Towards an ethically informed framework for managing patients with medically unexplained symptoms: developing boundary principles

by

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A thesis submitted in partial fulfilment of the requirements for the award of the degree of Doctor of Philosophy

June 2024

Keele University

Abstract

Introduction

Patients with medically unexplained symptoms (MUS), i.e., physical complaints not fully explained by somatic/psychiatric pathology, are well-documented as a significant problem in primary care. Yet, the issues these patients and their doctors face have rarely been examined from an ethical perspective.

Aim

Use the views and experiences of patients, and, empirical data from routinely recorded primary care consultations, to derive boundary principles – a series of normative statements that describe how ethical concerns around MUS should be characterized and responded to.

Methods

To ascertain facts and values that operate on the problem 1) a qualitative evidence synthesis of views and experiences of patients/doctors in diagnosing and managing patients with MUS, 2) identification of patients using routinely recorded electronic health records in primary care, and, analysis of epidemiological data as well as patterns of resource usage, and 3) systematic review of costs of patients with MUS in England and a cost of illness study, were carried out.

Results

Patients and doctors shared concerns about managing diagnostic uncertainty, emotional experiences (e.g., stigma, stereotyping), and resource availability. EHR data indicated support for these concerns: for e.g.: 55% of patients without a diagnosis continued to

consult for unexplained symptoms for five years consecutively; average annual consultation rate for patients who did not have their illness named was 22 cf. 12 for patients with a diagnosis; around a fifth of diagnosed patients had no investigations or referrals during five years of consulting, and around two-thirds of patients had a mental health issue on record. Estimated total cost of MUS to the NHS in 2021 was £4.6bn and the annual cost of each new patient cohort was £452m. Boundary principles derived from these values and facts were centered around building a therapeutic alliance based on a culture of respect, harm minimization and improved resources and capabilities.

ACKNOWLEDGEMENTS

This PhD journey truly has been one in which the journey was more important than the destination, for I learnt so much from great people; great not only because of their vast knowledge, expertise and experience, but because of their willingness to inspire, support, lend a hand, even when it caused considerable inconvenience. So, a heartfelt thank you to

- Professor Athula Sumathipala: When I count my blessings, you are right at the top of the list. Thank you so much, not only for what you have done for me, but for all that I have seen you do for others, even strangers. For portraying how fulfilling a life of knowledge-seeking and service to humanity can be.
- Professor Kelvin Jordan. You forced me to rethink, question, go from vague to precise. I could not have completed this thesis without your invaluable support, and more importantly, thank you for turning me into a more analytical thinker.
- Professor Sue Jowett. You supported me through masters' and PhD theses, and you were always helpful, encouraging and a friendly face to turn to when in need.
- Dr. Thomas Shepherd. You gave me the most practical advice right from the start.

I would like to thank Professor Christian Mallen, Professor Samantha Hider, Dr. Emma Healey, and Professor Oksana Kehoe of the Keele University for their kind support.

I thank the NIHR School for Primary Care Research for funding this research, and Dr. Georgina Fletcher, for her kind support.

Thank you James Bailey, Data Manager of Medical Records at the Keele University, for the critical support you gave in drawing down and analysing the data. This research could not

have been done without you. Thank you Dr. John Edwards and Dr. Ying Chen of the Academic Custodianship Committee of the CiPCA database, Jo Jordan, Dr. Nadia Corp and Dr. Opeyemi Babatunde of the Systematic Review Unit of the Keele University, for your kind support. Thank you Dr. Steven Blackburn and Adele Higginbottom of the PPIE team, and the members of the Research User Group at Keele University who helped make this research more relevant. Thank you Dr. Ross Wilkie, Dr. Lianne Wood, Dr. Tom Kingstone and Zara Richards of Keele University for your kind support.

Thank you Dr. Godwin Kodituwakku, Professor Gominda Ponnamperuma, Dr. Sudath Samaraweera, Dr. Kaushalya Jayaweera, Lasith Dissanayaka, Krishani Jayasinghe, Chamali Jayasinghe, Binoli Herath, Irushi Ediriweera, Maneesha Jayaweera, Aruna Walisundara, Ranisha Wimalasuriya, Sameeha Jabir, Dr. Enoka Wickramasinghe, Dr. Prabhath Ranasinghe, Dr. Asiri Hewamalage and all at IRD for your support over the years. Thank you Dr. Kalpani Abhayasinghe, who was there right from the start, to the very end, for all your help.

Thank you to my family, my much-loved fourteen-year-old son Dhiren Fernando whose immense kindness, support and love through the final sprint to finish this thesis will always be a treasured memory, to Lakmal Fernando, who has always been supportive of my academic ventures over the long years, to my sister Lakmalie Thilakaratne who looks out for me all the way from Australia, and to my very gentle mother Esha Vithanage who did everything she possibly can to make my life easier while I did this.

Thank you to my father Sandun Vithanage who instilled in me a lifelong love of books and learning – this is my gift back to you. I would not have completed this PhD if not for the memory of your trust in me.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AMED - Allied and Complementary Medicine Database

APA – American Psychological Association

CFS - Chronic fatigue syndrome

CiPCA - Consultations in Primary Care Archive

DSM-5 - Diagnostic and Statistical Manual of Mental Disorders-5

FM - Fibromyalgia

GBP – British pound sterling

GP - General Practitioner

EHR – Electronic Health Records

IBS – Irritable Bowel Syndrome

ICD-11- International Classification of Diseases-11

LHS – Left Hand Side

ME - Myalgic Encephalomyelitis

MEDLINE - Medical Literature Analysis and Retrieval System Online

MMS - Mortality and Morbidity Statistics

MUS - Medically Unexplained Symptoms

NHS – National Health Services

RHS – Right Hand Side

UK – United Kingdom

USA – United States of America

CHAPTER 01
INTRODUCTION, AIMS AND OBJECTIVES OF THE RESEARCH

1.1 Introduction

'Medically unexplained symptoms (MUS)' is a generic term used to describe what the Royal College of General Practitioners and the Royal College of Psychiatrists define as 'persistent bodily complaints for which adequate examination does not reveal sufficient explanatory structural or other specified pathology' (Chitnis et al, 2011, p.1).

In clinical practice, MUS is considered a working hypothesis that is adopted when a patient has complained of physical symptoms for several weeks, where appropriate medical examination and investigations have not indicated any medical or psychiatric pathology that adequately explains the symptoms, thus leading to the justified assumption that 'somatic or psychiatric pathology have been adequately detected and treated, but that the clinical condition presented by the patients was not adequately resolved' (Olde Hartman et al, 2018).

Considering MUS as a working hypothesis requires and allows for monitoring and revising the hypothesis if there is any change in the symptoms or any other cause for concern (Olde Hartman et al, 2013). This does not necessarily mean that a patient who complains of unexplained symptoms should not be given an explanation and a name about his complaint. For most patients, 'giving a medical name for their health problems is point zero' (Lian et al,

2021, p.7), since patients consider that receiving a diagnosis, or a name for their complaint, is the starting point for finding a solution to the problem.

Furthermore, it is important to recognise that following the changes in DSM-5 and ICD-11, that there can be somatic or psychiatric conditions concurrently with physical symptoms in some patients. In such patients, these physical symptoms are considered medically unexplained if they show greater severity or persistence than is expected according to the severity of the relevant condition (Olde Hartman et al, 2018).

The severity of MUS has been recorded in a spectrum ranging from mild and self-limiting to chronic, persisting and debilitating disorders, as well as to functional somatic syndromes, clusters of related symptoms specific to a certain organ system such as Irritable Bowel Syndrome, Fibromyalgia and Non-cardiac pain, though the concept of separate syndromes is questioned due to the significant symptom overlap in these syndromes (Wessely, 1999; Edwards et al, 2010; Rosendal et al, 2013; Olde Hartman, 2004; 2017; Leaviss et al, 2020).

Controversies in MUS: There is much dispute around MUS, starting with its epidemiology, and how it is conceptualised and classified (Rosendal, 2017; Jutel, 2010; discussed in detail in Chapter 3). Partly due to the wide-ranging terminology used to describe the illness (ranging from persistent physical symptoms, somatization, functional illness, psycho-somatic illness to malingerers, hypochondriacs, the "worried well" and hysterics), there is also limited consensus on the frequency of presentation of MUS: a systematic review found that MUS prevalence estimates in published research range from 0.1% to 60.7%, depending on the definition of MUS used (Haller et al, 2015). Management modalities for MUS are

disputed and so is operationalizing the term MUS – there is disagreement on what illnesses and which patients should be considered as falling within the umbrella term of MUS.

Diagnosis of MUS is a key point of contention: under both the DSM-5 (a frequently cited classification of mental illness, Diagnostic and Statistical Manual of Mental Disorders, DSM-5, 2013) and ICD-11 (a commonly used system of disease classification, ICD – 11 for Mortality and Morbidity Statistics, ICD-11 MMS, 2018), the current key diagnostic criteria are for the physician to consider that the patient has disproportionately intense and persistent thoughts about the seriousness of his/her symptoms, and a high level of health anxiety, typically for over six months. While patients state that they want a diagnosis, their illness named, since they perceive a diagnosis as a legitimisation of their illness, doctors may be reluctant to give a diagnosis of MUS, for fear of relaxation of clinical vigilance as well as due to concern for the patient who could be stigmatised through a diagnosis of MUS (Bayliss et al, 2016; Brownell et al, 2016; Pohontsch et al, 2018).

Due to the issues described above, some patients may not receive appropriate treatment, and illness can be perpetuated with repeated cycles of investigations and negative findings, leading to excessive resource usage for limited beneficial results (Smith et al, 2003; 2007; Collin et al, 2017). This is not necessarily due to a lack of evidence-based treatments for MUS (Sumathipala, 2007; Edwards et al, 2010).

It is also important to consider the limited number of patients who may be suffering from as yet undiagnosed somatic pathology, and it is to address this concern that doctors are given guidance to assess the necessity of a revision to the working hypothesis of MUS if there is any change in the symptoms (Olde Hartman et al, 2013). In one study, 12% of the

patients who received a diagnosis of MUS were found to have an underlying medical condition explaining their symptoms (van der Feltz-Cornelis et al, 2020). In another study, 51% of autoimmune disease patients reported that they were told the disease was “in your head” before the autoimmune disease was diagnosed (Ladd, 2014) and rare diseases, where diagnosis can be delayed up to seven years on average, often get categorised as MUS (Schmidt, 2011). A qualitative synthesis of 57 studies on fatigue in long-term conditions found that just over half of the patients complaining of fatigue in the studies had a cancer diagnosis (Whitehead et al, 2016). Eikelboom et al (2016) found in a systematic review and meta-analysis of 22 diagnostic evaluation and follow-up studies that 8.8% of patients initially diagnosed with a functional somatic syndrome had their diagnosis revised to account for underlying somatic disease. This should not be construed to mean that patients with MUS are patients with physical illness who are simply misdiagnosed. Indicating the complex, convoluted, nature of the problem of patients with MUS, Crimlisk et al (1998) reassessed patients with medically unexplained motor symptoms and found that, while the level of medical explanations for these patients was low, the level of psychiatric comorbidity was high.

The problem of MUS is frequently framed in the literature as an issue of resource utilisation and economics (Hiller and Fichter, 2004; DeWitt et al, 2009; Barrett et al, 2012). The 1.0% - 2.5% of MUS patients said to utilize a disproportionately high amount of the resources are frequently mentioned: in the UK, for example, the annual cost to the NHS has been estimated at over GBP3bn (Bermingham et al, 2010), whereas several published papers

quoted these estimates and extrapolated them incorrectly (and were subsequently corrected) to GBP12bn in 2015/16 (Chew-Graham et al, 2017; Payne & Brooks, 2018).

Issues in the diagnosis and management of patients with MUS: Qualitative research gives extensive evidence of the one matter related to MUS where there is almost unanimous agreement: that MUS is extremely difficult to manage. It is concerning that the patient experience across the world has been described as feeling 'frightened, ignored, belittled, accused, dismissed, or deeply and painfully humiliated by healthcare professionals on whose knowledge, skills and mercy we have depended when we were sick' (Atkins, 2010, p.xii, USA), that the patients' explanations regarding their illness was not taken in to account (Sumathipala et al, 2008, Sri Lanka), that their experience was met with 'disbelief, inappropriate psychological explanations, marginalisation of experiences, disrespectful treatment, lack of physical examination, not receiving appropriate treatment and receiving damaging health advice' (Lian & Robson, 2017, p.1, Norway), and that they felt it was necessary for the patient to prove worthy of being treated (Madden and Sim, 2016, UK).

Similarly, doctors face significant problems when managing patients with MUS. Doctors find these patients frustrating, difficult and demanding, feel powerless, fear missing an important physical diagnosis and face a moral dilemma – although the suffering of the patients is recognized, they trigger feelings of helplessness and guilt among practitioners as they struggle to help these patients (Dowrick, 2010; Johansen and Risor, 2016; den Boeft et al., 2016; Houwen et al, 2019). The lack of time and management options, the limited referral options, and the need to manage available resources efficiently exacerbate the problem for doctors (Bayliss et al, 2016; Brownell et al, 2016; Kromme et al, 2018; Rask et

al, 2021). When doctors speak of a relationship with patients being frustrating to the extent that it compromises their clinical judgment (Wileman, 2002; Atkins, 2010) and patients speak of being caused iatrogenic harm through consultations with their doctor (Page and Wessely, 2002; Stone, 2013), the problem warrants further investigation.

Do these issues amount to ethical concerns? Research on whether these problems amount to an ethical issue i.e., an issue of moral significance (Braunack-Meyer, 2001), and, if yes, primary ethical analysis of these issues, is limited.

Some guidance on whether these MUS related issues are indeed ethical concerns can be gained from their similarity to issues around which there is an ethical discourse. Some of the discussion around the ethical issues of epistemic injustice (Fricker, 2007; Drozdzowicz, 2021), justice and allocation of medical resources (Gillon, 1985), truth telling (Gillon, 1985; O'Leary, 2018), the ethics of diagnostic uncertainty and prescribing (Dowrick & Frith, 1999), ethical issues related to psychiatry (Shackle, 1985; Katz et al, 2014) and delivery of healthcare to stigmatised populations (Nikoo et al, 2015), are closely aligned with the issues related to MUS although they have not been discussed adequately except in relation to a few specific conditions. For example, epistemic injustice in healthcare encounters has been discussed as specifically applied to Chronic Fatigue Syndrome patients (Blease, 2016) and to Chronic Pain (Buchman et al, 2017).

Stone (2014) describes a few ethical issues related to MUS primarily in relation to the doctor-patient relationship, though without ethical analysis; Kanaan (2007) wrote one of few early papers on ethical issues in the management of somatoform disorders; Desai and Chaturvedi (2016) published a brief letter on the ethical dilemmas of MUS. The ethics of

MUS related issues such as informed consent, autonomy, and truth-telling are also discussed in the paper 'Why Bioethics should be concerned with Medically Unexplained Symptoms' (O'Leary, 2018), and the risk of misdiagnosis and harm is discussed in relation to the ethical psychotherapeutic management of patients with MUS (O'Leary & Geraghty, 2021).

It is important to assess and verify if patient and doctor concerns regarding MUS are indeed ethical issues, so that the weight of moral authority can be brought on to finding a solution to these problems. Based on these similarities, and working on the hypothesis that these issues could indeed be ethical concerns, the question arises of how they should be analysed, and to what end.

Dworkin (1978) helps clarify how to decide if an issue is indeed an ethical issue. To state that something is ethically wrong, and is an ethical concern,

i) it should be morally wrong, and not just a personal preference or prejudice,

ii) the reasons as to why it is a moral wrong, must meet the minimum standards of evidence and argument and must not be based on prejudice, alleged facts that may be false or implausible or on personal emotional reactions, and

iii) such reasons should presuppose a general moral principle or theory.

However, establishing that these MUS related issues are a moral wrong alone would be of limited use if there is no attempt to find a solution to such issues.

Available evidence on MUS related concerns not sufficiently comprehensive:

Qualitative research findings have clearly indicated that there are potential ethical issues in the way MUS patients are diagnosed and managed (as discussed in detail in Chapter 4); however, qualitative evidence is usually generated based on small samples which may not be representative of the wider population, and it has been said that there is a risk of the findings being a mere collection of personal opinions that is subject to researcher bias (Hammarberg, 2016, Noble & Smith, 2015). It is therefore necessary to assess if these findings are significant and present to the extent that they should be an ethical concern.

One of the ways this can be done is to consider if there are commonalities in the qualitative research findings, for example by carrying out an evidence synthesis of the available qualitative research on MUS issues. In addition, it may be possible to analyse quantitative data to support (or refute) some of the qualitative research findings, to ascertain if there is supporting evidence for these issues being present in the wider population; for example, it is possible to verify if there are indeed delays in naming the illness in the case of MUS patients, to assess the duration of their symptoms, and to calculate the costs incurred by these patients by looking at routinely collected consultation data.

The primary focus of this study is England, however, when analysing the data on MUS available for England, the published data on MUS prevalence, identification, management, costs etc., is confusing and not comprehensive, as discussed in detail in Chapter 3, due to

- the wide variation in defining, operationalising MUS,

- most data originating from patient sample groups included in trials, which are not necessarily representative of real-life situations (for e.g., patient selection into trials depends on the research protocol defining severity, duration, disease outcome and as a result, severe MUS patients alone may be included in the trial, or, alternatively, consent for research participation could be denied due to poor doctor-patient relationship in severe MUS patients, who may then be under-represented). Where population-based samples were used, data was mostly sourced from questionnaires, in which case data quality can be compromised due to recall bias varying with factors such as time and current intensity of symptoms (Schmier et al, 2004).
- GPs reluctance to record a diagnosis of MUS for patients can lead to systematic under-reporting of these patient populations in primary care data (Olde Hartman et al, 2013; Payne & Brooks, 2016); and despite the considerable amount of research on MUS carried out on large consulting populations (Ring et al, 2005; de Waal et al, 2008; Olde Hartman, 2011; van Eck van der Sluijs et al, 2015), there is further need for research covering timeframes longer than 2-3 years, using reliable longitudinal data.

The broader, longer-term perspective necessary to understand and manage widespread, chronic conditions such as MUS is therefore limited in England.

- very few cost estimates have been made on costs of MUS for England, and the most frequently cited numbers (Bermingham et al, 2010), were calculated based on Dutch, German and American data, where management and healthcare systems are very different, which could skew the estimates.

To summarise, the core MUS related concerns that prompted the work of this study, as evidenced in detail in Chapters 3 and 4, are as follows:

- Qualitative research provides evidence of
    - some patients with MUS feeling stigmatised, humiliated, particularly by the healthcare profession, suffering iatrogenic harm, and not receiving the appropriate care,
    - some doctors feeling frustrated and helpless due to difficulties in managing these patients.
- Furthermore,
    - Some patients are misdiagnosed as MUS patients due to diagnostic uncertainty and the lack of biological disease markers, and
    - MUS patients are considered to be costly and excessive users of scarce resources.
- However, qualitative research evidence carries the concern if the conclusions are representative of the wider population, and needs further corroboration.
- The data available currently on MUS prevalence, duration, recognition, management, and costs is not sufficiently comprehensive to arrive at a clear conclusion on the extent and significance of MUS as a concern in real-life practice, particularly in England.
- Globally, there has been limited discussion on whether the issues MUS patients face are an ethical concern and if attention ought to be drawn to these issues for example,

similar to the way the need for ethically sound management of psychiatric patients has been discussed (Lolas, 2006; Drozdzowicz, 2021). Moreover, there is limited guidance available on how best to manage these concerns ethically.

- Ethical analysis of MUS related issues is complicated due to the conflict between ethical principles involved – for example, the conflict between the principles of autonomy and beneficence in the question of patients' requests for a diagnosis, a naming of the illness. Another example is the conflict between the principles of autonomy and justice / fair resource distribution in the context of patients' requests for repeated investigations.

The research questions this thesis seeks to answer therefore are as follows (Table 1.1):

Table 1.1. Research questions
1. What are the issues faced in the recognition and management of MUS patients, from the perspective of patients, and physicians? 2. What does the empirical evidence from large consulting populations indicate about the extent and intensity of these issues? 3. What are the ethical principles that give guidance on deciding if these MUS related issues are ethical concerns? 4. Taking guidance from relevant ethical principles and empirical data, is it possible to develop the boundary principles that form the basis of a framework to better manage patients with MUS ?

To answer these questions, an appropriate methodology to investigate the issue needs to be selected.

A methodology to investigate MUS related concerns: Bioethics investigates ethical issues related to medicine, healthcare, research, and related subjects using relevant principles and methods of moral philosophy, and moral philosophy is considered the core method of carrying out bioethical inquiry (Harris, 2004).

Normative ethics specify the moral standards that define right and wrong conduct and morality is one of the normative systems; other normative systems, which set out the rules of correct conduct, include for example, the legal system, rules of religions, and even the rules of etiquette (Harris, 2004).

Bioethics, as a branch of applied ethics, cannot focus on ethical theories alone and must consider ethics in the context of how it is practiced in real life. Ethical theories, principalism, for example, set out how the situation 'ought' to be.

Such ethical reasoning that does not reference real life situations, can result in criticism that the ethical claims are impractical, reducing their perceived validity and limiting their application in policy and practice (Hedgecoe, 2004).

Glover (2000) stated that morality needed to be humanised by rooting it in human needs and human values and Ives et al (2017: ix) refer to this requirement as applied ethics needing to have 'real world purchase'; they state that in order for ethics to be relevant to the realities of morality as it is dealt with in day-to-day life, the research process used to analyse it in applied ethics needs to ensure meeting one or more of three conditions: that

the ethical issue is i) 'genuine and authentic', ii) analysed with reference to the circumstances of the case, iii) pragmatic and that there is an attempt to generate a solution to the problem of how one ought to act to address the ethical concerns in a way that is acceptable and implementable.

Descriptive ethics describe ethical issues, describing the situation as it 'is' but does not discuss or evaluate how the situation 'ought' to be, or instruct people on how they ought to act.

Empirical data, obtained through observation, can provide the real-life information of how people act/think and the context of the situation for the issue under consideration. However, 'doing ethics by head count', collecting information about the common viewpoint on an issue and considering the majority view as the 'right' (or wrong) conduct, is incorrect, particularly if the information is merely 'a collection of recorded prejudices or evidence of a slavish and uncritical adherence to a sectarian normative system' (Harris, 2004: 12).

Parker (2009) analyses this as descriptive ethics failing to distinguish clearly between describing and evaluating and therefore failing to give motivation to and to guide what ought to be done. Ives et al (2017: 3) give several examples of strategies used in empirical research on bioethical issues including 'empirical identification of ethical issues in practice, empirical substantiation of practical moral arguments and empirical evaluation of implementation of ethical arguments/interventions in practice.'

These research designs, however, do not lead to finding a solution to the ethical concern, or provide recommendations on what is the right thing to do in order to address the ethical issue.

Empirical bioethics attempts to integrate empirical enquiry, i.e., research to obtain information on how people act/think in real world situations, with normative enquiry, i.e., research on what ought to be done, the right thing to do/think.

The key differentiating factor of empirical bioethics as a research strategy is the combination of empirical and normative research to find a solution for ethical problems and concluding on what ought to be done; such conclusions are 'meaningfully informed by observation and understanding about the way the world currently is' (McMillan, 2016 in Ives et al, 2017: 8).

Reflexive Balancing (RBL) is a pragmatic empirical bioethics methodology that permits the drawing together of stakeholder views, empirical data and theoretical perspectives. It takes a consultative approach where the researcher consults the data and conducts the normative analysis, and although participants' views and experiences are incorporated in the analysis, the participants themselves are not involved in the process of forming normative conclusions (Ives, 2014; Davies et al, 2015; Ganguli-Mitra, 2017).

Furthermore, it provides a mechanism to find an acceptable compromise as a solution to the ethical dilemma of conflicting ethical principles when considering the point of view of doctors and patients (Davies et al, 2015).

RBL consists of three phases:

1) identifying a moral problem,

2) developing boundary principles that form the basis for a framework of a solution to the moral problem by conducting disciplinary naïve inquiry and ascertaining facts and values that operate on the problem, and,

3) generating normative solutions to the moral problem by trying to find coherence between the boundary principles and accepting / rejecting each principle by challenging it with alternative theoretical challenges and / or disconfirming empirical data.

1.2 Aims and Objectives of this Research

To fill the gaps in information about MUS to inform future guidance for better management of MUS patients in primary care in England, the overall aim of this thesis is

To integrate

i) empirical inquiry - research carried out to establish factual evidence of whether there are problems/issues specific to MUS recognition and management that are widespread

with

ii) normative inquiry – research on the ethical principles that give guidance on the right thing to do, in order to

iii) develop a framework of a solution to the moral problem by setting out the boundary principles, i.e. the set of facts and values that operate on the problem.

Table 1.2. Objectives
1. Describe key themes emerging from qualitative research studies regarding experiences of patients and clinicians in recognising and managing MUS. 2. Assess the extent to which real-life data can support the findings described in qualitative research by analysing the current patterns of recognition, management, healthcare resource utilisation and costs of MUS as routinely recorded in a consulting population in primary care in England. 3. Discuss the ethical principles and theories relevant to determining if MUS related issues identified are ethical concerns. 4. Apply relevant methods and principles of moral philosophy along with the findings from empirical data to develop the boundary principles that form the basis of a framework to better manage patients with MUS.

RBL requires carrying out disciplinary naïve inquiry in to the problem. Qualitative data on the values operating on the MUS-related concerns of both patients and doctors is sourced from an evidence synthesis of published qualitative research on MUS globally. Real-life quantitative data to support (or refute) these MUS related issues are examined for England, in primary care, where most MUS cases are first encountered, using electronic healthcare data routinely recorded in a primary care database. Conducting research using routine electronic healthcare records (EHR) provides cost-effective and reliable data on morbidity,

and enables monitoring changes in longitudinal studies, if recorded with high validity and integrity (Jordan et al, 2004; Khan et al, 2010). Research in a consulting population enables studying how MUS is recognised and managed in real life (as opposed to under trial conditions). A systematic review of published data on costs of MUS is carried out for England, and, actual costs incurred for MUS patients are calculated using EHR data from the primary care database. The research questions, objectives, and a brief description of the methods to achieve each objective is summarised below in Table 1.3, detailed methodology will be discussed under each chapter.

Table 1.3. Summary: Research questions, objectives, and methods	
Research question	**Objectives and methods**
1. What are the issues faced in the recognition and management of MUS patients, from the perspective of patients, and physicians?	Describe key themes from qualitative research on experiences of patients and clinicians in recognising and managing MUS by carrying out an evidence synthesis.
2. What does the empirical evidence from large consulting populations indicate about the extent and intensity of these issues?	Assess the extent to which real-life data supports qualitative research findings by analysing current patterns of recognition, management, resource utilisation and costs of MUS as routinely recorded in a consulting population in primary care in England.
3. What are the ethical principles that give guidance on deciding if these MUS related issues are ethical concerns?	Discuss the ethical principles and theories relevant to determining if MUS related issues identified are ethical concerns.
4. . Taking guidance from relevant ethical principles and empirical data, is it possible to develop the boundary principles that form the basis of a framework to better manage patients with MUS ?	Apply relevant methods and principles of moral philosophy along with the findings from empirical data to develop boundary principles that form the basis of a framework to better manage patients with MUS.

1.3 Importance of this research

MUS is a common problem in clinical practice, which can account for up to 61% of all consultations in primary care (Haller et al, 2015, as discussed in detail in chapter 3). Despite the evidence from patients of not receiving appropriate treatment, of stigma and discrimination, some evidence of excessive resource usage by these patients, and of the difficulties doctors face when managing MUS patients (as discussed in detail in Chapter 4), there has been very little discussion of these issues as an ethical concern, nor of how these issues can be handled in a more ethical manner.

This study is novel because it is tackling an area in medical ethics that has had limited investigation previously. It is important to discuss these concerns from an ethical perspective as it can help focus on the specific aspects of the issue that are contentious, give the justification for why ethically questionable behaviour should be avoided, provide a moral framework to guide on the correct actions, and, as it can affect the way doctors and patients behave in dealing with the issues related to MUS, to bring about better outcomes in patient management.

What is also new is that the final outcome of the study is to develop boundary principles that provide a framework of a solution to guide managing MUS more ethically, which has not been done before. The theory behind the ethical framework is grounded in real-world experiences of patients and clinicians using the methodology of reflexive bioethics and reflexive balancing, which too has never been done before.

Since a concern regarding qualitative data is that it may not be representative of the wider population, this study uses quantitative data to support (or refute) the findings of qualitative research, and to examine if the issues of MUS are severe and widespread under real-life conditions to merit being a public concern. Using quantitative data to validate findings of qualitative research is a methodological innovation in this area, which has not been seen in a horizon review of the relevant literature.

Quantitative data on MUS in England has some inconsistencies due to the lack of consensus on conceptualisation, definition, and operationalisation of MUS, with even prevalence data ranging from 0.1% to 60.7%, as discussed further in Chapter 3. Although there is a significant body of research on MUS on consulting populations, there is only a limited amount of research covering timeframes longer than 2-3 years. Research on MUS has mostly been carried out under trial conditions, in patients referred to secondary care or sometimes on population-based samples. Population based research is most often carried out through data sourced from questionnaires, where the data quality can be compromised, due to the restricted nature of questionnaires, and also due to recall bias; the outcome of the healthcare encounter can impact the way in which a patient remembers related events, and it is also coloured by the time that has passed since the event described (Pannucci & Wilkins, 2010, Janssens et al, 2018). Trial conditions may not always be representative of the real-life situation.

To fill these lacunae in MUS research, this study uses routinely recorded electronic healthcare data from a primary care database to examine the epidemiology of MUS and how it is being managed over a five-year timeframe, which has not been done previously.

This allows examination of time taken to name the illness in a patient as MUS, treatment given, duration of the complaints of MUS, as it has happened in real-life. This is also one of the few occasions when qualitative and quantitative data related to MUS are investigated in a combined approach.

This study examines the empirical data related to MUS comprehensively in order to develop the boundary principles that form the basis for a framework that helps manage MUS related issues more ethically, filling an important and urgent need to discuss and address the ethical issues around MUS.

CHAPTER 02
METHODOLOGY

2.1 Introduction

This chapter looks at the overall methodology of the thesis – the methodology to develop the boundary principles that form the basis of a framework to manage patients with MUS more ethically as well as effectively. Developing the boundary principles based on empirical data requires integrating empirical research with normative enquiry and therefore, several different types of methodologies are required: 1) the methodology of empirical bioethics leading to the method of reflexive balancing, 2) methodology of qualitative evidence synthesis, and 3) methodology to carry out electronic healthcare record analysis and collate cost data. The methodology to integrate the empirical research with normative enquiry is discussed in this chapter. Specific methods related to each of the empirical data analysis components of the research are described under the relevant chapters.

The primary motivation for the work described in this thesis was a 'moral intuition' that there is 'something' wrong in the way patients with medically unexplained symptoms are dealt with in healthcare systems. This intuition, or 'strong, stable, immediate moral belief' (Doris et al, 2010, p.246), however, was precipitated by engagement with hard evidence from the significant body of qualitative research that describes the experiences of these patients, as well as on the evidence of excessive resource usage by these patients from quantitative and economic research in a resource-constrained healthcare system. In addition to this engagement with the literature, in the context of research work carried out

as part of previous research projects related to patients with MUS, there was also anecdotal evidence gathered from listening to the lived experiences of both patients with MUS and with doctors, particularly general practitioners, during those research projects. The researcher being an ethnic minority female may have supported this intuition since the majority of patients with MUS are female. Since a moral intuition of 'a wrong' could predispose towards a bias in research conclusions, conscious effort was taken in designing the research methods to avoid such potential bias.

The problems patients with MUS and their doctors face are described extensively in qualitative research, and are remarkably similar around the world and over time, as discussed in detail in chapters 3 and 4. Secondly, it appeared wrong that the most frequent justification put forward for the need to better manage these patients, who are said to account for up to 61% of patients in primary care (Haller et al, 2015), was based on economic concerns. The discussion around the ethical aspects of the problems with patients with MUS is limited, and furthermore, the economic argument also appears futile: despite patients with MUS being a significant cost to the overall healthcare system, the financial gains of diagnosing and effectively managing a MUS patient was found to be insignificant for individual doctors or GP practices (Gathogo & Benjamin, 2013). Emphasis on economic gain was therefore not a particular incentive for a GP practice to better manage MUS patients.

Moral intuitions: Moral intuitions are immediate, strong beliefs about what is right or wrong; they are immediate because they arise without a process of conscious, rational thinking, are strong because the holder is confident about the belief, and it is a belief held

over time, not an idea held temporarily and then discarded (Sinnott-Armstrong et al, 2010). Moral intuitions are said to be useful and relevant to ethical judgment as they can be the foundation for further ethical deliberation and exploration (van Willigenburg, 1991, in Ives et al, 2017); but it is also said to be lacking credibility as the moral principle or theory built based on moral intuition alone could end up being nothing but a systematised statement of a person's judgement, subjective, biased and even wrong (Strong, 2010).

Ethical theories and principles in existing research: Since moral intuition alone is not a strong foundation to mandate ethical action, it was necessary to examine if there is a theoretical basis or framework that gives a coherent and comprehensive view of the concerns around the diagnosis and management of MUS patients. Research on these issues was found to be limited. One of the early papers on issues related to MUS discusses the ethical concerns of diagnostic uncertainty and of prescribing (Dowrick & Frith, 1999); other related ethical discussions include that on epistemic injustice (Fricker, 2007), ethics of psychiatry (Katz et al, 2014; Drozdzowicz, 2021), and healthcare delivery to stigmatised populations (Nikoo et al, 2015).

Kanaan et al (2007; 2009) discuss the ethical conflicts around MUS from the point of view of the clinician and relates them to the principles of autonomy, beneficence and non-maleficence. A paper on the ethical issues in managing MUS in developing countries brings in the issues of resource constraints and justice into the discussion (Chandra & Sathyanarayana, 2013). Discussion relating to epistemic injustice in CFS (Blease, 2016) informed consent, autonomy and truth telling (O'Leary, 2018, 2021), the ethics of diagnosis

and the doctor patient relationship (Stone, 2018), have contributed to initiating the discussion on MUS related ethical issues.

Need to formulate normative recommendations to guide ethical management of MUS: As discussed in chapter 1, it is important to establish that MUS-related concerns are indeed ethical issues so that the weight of moral authority can be brought on to find a solution to these issues. However, there has been limited attempt to provide a solid moral / ethical foundation for the concerns surrounding patients with MUS or to provide clear guidance on the actions to manage these patients *ethically*; though there is much literature on managing MUS patients, the focus is usually on clinical effectiveness and how to reduce symptoms and resource usage. Once established that they are indeed ethical concerns, it is necessary to formulate normative recommendations to guide action – what we 'ought' to do.

Need for 'Real-world purchase' for normative recommendations: The limited ethical literature on MUS related issues is mostly focused on ethical theories and principles which set out how the situation 'ought' to be. Ethical theories and principles are often not related to how things happen in real life, neither do they always guide on situations where two ethical principles are in conflict. Just as moral intuition alone is an insufficient foundation, ethical theories and principles alone too may not be robust enough to guide ethical action, since they may be perceived as impractical and not feasible in real-life. It is therefore necessary for any normative recommendations to have 'real-world purchase' through being authentic, being analysed with reference to the circumstances of the case and being pragmatic with the aim of answering the question of how one should act in order to be acting ethically (Ives et al, 2017: ix).

Empirical data provides 'real-world purchase': Research on what is actually happening in the real world in the diagnosis and management of MUS patients, empirical research, tells the actual 'is' situation. Such empirical research findings can help the normative ethical recommendations to be grounded in reality, however, this does not mean that the majority opinion is the ethically correct opinion – doing ethics by head count can lead to wrong conclusions.

How empirical research can inform bioethics: One of the simpler versions of how empirical research can inform bioethics is described by Kon (2009) as empirical research falling into four categories:

1) 'Lay of the land' research – uses qualitative or quantitative methods to describe the current situation (e.g., practices, beliefs). An early example of this type of research related to MUS is "Medically unexplained symptoms – GP's attitudes towards their cause and management" which surveyed GPs and found that their attitudes ranged from considering adequate investigations and referrals as necessary in order to exclude organic disease and to reassure the patient, the need for a multi-disciplinary approach with counselling for these patients, to 'Most of MUS are related to not wanting to go back to work and medical sick benefits' (Reid et al, 2001: 521). This type of research is more descriptive than analytical and can be useful to indicate necessity for further research.

2) 'Ideal vs Reality' research – begins with an ethical premise related to an established ethical norm and examines the current situation to assess to what extent reality matches the ideal. In 'A narrative review of the impact of disbelief in chronic pain' (Newton et al, 2013), the study starts with the ethical premise of epistemic injustice (although the term is

not used), explains the reasons why it is wrong to disbelieve patients, how the patient is disempowered by this disbelief and states that healthcare personnel have a responsibility to acknowledge and recognise a patients' suffering. They then carry out a narrative review of research containing first person accounts of patients who had their complaints of pain disregarded and disbelieved, reviewing the extent to which current practice extends such epistemic injustice.

3) 'Improving care' research – the next step in empirical research is to attempt to solve the problems discovered through the 'ideal vs reality' type of research. The aim here is to design and test new tools to help in the ethical management of patient concerns; this is critically important to effect change in practice, but it is much less common than the first two types of research. An excellent example of this type of research is the work described in 'Turning theory into practice: rationale, feasibility and external validity of an exploratory randomized controlled trial of training family practitioners in reattribution to manage patients with medically unexplained symptoms' (the MUST, Morris et al, 2006).

In this study, 'reattribution' was developed as a new approach to better manage MUS patients, GPs were trained in reattribution, and the impact of the training was examined. Further research was then carried out to find out the GP's opinions about reattribution training (Dowrick et al, 2008). Such research too is crucial in understanding if interventions are successful, and the reason why if they are not.

4) Changing Ethical Norms – this is where a synthesis of empirical research findings serve as the basis for a bioethical argument for changing ethical norms. It is not a mere meta-analysis. Kon (2009) uses the example of how, over the years, an extensive body of

empirical research on the ethics of medical decision making and of patient preferences, led from medical paternalism to patient autonomy in decision making, and then towards a shared decision-making model.

2.2 Integrating empirical research with normative enquiry

It is critically important to avoid taking an 'is' claim, and directly derive an 'ought' claim from it (Kon, 2009: 59). What is necessary is to figure out how the 'is' can inform the 'ought' and then to find a method to integrate empirical findings into normative ethical reasoning (Ives and Draper, 2009), to arrive at normative recommendations to guide ethical action.

Bioethics is a vast area combining a number of disciplines, empirical bioethics is even more complex. Research strategies, methodologies and methods used are so numerous and diverse, and described as sometimes so vague that 'making sense of it is a challenge for even the most seasoned researcher' (Ives et al, 2017).

Not being a 'most seasoned researcher', and undertaking this work as a sole researcher, the researcher and her supervisors decided that that the best way forward was to study a few of the research strategies and methodologies that appeared most suitable to manage the complex ethical dilemmas of MUS, to select one research strategy and one methodology from the literature that was comprehensive, well-justified and explained in sufficient detail, to adapt that process to the current research, and explain deviations from it, if any. Accordingly, this thesis uses empirical bioethics as the research strategy and broadly follows the theoretical reasoning and practical strategies described in detail in *Empirical Bioethics,*

theoretical and practical perspectives, edited by Jonathan Ives, Michael Dunn and Alan Cribb (2016).

It should also be mentioned that the final version of the research strategy, method and methodology described here were arrived at after many false starts. Different areas of focus and different ways of compiling and presenting this multi-stranded research project were trialled, and modified before arriving at the final version.

2.2.1 RESEARCH STRATEGY: EMPIRICAL BIOETHICS.

Empirical bioethics was chosen as the research strategy since the final outcome targeted from this research is to identify the facts and values that operate on the identified moral problem: is it possible to manage patients with MUS in a better, more ethical way?

Empirical bioethics alone has the primary objective of generating solutions, when compared to other research strategies (for example, empirical substantiation of practical moral arguments, empirical evaluation of implementing ethical interventions), as pointed out by Ives et al (2017). They also point out that in generating solutions, what is required is to not merely use facts to prove a point, but to integrate the facts about how the real world 'is' to work out how the real world 'ought' to be, going beyond merely having two separate phases of empirical and ethical research.

2.2.2 METHODOLOGY AND METHOD TO INTEGRATE EMPIRICAL FINDINGS WITH NORMATIVE PRINCIPLES

A comprehensive overview of methodologies used to integrate empirical research and normative inquiry based on a systematic review (Davies et al, 2015), revealed 32 different

types of empirical bioethics methodologies, which the authors classified in to two main groups: 1) dialogical – where the researcher generates normative conclusions through a dialogue with participants and justifies these claims through building consensus with the participants; and 2) consultative – where the researcher conducts empirical research to collect empirical data, analyses the data, draws normative conclusions from that empirical data, and justifies the normative conclusions by investigating the conclusions rationally and coherently.

In this research project, the objective is to remain consultative in approach, in keeping with the type of research carried out, collecting empirical data, analysing and drawing conclusions from it.

Choosing a methodological approach proved to be complicated. Four distinct methodological approaches were considered as potentially appropriate for this study:

1) **Feminist empirical bioethics**: Drawing from feminist bioethics which focuses attention on how discrimination based on factors such as gender, ethnicity, disability and economic power drives and perpetuates injustice in healthcare, public health and research, feminist empirical bioethics combines empirical research with feminist theory to build normative guidelines (Scully, 2017). Feminist bioethics is particularly suitable for dealing with the power imbalance, gender bias, epistemic injustice issues of MUS patients, as the focus is on bringing the views of disregarded, marginalised stakeholders into the process of analysing ethical issues, and finding solutions for it.

This research work, however, aims to incorporate the voices of those on both sides of the power balance equation; the mostly female patients, but also that of the doctors, and therefore requires a methodology with a broader approach than feminist empirical bioethics.

2) **Wide Reflective Equilibrium (WRE)**, described by John Rawls as an argumentative method for developing and justifying principles for a just society (Rawls, 1971, 1999). This approach to solving ethical problems was one of the earliest to deviate away from the 'top down' approaches that use moral theories and principles alone to justify solutions to ethical problems (Ives, 2014). There are many versions of WRE and the method proposed by Ebbesen and Pedersen (2007) using phenomenological hermeneutics to gather and interpret data along with WRE to conduct the analysis and generate normative conclusions appeared feasible for use in this situation.

A critical problem with reflective equilibrium, though, is that it is not possible to be certain that the final outcome is not merely a systematisation and justification of the researcher's own moral judgments. A key premise of this thesis is that it should bring out the voices of the key stakeholders and not of the researcher; WRE was found to be not suitable for this research project due to the risk of WRE merely justifying the researcher's views rather than stakeholder views.

3) **Normative – Empirical Reflective Equilibrium (NE-RE)**, brought forward by van Thiel & Van Delden (2017), is a modified version of Rawls' reflective equilibrium (RE) and proposes bringing together moral intuitions, moral principles, morally relevant facts and background theories coherently to build morally defensible arguments to justify solutions to ethical

problems. NE-RE was considered suitable as the methodology for this research for the two reasons that distinguish it from reflective equilibrium: 1) NE-RE incorporates moral intuitions from sources other than the researcher (whereas RE mostly considers the moral intuitions and considered moral judgments of the researcher), and 2) empirical research is used to obtain data on moral intuitions and morally relevant facts. The authors defend these features by explaining that incorporating the moral intuitions and considered moral judgements of different stakeholders brings in experiences and insights otherwise unavailable that can enrich the development of normative principles.

However, there is limited clarity on how to move from the stage of reflexive equilibrium to developing solutions / recommendations / guidelines to resolve the ethical problem/s at hand.

4) **Reflexive Bioethics**, Reflexive Bioethics was proposed as a methodology specifically for 'interdisciplinary and empirical bioethics' using 'the method of Reflexive Balancing (RBL)' and is 'primarily aimed at research projects that seek to produce recommendations for action' (Ives, 2014: 303).

The process of Reflexive Balancing starts with identifying a moral problem through experience, theoretical considerations or through empirical literature. The next step is to identify the core values that affect the stakeholders' views about the ethical problem through existing or new empirical research, and these become the 'boundary principles' formulating the initial hypothesis. Boundary principles can be characterised as a series of normative statements, where each normative statement characterizes a specific ethical concern and describes how that ethical concern should be responded to.

What differentiates Reflexive Bioethics is that the research at this stage is 'disciplinary naïve' (Ives, 2014: 311); the aim is to examine the ethical problem from multiple perspectives, and fully understand the context of the problem at a both micro and macro level, in the way that it is understood and defined by stakeholders. Formulating the most suitable research questions to elicit this information is the challenge at this stage. In the third stage of Reflexive-Balancing, the boundary principles are challenged systematically; akin to the way the null hypothesis is challenged and the researcher rejects / fails to reject the null hypothesis based on the evidence (Ives, 2014).

Reflexive bioethics as the methodology and the method Reflexive Balancing although used often with qualitative research, and to find solutions to a single ethical issue (Morley et al, 2021, moral distress in nurses), has also been used to explore broader themed multi-disciplinary projects. A case in point is a project involving ethical, legal and methodological aspects of best interests in decision making in healthcare, using not only empirical bioethics and research ethics methodologies, but also socio-legal scholarship, setting the precedent for its use in research of the type carried out in this study (BABEL, University of Bristol).

2.3 How the method of Reflexive Balancing is applied

This research uses empirical bioethics as the research strategy, reflexive bioethics as the methodology (Huxtable & Ives, 2019: 89), and uses the method of reflexive balancing.

Reflexive Bioethics and the method of RBL were selected since they align with several key features of this research: 1) RBL takes a pragmatic approach and permits inclusion of beliefs based on coherence, 2) the primary belief system incorporated in to a study – the boundary

principles - are derived from empirical data – permitting the voices of the stakeholders to be heard rather than that of the researcher, 3) incorporates interdisciplinary research, 4) the disciplinary-naïve inquiry formulation permits deviations from the standard method to incorporate the qualitative and quantitative research envisaged for this study, and, 5) the methodology permits limiting the research to the second stage of the RBL method to the extent that is feasible for a single researcher PhD project, so that the final outcome of this study is identifying the facts and values that operate on the moral problem, and developing a framework of boundary principles.

The framework of boundary principles developed from this research project could later be challenged and subjected to reflexive balancing to arrive at normative recommendations to manage MUS patients more ethically; this last phase of the reflexive balancing method would need to be carried out at a later stage and is out of the scope of this study.

Table 2.1 summarises the process of Reflexive Balancing as it was described in the original paper (Ives, 2014), and how it has been applied in this research.

Table 2.1: How the method of Reflexive Balancing is applied in this research	
Steps required	**Steps taken in this study**
RBL Step 1: Identify moral problem from theoretical considerations, practical experience, engagement with empirical literature, mix of all 3.	The moral problem: Is it necessary to develop an ethically informed framework for managing patients with MUS better? – is identified through engaging with the empirical and theoretical literature. ***Chapter 3 – A comprehensive overview of MUS***
RBL Step 2: Disciplinary-naïve inquiry into the problem from multiple perspectives Key aims at this stage: a) Uncover and explore, from multiple perspectives, all values operating on the problem. b) Fully understand the micro and macro context of the problem, the way it is constructed, experienced and lived through by stakeholders, with the aim of uncovering recalcitrant experience that has to be considered. c) Ascertain the facts and values that operate on the moral problem that then act as a framework of quasi-foundational boundary principles.	**1) Derive the ethical and empirical issues that impact on the problem:** i) Values of stakeholders derived from qualitative evidence synthesis of patients' and doctors' experiences in managing patients with MUS ***Chapter 4 – Qualitative Evidence Synthesis*** 2) **Elicit the factual data to support / refute the issues arising from the qualitative data using**: i) Analysis of real-life routinely recorded electronic healthcare records of consultations in a primary care data base. ***Chapters 5 – 10 MUS in Primary Care study*** ii) Systematic review of costs of MUS; cost of illness study - ***Chapters 11-12 Costs of MUS in England study*** ***3)*** **Based on these values and facts, and relevant ethical principles, derive the boundary principles, i.e. the series of normative statements that describe how ethical problem should be characterised and responded to *Chapter 13 – Moral principles relevant to MUS related concerns; Chapter 14 - Deriving Boundary Principles***
RBL Step 3: Reflexive Balancing Systematically challenge boundary principles by actively searching for disconfirming data to arrive at a set of normative recommendations that are coherent with each other.	This final phase is not undertaken in this study.

The objective of Step 2 – Disciplinary naïve inquiry is an in-depth analysis from many perspectives for a more holistic view of the problems at hand. In this project, the breadth and depth of the existing qualitative research evidence made further empirical data collection first-hand through stakeholder interviews superfluous, since there is a rich literature of in-depth qualitative exploration, from which it is possible to extract patients' and doctors' views and experiences regarding issues related to MUS. Such use of qualitative research in bioethics is well-established now (Wangmo and Provoost, 2017), and the views expressed in such primary research can be synthesised and used to extract the values of stakeholders on ethical issues. This research is detailed in *Chapter 4 – A Qualitative Evidence Synthesis of Patients' and Doctors' experiences in diagnosing and managing MUS.*

Next, in order to elicit the factual data to support /refute the issues discussed in the qualitative data, an in-depth analysis of real-life routinely recorded electronic healthcare records of consultations in a primary care data base was carried out – this study is detailed in *Chapters 5-10 – the MUS in primary care study.* This section takes up a large amount of space in this research since the validity of the findings depend on the methodological rigour under which this quantitative, electronic healthcare record (EHR) based research is carried out. A systematic review is carried out first to determine the mechanisms of identifying MUS patients in EHR data, and the findings from the review are incorporated into this research. The research design and process are examined and approved by both experts in MUS, Primary care and EHR-based research, and information on the methodology and processes leading to the findings are provided in detail in these chapters.

The facts related to resource usage and the costs of patients with MUS are investigated through a systematic review of the existing literature on the costs of MUS in England, followed by a cost of illness study of the costs of MUS in England, which again provides independent, real-life evidence, and is described in *Chapters 11 – 12 Costs of MUS in England study.* Similar to the MUS in Primary Care study, the methodology is detailed in the chapter and the study design and process were supervised and approved by a health economics expert to ensure methodological rigour.

Based on the values and facts identified from this disciplinary naïve enquiry, and using relevant ethical principles sourced from theoretical literature, the next step is to derive the boundary principles, i.e. the series of normative statements that describe how the ethical problem should be characterised and responded to, as described in *Chapter 13 – Moral Principles relevant to MUS related concerns and Chapter 14 - Deriving Boundary Principles.*

The process of how the ethical principles and facts that impact on the problem derived from empirical data can be used to formulate the boundary principles, and at a later stage subjected to the reflexive balancing process, to formulate an ethically informed framework to manage MUS, is illustrated here using an example, for clarity (although this is part of the findings of the research and is discussed in detail later on in Chapter 14).

The evidence synthesis revealed that a frequently repeated concern of MUS patients is that they do not receive a diagnosis, whereas they wish to have a diagnosis since they believe delayed diagnosis has an impact on legitimising their illness, and since naming the illness is perceived as a first step in finding a solution to their problems. To support (or refute) this complaint about delayed diagnosis, real-life recorded data of a consulting population of

patients with MUS was analysed, as described in Chapters 5-10. This revealed that, in the population investigated, 55% of the patients presenting to the GP with symptoms indicating MUS and who had their complaints recorded in the electronic records using symptom codes, continued to consult for MUS symptoms but did not have their illness named even five years after the first presentation; only 11% had their illness named as MUS within five years, and 3% received a diagnosis of an organic disease within five years. Only approximately one in ten patients had their illness named, supporting the claim of MUS patients expressed in qualitative research that there is a delay in naming their illness. Considering that respecting patient choices and their autonomy is a basic ethical tenet in the practice of healthcare, this leads to the derivation of a boundary principle: Respecting patient autonomy and supporting their choices requires naming the illness of patients as soon as it is clinically feasible.

However, the evidence synthesis of qualitative research found in-depth detail of the real-life experience of doctors who discuss reasons for delaying or not giving a diagnosis of MUS, to prevent the relaxation of clinical vigilance, and, usually with the objective of beneficence towards their patients, to save them from the stigma of being diagnosed with MUS. This leads to a conflicting boundary principle which would say: It is important to avoid giving a diagnosis of MUS to a patient to prevent them being harmed by stigma.

These two boundary principles that are in conflict with each other would then need to be systematically challenged 'by confronting these principles with the recalcitrant experience that generated the problem, with alternative theoretical perspectives, potentially disconfirming data' (Ives, 2014), so that the tensions between them can be resolved and

finding a solution so that these two principles can operate together coherently, alongside other boundary principles as well.

In a second example, the evidence synthesis indicated that high consultation frequency is one of the key problems of MUS for clinicians. The EHR data analysis showed that in the investigated population, the consultation frequency is consistently lower in patients who have received a diagnosis (15 consultations in Year 1) when compared to those that have not received a diagnosis (22 consultations in Year 1, Chapter 10).

However, the mean consultation frequency over five years for these GP-diagnosed MUS patients continued to remain over three times higher (11 consultations per year) than the population mean for that age group in the UK (3.1 consultations per year), despite 63% of these patients not complaining of MUS after the first year. These 63% of patients who complained of MUS only in the first year had a five-year mean consultation rate ranging from 4 – 45, i.e., some of the patients who consulted for MUS only in the first year, had 45 consultations per year on average in the next four years (although the consultations were not for MUS).

This raises the question of why they were consulting so frequently, if not for MUS, and the closest association was found with patients with psychological or mental health issues: GP-diagnosed MUS patients with psychological /mental health issues recorded had on average 13 consultations per year, whereas those without a record of mental health issues, had an average rate of 8 consultations per year.

The data from this patient population indicates that there could be a potential association between the high consultation rate and the presence of comorbid psychological/mental health issues, in this patient population, though there is no evidence for causation.

The calculation of the costs incurred by the patients in the investigated population show that the costs of consultations and associated prescriptions account for the majority of the costs in this patient group.

These findings, when combined with the cost data, show that the high costs of MUS may be due to the costs of consultations and associated prescriptions, leading to the boundary principle that managing comorbid mental health proactively in patients presenting with MUS could help reduce costs to the NHS, and lead to fairer resource allocation. However, as mentioned previously, it would be incorrect to assume causation, i.e. that mental issues are the cause for higher costs, and it would be necessary to challenge this boundary principle with recalcitrant data, to arrive at a final conclusion.

Using Reflexive bioethics and Reflexive balancing in a project combining ethical, qualitative and quantitative research, which deals with a large number of ethical issues surrounding patients with MUS and their clinicians, requires, what can be termed extensions, of the current applications of this methodology and method. Real-life quantitative data has not been used in empirical bioethics (as far as a horizon review indicated) to support or reject the empirical findings from qualitative research. As a field still in a growth phase, methodological innovation and adaptation is almost a given in this field (Ives et al, 2017), and could help broaden the scope of Empirical Bioethics.

2.4 Conclusion

This chapter described the methodology used to integrate empirical research with normative enquiry, and specified how the methodology of Reflexive Bioethics and the method of Reflexive Balancing (RBL) are used in this research. A summary of the research plan is given in Table 2.1.

The next chapter is the first step in the RBL process – a comprehensive overview of MUS to identify and understand the problem.

CHAPTER 03
A COMPREHENSIVE OVERVIEW OF MUS

3.1 Introduction

" I just want permission to be ill" "Isolation, frustration, unworthy of help.. Self-loathing, unemployable, living a lie….." "Guilt, being a fraud, time waster.. that the whole thing is something I've manifested and in some way I'm perpetuating.." (Nettleton, 2006: 207) ".. the deliberate, and sometimes aggressive, refusal of physicians to aid and treat an acutely ill and vulnerable patient" (Atkins, 2010: xxviii) 'My friends and family …knew I was sick but because the doctors couldn't come up with a name, they'd say 'maybe it is all in your head' or 'If the doctors can't find anything, it can't be too serious' (Wendell, 1996: 130)	Lisa Steen went to her GP in September 2012 after feeling unwell with dizziness, visual symptoms, feeling tired, palpitations, cramps, subtle cognitive impairments, memory problems and difficulty coping at work. She was referred to the eye clinic, a neurologist and a psychiatrist. No abnormality was detected on ultrasound, blood tests, MRI or neurological examination. The psychiatrist diagnosed depression and health anxiety. For two years, until June 2014, she received several months of psychotherapy and more anti-depressants. A GP, working in Cambridge, she died of a metastasized kidney cancer in 2015, aged 44. (BMJ blog, 2016) "You can get yourself into the position where you will never spot an illness in this patient if it was staring you in the face and they were dead on the floor, because you will feel it's just their bloody somatising." (Wileman, 2002: 181)

The narratives on the left, above, closely reflect the narratives of a significant proportion of patients in primary care, who are described using many, often derogatory, terms:

hypochondriacs, malingerers, hysteria, patients with medically unexplained symptoms, medically unexplained physical symptoms, persistent physical symptoms, somatoform disorder, somatic symptom disorder (SSD), somatic syndrome, bodily distress disorder (BDD), bodily distress syndrome, functional disorder, functional syndrome, health anxiety or conversion disorder (Greco, 2012; North, 2015).

The narratives on the right are what physicians are often concerned about in MUS: missing a serious disease manifesting as disparate physical symptoms for which test results are negative, resulting in prolonged frustration and helplessness to the extent that professional judgment can get impacted. The contradiction between the patients' experience and the professionals' knowledge results in unexplained symptoms appearing 'medically suspect even when they are experientially devastating' (Barker, 2008: 21).

These excerpts also illustrate the importance of considering MUS as a working hypothesis – where the hypothesis is arrived at after adequate examination and investigation has ruled out the possibility of somatic or psychiatric pathology, and it is also important to ensure that the working hypothesis is revisited and revised if evidence of any change in symptoms or in the symptom pattern is found subsequently (Olde Hartman et al, 2013). DSM-4 required the symptoms to be unexplained, however, DSM-5 has removed this requirement and focuses on the features of persistence of symptoms (over 6 months) and excessive and disproportionate concerns about the symptoms. Considering MUS as a working hypothesis is consistent with these definitions, and this permits the doctor to monitor somatic symptoms of unclear aetiology, their persistence, the patients' concerns about the symptoms and alter the diagnosis where necessary.

Patients with medically unexplained symptoms range from those with single, mild and transient symptoms to poly-symptomatic, chronic, debilitating illness (Smith & Dwamena, 2007; Olde Hartman et al, 2013; Henningsen et al, 2018). These patients most often complain of fatigue, pain, malaise, breathlessness, dizziness, gastrointestinal symptoms such as bloating, diarrhoea, constipation and neurological symptoms such as gait disturbances and pseudo seizures (Rosendal et al, 2015). In some patients, groups of severe symptoms seen together are considered a symptom syndrome, for example Fibromyalgia, Chronic Fatigue Syndrome and Irritable Bowel Syndrome (Wessely et al, 1999; Fink & Schroder, 2007).

The aetiology of MUS is not clearly established though it is believed to be multifactorial. MUS is also closely intertwined with physical illness: for example, non-cardiac chest pain is commonly seen after myocardial infarction and some patients with non-epileptic seizures can also have epilepsy (Mellers, 2005; Qintar et al, 2017). The risk of developing MUS is higher with childhood illness, adversity and abuse, certain personality traits, and infection, trauma or physical illness can act as triggers (Deary et al, 2007). Four categories of factors potentially associated with perpetuating illness symptoms have been described: social factors including medical uncertainty or secondary gains (e.g., chronic pain helps avoid carer burden); physiological factors which include autonomic dysregulation, central sensitisation; cognitive factors (e.g., catastrophising, maladaptive psychological coping); and behavioural factors such as avoidance behaviour (Page & Wessely, 2003; Husain & Chalder, 2021).

This chapter starts with a discussion of the ambiguity in the conceptualisation, nomenclature and classification of MUS, the prevalence of MUS, and then a brief discussion

of the interventions in managing MUS and the evidence on their effectiveness. It then examines why MUS are a problem for patients, clinicians and the NHS, and finishes with a discussion on why MUS should be reframed as an issue of ethics as much as a problem of cost and economics.

3.2 MUS – nomenclature, classification, conceptualisation and operationalisation

Medically unexplained symptoms (MUS) are an illness without a broadly agreed upon name or definition (Rosendal et al, 2017; Henningsen et al, 2018) and the term hysteria, dating back to the ancient Greeks, is still used colloquially to refer to MUS (Aybek & Vuilleumier, 2016; Bruno et al, 2021). MUS does not figure in either of the two main diagnostic manuals: American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or WHO's International Classification of Diseases and Health Related Problems (ICD-11).

The nomenclature and classification of Medically Unexplained Symptoms underwent multiple changes over the past forty years since the term 'hysteria' was removed from DSM-3 in 1980 (DSM-3). The illness is now covered under the category Somatic Symptom Disorder in DSM-5 and under Bodily Distress Disorder in ICD-11, with the diagnostic criteria shifting to persistent, disproportionate and excessive thoughts, feelings and behaviours regarding the symptoms in both classification systems.

The terms medically unexplained symptoms (MUS) or medically unexplained physical symptoms (MUS) remain the most commonly used terms to discuss the symptoms without

a medical explanation (Jones, 2019; Stortenbeker, 2020; Jungmann & Witthoft, 2020) and they are considered neutral descriptions (Olde Hartman et al, 2009). MUS is defined as 'physical symptoms that persist for more than several weeks and for which adequate medical examination has not revealed a medical condition that adequately explains the symptoms; (Olde Hartman et al, 2013).

In this thesis, the definition for the generic term 'medically unexplained symptoms – MUS', is used as described above by Olde Hartman et al (2013) and as it is understood most widely by clinicians and patients alike: this includes 1) physical symptoms without clear organic pathology 2) where the clinician believes excessive attention is paid to the symptoms 3) situations of psychogenic distress displayed in the form of somatic symptoms 4) functional somatic / symptom syndromes such as Chronic Fatigue Syndrome (CFS), Irritable Bowel Syndrome (IBS) or Fibromyalgia (FM) 5) transient mild symptoms as well as 6) disease due to biological causes as yet unrecognised. The rationale for operating under this broad definition is that the illness label given to a patient appears to be a matter of clinician or researcher preference rather than any specific feature of the patient's complaints or illness (Leaviss et al, 2020). Where the thesis refers to a particular category such as transient, mild symptoms or symptom syndromes, a specific description of the condition is used. Cases where the patient feigns symptoms, e.g., Munchausen's syndrome / factitious disorder are not considered MUS.

In some patients, groups of severe symptoms that frequently cluster together are considered a symptom syndrome, for example Fibromyalgia, Chronic Fatigue Syndrome and Irritable Bowel Syndrome (Wessely et al, 1999; Fink et al, 2007). Such clustering shows

significant overlaps, however, and it has been questioned if these are all manifestations of a single syndrome (Wessely et al, 1999; Olde Hartman et al, 2004).

3.2.1 Clinical definitions of MUS

The early definitions of MUS were based mainly on excluding any medical explanation for the symptoms patients complained of (Lipowski, 1988; Smith & Dwamena, 2007), whereas the recent definitions have shifted towards specific behaviours displayed commonly by patients with MUS such as disproportionately intense and persistent thoughts about the seriousness of his/her symptoms, and a high level of health anxiety, typically for over six months (ICD-11, DSM-5). These definitions allow for the presence of medically *explained* illnesses, usually chronic issues, that co-exist alongside the unexplained symptoms, with the focus now moved towards the behavioural traits accompanying the unexplained symptoms (ICD-11, DSM-5).

According to DSM-5, "presence of somatic symptoms of unclear aetiology is not in itself sufficient to make the diagnosis of somatic symptom disorder" and neither of these classifications any longer indicate a necessity for the symptoms complained of to be medically unexplained in order for a diagnosis of SSD/ BDD. Dimsdale et al (2013) state that diagnosis of SSD under DSM-5 requires three factors: distressing and impairing somatic symptoms, persistence of at least six months, and association with disproportionate and excessive thoughts, feelings and behaviours regarding these symptoms.

In ICD-11 – the diagnostic criteria for the new term Bodily Distress Disorder that replaced all ICD-10 somatoform disease related categories except hypochondriasis include persistent

and distressing bodily symptoms with the person devoting excessive attention to the symptoms and lack of resolution after appropriate clinical examination, investigations and reassurance.

Research studies undertaken recently too have shifted towards this definition, with, for example, Kitselaar et al (2021), defining patients with MUS as those whose complaints "are not *fully* explained by established biomedical pathology" and including patients who have other chronic physical conditions. This study, which used four different methods to identify patients with MUS in a consulting population, found that the prevalence of unexplained symptoms (referred to in the study as 'persistent somatic symptoms, PSS') is high in patients with chronic physical conditions, and concluded that it was undesirable to classify PSS on the basis of excluding chronic physical conditions. A similar conclusion was arrived at in a previous study which investigated the relevance of a distinction between medically unexplained symptoms (MUS) and medically explained symptoms (MES, Klaus et al, 2013).

It is necessary to clarify here that, in contrast to the above-mentioned studies, for the EHR research undertaken for this thesis (described in Chapters 5-10), it was decided to exclude patients with diagnosed co-existing medical conditions, as well as patients over the age of 50 years in whom undiagnosed chronic conditions are more likely, resulting in only patients with unexplained symptoms being included in the study. This was necessary in this study since the study attempts, for example, to count the number of consultations per patient per year caused by unexplained symptoms and to calculate the total cost of such consultations.

If patients with other diagnosed chronic conditions as well as unexplained symptoms were included in research, the patient may have consulted for the unexplained symptom or the diagnosed chronic condition or for both. Patients with co-existing medical conditions in the initial study population were included in a study on non-cardiac chest pain in Iceland, where the authors mention that physician's notes were referred to when there was no diagnosis specified in the electronic records (Flovenz et al, 2023).

However, when a symptom code is recorded as the reason for the consultation in electronic health records on the CiPCA database that was used for this research (as described in Chapter 5-10), it is not possible to differentiate whether the doctor considered the symptom to be medically unexplained or if he considered the symptom was due to the diagnosed chronic condition, since doctors' notes, which may have given further detail, are not available on the database.

Therefore, in order to find out the specific number of consultations due to unexplained symptoms, it was necessary to exclude patients with diagnosed chronic conditions. To minimise the risk of patients with undiagnosed chronic conditions being included in the study, patients over the age of 50 years where chronic conditions are more likely were excluded (Smith et al, 2001; Walker et al, 2016).

The findings of the Kitselaar study support this choice since MUS cases found by Method B used in the Kitselaar study (which is the patient identification method most similar to the method used in this study, i.e. Frequent consultations + record of Symptom Codes) – were the most likely to have a chronic physical condition. The study therefore concluded that

"differentiating which complaints are PSS (MUS) and which complaints are strictly related to a physical condition may be most challenging for cases selected by Method B" (Kitselaar et al, 2021, p. 6). Furthermore, the Klaus study (Klaus et al, 2013) found that "the aetiology as explained or unexplained symptoms changed from baseline to follow-up in many persisting symptoms (20% MUS changed to MES, and 50% MES changed to MUS)", indicating that isolating patients with MUS is harder when including patients with diagnosed chronic conditions (Klaus et al, 2013, p.1).

However, the disadvantage of using this method of patient selection is that all empirical findings of this study are likely to be applicable to this specific subset of patients alone, patients aged below 50 years with unexplained symptoms and without any other diagnosed chronic conditions, whereas the total population with MUS is highly heterogenous.

3.2.2 Confusion in MUS nomenclature

Tables 3.1 and 3.2 give the various terms associated with MUS and the diagnostic labels under different classification systems. The most ancient of terms related to MUS, the term hysteria, has been used to refer to the features associated with dissociation, conversion and somatisation, from the time of Hippocrates and Aristotle to Galen to the 20th century, though it is much less common now (North, 2015; Aybek & Vuilleumier, 2016; Bruno et al, 2021). Primarily an illness of females at the time (until Freud), hysteria was said to be caused by a 'wandering womb' (North, 2015). Diseases associated with MUS such as Briquet's Syndrome that were first described in 1859 persist to this date. Briquet described hysteria as a chronic, poly-symptomatic disorder with diagnostic criteria including the

presence of at least 25 symptoms out of a list of 59 symptoms, in at least nine of ten organ systems, and onset before the age of 30 years (Lipowski 1968 cited in Desai 2018). Briquet's syndrome is still taught in some medical schools today (e.g., Brown University, 2020).

The term medically unexplained symptoms is used to describe a range of widely different conditions: mild, non-specific symptoms (Roennenberg, 2019), to terms encompassing the most severe form of physical symptoms without organic explanation, Functional Somatic Syndromes such as fibromyalgia (FM), chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS) (Joint Commission Panel for Mental Health, JCMPH MUS guide, 2017). Somatisation, where a person interprets mental illness as a bodily issue, was first described as "the tendency to experience, conceptualize, and/or communicate psychological states or contents as bodily sensations, functional changes, or somatic metaphors" and updated to 'a tendency to experience and communicate somatic distress in response to psychosocial stress and to seek medical help for it' (Lipowski, 1988 cited in Desai, 2018). The Somatization disorder diagnosis based on research on Briquet's syndrome was added to DSM-3 for the first time; diagnosis required 14 out of 37 symptoms (Liskow, 1988). The Somatoform Disorders category also included conversion disorder, psychogenic pain disorder, hypochondriasis, and atypical somatoform disorders. The term 'Functional' disorder is used to indicate that the problem is in the alteration of the function of a given organ or bodily system rather than in the structure (Nimnuan et al, 2001).

Table 3.1. Terminology used in describing MUS	
Generic terms	**Definition**
Hysteria	Multiple recurrent unexplained physical symptoms presenting in many different organ systems (St. Louis criteria*)* (North, 2015). Removed from DSM-3 onwards.
Briquet's Syndrome	At least 25 clinically significant and medically unexplained symptoms from a list of 59 symptoms representing at least 9 of 10 organ systems; Starting before age 30; Almost exclusively in women (North, 2015).
Neurasthenia	An ill-defined condition with the symptoms of fatigue, headache and irritability. Not used commonly anymore. (Bankier, 2001). Removed from DSM-3 but retained in ICD-10.
Worried Well	Generic term to describe patients with complaints but where the GP believes the patient is well – i.e., no disease
Functional disorder	Suggesting an alteration in the function rather than in the structure of the organ / body system that is the source of the complaint. Used pejoratively to mean 'it's all in the mind' *(*Sharpe, 2001).
Somatisation	Implies a psychological problem is expressed somatically.
Conversion disorder	Used specifically to refer to a loss of function such as weakness of a limb. Implies that the symptoms are due to a conversion of psychological problems (Sharpe, 2001).
Dissociative disorder	Detachment from surroundings or from physical or emotional experiences (Evans, 2019).
Bodily Distress Syndrome	A unifying diagnosis that encompasses a group of closely related conditions such as somatisation disorder, fibromyalgia, IBS and CFS. It is based on identification of symptom patterns from four body systems: Cardio-pulmonary/autonomic arousal, gastrointestinal arousal, musculoskeletal tension and general symptoms (Fink, 2017).
Somatoform symptoms	Recurrent and multiple somatic complaints for which medical attention is sought but that apparently are not due to any physical disorder (North 2015).

Somatization disorder (DSM-3 & DSM-4)	DSM-3 : Lifetime history of 14 of 37 possible symptoms in 7 categories of symptom types. DSM-4: 4 pain symptoms, 2 gastrointestinal symptoms, 1 sexual symptom, 1 pseudo-neurological symptom. DSM-4-TR (text revision): Presence of 8 symptoms out of a list of 32 symptoms given as examples in four symptom groups starting before 30 years. Removed under DSM-5.
Undifferentiated somatoform disorder (DSM-4)	Removed under DSM-5.
Conversion disorder (DSM-4)	Chronic pseudo-neurological symptoms – motor or sensory symptoms e.g., seizures. Symptoms should be medically unexplained to qualify for the diagnosis.
Pain disorder (DSM-4)	Chronic pain; one or more pain symptoms as the predominant focus of the presentation; psychological factors involved and excluding factitious disorder, malingering or other psychiatric explanation. Removed under DSM-5.
Hypochondriasis (DSM-4)	Serious illness anxieties; No somatic symptoms; At least six months duration; The term hypochondriasis discarded in DSM-5 and considered under Illness Anxiety disorder.
Body Dysmorphic disorder (DSM-4)	Preoccupation with an alleged defect in appearance that causes the patient to feel ugly.
Somatoform disorder	Somatoform symptoms for <6 months not meeting criteria of the other specified somatoform diseases in DSM-4.
Factitious disorder	Deliberately feign or simulate illness to obtain medical care. (Sharpe, 2001).
Munchausen Syndrome	Eponym for factitious disorder (Sharpe, 2001).
Malingering	Not a medical diagnosis but the deliberate simulation or exaggeration of physical or psychiatric symptoms for obvious and understandable gain (e.g., monetary compensation) (Sharpe, 2001).

Table 3.2 Somatic symptom and related disorders in DSM-5 and ICD-11	
DSM-5 classification terms	
Somatic symptom disorder	≥1 distressing somatic symptoms significantly disrupting daily life; Excessive thoughts, feelings, behaviours related to the somatic symptoms or associated health concerns; Duration typically more than 6 months.
Illness anxiety disorder	Excessive or disproportionate preoccupation with serious illness; only mild or no somatic symptoms; high level of anxiety about health.
Conversion disorder - Functional Neurological Symptom Disorder	One of more symptoms of altered voluntary motor or sensory functions; significant distress or impairment in important areas of functioning.
Other specified somatic symptom and related disorder	Clinically significant distress or impairment in social, occupational or other important areas of function. Includes e.g. Brief somatic symptom disorder, Brief illness anxiety disorder. - In both cases above, symptom duration less than 6 months Illness anxiety disorder without excessive health-related behaviours (criteria for illness anxiety disorder not met).
Unspecified somatic symptom and related disorder	Predominantly somatic symptoms but where there isn't enough information to make a more specific diagnosis
ICD-11 classification terms	
Hypochondriasis	Located under obsessive-compulsive or related disorders (6B23); Involves repetitive and excessive health-related behaviours, and includes hypochondriacal neurosis and illness anxiety disorder.
Bodily Distress Disorder	Presence of bodily symptoms distressing to the individual and excessive attention directed to problems; manifested by repeated contact with healthcare providers (6C20).
Chronic Fatigue Syndrome	Chronic fatigue syndrome and benign myalgic encephalomyelitis are marked under other disorders of the nervous system (8E49).

One or more chronic symptoms of unknown aetiological origin diagnosed following consensus-based criteria related to the primary complaint are called functional somatic syndromes (FSS) or symptom syndromes, e.g., persistent abdominal pain and altered bowel habits are irritable bowel syndrome (IBS), widespread muscle pain and tenderness is fibromyalgia (Barsky & Borus, 1999; Wessely et al, 1999; Donnachie et al, 2020). Henningsen (2018) points out that there are no objective criteria for a physician to decide if a patient's complaints should be categorised as a FSS or as a medically unexplained symptom. The extensive overlap in symptoms between syndromes, the frequent co-occurrence of >1 syndrome and the different syndromes responding to the same therapies, have led some researchers to consider patients with FSS as suffering from a single, general, condition (Robbins et al, 1997; Wessely et al, 1999). Table 3.3 lists the most common FSS (Barsky & Borus, 1999; Henningsen, 2018).

Table 3.3: Symptom syndromes / Functional somatic syndromes according to body systems

Gastroenterology	**Cardiology & Respiratory medicine**	**Rheumatology**	**Neurology**	**Dentistry**
Irritable bowel syndrome	Atypical chest pain	Fibromyalgia	Tension headache	Atypical facial pain
Non-ulcer dyspepsia	Non-cardiac chest pain	Chronic Fatigue Syndrome	Non-epileptic attacks / pseudo seizures	Temporo-mandibular joint syndrome
	Hyperventilation syndrome	Chronic whiplash syndrome		
Ear, nose, throat	**Gynaecology**	**Allergy**	**Musculo-skeletal system**	
Globus Syndrome	Premenstrual Syndrome	Multiple chemical sensitivity	Chronic low back pain	
Globus Hystericus	Chronic pelvic pain	Sick building syndrome		

3.2.3. Classification of MUS is a long-standing problem

Based broadly on division of medical disciplines at a historical level, MUS are traditionally considered in two separate silos although there is significant overlap seen between the two. The first, medically unexplained symptoms related to neurological conditions (weakness, convulsions etc), which was Conversion disorder in DSM-4, is now named Functional neurological symptom disorder in DSM-5, with the requirements for diagnosis being duration over six months and "clinical findings provide evidence of incompatibility between the symptom and recognised neurological or medical conditions."

The second broad group, medically unexplained symptoms unrelated to neurological issues (gastro-intestinal issues for example), existed under DSM-4 as somatoform disorders and is now Somatic Symptom Disorder in DSM-5.

The generic term Medically Unexplained Symptoms is now primarily covered under the category Bodily Distress Disorder (BDD) in ICD-11 and the category of Somatic Symptom Disorder (SSD) in DSM-5. The diagnostic categories of Illness anxiety disorder, conversion disorder or functional neurological symptom disorder, psychological factors affecting other medical conditions, factitious disorder and other specified/unspecified somatic symptom and related disorders in DSM-5 can also be used to record MUS. Body dysmorphic disorder has been moved to obsessive-compulsive and related disorders in DSM-5.

3.2.4 Conceptualising MUS

This thesis conceptualises MUS as a working hypothesis – a hypothesis formulated once consultations and investigations have ruled out somatic or psychological pathology that could

be responsible for the symptoms complained of. Since it is possible that the symptoms may be linked to somatic pathology, it is always prudent to maintain MUS as a working hypothesis and be ready to change the diagnosis if there are any changes in the symptoms / symptom patterns (Olde Hartman et al, 2018).

MUS vary so widely in the way they are conceptualised and classified (Rosendal, 2017) that the illness category has been referred to as a 'waste basket diagnosis' (Jutel, 2010), as a category for illnesses that do not fit anywhere else. It has also been described as a 'junk drawer', i.e., a place where things that have no other place are kept (Rasmussen, 2020).

The core criterion to define MUS in the literature is the persistence of physical symptoms in the absence of sufficient explanatory pathology after adequate examination and investigation (Schaefert, 2010; Rosendal, 2017). Rasmussen (2020) points out that it is the usual expectation of concordance between the symptoms and pathology being violated that leads to ambiguity and doubt, causing MUS to be an anomaly and therefore problematic.

Rasmussen also points out two different ways of framing MUS:

1) doxic framing – where the focus is on symptoms and patients without reference to doctors e.g., "patients suffer from physical symptoms without sufficient organic findings…", or, "In 30-70% of cases no organic causes for the patient's symptoms can be found" (Burbaum, 2010), and
2) heterodoxic framing - where MUS is framed with reference to what doctors think or believe about the symptoms e.g., "10-20% of patients present physical symptoms in primary care that their general practitioners believe are not explained by physical disease" (Salmon et al, 2008).

MUS is conceptualised in a wide variety of ways in the literature. Firstly, although the term MUS literally refers to 'symptoms', MUS refers to the collective and overall, singular status of the patients' symptoms as 'medically unexplained' rather than to disparate individual symptoms. Furthermore, the frequent doxic framing, where the focus is on symptoms and patients, appears to 'shift the responsibility for the inability to explain the symptom from the doctor to the patient' (Hadler, 1996 quoted in Leaviss et al, 2020: 113). With the new definitions of Bodily distress disorder in ICD-11 and Somatic symptom disorder in DSM-5, framing MUS with reference to the doctors' opinion appears to have now gained primacy.

The Joint Commissioning Panel for Mental Health in the UK is co-chaired by the Royal Colleges of General Practitioners and Psychiatrists. Its Guidance for commissioners of services for people with MUS (JCPMH MUS guide, 2017) sees MUS as 'bodily complaints for which adequate examination does not reveal sufficiently explanatory structural or other specified pathology' and that it is 'common, with a spectrum of severity.' It then goes on to list the types of symptoms that can present and the associated syndromes, conflating MUS and Functional Somatic Syndromes such as Irritable Bowel Syndrome (IBS), Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME), and Fibromyalgia (FM). However, the Royal College of Psychiatrists and the Paediatric Mental Health Association guide on MUS in Children and Young People (CYP) states that MUS are 'the symptoms an individual describes that are not fully explained by physical examinations or investigations' (RCPsych Guide to MUS in CYP, 2018). It then goes on to specifically differentiate MUS from 'long-term conditions such as CFS, IBS and FM' – contrary to how the JCMPH MUS guide conceptualises MUS and also states that the term is not interchangeable with Somatic Symptom Disorder, Factitious disorder and Malingering.

The German clinical practice guidelines renewed and published in 2019 specifically differentiate "functional somatic symptoms" from 'commonly occurring transitionary indispositions" and state that FSS refer to three broad groups: 1) persistent unspecific symptoms that are burdensome enough for a patient to consult a doctor but are not classified as disease - referred to as medically unexplained symptoms or persistent physical symptoms 2) functional somatic syndromes which are defined symptom clusters presenting over an extended period such as FM or IBS. 3) the conditions that fulfil the criteria of 'pronounced (multi)somatoform disorders and the newly defined somatic stress disorders', associated with psycho-behavioural symptoms (Roenneberg et al, 2019). These are but a few examples of the wide variation in the conceptualisation of MUS in the literature.

3.2.5 Operationalising MUS: inclusive vs. restrictive interpretations

Operationalising MUS in research – how the core requirement of presence of somatic symptoms in the absence of explanatory pathology is defined to include patients in / exclude patients from research – varies widely. It is most often based on how the terms medically explained and unexplained are defined, and how ambiguity, where the distinction between medically explained and unexplained is not clear, is dealt with (Rasmussen, 2020). Some researchers take an inclusive approach – considering all symptoms that are "not fully explained by tissue abnormalities" as medically unexplained; for example, in Rask et al (2014) all patients where the GP could not establish a specific diagnosis are considered to be MUS patients, i.e. no specific disease diagnosis – then it is MUS.

Other researchers have used a more restrictive approach where MUS was operationalised to include only cases where MUS was diagnosed definitively. Ambiguous cases are excluded.

Contrary to Rask et al (2014), Houwen et al (2019) only included cases where the physical symptoms could not be explained by a recognisable disease, i.e., it is MUS only where the patient's condition is specifically diagnosed as MUS. Morriss et al (2012) asked GPs to categorise patients as 1) definitely / probably MUS 2) possibly MUS 3) unsure 4) unlikely to be MUS and 5) definitely not MUS and included categories 1 and 2 as MUS patients in their study.

Restriction is also applied by deciding to exclude patients based on age, and presence of co-morbidities in the form of concurrent somatic diseases such as diabetes, and/or psychiatric illness. For example, the Smith et al study (2001) included patients aged 21 – 55 years and excluded those with co-morbidities, pregnancy, substance abuse and psychiatric care. Other studies have included patients up to the age of even up to 70 years (Barends, 2020).

A third approach is to consider patients as MUS cases based on duration of symptoms, symptom count and frequency of consultations. Duration of symptoms varies widely from presence of unexplained symptoms for 'at least several weeks' (Barends, 2020) to 'over three months duration' (Aamland, 2014) and to over six months duration in others (Claassen-van Dessel et al, 2016). Consultation frequency as a criterion varies for example, 'at least twice in the previous 3 months' with MUS related complaints (Sitnikova et al, 2018) and 'more than 8 consultations per year over two years' (Smith et al, 2009). There is also an information bias created by the inclusion of participants into research studies based on questionnaire returns – e.g., in the Creed et al 2012 study, 58% of eligible participants completed the initial questionnaire; non-responders were predominantly male, of younger age, and only 30% of eligible participants completed follow-up questionnaires. This means that the study results will

primarily include data from older females, and represent only 30%-58% of the general population, as opposed to if consecutive consulters were included in the study.

Murray et al (2016) point out that MUS is used sometimes as a working hypothesis prior to making a formal diagnosis and that MUS researchers make up their own definitions of what constitutes MUS, complicating comparisons among research findings. Smith et al (2002), for example, created a new category in MUS – Minor Acute Illness, defining it as unexplained symptoms that resolve completely within six months, as opposed to patients who need to report symptoms for over six months for a diagnosis of Somatoform disorder.

Such differences in operationalisation affects research outcomes; for example, including patients with comorbidities will impact resource use data and effectiveness data.

3.3 Epidemiology of MUS

Prevalence: Given the wide variation in MUS conceptualisation, nomenclature and classification discussed in the previous sections, it is not surprising that there is a wide variation in the reported prevalence rates for MUS. Creed and Barsky (2004) carried out the first systematic review of prevalence of somatisation disorder and hypochondriasis and found prevalence ranging from 0.1% to 13.8% for somatisation disorder, from 0.03% to 35% for abridged somatisation disorder and 1.3% to 7.7% for hypochondriasis, as shown in Table 3.4. Haller et al (2015) carried out a systematic review and reported point prevalence for MUS ranging from 0.7% to 60.6%, and 0.0% to 79% for other MUS-related disease labels.

Table 3.4: Point prevalence of MUS reported in primary care (no. of research studies included in assessment)	
Creed & Barsky, 2004; systematic review	
Somatisation disorder (10)	0.1% - 13.8%
Abridged somatisation disorder (16)	0.03% - 35%
Hypochondriasis (4)	1.3% - 7.7%
Haller et al, 2015; systematic review	
Somatisation disorder (27)	0.0% - 35.2%
Undifferentiated somatoform disorder (7)	5.5% - 79%
Chronic pain disorder (7)	0.8% - 16.8%
Somatoform autonomic dysfunction (3)	4.3% - 12.5%
Somatoform disorder, unspecified (5)	4.2% - 27.2%
Abridged somatisation disorder (6)	5.9% - 21%
Multi-somatoform disorder (5)	8.2% - 23.5%
Somatoform disorder (7)	11.7% - 52.9%
Medically unexplained symptoms (2)	20.5% - 60.6%

Prevalence data reported for England was examined separately, given in Table 3.5, and the most recent data indicated that 18% of consecutive attenders in primary care had MUS (Taylor et al, 2012).

Table 3.5: Point prevalence of MUS reported for England				
Peveler et al, 1997	Primary care	17-81 years	175 GP surgery attenders	19% (GP review) 35% (screening instruments)
Taylor et al, 2012	Primary care	>=16 years	2,337 consecutive attenders	18% with MUS
Nimnuan, et al, 2001	Secondary care	16-65 years	550 hospital clinic consulters	52% with MUS
Aggarwal et al, 2006	General population		2,299 people registered with a GP practice	27% FSS

Prevalence rates have been reported for FSS separately: up to 15% for IBS (Drossman et al, 2002), 10%-15% of adults and 25% of gastroenterology appointments (Chey et al, 2015); Fatigue symptoms in 5%-20% of adults and 0.2% - 2.6% for CFS (Sullivan et al, 2005; Prins et al, 2006); fibromyalgia at 2% -8% of the general population (Branco 2010). These estimates show significant variations; a recent Danish study reported overall FSS prevalence at 9.3%, 3.8% for IBS, 2.2% chronic widespread pain, 6.1% chronic fatigue (Petersen et al, 2020). Prevalence rates for specific age groups also have been reported : Hilderink et al in 2013 found prevalence rates for Somatoform disorders in the age group <50 years ranging from 10.7% to 21.8%. In the same age group, the reported prevalence for persistent MUS (defined as $\leq$4 contacts for a functional symptom without medical diagnosis over one year), ranged from 1.6% in primary care (Verhaak et al, 2006) to 69.7% in a general population study (N=2,552) using Screening for somatoform symptoms, SOMS-7 (Hiller et al, 2006). Prevalence estimates based on clinician identification of MUS patients are much lower than when using questionnaires, and lower in consulting populations than in the general population as seen from these reviews.

It is well-documented that patients with MUS are under-diagnosed (Warren & Clauw 2012; Rief 2014); the Warren and Clauw study found that GPs had not identified 90% of patients with CFS, 77% of patients with Fibromyalgia and 69% of patients with IBS. This may however be with the best of intentions, GP reluctance to record MUS diagnosis can be out of concern for the negative effects it can have on patients (Robertson and Kerridge 2009; Levenson 2011). GPs appear to be recording patient symptoms as symptom codes, without recording a diagnosis (Harkness et al, 2013; Soubieres et al, 2015; Payne & Brooks, 2018). The Soubieres study (2015) for example found that while only 1,982 patients were recorded with IBS-specific codes in

Hospital Episode Statistics data in 2012-2013, there were 28,849 patients with records of IBS-related symptom codes. Similarly, the Harkness study (2013) found 8,444 patients with an IBS Read code and 42,490 patients with an IBS-related symptom code in a regional patient database (Salford Integrated Record).

Patient characteristics: MUS has been reported as most common among 'elderly women with a lower socio-economic status' (Verhaak et al, 2006) and those with MUS were reported to have more psychological distress, functional impairment and social isolation, and, to be high users of healthcare and welfare resources (Dirkzwager & Verhaak, 2007).

Prognostic factors, Course of MUS and outcomes

A systematic review on the course and outcomes of MUS found that 50%-75% of MUS patients improve during follow-up whereas 10% -30% of patients show worsening of disease (Olde Hartman, 2009). Outcome measures researched include the remission of illness, change in functional impairment and change in medical care utilisation (Gureje & Simon, 1999). For the patients who show worsening, the outcomes are poor with only 1 in 20 CFS patients estimated to recover fully, and one-third continue to be disabled (Cairns & Hotopf, 2005). Similarly, in Fibromyalgia, 30%-40% of patients stop or reduce work (Arnold et al, 2011).

The number of symptoms at base line and the severity of the presentation at baseline appear to indicate an unfavourable prognosis, whereas there is conflicting evidence on the role of gender and comorbid mental health issues in the prognosis of MUS (Olde Hartman, 2009). The Patient explanatory model, which describes the illness perceptions of patients, also helps to understand the distress of patients as their illness perception can affect the outcome (Sumathipala et al, 2008).

3.4 Interventions to manage patients with MUS

The management of the 10% -30% of MUS patients whose symptoms worsen, usually proceeds as follows: extensive and intensive investigations, referrals to multiple specialist consultations, inform the patient that there is nothing physically wrong with them and that they should see a psychologist / psychotherapist as the cause may be psychogenic, which is often disputed by the patient (Roenneberg et al, 2019). The challenge for the physician caring for the MUS patient is therefore to not only manage the individual complaints, but to arrive at a care plan for prolonged care for ongoing illness, which often includes dealing with psychosocial stressors as well as comorbid mental health issues such as depression, anxiety, and post-traumatic stress.

Evidence-based treatment is available, though there is a wide variation in that as well. Roenneberg et al (2019) summarised the evidence base for interventions to treat functional somatic symptoms and found: strong evidence for pharmacological treatment (Pregabalin and Milnacipran for Fibromyalgia, Linaclotide for IB with constipation); moderate evidence for exercise and aerobic training for CFS and Fibromyalgia; the evidence base for the use of self-help interventions, short-term psychotherapy, cognitive behavioural therapy (CBT) was found to be weak.

Psychological therapy: Leaviss et al (2020) provide a summary of the psychological treatment methods provided in England. Cognitive behavioural therapy (CBT) is one of the most common interventions offered and it focuses on alleviating the perpetuation of cognitive, behavioural and physiological responses that lead to continued symptoms, distress and disability. Reattribution therapy, which attempts to relate patients' symptoms to psychosocial problems

was designed for delivery by GPs and was found to be useful to increase GPs' competence and confidence to manage MUS patients (Dowrick et al, 2008). However, significant barriers to implementation, evidence of lack of effectiveness and intrinsic problems with the model have resulted in it not being delivered commonly anymore (Gask et al, 2011). Behaviour therapy is focused on reducing harmful behaviour such as the intense focus on symptoms and reassurance seeking from healthcare professionals. Relaxation therapy focuses on methods such as meditation-based stress reduction. The newer methods of therapy, called 'Third-wave CBT', comprise mindfulness and acceptance therapy which focus on self-regulation of attention and acceptance.

A review of seven studies found that CBT is efficacious for both symptom syndromes and the broader category of MUS, and that it reduced physical symptoms, psychological distress and disabilities (Sumathipala, 2007), as did a meta-analysis by Gerger et al (2015). Another meta-analysis found small-to-moderate effect size in short-term psychotherapy for multiple MUS (Kleinstauber et al, 2011). The van Dessel et al review (2016) found that non-pharmacological interventions could help reduce symptom severity when compared to usual care. The Leaviss study (2020), a comprehensive review, found that behaviour modification interventions, particularly high-intensity CBT and multimodal therapies have some beneficial impact on improving symptoms, but the authors commented that there were insufficient studies for each intervention type and that the significant heterogeneity between studies can be related to the diverse results of the reviews. Analysing the details of the studies included in these reviews and meta-analyses indicate that the differences can be explained by the types of patients included in the trials, the age, the disease intensity, duration of symptoms; furthermore, Gerger et al

(2015) found in their meta-analysis that psychotherapy delivered by psychologists appeared to have larger effect sizes than that delivered by GPs. In terms of cost-effectiveness, group CBT and collaborative group interventions appeared to be the most cost-effective (Wortman et al, 2018), although this review too was constrained by study-heterogeneity.

Pharmacological therapy: A Cochrane review of the efficacy of different types of antidepressants, antipsychotics and a combination of antidepressants and antipsychotics, found only low-quality evidence of these pharmacological therapies being effective as treatment of MUS (Kleinstauber et al, 2014). Industry funded studies indicated that Linaclotide was more effective in IBS patients compared to antidepressants, as was Duloxetine for Fibromyalgia (Wortman et al, 2018).

Physical therapy: Graded exercise was found to be effective for fatigue and multi-modal therapy was beneficial for physical functioning (Leaviss et al, 2020).

In summary, the current guidance for stepped, collaborative care based on the severity level leading from initial reassurance and basic care to multimodal therapies including psychotherapy and treatment for comorbid mental health issues must be strengthened through a convincing evidence base for the management options for MUS. NICE guidelines for managing CFS/ME is the most recent comprehensive guideline in the UK (NICE ME/CFS guidelines 2021) and the approach to diagnosis, communication and management is applicable to most MUS. The Royal College of General Practitioners issued Guidance on MUS (RCGP guidelines) as did the Royal College of Psychiatrists (RCP guidelines). More research is necessary and such research needs to be based on widely agreed criteria, so that there is less heterogeneity among the studies (Kleinstauber et al, 2019; Leaviss et al, 2020).

3.5 MUS: a problem to patients and doctors

Conceptualisation of MUS is confusing as is its classification; diagnosis is difficult due to this confusion, nomenclature changes frequently and management is difficult due to frequent resistance from patients themselves and further complicated by how MUS sits in the interface between medicine and psychiatry. As a result, we still do not have a widely accepted body of knowledge on MUS – even the prevalence estimates range from 0.1% to 60.6% of patients presenting in Primary Care as having MUS (Haller et al, 2015), the wide range is due to wide study heterogeneity.

Researchers agreed in 2007 that the three most critical problems in MUS are 1) lack of an unambiguous definition of MUS that can be applied globally 2) the best strategy to recognize MUS in primary care and 3) need for further research on effective interventions for MUS (olde Hartman, 2008); these problems are still unresolved. As a result, MUS is a problem not only for patients, but also for healthcare providers and society.

3.5.1 UNPREDICTABLE ILLNESS TRAJECTORY IN MUS

The majority of MUS patients present with transient and self-limiting conditions, which require a few consultations and reassurance of absence of disease (Roenneberg et al, 2019). Current literature shows that there are several common potential outcomes for MUS patients (Chitnis, 2011): some of these patients receive a diagnosis of MUS/hypochondriasis/health anxiety and are given anti-depressants/anxiolytics with only cursory investigations into their complaints; some may however be suffering from yet undiagnosed organic disease. In 2000, Nimnuan

reported in a study (n=529) that 17% of patients are mistakenly diagnosed as psychogenic at the first visit to a specialist (Nimnuan, 2000). Carson et al (2000) found that, of the patients referred to secondary care to confirm the GP's opinion that there was no neurological disease, 39% had organic disease. Other studies (Stone, 2005; Morris, 2007), found that an organic cause for disease is later revealed in 4% -10% of patients initially diagnosed with MUS. Though this is not the most common outcome, it is the most serious, since treatable organic disease is missed.

The second, and most common, outcome is that they are repeatedly referred for investigations, specialty care and have repeated secondary care admissions, resulting in iatrogenic harm. One study found that 25% of these patients persist in seeking care within the primary care system after 12 months and that an estimated 30% (range of 10% to 80%) are found to have an associated psychiatric issue, most commonly depression or anxiety (Chitnis, 2011). They are sometimes not referred for psychotherapy nor given the anti-depressants/anxiolytics that could help them, partly due to the resistance from patients themselves to being identified as in need of psychiatric help (Murray et al, 2016). The IAPT program, which included MUS patients on a wider scale since 2017, has however increased access to 'talking therapies' for MUS patients to some extent, a step in the right direction (Toffolutti et al, 2021).

The illness trajectory of MUS, however, is unpredictable – akin to the 'chaos' narrative where there is no clear beginning, no plot, no structure and no clear end to the disease story (Frank, 2013, Figures 3.1 and 3.2). Just as much as the onset of the symptoms is often uncertain, the numerous tests, consultations and referrals patients face, as well as the lack of acceptance of their suffering from authoritative sources, leave little room for resolution of the illness.

Figure 3.1. Usual restitution narrative for most patients

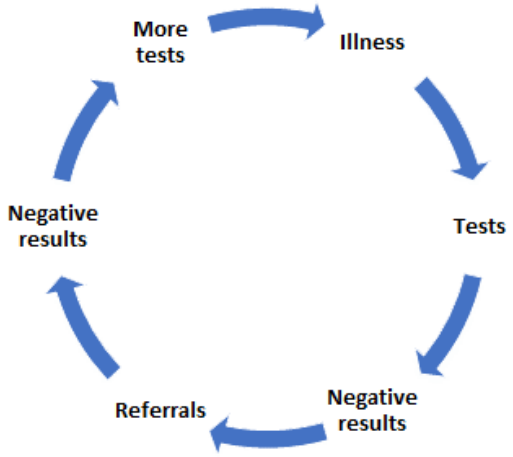


Figure 3.2. Chaos narrative common among MUS patients

3.5.2 MUS IS A PROBLEM FOR DOCTORS

It has been suggested that a patient whose symptoms cannot be medically explained is marginalised and punished due to the patient being unable to 'propose an illness that the doctor can recognise as a disease' (Balint, 1964 cited in Jutel, 2010:230). It is well documented that such MUS patients are a significant problem for doctors: given the uncertainty, doctors fear missing an important physical diagnosis and face a moral dilemma – although the suffering of the patients are recognized, they trigger feelings of helplessness and guilt in doctors as they struggle to help these patients (Johansen and Risor, 2016; Houwen et al, 2019), as indicated by qualitative research findings such as:

"Many doctors have the same basic feeling about these patients… exhaustion, desperation"

"When I think within two minutes 'I do not have a clue of what is going on here', then I start to think 'this can be MUS'." (den Boeft et al., 2016:58)

On the other hand, doctors sometimes avoid giving a diagnosis of MUS to patients, for fear of stigmatizing the patient, and as it could subsequently lead to a 'problematic relaxation of clinical vigilance' (Robertson and Kerridge, 2009:217) so that doctors disregard physical symptoms complained of as part of the manifestation of MUS (Levenson, 2011). This reluctance, and the confusion regarding terminology can lead to a systematic under-reporting of MUS patients (Warren & Clauw, 2012; Rief, 2014; Payne & Brooks, 2018). In some cases, having to deal with the discomfort MUS patients engender amidst the stress of a busy, resource constrained practice, doctors may even give up on these patients because 'their troubles are too complex, in both medical and social terms, for fixing' (Frank, 2013:114).

The dual problem of diagnostic uncertainty and fear of relaxing clinical vigilance, as well as the limited effective management options available for MUS patients, lead to the frustration many doctors face when having to deal with MUS patients. It is concerning that the antagonistic relationship that can develop between MUS patients and doctors where GPs see patients as undermining their authority and lacking trust appears to worsen to the extent that the physician's professional judgement can be compromised, as indicated by:

'You can get yourself into the position where you will never spot an illness in this patient if it was staring you in the face and they were dead on the floor, because you will feel it's just their bloody somatising.' (Wileman et al, 2002:181)

Just as much as there is evidence about the frustration of doctors and the difficulties they face in managing patients with MUS, there is also much evidence about strong positive relationships between doctors and patients with MUS as indicated by patients who state for example that:

"I'd built up quite a solid relationship with [the doctor], I just felt that he was very engaging and it felt [as if] he took me seriously" (Cooper and Gilbert, 2017), and, "She was a brilliant doctor.. she explained to me why she was.. (Harvey et al, 2018).

Similarly, there is also evidence on doctors who have a positive view on the challenge that patients with MUS present " I don't think I find them as difficult as some people do. I don't know why that is, but … with most people, ..I give people a little bit of time, .. I just try to be honest and if you are talking to a patient, they are an individual person, I'm just honest with them" and "I think they can be perceived as difficult, but I don't think they are by and large I don't think I have ever looked after anyone that you couldn't make some changes to (Maatz, 2016).

3.5.3 MUS PATIENTS STRUGGLE FOR LEGITIMACY, FOR TREATMENT

Some of the terms used to refer to these patients, for example, the worried well, heart sink patients, malingerers, hypochondriacs, themselves imply that these patients are not 'real' patients, but that it is 'all in their head,' whereas patients and doctors both worry that 'like Schrödinger's cat, disease may or may not be hiding behind medically unexplained symptoms' (Stone, 2018 (2):18). With this uncertainty, patients, deprived of the traditional trajectory of illness where the problem is identified through investigation, given a name through a diagnosis and resolved through treatment. i.e. the restitution narrative (Frank, 2013), feel that their

symptoms are discounted, their lived experience invalidated and suffer from shame and stigma. The relationship with the clinician is often adversarial rather than collaborative; patients feel they have to fight to access necessary care (Lian & Robson, 2017). These issues are discussed in detail in Chapter 4.

3.6 MUS: discussed primarily as a problem of resource usage

The problem of MUS is mostly framed in the literature as an issue of resource utilisation and economics (Hiller and Fichter, 2004; DeWitt et al, 2009; Barrett et al, 2012; Payne, 2018; Wortman et al, 2018; Leaviss et al, 2020). The 1%-2.5% of MUS patients said to utilize a disproportionately high amount of the resources are frequently mentioned. To cite a few examples, severe MUS patients were estimated to cost over GBP100m per annum in London (Rohricht 2014), and overall medical costs due to MUS in England were estimated at GBP3bn per year, escalating to GBP18bn when considering total economic cost, in 2008 (Bermingham, 2010). Within the cost and resource utilisation point of view, reduction of costs incurred by these patients has been the primary focus.

There are, however, multiple gaps in the assessment of actual costs of MUS. Taking the case of England, the frequently cited figure on MUS costs of GBP3bn per year, was calculated by applying prevalence estimates of MUS in primary care consultations in the Netherlands to calculate costs of MUS for England, due to lack of MUS prevalence data for England (Bermingham, 2010). The study was carried out using the best available data at the time, however, using Dutch (also US and German) data leaves room to question the accuracy of the cost calculations - the primary care systems of the Netherlands and England are prima facie

similar, but the two healthcare systems overall have significant differences: in contrast to the English system which is free at the point of usage, the Netherlands uses a healthcare insurance system where it is obligatory for every resident to take a basic health insurance from one of ten large insurance companies to cover the costs of GP and hospital visits, and to pay a mandatory excess (€385 in 2020) before the insurance reimburses costs (Bakx, 2016).

Several other studies that have attempted to assess the costs of MUS in England have done so using data recorded under trial conditions (details in Chapter 11), which is not necessarily a reflection of actual on-the-ground conditions; this essentially means that we have a limited understanding of the actual costs of MUS in England. Moreover, there is a certain amount of necessary costs associated with MUS. For example, if a patient presents with a suspected 'lump' in the breast, it is investigated and there is no concern that the cost of investigation is an unnecessary expense even if the 'lump' turns out to be benign. Similarly, if a patient presents with a legitimate concern, the cost of investigation and/or referral should not be concerned a 'waste of resources' merely because the results are negative or because it is not medically explainable. These costs should not be lumped together with the *avoidable costs* of perpetuation of MUS with repeated cycles of investigations and referrals.

The NHS commissioning support for London study carried out in 2011 estimated the cost of care for 227 severe MUS patients over a 2-year period at one million pounds – with an approximate 30:70 distribution between primary and secondary care and estimated that the early identification of 75 MUS patients could have saved a practice £1,320 per month through avoiding unnecessary investigations and repeated consultations (Gathogo & Benjamin, 2013). This means that the identifying a severe MUS patient saves a practice £18 per month or just

over £200 a year. This could partly explain the lack of incentive for busy GPs to spend time to identify and treat MUS patients: MUS has usually been framed as a question of cost – whereas in reality the financial incentive of identifying a MUS patient could be considered too low to have an impact, and the cost of interventions for effective management may well be higher.

3.7 Need to reframe MUS as an issue of ethics and economics

There is limited discussion of the ethical issues related to MUS among both medical professionals and medical ethicists; the very few references to the ethical issues related to MUS in the literature come primarily from social scientists, patient activists and less than a handful of medical professionals.

The modern practice of healthcare operates with a heavy emphasis on evidence-based medicine; in the case of MUS, however, lack of evidence of disease is interpreted as evidence of absence of disease (Alderson, 2004; O'Leary, 2018). Diagnostic uncertainty is a characteristic of MUS to a large extent resulting in conflating several distinctly different meanings of MUS (O'Leary, 2018): the term MUS can be used to refer to

1. We (the doctors) don't know why you (the patient) have these symptoms, or,
2. We know why you have these symptoms – it's a psychogenic problem, or even
3. We know why you have these symptoms – it's part of a defined symptom cluster called symptom syndromes, though we don't know why this happens.

Moreover, the diagnosing doctor does not have to justify this move from 'we don't know why you have these symptoms' to 'we know it's a psychogenic problem'; both DSM-5 and ICD 11

allow diagnosis of SSD/BDD based on the clinicians' belief of an excessive, disproportionate or maladaptive response to symptoms. This is in line with the view that 'the diagnosis of SSD, like every other diagnosis, relies on clinical experience and judgment' and that they have 'a wealth of clinical experience on which to judge whether a given patient's thoughts, feelings, and behaviours are indeed beyond the norm' (Dimsdale & Levenson, 2013: 588).

The disadvantages of such an approach is that it risks overriding the epistemic privilege of the patient, and does not give sufficient weight to the difficulties of diagnosing MUS due to the complex interplay of psychiatric and somatic features, and the diagnostic uncertainty that results. It should be noted that physicians were warned against the tendency to label problematic cases as medically unexplained as far back as 1893. For example, referring to medically unexplained neurological disease diagnosis, it was stated that 'the more slender and insecure the practitioner's knowledge of nervous diseases the more prone he is to regard strange or puzzling cases as instances of 'hysterical paralysis' (Slater 1965:1395). It has also been pointed out that there is a methodological difference between assessing the percentage of patients who had a psychogenic diagnosis reversed and that it is more accurate to check what percentage of patients receiving a medical diagnosis had their symptoms previously attributed to a psychogenic cause (O'Leary, 2018).

Equally importantly, it has been pointed out that the 'sensationalised media coverage, profound suspicion of medical expertise and physicians, mobilisation of parties with a vested self-interest (….), litigation and a clinical approach that overemphasises the biomedical and

ignores the social factors' can 'influence, exacerbate and perpetuate the somatic distress of patients, heighten their fears, prolong their disability' (Barsky & Borus, 1999:910). These differences of opinion only serve to indicate the controversies that exist in the diagnosis of diseases attributed to mental disorders and the extreme caution necessary in attributing symptoms to mental disorders.

The diagnostic uncertainty that prevails in the early stages of MUS means that clinicians need to balance two factors: 1) ensuring that the patient receives the necessary care, be it medical investigation, treatment and care, psychotherapy or psychiatric care as appropriate, and, 2) avoiding unnecessary investigations and treatment leading to iatrogenic harm. The latter is critically important so that patients can avoid being caught in the vicious cycle of repeated investigations and multiple consultations.

Given the increasingly limited nature of resources available and the need for resource allocation to be carried out in the most efficient way possible, MUS can be a burden on healthcare systems. MUS patients who insist on repeated and extensive investigations and referrals create a strain on available resources; it may be a waste of resources when they cannot necessarily benefit from it. Going through repeated investigations and referrals can lead to iatrogenic harm, and MUS patients could then be prevented from receiving the appropriate care required to manage their situation. When considering MUS from a benefit maximization point of view, primary care providers[1] not being fully-equipped to deal with this group of patients who are estimated to be up to 45% of total primary care presentations (Chew-Graham

[1] The primary care system, which is the first point of contact and which mediates the care of MUS patients in the long run is the focal point of this thesis, with references as necessary to the secondary and tertiary care systems.

et al, 2017; Haller et al, 2015), suggests the urgent need for further training. This can be a failure, not only towards the MUS patients, but also towards all other users of the healthcare system given that scarce resources are diverted towards MUS patients who cannot necessarily benefit from the care provided.

The literature on MUS shows frequent emphasis on the financial incentives for early identification and management of these patients and very little on the ethical issues at stake in the way healthcare systems deal with MUS patients.

3.7.1 MUS RELATED ETHICAL ISSUES DISCUSSED IN THE LITERATURE

The limited discussion found in the literature, though not always specifically termed so by the authors, revolve around several key concepts of bioethics: non-maleficence versus beneficence, justice and equity, respect for patient autonomy alongside consent issues and medical paternalism, epistemic privilege versus objective evidence, stigma, power imbalance and the role of gender in MUS.

3.7.1 Beneficence vs non-maleficence

The need for non-maleficence – to not to harm the patient through unnecessary investigations is discussed along with the equal or more important fundamental tenet of bioethics and medicine of beneficence - ensuring that patients receive the care they seek as well as the care they need (Gillon (1), (2), 1985; Page & Wessely, 2003; Kanaan et al, 2009).

3.7.2 Justice and equity

The patient's right to receive care may be compromised in this group of patients and they frequently complain of being denied legitimacy for their issues due to the lack of a diagnosis.

MUS figuring low in the hierarchy of disease prestige, not recognised as a disease deserving of support and care (unlike e.g. breast cancer or heart disease), and the resultant stigma as a malingerer or hypochondriac, is another ethical issue that has been pointed out and needs further discussion, particularly as the medical profession is partly responsible for how the public views MUS. The issue of equity also arises at a broader level when considering the limited resources allocated globally for mental disease (Stone (1), (2) 2018; Gillon (1), (2), 1985).

3.7.3 Epistemic privilege vs objective evidence

The normative and epistemic importance of patient perspectives is gaining increased importance in medical research (Schicktanz, 2007), with for example, the NIHR, and most research funding agencies including MRC UK and the Wellcome Institute, mandating Patient and Public Involvement and Engagement (PPIE) as a part of the research process. Similar trends are seen in Europe with, for example, the German National Ethics Council requiring the participation of people with disabilities and chronic or acute disease in the research arena. Qualitative research on patient perspectives can be seen more frequently now, however, there is limited research on how patient perspective can and should be incorporated into the research process works in practice.

This increasing recognition of the value of patient perspectives at a macro level – as indicated by the need to include PPIE in research, is yet in the process of being attributed to the patient experience at the individual level in clinical practice. ICD-11 and DSM-5 both for example give the clinician the power to decide if the attention paid to the disease is excessive – negating the patient's epistemic privilege – the lived experience of his/her own disease. Objective evidence as witnessed by the unbiased clinician may well be better placed to identify disease; however,

this must occur alongside an acknowledgment of the epistemic collaboration the patient provides. Failure to do so is to deny the patient a narrative, and at the same time, missing the opportunity to incorporate his lived experience in the form of a self-narrative and the patient explanatory model, both of which can help to build a stronger 'treatment alliance' between the patient and the clinician (Sumathipala et al, 2007; Taieb, 2009).

3.7.4 Autonomy, consent, medical paternalism, power and gender issues

MUS still suffers from the pejorative connotations of hysteria, and, as it was primarily attributed to women, who, at the time, were not considered autonomous, the tendency to entangle a psychogenic diagnosis with an 'assumed lack of autonomy in women' (O'Leary, 2018). Nearly three-quarters of MUS patients are women (Arnold et al, 2011); however, it is not clear if this is a result of doctors being more ready to assign a 'medically unexplained' diagnosis to women (Katz et al, 2010). It is well documented (mostly by non-clinicians) that physicians have shown scepticism regarding the credibility of women's illnesses (Werner and Malterud, 2005; Pryma, 2017). Despite the term hysteria being removed from the DSM, some in the medical profession still conflate conversion or functional disorders with hysteria as indicated by, for example: "the diagnosis is functional weakness, which might also be called conversion disorder or psychogenic weakness. In years gone by it would have been called 'hysteria' (Stone (2), 2005); 'The paradigm unexplained syndrome is hysteria, or "conversion disorder" as it is now known' (Kanaan et al, 2009:297).

The frustration patients feel can be worsened with the paternalistic attitudes that persist towards MUS patients in medicine. Using the term 'functional' to convey different meanings to patients vs healthcare professionals, and being deliberately ambiguous in the wording used

when discussing a psychogenic diagnosis is akin to doctors previously preferring to hide a critical illness diagnosis from the patient to spare the patient worry. Some researchers advocated a nuanced approach to 'remain respectful of autonomy while avoiding the conflict that comes with direct disclosure' – language that reinforces the paternalistic mentality that is tied to a perceived lack of autonomy in such patients (Kanaan et al, 2012). When a neurologist states that the rate of misdiagnosis of medical disease as psychogenic illness is 'only 4%, a rate no worse than for any other neurologic or psychiatric condition' (Stone et al, 2005), such an 'only 4%' translates to one in every 25 patients being misdiagnosed. When considering that up to 60.7% of consulting patients have been considered medically unexplained (Haller et al, 2015) – this is a significant number.

The power of the position the doctor occupies in the doctor-patient relationship by virtue of his/her professional knowledge and experience is intensified in the case of MUS patients due to the lack of credence given to the patient narrative when objective evidence to support that narrative cannot be found via investigations (Swartz, 2018).

On the other hand, doctors too perceive a power imbalance that is in favour of MUS patients, making them feel discomfort, inadequacy, resentment and fear of such patients who could dominate and manipulate the course of the consultation (Wileman, 2002; Johansen, 2017). The collective power patients feel they have gained through online forums and patient advocacy organisations may well have a role in this (Barsky & Borus, 1999; Stone, 2018).

3.8 Need a framework to address MUS-related ethical issues

The discourse around ethics as related to MUS itself appears adversarial. On the one hand, patients, activists, social scientists and advocates of feminist bioethics deplore the power, justice, autonomy and gender bias related issues around MUS that they believe the medical profession continue to propagate. They point out the vulnerability and disempowerment patients feel when facing an 'out-of-the-norm' illness, succinctly expressed as 'the confluence of a medical culture that is all-knowing and a societal tendency to view the individual as the vessel of all possibility means that it becomes too easy to blame patients for symptoms that are seemingly inexplicable' (Atkins, 2010:xxv).

Not much has been written from the perspective of the medical profession on the ethics of MUS. Kanaan et al (2009) discussed the 'shift in ethical obligations on doctors' from the paternalistic position of protecting patients from distressing news to 'respect for patient autonomy in the form of truth-telling.' However, in a reflection of the realities clinicians face regularly in their practice with MUS patients, they then question if the principle of beneficence ought to take priority over the principle of respect for autonomy, given the propensity of patients to reject psychiatric diagnoses and drop out of treatment. Cole et al (2014) discuss such ethical dilemmas as related to psychogenic non-epileptic seizures.

Clinicians have also researched the risk of iatrogenic harm, and the risk of relaxing clinical vigilance alongside psychiatric diagnoses (Robertson & Kerridge, 2009). Sankary and Ford (2018) discussed the ethical implications of 'the blurred distinction between diagnosis and intervention', as well as the co-occurrence of psychogenic causes and organic symptoms. Stone

is one of the few clinicians to tackle the ethical issues related to MUS recently, discussing the patient's lack of validation in the absence of a named disease, as well as the resultant lack of guidelines, protocols and resources to deal with the patient's disease (Stone, 2018). Importantly, she discusses the 'challenge of individualising evidence-based treatment' so that the focus can move from disease guidelines to individual patient needs whilst acknowledging the need for clinicians to attempt care even in the absence of evidence (Stone, 2013: 501).

This limited discourse on MUS-related ethical issues was carried out primarily by academic clinicians and patient advocates. However, these same themes, for example, power, epistemic injustice, vulnerability, appear in the qualitative research describing patient and clinician experiences (detailed in Chapter 4), though not expressed in ethics-related terminology. Such 'moral intuitions' from the key stakeholders can be used alongside moral principles to construct a richer ethical framework around the issues related to MUS (van Thiel & van Delden, 2017). It is critically important for medicine to acknowledge the necessity to engage with these patients with an acknowledgment of their suffering given both the high prevalence of medically unexplained disease in medicine, and the fact that these patients may not receive the care they need. At the same time, these patients also need support in better understanding their illness and their contribution towards its management. Current clinical ethics frameworks are not necessarily equipped to deal with the specific issues related to MUS. For a paradigm shift in the approach towards MUS patients, an ethical framework that considers the unique features of MUS is needed. It needs to guide the change in the negative approach learned from the time healthcare staff are students, and support clinicians to deal with the challenge of informed consent given that these patients remain fully autonomous despite receiving a psychiatric

disease diagnosis. Such an ethical framework also needs to support clinicians to accept and deal better with the ambiguity inherent in medically unexplained symptoms, to support the learning of management of these patients with greater confidence, and to consider the ethical nuances of assigning a psychiatric disease label to the patient given the stigma and restricted access to care these patients subsequently face.

3.9 Conclusion

This chapter provided an overview of the problem of MUS, discussed its aetiology, epidemiology, management, the current focus on the economic impact of MUS and initiated the discussion on why MUS related issues need to be reframed as an ethical issue. The next section describes the qualitative evidence synthesis (Chapter 4), and is followed by the analysis of real-life, routinely recorded data on the consultations of patients with MUS in a primary care database (Chapters 5-12).

CHAPTER 4

PATIENT AND CLINICIAN EXPERIENCES IN RECOGNISING AND MANAGING MUS: A QUALITATIVE EVIDENCE SYNTHESIS

4.1 Introduction

The focus of this thesis is to ascertain the facts and values that operate on the problems faced by patients and doctors in the diagnosis and management of patients with MUS with the objective of developing boundary principles as described in Chapter 2.

The boundary principles must be identified through 'robust and reflexive empirical research which accesses and lays bare the nature of the problem from the perspective of the stakeholders which allows the researcher to identify 'the central and overriding values that inform stakeholders' thinking about the problem and specifies key considerations' (Ives, 2014).

In order to achieve such an understanding of both the micro and macro aspects of the problem, in the ways it is experienced and perceived by the stakeholders, the researcher needs to explore the issue from all angles, investigating the problem broadly, to uncover all aspects impacting on the issue.

New research is usually necessary to identify the facts and values that operate on an issue. However, there is a large body of qualitative research published on the focus of this thesis, experiences of patients and doctors in identifying and managing MUS (Eccleston et al, 1997; Asbring, 2002; Nielsen 2020, Rask 2021), which permits extracting the facts and values important to the key stakeholders, doctors and patients, making the incremental value of any further primary research quite limited.

The quality of this evidence, though extensive, could potentially be criticised based on the usual criticisms aimed at qualitative research: the unique demographic, psycho-social, cultural and contextual characteristics of each of the individual research papers that could lead to poor transferability, and methodological issues such as small sample sizes (Dixon-Woods & Fitzpatrick, 2001; Campbell, 2003; Thomas & Harden, 2008; Ring et al, 2011).

Carrying out an evidence synthesis which collates the findings of a number of primary qualitative studies in a systematic manner (akin to systematic reviews carried out for quantitative data) permits consolidating evidence, helps to identify the core concerns and contributes to a deeper understanding of complex situations such as the issues faced by clinicians and patients in this case (Johansen & Risor, 2016; Flemming & Noyes, 2021; Talbot et al, 2022). Furthermore, it helps assess the generalisability and transferability of disparate research findings (Dixon-Woods et al, 2006; Noyes et al, 2021). Noyes et al (2021) state in the Qualitative Evidence chapter of the Cochrane Handbook for Systematic Reviews of Interventions that qualitative evidence synthesis helps assess patients' core areas of concern, identify areas where further research is necessary and provides further evidence to understand the complexity, contextual variations, and implementation of interventions in order to inform policy making decisions.

4.2 Why it is important to carry out this review

Evidence synthesis of patient and clinician experiences in MUS in the literature is limited with syntheses carried out only related to a few specific criteria for specific conditions: chronic

fatigue syndrome (Larun & Malterud, 2007; Anderson et al, 2012, Bayliss et al, 2016), the nature of fatigue across long-term conditions (Whitehead et al, 2016), the problems GPs face with MUS (Johanson and Risor, 2016), living with psychogenic non-epileptic pain (Rawlings & Reuber, 2016), and, experiences and needs of patients with IBS (Shorey et al, 2020). Murray et al (2016) carried out a review of barriers to diagnosis of MUS and Hanssen et al (2021) a review of barriers and facilitators to implementing interventions for MUS, which are related to this review; however, here the focus is on the patients' and clinicians' experiences of the process. There is a significant body of qualitative research on MUS overall, yet the evidence from qualitative research remains as 'islands of knowledge' (Parslow et al, 2017, p.2), which have not been synthesised into producing outcomes that can be used to improve the diagnosis and management of MUS patients.

This thesis aims to synthesise existing evidence pertaining to the reality of patients' and doctors' lived experiences in comparison to the ethical ideal of how patients should be managed. It is important in this context to consider the issue from the viewpoint of doctors as well as patients, since they face multiple difficulties when attempting to manage MUS patients, and understanding doctors' experiences is just as critical to finding a solution to these concerns as that of patients.

This qualitative evidence synthesis, which puts together the views and experiences of both patients and doctors on recognising and managing MUS can help provide a broader understanding of the extent and severity of the problem, identify the gaps in knowledge, the areas that need further investigation, and positively impact patients' lives by improving their diagnosis and management.

In the context of this thesis, carrying out an evidence synthesis helps achieve the requirement of the RBL method to investigate the issue from multiple angles and to extract the values of key stakeholders, patients and doctors, as they are 'lived through and experienced' (Ives, 2014). Boundary principles are derived from the values of key stakeholders thus extracted. Deriving boundary principles from empirical data in this manner helps guard against bias (Ives, 2014) and brings out stakeholder views as opposed to that of the researcher.

4.3 Objective

To conduct a synthesis of existing evidence on patients' and doctors' views and experiences of recognising and managing MUS.

4.4 Methods

Many approaches to synthesizing the findings of qualitative research have been developed over the years since the first method of meta-ethnography was published by Noblit and Hare (1988). Dixon-Woods et al (2005) analysed the strengths and weaknesses of these methods and analysed the difference between integrative and interpretive syntheses. Integrative syntheses focus on summarizing data, in cases where the key concepts of the synthesis would be defined at an early stage, and these concepts form the categories under which the data extracted from the empirical studies would be summarised. Interpretive syntheses do not specify concepts before the synthesis and aim to generate theories that are based upon the data from the studies. They include Thematic synthesis as one of the forms of interpretive synthesis (Narrative summary, grounded theory, meta-ethnography among others).

Thomas and Harden (2008) took the term Thematic analysis which usually refers to the method used in analysing primary research and developed the methodology of Thematic synthesis which is carried out in three steps:

1) free line-by-line coding of the findings in each primary study

2) organising the free codes into related areas to develop descriptive themes

3) developing analytical themes

Thomas and Harden (2008) state that 'going beyond' the content of original studies is a necessary component of synthesising qualitative research. This is achieved by interpreting the descriptive themes emerging from the analysis of the line-by-line coding iteratively until the new analytical themes that emerge are 'sufficiently abstract' to describe and explain all the initial descriptive themes. It is important here to ensure that these analytical themes that emerge are based on the descriptive themes and that they do not result in a 'purely theoretically driven review that goes beyond existing knowledge (Talbot et al, 2022).

A University of Oxford team modified the Thomas and Harden approach when synthesising the evidence on experiences of treatment-resistant mental health conditions in primary care (Talbot et al., 2022), using a 'descriptive and interpretative approach' which incorporated interpretation of the existing evidence to develop 'novel insights' from the existing evidence, rather than 'going beyond' the original data. Another example of where this interpretive approach to develop analytical themes is employed is a thematic synthesis of qualitative studies of GP/nurse perspectives on discussing weight with obese patients in primary care (Warr et al, 2020).

In this synthesis, it is important to ensure that the evidence emerges from the primary studies. Early defining of key concepts/categories by the researchers as is usual in integrative synthesis is therefore not suitable for this synthesis, and an interpretive approach is taken. The analytical or high-order themes need to be developed based on the lived experience of doctors and patients as described in the primary studies.

This synthesis therefore follows Talbot's interpretation of the Thomas and Harden approach to thematic synthesis of systematic coding of data, developing descriptive themes and generating higher-order themes based on the descriptive themes, since this modification allows retaining the voices of the stakeholders, and to interpret their views and experiences to bring in new insights. This approach is also supported by the Cochrane Collaboration Qualitative Methods Group, which suggests that a synthesis should produce new 'synthetic constructs, which are a consequence of reshaping, or interpretation, of data from individual studies to create a new model or framework (Noyes & Lewin 2011).

The SPIDER tool (Sample, Phenomenon of Interest, Design, Evaluation, Research type, Cooke et al, 2012), modifying the PICO approach to make its use more amenable in qualitative evidence synthesis, was used in this review.

4.4.1 INCLUSION CRITERIA

Sample: The focus is on adult patients with MUS and doctors who diagnose and manage MUS patients.

Phenomenon of interest: The review focuses on the views and experiences of two key stakeholders (patients and clinicians) in the diagnosis and management of MUS. Both patients

and doctors are included in this single study to compare and contrast the issues from the two different viewpoints. An inclusive approach to the definition of MUS is taken in this review, encompassing all definitions of MUS as described previously in Chapter 3.2.

Design, evaluation, and research type:

Included: Primary studies that used qualitative methods to collect data (interviews, focus group discussions, diaries, open-ended survey questions and observations) and to analyse the data (for example, thematic analysis, grounded theory) related to the diagnosis and management of patients with MUS; personal accounts of experiences of MUS patients or doctors; Mixed-method studies where it was possible to extract data on themes identified; primary studies.

Excluded: Systematic or other reviews that carry an interpretation of original research that could bring in an additional level of bias; studies that used quantitative methods (e.g., descriptive statistics) to analyse data collected using qualitative methods such as open-ended survey questions excluded if there was no qualitative analysis of the responses; studies that lacked in-depth qualitative data; studies focusing on specific outcomes of MUS conditions (rather than on the diagnosis and management as whole, e.g. sleep in chronic fatigue or the response to a specific therapy such as hypnotherapy); studies which focused on multiple conditions which included organic disease or psychiatric illness (e.g., Irritable Bowel Syndrome and inflammatory bowel disorder studied in combination); papers based on data sourced from web pages and online chats (and did not have a defined strategy to exclude bias when carrying out research).

4.4.2 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

The standard, structured search strategy approach of conventional systematic reviews has been found to be of limited use in qualitative research as it risked missing relevant research papers (Greenhalgh et al, 2005; Dixon-Woods et al, 2006). Dixon-Woods et al (2006) suggested that a more organic process of search methods would fit in better with the exploratory nature of the review question in evidence synthesis. A combination of electronic data base searches, reference chaining, and website searches was therefore used to find relevant studies.

The search strategy (Appendix 4.1) was kept intentionally broad so that a range of studies could be captured. The time frame was limited from 1 January 2016 to 31 December 2022 (past seven years) to capture recent experiences without compromising the comprehensiveness of the search. Studies were limited to peer-reviewed articles in the English language and to studies on adults over 18 years, without any geographic restriction. The databases Academic Search Complete, Ageline, the Allied and Complementary Medicine Database (AMED), CINAHL Plus with Full Text, MEDLINE, APA Psycinfo, SPORTDiscus with Full Text, APA PsycArticles, and Philosopher's Index were searched using the EBSCOhost search interface.

4.4.3 STUDY SELECTION

Following the removal of duplicates, a title and abstract review was carried out screening the articles against the inclusion criteria. The articles selected for full text screening were reviewed by both the thesis writer and the lead supervisor.

In qualitative primary research, data saturation is the point at which further research is deemed to not yield further new information and in qualitative evidence synthesis, the focus is on

identifying themes/concepts rather than exhaustively summarising all data (Dixon-Woods et al, 2006; Ames et al, 2019). However, this evidence synthesis is nested within a PhD research study where one of the objectives is to assess the extent of the problems faced by MUS patients and their doctors. Therefore, in order to be as comprehensive as possible, and to assess if these are widespread issues, all relevant papers were included in the synthesis. The author reviewed all the studies and the lead supervisor independently reviewed data from random samples. Conflicts were resolved through discussion.

The studies were separated into two groups: doctors' views and patient views; studies containing both doctor and patient views were included in both categories.

4.4.4 DATA EXTRACTION

The more inclusive method of data extraction is to include all themes and qualitative data given in the primary study regardless of the presence or absence of a direct quotation illustrating the point. With this method, however, it is difficult to assess whether the themes have actually arisen from the primary data or to assess the validity of the themes generated, i.e. whether the themes developed in the primary studies emerged from data and its analysis rather than from 'armchair theorizing' by researchers" (Noyes & Lewin, 2011).

Within the overall theme of this thesis, it is more important to ensure that the themes generated are based on stakeholder views, therefore it was decided that the best option is to use the more restrictive form of data extraction: data points illustrated by a direct quotation from a respondent, i.e., first-order constructs alone, were extracted from the primary study (Flemming & Briggs, 2007).

A data extraction tool consisting of the following study characteristics was used for the extraction of descriptive data of each study:

Data extraction field	Information extracted
Context and participants	First author, year of publication and title; Country; Setting – Primary / Secondary Care / Other; Study Focus – Patient / Health Care Provider (HCP); Type of MUS of concern – CFS/ME/FM, IBS, or other MUS
Study design and methods used	Sample size and sampling method Data collection methods: Interview / focus group discussion / survey Data analysis methodology (ethnography, phenomenology etc)
Study Quality	Quality assessed using CASP quality assessment tool and the result included in data extraction table
Findings	The Findings or Results section of each study was extracted. Direct quotations from participants (first-order constructs) were extracted after detailed study of this section.

4.4.5 QUALITY ASSESSMENT

The methodological quality of the included studies were assessed using a quality appraisal framework adapted from the Critical Appraisal Skills Programme (CASP) quality assessment tool for qualitative studies (CASP 2018), given in Appendix 4.2. This has been previously used in a number of qualitative studies (Houghton, 2020; Glenton, 2013; Lewin, 2018).

Methodological limitations were assessed for each article by two reviewers separately, compared and disagreements resolved through discussion. An inclusive policy was followed when deciding whether to include studies in the research. Methodological limitations resulted in the exclusion of studies only where there were serious concerns, since even studies where there are concerns about methodology could provide 'useful and authentic accounts of a

phenomenon despite it being poorly reported' (Dixon-Woods et al, 2005; Noyes et al, 2008; Soilemezi, 2018, p. 9; Houghton, 2020).

4.4.6 ASSESSMENT OF CONFIDENCE IN THE REVIEW FINDINGS

Two reviewers (the author and the lead supervisor) independently assessed the confidence in the findings based on the four components of the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) approach (Lewin 2018), based on the assessment of methodological quality, coherence, relevance and adequacy.

1. Methodological limitations of included studies: concern on the design, conduct of the studies

2. Coherence of findings – assess how clearly the data from the articles fit the review findings

3. Adequacy of data – assess the degree of richness of the data

4. Relevance of data to the review question

Overall confidence in findings were compared and differences resolved through discussion.

4.4.7 DATA SYNTHESIS

The process described below developed from Cochrane Guidance for data extraction (Noyes & Lewin, 2011) and a modified form of Thomas & Harden's methodology for thematic synthesis (Thomas & Harden, 2008 as modified by Talbot et al, 2022) was followed separately for the two groups – doctors' experiences and patient experiences.

All the text from the section 'results' or 'findings' in each paper was extracted. These were studied in detail to understand the context of the direct quotations provided and then the

direct quotations were separated for line-by-line coding. An inductive coding approach was taken allowing the narrative to emerge from the raw data.

The synthesis was carried out in three stages:

i) Free line-by-line coding of the findings of primary studies – each line of the first-order constructs was given a code that captures its meaning and content. They were collected as 'free codes' without organising the codes in a hierarchical structure. At the end, all the text was re-examined to check that the interpretation was consistent. The code development was done manually and the free codes from each paper were coded with a single colour for ease of keeping track of the origin of the code.

ii) Similarities and differences among the codes were examined and similar codes were identified and aggregated under similar concepts. Where necessary, new codes were created to represent a group of codes similar in meaning and concept resulting in a set of descriptive themes, which too remained close in meaning and concept to the original findings of the primary studies.

iii) A mind-mapping approach (OSOP – one sheet of paper method) was used to identify conceptual links among the descriptive themes leading to the development of overarching 'higher-order' or analytical themes. The themes were initially developed by the thesis writer and subsequently the lead supervisor reviewed the codes independently in order to ensure that all relevant issues arising from the data was captured.

4.5 Results

4.5.1 SEARCH RESULTS

The search resulted in 2,476 records after removal of duplicates. A title and abstract review resulted in 61 potentially relevant articles. Other sources yielded 4 articles. Of the 65 articles where full-text search was done, 35 papers were excluded and 30 papers were selected for inclusion in the qualitative evidence synthesis (Appendix 4.3).

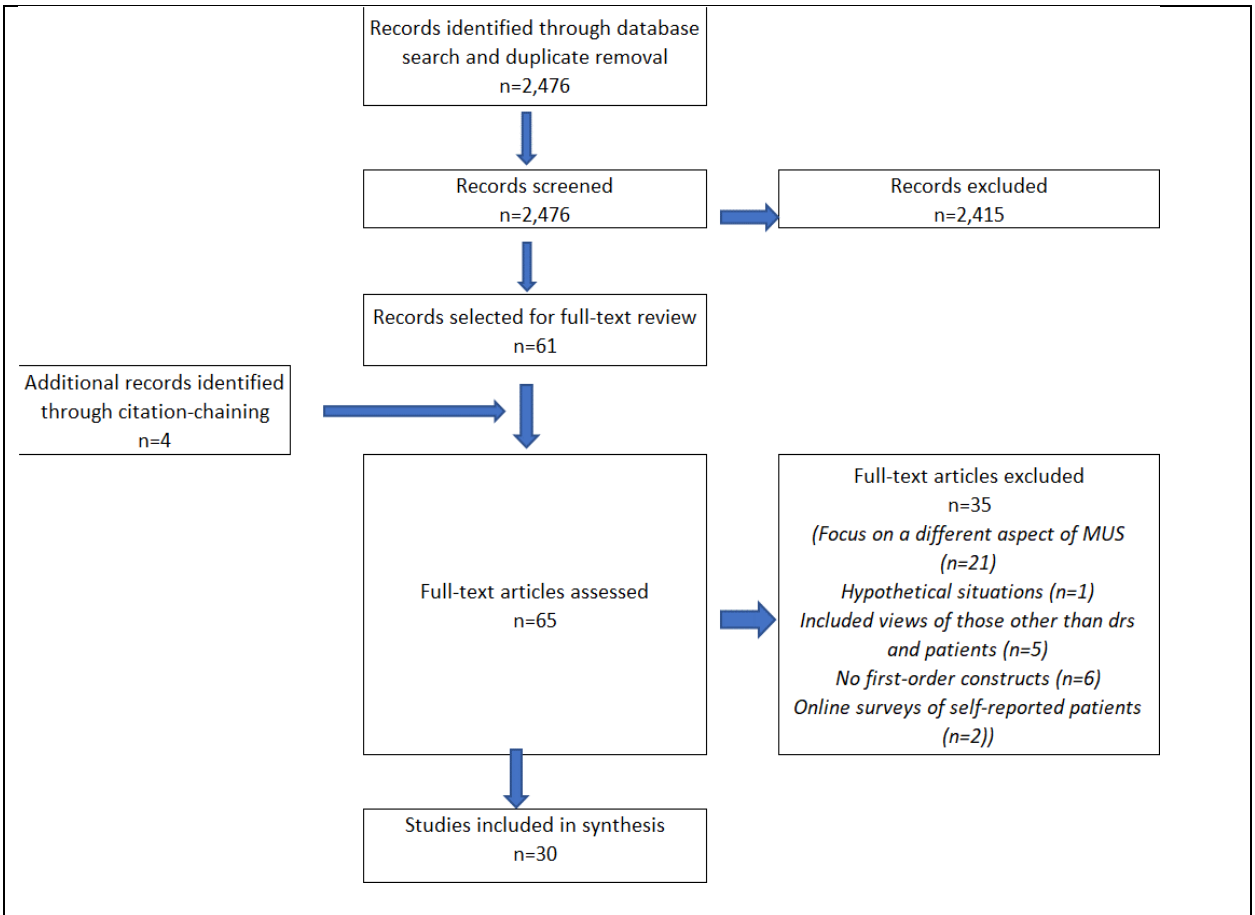


Figure 4.1: PRISMA flow diagram and identification of studies

These 30 studies represented the views and experiences of 1,775 patients and 213 doctors. The data extraction sheet mentioned in Section 4.4.4 is reproduced in Appendices 4.4 to 4.6,

separately for papers discussing experiences of patients, doctors, and both. There were 18 papers which discussed the views and experiences of patients, 10 papers that of doctors and 2 papers which discussed both. Apart from a large survey of 1,163 male patients (Muraleetharan), the vast majority of participants were female (571 cf. 16 male patients).

Data collection: Most of the studies used interviews except three which used Focus Group Discussions (1, 9, 24), one that carried out a qualitative survey (21) and one that used written submissions (15).

Geographic origin: Two papers were from LMIC countries, Iran (19) and South Africa (8), the remainder from HIC: Norway (1, 10, 15), Sweden (3), Denmark (26), Netherlands (9, 13, 14), Finland (27), Germany (24), Spain (4, 20), UK (2, 5, 12, 16, 17, 18, 22, 23, 28, 29, 30), Canada (6) and USA(7, 11, 21, 25).

Setting: Nine of the studies were carried out in a primary care setting (1, 2, 4, 9, 13, 19, 24, 26, 27), nine in a secondary care setting (5, 11, 14, 16, 17, 20, 22, 23, 29) and the remainder in other settings such as universities (3, 6, 7, 8, 10, 12, 15, 18, 21, 25, 28, 30).

Method of analysis: Seventeen studies used a form of thematic analysis to analyse data, the most common analytic approach, and the remainder of the studies used a variety of approaches; four used a phenomenological approach, three used content analysis, two used narrative analysis, and one each used a framework approach, systematic text condensation, discourse analysis, and constant comparative analysis.

Disease condition studied: The research was categorised into three groups: 1) Chronic Fatigue Syndrome / Myalgic Encephalitis / Fibromyalgia (CFS/ME/FM), were considered within a single

group, 2) Irritable Bowel Syndrome, 3) Generic medically unexplained symptoms and other: unspecific conditions such as chronic pain, chronic low back pain, unexplained neurological conditions were considered together. Eleven of the papers focused on patients with Fibromyalgia / Chronic Fatigue Syndrome / Myalgic Encephalitis (FM/CFS/ME, 2,4,5,7, 8,15, 18,20,21,27, 30), four on Irritable Bowel Syndrome (IBS, 3,12,19,28) and the remainder on MUS and other (1, 6, 9, 10, 11, 13, 14, 16, 17, 22-26, 29).

4.5.2 ASSESSMENT OF METHODOLOGICAL LIMITATIONS IN PRIMARY STUDIES

The concerns about the methodologies used were primarily regarding the recruitment strategies: Convenience sampling, purposive sampling, and snowball sampling were the most commonly used sampling methods. Recruitment in some cases was through personal contacts, previous study participants etc, without considering how bias was to be avoided.

There were 19 studies without any methodological concerns (Appendix 4.7). Nine studies (4, 12, 13, 14, 16, 18, 19, 20, 28) where convenience sampling was done were marked as “mild concerns” although there is argument for convenience sampling not having a negative impact in qualitative studies (Marshall, 1996; Luborsky, 1995; Palinkas, 2013). There were “moderate concerns” about the sampling and recruitment strategy in two studies (7, 26) where recruitment was through personal contacts, or through internet-based recruitment, where there is less confidence about the participants’ true credentials than when recruited through primary/secondary care. The summary findings of the assessment are given in Appendix 4.7.

4.5.3 ASSESSMENT OF CONFIDENCE IN THE REVIEW FINDINGS

The studies were assessed for overall methodological quality, coherence and relevance as shown in Appendix 4.8. The two reports where there were mild concerns about methodology were marked as 'Moderate confidence'; there was high confidence in the evidence in all other reports.

Prior to selection of the final studies to be included in the research, three reports were excluded due to serious methodological concerns and very low confidence; two were reports of the same industry designed, sponsored and conducted survey, written in two different years with industry funded medical writing support, and the third, one where patients were recruited through personal contacts without any further detail on how bias was to be avoided.

4.5.4 SUMMARY OF QUALITATIVE FINDINGS

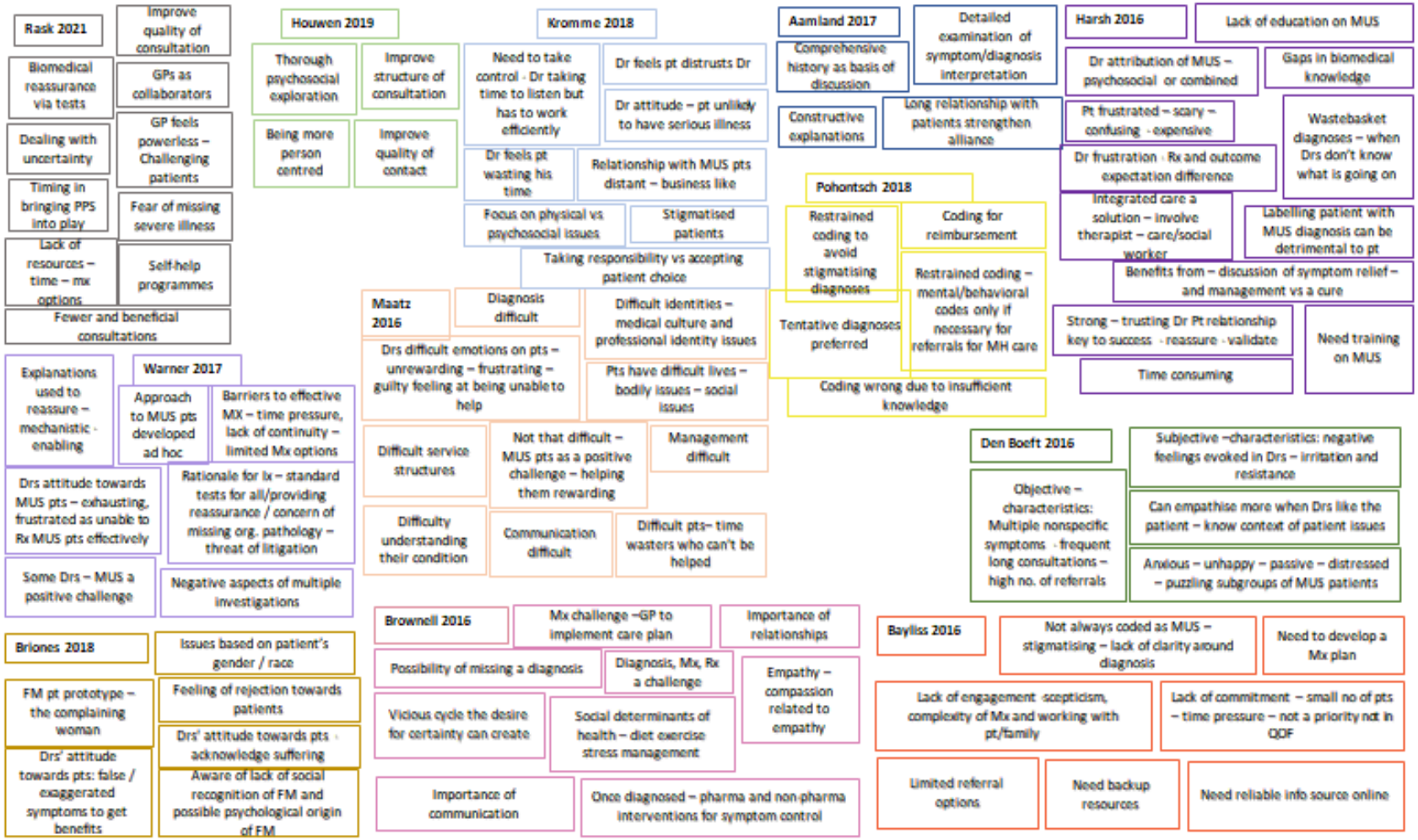
4.5.4.1 Doctors' experiences in diagnosis and management of patients with MUS

Examination of the direct quotations by participants in the Findings/Results segments in the papers yielded 168 relevant direct quotes. Each of these were assigned a code that captured its meaning and context. These were collected as free codes without hierarchy. An example of the coding of a paper is shown below in Figure 4.2 and the full list of quotes and codes in Appendix. 4.9.

Figure 4.2: Developing codes through line-by-line coding of direct quotations	
"our medical education is not doing a very good job of teaching us to treat patients with medically unexplained illness; side of medicine that we don't learn in textbooks"	Lack of education on MUS (Harsh)
"having a psychologist or psychiatrist or somebody to whom I could say 'How would you . . . kind of deal with this with the patient?' to kind of help me out along the way"	Integrated care as a solution – involve therapist – care/social worker (Harsh)
"multidisciplinary approach"	
"stems from the fact that I have some resources available to me in my clinic,"	
"partner up and help these patients,"	
"having available a behavioural health component is enormously helpful"	
"provide social support, maybe doing less medically and more socially and more psychosocially."	Potential solutions - biomedical therapies combined with psychosocial support
"combined approach (biomedical therapies + psychosocial treatments)"	
"not just quickly say, 'Oh it's just from stress and depression or something else that's going on'"	Differentiate between diagnostic uncertainty and psychosocial aetiology (Harsh)
"appropriate medical evaluation' prior to assuming symptoms stem from psychosocial aetiology"	
"a haphazard chicken or egg situation where you don't know whether it is the symptoms that are causing you to be depressed and frustrated or whether this is a manifestation of something else."	
"frustrating" for patients	Acknowledgement of patient concerns - frustrated (Harsh)
"obviously scary"	Patients scared (Harsh)
"perhaps with an appropriate chip on their shoulder toward the health care system that has failed them so far"	Acknowledgement of patient dissatisfaction (Harsh)
"feel confused"	Patients confused (Harsh)
"a very expensive process for the patient"	Patients find it expensive (Harsh)
"We almost just hang these on people when they have pain we can't explain or belly pain we can't explain"	MUS diagnoses given when symptoms unexplainable (Harsh)
"more demanding", "needy,"	Patients are demanding (Harsh)
"'high utilizers' of the medical system"	Patients are high utilisers of the medical system (Harsh)
"resistant about opening up and accepting that maybe these are somatic complaints"	Patient refusal to accept MUS diagnosis (Harsh)
"can be kind of fun at times, like a challenge, like, 'Okay can I help them somehow?"	MUS as a positive challenge (Harsh)

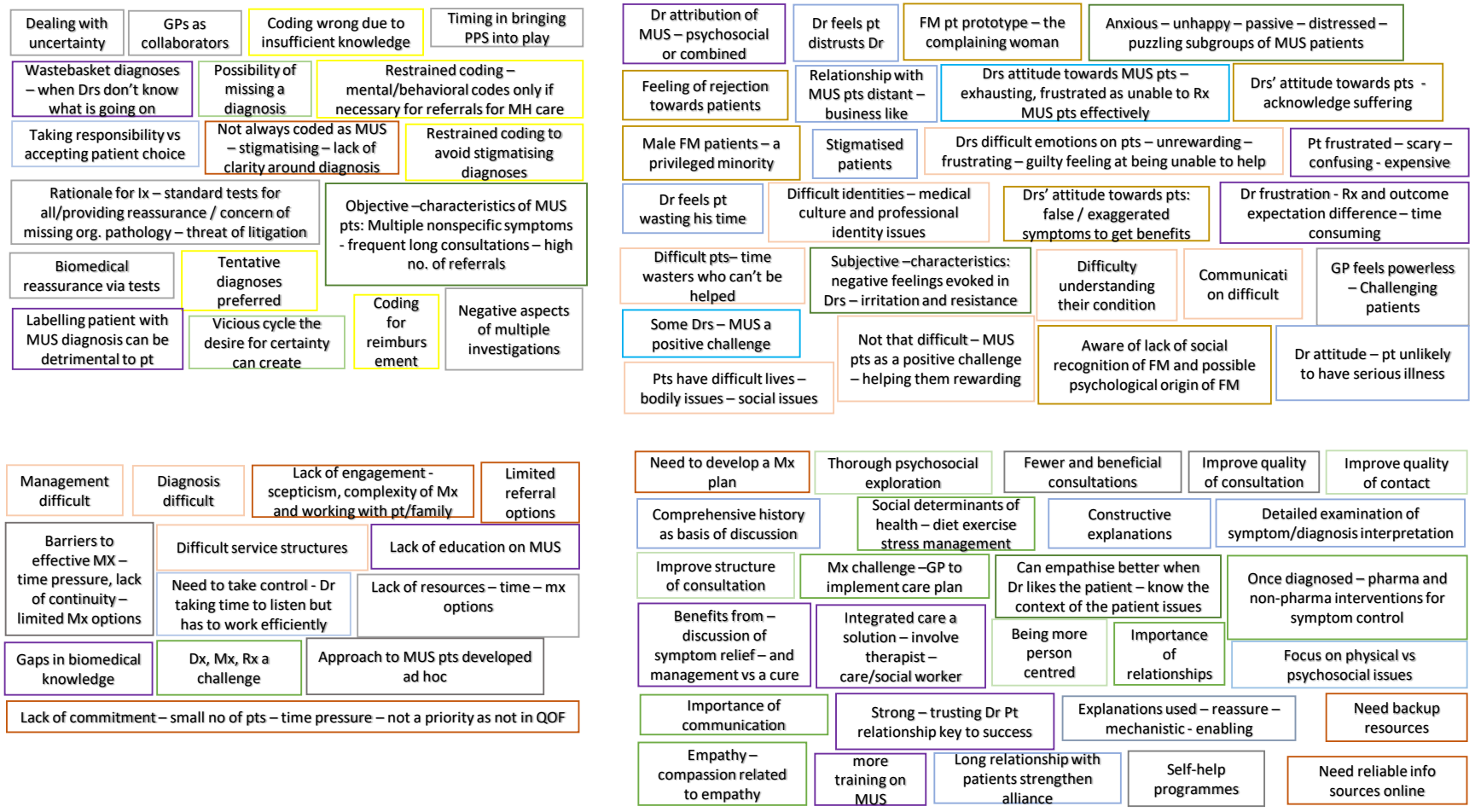
Free codes were developed from direct quotations of participants in the primary studies (an example shown in Figure 4.3).

Fig. 4.3 Free codes developed from direct quotations of participants in primary studies – Doctors experiences



These free codes were then consolidated in to related areas to develop descriptive themes as illustrated below in Figure 4.4.

Fig 4.4 The process of developing descriptive themes using mind map – Doctors' experiences



The descriptive themes arising from the codes generated based on doctor's experiences were as follows:

Figure 4.5 Doctor's views: Three Descriptive themes emerged from the primary data

Managing Diagnostic Uncertainty

- Acknowledge importance of diagnosis to patients (Pohontsch, Aamland)
- Restrained coding necessary (Pohontsch, Bayliss)
- Patients refuse to accept MUS diagnosis (Harsh)
- Need for reassurance via tests (Rask, Warner)
- Need to exclude organic illness (Rask, Warner)
- Need to avoid risk of litigation (Warner)
- Need to consider harm arising from repeated investigations (Harsh, Brownell, Warner)
- Need to accept diagnostic uncertainty as an integral part of MUS (Brownell, Maatz, Warner)
- Need to accept possibility of gaps in biomedical knowledge (Harsh, Brownell, den Boeft)
- Need to differentiate between diagnostic uncertainty and psychosocial aetiology (Harsh)
- Taking responsibility vs simply accepting patient choice (Rask)

Emotional experiences in doctor-patient encounter

- Frustration, irritation, and desperation of doctors (Briones, Brownell, den Boeft, Harsh, Maatz)
- Feeling of powerlessness (den Boeft)
- Guilt at being unable to help (Maatz)
- Patients seen as time wasters (Kromme, Maatz)
- Patients seen as difficult and demanding (Kromme, Briones, Harsh)
- Patients seen as complainers (Briones)
- Disbelief and prejudiced towards MUS patients (Briones, Bayliss)
- Problem complicated by gender issues (Briones)
- Lack of commitment towards unrewarding work (Bayliss, Maatz)
- Recognising patient difficulties (Briones, den Boeft, Harsh, Maatz)
- MUS seen as a positive challenge (Harsh, Maatz, Warner)

Resource related issues

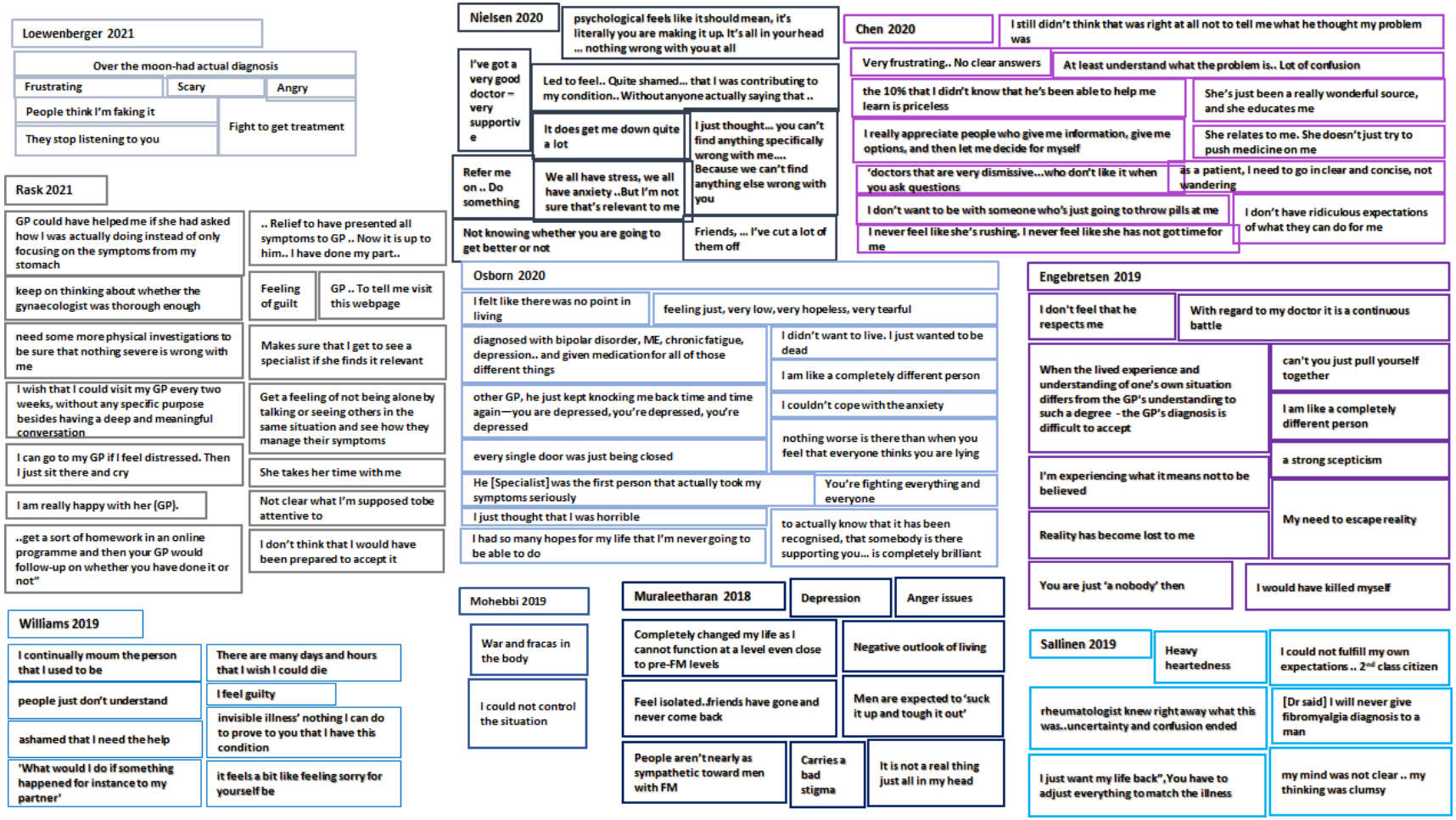
- Limited time and management options are a constraint (Brownell, Kromme, Rask)
- MUS patients heavy users of resources (Harsh, Maatz)
- Limited referral/support services (Bayliss, Maatz)
- Limited awareness/training on MUS (Harsh, Pohontsch, Warner)

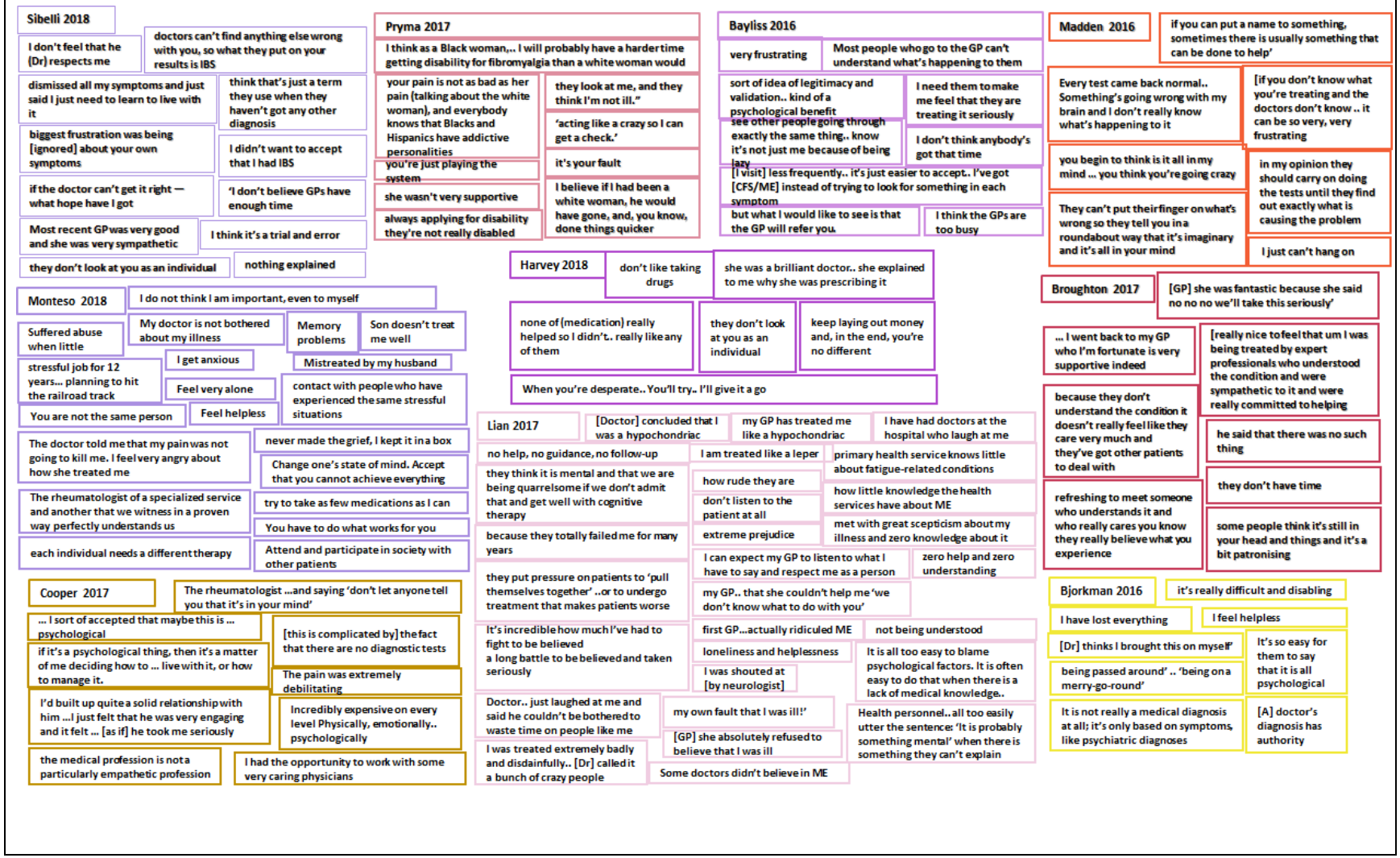
4.5.4.2 Patients' experiences in diagnosis and management of patients with MUS

Direct quotations by participants in the Findings/Results segments in the papers yielded 195 relevant direct quotes. Each of these were assigned a code that captured its meaning and context. Where the same paper had multiple quotes with similar meaning, they were categorized under the same code, resulting in 106 final codes. These were collected as free

codes without hierarchy and all codes from a given paper were assigned a single colour code (illustrated in Fig. 4.6). The full list of quotes and codes is given in Appendix 4.10.

Figure 4.6: Free codes developed from direct quotations of participants in primary studies – Patients' experiences




Sibelli 2018
I don't feel that he (Dr) respects me
doctors can't find anything else wrong with you, so what they put on your results is IBS
dismissed all my symptoms and just said I just need to learn to live with it
think that's just a term they use when they haven't got any other diagnosis
biggest frustration was being [ignored] about your own symptoms
I didn't want to accept that I had IBS
if the doctor can't get it right — what hope have I got
'I don't believe GPs have enough time
Most recent GP was very good and she was very sympathetic
I think it's a trial and error
they don't look at you as an individual
nothing explained
Pryma 2017
I think as a Black woman,.. I will probably have a harder time getting disability for fibromyalgia than a white woman would
your pain is not as bad as her pain (talking about the white woman), and everybody knows that Blacks and Hispanics have addictive personalities
they look at me, and they think I'm not ill."
'acting like a crazy so I can get a check.'
you're just playing the system
it's your fault
she wasn't very supportive
I believe if I had been a white woman, he would have gone, and, you know, done things quicker
always applying for disability they're not really disabled
Bayliss 2016
very frustrating
Most people who go to the GP can't understand what's happening to them
sort of idea of legitimacy and validation.. kind of a psychological benefit
I need them to make me feel that they are treating it seriously
see other people going through exactly the same thing.. know it's not just me because of being lazy
I don't think anybody's got that time
[I visit] less frequently.. it's just easier to accept.. I've got [CFS/ME] instead of trying to look for something in each symptom
but what I would like to see is that the GP will refer you.
I think the GPs are too busy
Madden 2016
if you can put a name to something, sometimes there is usually something that can be done to help'
Every test came back normal.. Something's going wrong with my brain and I don't really know what's happening to it
[if you don't know what you're treating and the doctors don't know .. it can be so very, very frustrating
you begin to think is it all in my mind ... you think you're going crazy
in my opinion they should carry on doing the tests until they find out exactly what is causing the problem
They can't put their finger on what's wrong so they tell you in a roundabout way that it's imaginary and it's all in your mind
I just can't hang on
Harvey 2018
don't like taking drugs
she was a brilliant doctor.. she explained to me why she was prescribing it
none of (medication) really helped so I didn't.. really like any of them
they don't look at you as an individual
keep laying out money and, in the end, you're no different
When you're desperate.. You'll try.. I'll give it a go
Broughton 2017
[GP] she was fantastic because she said no no no we'll take this seriously'
... I went back to my GP who I'm fortunate is very supportive indeed
[really nice to feel that um I was being treated by expert professionals who understood the condition and were sympathetic to it and were really committed to helping
because they don't understand the condition it doesn't really feel like they care very much and they've got other patients to deal with
he said that there was no such thing
refreshing to meet someone who understands it and who really cares you know they really believe what you experience
they don't have time
some people think it's still in your head and things and it's a bit patronising
Monteso 2018
I do not think I am important, even to myself
Suffered abuse when little
My doctor is not bothered about my illness
Memory problems
Son doesn't treat me well
I get anxious
Mistreated by my husband
stressful job for 12 years... planning to hit the railroad track
Feel very alone
contact with people who have experienced the same stressful situations
You are not the same person
Feel helpless
The doctor told me that my pain was not going to kill me. I feel very angry about how she treated me
never made the grief, I kept it in a box
Change one's state of mind. Accept that you cannot achieve everything
The rheumatologist of a specialized service and another that we witness in a proven way perfectly understands us
try to take as few medications as I can
You have to do what works for you
each individual needs a different therapy
Attend and participate in society with other patients
Lian 2017
[Doctor] concluded that I was a hypochondriac
my GP has treated me like a hypochondriac
I have had doctors at the hospital who laugh at me
no help, no guidance, no follow-up
I am treated like a leper
primary health service knows little about fatigue-related conditions
they think it is mental and that we are being quarrelsome if we don't admit that and get well with cognitive therapy
how rude they are
how little knowledge the health services have about ME
don't listen to the patient at all
because they totally failed me for many years
extreme prejudice
met with great scepticism about my illness and zero knowledge about it
I can expect my GP to listen to what I have to say and respect me as a person
zero help and zero understanding
they put pressure on patients to 'pull themselves together' ..or to undergo treatment that makes patients worse
my GP.. that she couldn't help me 'we don't know what to do with you'
It's incredible how much I've had to fight to be believed a long battle to be believed and taken seriously
first GP...actually ridiculed ME
not being understood
loneliness and helplessness
It is all too easy to blame psychological factors. It is often easy to do that when there is a lack of medical knowledge..
I was shouted at [by neurologist]
Doctor.. just laughed at me and said he couldn't be bothered to waste time on people like me
my own fault that I was ill!'
Health personnel.. all too easily utter the sentence: 'It is probably something mental' when there is something they can't explain
[GP] she absolutely refused to believe that I was ill
I was treated extremely badly and disdainfully.. [Dr] called it a bunch of crazy people
Some doctors didn't believe in ME
Cooper 2017
The rheumatologist ...and saying 'don't let anyone tell you that it's in your mind'
... I sort of accepted that maybe this is ... psychological
[this is complicated by] the fact that there are no diagnostic tests
if it's a psychological thing, then it's a matter of me deciding how to ... live with it, or how to manage it.
The pain was extremely debilitating
I'd built up quite a solid relationship with him ...I just felt that he was very engaging and it felt ... [as if] he took me seriously
Incredibly expensive on every level Physically, emotionally.. psychologically
the medical profession is not a particularly empathetic profession
I had the opportunity to work with some very caring physicians
Bjorkman 2016
it's really difficult and disabling
I have lost everything
I feel helpless
[Dr] thinks I brought this on myself'
It's so easy for them to say that it is all psychological
being passed around' .. 'being on a merry-go-round'
It is not really a medical diagnosis at all; it's only based on symptoms, like psychiatric diagnoses
[A] doctor's diagnosis has authority

The descriptive themes that emerged from aggregating the primary codes were close in nature to the descriptive themes generated from the doctors' experiences and were aggregated under the same headings as shown in Figure 4.7 below.

Figure 4.7: Aggregating codes based on direct patient quotes led to descriptive themes

Dealing with Diagnostic Uncertainty

Importance of receiving a diagnosis (Bayliss, Bjorkman, Chen, Loewenberger, Madden, Osborn)

Unwilling to accept diagnosis (Bjorkman, Broughton, Engebretsen, Lian, Madden, Nielsen, Rask, Sibelli)

Lack of confidence in doctors (Bjorkman, Engebretsen, Harvey, Lian, Muralee, Osborn, Pryma, Rask)

Onus on patients to get better (Bjorkman, Engebretsen, Lian, Muralee, Pryma)

Emotional experiences in doctor-patient encounter

Sad (Bjorkman, Engebretsen, Harvey, Madden, Monteso, Muralee, Nielsen, Osborn, Sallinen, Sibelli, Williams)

Angry (Bayliss, Chen, Loewenberger, Madden, Muralee, Sibelli)

Scared (Bayliss, Chen, Loewenberger, Monteso, Nielsen, Osborn, Sallinen, Sibelli)

Disbelieved (Broughton, Cooper, Engebretsen, Lian, Loewenberger, Muralee, Osborn, Pryma, Williams)

Not listened to and misunderstood (Lian, Loewenberger)

Felt disrespect and dismissive attitude (Chen, Cooper, Engebretsen, Harvey, Lian, Monteso, Sibelli)

Problems worsened by race/gender (Muralee, Pryma, Sallinen)

Adversarial relationship with doctors (Engebretsen, Loewenberger, Osborn)

Resource related issues

Difficult to get tests and referrals (Bayliss, Nielsen)

Lack of time (Bayliss, Broughton, Sibelli)

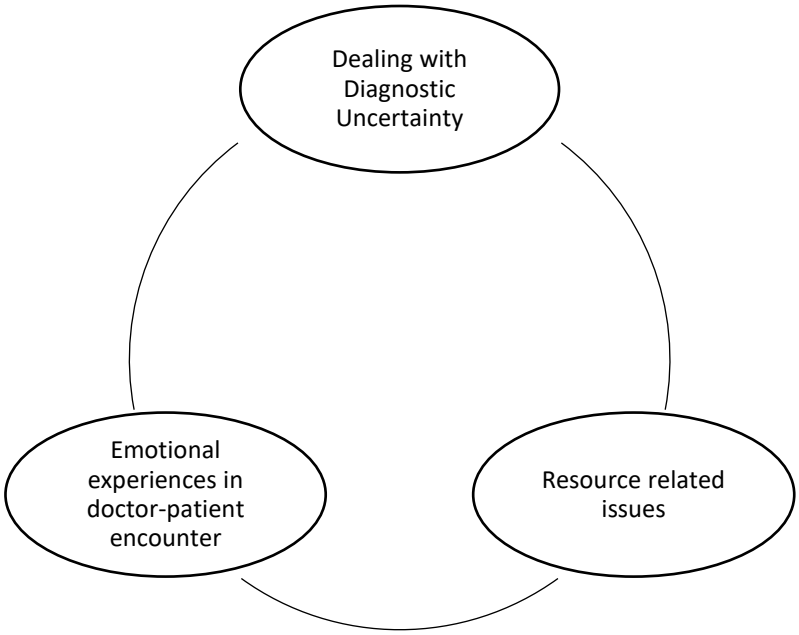
Expensive (Cooper, Harvey)

Accused of feigning illness for financial benefit (Pryma)

4.5.4.3 Descriptive themes – combining data from doctors and patients

Coding and aggregating the direct quotes from each of the two groups (patients and doctors) separately, showed that in both cases the experiences were centred around three main descriptive themes: 1) Dealing with diagnostic uncertainty 2) Emotional experiences around the doctor-patient encounter and 3) Resource related issues.

Figure 4.8: Descriptive themes arising from doctor and patient quotes from primary research



Discussion of the key themes was distributed across the 30 papers shown in Table 4.1.

Table 4.1 shows that 27 of the papers included discussion of the emotional experiences around the doctor-patient encounter. Eight discussed the issue of diagnostic uncertainty and 13 discussed resource related issues.

Table 4.1: Distribution of key themes across the primary studies

	Paper	Dealing with Diagnostic uncertainty	Emotional experiences in doctor-patient encounter	Resource related issues
1	Aamland 2017	Yes	-	-
2	Bayliss 2016	- / -	Yes / -	Yes / Yes
3	Bjorkman 2016	-	Yes	-
4	Briones 2018	-	Yes	-
5	Broughton 2017	-	Yes	Yes
6	Brownell 2016	Yes	Yes	Yes
7	Chen 2020	-	Yes	-
8	Cooper 2017	-	Yes	Yes
9	den Boeft 2016	Yes	Yes	-
10	Engebretsen 2019	-	Yes	-
11	Harsh 2016	Yes	Yes	Yes
12	Harvey 2018	-	Yes	Yes
13	Houwen 2019	-	-	-
14	Kromme 2018	-	Yes	Yes
15	Lian & Robson 2017	-	Yes	-
16	Loewenberger 2021	-	Yes	-
17	Maatz 2016	Yes	Yes	Yes
18	Madden 2016	-	Yes	-
19	Mohebbi 2019	-	Yes	-
20	Montesó 2018	-	Yes	-
21	Muraleetharan 2018	-	Yes	-
22	Nielsen 2020	-	Yes	Yes
23	Osborn 2020	-	Yes	-
24	Pohontsch 2018	Yes	Yes	Yes
25	Pryma 2017	-	Yes	-
26	Rask 2021	Yes	- / -	Yes / -
27	Sallinen 2019	-	Yes	-
28	Sibelli 2018	-	Yes	Yes
29	Warner 2017	Yes	Yes	Yes
30	Williams 2019	-	Yes	-
	Total no. of papers	**8**	**27**	**13**

These three descriptive themes are discussed in detail below, illustrated by direct quotes extracted from the primary research and comparing and contrasting the perspectives of doctors and patients.

Theme 1 - Dealing with diagnostic uncertainty

Figure 4.9 brings together the viewpoints of both patients and doctors in detail for ease of reference. Patients described the importance of receiving a diagnosis in six of the studies ((Bayliss, Bjorkman, Chen, Loewenberger, Madden, Osborn). Whilst some expressed their happiness in receiving a diagnosis, "*over the moon I had an actual diagnosis*" (Loewenberger), others elaborated on the reasoning behind wanting a diagnosis, stating that it was because "*a doctor's diagnosis has authority*" (Bjorkman), that a diagnosis gave "*legitimacy and validation*," (Bayliss) and that it gave a sense of being supported: "*to actually know that it has been recognised, that somebody is there supporting you… is completely brilliant*" (Osborn). A diagnosis is seen as the first step in obtaining help for the condition: "*if you can put a name to something.., there is usually something that can be done to help*", (Madden).

Doctors acknowledged the importance of a diagnosis to a patient (Pohontsch, Aamland), and specified that they were reluctant to give a diagnosis code of MUS to a patient due to the stigmatising effect it had (Bayliss, Pohontsch) and due to their awareness that patients were reluctant to accept a diagnosis of MUS (Harsh). Due to these concerns, doctors would usually give a mental health / behavioural issue related illness code to a patient only where it was necessary for a referral to obtain mental health care (Pohontsch).

Doctors then discussed the ways in which they dealt with managing diagnostic uncertainty.

Figure 4.9: Dealing with diagnostic uncertainty from the perspective of:
Patients
Importance of receiving a diagnosis (Bayliss, Bjorkman, Chen, Loewenberger, Madden, Osborn)
Unwilling to accept Dr's diagnosis
Not prepared to accept diagnosis (Engebretsen, Nielsen, Rask, Sibelli)
Perception that MUS diagnosis given as the easy option (Bjorkman, Lian, Sibelli)
MUS diagnosis given when doctors can't find cause of illness (Broughton, Lian, Madden, Nielsen, Sibelli)
Accepting psychological diagnosis implies acceptance of faking illness (Nielsen)
Lack of confidence in doctors
Perception of lack of knowledge (Lian)
Dissatisfied with referrals and investigations (Harvey, Rask)
Feeling that health services failed the patient (Lian)
Perception of misdiagnosis (Bjorkman, Osborn)
Onus on patients to get better (Bjorkman, Engebretsen, Lian, Muralee, Pryma)
Doctors
Delaying diagnostic coding of MUS
Acknoweldge importance of diagnosis to patients (Pohontsch, Aamland)
Restrained coding necessary (Pohontsch, Bayliss)
Patients refuse to accept MUS diagnosis (Harsh)
Managing diagnostic uncertainty
Need for Reassurance via tests (Rask, Warner)
Need to exclude organic illness (Rask, Warner)
Need to avoid risk of litigation (Warner)
Need to consider harm arising from repeated investigations (Harsh, Brownell, Warner)
Need to accept diagnostic uncertainty as an integral part of MUS (Brownell, Maatz, Warner)
Need to accept possibility of gaps in biomedical knowledge (Harsh, Brownell, den Boeft)
Need to differentiate between diagnostic uncertainty and pyschosocial etiology (Harsh)
Taking responsibility vs simply accepting patient choice (Rask)

Some GPs in Primary Care dealt with uncertainty by referring the patient on for further testing even when they believed it was unnecessary since this provided reassurance to patients: "*refer the patient to further tests at the hospital even though you have a clear expectation that everything is normal. But when blood tests and a scan confirm this, the patient is reassured to a higher extent*" (Rask). Some secondary care physicians on the other hand viewed their role as providers of reassurance: "*I see my main function in the heart*

clinic as reassuring," (Warner) and doctors also believe that this helps to establish trust with the patient and to show that they are being taken seriously (Warner).

Such reassurance is necessary not only for the patient but also for the doctor as they are concerned about missing organic pathology: "*we have to hedge our bets because we are so afraid of missing severe illness*" (Rask). This concern was exacerbated by the threat of litigation, leading to doctors practising medicine defensively "*if we were in an era where the lawyers weren't so prominent...then I probably wouldn't be so defensive*" (Warner). While pointing out that sometimes the diagnosis was for the doctor's peace of mind and administrative reasons rather than necessary for the patient "*sometimes the patients don't need a diagnosis and the doctor is the one that needs the diagnosis for their own mental comfort*" (Brownell), doctors also pointed out the necessity to consider the harm due to repeated investigations and to consider a limiting point for investigations: "*at some stage be quite firm and say, 'I don't think I want to do any more tests. I think they are unnecessary. I think potentially they're dangerous*" (Warner). Similarly, doctors warn of "*how much harm we can do and how much worse we can make these situations a lot of times"* in a *"'well-intentioned' effort to help patients*" (Harsh).

Pointing out that "*a lot of the patients tend to keep looking for an answer and they keep going doctor to doctor to doctor*", Brownell (2016) discusses "*the vicious cycle the desire for certainty can create*," and the necessity to accept diagnostic uncertainty as an integral part of MUS: "*a lot of times you have to say, look, you know, we don't have the answer for everything. We don't have the tests for everything.*.". They point out that the failure to acknowledge the uncertainty inherent in MUS leads to "c*reating overly anxious people who*

want certainty in […]every encounter". Some papers (den Boeft, Harsh, Brownell), also point out the necessity of acknowledging that there may be gaps in current biomedical knowledge which contribute to this uncertainty: "*certain things still unexplainable now, but maybe not in another 100 years. Lyme is always a good example*" (den Boeft).

Doctors participating in one study (Harsh) emphasized the need to differentiate between diagnostic uncertainty and psychosocial aetiology stating that doctors should not "*just quickly say 'oh it's just from stress and depression'*" and that "*appropriate medical evaluation*" is essential "*prior to assuming that symptoms stem from psychosocial aetiology*." They also stated that there is a tendency among some doctors to treat conditions e.g., IBS, FM, chronic pain, as '*waste basket diagnoses'* when the cause for symptoms cannot be easily explained.

Patients' apparent response to these difficulties doctors discuss is by being unwilling to accept the doctor's diagnosis (Engebretsen, Nielsen, Rask, Sibelli). They have a perception that the MUS diagnosis is given as an easy option: "*Health personnel.. all too easily utter the sentence 'It is probably something mental' when there is something they can't explain*" (Lian) and "*It's so easy for them to say that it is all psychological*" (Bjorkman); or that it is a diagnosis given when doctors can't find the cause of the illness (Broughton, Lian, Madden, Nielsen, Sibelli): *"They can't put their finger on what's wrong so they tell you in a roundabout way that it's imaginary and it's all in your mind" (Madden); "I think that's just a term they use when they haven't got any other diagnosis" (Sibelli).*

In some studies doctors specifically rejected this idea: "*I do think that family doctors look at these cases as an interesting challenge and we do not look at them as cases we can just wash our hands off if we can't explain [their symptoms]*" (Brownell).

Such perceptions have also led to an apparent lack of confidence in doctors where patients believe that doctors lack knowledge about MUS ("*how little knowledge the health services have about ME"*, Lian), and feel dissatisfied with the referrals and investigations carried out ("*keep on thinking about whether the gynaecologist was thorough enough*," Rask). Some report a feeling that the health services have failed them ("*they totally failed me for many years*," Lian). Related to this issue, some patients have reported a perception of misdiagnosis. Osborn reports on a patient who claims to have been '*diagnosed with bipolar disorder, ME, chronic fatigue, depression.. and given medication for all of those different things,"* which appears to be a valid concern, and it is this perception that appears to have led to patients reporting of a feeling of "*being passed around*" (Bjorkman).

In the same vein, patients report feeling that the onus is on them to get better: "*can't you just pull yourself together*" (Engebretsen); "*[Dr] thinks I brought this on myself*" (Bjorkman); "*it's your fault*" (Pryma); "*they think it is mental and that we are being quarrelsome if we don't admit that and get well with cognitive therapy"* (Lian).

Lastly, Rask reported on the concern that some GPs brought out that sometimes GPs tend to act as "*collaborators*", accepting the patient's choice rather than taking responsibility for patient management: "*none of us dare say that we don't expect a physical explanation for their symptoms. Instead, the patients become more and more nervous as we all keep*

searching for an answer that isn't there" because "*we are afraid of how the message will be received by the patient and whether we will get dismissed by him or her."*

Theme 2 – Emotional experiences in doctor-patient encounter

Patients said that they felt sad, angry and frightened (Figure 4.10).

Figure 4.10: Emotional experiences in doctor-patient encounter
Patients
Sad
Depressed (Muralee, Nielsen, Osborn, Sallinen)
Isolated, lonely, and helpless (Bjorkman, Lian, Monteso, Muralee, Nielsen, Sibelli)
Guilty (Rask, Williams)
Loss of sense of self (Engebretsen, Madden, Monteso, Osborn, Sallinen)
Negative self-worth (Engebretsen, Monteso, Muralee, Osborn, William)
Shamed (Nielsen)
Stigmatised (Muralee)
Suicidal (Engrebretsen, Monteso, Osborn, Williams)
Unachieved potential (Muralee, Osborn, Sallinen, Williams)
Abused/ ill-treated (Monteso)
Angry
Angry (Loewenberger, Muralee)
Frustrated (Bayliss, Chen, Loewenberger, Madden, Sibelli)
Scared (Bayliss, Chen, Loewenberger, Monteso, Nielsen, Osborn, Sallinen, Sibelli)
Anxious (Monteso, Osborn)
Confused (Bayliss, Chen, Sibelli)
Frightened (Loewenberger)
Memory issues/Brain Fog (Monteso, Sallinen)
Uncertainty (Nielsen, Sallinen)
Not believed (Broughton, Cooper, Engebretsen, Lian, Loewenberger, Muralee, Pryma, Williams)
Not listened to and misunderstood (Lian, Loewenberger)
Felt disrespect and dismissive attitude
Dismissive attitude (Chen)

Lack of respect (Engebretsen)
Not treated as an individual (Sibelli)
Treated rudely and badly (Lian)
Ridiculed (Lian)
Lack of empathy (Cooper)
Lack of support (Lian)
Prejudiced (Lian)
Problems worsened by race/gender (Muralee, Pryma, Sallinen)
Adversarial relationship with doctors (Engebretsen, Loewenberger, Osborn)
Doctors
Frustration, irritation, and desperation of doctors (Briones, Brownell, den Boeft, Harsh, Maatz)
Feeling of powerlessness (den Boeft)
Guilt at being unable to help (Maatz)
Patients seen as time wasters (Kromme, Maatz)
Patients seen as difficult and demanding (Kromme, Briones, Harsh)
Patients seen as complainers (Briones)
Disbelief and prejudiced towards MUS patients (Briones, Bayliss)
Problem complicated by gender issues (Briones)
Lack of commitment towards unrewarding work (Bayliss, Maatz)
Recognising patient difficulties (Briones, den Boeft, Harsh, Maatz)
MUS seen as a positive challenge (Harsh, Maatz, Warner)

They spoke of being depressed ("*feeling just very low, very hopeless, very tearful,"* Osborn; "heavy hearted," Sallinen), of being isolated, lonely and helpless ("*feel helpless, feel very alone,"* Monteso; "*Feel isolated... friends have gone and never come back*", Muralee; "*Friends, … I've cut a lot of them off*," Nielsen; "*feel helpless",* Bjorkman), of the loss of sense of self ("*I am like a completely different person,"* Osborn; "*My need to escape reality… reality has become lost to me,"* Engebretsen; "*I just want my life back*," Sallinen) and of negative self-worth ("*You are just a nobody then",* Engebretsen; "*I do not think I am important, even to myself*," Monteso). Patients spoke of shame ("*led to feel ashamed that I*

need the help", Williams; "*Quite shamed… that I was contributing to my condition.. without anyone actually saying that*", Nielsen), and feeling stigmatised ("*carried a bad stigma,* Muralee). In one study, patients spoke of abuse suffered ("*Suffered abuse when little"; "mistreated by my husband,"* (Monteso).

They also spoke of potential that was unachieved because of the illness ("*I had so many hopes for my life that I'm never going to be able to do,"* Osborn; "*I could not fulfil my own expectations .. [feel like] a 2nd class citizen,"* Sallinen; "*I continually mourn the person that I used to be*," Williams). Feeling suicidal was also a repeated theme ("*I felt like there was no point in living; I didn't want to live. I just wanted to be dead*," Osborn; "*I would have killed myself,"* Engebretsen; "*planning to hit the railroad track,"* Monteso; "*there are many days and hours that I wish I could die*," Williams).

Some patients discussed feeling angry (Loewenberger, Muralee) and frustrated ("*biggest frustration was being [ignored] about your own symptoms*," Sibelli; "*if you don't know what you're treating and the doctors don't know .. it can be so very, very frustrating,*" Madden). They also described feeling frightened, anxious ("*I couldn't cope with the anxiety*," Osborn; "*I get anxious,"* Monteso), and confused ("*Most people who go to the GP can't understand what's happening to them*," Bayliss). Patients spoke of the uncertainty felt ("*Not knowing whether you are going to get better or not,"*(Nielsen) and reported feeling unable to think clearly ("*my mind was not clear .. my thinking was clumsy*," Sallinen).

Doctors, on the other hand spoke relatively less about their feelings in the primary research, though they mentioned that they sometimes had negative feelings such as frustration and

irritation towards these patients: "*I often use it as a diagnostic tool for MUPS, that I get irritated by patients*" and "*many doctors have the same basic feeling about these patients - exhaustion, desperation….the way they easily get into a fight with these patients* (denBoeft).

This frustration appears to stem at least partly from the doctors' feeling of being unable to help these patients ("*I think it is frustrating … because you like to be able to help people"; "we don't know what the diagnosis is - we can't do anything and that is frustrating for me",* Maatz), and a perception that "*things are probably not going to go well, no matter what you do, no matter what treatment you apply, whatever approach you use*" (Briones), leading to a feeling of powerlessness ("*It makes me feel powerless, because I do not get a way in,*" den Boeft) and guilt at being unable to help ("*you just feel really, really upset,*" Maatz). For a doctor in the Brownell study, managing patients with MUS felt like such patients could "*burn you out for the rest of the day.*"

Epistemic injustice towards patients was a key concern, cited by patients in nine of the studies: scepticism about their illness (Lian, Engebretsen) extended to being told that "*it is not a real thing and just all in my head*" (Muralee), and a feeling of "*people think I'm faking it*" (Loewenberger). A patient stated that "*it's incredible how much I've had to fight to be believed"* (Lian) and others spoke of the invisible nature of the illness where there is "*nothing I can do to prove to you that I have this condition"* (Williams). They also spoke of feeling that they were not listened to and that they were misunderstood (Lian, Loewenberger).

A doctor in the Brownell study offered a possible explanation as to why patients feel disbelieved, stating that confronting a patient with a statement such as "*there is no neurological evidence that could possibly explain this*" could result in the patient assuming that the doctor is saying that "*they are lying or that they are crazy or that they have some other defect of their character*" (Brownell). Some doctors agreed that they had colleagues who did not believe in MUS, for example, "*there are many professional people who do not believe in FM - they think it is a type of hysteria, a neurosis* (Briones)".

Another key concern among patients was that they felt doctors had a dismissive attitude and had no respect for them as patients or individuals; this was expressed in several different ways: "*doctors dismissed all my symptoms and just said I just need to learn to live with it"* (Sibelli); "*doctors that are very dismissive...who don't like it when you ask questions"* (Chen); "*I don't feel that he respects me*" (Engebretsen, Sibelli); "*they don't look at you as an individual*" (Sibelli and Harvey). Others stated how they were treated rudely and ridiculed: "*I was treated extremely badly and disdainfully.. [Dr] called it a bunch of crazy people"* (Lian); "*The doctor told me that my pain was not going to kill me. I feel very angry about how she treated me"* (Monteso); "*the doctor.. just laughed at me and said he couldn't be bothered to waste time on people like me*" (Lian). Patients felt that there was a lack of empathy from doctors: "*the medical profession is not a particularly empathetic profession"* (Cooper); that doctors did not provide support with the doctor stating that "*she couldn't help me 'we don't know what to do with you'*" (Lian) and that doctors were prejudiced against them "*felt extreme prejudice"* (Lian).

Primary research among doctors indicated that some doctors admitted to the attitudes patients complained about; for example, participants in the Briones study stated that "*I have to admit that it comes down to my own prejudice. I hold it against this sort of patient to a certain degree they're soft, you have to put pressure on them so that they will liven up their act*" and that "*They are patients that … towards whom I feel rejection , I have to admit it*". Some doctors also spoke of patients with MUS as time wasters: "*patients were time wasters who we can't help"* (Kromme); as complainers: "*they have a lot of complaints ; their way of life is a continual complaint"* (Briones); as difficult and demanding: "*these people are also very, very demanding*" (Briones), "*needy and demanding*" (Harsh), "*it is a difficult group"* (Maatz), and questioned the patients' sanity: "*the classic orthopaedic approach … is 'they're mad'" (Maatz).*

Comments from both doctors and patients indicated that these problems could be worsened by issues of race and gender. Two of the studies focused on MUS in male patients and in both cases patients felt that there was an extra layer of prejudice against men with MUS: "*People aren't nearly as sympathetic toward men with FM*" (Muralee) and "*[Dr said] I will never give fibromyalgia diagnosis to a man*" (Sallinen). The study by Pryma provided evidence from a number of black women who believed that there was an extra layer of prejudice against black people with MUS with reports of discrimination by doctors: "*your pain is not as bad as her pain (talking about the white woman), and everybody knows that Blacks and Hispanics have addictive personalities"; "I believe if I had been a white woman, he would have gone, and, you know, done things quicker"; "I think as a Black*

woman,.. I will probably have a harder time getting disability for fibromyalgia than a white woman would" (Pryma).

There was some evidence from doctors regarding this claim from the Briones study: "*They have a profile of complaining which, figuratively speaking, is more readily accepted by society in women than in men:* and "*I think that in cases of women with fibromyalgia you're conditioned to think twice about granting them work leave*" (Briones).

Such conflict-driven interactions appear to have led to an adversarial relationship between doctors and patients with patients making statements such as: "*With regard to my doctor it is a continuous battle*" (Engebretsen); *"It's a fight to get treatment*" (Loewenberger) and "*You're fighting everything and everyone*" (Osborn).

Research by Bayliss and Maatz attempted to uncover the reasoning behind this adversarial doctor-patient relationship some patients and doctors describe and suggested several factors: doctors find the work with MUS patients unrewarding: "*it's pretty unrewarding and I mean I'm sure they find me unrewarding and I find dealing with them unrewarding"* (Maatz) and "*It doesn't feel like there's a big win for the doctor since the level of commitment required to manage patients over the longer term is too much for a primary care professional; it's just a workload issue; It's not top of anyone's agenda ; the amount of importance you can give it isn't that much*" (Bayliss). The Bayliss study also points out the issues of time pressure and that activities required by regulators (e.g. Quality and Outcomes Framework) criteria attract more attention. Overall, the issue appears to be that it is

difficult to get doctors interested in patients with MUS because "*it is not sexy and it is not perceived that there is an awful lot that you can do for them*"(Maatz).

Contrary to this, some doctors showed empathy and recognised the difficulties patients face: they acknowledged the stigma ("*they have the feeling that they are stigmatized; they fear that the doctors are going to say: 'ah, another hypocrite,"* Briones), the difficult lives patients have (Maatz), their frustrations, fears, the expenses incurred (Harsh) and acknowledged the epistemic justice due to the patient ("*I know she is not putting me on now … I'm not saying that she is not telling the truth, the feeling that she has is real*," Briones). Some doctors viewed patients with MUS as a positive challenge: "*I like them (MUS patients). I think it's a challenge actually ... managing them over quite a long period of time you can, you feel as if you're achieving something*" (Harsh) and found that effective management of these patients was rewarding "*I don't think I find them as difficult as some people do; .. I'm just honest with them; it can sometimes be quite rewarding*" (Maatz).

Theme 3 – Resource related issues

The third descriptive theme centred around the issue of resources, mainly appointments, referrals and investigations. Some patients wanted more referrals and investigations ("..*what I would like to see is that the GP will refer you*", Bayliss; "*Refer me on .. do something*", Nielsen) and more time with the GP ("*they don't have time,"* Broughton; "*I don't believe GPs have enough time*, Sibelli), whereas GPs mostly found the lack of time and resources for managing patients with MUS a problem and viewed managing resource constraints as a necessity ("*Need to take control for efficient resource management*",

Kromme; "*lack of management options,"* Rask). Some doctors found that patients with MUS were heavy users of resources ("*these patients are high utilisers of the medical system*" Harsh); "*been to a number of doctors"* Maatz), although they recognised the need for referrals "*I have a great deal of respect for the physicians and the services that make referrals to me. They need to work with these patients*" (Brownell), whereas other doctors did not necessarily accept the role of gatekeeper for resources: " *I don't feel at all that I'm the policeman for the system"* (Brownell).

Patients also commented on the expenses they had to incur ("*Incredibly expensive on every level Physically, emotionally.. psychologically,*" (Cooper), "*keep laying out money and, in the end, you're no different,*" Harvey) and in one of the studies, patients discussed the problem they faced of being accused of feigning illness in order to obtain financial payoffs from the government (Pryma).

Doctors found that the limited availability of referral options and difficult service structures contributed to the difficulties in managing these patients, as did the limited education and training on MUS (Harsh, Warner, Pohontsch), and in the case of doctors in secondary care, some of them believed that the difficulty in maintaining any continuity in the care of the patient led to limitations in what they could do for the patient (Warner).

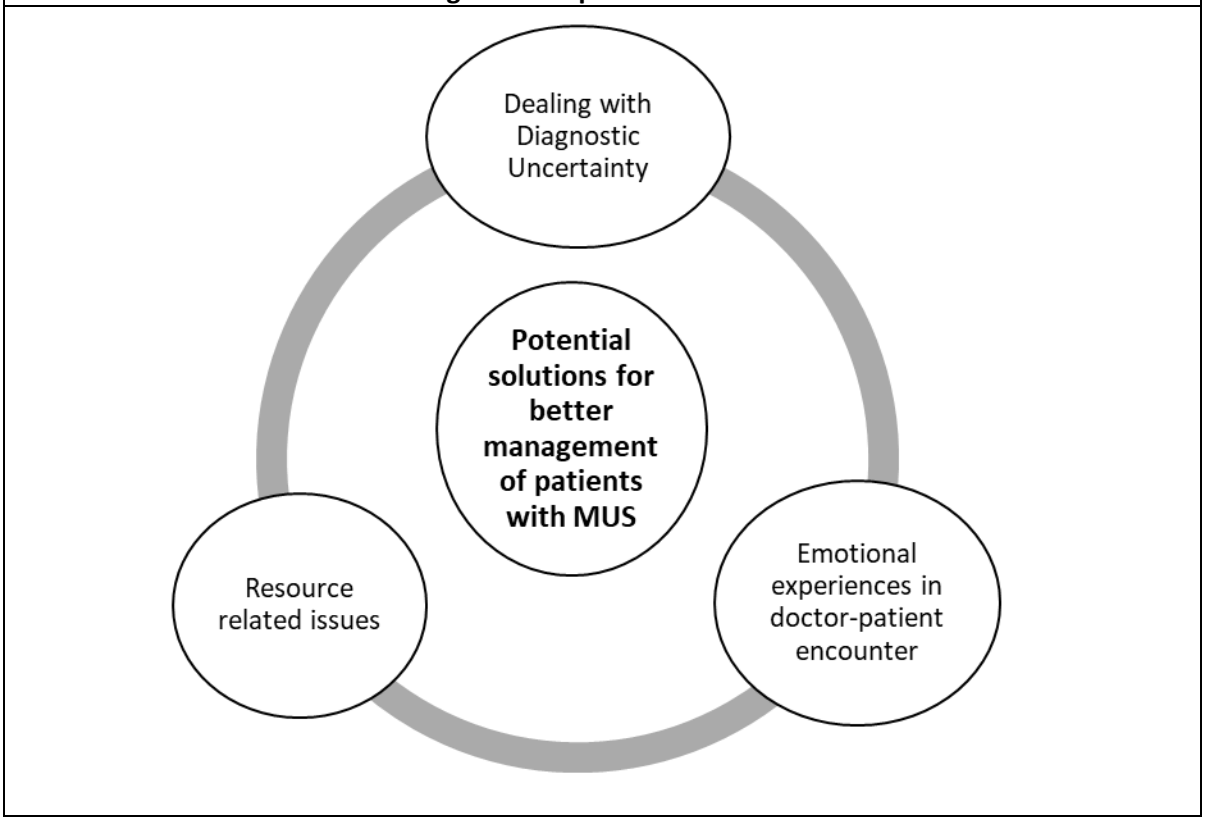
Figure 4.11: Resource related issues from the perspective of:
Patients
Difficult to get tests and referrals (Bayliss, Nielsen) Lack of time (Bayliss, Broughton, Sibelli) Expensive (Cooper, Harvey) Accused of feigning illness for financial benefit (Pryma)
Doctors
Limited time and management options a constraint Lack of resources - time and management options (Rask) Need to take control for efficient resource management (Kromme) Managing resource constraints (Brownell) MUS patients heavy users of resources Been to a number of doctors (Maatz) Patients are high utilisers of the medical system (Harsh) Limited referral/support services Difficult service structures (Maatz) Limited referral options (Bayliss) Limited awareness/training on MUS Lack of training on MUS (Warner) Lack of education on MUS (Harsh) Lack of continuity (Warner) Insufficient knowledge (Pohontsch)

4.5.4.4 Analytical / High-order theme summary – Potential solutions for better management of patients with MUS

Mind-mapping the descriptive themes led to the development of a higher-order theme arising from the data. It was found that the over-arching theme that bound together the primary quotes and the descriptive themes was the search for potential solutions to better manage patients with MUS. In the original studies these were expressed by patients as positive experiences and as what they needed to receive / experience in a medical encounter. In this synthesis, these opinions were interpreted as patient-suggested potential solutions for improved management of MUS patients. Similarly, viewpoints expressed by

doctors in multiple different contexts have been analysed and interpreted as to how they can lead to the better management of patients with MUS.

Figure 4.12: Analytical (High-Order) theme arising from doctor and patient experiences: Potential solutions for better management of patients with MUS



The potential solutions suggested by stakeholders were grouped together: a culture of respect, harm minimisation, and improved resources and capabilities, forming the basis of a therapeutic alliance.

Potential solutions: A culture of respect

Both patients and doctors believed a culture of respect is an important factor that supports better management of patients with MUS. Doctors and patients defined respect as a broad concept consisting of respect for the epistemic privilege of the patient, respect for their autonomy, protecting their dignity and minimising the risk of stigma, prejudice and stereotyping, and also as incorporating the patients' cooperation through respect for the expertise, experience and service of doctors.

Figure 4.13: Potential solutions: a culture of respect

- **Respect for epistemic privilege of patient**
  - Indicate belief in patient
    - Paying attention and believing the patient (Warner)
    - Acceptance and belief in patient(Aamland)
    - Accept lived experience of the patient (Brownell)
- **Respect for patients' autonomy**
  - Takes patients seriously (Broughton, Chen, Cooper, Bayliss, Osborn)
  - Need to be treated as an individual (Lian, Monteso)
- **Protecting patients' dignity**
  - Respect the patient as a person (Lian, Engebretsen)
  - Not to shame or ridicule patients (Lian)
- **Minimising stereotyping, stigma, prejudice**
  - Awareness of own bias (Harsh)
  - Drs recognize patients' stigma and problems (Briones)
  - Patients' co-operation towards developing respect for doctors' experience / service (Lian)

Doctors pointed out that respect for the epistemic privilege of the patient is a key aspect of a culture of respect and they put into practice by indicating to the patient that the patient is believed and accepted ("*That you're looking at and believing them*," Warner; "*I accepted*

and believed that he experienced the symptoms … If I had rejected him and told him that his symptoms didn't fit with any medical condition, that I didn't believe him, then I guess he would have found a new GP. In this way, we have kept the alliance" Aamland; "*you have to have the trust that what they are experiencing is what they are experiencing*." Brownell).

Doctors also recognised that failing to accord epistemic privilege to the patient is unhelpful in resolving the patient's issues ("*To confront the patient with*, '*Well there is no neurological evidence that could possibly explain this,' is not a helpful explanation [….] This is actually hurtful to some patients because they might assume that you're saying that they're lying, or that they're crazy, or that they have some other defect of their character,"* Brownell).

Patients believed that a doctor indicated respect for the patient's autonomy by showing that patients were taken seriously ("*I need them to make me feel that they are treating it seriously,"* Bayliss) and treated as an individual ("*each individual needs a different therapy*," Monteso). Similarly, doctors protect a patient's dignity by respecting the patient as a person and by not shaming or ridiculing the patient (Engebretsen, Lian & Robson).

Avoiding stereotyping operates in both directions: doctors by avoiding the assumption that patients are faking illness for example for financial benefit (Bayliss, Pryma, Engebretsen) and for patients to avoid assuming lack of awareness on the part of doctors (Lian & Robson). Doctors are aware of the stigma and prejudice patients with MUS face and recognise the necessity to eliminate such stigma ("*they have the feeling that they are stigmatised; they fear that the doctors are going to say: 'ah, another hypocrite; some people prefer not to use this diagnosis, because it will stigmatise the patient,"* Briones). Being aware of one's own biases was said to help minimise stigma and avoid prejudice (Harsh).

Potential solutions: Harm minimisation

Doctors and patients identified three key elements necessary to minimise harm to patients.

Figure 4.14: Potential solutions: Harm minimisation

Investigations and referrals – Balance need for reassurance vs risk of iatrogenic harm

Need for Reassurance via tests

- Biomedical reassurance via tests to deal with uncertainty (Rask)
- Rationale for Ix and referrals– standard tests for all for reassurance (Warner)

Need to consider harm arising from repeated investigations

- Consider a limiting point of investigations (Warner)
- Vicious cycle the desire for certainty can create (Brownell)
- A limiting point for investigations (Harsh)

Effective management of the patient's need for a diagnosis

Acknowledge importance of diagnosis to patients

- Patients like a diagnosis (Pohontsch)
- Importance of diagnosis to a patient (Aamland)

Importance of receiving diagnosis

- Doctor's diagnosis validates and legitimises illness (Bayliss)
- Doctor's diagnosis has authority (Bjorkman)
- Potential for effective treatment increases with a diagnosis (Madden)

Differentiate between diagnostic uncertainty and psychological illness

- Differentiate between diagnostic uncertainty and psychosocial aetiology (Harsh)
- Wastebasket diagnoses – when Drs don't know what is going on (Harsh)
- Perception that MUS diagnosis given as the easy option (Bjorkman, Lian, Sibelli)
- MUS diagnosis given when doctors can't find cause of illness (Broughton, Lian, Madden, Nielsen, Sibelli)

The first was the requirement to **balance the need for reassurance against the risk of causing iatrogenic harm**. Though both patients and their GPs needed reassurance that they did not have any serious illness and these concerns were addressed usually by ensuring that

patients received the standard tests necessary (Rask, Warner), it is also necessary to set a limiting point for investigations, so that repeating investigations to an extent that could harm the patient, which one doctor explained as a 'vicious cycle the desire for certainty could create (Brownell),' was avoided (Harsh, Warner).

Effectively managing the patients' need for a diagnosis was the second key element of harm minimisation. Doctors acknowledged the importance of a diagnosis to the patient (Aamland, Pohontsch); patients explained that receiving a diagnosis was important due to the legitimacy and validation it provided for their illness (Bayliss, Bjorkman), and that they perceived receiving a diagnosis as an indication that increased the possibility of finding effective treatment for their illness (Madden).

Doctors and patients both recognised that there is a **need to distinguish between diagnostic uncertainty and psychological illness** when managing patients with MUS. Doctors mentioned that MUS diagnoses can sometimes be 'waste-basket' diagnoses which are given out of convenience when diagnosis is difficult (Harsh); patients discussed their perception that MUS diagnoses are given 'as the easy option' (Bjorkman, Broughton, Lian, Madden, Nielsen, Sibelli) and that both doctors and patients should work towards dispelling such perceptions.

Better resources and capabilities

The need for better resources and capabilities to manage patients with MUS was pointed out by both doctors and patients.

Figure 4.15: Potential solutions: Better resources and capabilities

Doctors awareness and knowledge should improve

- Lack of training on MUS (Warner)
- Lack of education on MUS (Harsh)
- Lack of continuity (Warner)
- Insufficient knowledge (Pohontsch)
- Gaps in biomedical knowledge (den Boeft, Harsh)
- Awareness of limits of medicine (Brownell)

Improving self management capacity of patients

- Acceptance of condition (Bayliss, Chen, Monteso)
- Manage one's state of mind (Chen, Monteso, Cooper)
- Explore potential for peer support (Bayliss, Monteso, Rask)
- Balance need for GP support at a realistic level (Rask)

Integrated care

Better management plan

- Collaboration among doctors to manage MUS beneficial (Rask)
- Benefits from – discussion of symptom relief – and management vs a cure (Harsh)

Facilitating factors

- Self help programmes useful (Rask)
- Involve therapist – care/social worker (Harsh)
- Need reliable info source online (Bayliss)
- Need backup resources (Bayliss)

Manage psychological issues and social determinants of health

- Combine biomedical therapies with psychosocial support (Harsh)
- Role of depression and its management in MUS patients (Brownell)
- Social determinants of health – diet exercise stress management (Brownell)

Improving awareness and knowledge about MUS was constrained by the lack of training and education on MUS leading to gaps in biomedical knowledge (den Boeft, Harsh,

Pohontsch, Warner). One study pointed out the need for both patients and doctors to be aware of the limits of medicine (Brownell).

Improving self-management capacity of patients involves the need for patients to accept the reality of their situations and managing their state of mind with the support of doctors (Bayliss, Chen, Cooper, Monteso).

Some patients also expressed a need for peer support that GPs could potentially help organise ("*Get a feeling of not being alone by talking or seeing others in the same situation and see how they manage their symptoms*," Rask; "*see other people going through exactly the same thing.. know it's not just me because of being lazy, "*Bayliss; "*contact with people who have experienced the same stressful situations*," Monteso). Lastly, in one of the studies, patients expressed a need for support beyond medical treatment alone from GPs ("*GP could have helped me if she had asked how I was actually doing instead of only focusing on the symptoms from my stomach*", "*I wish that I could visit my GP every two weeks, without any specific purpose besides having a deep and meaningful conversation*", "*get a sort of homework in an online programme and then your GP would follow-up on whether you have done it or not*", "*I can go to my GP if I feel distressed. Then I just sit there and cry* ," Rask). Some doctors pointed out however, that such expectations need to be considered against the realities of the healthcare system ("*I have neither the time, nor the tools to help them sufficiently*," Rask).

Several important strategies in patient management were discussed: **Collaboration among doctors to manage MUS** ("*The more we [healthcare professionals] act in compliance with*

each other, the more reassured the patient gets, and the safer we feel as physicians," Rask), and integrated care ("*having a psychologist or psychiatrist or somebody to whom I could say 'How would you . . . kind of, deal with this with the patient?' to kind of help me out along the way*", "*stems from the fact that I have some resources available to me in my clinic*,", "*partner up and help these patients*,"; "*having available a behavioural health component is enormously helpful*," Harsh).

One study emphasized on the need for back up resources (*I'd like to know the specific details, in terms of, the waiting time for an assessment, and the referral criteria", "I think you need more backup; oh, you need graded exercise, you need a bit of physio, and you think; well, where the bloody hell are you going to get it?*" Bayliss) and the need for reliable online information sources ("*what I'd like is that you had all that information on the website and I can give people the address… I can say to patients, look, this is…I know this is a good website and the information, I believe is up to date*", Bayliss). Another suggested that self-help programs could be useful (Rask).

The necessity for **addressing the social determinants of health** ("*some exercise, and consider your social circumstances and address those.*.", "*A lot of people that I see they're overweight, they have terrible lifestyles, they smoke too much, drink too much, don't eat the right food, they get no exercise. … I'll talk a lot about stress relief, because I think the chronic stress response plays a central role*", Brownell), as well as the role of depression and its management in patients with MUS ("*there's something here that made me think of depression, and I think we should look at that today*," Brownell) were discussed. Combining biomedical therapies with psychosocial support was seen as beneficial ("*provide social*

support, maybe doing less medically and more socially and more psychosocially", "*combined approach with biomedical therapies and psychosocial treatments*," Harsh).

Therapeutic Alliance

Developing a therapeutic alliance based on the suggested components of a culture of respect, harm minimisation, and improved resources and capabilities as a mechanism for improving the management of MUS patients emerged as the final component of the overarching theme of the research synthesis. This involved improving the quality of the patient consultation, improving the structure of the consultation, shared decision making and brought out the need for patients to actively contribute towards better consultations.

Figure 4.16: Potential solutions: Therapeutic Alliance

- **Improve quality of patient contact**
  - Develop good relationship with patient
    - Good relationship with patient a positive (Brownell)
    - Trust as key to patient relationship (Warner)
    - Relationship based on trust (Aamland)
  - Indicating empathy and compassion
    - Awareness of patient context gives greater empathy (den Boeft)
    - Recognition of different subgroups of MUS patients - anxious – unhappy – passive – distressed –helps with greater empathy (den Boeft)
- **Improve communication (Aamland, Brownell, Harsh)**
- **Manage the role of collaborator (Rask)**
- **Improve structure of consultations**
  - Comprehensive history as basis of discussion (Aamland)
  - Show that the patient is taken seriously through a thorough examination (Aamland)

Summarise consultation - clear instructions (Houwen)

Thorough psychosocial exploration (Houwen)

Help facilitate peer support (Bayliss, Rask, Monteso)

Support beyond medical treatment alone (Madden, Rask)

Allocate sufficient time (Harsh, Maatz, Warner)

Need to develop a Mx plan (Bayliss)

Shared decision making

Explain, share information, give guidance (Chen, Harvey, Rask)

Listen and incorporate patient wishes into management plan (Chen, Lian)

Patient contributions to improved consultations

Patients to manage realistic expectations (Chen)

Work towards acceptance and confidence in doctors (Lian, Osborn, Rask)

Improving the quality of the consultation included key solutions offered as potential improvements to patient care: firstly, for doctors to be more caring, understanding and supportive ("*really nice to feel that.. I was being treated by expert professionals who understood the condition and were sympathetic to it and were really committed to helping*," Broughton; "*Most recent GP was very good and she was very sympathetic*," Sibelli; "*I had the opportunity to work with some very caring physicians,"* Cooper; "*I've got a very good doctor – very supportive*" Nielsen).

Doctors spoke of their understanding that a good relationship with the patient ("*it is really important with establishing the right sort of relationship*," Brownell; "*You need to develop a relationship with patients*," Warner) and that it needed to be based on trust ("*the key is to have a trusting relationship with the patient, that they're confident, they're happy that you have their best interests at heart*," Warner; "'*Oh yeah, I trust you!' This makes me feel that we have been through something together that enables me to soothe [the patient]*,"

Aamland). Providing reassurance to both the patient and their GP was seen as a necessity to improve the therapeutic relationship ("*I'm going to do an evaluation to make sure that the things I know how to treat or the things I know are going to kill you—I look for them and make sure that they're not there,*" Harsh; "*they and their GP . . . need reassurance that still nothing is wrong*," Kromme). Behavioural aspects such as being more person centred was also given as factors improving the quality of the consultation ("*maintain contact with the patient rather than looking at the computer. I can imagine now that he might say the doctor showed a lack of interest*," Houwen).

Doctors spoke of empathy and compassion as factors that help better manage clinical encounters ("*You hope to establish some sort of rapport with that person, you actually do feel a sense of sort of empathy for the situation they are in*," Brownell). They also spoke of the necessity of being aware of, on the one hand the patients' context, and on the other, of one's own biases, both of which help practice greater empathy and compassion ("*you actually do feel a sense of sort of empathy for the situation they are in* ," Brownell; "*if you know more about the context, you can better empathise*," den Boeft; "*recognize my own bias toward the patients more readily*," Harsh; recognise needs of different subgroups of patients, den Boeft). The importance of taking the responsibility for managing the patient instead of simply accommodating the patient's wishes was pointed out as a part of maintaining a therapeutic alliance ("*What you need is to acknowledge the patient and introduce [the concept of MUS] with respect… sometimes we are afraid of how the message will be received by the patient and whether we will get dismissed by him or her*, " Rask).

Improving communication was stated by several doctors as a key necessity to improve the quality of the patient contact ("*communicative dialogue between me and my patients with MUPS is far more important than what I actually do with them*," Aamland) and that it was necessary to clearly communicate the attempt to help the patient ("*We may not have an answer but we're both working towards the answer or we're at this point where we know we don't have an answer but we're willing to say, 'Okay, fair enough, but I'll continue to try and help'*," Brownell).

Improving the structure of the consultation, in the opinion of doctors included incorporating a comprehensive history as the basis of discussion ("*I try to be very systematic when I write the summary.. I feel this as a strength when I can tell the patient that we have done this and that.. I sometimes browse through the summary to memorise what we actually have done*," Aamland); showing that the patient is taken seriously by carrying out a thorough examination ("*I do more regular examinations; touch the belly, listen, and examine. I do not expect to find anything, but then I come a bit further in getting good contact with the patient*," Aamland); a thorough psychosocial exploration ("*I could have spent a bit more time on the anxiety and emotions; I feel I didn't ask her enough about why she's so worried*," Houwen); and to summarise the consultation and give clear instructions ("*first give the summary, then the conclusion, then the course of action*," Houwen).

Doctors recognised this necessity to give sufficient time to the patient and to maintain regular contact with the patient ("*more present with them . . . not as rushed*," Harsh; "*To treat them properly you need to give them more time than anybody else*," Warner; "*I think you have got to give people extra time when they are proving to be difficult patients ...got to*

be persistent and manage to break down the barriers to find out why," Maatz; "*I try to see her regularly because it seems to be one of the few things that will actually keep her out of the ED*," Harsh; "*I think that one way to manage these patients is to offer them some follow-up appointments and just talk with them*," Rask). However, this need has to be balanced against the reality of time and resource constraints with in the system ("*I think part of the problem is the system's so volume driven that being able to spend that time is a challenge*," Brownell).

They discussed the necessity of developing a plan for the management of these patients, with an emphasis on managing the symptoms rather than searching for a cure ("*[I have] a more clear idea in my own mind of how to manage it, as opposed to how to treat it, then I can follow up with saying; and this is what it means, and this is what we're going to do, and this what's likely to happen,"* Bayliss; "*a little bit of progress*", "*The longer I can get them to stay out of the ED the better*," "*patch a few holes here and there,*" Harsh*).*

Spending time and resources on them were the key criteria that patients recognised as capable of improving the structure of the patient contact ("*I never feel like she's rushing. I never feel like she has not got time for me*," Chen; "*Makes sure that I get to see a specialist if she finds it relevant*," Rask).

Shared decision making was proposed as an element that could lead to better patient relationships, with a doctor who listens, explains, shares information, gives guidance, and incorporates the patient's wishes in to the management plan described as one driving a positive relationship ("*she was a brilliant doctor.. she explained to me why she was prescribing it*,"; "*I really appreciate people who give me information, give me options, and*

then let me decide for myself"; "*need information.. I don't want to be with someone who's just going to throw pills at me; the 10% that I didn't know that he's been able to help me learn is priceless,"* Chen, Lian, Harvey, Rask*).* The study by den Boeft also found that doctors categorised patients with MUS in to different groups, anxious, unhappy, passive, distressed etc., and dealt with such patients accordingly.

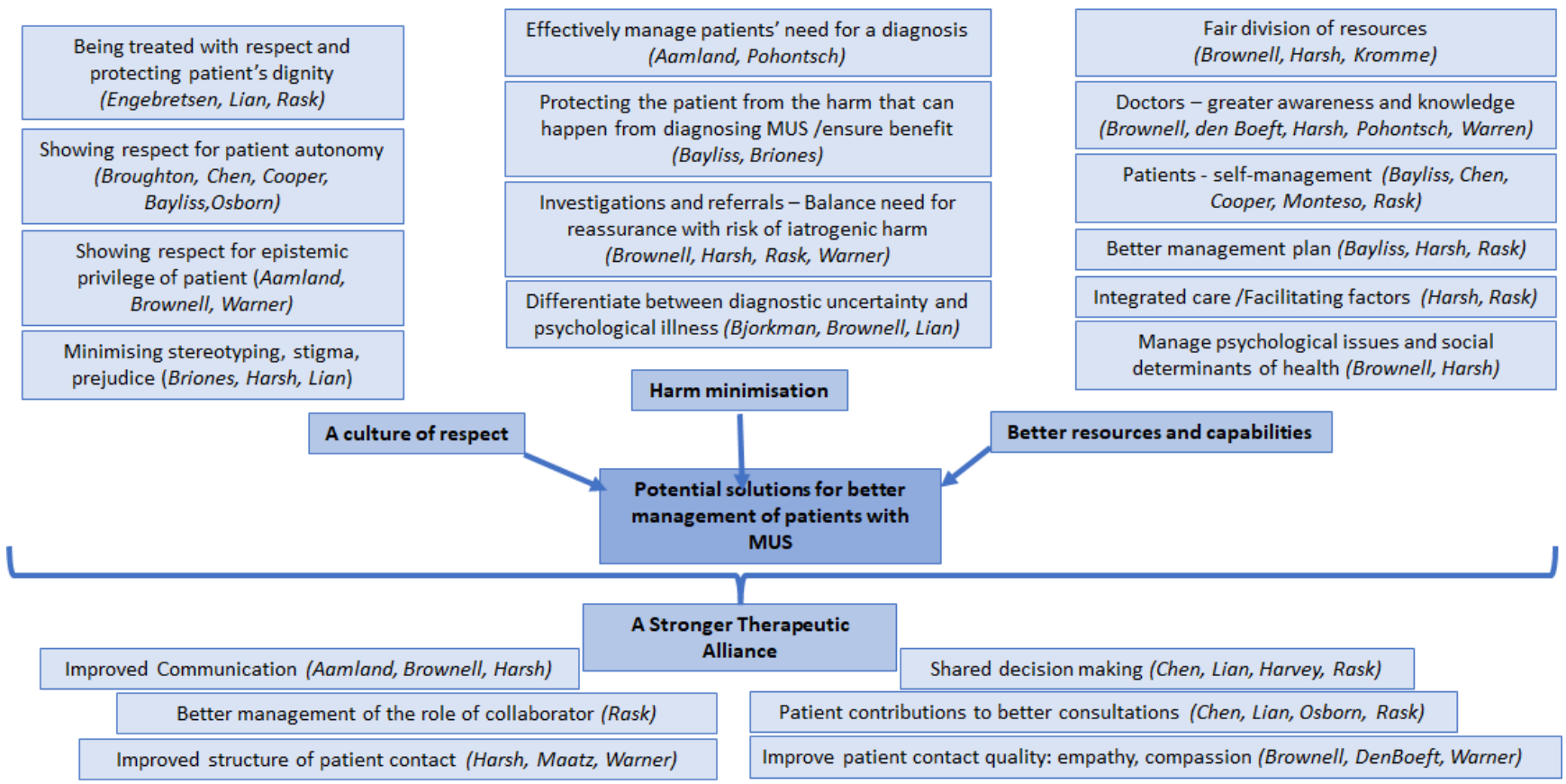
Based on patient comments, it was also possible to derive their ideas on the **ways in which patients could contribute to better and more useful encounters** with doctors. They spoke of having realistic expectations of what doctors can do ("*I don't have ridiculous expectations of what they can do for me*," Chen), of acceptance ("*I sort of accepted that maybe this is … psychological*," Cooper; "*Accept that you cannot achieve everything*," Monteso) and of the need to manage one's own state of mind when dealing with doctors ("*as a patient, I need to go in clear and concise, not wandering*," Chen; "*if it's a psychological thing, then it's a matter of me deciding how to … live with it, or how to manage it,*" Cooper). The need for patients to work towards increased acceptance and confidence in doctors is also apparent based on patients' comments about a perception of lack of knowledge in doctors (Lian), perception of misdiagnoses (Bjorkman, Osborn) and the dissatisfaction with referrals and investigations (Harvey, Rask).

4.6 Discussion

4.6.1 STATEMENT OF PRINCIPAL FINDINGS

This synthesis attempted to bring together the evidence on patients' and doctors' experiences on diagnosing and managing patients with MUS. As shown below in Figure 4.17, discussion of experiences of both patients and doctors centred around three key themes: dealing with diagnostic uncertainty, emotional experiences during the doctor-patient encounter, and resource related issues. The research also enabled the elicitation of a higher-order theme – the potential solutions offered by both doctors and patients on how to manage these encounters better: by inculcating a culture of respect in the healthcare system, by minimising harm and improving resources and capabilities in both doctors and patients, all leading to a therapeutic alliance, thereby improving the quality and structure of the doctor – patient encounter, improving communication, empathy, trust and belief in the patient.

Figure 4.17: Potential solutions for better management of patients with MUS



4.6.2 STRENGTHS AND LIMITATIONS

An extensive search indicated that this is the first synthesis that brought together the evidence on the experience of diagnosing and managing MUS from the perspectives of both patients and doctors. The findings show that doctors and patients share similar concerns and offered potential solutions that were mostly compatible with each other's expectations. The review includes research on patients with a wide range of MUS including specific symptom syndromes, includes the views of both primary and secondary care doctors so as to be as widely inclusive as possible.

There are a few methodological limitations that may have an impact on the research findings. Firstly, synthesising evidence based on first-order constructs reported in studies is a limitation since they may not necessarily represent the entire experience of the stakeholders as the published quotations are selected by the study authors (Atkins et al, 2008). Secondly, by selecting to base the synthesis on first-order constructs alone, there may have been some data loss, if the authors of the primary studies had not selected to illustrate their point using a direct quote from the participants.

The definition of MUS in the primary research studies may also have an impact on the nature of the experiences the patients described. The synthesis was able to capture a wide range of MUS in the studies included – CFS/ME/FM (11 papers), IBS (4 papers) and a wide variety of issues including chronic pain and neurological conditions such as functional seizures and functional motor disorders in 15 papers. However, in the unspecified MUS category, there is limited information on how the diagnosing doctors defined MUS –

meaning there may be significant differences in patient selection – some studies may include patients with severe MUS whereas others could include patients with mild/moderate MUS. A range of perspectives could be a positive however there is the risk that the patient population is not necessarily representative of the total population and for example, may be limited to sufferers of the most severe forms of MUS alone.

The study was limited to research published in the past seven years, leading to loss of information published before this period. The study participants were mostly white and female, which could limit the applicability of the findings in other contexts, although there was one study which included a significant male population (Muraleetharan), one study which included a significant number of people of Black ethnicity (Pryma), one study from Iran (Mohebbi) and another from South Africa (Cooper).

4.6.2 COMPARISON WITH EXISTING LITERATURE

Although there are no syntheses simultaneously reviewing doctors and patients experiences, existing literature addresses some of the key issues emerging from the synthesis.

A qualitative meta-summary of the research on the patient experience of living with MUPS (Polakovska & Rihacek, 2021) mirrors this review's findings on the ambivalence about receiving a diagnosis of MUS as it can reassure patients despite the risk of stigma. A second key point was the patients' dissatisfaction with the healthcare system, with the loss of faith in their doctors' competence which, in turn, led to a loss of hope of recovery.

A meta-synthesis of qualitative studies on GP's perceptions on the management of MUS made similar observations to this review on the parallel negative experiences of doctors and patients (Johansen & Risor, 2016).

A synthesis of guidelines and systematic reviews on the management of MUS in primary care based on doctors' views (olde Hartman et al, 2017) found limited evidence for the effectiveness of enhanced care by primary care physicians and stated that further evidence was necessary particularly on 1) the effects of strengthening the doctor-patient relationship on the course and prognosis of MUS and 2) on the influence of specific consultation skills such as the systematic exploration of patient ideas, concerns and expectations as well as providing a summary and personalised explanations during consultations. This synthesis found that both patients and doctors believe a stronger doctor-patient relationship is one of the ways to better manage patients with MUS. Patients have also emphasized that they valued a personalised approach with the doctor taking into consideration the patient's ideas, concerns and expectations (Chen, Harvey, Lian, Rask).

4.6.3 IMPLICATIONS FOR RESEARCH, PRACTICE AND POLICY

This synthesis clarifies the concerns of both patients and doctors on issues related to MUS diagnosis and management and provides suggestions on how this can be improved. Further research is necessary on how such improvements can be implemented.

Developing a culture of respect with working towards minimising stereotyping and prejudice is important, particularly since research indicates that negative emotions about patients can impact clinical decision making and patient safety (e.g., Isbell et al, 2020).

Further research on for example, integrated care, promoting support for patients' self-management, and on the association between managing psychological issues and social determinants and MUS, and establishing practice and policy based on such further research could help improve care for patients with MUS.

4.7 Conclusion

Based on a thematic synthesis of 30 qualitative studies, three key themes (dealing with diagnostic uncertainty, resource related issues and emotional experiences during the clinical encounter) describing the experiences of doctors and patients were identified. Arising from around these themes, potential mechanisms of improving the management of patients with MUS were identified. These findings can be used to improve guidelines on clinical encounters and management of patients with MUS.

CHAPTER 05
THE MUS IN PRIMARY CARE STUDY - OVERVIEW

5.1 Introduction

Chapter 2 explained that the second step in the process of reflexive balancing is to engage in disciplinary-naïve enquiry in to the problem. Chapter 4 described the qualitative evidence synthesis of views and experiences of patients with MUS and doctors who treat them. Their key concerns included: delay in diagnosis, delay in investigations and referrals, presence of mental health issues, stereotyping as faking illness to obtain benefit payments from the government, excessive usage of resources by these patients.

Analysing data on patients diagnosed with MUS and on patients who continue to complain of MUS sourced from real-life, routinely recorded data in a primary care database, could potentially provide evidence to support or refute these claims. This part of the research – the MUS in primary care study, aims to examine the evidence on diagnosis, management, outcomes and costs in real life, using real-life data of MUS patients (rather than under trial conditions) in a large consulting population.

To support or refute the claims of patients and doctors that emerged from the evidence synthesis, it is critically important that this empirical research is carried out to the highest standards of conduct of quantitative, and electronic healthcare data research. This was termed as a requirement that 'empirical bioethics research ought to attend to the rigorous implementation of empirical methods, and import accepted standards of conduct from

appropriate research paradigms' in the consensus finding project on empirical bioethics (Ives et al, 2018, Standards of Practice).

A scoping study of available research on MUS in England indicated that the epidemiological data available on MUS is patchy and confusing (due to multiple reasons as discussed in detail in Chapter 3), including the wide variation in defining and operationalising MUS, as indicated for example by published MUS prevalence data for a consulting population ranging from 0.7% for somatisation disorder to 60.7% for MUS (Haller et al, 2015). Furthermore, research on MUS has mostly been carried out on population-based samples, in patients referred to secondary care or under trial conditions. Population based research is most often carried out through data sourced from questionnaires, where the data quality can be compromised due to recall bias, whereas trial conditions are frequently not representative of real-life situations (olde Hartman, 2009, Konnopka & Konig, 2019). Although there is considerable research on MUS in consulting populations in primary care, longitudinal studies on periods longer than 2-3 years is limited in the literature. Long-term research can be helpful in MUS as it can help to track disease progression and assess longer-term outcomes.

Using routinely recorded electronic healthcare record (EHR) data for research has the advantage (discussed in further detail in chapter 5.2), that it can provide cost-effective and reliable data reflecting the real-life situation on morbidity and can enable monitoring changes in longitudinal studies, if recorded with high validity and integrity (Jordan et al, 2004; Khan et al, 2010). However, EHR data differs from research data in terms of structure, purpose and collection methods, and therefore has some limitations when compared to

primary research data: 1) it is recorded for clinical purposes and may not include all relevant information, 2) the quality of the data depends on accurate, complete and consistent data input, 3) it misses out on picking up people with illnesses who do not consult, and 4) EHR data analysis can differ significantly between studies, as EHR data analysis methodology is not well-defined in many research areas (Weiskopf & Weng, 2013; Kotz et al, 2022).

As discussed in Chapter 3, MUS patients are frequently under-diagnosed, and this may be intentional on the part of GPs who refrain from recording a diagnosis of MUS out of concern for the negative effects it can have on patients, and record patient symptoms as symptom codes, without recording a diagnosis (Harkness et al, 2013; Soubieres et al, 2015; Payne & Brooks, 2018). The Soubieres study (2015) for example found that while only 1,982 patients were recorded with IBS-specific codes in Hospital Episode Statistics data in 2012-2013, 28,849 patients had records of IBS-related symptom codes. Similarly, the Harkness study (2013) found 8,444 patients with an IBS Read code and 42,490 patients with an IBS-related symptom code in a regional patient database (Salford Integrated Record).

In this context, conducting research using electronic healthcare databases that routinely collect primary care data is advantageous, as it can be used to find records of both GP-diagnosed MUS patients and those who may be suffering from MUS, but did not receive a GP-diagnosis of MUS. Due to the lack of definitive disease markers for patients with MUS, the standard for diagnosis of patients with MUS has been by a clinician examining patient records of consultations, diagnostic tests and hospital visits in order to verify if the patient's complaints have been fully investigated so that a medical explanation can be definitely ruled out (Brown, 2007). This requirement has now been updated so that it is the clinician's

opinion that a patient displays disproportionate and persistent concerns about the seriousness of the symptoms or excessive time and energy devoted to the symptoms or health concerns, that leads to a diagnosis of MUS – (specifically the updated term 'Bodily Distress Disorder' under ICD-11 and similar conditions to diagnose 'Somatic Symptom Disorder' under DSM-V). Therefore, given that the clinician's opinion has been accepted as the standard for diagnosing MUS, if a GP has recorded a MUS specific Read code (e.g., Read codes for MUS Symptom Syndromes, codes referring to "psychogenic", "functional" or "pseudo" conditions, or codes referring to a general condition of "medically unexplained", "hypochondria", "somatising", in this study, it is considered informed decision making by the GP and a definitive diagnosis of MUS.

Using electronic health records has been proposed as a mechanism to identify MUS patients at an early stage (Kroenke, 2003; Smith et al, 2001, 2009; den Boeft et al, 2014; Westrienen et al, 2020). Current research indicates that MUS can be identified using electronic health records based on criteria such as the type of symptom recorded, the duration of symptoms and the number of GP visits etc (Smith et al, 2001, 2009; Morriss et al, 2012; van Westrienen, 2019).

Given the paucity of relevant data from published research, and the advantages of research using electronic healthcare records (EHR data), this MUS in Primary Care study aims to investigate the data available on the real-life diagnosis and management of patients with MUS in primary care in England using an electronic healthcare record database. To ensure that the research is carried out to the best standards possible, a systematic review on the methods of using EHR data to recognise patients with MUS was carried out. The information

from this systematic review was used to inform the EHR data analysis methodology used in this study, along with a further rapid review of related literature. The study will help to support or refute the data generated from qualitative research about the issues regarding the diagnosis and management of patients with MUS.

For example, qualitative research findings indicate patients often complain about not receiving a diagnosis; whether this is true can be determined by looking at the number of patients who present to their GP with symptoms suggesting MUS, but who receive a diagnosis only after a long time, or not at all. Furthermore, findings indicate that doctors believe MUS patients are mostly from lower socio-economic groups and exaggerate symptoms to qualify for social security payments; whether this is true can be determined by examining where the MUS patients in this primary care database are positioned on the Indices of Multiple Deprivation. Patients complain that they do not receive appropriate investigations and referrals as some doctors believe MUS patients' complaints are unfounded; to what extent this patient complaint is true can be assessed by examining what percentage of these patients undergo examinations and are referred for further care.

5.2 Overview of methods and datasets for the MUS in primary care study

Primary care data for this study is sourced from electronic healthcare data routinely recorded from 2005 to 2015 in a regional primary care database, the Consultations in Primary Care Archive (CiPCA) database. This database was selected as it is sufficiently extensive to provide population level data; data collected from multiple practices has been

found to be representative of the population (Herrett et al, 2015). Furthermore, the CiPCA database specifically has been found to be generalisable to English population level data for some conditions such as musculoskeletal disorders (Jordan et al, 2007). At the same time, this database is also not too large for in-depth analysis carried out within a PhD study by an individual researcher. It is also for convenience as the database is held at the School of Medicine at the Keele University, where the PhD study is carried out.

It is important to note that when referring to 'identifying' patients with MUS or any other similar condition in this study, there is no attempt at any point to break the anonymity of the patient to discover his/her identity. 'Identifying' as a patient with MUS refers to separating out such patients from patients without MUS.

5.2.1 THE CIPCA DATABASE

The CiPCA database contains pseudo-anonymized, routinely collected primary care data for an annual registered population of c.90,000 patients from nine GP practices in North Staffordshire. Morbidity, symptom, and process of care data is captured using the Read code framework, which was used in primary care until April 2020. Pursuant to a research agreement with the Keele University Research Institute for Primary Care and Health Sciences (now part of the School of Medicine), these practices followed a programme on consultation data audit, training and validation and generally adhere to high standards in coding clinical activity. The data is regularly audited and has been shown to have data quality comparable to national general practice databases (Porcheret et al, 2004). The North Staffordshire Research Ethics committee (reference 03/04) granted approval for the

broad use of data for research purposes at the Keele University and this was most recently updated by the Haydock Park Research Ethics Committee (reference 17/NW/0232) in April 2017. A formal data request form and a request proposal outlining the research question and research methodology was submitted to the CiPCA Academic Custodianship Committee and was approved on 11 September 2018.

Full-year data was available from 2000 to 2015 at the time of the start of this study. A unique anonymised patient identifier is allocated to each patient, and each contact with the GP practice is recorded with a unique consultation ID, which allows the patient data to be tracked over time. Entering at least one code is required per contact event. Morbidities and symptoms are coded using the Read Code system. The database also carries information on prescriptions including date of prescription, BNF code, drug item issued, number of issues and last date of dispensation.

5.2.2 THE READ CODE SYSTEM

This 'coded thesaurus of clinical terms' is a standardised vocabulary for clinical terms that was used in the NHS to electronically record patient data in England from 1985 until April 2020 when it was replaced by the Snomed codes (www.data.gov.uk, www.scimp.scot.nhs.uk).

Read Codes are arranged in Chapters as shown in Table 5.1 below; Chapters 1-9 (processes of care) provide the terminology for history, symptoms, examination, procedures and administration; Chapters A to U provide the terms to record disorders, i.e., diseases, conditions and injuries, based on bodily systems. Chapter Z is for unspecified conditions.

Table 5.1: Order of arrangement of Read Code chapters					
Processes of care		**Diagnosis codes**			
0	Occupations	A	Infectious / parasitic diseases	L	Pregnancy, childbirth, and puerperium
1	History / symptoms	B	Neoplasms	M	Skin and subcutaneous tissue diseases
2	Examinations and signs	C	Endocrine, nutrition and metabolic diseases	N	Musculoskeletal and connective tissue diseases
3	Diagnostic procedures	D	Blood and blood forming organs diseases	P	Congenital anomalies
4	Laboratory procedures	E	Mental and behavioural disorders	Q	Perinatal conditions
5	Radiology / physics in medicine	F	Nervous system and sense organ diseases	R	[D] Symptoms, signs, and ill-defined conditions
6	Preventative procedures	G	Circulatory system diseases	S	Injury and poisoning
7	Operations, procedures, sites	H	Respiratory system diseases	T	Causes of injury and poisoning
8	Other therapeutic procedures	J	Digestive system diseases	U	[X] External cause of morbidity and mortality
9	Administration	K	Genitourinary system diseases	Z	Unspecified conditions

The codes are arranged in a hierarchical structure, expanding for up to five levels, with increasingly specific terminology as shown in an example below. This structure was adopted to help GPs select the most appropriate Read Code, as well as to help search and report on recorded data.

Table 5.2: Hierarchy in Read Codes	
Read code Hierarchy	
1….	History/symptoms
17…	Respiratory symptoms
171..	Cough
174.	Productive cough

Two types of Read codes refer to MUS: MUS-specific Read codes – diagnosis codes used when a GP diagnoses a patient as suffering from MUS, and, MUS-related symptom codes, usually located under Processes of care, in Chapter 1 - History and symptoms and Chapter 2

- Examinations and signs; these are discussed in detail in Chapter 6 – Read codes used to record MUS and related symptoms in primary care.

5.3 Aims and objectives of the MUS in Primary Care Study

This section aims to answer Research Question 2: *What does the empirical evidence from large consulting populations indicate about the extent and intensity of these issues?* to achieve the following objective.

Objective 2 – Assess the extent to which real-life data can support the findings described in qualitative research by analysing the current patterns of recognition, management, healthcare resource utilisation and costs of MUS as routinely recorded in a consulting population in primary care in England.

This longitudinal cohort study aims to carry out a comprehensive analysis of patients with medically unexplained symptoms in a consulting population in England over five years, using the routinely recorded data from the CiPCA database to generate empirical evidence from real-life primary care practice, and in turn, to assess the extent to which real-life quantitative data from a large consulting population can help to support (or refute) the findings in Chapter 4 from qualitative research, trials and population studies from the current literature on MUS. Table 5.3 considers how each of the MUS-related factors in the first column is described in qualitative research (Column 2), The third column gives the information that can be found from the real-life data in primary care electronic health records on each of these factors.

For example, qualitative research findings indicate that incidence and prevalence of MUS is high, despite significant under-reporting of MUS. The incidence of MUS can be calculated

using the primary care database information on the number of new patients for whom the GP has recorded a MUS-specific code. The extent of under-reporting can be evaluated by the number of new patients who are potentially patients with MUS, although GPs have not recorded an MUS diagnosis but have recorded MUS-related symptom codes.

Qualitative evidence indicates that the diagnosis of MUS is often delayed. EHR data can be used to support or refute this finding by examining how quickly a patient is given the diagnosis of MUS, and, by assessing the number of patients with MUS-related symptom codes recorded who subsequently receive a diagnosis of MUS, and how long it takes for this diagnosis to be given.

Table 5.3: Comparing qualitative evidence of MUS related factors to quantitative, real-life data		
MUS related factor	**Qualitative / existing evidence**	**Real-life data sought from primary care electronic health records**
Incidence / Prevalence	• High • Significant under-reporting	Incidence of MUS; for each of years 2007 - 2010 • No. of new patients with a GP recording of MUS code • No. of patients fulfilling criteria for potential MUS but without a GP-recorded MUS code
Diagnosis	• Diagnosis delayed	• Number of patients with symptom codes later identified as patients with MUS with a recorded MUS code, and time taken to do so • Recorded use of diagnostic tests for MUS (e.g. PHQ15)
Socio-demographic characteristics	• Mostly female • Younger age • Lower socio-economic status	• Patient count male/female • Age distribution of patients • Socio-economic status as measured by Indices of Multiple Deprivation ranking
Investigations	• Repeated, or, • Denied	• Investigations recorded for patients with MUS/symptom codes
Consultations	• Excessive	• No. of consultations per patient per year
Comorbid mental illness	• Common	• % of patients with a mental health / psychological issue related code on record
Vulnerability	• Common	• % of patients with a record of childhood, sexual or domestic abuse
Disease perpetuation	• Prolonged complaints of illness without resolution	• % of patients who continue to have an MUS code recorded for each of next 5 years after diagnosis • % of patients with MUS-related Symptom codes on record over 5 years • % of patients with MUS-related Symptom codes who are subsequently diagnosed with MUS within 5 years
Costs to primary care	• High	• Analysis of costs to primary care – consultations, investigations, prescriptions (In chapters 11-12)

5.3.1 RESEARCH PROCESS: FLOW CHART OF THE MUS IN PRIMARY CARE STUDY

The research process was conceptualised by the researcher in close consultation with the lead supervisor, Professor Sumathipala, a global expert in MUS and also a consultant psychiatrist, and, Professor Kelvin Jordan, Professor of Biostatistics at Keele University. The aim is to study the diagnosis and management of the two key patient groups with MUS:

1) where a GP has recognised and recorded a patient as a patient with MUS – a 'GP-diagnosed MUS patient', and,

2) where the GP has recorded MUS related symptom codes, but there is evidence to indicate that the patient has MUS – an 'EHR-defined MUS patient'.

The first step of the study is to find such MUS patients in the primary care database.

- As detailed in **Chapter 6**, a systematic review was carried out to learn about the mechanisms used previously using electronic health records to define MUS patients, and, to validate the accuracy of such searches. The systematic review findings inform and support the creation of an electronic health record (EHR) database search mechanism to define 1) GP-diagnosed MUS patients, and, 2) EHR-defined MUS patients.

- In the next step, **Chapter 7,** two lists of Read codes GPs had used in the primary care database to record patients as suffering from MUS or MUS related symptoms are derived, using information from the systematic review and further literature review:

  1) "MUS-specific Read codes" - the list of codes GPs may use to record MUS in the database where GPs have recorded the patients as suffering from MUS –and,

2) "MUS-related symptom codes" - the list of symptom codes GPs recorded in the database that may indicate the presence of MUS in patients.

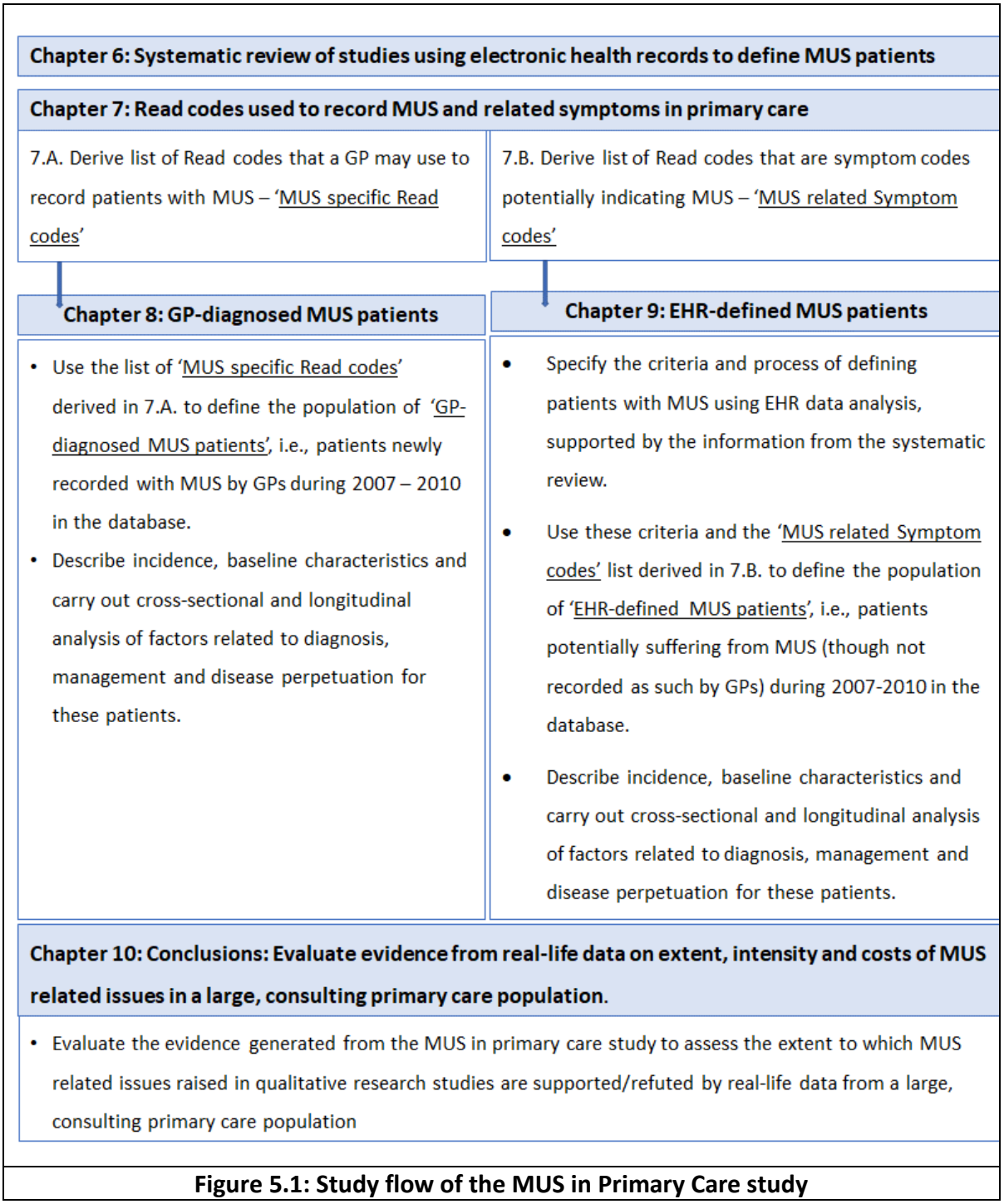


Figure 5.1: Study flow of the MUS in Primary Care study

- **Chapter 8**: The list of 'MUS specific Read codes' derived in Chapter 7 is used to define the population of GP-diagnosed MUS patients, i.e., patients newly recorded with MUS by GPs during 2007 – 2010. MUS is conceptualised here as a working hypothesis that can be revised based on changes in symptoms rather than as disparate symptoms, as defined by Olde-Hartman et al (2018). The chapter then describes the prevalence, baseline characteristics and the cross-sectional and longitudinal analysis of factors related to diagnosis, management, and disease perpetuation of this GP-diagnosed MUS patient group.

- **Chapter 9**: This chapter describes the process of deriving a mechanism to recognise patients who are likely to be suffering from MUS (though a GP has not recorded such a diagnosis), using a set of defined criteria, including the list of 'MUS related Symptom codes' collated in Chapter 7, and the information from the systematic review in Chapter 6. This search mechanism is then applied to the primary care database population to separate out a list of potential MUS patients – defining the population of 'EHR-defined patients with MUS'. This will capture the information of the number of patients who potentially suffer from MUS, but who have not been recorded by their GP as a MUS patient, giving a more comprehensive view of all the patients with MUS in the consulting population. Finally, it describes the prevalence, baseline characteristics and the cross-sectional and longitudinal analysis of factors related to diagnosis, management and disease perpetuation.

Lastly, in **Chapter 10**, the findings from the MUS in primary care study in chapters 8 and 9 are evaluated to assess if the MUS related concerns raised in qualitative research studies in

chapter 4 are supported or refuted by the real-life data from the large, consulting primary care population studied. Cross sectional analysis to compare the two different groups of patients on demographic characteristics, as well as longitudinal analysis to investigate times to identification and resolution is carried out. This gives information on the real-life situation of MUS – and could either support or refute some of the issues emerging from the qualitative research – on delayed diagnosis, disease perpetuation and other associated factors such as presence of mental health issues.

The specific objectives of the MUS in Primary care study are summarized in Table 5.4.

Table 5.4: Specific objectives of MUS in primary care study	
1. Analyse the mechanisms used in previous studies using electronic health records to define MUS patients, and to validate the accuracy of such searches; strengths and weaknesses of the different methods.	Chapter 6: Systematic review of studies using electronic health records to define MUS patients
2. Analyse use of Read codes to record MUS / related symptoms. • Derive lists of Read codes that ○ a GP may use to record patients with MUS – 'MUS specific Read codes' ○ are symptom codes potentially indicating MUS – 'MUS related Symptom codes.'	Chapter 7: Read codes used to record MUS and related symptoms in primary care
3. Use the list of 'MUS specific Read codes' to define the population of patients newly recorded with MUS by a GP in each of the years 2007 – 2010 and for the defined patient group ○ describe prevalence and baseline characteristics ○ carry out cross-sectional and longitudinal analysis of factors related to diagnosis, management and disease perpetuation (as detailed in outcome measures below).	Chapter 8: GP-diagnosed patients with MUS

4.a. Derive a mechanism to recognise patients with MUS via EHR data analysis, supported by the information from the systematic review. 4. b. Use the derived mechanism and the list of 'MUS-related symptom codes' to define the population of patients potentially having MUS (though not recorded as such by GPs), and, for the defined patient group 'EHR-defined patients with MUS' o describe prevalence and baseline characteristics o carry out cross-sectional and longitudinal analysis of factors related to diagnosis, management and disease perpetuation (as detailed in outcome measures below).	Chapter 9: EHR-defined patients with MUS
6. Evaluate the evidence generated from the MUS in primary care study to assess the extent to which the real-life data from a large population helps to validate or refute the MUS related concerns raised by small samples of patients / doctors in qualitative research studies.	Chapter 10: Conclusions: evidence from real-life data on extent and intensity of MUS related issues in a large, consulting population.

5.3.2 OUTCOME MEASURES FOR THE MUS IN PRIMARY CARE STUDY

The following are the outcomes to be measured from the MUS in Primary care study – as given briefly in column 3 of Table 5.3.

Incidence

- For each of years 2007 - 2010, per 1000 population
    - No. of patients with a GP recording of MUS-specific Read code – GP-diagnosed MUS patients
    - No. of patients fulfilling criteria for potential MUS without a GP-recorded MUS code – EHR defined MUS patients

Cross-sectional analysis after combining patients across each year 2007-2010, for the two groups of patients GP-diagnosed MUS patients and EHR-defined MUS patients separately:

- Socio-demographic characteristics
    - Describe patient groups by calendar year diagnosed/identified, gender, age, quartile in Index of Multiple Deprivation.
- Diagnosis
    - Time taken for patients with symptom codes to be identified as patients with MUS with a MUS-specific Read code recorded by a GP.
    - Recorded use of diagnostic tests for MUS (e.g., PHQ15)
- Management
    - Investigations recorded for the two groups of patients
    - Comorbid mental health / psychological issues: % of patients with a mental health / psychological issue related Read code on record
    - Vulnerability: % of patients with a record of childhood, sexual, domestic abuse or drug abuse

Longitudinal analysis

- Disease perpetuation
    - For GP-diagnosed MUS patients, descriptive analysis, stratified by age, gender and calendar year and number of following 5 years defined as an MUS patient
    - For EHR-defined MUS patients, descriptive analysis, stratified by age, gender and calendar year, of:
        - Number of following 5 years defined as unrecognized MUS patient
        - Percentage recognized as patients with MUS by GP in subsequent 5 years

5.4 Validation of the Research process

Validation of the research process, the code list generation process and the resulting code lists was carried out in two stages by two consultants with experience in patients with MUS and expertise in psychiatry and primary care, along with two experts on research using electronic health records. This is in line with the methodology used in similar reviews where two groups of experts, ones with clinical expertise and others with methodological expertise are involved (Buscemi et al, 2006; Khangera et al, 2012).

- In the first stage of the validation process, the research process and preliminary lists of all codes included in the lists as well as the excluded codes were examined and refined by a consultant psychiatrist who is a global expert in MUS and with extensive family medical practice qualifications and experience as well - Prof. A. Sumathipala, Professor of Psychiatry and supervisor of the study, in a series of one-on-one meetings.
- The code generation process and the code lists revised after the first review were then submitted for approval to an advisory panel formed from among the custodians of the CiPCA database, including Dr. J. Edwards, an NIHR Academic Clinical Lecturer in Primary Care and a GP, Dr. Ying Chen, a biostatistician and Prof. K. Jordan, Professor of Biostatistics and supervisor of the study.
- The work related to the costs and economics components of the research were conceptualised with the support of the third supervisor of the PhD research, Professor Sue Jowett of the Health Economics Unit, Institute of Applied Health Research, University of Birmingham, and subsequently supervised and reviewed.

CHAPTER 06
IDENTIFYING MUS PATIENTS USING ELECTRONIC HEALTH RECORDS – A SYSTEMATIC REVIEW

6.1 Background

The reported worldwide prevalence of primary care patients presenting with Medically Unexplained Symptoms (MUS) ranges from 0.7% to 60.7% (for the various terms for MUS, Haller et al, 2015). These patients are said to consume a disproportionate amount of health resources, often due to unnecessary investigations and inappropriate symptomatic treatments (Konnopka, 2013).

Early identification as an MUS patient can help to avoid the frequent referrals, which reinforce and prolong somatising behaviour, which in turn reduces the take-up of limited resources (van Westrienen et al, 2019). There is no standardised procedure for the recognition of MUS (Smith, 2001).

Identifying MUS is essentially assessing the probability of presence/absence of MUS in the patient by considering their clinical and non-clinical features (Moon et al, 2012). Such research is diagnostic research if the disease is identified as currently present and prognostic research if the disease or outcome occurs within a specified future period (Hendriksen et al, 2013). This review considers diagnostic research carried out to identify MUS using electronic health records, by using a search strategy to analyse electronic health records in electronic healthcare record databases.

6.2 Identifying patients with MUS using electronic health record data

Conducting research using electronic healthcare databases that routinely collect primary care data is advantageous as they can provide cost-effective and reliable data on morbidity and enable monitoring changes in longitudinal studies, if recorded with high validity and integrity (Jordan et al, 2004; Khan et al, 2010). Using information routinely recorded in electronic health records (EHR) to identify MUS patients is important as it can facilitate earlier recognition of these patients, and using EHR data for recognition of morbidity is convenient, economical and has been shown to be feasible in multiple applications in other 'at risk' populations such as cardiovascular disease and diabetes (Drubbel et al, 2012; Feldstein et al, 2010).

Several attempts have been made to develop a mechanism for the identification of MUS patients using healthcare records (Smith, 2001; Verhaak, 2006) effectively with appropriate sensitivity and specificity; however, there is no generally accepted procedure to identify MUS patients using EHR. Before introducing a test to identify MUS patients into clinical practice, it is necessary to show that the test works accurately in the intended population in clinical practice – i.e. demonstrate clinical validity, and that it is useful to improve patient outcomes – i.e. demonstrate clinical utility.

6.2.1 CLINICAL VALIDITY - DIAGNOSTIC ACCURACY OF TESTS USING EHR TO IDENTIFY MUS PATIENTS

Diagnostic accuracy tests are used to assess clinical validity – to see if the index test (i.e., the test that is being checked for validity), can accurately distinguish between patients who have a given disease and those who do not have the disease. For the purposes of this review, an EHR search method is viewed as a diagnostic test, which helps a clinician to determine the presence or absence of the MUS disease condition in a patient. Sensitivity and specificity of the new 'index test' are measured by comparing the results of the index test to the results of the reference standard, i.e., the best method available currently to recognise MUS patients. Sensitivity of the test refers to the percentage of patients with MUS according to the reference standard, who are correctly recognised by the index test as suffering from MUS. Specificity refers to the ability of the test to accurately recognise patients who do not have MUS. If the sensitivity and specificity of such a reference standard is high and it is the best available test under reasonable conditions, it is used as the gold standard, i.e., a test that is capable of best differentiating between patients with MUS and those without MUS (Versi, 1992; Cardoso et al, 2014; Rutjes et al, 2007; Umemneku et al, 2019).

6.2.2 CLINICAL UTILITY - IMPORTANCE OF USING ELECTRONIC HEALTH RECORD DATA TO IDENTIFY MUS

Using electronic records to identify MUS can simplify the process of recognising MUS patients at an early stage, based on criteria such as age, gender, the type of symptoms recorded, and the number of visits. When choosing between sensitivity and specificity in

setting the cut-off points for identifying MUS patients, sensitivity is important to avoid missing out patients, but at the same time specificity is critically important, as false classification can prevent the patient's actual organic disease being diagnosed and treated. Where the sensitivity and the specificity of the search mechanism is high, it can be used as a simple, quick mechanism to identify MUS patients; where the sensitivity/specificity is lower, an EHR search mechanism could potentially be used to provide a preliminary identification which can be subsequently verified by a clinician.

Identifying MUS patients early on in the process can help provide appropriate services to these patients, avoid unnecessary cycles of tests and referrals and thus avoid the perpetuation of disease, which is harmful to the patient, this ultimately helps maximise utility of available resources in the healthcare system.

6.2.3 REFERENCE STANDARD / GOLD STANDARD FOR MUS IDENTIFICATION

Diagnosis by a clinician: MUS is a syndromal diagnosis, for which, currently, the most reliable method to diagnose MUS is for a clinician with training and experience in identifying MUS to examine the records of consultations, diagnostic tests and hospital visits in order to verify if the patient's complaints have been fully investigated so that a medical explanation can be definitely ruled out (Nimnuan, 2000; Creed & Barsky, 2004; Brown, 2007). This The reliability of such chart review by a physician has been established in several studies (Smith, 2001; Rask, 2010; Morriss, 2012). Chart review, however, is a time-consuming process that is not practical for use in large patient groups.

Diagnostic questionnaires: Patient self-reports of symptoms using questionnaires such as the Patient Health Questionnaire -15 (PHQ-15) are also used to identify MUS patients, and

this method has been enhanced in some studies by a secondary check where a physician rates the patient charts to confirm if the symptoms are indeed medically unexplained (den Boeft, 2014). Questionnaire-based methods are considered less effective diagnostic methods since patients' recollection of their symptoms can be unreliable, varying with factors such as time and current intensity of symptoms. However, PHQ-15 was found to be a moderately reliable and valid questionnaire to identify MUS (Kroenke et al, 2002; van Ravesteijn et al, 2009); PHQ-15 and the somatisation subscale of the Symptom Checklist 90-item version (SCL-90SOM) were considered the best options to be used in large-scale population-based studies as they use 'well-established psychometric properties, contain relevant symptoms, are relatively short, and are available in multiple languages' (Zijlema et al, 2013, p. 459). Similarly, Sitnikova et al (2017) found the PHQ-15 and the Four-Dimensional Symptom Questionnaire (4DSQ) somatisation subscale to have the best internal consistency, structural and construct validity. The Whitely Index and the Health Anxiety subscale of the Illness Attitude Scales were found to be effective in differentiating between patients with and without hypochondriasis (Speckens et al, 1996). However, it has also been noted that standardised psychiatric interviews for somatoform disorders can show low correlation with GP-identified MUS cases (Hosmer & Lemeshow, 2000, cited in Morriss, 2012). Chart review by physicians with clinical knowledge and experience of MUS has been established as the best available with some studies referring to this method as the gold standard (Smith et al, 2001, 2003, 2009; Morriss et al, 2012).

6.3 Rationale

This systematic review therefore attempts to carry out an evidence synthesis of methods that use EHR to identify MUS patients, evaluate the quality of these studies, and, to examine the reasons for differences in findings among the studies, if any. An extensive search of Medline, Embase and the Cochrane Library medical databases did not reveal any previous reviews of the methods of identification of MUS patients using EHR.

6.4 Objectives

1. To summarise the ways in which electronic health records (EHR) have been used to identify and research patients with MUS.
2. To determine the diagnostic accuracy of using electronic medical records to detect MUS in primary care patients compared against reference standards used by researchers
3. To critically analyse the characteristics and effectiveness of the different mechanisms employed in using EHR to identify and research MUS patients

6.5 Methods

The protocol and search strategy for this study was developed by the researcher, reviewed and approved by the Systematic Review team of the Keele University School of Primary, Community and Social Care and registered on the Prospero International prospective register of systematic reviews (Registration No. CRD42018103489).

6.5.1 INCLUSION / EXCLUSION CRITERIA

Studies that used an EHR search method to analyse electronic health record databases to identify MUS patients, and compared the search results to the findings from a reference standard that has previously been validated and shown to be reliable (with publication in a peer-reviewed journal and independently verified as detailed in 6.2.3 above), so as to establish the accuracy of the EHR search method were included. Studies where consecutive series of patients who presented in primary care were recruited into the study, both prospective and retrospective, were included. Diagnostic cross-sectional studies were included. Diagnostic case-control studies were excluded, as the case selection process could introduce bias by selecting only specific types of MUS patients (Bossuyt and Leeflang, 2008). Study designs where the index test was carried out on all patients presenting to the primary care practice, and those where the index test was carried out only on people who were indicated as potential MUS patients by a prior test were both included.

Table 6.1: Summary of inclusion criteria

Studies should:

- focus on adults over 18 years of age
- focus on patients with the condition of medically unexplained symptoms
- be reported in English
- be carried out after 1 January 2000
- aim to identify patients with MUS using electronic health records (EHR)
- compare the identification method using EHR to a reference standard that has previously been validated and established as reliable (clinician assessment or validated questionnaires)

To be included in the review, a study needed to have the EHR-based identification method compared against a reference standard, an approach currently used in practice to identify MUS patients; these include

i) Diagnosis by a clinician through clinical assessment after comprehensive testing and clinical interview/s with patient

ii) Diagnosis by a clinician following manual chart review of complete medical records

iii) Patients meeting the cut-off scores on a previously validated self-report questionnaire: PHQ15 (Interian et al, 2006), the Whiteley Index (Pilowski, 1971; Pilowsky and Spence, 1994) and the Illness Attitude Scale (IAS, Kellner, 1986).

All studies carried out on adult patients were included. Patients with the condition of medically unexplained symptoms are considered the target condition to be detected by the search strategies. Studies that differentiate between the different stages of MUS (mild, moderate, chronic, based on condition severity) are included.

Exclusion Criteria

Studies that:

- identify only a specific type of MUS or MUS Symptom Syndrome alone (e.g., chronic pain or IBS identification alone)
- do not compare the selection criteria for identifying MUS against an established standard measurement to confirm validity of the criteria
- focus on or included children and adolescents

6.5.2 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

The first comprehensive electronic data search for this review was carried out in April 2018 searching Medline, Embase, Psychinfo and CINAHL healthcare databases using OvidSP and EBSCO, the Prospero register of systematic reviews and the Cochrane Library. The data search was restricted to the English language in peer reviewed journals and for studies carried out after 1 January 2000. Search strategies included the combined terms related to electronic health / medical records and to terms referring to medically unexplained symptoms (Appendix 6.1). The search was restricted to after 2000 since quality and completeness of electronic health records are likely to have increased from around the year 2000. The reference lists of key studies on the subject matter were searched in order to identify further studies. The search was repeated to identify any new studies in May 2021. The reference lists of studies thus identified were checked for further relevant studies. Searches were also conducted in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessments Database (HTA Database) at www.crd.york.ac.uk/CRDWeb/ for other relevant articles.

6.5.3 DATA COLLECTION AND ANALYSIS

Selection of studies

The first reviewer carried out the data base search and examined the titles from the search to exclude the irrelevant articles. Two independent reviewers carried out the abstract and full text review of the relevant articles and full text review. Disagreements were resolved through discussion.

Data extraction and management

The following data was extracted into a modified form of the STARD checklist, Standards for Reporting of Diagnostic Accuracy (Bossuyt et al, 2003), where available (Table 6.2).

Table 6.2. Data extracted from selected studies	
Bibliographic details of paper	Title of study, first author, year, citation/link
Introduction	Scientific and clinical background, intended use and clinical role of index test, study objectives and hypotheses
Study design	Prospective/Retrospective, Randomized/not, Cluster/Cross-over design, duration
Participants	Eligibility criteria, basis of identification, enrolment procedure (consecutive/random), setting, location, start and end dates, number receiving index test and reference standard, demographic data (gender, age, etc.), co-morbidities
Index test	Details of index test screening method carried out to identify patients with MUS; how the tests were carried out, assessors' experience, expertise and training
Reference test	Details of reference test/s carried out, rationale for test positivity cut-offs or result categories
Cross-tabulation of index test results	As reported when published; calculated using information from available data e.g., sensitivity, specificity or predictive values
Study limitations	Sources of potential bias, statistical uncertainty, generalisability (reviewer's conclusions and those reported by the authors)
Implications for practice	Intended use and clinical role of index test (reviewer's conclusions as well as those reported by the authors of the original papers)

The researcher carried out the data extraction and the lead supervisor checked the data extracted; disagreements were resolved through discussion.

6.5.4 ASSESSMENT OF METHODOLOGICAL QUALITY

The methodological quality of the studies was assessed using the QUADAS-2 tool (Whiting, 2011) recommended by the Cochrane Collaboration. The four domains, participant selection, index test, reference standard and participant flow were each assessed for risk of bias and for applicability in the case of the first three domains. As recommended by the developers of the Quadas-2 tool, the tool was reviewed for suitability for this study and it was decided to retain all questions. Two independent reviewers rated the studies based on pre-agreed operationalising criteria and disagreements resolved through discussion. A narrative summary of the risk of bias/applicability is provided rather than a summary quality score in order to ensure the limitations of each study are considered transparently.

6.5.5 DATA SYNTHESIS AND STATISTICAL ANALYSIS

A narrative synthesis of the studies is provided. In this review, all methods that use electronic health records to identify patients with MUS were considered index tests. This review is structured as a comparison of accuracy of multiple index tests. The review considered all available studies and carried out indirect comparisons of the different index tests in relation to reference standards, despite the risk of confounding due to differences in patient and study characteristics.

For the index tests, an explicit threshold to separate cases of MUS patients from those without MUS is not always specified; an implicit threshold based on the levels of certainty of presence or absence of disease driven by clinical judgment is considered acceptable. As the review includes more than one index test, the diagnostic accuracy of each test was

analysed individually, with a 2-by-2 table presented for each study, where feasible. A narrative assessment of the differences in accuracy between the tests is then carried out. A patient is considered the unit of analysis in each of the studies. Meta-analysis is not carried out due to the heterogeneity, the low number of studies identified and the different methods used.

This review will provide a descriptive analysis of the results, including the measures of diagnostic performance of the diagnostic tests. The number of eligible studies is limited and the heterogeneity in the methods of identifying MUS within EHR, settings and design utilised in the different studies make pooling of diagnostic accuracy data, and generating an average estimate of sensitivity and specificity to be of limited validity.

6.6 Results

6.6.1 SEARCH RESULTS

The electronic searches and other searches provided 1,932 articles for initial screening; 1,896 records were excluded after an initial title review. Of the 36 articles remaining, assessing the abstract for eligibility resulted in 16 articles being excluded. The remaining 20 articles were subjected to full-text review; 15 articles were excluded (reasons for exclusion given in Appendix 6.2) and 5 studies were included in the review. The study flow diagram below indicates the number of studies selected at each point.

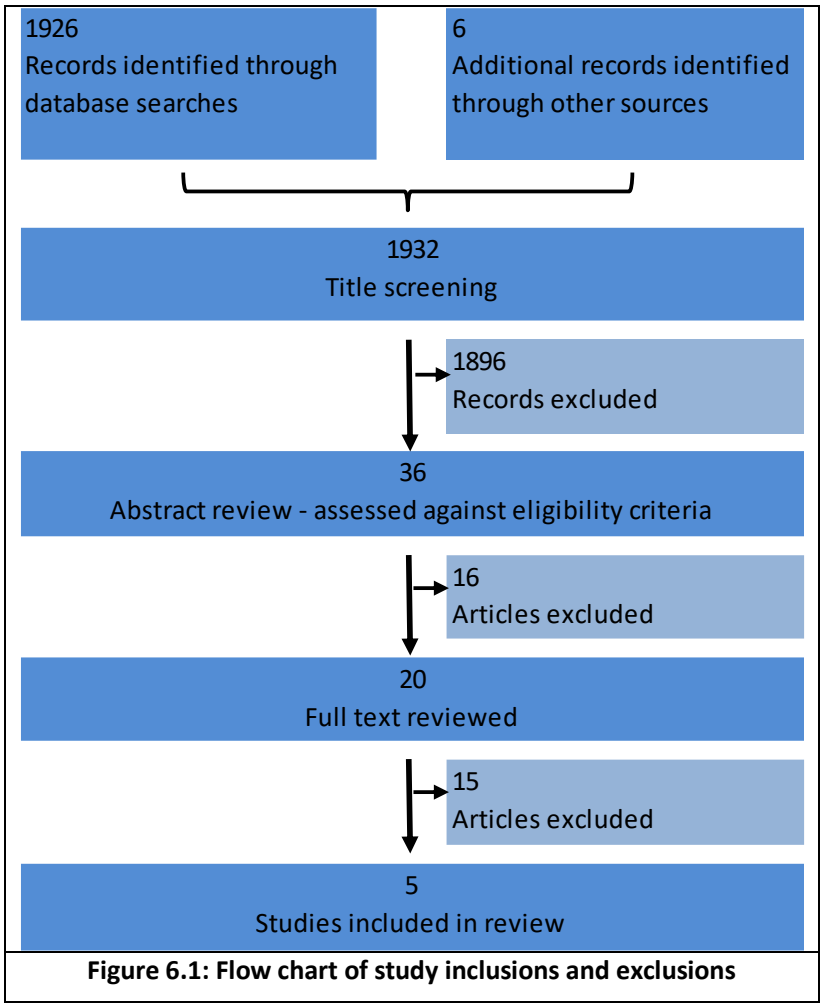


Figure 6.1: Flow chart of study inclusions and exclusions

6.6.2 INCLUDED STUDIES

Table 6.3 below gives the details of the five included studies, published over 2001 -2020. Robert Smith et al carried out the three earliest studies in 2001, 2004 and 2009 in the USA (Smith et al 2001; Smith et al 2004; Smith et al, 2009). One study was carried out in England (Morriss, 2012) and the most recent in the Netherlands (den Boeft, 2014).

Table 6.3: Studies selected for the review				
Study	**First Author**	**Year**	**Citation**	**Study Objective**
Screening for high utilizing somatising patients using a prediction rule derived from the management information system of an HMO: a preliminary study.	Robert C. Smith	2001	Medical Care Volume 39, Number 9, pp 968-978	Develop and validate Prediction* rule to identify high-utilising somatising patients.
A method for rating charts to identify and classify patients with medically unexplained symptoms.	Robert C. Smith	2004	Psychotherapy and Psychosomatics 2004; 73 (1): 36-42	Identify and classify MUS patients using a chart rating method.
The diagnostic accuracy of predicting somatisation from patients ICD-9 diagnoses	Robert C. Smith	2009	Psychosomatic medicine. 2009; 71(3): 366-371	Develop and validate prediction rule to evaluate contribution of database correlates to a diagnosis of somatisation.
Estimating the prevalence of medically unexplained symptoms from primary care records.	R. Morriss	2012	Public Health 2012; 126: 846-854	Develop models to estimate the prevalence of medically unexplained symptoms and severe MUS in a primary care practice from existing patient electronic records
Identifying patients with medically unexplained physical symptoms in electronic medical records in primary care: a validation study.	M. den Boeft	2014	BMC Family Practice 2014; 15:109	Validate EMR screening method to identify MUS patients using PHQ-15 as a reference test
* The 'Prediction Rule' referred to here is a rule to predict if a patient has / does not have MUS at that given time, does not refer to a prediction of whether or not the patient will develop MUS in future as defined in prediction studies, and was therefore selected for this review.				

Demographic characteristics of the study patients are given in Table 6.4. The study involved large numbers of patients, ranging from 883 to 1,400. Only adult patients were included;

the lowest mean age at 38.8 years was reported in the den Boeft study and the oldest mean age of 52.4 years in the Morriss study, which included patients up to 95 years of age.

Table 6.4: Demographic characteristics of patients in included studies

Study	Location	Patients in study	Age (years) mean / range	Gender (Female %)	No. of visits - mean (inter-quartile range)
Smith 2001	USA	883	40.3 (21-55)	67.0%	10.7 (7-13) visits / year
Smith 2004	USA	1,400	Not reported	Not reported	≥ 8 visits / year
Smith 2009	USA	1,364	47.1 (18-65)	71.6%	12.8 visits / year
Morriss 2012	UK	828	52.4 (19-95)	59.3%	Not reported
den Boeft 2014	Netherlands	1,223	38.8	61.8%	≥ 5 visits / year

6.6.3 SELECTION OF ELIGIBLE PATIENTS IN INCLUDED STUDIES

Age and consultation frequency were the key criteria used to identify patients eligible for the studies.

Table 6.5: Method of selection of eligible patients for the study	
Study	**Method to identify eligible patients**
Smith 2001	1. Step 1 - Patients aged 21 - 55 years with at least one primary care / emergency visit during the year 2. Step 2 - Identify patients with ≥6 visits / year (65th percentile) - 5,423 patients selected out of 15,505 eligible patients 3. Randomly select 1,000 out of the 5,423 patients 4. Of the 1,000 random selections, 94 patients excluded for pregnancy, substance abuse, psychiatric issues, employees of HMO; 23 excluded due to incomplete data - 883 patients selected for study 5. 2/3rds of 883 - 533 patients randomly selected to derive the prediction rule – the 'derivation set' - the remainder used for rule validation – the 'validation set'
Smith 2004	Patients with ≥8 primary care visits in preceding 24 months - 1,646 patients; Excluded patients with obvious organic disease - 246 excluded, remaining 1,400 patients included in the study
Smith 2009	1. Age 18 - 65 years; Patients with ≥8 primary care visits / year in preceding 24 months - identified 1,646 patients 2. Excluded patients with obvious organic disease - 246 excluded; 36 excluded for incomplete medical records; remaining 1,364 patients included in the study 3. 2/3 of sample (N=901) used as a derivation set - to develop a regression model; the remaining 1/3 (N=463) served as validation set
Morriss 2012	1. Patients aged ≥18 years with complete primary care consultation data for preceding 24 months 2. All patients who attended at five consecutive surgeries in eight GP practices - 828 patients included in study
den Boeft 2014	1. Patients aged ≥18 years with ≥5 primary care consultations in preceding 12 months 2. Completed a PHQ-15 during 2005-2007 3. No COPD, HT, Diabetes, established psychiatric diagnosis - 1,223 patients identified for the study

Four studies excluded patients with organic disease as shown below in Table 6.6, whereas the Morriss 2012 study had patient age over 18 years as the only eligibility criterion and included all patients attending five consecutive surgeries at eight GP practice surgeries.

Table 6.6 : Criteria for patient selection in included studies			
	Age	Frequent users (No. of consultations)	Exclude patients with obvious organic disease
Smith 2001	21-55 years	≥ 6 / year	No
Smith 2004	≥18 years	≥ 8 / year for 2 years	Yes
Smith 2009	18-65 years	≥ 8 / year for 2 years	Yes
Morriss 2012	≥18 years	No	No
den Boeft 2014	≥18 years	≥ 5 / year	Patients with COPD, HT, Diabetes, Psychiatric disease excluded

6.7 Summary of Index tests, Reference tests and results in the selected studies

Three studies, Smith 2001, Smith 2009 and the Morriss studies, developed logistic regression models to assess the probability of a patient having MUS. The summary details of these studies is given in Table 6.7 below.

The Smith 2004 and the den Boeft studies did not develop regression models. The Smith 2004 study trained raters to consistently rate consultation data to identify and classify MUS – and compared it against intensive chart rating by a physician. The den Boeft study used an EHR screening method to identify MUS patients and compared it against PHQ-15 scores. Summary details are given in Table 6.8.

Detailed information on these studies is given in Appendix 6.3.

Table 6.7: Logistic regression models developed to assess a patient's probability of having MUS (Details in Appendix 6.3)			
	Smith 2001	**Smith 2009**	**Morriss 2012**
Participant selection	All patients, 21-55 years, ≥ 6 consultations / year; 883 patients chosen, of which, 2/3, 588 taken as 'derivation set', remainder test set	Patients without organic disease, 18-65 years, ≥ 8 consultations/ year for 2 years; 1,346 patients chosen, 901 taken as derivation set	All patients aged ≥18 years; 828 consecutive consulters
Index test	Model variables: gender, no. of visits, somatisation potential (greater % of visits are for neuro, gastrointestinal, musculoskeletal or ill-defined conditions)	Model variables: Age, female gender, no. of visits, Somatisation potential (greater % of visits are for neuro, GI, MSK, ill-defined conditions)	Model variables: Age, female gender, anti-depressants in past 2 years, multiple pain sites, depression
Reference test	Diagnosis of somatisation by physician (>1 physical symptom, ≥6 months duration; tests, referrals show no organic disease)	Diagnosis of somatisation by physician (no documented organic disease to explain ≥1 symptom for ≥6 months)	Diagnosis of somatisation by physician
Results	Patient considered a somatiser if model indicates at least a 40% probability of a patient being a somatiser, model sensitivity 49%; specificity 96%. PPV 26%, NPV 99%	Patient considered a somatiser if model indicates at least a 30% probability of a patient being a somatiser, model sensitivity 47%; specificity 83%. PPV 39%, NPV 87%	Estimated MUS prevalence according to index test regression model: 18.4%; Observed MUS prevalence according to clinician rating: 19%

Table 6.8: Numerical rating / Screening methods to assess a patient's probability of having MUS (Details in Appendix 5.3)		
	Smith 2004	**Den Boeft 2014**
Participant selection	Patients without organic disease, ≥ 18 years, ≥ 8 consultations / year for 2 years; 1,400 patients selected	Patients with established chronic disease excluded; ≥ 18 years, ≥ 5 consultations / 12 months preceding PHQ-15 completion; 1,223 patients.
Index test	Numerical method for chart rating: Separate patients who 1) had definitive testing/referral vs had few/no tests 2) in those who had testing/referrals, patients with organic disease vs little/no organic disease Patients with higher % of symptoms but having no organic disease after testing/referrals considered patients with MUS	EHR screening method to analyse consultation data: 1) all patients ≥ 18 years, ≥ 5 consultations / 12 months preceding PHQ-15 completion; exclude those with established chronic disease 2) 2 sub-groups of patients: i) Syndrome-based confirmed MUS: ≥ 1 consultation for IBS, Fibromyalgia or Chronic Fatigue ii) High-Risk MUS - patients with ≥3 consultations for ≥1 of 104 ICPC codes suggestive of MUS
Reference test	Diagnosis of somatisation by physician	PHQ-15 scores of ≥ 5 and ≥10
Results	Numerical rating method found 1,025 patients with MUS; physician diagnosed 709 patients with MUS. Numerical rating method has sensitivity 100%; specificity 54%. PPV 69%, NPV 100%	Comparing EHR analysis to PHQ cut-off scores of 1) ≥ 5, Screening method sensitivity 17%; specificity 95%. PPV 78%, NPV 54% 2) >10, Screening method sensitivity 30%; specificity 93%. PPV 40%, NPV 89%

Table 6.9: Risk of Bias assessment using QUADAS-2					
	Smith 2001	**Smith 2004**	**Smith 2009**	**Morriss 2012**	**Den Boeft 2014**
Domain 1: Patient selection					
Consecutive / Random sampling	Random	Consecutive	Consecutive	Consecutive	Consecutive
Case control design	No	No	No	No	No
Avoid inappropriate exclusions	Yes	Yes	Yes	Yes	Yes
Risk of bias	Low	Low	Low	No	Low
Applicability concerns	Low	Low	Low	Low	Low
Domain 2: Index test					
Index test results interpreted without reference test results	Yes	Yes	Yes	Yes	Yes
Threshold specified	Yes	Yes	Yes	Yes	Yes
Risk of bias	High	Low	Low	High	Low
Applicability concerns	High	Low	Low	High	Low
Domain 3: Reference test					
Correct classification of condition	Yes	Yes	Yes	Medium	Yes
Reference test results interpreted without index test results	Yes	No	Yes	Yes	Yes
Risk of bias	Low	Medium	Low	Low	Low
Applicability concerns	Low	Low	Low	Low	Low
Domain 4: Flow and timing					
Time interval and interventions between index and reference test	Same period	Up to 24 months	Up to 24 months	Up to 24 months	Up to 12 months
Appropriate interval between index test and reference test	Yes	Yes	Yes	Yes	Yes
All patients receiving the reference test	Yes	Yes	Yes	Yes	Yes
All patients included in the analysis	Yes	Yes	Yes	Yes	Yes

6.8 Risk of Bias

The study used the QUADAS-2 tool (Whiting, 2011) to assess risk of bias as recommended by the Cochrane Collaboration to assess methodological quality of diagnostic accuracy studies (Appendix 6.4 gives details on the factors considered in the risk of bias assessment). The Quadas tool uses four domains: i) Patient selection ii) Index test iii) Reference test and iv) Participant flow and timing to assess risk of bias, and secondly, assesses applicability (Table 6.9). Two raters assessed the methodological quality of the studies for risk of bias using the Quadas-2 tool, and resolved disagreements through discussion.

The risk of bias is high in the index test of the Smith 2001 and the Morriss studies. In the Smith 2001 study, the calculation for high somatisation potential does not differentiate between patients with organic disease and somatisation, which means patients with organic disease can be considered a somatiser. In the Morriss study, the final model contains variables which have p-values greater than 0.05 (opiate use and chronic fatigue in the MUS model, and obesity and opiate use in the severe MUS model) when the multi-variate associations of variables are considered.

The reference test in the Morriss study was also classed as medium risk of bias since the patients considered 'possibly MUS' by the GP, i.e., where the GP was uncertain whether it was a patient with MUS, were also considered MUS patients. The risk of bias was considered medium in the Smith 2004 study since the reference standard test examined cases that were already identified by the index test patients with MUS. Other than that, the risk of bias is low in the studies.

6.9 Discussion

As far as is found in the published literature, this is the first study to systematically review the use of electronic health records to identify patients with medically unexplained symptoms. The five identified studies all targeted developing a mechanism to separate patients with MUS from those without MUS by analysing electronic health record data and to assess the accuracy of these mechanisms by comparing the results against a validated and reliable patient identification mechanism as the reference test. Clinicians' opinions after reviewing results of appropriate diagnostic investigations or results of validated instruments such as PHQ-15 were used as the reference tests. Three of the studies built a regression model; one used a chart rating method and the last used specified ICPC codes along with clinical and consultation characteristics to identify MUS patients. The studies indicated that patients with MUS can be recorded in the database either with a diagnosis code, where the GP has recognised the person as a patient with MUS, or, they may simply have symptom codes recorded; these MUS related symptom codes can be used in conjunction with other correlated variables such as consultation frequency, age or gender to find this second group of unrecorded MUS patients.

6.9.1 CONSULTATION FREQUENCY AND SYMPTOM CODES COULD POTENTIALLY BE USED TO IDENTIFY MUS PATIENTS USING EHR DATA

In summary, it appears that a method incorporating the number of visits and the type of complaint could potentially be used as variables to identify MUS patients. Although no single variable was found to be associated with MUS in all studies (Table 6.10), the number

of visits was correlated with the presence of MUS in four of the studies (Smith 2001, 2004, 2009 and den Boeft, 2014). Two Smith studies (2001 and 2009) found that somatisation potential, defined as a high percentage of consultations for any disorder in the nervous, gastro-intestinal, musculoskeletal systems or ill-defined complaints, which were recorded in EHR using MUS related symptom codes, were associated with the presence of MUS. The den Boeft study found that 101 ICPC codes suggestive of MUS could be used to identify patients with MUS.

Table 6.10: Variables correlated with presence of MUS as identified by the studies

	Positive statistically significant correlation	Negative statistically significant correlation
Smith 2001	Female gender, number of visits, Somatisation potential*	-
Smith 2009	Female gender, number of visits, Somatisation potential, age	Age X Age
Morriss 2012	In the previous 2 years - prescription for opiates, multiple pain sites, chronic fatigue, prescription for anti-depressants	Age
Smith 2004	Number of visits	-
den Boeft 2014	Number of visits, ICPC codes clinically suggestive of MUS	-
	*Somatisation potential – high percentage of consultations for any disorder in the nervous, gastro-intestinal, musculoskeletal systems or ill-defined complaints.	

The Morriss study, however, goes contrary to the other four studies, and found no association between female gender, the number of visits and the presence of MUS. The variables found associated with MUS in their final model were antidepressant use, multiple pain sites, opiate use and chronic fatigue and age as a negatively correlated variable.
The findings of this study that the number of visits can be an indicator of the presence of MUS is similar to the findings of a 2021 study (Kitselaar et al, 2021) where a patient

identification method based on MUS related symptom codes (Robbins list) and consultation frequency identified the highest percentage of patients with persistent physical symptoms (7%), compared to other methods including identifying MUS patients based on GP recorded symptom syndrome codes, persistent physical symptom related terminology on record and >=20 points on the 4DSQ somatisation subscale. This is not necessarily conclusive though, since, as the authors too point out, these methods are not externally validated.

This study by Kitselaar et al (2021) is not included in the study as it does not compare the methods of identification to a reference standard as required by the inclusion criteria.

6.9.2 NO STUDY FOUND A METHOD WITH SPECIFICITY AND SENSITIVITY ADEQUATE FOR CLINICAL USE

All five studies reported (or provided sufficient data) to calculate sensitivity and specificity as well as positive/negative predictive values. None of the studies found a method that would by itself be viable in clinical practice to identify MUS patients using electronic health record data with adequate specificity and sensitivity. Sensitivity was near 100% in the Smith 2001 and 2004 studies; however, both had low specificity of 54% and the sensitivity of 98% in the Smith was achieved only when considering a very low, 4% probability of a patient being a MUS patient. Although the c-statistic was at acceptable levels in the Smith 2001, 2009 and Morriss 2012 studies (0.90/0.78, 0.72/0.68 and 0.70/0.76 respectively), these were also arrived at with low probability cut-off points below 0.4. The positive predictive values were low in all three regression models (26% when sensitivity is 98% in Smith 2001, 39% in Smith 2009 and 34% in Morriss 2012), meaning there would be many false positives,

making these unsuitable for clinical screening to identify MUS patients as it would lead to patients with organic disease being considered MUS patients and not receiving necessary treatment.

Table 6.11: Sensitivity, specificity and predictive values of the different studies

	MUS observed prevalence	Cut-off point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	c-statistic
Smith 2001	14%	0.04	98%	54.0%	26%	99%	Derivation: 0.9
		0.3	56%	93.1%	57%	93%	Validation: 0.78
		0.4	49%	95.9%	66%	92%	
Smith 2009	19.4%	0.3	47%	83%	39%	87%	Derivation: 0.72 Validation: 0.68
Morriss 2012	MUS: 18 - 20%; Severe MUS: 3%	0.24	40%	86%	34%	89%	
Smith 2004			100%	54%	69%	100%	
den Boeft 2014		PHQ-15 >5	17%	95%	78%	54%	
		PHQ-15 > 10	30%	93%	40%	89%	

The Smith 2001 study reported the sensitivity and specificity of the regression model at 98% and 54% respectively at a probability cut-off value of 0.04. A 4% probability of being an MUS patient is far too low and increasing the cut-off value to a more realistic 40% probability reduced the sensitivity to 49%, making this model unsuitable for practical use, as stated by the authors as well. Similarly, in the Smith 2009 study, the authors concede that the results are not sufficient to support wide scale screening, given the low sensitivity of 47%.

The Morriss 2012 study reported 40% sensitivity and 85% specificity at a 24% probability cut-off level of the model, and the authors considered the model had reasonable ability to

discriminate between MUS cases and non-cases given the c-statistic of 0.70. The positive predictive value was 34% and the negative predictive value 89%. However, the low positive predictive value suggests that the model is picking up too many non-cases, and would therefore be too risky to use in clinical practice.

The den Boeft study reported sensitivity of 30% even at the higher cut-off of PHQ-15 ≥10 and a positive predictive value of 40%. The Smith 2004 study had a calculated sensitivity of 100% but specificity was low at 54%. Positive predictive value was 69% i.e., a false positive rate of 31% as reported in the study. The authors stated that the high false positive rate was expected as they deliberately set the threshold so as to identify as many MUS patients as possible; they suggest adopting a more specific scoring rule which would identify fewer cases overall but reduce the false positive rate. They specifically state that the index test is not suitable for clinical use due to the required high skill level (senior internal medical residents or experienced clinicians) and time-consuming nature (40 hours of training and 15-20 minutes per chart) of the method.

6.9.3 KEY ISSUES IN COMPARING DIAGNOSTIC ACCURACY OF METHODS IN THE SYSTEMATIC REVIEW

6.9.3.1 Electronic health record data and MUS rating depend on GP definition of MUS

The usefulness of electronic health data depends on the quality and accuracy of the data recorded by GPs. The definition a given GP assigns to MUS as a condition, to individual unexplained symptoms, and how the GP operationalises such definition determines how a

patient's condition is recorded in the EHR system. Similarly, the definition and operationalisation of MUS adopted by a physician carrying out chart rating will determine whether or not a patient is considered MUS. This in turn affects the sensitivity and the specificity of the developed method.

For example, in the Morriss study, being considered a potential MUS patient requires unexplained physical symptoms lasting >3 months whereas the Smith 2001 study defines 'somatisation' as 'presence of unexplained physical symptoms of at least 6 months duration or, occasionally, where an organic disease is present but does not fully explain the frequency or intensity of a patient's symptoms.' This results in different types of patients being included in the studies. The Smith 2004 study added another layer of complexity as it distinguished MUS patients from what they termed 'Minor Acute Illness' based on the level of diagnostic investigations – if the patient's regular physician had not investigated the complaints, that was judged to be a 'marker of lack of severity' and therefore not MUS. In the Smith 2009 study, somatisation is defined as 'physical symptoms with little or no documented basis in underlying organic disease', without any time limit on the duration of symptoms. Lastly, the den Boeft study grouped together Syndrome-based confirmed MUS patients and those with symptoms suggestive of MUS in the study population.

Any future research undertaken on MUS using EHR should clarify the definition and operationalisation of MUS in the study, a task further complicated by the current nomenclature and definition of MUS, which clubs together both medically explained, and unexplained symptoms based on the patients' level of distress.

6.9.3.2 General population vs. selective population affects predictive values

Each of these methods should be evaluated based on the population used in the study. The positive and negative predictive values are influenced by the prevalence of MUS; a selective population where the prevalence of MUS is high will increase the reported positive predictive value. The Morriss study alone used a general population with age ≥18 years as the only criterion. The den Boeft study used patients with ≥ 5 consultations per year, Smith 2001 ≥ 6 / year, and Smith 2004/2009 further restricting the population to those with ≥ 8 consultations per year. Such a high utilizing population is likely to have a higher prevalence of MUS, and result in a higher positive predictive value.

6.9.3.3 Sensitivity vs specificity

Diagnostic instruments, models, questionnaires etc, when used as a screening instrument and assessed against a reliable standard, often display high sensitivity but low specificity. The balance between the two is context specific and in this case, sensitivity can be more important – in order to not to miss patients. The problem is that this also results in too many false positives, with non-cases being identified as MUS patients. Unless there is a confirmatory gold standard diagnosis, this leads to non-MUS patients being considered MUS patients, leading to a relaxation of clinical vigilance, patients not receiving the necessary diagnostic work-up and treatment as well as unnecessary costs to the healthcare system.

6.9.3.4 A gold standard for reference tests for MUS

The term gold standard originally meant a test that is 100% accurate, without error, with 100% sensitivity and 100% specificity, though now it is understood that most tests will not meet such criteria and the standard is considered as the best available test under

reasonable criteria, as discussed previously ((Versi, 1992; Cardoso, 2014; Rutjes et al, 2007; Umemneku et al, 2019). Opinion is divided as to whether a gold standard can be achieved in diagnosing mental health related conditions. Some researchers believe a structured clinical interview to establish the presence of a mental disorder can be considered a gold-standard (Richardson et al, 2015) whereas others have pointed out the problems inherent in considering single instruments and GP opinion as gold standard in mental disorders (Magpie Research Group, 2004; den Boeft, 2014).

In the case of identifying MUS, there are 2 key factors which can bring error into each of the two types of reference tests. Recall bias can affect the result in diagnostic instruments such as PHQ-15 and there is a certain amount of subjectivity inherent when GP opinion is the basis for the identification.

Assessing the quality of the reference test is therefore important in this type of review, and it has been suggested that it is more appropriate to use the term 'reference standard' rather than 'gold standard' when discussing reference tests where there is potential for misclassification based on the reference test (Rutjes et al, 2007).

Limitations in carrying out this review are the exclusion of publications in languages other than English and in the grey literature.

6.10 Conclusions and next steps

The attempts to identify MUS patients using electronic health record data analysis have not yet succeeded at producing a method that is adequate for clinical use. At best, a method with high sensitivity can be used to identify patients, along with a second GP review type of

mechanism to identify and separate out the false positives, accepting that there will be a high false positive rate.

The importance and necessity of an objective method to identify MUS, however, is greater than ever before, with the subjective opinion of the GP now being the primary criteria to diagnose an MUS patient following the change in definition of patients with medically unexplained symptoms under both the DSM-5 and the ICD-11 classification systems.

The information from the systematic review is used to generate search mechanisms to find patients with MUS in primary care using the CiPCA database (described in detail Chapters 7, 8 and 9). Using the findings from the systematic review in Chapter 6, and further literature searches, Chapter 7 discusses the process of deriving lists of 1) MUS specific Read codes, and 2) MUS related symptom codes – which are symptom codes that potentially indicate MUS, that have been used in the CiPCA data base.

These lists of codes will then be used to define two patient groups in this primary care consulting population and discuss their data:

1) patients for whom the GP has recorded MUS specific Read code/s – "GP-diagnosed patients with MUS" in Chapter 8, and,

2) patients potentially suffering from MUS for whom the GP has recorded MUS related symptom codes – "EHR-defined patients with MUS" in Chapter 9.

Chapter 9 will also discuss developing a mechanism to recognise potential MUS patients, using MUS related symptom codes and discuss their data.

CHAPTER 07
READ CODES USED TO RECORD MUS AND RELATED SYMPTOMS IN PRIMARY CARE

6.1 Background, aims and objectives

This chapter aims to define a population of patients with MUS in a primary care consulting population using electronic healthcare records. The systematic review in Chapter 6 indicated that the reference standard (or gold standard in some cases) for the identification of patients with MUS is for a clinician with experience and knowledge on the subject to review the patient's history and investigations to rule out the presence of organic disease, and, with the new changes to the diagnostic criteria, for him to determine that the patient displays disproportionately high health anxiety. In this context, it is accepted for the purposes of this study that a GP recording a MUS specific Read code for a patient indicates an accurate diagnosis that the GP has recognised him/her as a patient with MUS (even though there is a certain possibility, as for any other diagnosis, that the GP might be wrong). MUS is characterised by diagnostic uncertainty, at least in the early stages of the condition. Doctors often record symptom codes to avoid recording a diagnosis of MUS or somatoform / functional disorder as discussed previously (Chapter 4). The systematic review showed that the multivariate associations of younger age, high consultation frequency and such MUS related symptom codes indicated a higher probability of presence of MUS (with p values <0.05), and that they can potentially be used in combination to find patients with MUS in EHR databases, even where the GP has not recorded a diagnosis of MUS.

The systematic review in Chapter 6 was limited to using electronic health records to identify patients with MUS, and therefore did not include other studies that provided lists of MUS disease labels, symptoms, or symptom codes (Read, ICPC, ICD) which did not use electronic health records. The findings from the systematic review were therefore supplemented by a further evidence summary carried out to find in the existing literature, lists of Read codes, ICPC codes or lists of disease labels referring to both 1) diagnosed MUS, and, 2) symptoms related to MUS.

AIMS AND OBJECTIVES OF THE CHAPTER

1. Generate an evidence summary of lists of Read codes, ICPC codes or lists of disease labels in the existing literature referring to i) diagnosed MUS, and ii) symptoms that are most likely to indicate the presence of MUS.

2. Using the information from the systematic review and the evidence summary, derive two lists of Read codes:

i) A list of Read codes used in primary care to indicate a diagnosis of MUS in patients – 'MUS specific Read code list' (detailed in Chapter 7.3.3.1). ii) A list of Read codes of codes of non-specific symptoms used in primary care that could indicate an MUS patient (though the GP has not given a diagnosis) – 'MUS related Symptom code list' (detailed in Chapter 7.3.3.2). The 'MUS specific Read code list' is then used to define 'GP-diagnosed MUS patients' (Chapter 8) and the 'MUS related Symptom code list' is used to define 'EHR-defined MUS patients' (Chapter 9).

7.2 Evidence summary of lists of Read, ICPC, ICD codes and disease labels used to record MUS found in the literature

The systematic review on identifying MUS in primary care using electronic health records yielded only one study that provided ICPC codes that inferred diagnosed MUS (den Boeft, 2014). Therefore, an evidence summary in the form of a rapid review (Khangura et al, 2012) was carried out to find out any list of Read codes, ICPC codes or lists of disease labels referring to MUS. This type of review was undertaken rather than a systemic review as the purpose was to answer the questions "what has been done previously? what does the literature say?" (Khalil et al, 2021, p.1). The initial survey too indicated that such lists were found in widely different types of research (Tricco et al, 2018; Munn et al, 2018), and therefore was harder to source based on a systematic review.

- Research question: What are the Read codes / ICPC codes/ lists of disease labels doctors / researchers have used to record patients with MUS?

- Systematic search of literature: a broad-based search was carried out with the words related to the various disease labels for MUS used in the systematic review of identifying MUS using EHR and the words "Read code" or "ICPC code" or "ICD code" as the search terms (Search strategy in Appendix 7.1). This generated 3,595 results. Title review excluded 2,671 studies and there were 924 studies remaining. Reference chaining yielded 3 further studies included in the results. Given the very large number of studies, the studies were reviewed using a qualitative research

methodology, reaching the point of saturation, which was assessed as twenty consecutive studies not providing any new data.

- Risk of bias assessments irrelevant: these codes are usually mentioned in studies on prevalence, illness management or in commentaries, where the code list is not related to risk of bias in the study.

7.2.1. Results:

The findings were grouped into two: i) Diagnosed MUS codes / illness labels to indicate where there is a diagnosis of MUS, and ii) MUS related symptom codes (symptom codes), which are symptom codes for non-specific complaints/conditions, which have been found, in the experience of clinicians and researchers, to be frequently associated with MUS patients. Many lists were a combination of the two types of records and were separated, in consensus with the supervisor.

1) Codes / disease labels to indicate diagnosed MUS

i) *codes / illness labels recording the presenting complaints as part of a specific MUS Symptom Syndrome* (e.g. Irritable Bowel Syndrome, Fibromyalgia, Chronic Fatigue Syndrome)

ii) *where a psychiatric / psychological causation is attributed to the presenting complaint*, referring to “psychogenic”, “functional”, “neurogenic” or “pseudo” conditions (e.g. psychogenic hyperventilation, functional diarrhoea, neurogenic bladder, pseudo seizures)

iii) where an organic explanation cannot be found for the symptoms, but the clinician refers to a general condition of “medically unexplained”, “somatisation” or “hypochondria”.

Wessely et al (1999) provided a comprehensive list of MUS symptom syndromes in ten different bodily systems, which has since been referred to frequently in MUS studies. Fink et al (2010) and Creed et al (2012) added Chronic pain to the syndrome list. Warren & Clauw (2012) added panic disorders and migraine as symptom syndromes; migraine, however, was excluded from this study of MUS as it has known pathologic abnormalities such as blood vessel diameter changes (Bulow-Olsen, 2013; Wijeratne et al, 2019). Read code lists used to record patients with diagnosed MUS were found reported in two studies: Harkness et al (2013) reported Read codes for IBS whereas Shraim (2013) reported code lists for IBS, FM, CFS, somatoform and conversion disorders. ICPC codes for some somatic syndromes (den Boeft et al, 2014) and ICD codes for somatoform and dissociative disorders were found (Schaefert et al, 2010), as shown in Table 7.1.

Table 7.1: Lists of Read, ICPC, ICD codes and disease labels used to record *diagnosed* MUS found in the literature (Read codes in Bold lettering)											
	Wessely 1999 /Nimnuan 2001	**Schaefert 2010**	**Fink 2010**	**Warren 2012**	**Creed 2013**	**Harkness 2013**	**Shraim 2013**	**den Boeft 2014**	**Haller 2015**	**Schroder 2015**	**Picariello 2015**
Gastro enterology	Irritable bowel syndrome, non-ulcer dyspepsia		IBS	IBS	IBS	IBS: Read codes **14CF, J521** + sub headings	**J521, J5210, 14CF, Eu453**	IBS - ICPC D93		IBS	IBS
Gynaecology	Premenstrual syndrome, chronic pelvic pain						**R090G**				
Rheumato-logy	Fibromyalgia (FM)		FM	FM			**N248, N2480**	FM - ICPC L18.01		FM	FM
Cardiology	Atypical or non-cardiac chest pain		Non-cardiac chest pain				**R065B, 1828**			Non-cardiac chest pain	Non-cardiac chest pain
Respiratory medicine	Hyperventilatio n syndrome		Hyperventil ation syndrome				**R0601**			Hypervent ilation syndrome	
Infectious diseases	Chronic (post viral) fatigue syndrome										
Neurology	Tension headache (TH)						**F2626**			TH	Chronic TH
Dentistry	Temporomandi bular joint dysfunction, atypical facial pain						**J0464**				
Ear, nose, and throat	Globus syndrome										

Allergy	Multiple chemical sensitivity										
Chronic Fatigue			Chronic Fatigue Syndrome (CFS)	CFS	Chronic Fatigue		CFS: **F286, F2860, F2861, F2862, Eu460**	CFS ICPC A04.01			CFS
Pain			Chronic pain syndrome		Chronic widespread pain						
Somatoform disorders		ICD: F45.0-45.9					**Eu45, Eu450, Eu451, Eu454, Eu45z, Eu45y**		ICD-10 - F45.0/45.9/ 300.81/300.11		
Conversion disorders							**Eu44**				
Hypochondriacal disorders									ICD-10 - F45.2		
Body dysmorphic disorders									ICD-10: 300.7		
Dissociative disorders		ICD: F44									
Panic disorders				Panic disorder							
Other				~~Migraine~~							

2. MUS related symptoms / symptom code lists

The second group of Read codes and illness labels found in the literature are for MUS related symptoms - which are non-specific complaints/conditions that have been found as most likely to indicate the presence of MUS in patients. Table 7.2 below gives a summary of these symptoms, Table 7.1 above presented the disease labels, Read, ICPC, ICD codes used once MUS is *diagnosed* and thus recorded. Two of the studies in the systematic review used lists of MUS related symptom codes (Smith et al, 2009; den Boeft, 2014) combined with age and consultation frequency to identify MUS patients.

These lists are similar in overall structure to the symptom code lists associated with MUS in several validated mental health screening instruments and in other symptom code lists used in research studies: The Patient Health Questionnaire, PHQ-15, assesses the severity of somatic symptoms using a self-administered subscale of 15 somatic symptoms in the digestive, musculoskeletal, genito-urinary, neurological, cardiac & respiratory systems (Kroenke et al, 2002; validated in over 40 studies, Kocalevent et al, 2013), that is based on the full PHQ scale (Spitzer, 1999). Escobar et al (2010) used a list of 14 somatic symptoms very similar to the PHQ-15 in a research study to assess the ability of concurrent somatic symptoms to predict psychopathology and service use. The Four-Dimensional Symptoms Questionnaire (4DSQ) contains a somatisation scale of 16 symptoms associated with MUS (Terluin, 2006). The Robbins list (1997) of 23 somatic symptoms is broadly similar to the PHQ-15. The list of 59 codes indicative of Briquet's syndrome (cited in North, 2015) and the list of 37 somatic symptoms in Nimnuan et al (2001) indicate somatic symptoms predictive of MUS. The Bodily Distress Syndrome checklist (Budtz-Lilly et al, 2015) identifies symptoms

in four groups: cardio-pulmonary/ autonomic, gastrointestinal, musculoskeletal and general symptoms.

In addition to these studies, the evidence summary revealed two published lists of MUS related symptom Read codes. Shraim (2013) included a list of 301 Read codes used to identify MUS in a doctoral thesis and Mansfield (2017) identified 335 Read codes corresponding to 40 out of the 42 somatic symptoms listed in the ACR-2010 criteria for Fibromyalgia (Wolfe et al, 2010) in her doctoral thesis. These lists collated the Read codes available in the Read code system to record MUS. They, however, gave no indication of whether or not the codes were actually used in practice by GPs to record MUS, nor the extent and frequency of their usage.

Table 7.2: Somatic symptoms identified in literature as most likely to be associated with MUS						
Gastro-intestinal	**Cardiac/ Respiratory**	**Genito-urinary**	**Neurological**	**Fatigue**	**Pain**	**Miscellaneous**
PHQ15 2002						
Constipation, loose bowels or diarrhoea Nausea, Gas or indigestion Stomach pain	Feeling heart pound or race Shortness of breath Chest pain	Menstrual cramps or other problems with periods Problems during intercourse	Dizziness Fainting spells	Feeling tired or having low energy	Pain in arms, legs, or joints Headaches Back pain	Trouble sleeping
Robbins (1997)						
Loss of appetite Nausea, loose bowels, Gas or bloating Constipation Abdominal pain	Shortness of breath Palpitations Chest pain		Numbness Dizziness	Weakness fatigue CFS	Back pain Joint pain Extremity Pain Headaches	Sleep disturbance Restlessness, Slow thoughts Difficulty concentrating Lump in throat
Nimnuan et al 2001						
Heartburn, throat discomfort abdominal pain, nausea, vomiting,	Palpitations, chest pain, breathing difficulties	Menstrual symptoms, pelvic pain	Trembling, dizziness, mood swings, numbness mental fatigue, irritable, forgetful itching, headache	Physical fatigue, daytime sleepiness	Persistent, multi-site pain, stiffness, low back pain, facial pain	Sleep problems, photo/phono sensitivity, dry mouth, taste disturbed, tinnitus
Kroenke et al 2002						
Nausea, gas, indigestion, diarrhoea, constipation, abdominal pain	Chest pain, heart pounding, dyspnoea,	Painful intercourse, period problems	Fainting spells Dizziness		Pain in arms, legs, headaches, back pain	

den Boeft ICPC codes (2014)						
Flatulence/ gas/ belching Nausea Diarrhoea Constipation Change faeces / bowel movements Loss of appetite Weight loss Abdominal pain/ cramps Abdominal pain epigastric / localised Rectal/ anal pain	Pressure/ tightness of heart Palpitations/ awareness of heartbeat Irregular heartbeat Chest symptom / complaint	Urinary frequency/urgency Urination problems Genital pain female Menstruation related pain Painful intercourse Premenstrual symptom/complaint Menopausal symptom/complaint Vaginal / vulval symptom/complaint other Pain/complaint in pelvis Pain penis/ testis/ scrotum	Tingling toes/ fingers/feet Vertigo/dizziness Sensation of unsteadiness Lightheaded-ness	Weakness/ tiredness general	Muscle pain Sprain/ strain of joint NOS Cardiovascular pain NOS Heart pain Pain general / multiple sites Headache Pain in face Complaints of chest, neck, back, low back, flank, axilla, jaw, elbow, wrist, hand, hip, leg, knee, foot	Whiplash trauma / cervical spine Eye sensation abnormal Hearing complaint Tinnitus ringing/buzzing ear Pruritis Sleep disturbance Fear of disease

These code lists found in the literature are then used to inform and confirm the MUS-specific Read codes list and the MUS-related symptom codes lists built using the recorded data in the primary care database.

7.3 Deriving Lists of MUS Specific Read Codes and MUS-related Symptom codes

7.3.1 Study setting and population

The study was carried out using the routine healthcare data recorded in the CiPCA database. The data was obtained from the CiPCA data manager (James Bailey) following a formal request for data approved by a sub-committee formed from among the CiPCA custodians as described in chapter 5.2.1.

7.3.2 METHODS

7.3.2.1 Operationalise 'MUS-specific Read codes', 'MUS related symptom codes'

A MUS specific Read Code was defined for this study as

- any Diagnostic code referring to specific MUS Symptom Syndromes
- any Diagnostic code referring to specific "psychogenic", "functional" or "pseudo" conditions
- any other code referring to a general condition of "medically unexplained", "hypochondria", "somatising" or other related term naming the condition.

A MUS related Symptom code was defined for this study as:

- any non-specific history/complaint/referral code that could potentially indicate MUS in a patient

7.3.2.2 Study design: process

The researcher designed the process in consultation with the lead supervisor to generate the two Read code lists and included two stages of validation.

Step 1. Reviewed Read codes used in the database: The data manager (James Bailey) provided the list of 30,406 Read codes that had been used in the database during 2000-2015 and the frequency of use of each Read code during the period. The researcher first reviewed all codes that had been used at least 10 times in the database amounting to 10,352 codes. The cut-off point, the code being used ≥ 10 times, was selected arbitrarily for two reasons. Firstly, considering that if a code had been used less than 10 times over a 16-year period, the frequency of its use in the database is negligibly low; secondly, for convenience, to keep the number of codes to be examined manageable.

Step 2: Deriving MUS specific Read code list: All Read codes meeting the definition for MUS specific Read codes found in the list of 10,352 most frequently used codes were included in the MUS specific Read code list. The search for MUS specific Read codes was then extended to the entire Read code list, as it was noted that there were a number of MUS specific Read codes that had been recorded less than 10 times in the database.

Step 3: Deriving MUS related Symptom code list: The systematic review and evidence summary indicated that the symptoms related to MUS could be categorised in to seven groups based on bodily systems: gastro-intestinal, cardiac/respiratory, genito-urinary system, nervous system, musculoskeletal system, fatigue and a miscellaneous group. All

pain codes were placed in the specific related body system. A step-by-step elimination process was used to identify codes in each category used in the database (Table 6.3).

Table 7.3: Process of elimination to arrive at MUS related Symptom codes list	
A	Of the 10,352 codes used >=10 times in database, removed all Read code groups related to i. Processes of care Read codes except History / Examination (Chapters 0, 3-9) ii. Chapters related to medically explainable disease (Chapters A-D, L, P, Q, S, T) iii. Local codes (e.g., EMIS codes) Shown in detail in Table 7.4.
B	Remaining codes from: i. History/ Examination chapters ii. Diagnostic code chapters E,F, G, H, J, K, M, N, R, U, and Z further studied in detail and excluded all codes • clearly referring to organic diseases (e.g., 1252 FH: Diabetes mellitus) • clearly unrelated to MUS (e.g., 22J2 Death; 136R Binge drinker)
C	Remaining non-specific history, complaint, symptom, diagnosis, or referral codes suggestive of MUS included into MUS related Symptom codes list
D	MUS related Symptom codes categorised in to seven groups: 1) Gastro-intestinal system 2) Cardiac/Respiratory systems 3) Genito-urinary system 4) Neurological symptoms 5) Fatigue 6) Musculoskeletal system 7) Miscellaneous

From the list of 10,352 Read codes used >=10 times in the database, groups of codes not relevant to MUS were first excluded from the Read codes list as shown in Table 7.3.

- All the processes of care Read codes starting from the digits 0 (occupations), 3 (diagnostic procedures), 4 (laboratory procedures), 5 (radiology), 7 (operations and procedures), and, 9 (administrative data) were removed.
- All diagnosis codes starting from A – D, indicating Chapter A (Infectious and parasitic disease), Chapter B (Neoplasms), Chapter C (Endocrine, nutrition and metabolic diseases) and D (Blood and blood forming diseases) were removed since they clearly referred to medically explainable conditions, as were codes starting with L (Pregnancy and childbirth), P (Congenital anomalies), Q (Perinatal conditions), S and T (injury and poisoning).
- All EMIS and local codes on record were excluded to ensure generalisability.

Table 7.4: Read code chapters unrelated with MUS were first excluded

Processes of care	**Diagnosis codes**	
~~0 Occupations~~	~~A Infectious / parasitic disease~~	~~L Pregnancy, childbirth and puerperium~~
1 History / Symptoms	~~B Neoplasms~~	M Skin and subcutaneous tissue diseases
2 Examinations and signs	~~C Endocrine, nutrition, and metabolic disease~~	N Musculoskeletal and connective tissue diseases
~~3 Diagnostic procedures~~	~~D Blood and blood forming organs' diseases~~	~~P Congenital anomalies~~
~~4 Laboratory procedures~~	E Mental and behavioural disorders	~~Q Perinatal conditions~~
~~5 Radiology~~	F Nervous system and sense organ diseases	R Symptoms, signs and ill-defined conditions
~~6 Preventative procedures~~	G Circulatory system diseases	~~S Injury and poisoning~~
~~7 Operations, procedures, sites~~	H Respiratory system diseases	~~T Causes of injury and poisoning~~
~~8 Other therapeutic procedures~~	J Digestive system diseases	U External cause of morbidity and mortality
~~9 Administration~~	K Genitourinary system diseases	Z Unspecified conditions

- The remaining codes from Chapters 1 / 2 and chapters E, F, G, H, J, K, M, N, R, U and Z were examined further and all codes related to organic disease, injuries, poisoning or were clearly unrelated to MUS were removed.

- This resulted in a list of non-specific history, complaint, symptom, diagnosis or referral codes suggestive of MUS and they were included into the MUS related Symptom codes list.
- These codes were categorised into seven categories: gastrointestinal, cardiac/respiratory, genito-urinary system and musculoskeletal systems, neurological symptoms, fatigue and miscellaneous.
- Read codes that refer to symptoms that could indicate MUS in body systems other than the systems mentioned above were included in the miscellaneous group. Literature indicated sleep disturbances, difficulty concentrating, pruritus, whiplash and other sensory related disorders as commonly seen MUS related symptoms. Codes related to sweating, feverishness / cold / flushing and other general complaints that could indicate MUS were added to the list.

7.3.1.3 Study design: validation of code list generation process and code lists

- There were no queries from the panel (details of panel in chapter 5.4), on the MUS specific codes list generated except on one obvious error, which was corrected. On the advice of the panel, all MUS specific codes that had been used less than five times in the database were removed, as a measure of good practice in EHR data research.
- The few queries on the categorisation of symptoms in the MUS related Symptom code list were resolved in a group meeting where consensus was achieved through discussion. The queries raised were mostly related to categorisation of symptoms: the category 'pain' was cancelled and a new category musculoskeletal system was

created. The pain codes were categorised into the respective bodily system, and those that did not fit in any of the key bodily systems were placed in a miscellaneous category. There were 18 symptom codes which had been included in the miscellaneous category previously (e.g., codes denoting stiffness, discomfort), which in the opinion of the panel were better placed in the musculoskeletal system category, and were changed accordingly.

7.3.3 RESULTS

7.3.3.1 MUS Specific Read code list: A list of 55 MUS specific Read codes were found used in the primary care database to record GP-defined patients with MUS, given in Appendix 7.2. Twenty-one Read codes used to record Symptom syndromes – IBS, Fibromyalgia and Tension headache, were the most frequently recorded. There were 18 different diagnostic codes used to record morbidities GPs identified as specific psychogenic, functional or somatoform conditions such as functional constipation and psychogenic hyperventilation which were the most frequently recorded. The remaining 16 codes denoted conditions that were diagnosed as generic medically unexplained conditions, hypochondria or psychosomatic conditions.

7.3.3.2 MUS related Symptom Codes list: A list of 562 MUS related Symptom codes were found recorded in the database, of which the most frequently recorded were codes for abdominal pain, low back pain and headache. These codes were categorised in to seven mutually exclusive groups, provided in Appendix 7.3. under the different subcategories.

Table 7.5: No. of MUS related symptom codes in seven mutually exclusive groups	
	No. of different MUS related Symptom codes recorded in database
Musculoskeletal system	153
Gastrointestinal symptoms	116
Miscellaneous	89
Neurological symptoms	83
Cardiac/Respiratory symptoms	59
Genitourinary system symptoms	45
Fatigue	17
Total	562

As shown in Table 7.5, MUS related symptom codes recorded for Musculoskeletal system symptoms were the most frequent, 153 codes. There were 116 MUS related symptom codes recorded for gastro-intestinal symptoms and 83 MUS related symptom codes for neurological symptoms; MUS related symptoms codes for cardiac and respiratory system symptoms were recorded using 59 different codes.

7.4 Code lists for investigations, chronic organic disease, referrals and vulnerability

These code lists were prepared by the researcher in consultation with the lead supervisor. The lead supervisor carried out the first review and the panel then reviewed and approved the code lists.

The data was searched for records of non-pharmacological treatment options for MUS for these patients; however, except for the code for Cognitive Behavioural therapy recorded 43 times over the 16- year period of primary care database records, there were no meaningful

numbers of records of such treatment, and therefore the search for treatment given to MUS patients was cancelled.

7.4.1 INVESTIGATIONS

It was necessary to develop a code list to find out what investigations were carried out for MUS patients. These codes are found in chapters 3-8 in the Read code system. Read code system Chapter 9 includes records of results reports of these investigations .

Table 7.6: Read code chapters where investigations are recorded
3 Diagnostic procedures
4 Laboratory procedures
5 Radiology
~~6 Preventative procedures~~
7 Operations, procedures, sites
8 Other therapeutic procedures
9 Administration

All codes from these chapters 3-5 and 7-9 found in the 10,352 Read code list mentioned above were reviewed to collate a list of all investigation codes used in the primary care database. The list was submitted to the panel for validation and a list of 650 Read codes used to record investigations in the database, was finalised after removing 25 codes that had been erroneously included. This code list, given in Appendix 7.4, was used to record the number and type of investigations carried out for MUS patients in chapters 8 and 9 and to calculate the costs of MUS patients in chapter 12.

7.4.2 REFERRALS

Similar to analysing the investigations that were carried out on these patients, it was necessary to develop a code list to find out how frequently MUS patients were referred for further care. These codes are found in Chapter 8 in the Read code system. The 10,352 Read codes used most frequently on the CiPCA database (each used $\geq$ 10 times) were analysed and all the codes starting with the number 8 denoting referrals for further care were separated out into a list submitted to the panel for validation. Codes clearly unrelated to MUS were excluded (e.g., codes relating to obstetrics), and the finalised list is given in Appendix 7.5, along with the costs for each referral during 2007-2014, used to calculate the costs of referrals for MUS patients in Chapter 11.

7.4.3 CHRONIC ORGANIC DISEASE

Frequent consultations were found to be highly correlated with the presence of MUS in the systematic review and evidence summary. However, in some patients, the high consultation rate may be due to the presence of chronic organic disease, and such patients need to be excluded from the study population of patients with MUS.

Chronic organic diseases identified as causing high consultation frequency in the literature are mainly chronic respiratory problems and chronic cardiovascular disease (Smits et al, 2016; Santalahti et al, 2021). The den Boeft study (2014) excluded patients with chronic obstructive pulmonary disease, hypertension or diabetes mellitus to isolate MUS patients.

Presence of organic disease is assessed in this study to exclude patients with chronic disease when identifying potential MUS patients based on consultation frequency and to assess if

there is misdiagnosis of chronic organic disease as medically unexplained symptoms. Therefore, all diseases and records of chronic organic disease that can cause increased consultation rates are included in the list. Other studies on the prevalence of MUS excluded patients with organic illness by removing all patients with a record of a medical diagnosis defined for example as an ICPC-code >70 in the Verhaak study on persistent presentation of MUS in general practice (2006). However, relying on such a blanket exclusion was not possible in this study since some cases in this database indicated the presence of organic illness using history codes rather than diagnosis codes for example (1Z codes for chronic kidney disease). The 10,352 Read codes used most frequently on the CiPCA database (each used $\geq$ 10 times) were analysed and all the codes denoting chronic organic disease were separated out and are given in Appendix 7.6.

Depression and anxiety too have been identified as causing high consultation rates, however, mental health issues are also highly prevalent among MUS patients, therefore patients with these mental health codes are retained within the study and analysed separately.

7.4.4 READ CODES TO RECORD MENTAL HEALTH / PSYCHOLOGICAL ISSUES

To assess the frequency of consultations for mental health conditions during the study period, a list of all mental health codes on record in the CiPCA database was collated. Preparation of the mental health code list was based on the comprehensive list of mental health codes used in the primary care database provided by the custodians. The 30,406 Read codes that were used in the CiPCA database during 2000-2015 was checked and all

codes that had been used to record mental health issues in the database resulted in the comprehensive list of 1,102 mental health codes in Appendix 7.7.

7.4.5 VULNERABILITY

Qualitative research findings indicated that patients with MUS can have a history of childhood, domestic or sexual abuse or substance abuse (Katon et al, 2001; Lowe et al, 2008). Although these issues are not always disclosed to a GP or recorded in a database, the Read code system has specific codes to record such trauma, and this study created a list of such codes to assess the frequency of such records in the defined study population. The 10,403 codes used >=10 were analysed to collate the list, given in Appendix 7.8. Codes indicating vulnerability in any form, childhood, domestic or sexual abuse, drug addiction and suicide attempts (except Read codes starting with an E, in the E chapter of Mental health related problems, which are already included in the mental health related codes), homelessness, asylum seekers, torture victims were all included in this list.

7.4.6 USE OF DIAGNOSTIC INSTRUMENTS TO DIAGNOSE MUS

The systematic review and evidence summary were used to collate a list of diagnostic instruments used to diagnose MUS (Hiller & Janca, 2003; Sitnikova et al, 2017), in order to check if there were records of GPs using diagnostic instruments to identify MUS patients (Table 7.7). Some of these (SCID, CIDI, IDCL, SDS, SCAN and PRIME-MD) are primarily used for classification, others for screening (SOMS-7) and for symptom severity (BSI, WI).

Table 7.7: Diagnostic instruments available to diagnose MUS	
Patient Health Questionnaire (PHQ-15) Four-Dimensional Symptom Questionnaire (4DSQ) Somatisation subscale Bodily Distress Syndrome checklist Physical symptom checklist (PSC-51) Symptom Check List (SCL-90-R) SOMS-7 Bradford Somatic Inventory (BSI) Whitely Index/Illness Attitude Scales (WI/IAS)	Structured Clinical Interview for DSM-IV – somatoform disorder subscale (SCID) Composite International Diagnostic Interview (CIDI) – somatoform disorder subscale – Somatoform Disorders Schedule (SDS) International Diagnostic checklists (IDCL) Primary Care Evaluation of Mental Disorders (PRIME-MD) Health Anxiety Questionnaire (HAQ)

7.4.7 VALIDATION OF INVESTIGATIONS, REFERRALS, CHRONIC ORGANIC DISEASE, MENTAL HEALTH AND VULNERABILITY CODE LISTS

The code list selection was verified by the lead supervisor (list of 10,352 codes) and the selected code list was then validated by the custodian panel of the primary care database.

7.5 Conclusions and Next steps

This chapter detailed the processes of deriving code lists for i) MUS specific Read codes used where GPs had diagnosed a patient as MUS, and, ii) MUS related Symptom codes, which are non-specific codes that could potentially indicate a patient with MUS, informed and supported by the findings of the systematic review in chapter 6 and a further evidence summary.

The next chapter, Chapter 8, describes the process of how the MUS specific Read code list developed in this Chapter 7 was used to define the study population of GP-diagnosed MUS patients and to analyse their data for five years including the index year.

CHAPTER 08
GP-DIAGNOSED MUS PATIENTS

8.1 Background

The selection of patients is informed by the findings of the systematic review in Chapter 6, and the evidence summary described in Chapter 7. The findings indicated that GPs record MUS patients either with a specific diagnosis using MUS specific Read codes or record MUS-related Symptom codes without giving a definite diagnosis of MUS. Younger age, and high consultation frequency had the most significant correlation with the presence of MUS in patients. This chapter defines and describes the patients who receive a MUS diagnosis from their GP, 'GP-diagnosed MUS patients' and the next chapter, Chapter 9 will describe patients who did not receive a MUS diagnosis from their GP, but are potentially MUS patients.

MUS is seen more commonly in younger adults, therefore adult patients aged =<55 years were included in defining the study population for MUS (Smith 2001); age is negatively correlated with the presence of MUS in patients (Morriss, 2012). This is also due to the presence of chronic conditions (e.g., diabetes, heart disease) being known to increase in line with age; for example, Walker et al (2016) found that chronic conditions occur more frequently after 55 years. It is not possible to differentiate if the symptoms displayed are due to MUS or due to the chronic conditions or both and the presence of chronic conditions

can directly increase the consultation, investigation and prescription information that this study aims to assess for MUS patients. The upper age limit was set at 50 years to limit the confounding impact on the data from chronic co-morbid diseases: for example, the increase in consultation rate in a patient with MUS such as IBS may be due to a comorbid condition such as heart disease rather than due to the IBS.

There is no generally accepted definition of frequent attendance (Vedsted & Christensen, 2005) and frequent attenders have been identified in the literature in one of two ways: using a cut-off point in the number of visits e.g., >10 visits (>=8, Smith et al, 2009; >=5, den Boeft et al, 2014) or using a cut-off point in the distribution of number of consultations in the given patient population – e.g., top 10%, top quartile (top 3%, Smith et al, 2008; top 10%, Luppa et al, 2020).

8.2 Aims and objectives of the chapter

This chapter aims to use the MUS specific Read code list developed in Chapter 7 and the other criteria derived from the systematic review such as age and comorbid organic disease to define the study population of GP-diagnosed MUS patients and to analyse their data for five years including the index year.

The real-life data on consultations, investigations and referrals for these GP-diagnosed MUS patients is used to assess the extent to which data from a large consulting population can help to support (or refute) the findings in Chapter 4 from qualitative research.

The specific objectives of this chapter, are to generate the following data for GP-diagnosed MUS patients as described in Table 5.3, Qualitative evidence of MUS related factors

compared to real-life data, to assess to what extent this real-life data supports the qualitative research findings.

1. Calculate incidence rate per 1000 population for each of years 2007 – 2010 using no. of patients with a GP recording of MUS Specific Read code.

2. Assess the extent to which the use of diagnostic tools (e.g. PHQ-15, and those given in Chapter 7.4.6) is recorded in the primary care database.

3. Determine socio-demographic characteristics of this patient group: Patient count male/female, age distribution of patients, Socio-economic status as measured by the English Indices of Multiple Deprivation ranking.

4. Determine the number of patients for whom investigations and referrals have been carried out to support diagnosis and management.

5. Determine the number of consultations per patient per year.

6. Determine the percentage of patients with a mental health / psychological issue related code on record.

7. Determine the number of patients with a record of childhood, sexual or domestic abuse

8. Determine the percentage of patients who continue to have an MUS-specific Read code recorded for five years (index year + four years).

9. Determine the number and percentage of patients who are diagnosed with organic disease within five years (index year + four years).

8.3 Methods

8.3.1 DERIVATION OF STUDY POPULATION

The study targeted selecting new patients who were recorded by their GPs as MUS patients in each year. Patients who had a new record of one or more of the 55 codes in the MUS Specific Read code list derived in the previous section recorded during the years 2007 to 2010 were considered for the study. A wash-out period of two years was applied – i.e. only patients who did not have an MUS code on record for two years prior to the index year were selected, to ensure that the cases selected in each year were all new cases (for example, a patient with a record of a MUS specific Read code in 2007 was not selected for the study if there was a record of a MUS specific Read code in either 2005 or 2006). The patients' records for five years including the index year were analysed.

The CiPCA data manager (James Bailey) carried out the initial patient selection, using the following inclusion criteria for each of the years 2007 to 2010.

- All patients aged 18-50 years during the relevant index year, based on year of birth (e.g., Year of birth between 1957 and 1989 for the patients selected in the index year 2007)
- Patients registered with the practice for at least two years prior to and five years including the index year (i.e. for 2007 patients, registered at least since 2005 and until at least 2011)

- Patients who have at least one of the list of 55 MUS Read codes identified in chapter 6 above recorded during the index year (e.g. for 2007, at any time during 2007) indicating that the patient was diagnosed by a GP as a MUS patient
- Patients who did not have any of the 55 MUS Read codes recorded during the two preceding years from the index year (i.e. for 2007 patients, no MUS Read codes recorded in 2005-2006)
- Patients who did not have any of the chronic organic disease Read codes listed in Appendix 7.6 in the index year

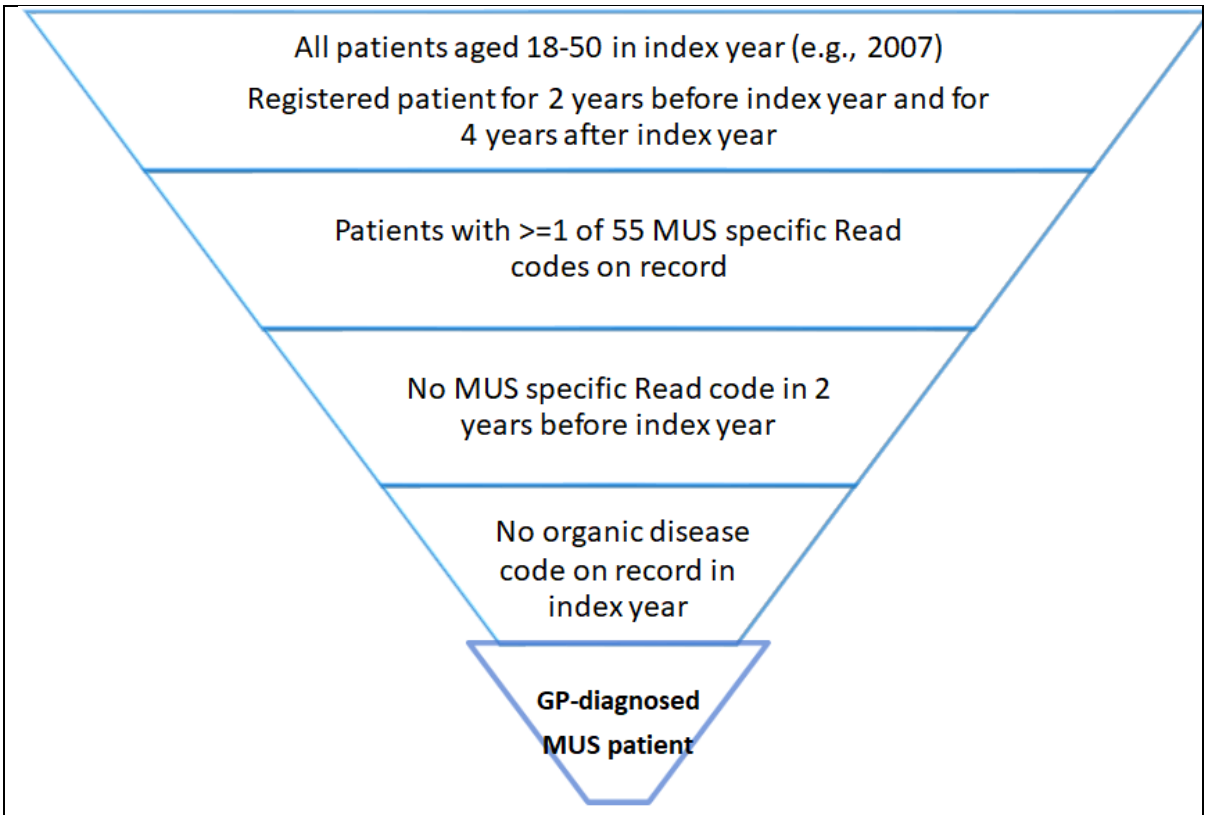


Figure 8.1: Process of deriving list of GP-diagnosed MUS patients

Data cleansing and checking the accuracy of the data search was carried out to ensure that only the relevant codes were included, and that the washout period and the age

requirements were met. For all patients meeting the above criteria, the following data was obtained from the CiPCA database.

- Patient code (unique code assigned to each patient)
- Year of birth
- Date of registration and date of end of registration (if already ended)
- Code for GP Practice where the patient is registered (1-9)
- Index of Deprivation (the English Indices of Multiple Deprivation 2015
- Referral data
- Consultation data: date of consultation, Read code, Read term, Job category of healthcare practitioner (HCP), consultation code.

The electronic clinical records from the CiPCA database were provided by the CiPCA data manager in four separate files: 1)Patient information – Unique anonymised patient identifier, sex, year of birth, date of registration, date of end of registration where relevant, code of GP practice and Indices of Multiple Deprivation ranking 2) The consultation data – with the date of consultation, Read code, description, job category, event value, event unit and consultation code 3) Referral data. Patients were matched using the unique identifier on the patient information file and the consultation / referral data files for this section.

8.3.2 DATA ANALYSIS

Data was analysed using SPSS for Windows 2018 and Excel 2019. The patient population was described using descriptive statistics. Consultation data of these patients for five years, index year + 4 years, were obtained and the following were assessed.

Incidence: For each of the years 2007-2010 the incidence rate per 1000 population is calculated using the number of new cases during the year as the numerator and the population at risk during the same time as the denominator – i.e. the number of registered patients aged 18-50 years during that year.

Diagnosis related: The 30,406 Read code list was checked to find out if any of the diagnostic tools for MUS (e.g., PHQ-15, 4DSQ), were found recorded in the primary care database and if so, how frequently.

Socio-demographic characteristics: The baseline characteristics of age and gender were established. Assessing socio-economic status was based on the English Indices of Multiple Deprivation 2015 (IMD). The IMD ranks 32,844 Lower-layer Super Output Areas in England (small areas of relatively even size containing approximately 1,500 people) according to their Deprivation score, with the most deprived area given a rank of 1, and the least deprived area a rank of 32,844. Deprivation is measured based on seven weighted domains of Deprivation: income (22.5%), employment (22.5%), health deprivation and disability (13.5%), education, skills and training (13.5%), barriers to housing and services (9.3%), crime (9.3%) and living environment (9.3%).

Investigations recorded: The code list used to record investigations (as described in 7.4.1) was checked against patient records for five years (Index year + 4 years), to determine the type and frequency of investigations carried out.

No. of consultations per year: Each consultation has a separate code recorded on the database. The unique, anonymised patient identifier data was matched against the consultation code list for each year 2007-2010 to find out the number of consultations per

patient per year. Multiple records under the same consultation code were considered to be a single consultation. Consultations carried out by GPs and those by other staff categories were counted separately. The number of consultations per patient were counted for the Index year (which is the first year a patient is diagnosed by a GP, or by the EHR-defined search mechanism, as a MUS patient), and for five years including the index year.

Comorbid mental illness: The consultation records of the GP-diagnosed MUS patients were examined to see if they had any of the 1,102 mental health codes recorded

1. At least once during the seven years of the study
2. At least once during the two years prior to diagnosis
3. At least once during the index year (year of diagnosis)

Vulnerability: The code list used to record history of childhood, domestic or sexual abuse, drug abuse and other indications (as described in chapter 7.4.5) was checked against patient records for five years (Index year + 4 years), as an indicator of a patient being in a vulnerable state.

Disease perpetuation: The percentage of patients who continue to have an MUS/symptom code recorded for each of 5 years from diagnosis (Index year + 4 years), were checked.

8.3.3 MISSING DATA

Complete case analysis was carried out – including only patients who had remained registered with the practice for at least five years starting from the index year. Imputation (single or multiple) in this case could result in distortion of data by overestimating for example the number of patients or the conditions that they have, and negate the purpose

of the study, which aims to assess the on-the-ground realities of the MUS patients' consulting behaviour. Furthermore, data cannot be imputed for people who had died during the five years. There was no data available to find out whether in the final year of available data if the patient had 1) ended the registration with the practice or 2) died. Therefore, complete case analysis was decided to be the best option. All patients with an end of registration date within five years of the index year were excluded from the study.

8.4 Results

The consultation data search had generated 6.84 million lines of data on these patients, which were matched with the patient information using the unique patient identifier.

667 patients who had a MUS Specific Read code recorded by their GP in each year during 2007-2010 and who had four years of data after the index year (five years of data in total) on record were included in the study population.

Table 8.1: No. of GP-diagnosed MUS patients each year, gender and mean age

No. of new patients meeting criteria for "GP-diagnosed MUS patient " each year			Total no. of patients 18-50 years in database for the given index year	Incidence rate of GP-diagnosed MUS patients per 1000 registered population aged 18-50 years
2007	168		37,338	4.5
2008	158		37,522	4.2
2009	161		37,910	4.3
2010	180		37,873	4.8
Total	**667**		**Mean 2007-2010**	**4.4**
Gender	No. of patients	Percentage		**Age**
Female	493	74%	Mean age	35.0
Male	174	26%	Standard deviation	8.8

Of the 667 patients, 74% were female, the mean age was 35 years with a standard deviation of 8.8. The number of patients newly diagnosed by a GP in each index year was compared

to the total number of patients aged 18-50 years in the database; this indicated that 0.4% to 0.5% of the total population were newly diagnosed each year as MUS patients.

8.4.1 GP-IDENTIFIED MUS PATIENTS – RECORDED CONDITIONS

The study analysed the codes that were recorded during the index year for the GP-diagnosed MUS patients, some of these patients had multiple MUS codes on record, which were counted separately for this purpose. The vast majority of patients, 67%, were recorded with Gastroenterology related symptoms – primarily with IBS. Most patients were recorded with a symptom syndrome: 61% of patients were recorded as suffering from Irritable Bowel Syndrome (IBS) related conditions using the codes J521-1 for Irritable Bowel Syndrome, J521 for Irritable Colon – Irritable Bowel Syndrome, and J5210 for Irritable Bowel Syndrome with diarrhoea. Atypical chest pain was the second most frequently recorded condition, in 11% of patients, 6% of patients with Fibromyalgia and another 1% with Chronic Fatigue Syndrome related conditions as seen below in Figure 7.2. Temporomandibular joint (TMJ) pain-dysfunction syndrome was recorded in 3% of the patients.

Table 8.2: Most common terms used for GP-diagnosed MUS patients in CiPCA 2007-2010

System (example)	No. of patients recorded	Percentage
Gastroenterology (Irritable Bowel Syndrome)	473	67%
Cardiology (Atypical chest pain)	81	11%
Rheumatology (Fibromyalgia)	46	6%
Dentistry (TMJ pain-dysfunction syndrome)	23	3%
Gynaecology (Premenstrual tension syndrome)	16	2%
Ear, nose, and throat (Globus hystericus)	16	2%
"Medically unexplained" (“Worried Well”)	14	2%
Pain (Hypochondrial pain)	13	2%
Neurology (Tension headache)	9	1%
Chronic Fatigue	9	1%
Adjustment/Body Dysmorphic disorders	9	1%

There are records of 89 patients where GPs attributed psychogenic causation to the presenting complaints such as functional constipation, psychogenic dyspareunia. Generic or collective terms for medically unexplained symptoms such as adjustment disorders and terms such as “worried well” were also used to record these patients.

Diagnostic tools: Other than the short health anxiety inventory, of which the use was recorded less than five times in the entire database in over 15 years, there was no record of any diagnostic tool used for MUS (e.g., PHQ-15, 4DSQ) recorded in the database.

8.4.2 SOCIO-DEMOGRAPHIC CHARACTERISTICS – GENDER, AGE, SOCIO-ECONOMIC STATUS

8.4.2.1 Age

The number of patients per age group increased with age. The age group of 31-40 years accounted for 34% and 41-50 years accounted for 39% of the patients (Figure 8.2).

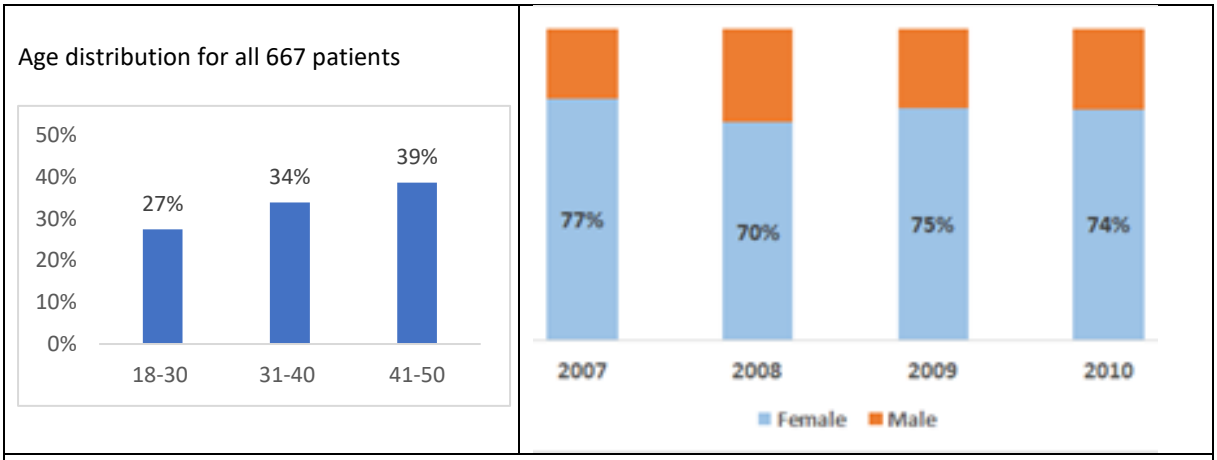


Figure 8.2: GP- identified MUS patients – age and gender distribution

8.4.2.2 Gender

Of the 667 GP-diagnosed MUS patients, 26% were male and 74% female. This distribution was similar across all index years with 74%-77% of the patients being female (Figure 8.2).

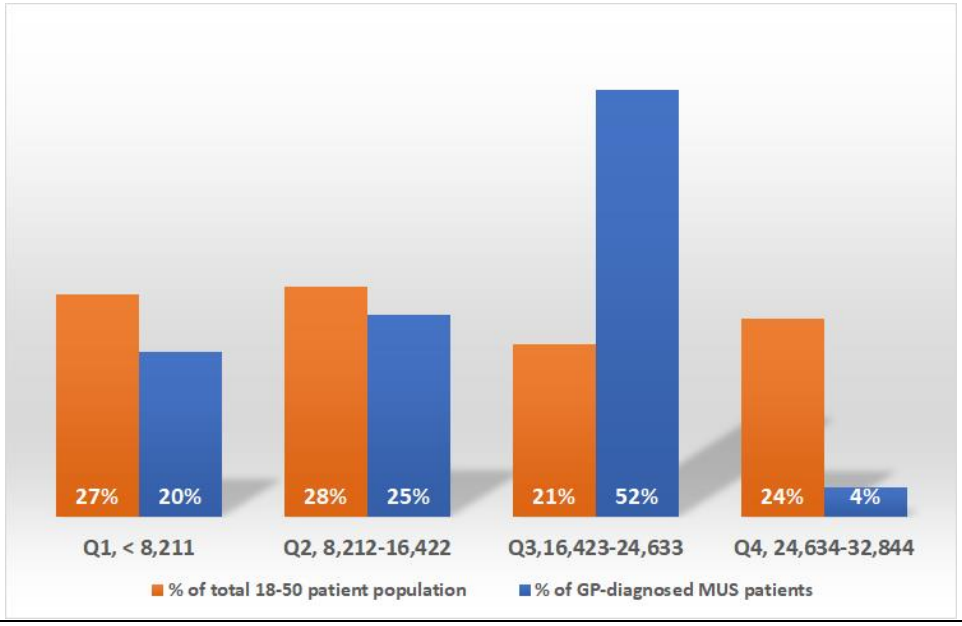


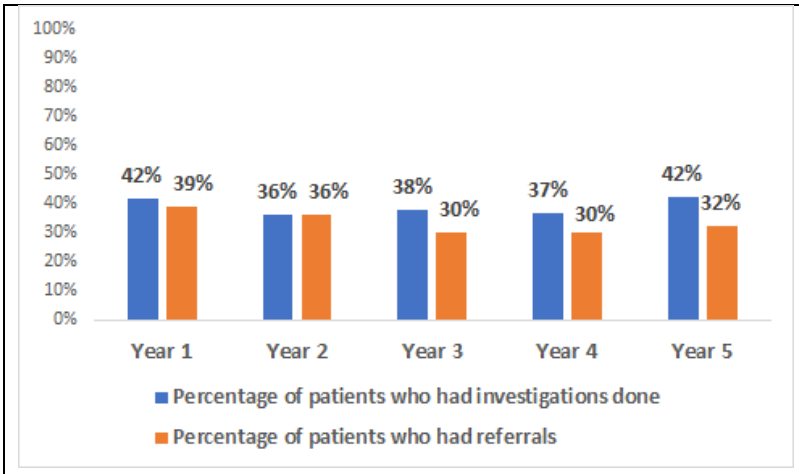
Figure 8.3: GP-diagnosed MUS patients –77% in 2nd or 3rd quartile of Deprivation index

8.4.2.3 Socio-economic status

Assessing socio-economic status is based on the English Indices of Multiple Deprivation 2015 (IMD), ranging from 1-32844. Based on the IMD ranking, the patients were grouped into quartiles: 20% of the GP-diagnosed MUS patients were found in the most-deprived quartile, whereas 27% of the total population aged 18-50 years in the primary care database were in this lowest quartile (Figure 8.3). The majority, 77%, of the patients were in the second and third quartiles and 4% of the patients were in the least deprived quartile, compared to 24% in the fourth quartile out of the total population aged 18-50 years in the database.

8.4.3 INVESTIGATIONS AND REFERRALS CARRIED OUT

Of the GP-diagnosed MUS patients, 42% had investigations carried out and 39% had referrals in the index year to support the diagnosis and management of MUS, and ranged over 30% - 42% over the next four years. Of these patients, 17% had no investigations carried out over the entire five years, and 21% had no referrals during the period.



No investigations carried out during five years: **17%**

No referrals made over five years: **21%**

Figure 8.4: GP-diagnosed MUS patients – % who had investigations and referrals

The most common investigations were urine testing, cervical smears, x-rays and ultrasound scans. This data was used to calculate total costs incurred by these patients in Chapter 11.

8.4.4 CONSULTATION FREQUENCY

The mean number of consultations per person per year over the five-year period (index year + 4 years) ranged from 1 to 45, excluding one extreme outlier (Figure 8.5). Of these patients, 30% had between 6-10 consultations per year during the five years and 28% less than five consultations per year. Thus, 58% of the patients had 10 consultations or less per year over the five years, whereas the most frequent consulting 10% of the patients, had a mean annual consultation rate of over 20 consultations each.

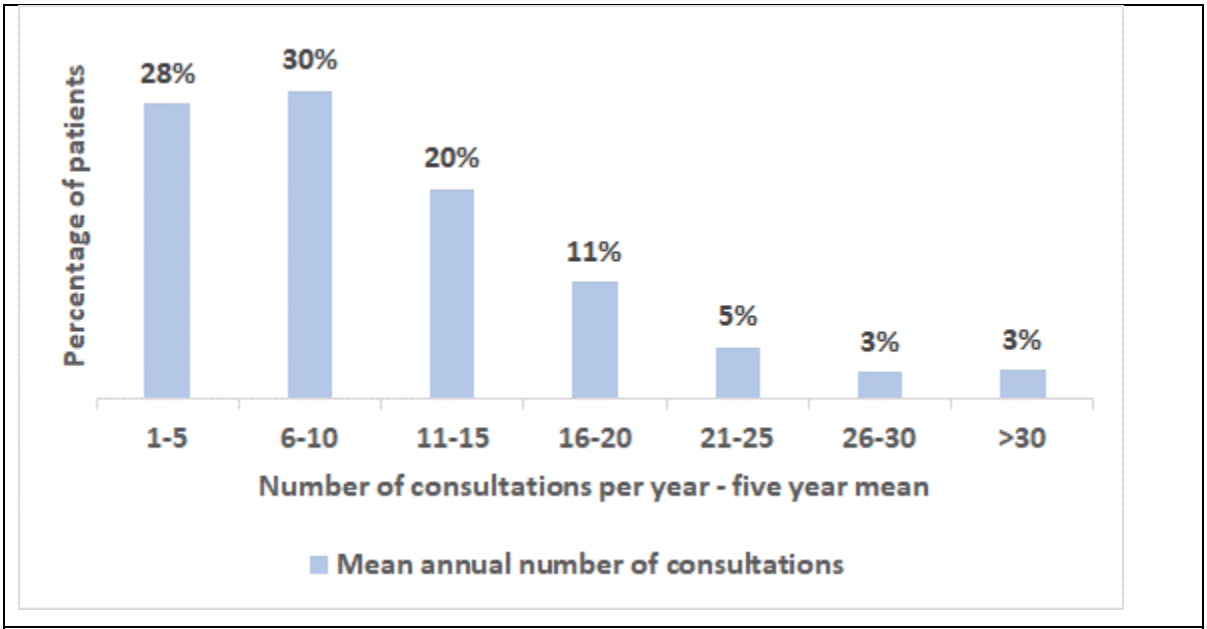


Figure 8.5: GP-diagnosed MUS patients: Mean number of consultations per year over five years

The mean number of consultations per year was 12 in the index year, reduced to 10 by the third year, and then increased again to 12 by the fifth year, as seen below in Table 8.3. Overall, the mean number of consultations remained at 11 over the five-year period.

Table 8.3 GP-diagnosed MUS patients: Mean number of consultations, index year + four years

		Index year	Year 2	Year 3	Year 4	Year 5
Patient group	2007	12	11	11	11	12
	2008	12	12	11	12	14
	2009	13	11	10	11	11
	2010	11	9	9	10	11
Mean		**12**	**11**	**10**	**11**	**12**

8.4.5 ASSESSING THE PRESENCE OF COMORBID MENTAL HEALTH ISSUES IN GP-DIAGNOSED MUS PATIENTS

As seen in Figure 8.6, out of the 667 GP-diagnosed MUS patients, 425 patients, 64% of the total, had at least one mental health or psychological issue related Read code on record during the 7-year period of the study (five years of study + 2 years prior to index year washout period). 68% of the female patients had at least one mental health code on record

(335 out of 493 female patients), whereas only 52% of the male patients did so (90 out of 174 male patients).

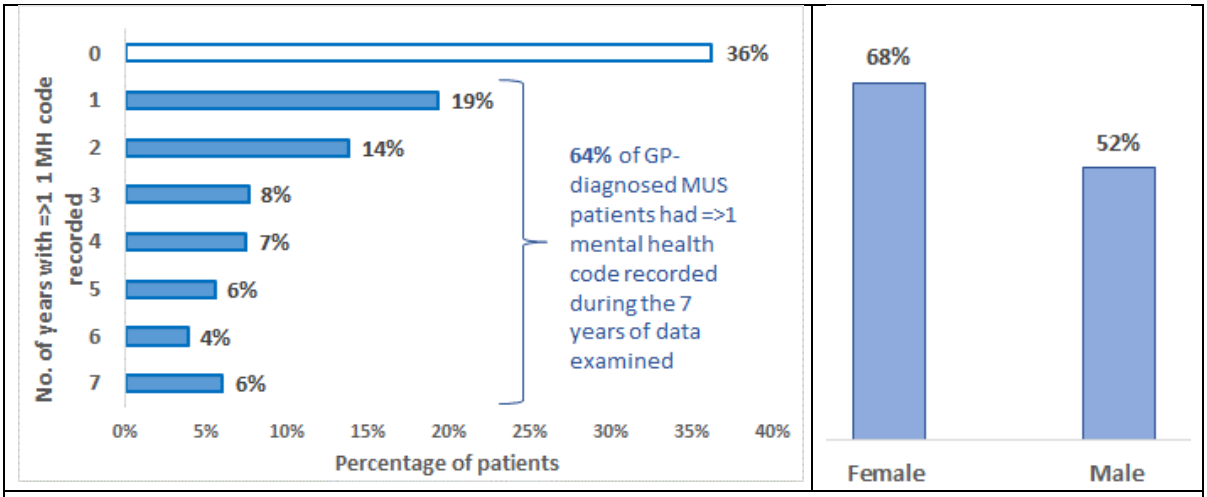


Figure 8.6: GP-diagnosed MUS patients with mental health issues during the 7-years of the study

Out of the 667 GP-diagnosed patients, 32% (216 patients) also had a mental health Read code on record during the Index year. 36% of the patients had at least one mental health Read code recorded during the two years prior to the Index year.

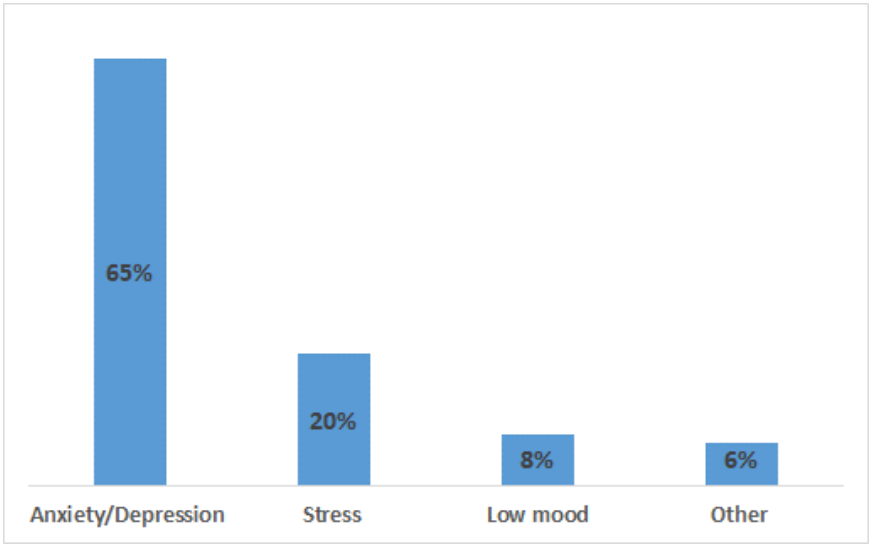


Figure 8.7: Complaints of patients with mental health issues in index year

As shown in Figure 8.7, of the 216 patients who had a mental health Read code on record in the index year i.e., the year of their diagnosis, 65% had a mental health issue that was related to anxiety and / or depression. 20% of the patients had a stress-related complaint and 8% a complaint related to sadness/low mood.

8.4.6 VULNERABILITY

Out of the 667 GP-diagnosed MUS patients over 2007-2010, less than five patients had at least one record of domestic violence or sexual abuse.

8.4.7 DISEASE PERPETUATION: NUMBER OF YEARS AS A MUS PATIENT FIVE YEARS AFTER DIAGNOSIS

The percentage of patients who had an MUS code recorded declined steadily in the years that followed the index year; 23% of the patients had a MUS code recorded in Year 2, and this percentage declined to 13%, in the fifth year. The pattern was however erratic, for example, some patients had no MUS code in Years 2 and 3 and but had one in Year 4. There were 417 patients (63%) who had a MUS specific Read code recorded only during the index year, and no MUS code recorded at all during the next four years.

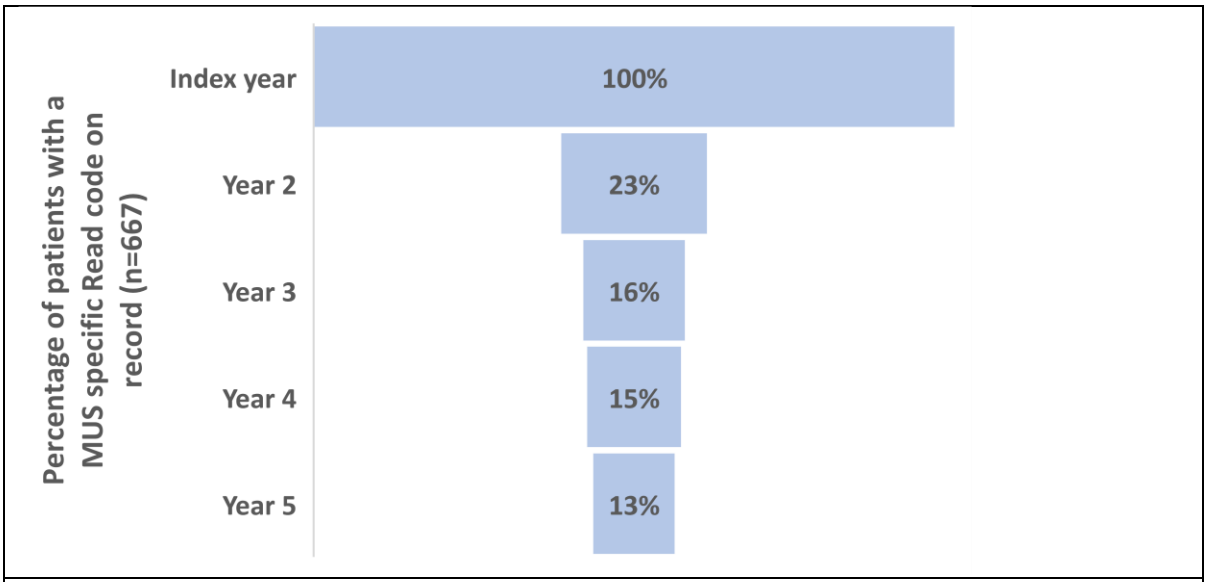


Figure 8.8: GP-diagnosed MUS patients – Percentage of patients with a MUS specific Read code recorded during the five years of the study period

8.4.8 PATIENTS DIAGNOSED WITH ORGANIC DISEASE WITHIN FIVE YEARS OF RECEIVING AN MUS DIAGNOSIS

Of the 667 GP-diagnosed MUS patients, 7% received a diagnosis of an organic disease in the year after the index year – Year 2; 22% in the four years that followed (Figure 8.9).

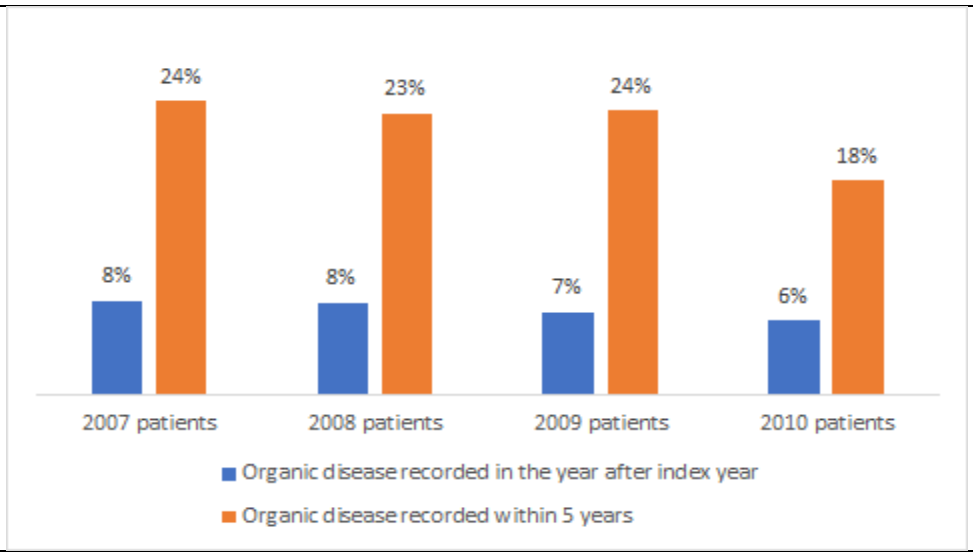


Figure 8.9. GP-diagnosed MUS patients with organic disease diagnosis - Year 2, within 5 years

8.5 Conclusions and next steps

This chapter described the process of using the MUS specific Read code list to define the study population of GP-diagnosed MUS patients – i.e., patients recognised and recorded by their GPs as patients with MUS, and the analysis of their consultation data to assess factors related to the diagnosis and management of these patients in real life. Records of 667 newly diagnosed MUS patients during 2007 – 2010 in the age group of 18-50 years, without any chronic disease in the index year were taken from the database. Of these patients, 74% were female, and 52% were in the third quartile of the English Indices of Multiple Deprivation. Irritable Bowel Syndrome was the main condition diagnosed in 67% of the patients, and secondly, atypical chest pain (11%). They had a mean annual consultation rate per patient of 12 in the index year and a five-year mean consultation rate of 11 consultations. Of these patients, 77% had a MUS specific Read code only during the Index year, 13% continued to have a MUS specific Read code recorded each year for five years,

22% were subsequently diagnosed with an organic illness within the five-year period, and 64% had a mental health or psychological issue related Read code on record at some point during the study period. Interpretation of these findings, including if and to what extent they support the findings of the qualitative research is discussed in Chapter 10.

The next chapter, Chapter 9, uses information from the systematic review and the evidence summary, and the MUS-related Symptom code list to derive a mechanism to define patients in the primary care database who potentially have MUS but haven't had their illness named by a GP, and to analyse their data for five years, similar to the analysis for the GP-diagnosed MUS patients.

CHAPTER 09
EHR-DEFINED PATIENTS WITH MUS

9.1 Background

As discussed in Chapters 3 and 4, patients do not always receive a MUS diagnosis from their GP. The systematic review findings indicated that such potential MUS patients, who do not have a record of a MUS diagnosis by their GP, but have only symptom codes on record, might be found through electronic health record analysis, by searching for young age, high consultation frequency and MUS-related symptom code records, the factors which have the most significant correlation with the presence of MUS in patients (Smith et al, 2009; Morriss, 2012; den Boeft, 2014). A recent study in 2021 confirmed these findings, that patients with MUS (termed Persistent Somatic Symptoms) can be identified from EHR databases using high consultation rate (=>6 consultations over six months), and records of MUS related symptom codes; the study used codes based on the Robbins list mentioned above in Chapter 7.2 (Kitselaar et al, 2021).

The analysis presented in this chapter aims to define undiagnosed MUS patients in the EHR database using the criteria of age, high consultation frequency and records of MUS-related symptom codes. It will then analyse the real-life data of these 'EHR-defined MUS patients' for five years including the index year, on consultations, investigations and referrals, to assess the extent to which data from a large consulting population can help to support (or refute) the findings from qualitative research.

9.2 Aims and objectives of the chapter

The specific objectives of this chapter are to generate the following data for GP-diagnosed MUS patients as described in Table 5.3, Qualitative evidence of MUS related factors compared to quantitative, real-life data, to assess to what extent this real-life data supports qualitative research findings.

1. To define the study population of 'EHR-defined MUS patients'.

2. To describe the process of distilling EHR data to derive the study population.

3. To analyse the consultation data of these patients for the outcomes:

i. Calculate incidence rate per 1000 population for each of years 2007 – 2010 of potential MUS patients using the number of EHR-defined MUS patients.

ii. Determine the number of patients with MUS related symptoms codes who are subsequently diagnosed as MUS patients with a MUS-specific Read code recorded.

iii. Determine socio-demographic characteristics of this patient group: Patient count male/female, age distribution of patients, socio-economic status as measured by the Indices of Multiple Deprivation ranking.

iv. Determine the number of patients for whom investigations and referrals have been carried out to support diagnosis and management.

v. Determine the number of consultations per patient per year.

vi. Determine the percentage of patients with a mental health / psychological issue related code on record.

vii. Determine percentage of patients with a Read code related to abuse.

viii. Determine the percentage of patients who continue to have an MUS code recorded for five years (index year + 4 years).

ix. Determine the number and percentage of patients who are diagnosed with organic disease within five years (index year + 4 years).

9.3 Describe study population of 'EHR-defined MUS patients'

Based on the findings of the systematic review and the evidence synthesis carried out, this study describes a EHR-defined MUS patient using the criteria of age, high consultation frequency and records of MUS-related symptom codes.

Age: As discussed in Chapter 7, the age limit was set at 18-50 years.

High consultation frequency: There is no generally accepted definition of frequent attendance (Vedsted & Christensen, 2005) and frequent attenders have been identified in the literature in one of two ways: using a cut-off point in the number of visits e.g., >10 visits (>=8, Smith et al, 2009; >=5, den Boeft, 2014) or using a cut-off point in the distribution of number of consultations in the given patient population – e.g. top 3%, Smits et al, 2016; top 5%, Reid et al, 2001; top 10%, Luppa et al, 2020. This study uses the top 10% of patients with the highest number of consultations in each GP practice as the criterion to define the frequent consulters to ensure selecting the most frequent consulters whilst avoiding the impact from variation in recording habits between practices. A key reason for selecting the top 10% of most frequent consulters (rather than e.g., the top 20%) emerged from the systematic review: setting the cut-off limit for consultations at 1-8 consultations per year

when attempting to identify MUS patients using EHR resulted in models with low specificity (Smith et al, 2001, den Boeft 2014). Setting a higher threshold on the number of consultations could help reduce selecting non-cases in this study.

MUS-related Symptom codes: The patient should have >=1 MUS-related Symptom code on record in the index year.

9.4 Process of using EHR data to derive the 'EHR-defined patients with MUS' study population

9.4.1 METHODS

The top 10% of most frequent consulters in each GP practice was taken from EHR for each of years 2007 -10 and the process in Figure 9.1 followed for an 'EHR-defined MUS patient.'

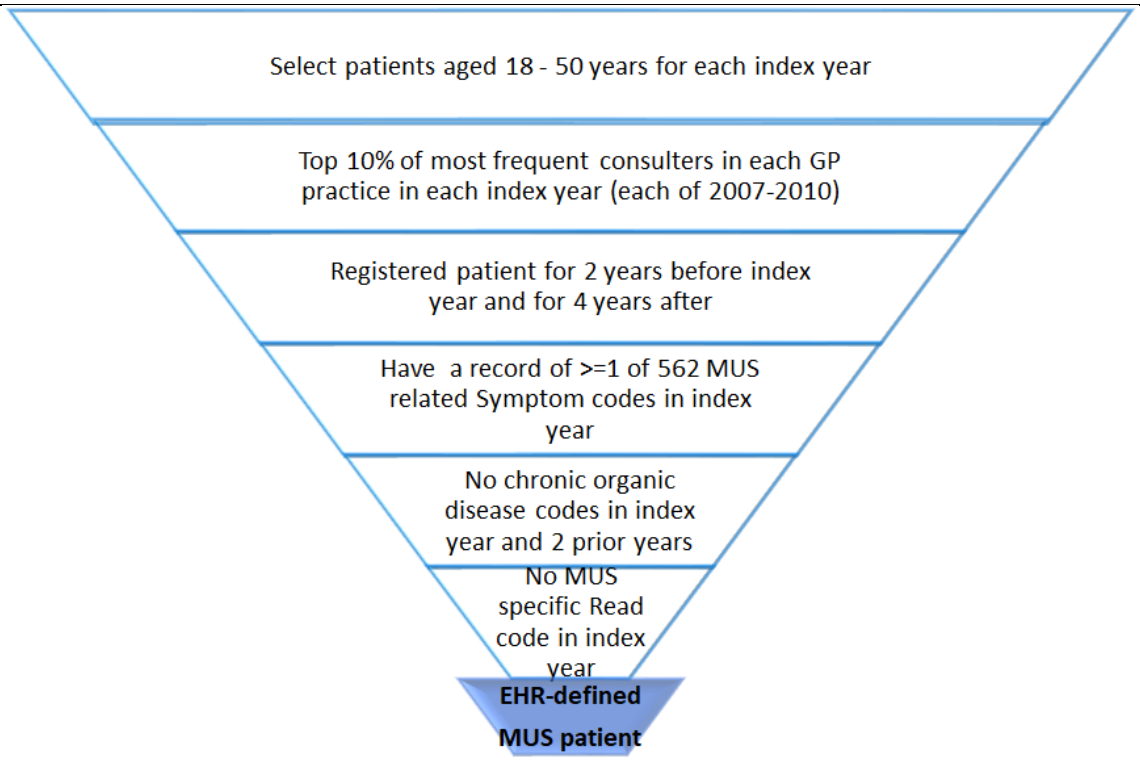


Figure 9.1 Process of using EHR to find patients with MUS

The database has a separate consultation code assigned per consultation; consultation frequency was defined as the number of consultation codes on record for each year and a consultation could be face to face (clinic or surgery), by telephone or a home visit). All patients below the age of 18 and over the age of 50 years for the given index year were excluded. To ensure complete cases, only patients who were registered with the practice for 2 years before the index year and four years after the index year were included. In order to include only new patients in the study, a washout period of two years was applied and patients who have a record of MUS specific Read codes in the two years prior to the index year were excluded using the list of MUS specific Read codes developed in Chapter 7 (Appendix 7.2). Patients who have a record of at least one of the 562 MUS related Symptom codes (in Appendix 7.3) list in the index year were selected.

However, in some patients, the high consultation rate is due to the presence of chronic organic illnesses (e.g., diabetes, ischaemic heart disease). Such frequent consulters, with a record of a Read code in the list of chronic organic disease in Appendix 7.6 recorded in the index year and the two previous years were excluded.

Validation: The original method of defining the patient population, patient selection process and analysis plan was developed in consultation with the lead supervisor. This research plan was submitted to an advisory panel formed from among the custodians of the CiPCA database, described in Chapter 5.4. The original research plan was extensively modified to arrive at the panel-approved current plan presented in this chapter, based on review comments and advice from the panel, primarily from Professor Kelvin Jordan.

Once the EHR-defined MUS population was selected based on the above process, the consultation data of the selected patients of the index year was manually reviewed by the researcher to validate the findings of the EHR-screening method. The purpose of this manual review was to ensure that there were no patients with medically explained disease included in the EHR-defined MUS patients list. The Read codes recorded against each consultation code in the index year were checked to see if any code indicating the presence of medically *explained* symptoms were noted in the records. In an early version of the research, it was noticed that when the study search mechanism looked for the presence of chronic organic illness in the index year alone, there were patients with chronic diseases included. The search mechanism was therefore amended to mark and exclude patients with a record of chronic illness in the two previous years. Fifty-one such patients were therefore excluded from the study.

The lead supervisor reviewed two hundred of the selected patient list randomly to further check the findings of the researcher.

9.4.2 DATA ANALYSIS

Incidence: For each of the years 2007-2010 the incidence rate per 1000 population is calculated using the number of new cases during the year as against the population at risk during the same time – i.e. the number of registered patients aged 18-50 years during that year.

Delayed diagnosis: The number of patients who had MUS related symptom codes recorded in the index year and were subsequently diagnosed as MUS patients was assessed by

counting the number of patients with a GP-recorded MUS specific Read code within the next four years after the index year.

Disease perpetuation: The percentage of patients who continue to have an MUS related Symptom code recorded for each of next four years after the index year were checked. Diagnostic tools, socio-demographic characteristics, investigations recorded, no. of consultations per year, comorbid mental illness, and vulnerability related data were analysed as described in Chapter 8.3.2 for the GP-diagnosed MUS patients.

9.4.3 MISSING DATA

Only complete cases, with data for the 2 years prior and four years post the index year were included – as described in Chapter 7.3.3.

9.5 Results

The consultation data of these patients was matched with the patient information using the unique patient identifier. There were 2,044 patients who met the defined criteria of a "EHR-defined MUS patient" in each year during 2007-2010 who were included in the study population. Of these, 77% were female; the mean age was 35 years with a standard deviation of 9.3. The number of EHR-defined MUS patients in each index year were compared to the total number of patients aged 18-50 years in the database to calculate the incidence rate of undiagnosed potential MUS patients in the registered population; an average incidence rate of 13.6 per 1000 registered population was recorded.

Table 9.1: No. of EHR-defined MUS patients each year, gender and mean age				
	No. of patients annually meeting the criteria for "EHR-defined MUS patient"		No. of patients 18-50 years in database for the given index year	Incidence rate of EHR-defined MUS patients per 1000 registered population aged 18-50 years
2007	593		37,338	15.9
2008	557		37,522	14.8
2009	471		37,910	12.4
2010	423		37,873	11.2
Total	**2044**		**Mean 2007-2010**	**13.6**
Gender	No. of patients	%	**Age**	
Female	1,577	77%	Mean age	34.9
Male	467	23%	Standard deviation	9.3

9.5.1 EHR-DEFINED MUS PATIENTS – NUMBER OF DIFFERENT SYMPTOMS

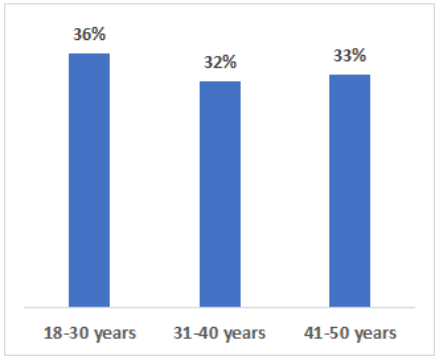
The study analysed the number of MUS-related symptom codes that were recorded during the index year for the EHR-defined MUS patients, to assess the complexity of the issues these patients report. As shown below in Table 9.2, 55% of these patients had more than one MUS-related Symptom code recorded. Two different symptom codes were recorded in 29% of all patients, 16% had three codes, and 12% of the patients had 4-9 different MUS-related Symptom codes recorded.

Table 9.2 No. of patients with different MUS-related symptom codes recorded in Index year								
No. of symptom codes		**1**	**2**	**3**	**4**	**5**	**6 - 9**	**Total**
Index year	2007	270	171	84	42	24	2	593
	2008	273	149	80	38	11	6	557
	2009	205	148	73	24	11	10	471
	2010	192	120	66	32	7	6	423
	Total	940	588	303	136	53	23	**2044**
		45%	**29%**	**16%**	**7%**	**3%**	**2%**	

9.5.2 SOCIO-DEMOGRAPHIC CHARACTERISTICS – GENDER, AGE, SOCIO-ECONOMIC STATUS

9.5.2.1 Age

The patients are divided fairly evenly across the three age groups.



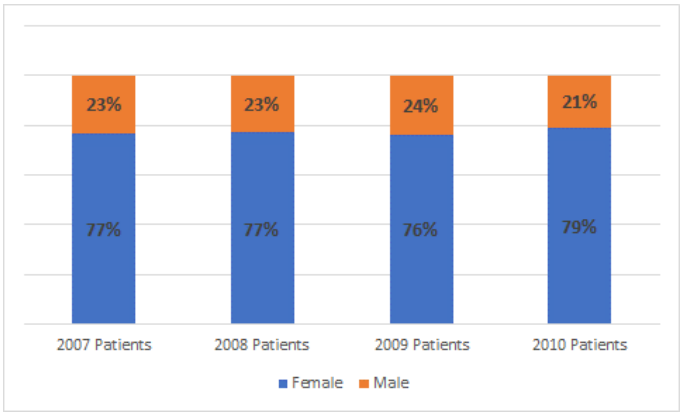


Figure 9.2: EHR-defined MUS patients – age and gender distribution

9.5.2.2 Gender

Of the 2,044 EHR-identified MUS patients, 23% were male and 77% female. This distribution was similar across all years with 76%-79% of the patients being female.

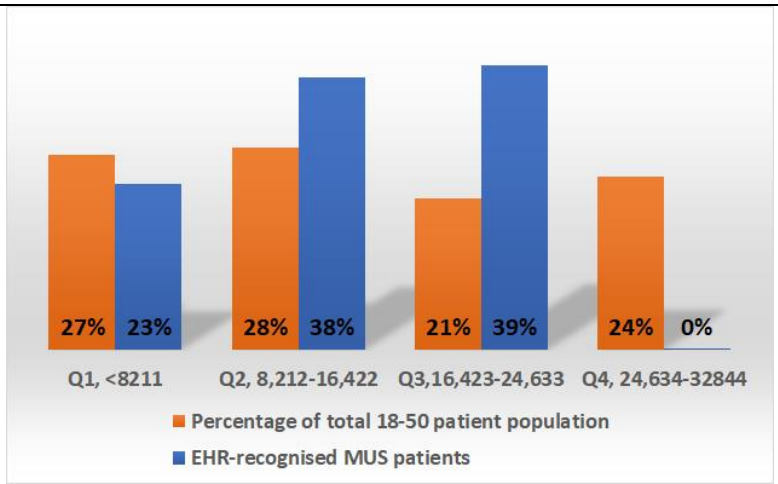


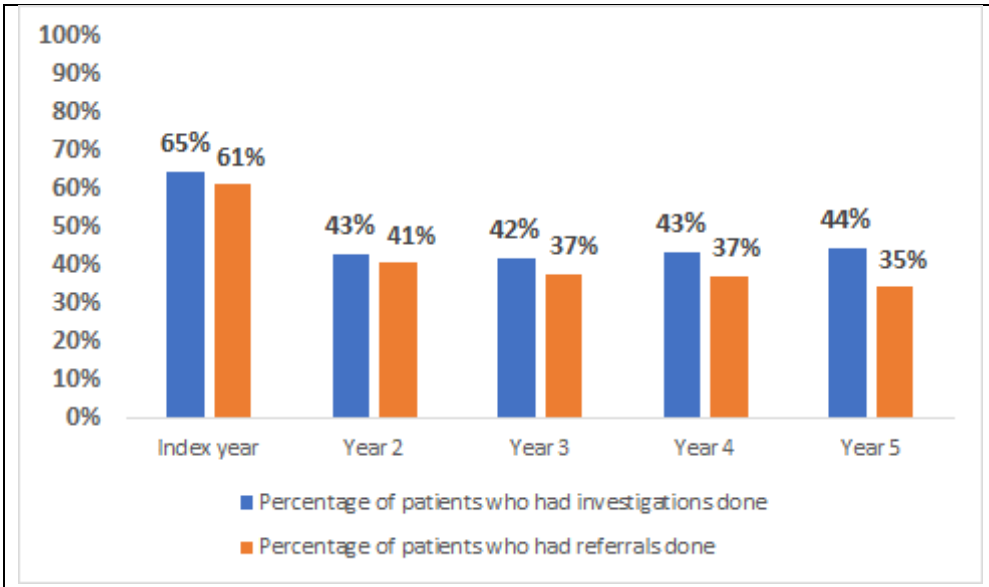
Figure 9.3: EHR-defined MUS patients – 77% in 2nd or 3rd quartile of Deprivation index

9.5.2.3 Socio-economic status

Assessing socio-economic status based on the English Indices of Multiple Deprivation 2015 ranking, the patients were grouped into quartiles: 23% of the EHR-defined MUS patients were found in the most deprived quartile, whereas 27% of the total population aged 18-50 years in the database were in this lowest quartile. The majority, 38% and 39% of the patients were in the 2nd and 3rd quartiles; none in the least deprived quartile, compared to 24% in the fourth quartile out of the total population aged 18-50 years in the database.

9.5.3 INVESTIGATIONS AND REFERRALS CARRIED OUT

Of the EHR-defined MUS patients, 65% had investigations carried out and 61% had referrals during the index year, to support the diagnosis and management of MUS, and ranged over 35% - 44% over the next four years. Of these patients, 10% had no investigations carried out over the entire five years, and 12% had no referrals.



No investigations carried out during five years: **10%**

No referrals made over five years: **12%**

Figure 9.4: EHR-defined MUS patients – % who had investigations and referrals

9.5.4 CONSULTATION FREQUENCY

The mean annual number of consultations per person ranged from 2 to 92. The majority of patients, 30%, had between 11-15 consultations per year over the five-years of the study. Only 5% of the patients had between 1-5 consultations; the top 4% of patients had over 30 consultations annually during the five year period.

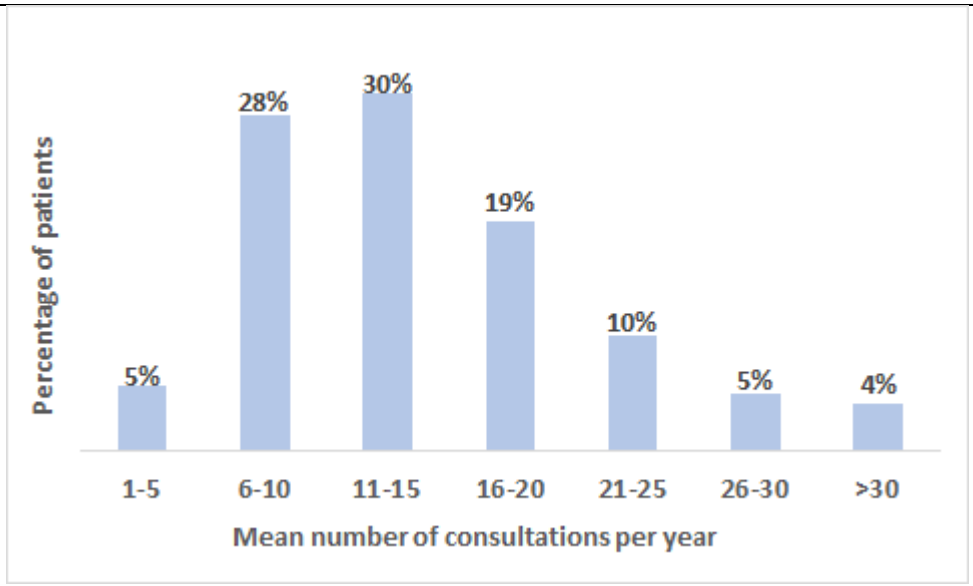


Figure 9.5: EHR defined MUS patients – consultation frequency over five years

The mean number of consultations was 22 in the index year, reduced to 15 per year in the following year and 13-14 per year in the three years thereafter.

Table 9.3: EHR-defined MUS patients: Mean number of consultations, index year + four years

	Index year	Year 2	Year 3	Year 4	Year 5
2007	21	15	14	14	14
2008	22	15	12	11	11
2009	23	15	15	14	14
2010	21	14	13	14	13
Mean	**22**	**15**	**14**	**13**	**13**

9.5.5 ASSESSING THE PRESENCE OF COMORBID MENTAL HEALTH ISSUES IN EHR-DEFINED MUS PATIENTS.

Out of the 2,044 EHR-defined MUS patients, 1,449 patients, 71%, had at least one mental health related Read code on record during the seven years of the study (2-year washout period + index year + 4 years after). 72% of the female patients had at least one mental health code on record (1,133 out of 1,577 female patients), as did 68% of the male patients (316 out of 467 male patients).

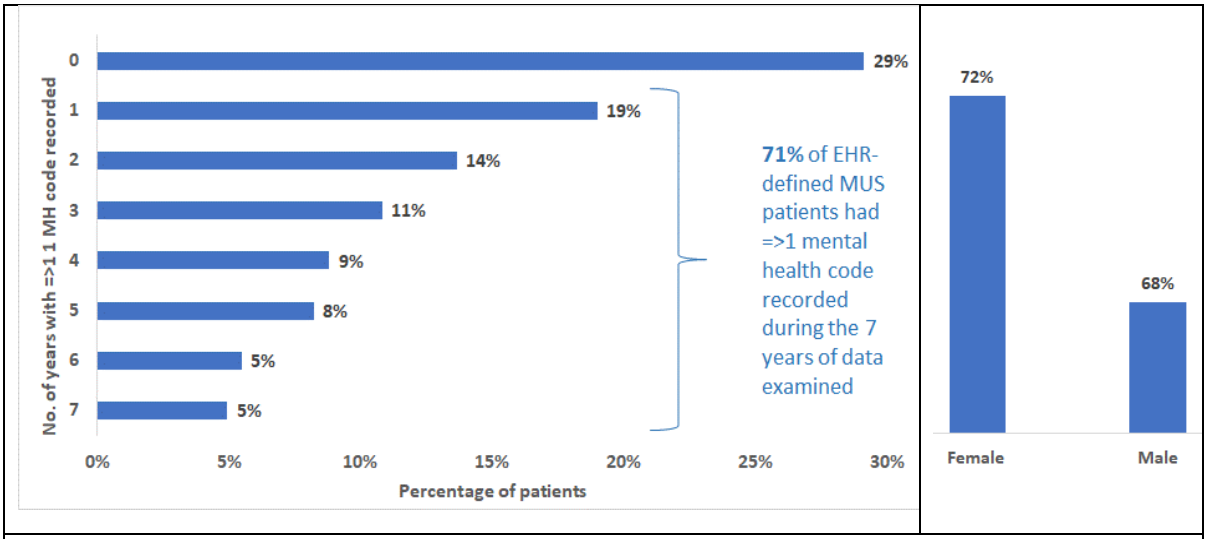


Figure 9.6: EHR-defined MUS patients with mental health conditions during the 7-years of study

Of the 844 patients who had a mental health Read code on record in the index year i.e. the year of their diagnosis, 45% had a mental health issue that was related to anxiety and / or depression. 19% had psychological conditions such as phobias, and 14% were recorded with severe psychiatric issues such as schizophrenia, suicide attempts; stress-related complaints were recorded in 9% of the patients, alcohol and drug dependence related issues were recorded in 4% of patients.

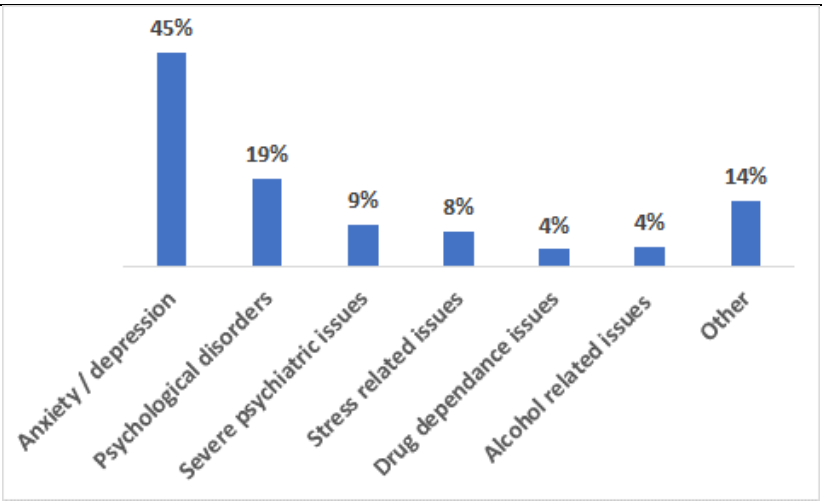


Figure 9.7: Complaints of patients with mental health issues in index year

9.5.6 VULNERABILITY

Out of the 2,044 EHR-defined MUS patients over 2007-2010, 22 of the patients, 1.1% were found to have a record of vulnerability. 14 patients had at least one record of domestic violence or sexual abuse and 8 others were marked as vulnerable due to other reasons such as homelessness.

9.5.7 DISEASE PERPETUATION: SYMPTOM PERPETUATION IN FIVE YEARS

Of the total 2,044 patients, 37% had a MUS-Related Symptom code recorded only during the index year and no MUS-related Symptom code recorded during the next four years. 63% of the patients continued to have MUS-related Symptom codes in the year after the index year. This level continued over the next three years and 55% of the patients continued to have a record of consulting, with a MUS-related symptom code even in Year 5, as shown below in Figure 9.8.

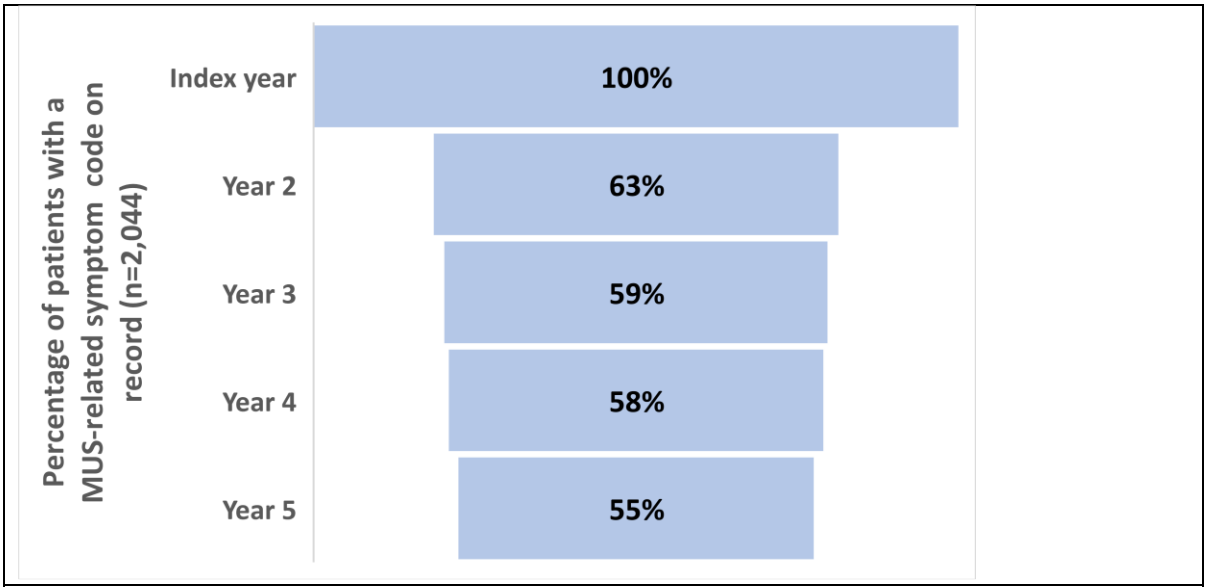


Figure 9.8: EHR-defined MUS patients – Percentage of patients with a MUS specific Read code recorded during the five years of the study period

9.5.8 DELAY IN DIAGNOSIS AS A MUS PATIENT

In the year following the index year, 4% of the EHR-defined patients were recorded by their GP as a patient with MUS, using a MUS specific Read code. GPs diagnosed 13% of the EHR-defined MUS patients as patients with MUS within five years as shown in Table 9.4.

Table 9.4: Subsequent diagnosis as an MUS patient by GP

	One year after Index year	Within 5 years of index year
2007 patients	2%	9%
2008 patients	1%	8%
2009 patients	3%	14%
2010 patients	5%	12%
Mean	**3%**	**11%**

8.6 Conclusions and next steps

This chapter described the process of using routinely recorded primary care data to define the study population of EHR-defined MUS patients – and the analysis of their consultation records to assess factors related to the diagnosis and management of these patients in real

life. There were 2,044 patients designated as EHR-defined MUS patients in the years 2007 to 2010, based on the criteria of age of 18 to 50 years, being in the top 10% of most frequent consulters in their registered GP practice, absence of chronic organic illness during the index year and two years prior, and lastly, a record of >=1 MUS related symptom code. Of these patients, 77% were female, and 77% were in the second and third quartiles of the English Indices of Multiple Deprivation. They had a mean annual consultation rate per patient of 22 in the index year and a five-year mean consultation rate of 15 consultations; 71% had a mental health or psychological issue related Read code on record. Of these patients, 37% had a MUS related symptom code during the Index year alone, 55% continued to have a MUS related symptom code recorded even in the fifth year; 11% were subsequently diagnosed as MUS patients (with a MUS specific Read code on record during the five-year period.

Interpretation of these findings, including if and to what extent they support the findings of the qualitative research, and comparing the findings in these patients to that of GP-diagnosed MUS patients is discussed in Chapter 10.

CHAPTER 10
DISCUSSION: EVALUATE EVIDENCE FROM QUANTITATIVE REAL-LIFE DATA ON EXTENT AND INTENSITY OF MUS RELATED ISSUES IN A LARGE, CONSULTING PRIMARY CARE POPULATION.

This concluding chapter of the MUS in Primary care Study, discusses the evidence generated from the MUS in primary care study detailed in the two previous chapters to evaluate the extent to which MUS related concerns raised in qualitative research studies are supported or refuted by real-life data from a large, consulting primary care population. The best evidence available from the literature was used in defining the study population. All GP-diagnosed MUS patients in the study within the defined age limits were included since the current best available standard for MUS diagnosis is based on physician's view of a patient's condition. For the EHR-defined patient group, the focus was to ensure a high level of specificity, which may have resulted in some potential MUS patients being excluded from the study. This is considered acceptable since the aim of the study is to analyse the real-life situation of MUS patients, and it is more important to exclude patients who do not have MUS. The chapter next discusses the strengths and limitations of the study.

10.1. Evaluating evidence from the MUS in primary care study

10.1.1 INCIDENCE / PREVALENCE

The mean annual incidence of GP-diagnosed MUS patients was 4.4 per 1000 registered population aged 18-50 years and 13.6 for EHR-defined MUS patients.

Table 10.1: Incidence rate of GP-diagnosed and EHR-defined MUS patients					
	Total no. of patients 18-50 years in database for the given index year	No. of new patients meeting criteria for "GP-diagnosed MUS patient " each year	Incidence rate of GP-diagnosed MUS patients per 1000 registered population aged 18-50 years	No. of new patients meeting the criteria for "EHR-defined MUS patient" each year	Incidence rate of EHR-defined MUS patients per 1000 registered population aged 18-50 years
2007	37,338	168	4.5	593	15.9
2008	37,522	158	4.2	557	14.8
2009	37,910	161	4.3	471	12.4
2010	37,873	180	4.8	423	11.2
Total		**667**		**2,044**	
Average	**37,661**	**167**	**4.4**	**585**	**13.6**

This study focused on newly diagnosed cases (therefore calculates incidence rates), and selected patients aged 18-50 years alone, finding an incidence rate of 4.4 patients per 1,000 population for GP-diagnosed MUS patients. Including the EHR-defined MUS patients increases the incidence rate to 18 per 1000 population. No comparable data on incidence rates for MUS in England were found despite an extensive literature search. As highlighted in chapter 3, reported prevalence rates for MUS range from 0.7% - 60.7% (Haller et al, 2015). Two studies reported data for a general population in primary care in England: Peveler et al (1997) reported 19% of booked consultations being for MUS and the reported prevalence rate of 18% of consecutive attenders (Taylor et al, 2012).

Whether a patient receives a diagnosis of MUS and if that is recorded as an MUS case is entirely dependent on the physician in an electronic health record database. It is not known if this recorded diagnosis of MUS was conveyed to the patient. This data cannot reveal the basis of this diagnosis, e.g. if any tests, chart review was undertaken since access to free text is not available in CiPCA and typically is not for other primary care research databases; it is very unlikely that any diagnostic instrument was used for this identification of MUS

since there are no records of using the relevant diagnostic instruments for MUS in the CiPCA database. There is also no indication of what definition of MUS a GP used when recording a patient as MUS, and if such definition was operationalised consistently by the recording GPs. Swanson (2010) carried out a study to characterise physicians' estimates of MUS and indicated how much the estimate numbers varied based on the definition of MUS. He found that applying the least restrictive definition of MUS gave a prevalence rate of 11% for MUS and a c. 3% rate for chronic MUS.

Low incidence of recorded incidence/prevalence similar to this study were found in a database study by Harkness et al (2013) on IBS using the Salford Integrated Record system (SIR), a local patient data record system from Salford, England, using data from 2002-2011. They found an age standardised prevalence rate for IBS per year per 100,000 population of 616 (equating to 0.6%), whereas the literature indicated IBS prevalence rates of ranging from 2.1% - 22% (Rey & Talley, 2009). They also reported finding similar low incidence rate for data from a third database, the Manchester Primary Care Organisation data, giving them reassurance that the findings of low incidence were not necessarily a data artefact.

The low incidence rates of MUS found in this study may be due to one of several factors or their combined effect:

1) excluding patients with comorbid organic disease: comorbid organic disease is common in patients with MUS (Smith & Dwamena, 2007). However, GP-diagnosed MUS patients who had comorbid organic disease in the index year and EHR-defined MUS patients who had it in the index year or two prior years were excluded from this study in order to ensure that the

resource use criteria were limited to data for MUS patients alone, to avoid confounding from factors related to organic illness.

2) the GP not recording a diagnosis code for MUS or using free text to record the diagnosis: GPs may be intentionally under-recording MUS conditions to avoid the potential relaxation of clinical vigilance, to protect patients from the stigma and the disadvantages of a recorded MUS condition; or simply to avoid the hostility from patients that is common when a diagnosis of MUS is provided (as discussed in Chapter 3). Harkness et al (2013) also point out that gastro-intestinal symptoms and IBS are not included in the Quality Outcomes Framework (QoF) scheme that incentivises GPs to diagnose specific diseases; neither are MUS. This may mean that diagnosis and recording of MUS is not a priority for GPs. GPs may have used free text in lieu of using a diagnosis code (Kotz et al, 2022), however, such patients would not be included in the study as the study did not analyse 'free text' to estimate the level of disease recorded in free text and it has been shown that failing to include free text in an analysis can result in underestimation of prevalence (Jordan et al, 2006). Nimnuan (2000) established that doctors are more likely to under-diagnose MUS in patients, rather than over-diagnose, and that finding appears to be replicated in this study as well.

3) the method of diagnosis of somatoform disorders and MUS in the literature: It may be due to the over-estimation of disease levels in the trials/population-based studies that frequently estimate prevalence based on self-report questionnaires which are subject to recall-bias. Furthermore, the presence of a MUS related symptom in a patient does not always lead to a consultation, therefore prevalence in consulting populations will usually be

lower than the prevalence recorded through a self-report questionnaire in the general population. Jordan et al (2006) found that recalled consultation prevalence (for knee problems) in the 'past year' was 33% vs. only 15% when medical records were assessed and they concluded that 'the disparity in estimates of consultation prevalence' were due to inaccuracy of recall when assessed by survey and by discrepancies in the records GPs made. Peveler et al (1997) found that screening instruments identified 35% of patients in their study as MUS patients, whereas GPs only identified 19% of the sample as MUS patients. Haller et al (2015) found that the prevalence rates were higher in studies reporting questionnaire-identified MUS patients than in those with GP-diagnosed patient rates in their systematic review of prevalence of MUS and related illness labels, and cautioned against the use of questionnaires alone to diagnose MUS.

4) Patient behaviour may also contribute to the low recording rates. As noted previously 63% of patients receiving a diagnosis of MUS in the index year have no further record of MUS. This may be due to resolution of the complaint, consistent with what is described in the literature as minor acute illness (Smith & Dwamena, 2007) or self-limiting symptoms (Rosendal et al, 2017). It is equally possible that some of these patients do not consult further about the MUS conditions due to resistance to a MUS diagnosis, stigma, due to a feeling that their GP cannot help them further or even that the GPs have worsened the situation through poor management (Stenner et al, 2000; Harkness et al, 2013).

The methodology of the study does not permit calculation of prevalence rates. However, even under the strict conditions of patient inclusion in the study, in total, 2,711 patients out

of an average of 37,661 patients, or 7.2% of the patient population, were found to be either GP-diagnosed or EHR-defined MUS patients, over the four-year period 2007-2010.

The findings of this study support the qualitative research findings of doctors complaining about a high prevalence of patients with MUS. Similarly, the number of recorded diagnosed MUS patients (4.4 per 1,000) is much lower than the number of MUS patients without a recorded diagnosis (13.6 per 1,000), supporting the claim of under-diagnosing of MUS.

10.1.2. SOCIO-DEMOGRAPHIC CHARACTERISTICS

In line with other research findings, 74% of GP-diagnosed MUS patients and 77% of EHR-defined MUS patients were female. The GP-diagnosed MUS patient group had 27% of the patients in the 18-30 years age category whilst the EHR-defined MUS patient group had 36%, likely an indication of GPs being more reluctant to give a diagnosis of MUS to patients below 30 years of age. Such a bias towards older, female patients has been noted previously as being a result of choosing the top 10% in terms of frequency of attendance, rather than stratifying by age and gender (Schrire, 1986). To circumvent this issue, Dowrick et al (2000), for example, selected their patient sample by defining frequent attendance as 'an annual rate of consultation at least twice as high as the practice sex- and age- related mean.'

The socio-economic status of the patients as measured by the Deprivation index indicated that the majority of GP-diagnosed MUS patients (52%) were placed in the third quartile, and 25% in the second quartile (Figure 9.1). In the EHR-defined MUS patient group (39%) were placed in the third quartile of the Deprivation index, 38% in the second quartile. The first quartile indicating the lowest socio-economic status contained 20%-23% of the MUS patient population, less than the 27% of the total population aged 18-50 years in the primary care

population in this category; on the other hand, the 4th quartile, indicating the highest socio-economic status, which contained 24% of the primary care population, had only 4% of the GP-diagnosed MUS patient population, and none in the EHR-defined group.

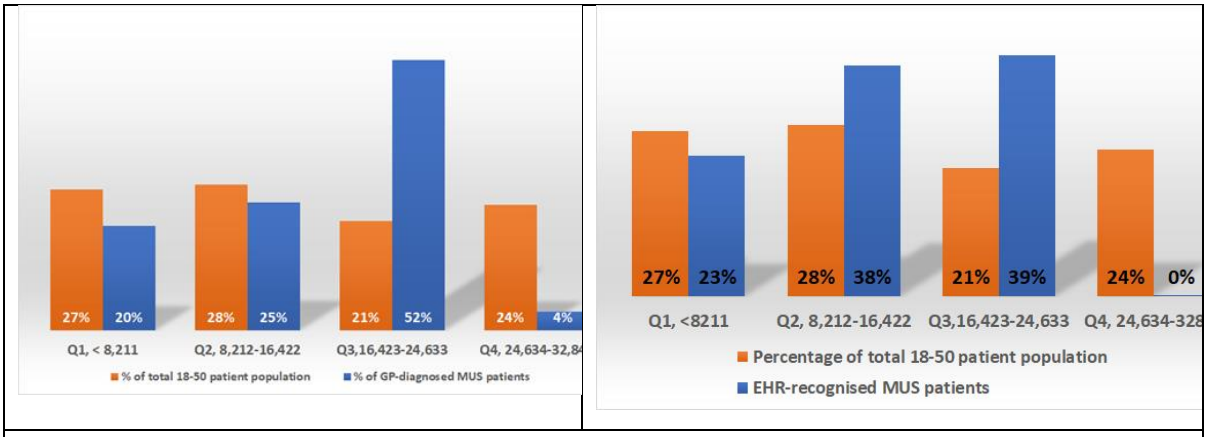


Figure 10.1: Comparison of the Deprivation index status of GP-diagnosed and EHR-defined MUS patients against the total population aged 18-50 years in the primary care database

Qualitative research indicated that some GPs viewed MUS patients as those who faked / exaggerated illness in order to get financial benefit from the government (Chew-Graham & May, 1999; Nettleton, 2006; Bayliss, 2016; Pryma, 2017). The third quartile of the Deprivation index, where the majority of MUS patients are located, is less likely to include people on benefits, whereas the first quartile, with the lowest socio-economic status, had a lesser percentage of MUS patients than the total population of the database; the findings of this study do not support the perception some GPs have about patients with MUS being primarily from lower socio-economic groups, nor some studies which found that MUS and related frequent attendance was 'most common among elderly women with lower socio-economic status' (Verhaak et al, 2006). However, Nimnuan (2000) found that doctors rated younger, unmarried patients receiving benefits, for whom they rated the clinical encounter

as negative, as having MUS, indicating that the negative perceptions about patients have an impact on diagnosing patients with MUS.

10.1.3. INVESTIGATIONS AND REFERRALS

The percentage of patients who had some form of investigation or a referral for further care was significantly lower in the index year in GP-diagnosed MUS patients, 42% and 39%, compared to 65% and 61% in EHR-defined MUS patients (Figure 10.2). The percentage of patients who had an investigation or a referral at any time during the five-year period was also lower in this group at 83% and 79% compared to 90% and 88% in EHR-defined patients.

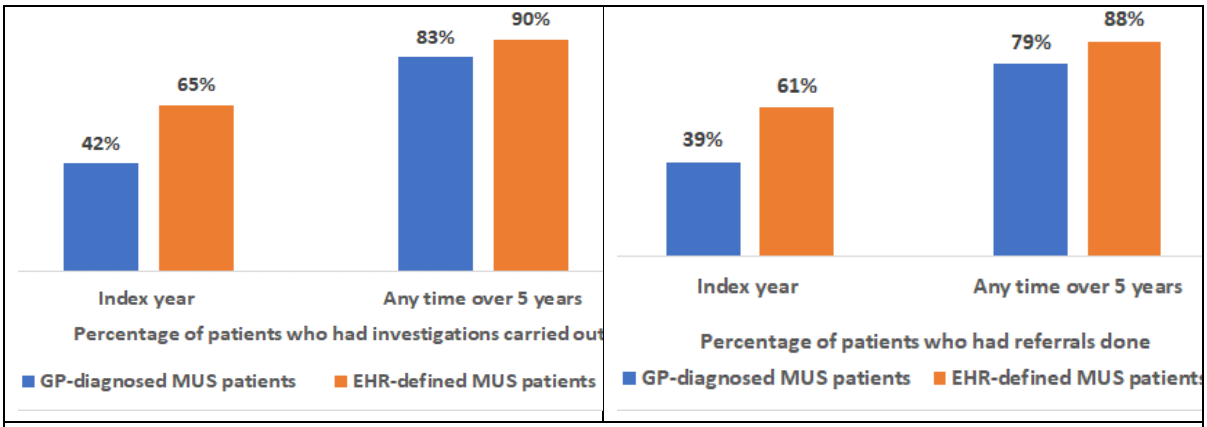


Figure 10.2: Investigations and referrals carried out for GP-diagnosed and EHR-defined MUS patients

This low level of investigations and referrals in the GP-diagnosed MUS patients in the Index year (42% and 39%) is concerning. These patients are presenting with MUS related symptoms for the first time (a two-year washout period was incorporated to ensure only patients presenting for the first time were included in the study, i.e. without any MUS related complaints in the two preceding years). As discussed in Chapters 1 and 3, MUS is considered and ongoing working hypothesis, where 'adequate medical examination or investigation has not revealed any condition that sufficiently explains' symptoms that last

for several weeks (Olde Hartman et al, 2018). The data shows that 58% of patients were diagnosed as patients with MUS without any investigations and 61% of patients were diagnosed as patients with MUS without any further referrals. This may indicate that these patients are categorised as MUS patients without adequate investigation or referral to a relevant specialist.

Although the EHR-defined MUS patients had more investigations and referrals done in the index year, 65% and 61%, this too declines to a 35%-44% range in the following four years (Table 10.2); a low level of investigations and referrals is concerning in this group of patients as they have not received a diagnosis – but 55% to 63% of this patient group continue to have MUS related symptom codes recorded over the next four years after the index year.

Of the GP-diagnosed MUS patients, 17% had no investigations carried out even once over the five-year period; 21% had no referrals. In the EHR-defined group, 10% had no investigations and 12% had no referrals at any time over the five years. Details of investigations and referrals for each index-year based patient sub-group is in Appendix 10.2.

Table 10.2: Investigations and referrals carried out for GP-diagnosed and EHR-defined MUS patients

Percentage of patients who had Investigations or referrals - for all patients / (No. of patients in group)						**No referrals / investigations for 5 years**
Investigations	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	
GP-diagnosed MUS patients (667)	42%	36%	38%	37%	42%	17%
EHR-defined MUS patients (2,044)	65%	43%	42%	43%	44%	10%
Referrals						
GP-diagnosed MUS patients (667)	39%	36%	29%	30%	32%	21%
EHR-defined MUS patients (2,044)	61%	41%	37%	37%	35%	12%

Interpreting the rate of investigations and referrals is not straightforward. What has been well-established is that investigations and referrals with minimal delay are a necessary part

of the diagnostic process, but that higher investigation and referral rates do not necessarily mean better care (Foot et al, 2010; Rubin et al, 2015). It has also been stated that under-referrals are a bigger problem than the small percentage of patients who are referred unnecessarily (Wilkin et al, 1989; O'Donnell, 2000).

Evidence from consulting populations indicate that investigations were carried out on 64% of cases (when examining the rates for patients subsequently diagnosed with cancer, Rubin et al, 2015) and that one in twenty cases, or 5%, results in a referral (Foot et al, 2010).

Qualitative research frequently discussed the problem of repeated investigations and referrals from the point of view of clinicians; patients often complain that they do not receive appropriate investigations and referrals. The real-life data on these two groups of patients show that around 60% of GP-diagnosed MUS patients receive that diagnosis without investigations or referrals and that around 60% of EHR-defined MUS patients, who do not have a diagnosis of MUS, do not have investigations carried out or referrals for specialist care, to attempt to resolve their complaints, even though 55% of the latter group continue to complain of MUS symptoms during the next five years. The percentage of patients who do have investigations and referrals remains around the same level in the high thirties to the low forties over the next four years. This real-life data serves to support both the physicians and the patients' concerns regarding investigations and referrals.

10.1.4. CONSULTATION FREQUENCY

The mean number of consultations of 22 in the Index year, for EHR-defined MUS patients, was 78% higher than the mean number of consultations of 12 for GP-diagnosed MUS

patients (Table 10.3). The number of consultations remained at a similar level, 10-12, in the GP-diagnosed patient group; in the EHR-defined MUS patient group, it reduced from 22 consultations in the index year to 15 in Year 2 and further in Year 4/5. The five-year mean of 15 in the EHR-defined group was 35% higher than that of 11 in the GP-diagnosed group.

Table 10.3. Mean annual consultations in GP-diagnosed /EHR-defined MUS patients

Mean number of consultations for all patients / (No. of patients in group)						**5-year mean**
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	
GP-diagnosed MUS patients (667)	12	11	10	11	12	11
EHR-defined MUS patients (2,044)	22	15	14	13	13	15
EHR-defined group greater than GP-diagnosed group by	**78%**	**37%**	**31%**	**18%**	**9%**	**35%**

Of the GP-diagnosed patients, 28% had less than the five consultations per year, less than the average annual consultation rate for England of 3.1 for the age group 18-55 years for 2008. Only 5% of the EHR-defined MUS patients had a mean recorded annual consultation rate less than the country's average consultation rate (Figure 10.3).

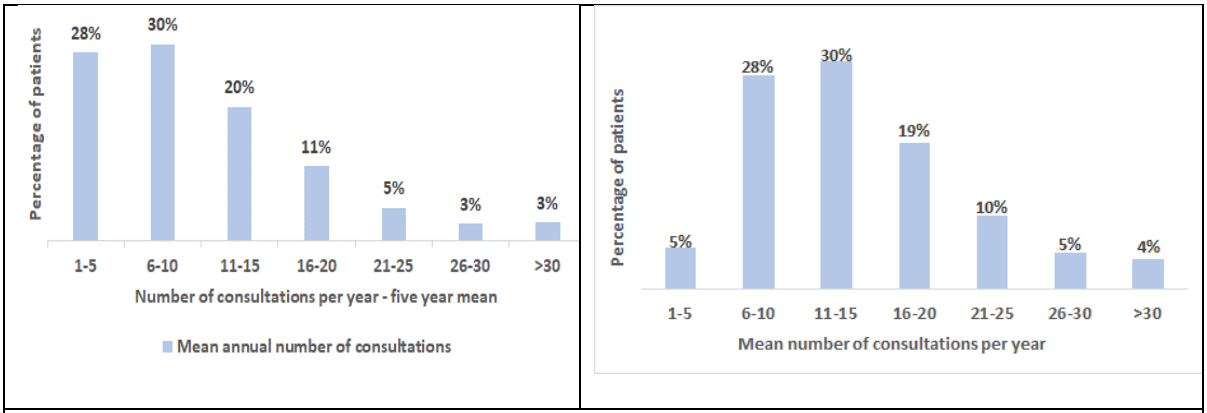


Figure 10.3: GP-diagnosed and EHR-defined MUS patients – 5-year mean consultation rate

Details of consultations for each index-year based patient sub-group is in Appendix 10.1. As described in chapter 8.4.7 when looking at disease perpetuation, 63% of GP-diagnosed MUS patients do not have a MUS-specific Read code recorded after the index year, indicating that they are not complaining of MUS after the first year. This corresponds to patients with 'Minor Acute Illness', i.e. those with normal to mild symptoms and low utilisation (Smith et al, 2002), to those with 'Self-limiting symptoms' (Rosendal et al, 2017). However, if 63% of GP-diagnosed MUS patients do not consult for MUS after the first year, then the number of consultations for the total GP-diagnosed MUS patient group should have declined in the following years. However, the mean number of consultations per year per patient continues to remain high at 10-12 in this patient group.

The number of consultations in this patient group shows a wide range, irrespective of the number of years a GP has recorded a MUS-specific Read code for a patient. As shown in Figure 10.4, the mean number of consultations per year per patient during the five-year period ranges from 1-46 for patients who had a MUS-specific Read code recorded in the Index year alone, whereas the patients who had MUS codes recorded each year for five years also had a mean number of consultations ranging from 4-45.

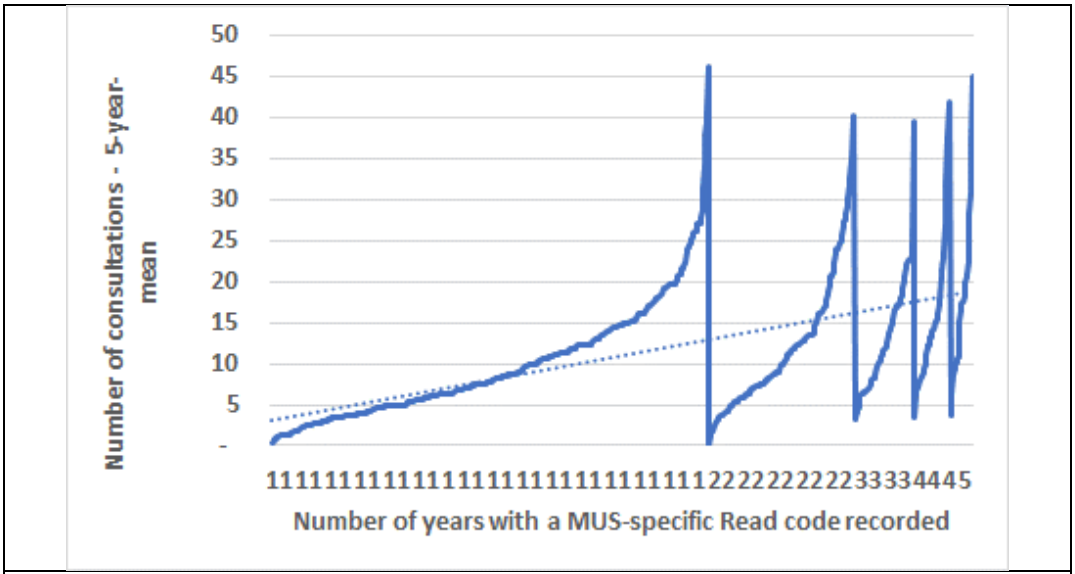


Figure 10.4: Number of years with a MUS code recorded compared to the mean no. of consultations per patient per year during the five years of the study period (n=667)

To find an explanation for the increased number of consultations despite 63% of MUS patients in the GP-diagnosed patient group not consulting for MUS after the index year, the relationship between age, gender, deprivation index state and comorbid mental health/psychological issues was carried out. Gender and the number of years a mental health or psychological issue related code is recorded appeared to be most closely linked to the number of consultations.

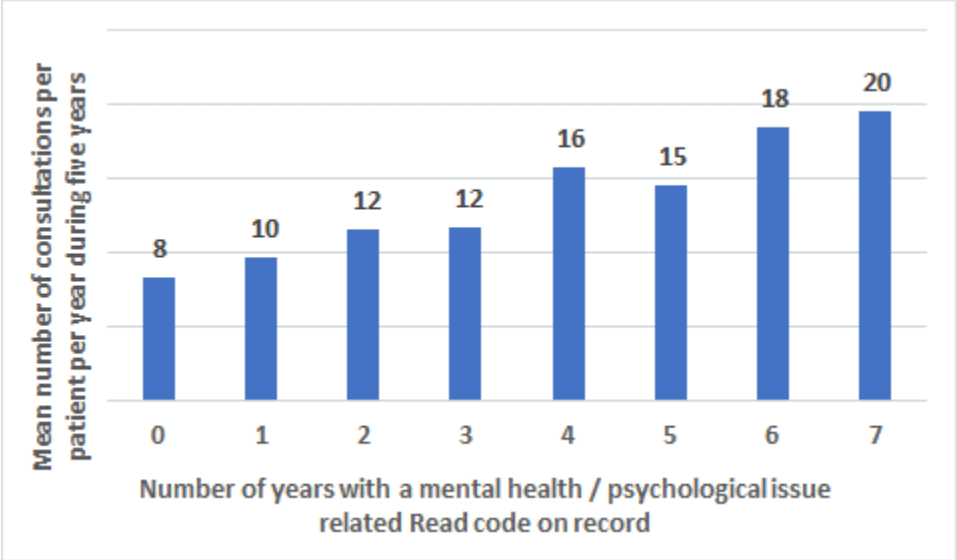
Gender and age-group specific mean consultation rates: This study found that MUS patients have a much higher overall mean consultation frequency: compared to the England's age-group specific mean consultation rate for 18-55 years of 3.1 per patient per year, 2.1 for males and 4.1 for females, for England (Hobbs et al, 2016), MUS patients' five-year mean consultation rates were nearly four times higher at 11 in the GP-diagnosed patient group, and five times higher at 15, for the EHR-defined patient group (Table 10.4).

Table 10.4. Mean no. of consultations per patient per year compared for GP-diagnosed and EHR-defined MUS patients against the mean data for England						
	England, age 18-55 years (2007 – 2014)	England, top 10% of most frequent consulters	GP-diagnosed MUS patients		EHR-defined MUS patients	
			Index year	Five-year mean	Index year	Five-year mean
Male	2.1		9	7	22	14
Female	4.1		13	13	22	15
Total	3.1	36.7	12	11	22	15

In the GP-diagnosed patient group, males had a lower consultation rate of 9 in the Index year, and a five-year mean of 7, compared to 13 for females in both cases. In the EHR-defined MUS patient group, the mean number of consultations of 22 was the same for both males and females in the index year; the five-year mean of 14 for males and 15 for females.

However, the consultation frequency of MUS patients was lower than 36.7, the mean consultation frequency of the top 10% of the most frequent attenders in England during 2007-2014 (Kontopantelis et al, 2021).

Mean number of consultations compared to duration of recorded mental health / psychological issues: As shown in Figure 10.5, the mean number of consultations per year per patient increases from 8 to 20 in line with the increasing duration of mental health / psychological issues, when examined for the five years of the study and the two prior years washout period. The average number of consultations for GP-diagnosed MUS patients with a record of a mental health / psychological issue ranges between 10 to 20, with an average of 13, compared to only 8 in patients without such a record.



Mean Consultation rate during five years for patients:

a) with a mental health code: 13

b) without a mental health code: 8

Figure 10.5. GP-diagnosed MUS patients - mean number of consultations per patient per year according to duration of mental health / psychological issue related Read code recorded

Duration of mental health issues compared to the duration of MUS: Table 10.5 shows the complexity of the association between MUS and mental health/psychological issues. In the GP-diagnosed MUS patient group, out of the patients who consult for MUS in the index year alone, 58% of the patients have a record of a mental health / psychological issue recorded over the five years of the study and the 2 years of the prior washout period.

The percentage of patients with a mental health / psychological issue increases in patients who continue to consult for MUS for longer, so that 74% of the patients who have MUS for 4 years, have also had mental health issues. It is also noticeable that over a third of patients, 36%, consulting for 5 years for MUS do not report mental health issues.

Table 10.5. Percentage of patients with a mental health/psychological issue cf. MUS duration						
Percentage of patients (n=667=100%)		Duration of MUS (No. of years with a MUS-specific Read code recorded)				
		1	2	3	4	5
No. of years with Mental Health / Psychological issue code recorded	0	42%	36%	30%	26%	36%
	1	21%	15%	14%	24%	14%
	2	13%	15%	12%	12%	18%
	3	6%	9%	12%	6%	14%
	4	6%	9%	14%	9%	0%
	5	5%	7%	7%	9%	5%
	6	4%	3%	4%	6%	0%
	7	4%	6%	7%	9%	14%
Percentage of patients with mental health / psychological issue in each year group 1- 5		**58%**	**64%**	**70%**	**74%**	**64%**

Qualitative research indicates that a primary concern regarding MUS patients is the high rate of consultations in this patient group. It is necessary to first clarify that evidence of association is not evidence of causation, and then to discuss the association between higher consultation rates and the several factors given below.

Firstly, lack of a diagnosis of MUS appears to be associated with higher consultation rates and disease perpetuation: consultation rates in patients without a diagnosis were 78% higher in the index year and 35% higher over 5 years; 55% of patients without a diagnosis continued to consult for MUS-related symptoms even in Year 5, cf. only 13% of diagnosed MUS patients consulting for MUS in the Year 5. The consultation rate in undiagnosed MUS patients is higher for both males and females, but lower in male diagnosed MUS patients. Secondly, the consultation rate continues to be high in diagnosed patients too even though 63% of diagnosed MUS patients consulted for MUS only in the index year. This high rate does not appear to be associated with disease perpetuation (Figure 10.4), whereas the

mean consultation rate increases with the increase in duration of mental health/psychological issues (Figure 10.5). The percentage of patients with mental health issues also increases as the duration of MUS is prolonged (Table 10.5).

10.1.5. COMORBID MENTAL HEALTH / PSYCHOLOGICAL ISSUES

The previous section discussed the extent of co-morbidity of mental health / psychological issues in patients with MUS. Furthermore, female patients with MUS are disproportionately burdened with mental health issues, 68% and 72% in the two groups (Figure 10.6).

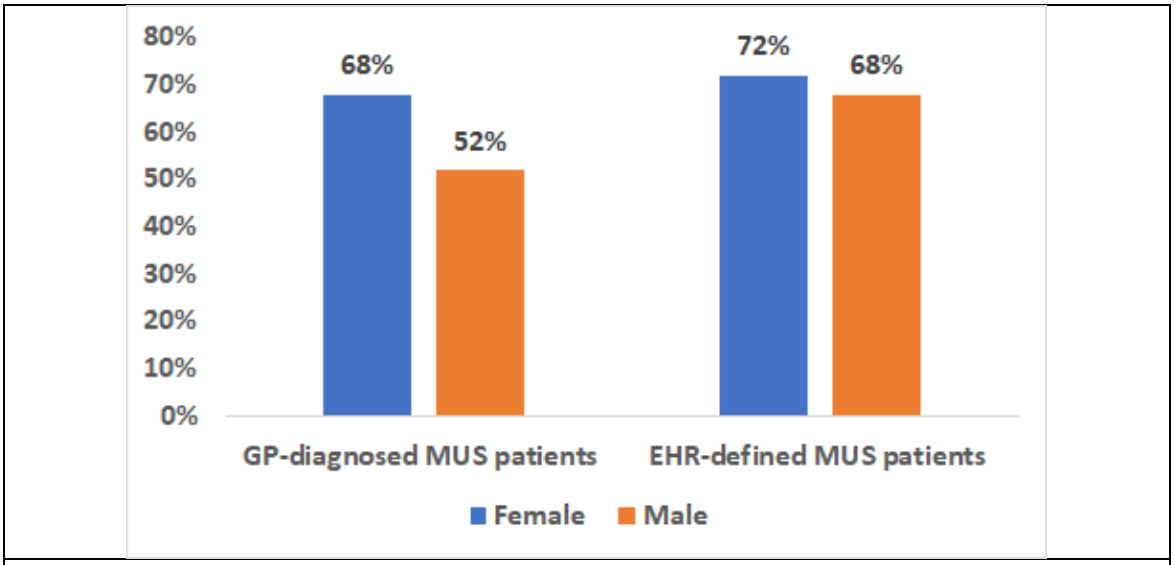


Figure 10.6: Percentage of patients with a mental health related Read code on record

The well-established finding that patients with diagnosed depression, anxiety and somatoform disorders were more often female (Lowe et al, 2008; Hanel et al, 2009; Vedat et al, 2010) was reiterated in the current study, though an additional noteworthy point is the 68% of male patients with mental health issues in the undiagnosed MUS patient group.

Depression and anxiety were the most frequently recorded mental health issues – 65% of all GP-diagnosed MUS patients had an issue related to anxiety and / or depression in the index year. However, in the EHR-defined MUS patient group, only 45% had an anxiety and depression related issue; 19% were psychological issues e.g., phobias, personality disorders. This finding is in line with the reported findings in the literature of the 'somatisation, anxiety, depression triad' (Kohlmann, 2016), where patients present with 'an overlap of somatic, anxiety and depression symptoms.' The percentage of patients with co-morbid mental health issues is however higher than found in the literature. In primary care, 54% of patients with somatisation had co-morbid depression, anxiety or both in study of 2,091 patients in 15 primary care clinics in the USA (Lowe et al, 2008). Van Eck van der Sluijs et al (2015) conducted a study in the general population, calculated 3-year incidence rates and found that 8.7% of people with MUS had a mood disorder, 5.7% an anxiety disorder and 4.7% a substance use disorder. Kohlmann (2016) found that 9.4% patients out of a total of 2,510 participants reported one of either somatic, anxious or depressive syndromes. The higher level in this study could be due to the longer study period of 7 years.

10.1.6. VULNERABILITY

There were very limited records on vulnerability – not sufficient to assess the qualitative findings of childhood, sexual or domestic abuse being common among these patients. This may be due to such issues not being comprehensively recorded using Read codes.

10.1.7. DELAYED DIAGNOSIS AND DISEASE PERPETUATION

As shown in Figure 9.4 in the previous chapter, of the EHR-defined MUS patients, only 3% were given a MUS diagnosis by their GP in the following year, and only 11% received a MUS

diagnosis by their GP within the five years that follow, indicating the extent of the delay in diagnosis of MUS. However, 55% of these EHR-defined patients continued to have a record of a MUS-related symptom code even in the fifth year, indicating that this low level of MUS diagnosis is not necessarily due to the absence of MUS in the patients.

Similarly, in the GP-diagnosed MUS patient group, 13% of the patients continued to have a record of a MUS specific Read code even in the fifth year, indicating the extent of disease perpetuation in this study population.

Delayed diagnosis has been associated with worse clinical outcomes and with patients' distress (Torring et al, 2012). The extent of the disease perpetuation found in this study population well exceeds the reported numbers in previous research: MUS was found to persist for one year in 51% of patients (Steinbrecher and Heller, 2011); for 2 years in 57% of patients (Budtz-Lilly et al, 2015) both in primary care but Verhaak et al, however, found in 2006, that only 2.5% of patients in a general practice who presented with MUS met the criteria for chronicity, measuring chronicity as presenting to the GP at least 4 times per year with symptoms considered to be medically unexplained. In this study, 13% of the GP-diagnosed MUS patients had a record of a MUS-specific Read code even in Year 5, indicating no resolution in their illness situation even in the fifth year of being diagnosed as a patient with MUS. The situation is worse in EHR-defined MUS patients, with 55% having a MUS-related symptom code recorded even in year 5 (Figure 9.8), and only 11% receiving a MUS diagnosis code within the five-year period. This finding is in line with the patient complaint detailed in qualitative research that diagnosis is delayed and that there is no effective resolution of the condition even once diagnosed.

10.2 Strengths and limitations of MUS in primary care study

This is the first research in England to use quantitative real-life data from routinely recorded data in a large, consulting primary care population to investigate the extent and intensity of issues related to the diagnosis and management of MUS patients described in qualitative research. This is one of the most comprehensive studies on MUS as it studies MUS in all its forms, ranging from transient, mild illness to symptom syndromes, and one of the largest, analysing data for over 188,000 person years (37,600 average patients x 5 years). Its value also lies in the analysis of 'real-world' data, as opposed to trial data, which can be skewed based on patient selection, methodology and other choices. A key strength of the study is the methodological rigour employed: the research process and analysis plan were subject to appraisal by both clinical and methodological experts and was undertaken only after their approval.

Stratification by age and gender was not carried out in this study, and that can bias the population in to including a greater number of older females.

10.2.1. VALIDITY OF THE RESEARCH APPROACH

One of the key concerns at the outset was the validity of the approach taken, if all MUS patients in the population are included in the study, and if patients without MUS could have been included. Since there are no biomarkers nor objective criteria to diagnose MUS, diagnosis is always on a balance of probability, it is not possible to diagnose MUS with 100% certainty. Diagnosis by a GP, as is carried out for the GP-diagnosed MUS group, is generally accepted as a reference standard for MUS diagnosis, accurate patient selection is more of a

concern in the EHR-defined MUS patient group. For example, if the top 20% of the most frequent consulters in each practice had been considered as the EHR-defined MUS patient for the study, the number of potential MUS patients could have been much higher, or much lower if the top 5% alone were considered.

The study is intended to ensure higher specificity, to ensure patients with MUS are not included: the choice of age limit of 18-50 years, excluding patients with organic illness and selecting the top 10% of most frequent consulters could result in exclusion of some MUS patients, and underestimating the actual numbers in incidence data. This is considered acceptable for this study since the primary aim is not to assess incidence but to carry out a detailed analysis of the diagnosis and management data for MUS patients and therefore it is more important to ensure only MUS patients are included. The criteria for inclusion are also what has been indicated by previous research to be associated most closely with the presence of MUS in patients, as established by a systematic review. Studies in the systematic review considered patients with minimum mean annual consultation rates of 6; considering the top 10% of frequent attenders resulted in patients with mean annual consultation rates over 8 being included in this study.

Regarding validation – the two methods used to validate if patients selected for a study are indeed MUS patients are to either use chart review by a physician or through a diagnostic questionnaire such as PHQ-15. Since this is database research, a questionnaire approach is not feasible. A process akin to chart review was undertaken here, with the researcher manually checking the index year data for the 2,044 patients, and the lead supervisor examining 10% of the cases, 204 patients' data.

10.2.2. USE OF ROUTINELY RECORDED DATA FROM PRIMARY CARE ELECTRONIC HEALTH RECORD DATABASES FOR RESEARCH

Primary care databases from which routinely recorded data can be extracted for research can provide cost-effective and reliable data on morbidity (Menachemi & Collum, 2011; Rubin et al, 2020). Databases provide 'real-world' data leading to a high level of external validity, as opposed to trials where findings can be skewed due to various reasons: patient selection methods, for example where patients with highest intensity of disease, who are not representative of the wider patient population, are selected for the trial (Kotz et al, 2022), or use of questionnaires which can lead to recall bias are used (olde Hartman, 2009). It is also useful as it avoids the "Hawthorne effect', where the mere fact of the participation in a trial alters the normal behaviour of a person (Roethlisberger & Dickson, 1939). The ability to interlink information from multiple data sources relatively easily, e.g., to link primary care data to Hospital Episode Statistics (HES) database, to cancer registries, death registrations, can increase the breadth of a research study considerably (Padmanabhan et al, 2019).

Database research also gives a high level of statistical power, that would be very costly, time and resource intensive, to achieve in a trial or in observational research such as surveys; for example, the CiPCA database used in this study permitted the analysis of data for c. 37,000 patients in the target population, a number which is impossible in any other context but database research in a PhD research. The use of other primary care databases such as the CPRD allows analysis of millions of patients, as well as to find sufficient numbers of rare cases (Herrett et al, 2015). Database research can enable monitoring changes in longitudinal

studies, if recorded with high validity and integrity (Jordan et al, 2004; Khan et al, 2010), which is very important for research on chronic diseases, or those with a long latency period (Herrett et al, 2015; Katz et al, 2022). This aspect strengthened this research by enabling the study of data two years prior to and five years follow up from the index year, again not feasible except with database research in a PhD study.

However, database research does have some limitations: three core factors should be considered when assessing the quality of primary care data in databases – completeness, accuracy and timeliness (Weiskopf & Weng, 2013). Data is only as good as the recording quality of those who input the data, and completeness and accuracy can vary, particularly since there are very limited scientifically based guidelines for researchers of primary care databases for many illnesses (Menachemi & Collum, 2011). Regarding the data used in this study, the participating primary care practices followed the Keele clinical data audit, training and validation programme, and are committed to recording clinical activity to a high standard (Porcheret et al, 2004 ; Jordan et al, 2004). However, the Read code system permits recording data using different diagnostic or symptom codes in different places as well as by writing in free text. The problem of using different codes has been addressed by comprehensively listing all relevant codes used in the database during the period, however, any record of a diagnosis in free text form is missed in the research since free text has not been analysed and is not available for research. Moreover, the completeness of the records will be affected by the way a problem is presented to the GP, who may record the new or most significant complaints addressed during the consultation in cases of people presenting with multiple problems (Jordan & Croft, 2008).

This leads to the next problem encountered in database research: differences in recorded incidence and prevalence levels calculated using databases and primary research. Prevalence data is underestimated most likely in chronic conditions (Jordan & Croft, 2008), multi-morbidity (Stewart et al, 2013), and in medically unexplained symptoms as in this study. Presence of illness in the general population, which is measured by surveys for example, does not always translate to a consultation. A GP may refrain from recording a diagnosis code for MUS to prevent the stigma of MUS to the patient, to prevent the relaxation of clinical vigilance that follows a diagnosis of MUS, as discussed in Chapter 3. Analysis of the data requires an in-depth understanding of the database structure and architecture (Prada-Ramallal et al, 2019), and this study overcame this problem by obtaining advice and instruction from the database manager and custodian committee, who have in-depth knowledge of the system.

10.3 Conclusions and next steps

The purpose of this section was to evaluate if the concerns raised by patients with MUS and doctors as described in qualitative research, are supported by the real-life data on large populations. The findings indicated that even within the strict criteria of age 18-50 years and absence of organic illness, 7% of the total patient population had either a recorded diagnosis of MUS or a symptom code indicative of MUS recorded within the five years of the study, that 13% of GP- diagnosed MUS patients and 55% of EHR-defined MUS patients, were still complaining of MUS in the fifth year from diagnosis, providing evidence of the extent of disease level in the population and its perpetuation. Consultation rates are much higher in this group of patients, with GP diagnosed patients reporting 15 consultations on

average per year, and EHR-defined MUS patients reporting 22 consultations on average per year, well above the country average of 3.1 per year for that age group. These patients also show high levels of comorbid mental health issues, and it was found that the consultation rates were much higher in patients who had a record of comorbid mental health issues. However, it is clarified here again that these findings are associations and that no research has been carried out to determine if there is a causative relationship between these two associated factors.

The data also showed that, contrary to common perception, the majority of MUS patients are not from the lowest socio-economic groups. These findings serve to establish that there is some supporting evidence from real-life data for the difficulties patients with MUS claim to face in relation to the diagnosis and management of their illness as discussed in qualitative research.

The next section, chapters 11 and 12, attempts to quantify the costs of MUS in England: it first undertakes a systematic review of the published data on costs of MUS in England, and in the second section, summarises the resource utilisation data from this study to estimate the costs of MUS to primary care.

CHAPTER 11
SYSTEMATIC REVIEW OF COSTS OF PATIENTS WITH MUS IN ENGLAND

11.1 Introduction

This section examines the issues related to the resource constraints and the costs of MUS to the NHS. The previous section, Chapters 5-10, described the process of separating out patients with MUS in a primary care database and collating real-life data on the time taken for diagnosis, service use rates, number of consultations, investigations and referrals, presence of comorbid mental health issues and disease perpetuation of these patients; chapter 8 discussed GP-diagnosed MUS patients (patients who were diagnosed as patients with MUS by their GP), chapter 9 the EHR-defined MUS patient group (patients who met the criteria for MUS but had not received a diagnosis from their GP) and chapter 10 compared the findings for these two patient groups, and discussed if the real-life data from this large consulting population were able to support the findings of qualitative research about the diagnosis and management of MUS patients.

Calculating the costs of MUS patients to the NHS is the next key step of the study. The first step, in this chapter, **Chapter 11**, was to collate available information on the costs of patients with MUS to NHS England through a systematic review. This did not provide comprehensive data about these costs, therefore, **Chapter 12** collated electronic healthcare record data from the primary care database on the use of healthcare utilization (on consultations, investigations, prescriptions and referrals), and publicly available data on

the costs for such utilization, to calculate the annual mean cost per MUS patient to the NHS, for each of the GP-diagnosed and EHR-defined MUS patient groups separately.

As discussed in detail in Chapter 3, prevalence of MUS is high, ranging from 0.7% to 60.7% globally (Haller et al, 2015), and reported at 18% of consecutive attenders at GP practices (Taylor et al, 2012). Consequently, these patients are said to consume a disproportionate amount of health resources, often as a result of unnecessary investigations and inappropriate symptomatic treatments (Bermingham et al, 2010; Payne & Brooks, 2018).

The primary aim of cost of illness studies is to quantify the direct and indirect costs of an illness (Jo, 2014; Wang et al, 2017, further detail on cost of illness studies in chapter 11.2). They have been criticised for quantifying costs without considering the benefits gained from such expenditure, as knowing the costs alone do not help support decision making on healthcare expenditure allocation decisions (Byford et al, 2000; Currie, 2000). They are, however, considered useful in quantifying the costs of chronic diseases which incur expensive and repeated healthcare expenditure, and as the basis for further in-depth economic evaluations (Clabaugh & Ward, 2008; Zemedikun et al, 2021).

The earliest study related to the costs of MUS in England, termed the cost of neurosis in general practice in England, assessed the total cost at GBP370m in 1985, with a third of it the cost of treatment and two-thirds accounting for the cost of lost production (Croft-Jeffreys & Wilkinson, 1989). At the time, GP consultations accounted for 60% of the treatment cost and 40% for drugs. Although the problem of MUS is frequently framed in the literature as an issue of resource utilisation and economics (Hiller and Fichter, 2004; DeWitt et al, 2009; Barrett et al, 2012; Chew Graham et al, 2017), there is limited information on

costs of MUS in England. The 1%-2.5% of MUS patients said to utilise a disproportionately high amount of the resources are frequently mentioned; Bermingham et al estimated the costs of MUS at GBP2.89bn for 2008/2009, and the annual cost of sickness absence and the poorer quality of life at over GBP14bn. Subsequent publications extrapolated this data inaccurately to cite costs related to MUS of GBP11.64bn, or as 11% of total NHS spend for 2015/2016, and were corrected a few years later (Payne & Brooks, 2018; Chew-Graham et al, 2017).

Furthermore, the Bermingham estimates were derived using Dutch, German and US data due to the absence of data for England at the time. Similarly, citing lack of UK data, Fineberg et al (2013) estimated the costs of somatoform disorders using prevalence data from Central Europe, as part of a study on costs of disorders of the brain in the UK. Apart from these studies, there is one systematic review of costs of medically unexplained symptoms carried out by Konnopka et al in 2012, which included two cost of illness studies from the UK (Morriss et al, 1998; Seivewright et al, 2008).

The most significant problem in collating information on costs of illness is the heterogeneity of methodologies used in the different studies (Costa et al, 2012; Konnopka & Konig, 2019). Therefore, this chapter collates information on and analyses the characteristics of cost of illness studies, including the key factors affecting heterogeneity and how they can impact cost of illness estimates. It then carries out a systematic review to collate all published information regarding the costs of MUS in England. The time frame is limited to studies after 2000, since data prior to that is too historical to be relevant. The primary focus is cost-of-illness studies, however, given the paucity of published studies in this area, all studies

including cost-effectiveness evaluations were reviewed to extract available data related to the healthcare system and societal cost of MUS. The quality of the studies is reviewed, not with the intention of excluding studies but to explore their relevance and credibility (Stuhldreher et al, 2012; Zemedikun et al, 2021).

11.2 Characteristics of cost of illness studies

The key factors accounting for the majority of study heterogeneity include: illness/disease definition, epidemiological approach, study perspective, type of costs, methodological approach to costing, valuing unit costs, and in discounting costs (Costa et al, 2012; Christensen et al, 2020; Konnopka & Konig, 2019; Wang et al, 2017). How these factors can impact cost of illness studies on MUS is briefly examined below:

Illness definition: The way an illness is defined in a cost of illness study impacts the types of patients included in the study, and therefore the reported costs. In the case of MUS, which are an illness without a broadly agreed upon name or definition; although it is now covered under the category Somatic Symptom Disorder under DSM-5 and under Bodily Distress Disorder in ICD-11, the terms MUS or MUS remain the most commonly used, neutral description to discuss the clinical presentation of symptoms for which significant pathology cannot be detected (Jones, 2019; Stortenbeker, 2020; Jungmann and Witthoft, 2020; olde Hartman et al, 2009). A scoping review indicated that there are a number of studies specifically focusing on one of the medically unexplained symptom syndromes, irritable bowel syndrome, fibromyalgia and chronic fatigue. Other studies focused on health anxiety, on generic medically unexplained physical symptoms or a specific type of MUS such as non-cardiac chest pain.

Epidemiological approach: Prevalence based studies, which measure the costs related to the illness during a specific time period (e.g. one year), are the most common approach and can help in healthcare expenditure planning; incidence-based cost-of-illness studies, which measure the life-time costs of an illness, can be useful in planning long-term management and prevention of an illness (Jo, 2014; Christensen et al, 2020).

Types of costs: Direct costs include direct healthcare costs incurred in diagnosing and treating the illness (e.g., for MUS, primary care: GP, nurse, therapist, pharmaceutical and imaging costs; secondary care: inpatient costs, emergency treatment, specialist doctor costs). Direct non-healthcare costs refer to additional costs incurred in providing / gaining access to treatment such as social services, counselling, transportation costs, child-care costs. Indirect costs refer to productivity losses that can be monetarily measured resulting from morbidity and mortality, absenteeism etc. Although intangible costs (e.g., psychological pain patients and their families suffer) are important, they are quite difficult to quantify and therefore are very rarely incorporated in to cost-of-illness studies (Tarricone, 2006; Jo, 2014; Christensen, 2020).

Cost Perspective: Most cost-of-illness studies are carried out from the perspective of the healthcare system – for which all medical costs incurred by for example the NHS in England are considered. Where a societal perspective is considered, in addition to medical costs, all costs of morbidity, mortality, and non-medical costs such as transportation costs need to be included in the cost assessment. Expanding this to the Government perspective would require including costs such that those related to criminal justice, rehabilitation as well.

In countries such as the USA where health insurance plays a key role, the third-party payer perspective may be considered, in which case, covered medical and mortality costs would be included. When assessing from a business owner's perspective, all covered medical costs and productivity losses due to absenteeism and mortality would be considered. Lastly, a study may take the perspective of the patient and the family, in which case, the out-of-pocket costs for medical care, loss of wages and household production due to morbidity and mortality, out of pocket payments for non-medical costs would all be considered. Jo (2014) refers to Luce et al (1996) and provides a detailed list of each type of cost and describes which costs are included in each different perspective.

Methodological approach to costing: Where the cost-of-illness study is prospective, costs are usually estimated using the bottom-up, micro-costing approach: using clinical trial data, patient/caregiver questionnaires and detailed records, the healthcare resource use data is collected for an individual patient during the time period, the unit cost for each type of use is then estimated, and the total cost for each patient is calculated by multiplying the unit costs by the usage. Micro-costing involves identifying resource usage at a detailed level, whereas gross costing involves identifying aggregated resource usage.

Where the study is retrospective, studies can use either the bottom-up approach or a top-down approach; the top-down approach calculates the cost of an illness by multiplying total health expenditure by the rate of utilisation of health services by all the patients with that disease to arrive at disease specific costs (Jo, 2014; Spacirova et al, 2020; Tekin et al, 2021). Each of these approaches have their own problems: results from top-down approaches vary depending on population size, healthcare system type, prices and frequency of treatment

considered. The bottom-up approach can be problematic as these studies are carried out usually from a payer/healthcare system perspective, with widely varying population sizes, types of costs included varying between studies, resulting in considerable heterogeneity. Furthermore, the small sample sizes of clinical trials which employ the bottom-up approach can lead to skewed data. (Drummond, 1992; Tarricone, 2006; Jo, 2014).

A third method, the econometric approach estimates the difference in costs in two matched groups with and without the disease, either a mean differences approach or a multiple-stage regression approach to determine the incremental difference that can be attributed to the disease (Jo, 2014).

Valuing unit costs: The unit cost of each direct and indirect cost types need to be assessed so that the number of units of usage can be multiplied by the unit cost to arrive at the total cost of a given treatment or procedure. For studies based in England, this is usually taken from aggregated and summarised NHS data. The Human Capital Approach (Weisbrod, 1961), the Friction Cost method (Koopmanschap, 1992) are the methods most commonly used to assess indirect costs (Krol & Brouwer, 2014; Versteegh et al, 2016).

The Human capital approach considers productivity losses to be equal to the value of a person's earnings had he been able to work during the entire time the person is unable to work, whereas the friction-cost approach equates productivity losses to the value of the person's earnings over the time taken to replace the absent worker. The willingness to pay approach has been used to estimate the monetary value of intangible costs (Xie et al, 2008) whereas informal care time can be valued using a number of methods including the

opportunity cost approach or the replacement cost approach (Van de Berg et al, 2006; Koopmanschap et al, 2008).

11.3 Systematic review: costs of patients with MUS in England

11.3.1 OBJECTIVES

To collate available information on the costs of patients with MUS in England.

The systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Liberati et al, 2009) guidelines.

11.3.2 SEARCH STRATEGY

A literature search was carried out on electronic databases (Embase, Medline, CINAHL Plus, APA Psycinfo, Pubmed, Econlit, Cochrane database of systematic reviews, NICE Evidence Service and NHS EED) for peer reviewed papers published in English between 2000 and December 2021. The searches were carried out using a combination of keyword searches and medical subject headings (MeSH) with the search strategy focused around three themes:

1) Geographic location: Search keywords include all four parts of the United Kingdom to ensure a comprehensive search; however, only studies carried out in England were included in the study.

2) Disease focus: Medically Unexplained Physical Symptoms and the three most commonly discussed Symptom Syndromes, Irritable Bowel Syndrome, Chronic Fatigue Syndrome and Fibromyalgia, and

3) Cost focus - costs or expenses.

The key terms of these three components were combined using the Boolean logic terms ("OR" / "AND") as shown below in Figure 11.1.

S1 – (england or britain or uk or united kingdom or great britain or wales) OR (scotland or scottish or scots) OR (northern ireland or ni or north ireland)

S2 - ('somatoform disorders' or 'somatization disorders' or 'medically unexplained symptoms') OR ('hypochondriasis' or 'hypochondriac' or 'hypochondria' or 'illness anxiety disorder' or 'health anxiety' or 'somatic symptom disorder') OR ('functional somatic symptoms' or 'functional somatic disorders' or 'functional somatic syndrome') OR 'persistent physical symptoms' OR ('medically unexplained physical symptoms' or 'multiple unexplained symptoms') OR ('psychosomatic disorders' or 'psychosomatic symptoms' or 'psychophysiological disorders') OR ('bodily distress syndrome' or 'bodily distress disorder') OR ('irritable bowel syndrome' or ibs) OR ('chronic fatigue syndrome' or 'myalgic encephalomyelitis' or me/cfs) OR (fibromyalgia or 'fibromyalgia syndrome' or fms or fm) OR ('non cardiac chest pain' or 'premenstrual syndrome' or 'temporomandibular joint dysfunction syndrome') OR ('functional neurological disorder' or 'conversion disorder')

S3 – (costs or cost or expense or financial burden) OR economic burden OR resource utilization

Figure 11.1: Sample search strategy – AMED, MEDLINE, APA Psycinfo, CINAHL Plus, APAPsycArticles, EconLit via EBSCOhost interface

The database search was complemented by citation chaining, searching the reference lists of key papers identified. Studies were limited to peer reviewed studies, to the English language alone and to studies published between 2000 and December 2021.

11.3.3 INCLUSION AND EXCLUSION CRITERIA

Participants: Studies published between 2000 and 2021 on adult patients with medically unexplained physical symptoms including symptom syndromes without any restrictions based on the type of MUS were included. Studies focusing specifically on children or young adults, below 18 years,, and those that included both patients with organic illness as well as patients with MUS were excluded. In the case of studies using top-down approaches for cost estimation, studies calculating costs for UK or for England were included. In the case of bottom-up approaches, studies with patients located in any part of England were included.

Interventions and comparators: All economic evaluations or cost-of-illness studies were included, as the number of cost-of-illness studies are limited. Cost data for patients prior to the intervention, or data for the treatment-as-usual arm were extracted in the case of cost-effectiveness studies to ensure that the costs considered were those under normal conditions (rather than during the intervention). Cost-effectiveness studies which did not provide sufficient data to assess the cost-of-illness under usual conditions were excluded.

Outcomes: Papers reporting outcomes including data on resource usage as well as cost estimates or calculations for patients with MUS under usual conditions (either as a 'treatment as usual' group or pre-intervention costs) were included.

Study design: Longitudinal or cross-sectional data from trial or non-trial data was included as were studies that reported on economic evaluations carried out in isolation or as part of

a trial on effectiveness. Studies that used top-down and bottom-up approaches to estimating cost of illness were included. Studies that did not include original data analysis, published protocols, dissertations, qualitative studies, reviews, abstracts, opinion pieces, and commentaries were excluded.

11.3.4 STUDY SELECTION

The search was carried out and duplicates were removed electronically and manually. Title and abstract screening was followed by full text review of identified relevant articles to select articles for inclusion in the study. Study selection and review was carried out by the researcher. The supervisor retrieved and reviewed a random sample of 25% of the studies for each stage of the selection process to confirm agreement, discrepancies resolved by discussion – following the process in Zemedikun et al, (2021).

11.3.5 DATA EXTRACTION

For the selected papers, study characteristics, illness definition used, epidemiological approach, types of costs included, cost perspective, the methodological approach to costing, and unit cost valuation were extracted using a template that was piloted using several key studies. Where the cost of illness data was to be extracted from trials, mean costs at baseline, prior to the intervention, which most closely approximates the service use and costs under normal conditions, were taken. Where the data was presented for two or three separate trial arms, the average across these arms was included.

11.3.6 ANALYSIS

Given the wide variety in the studies, they were categorised first in to three distinct groups: studies focusing on 1) Irritable Bowel Syndrome and its variants 2) Fatigue related studies including Fibromyalgia and 3) Generic medically unexplained symptoms and other. Then, the studies under each of these three groups were marked either as 1) Cost of Illness studies – where the primary aim of the study was presented as assessing the costs of illness and 2) Economic evaluations – where data on cost of illness for an MUS condition could be extracted, but this was not presented as the primary aim of the study. Thirdly, the studies were categorised based on their approach to calculating costs – a top-down approach or a bottom-up approach, and lastly, based on their perspective, NHS alone, or NHS and societal perspective. Where necessary, when cost data was provided for a period less than an year, the costs were extrapolated to estimate annual costs for comparability. The costs were reported alongside the costing year to obtain an overview of the evolution of costs over the past 20 years.

The findings are presented in the form of a narrative synthesis rather than a meta-analysis due to the heterogeneity of the studies. A descriptive summary of the studies and an overall assessment of the evidence generated from the study was presented.

11.3.7 QUALITY ASSESSMENT

There is no clear consensus on what tool is best for quality assessment in cost-of-illness studies; the Drummond checklist was adapted to COI studies by Molinier et al (2008) and by Stuhldreher et al (2012), both of which are frequently cited (Costa et al, 2012; Christensen et al, 2020; Angeles et al, 2021; Hajek et al, 2021). This study used the

Stuhldreher checklist as modified by Christensen et al (2020, Appendix 1) and assessed the quality of the selected papers. However, since the purpose of the study is to identify the costs of MUS, the intention was to be as inclusive as possible, and no studies were excluded from the review due to quality concerns.

11.4 Results

11.4.1. PRISMA flow diagram

The PRISMA flow diagram indicating the search and selection process of articles is shown in Figure 11.2.

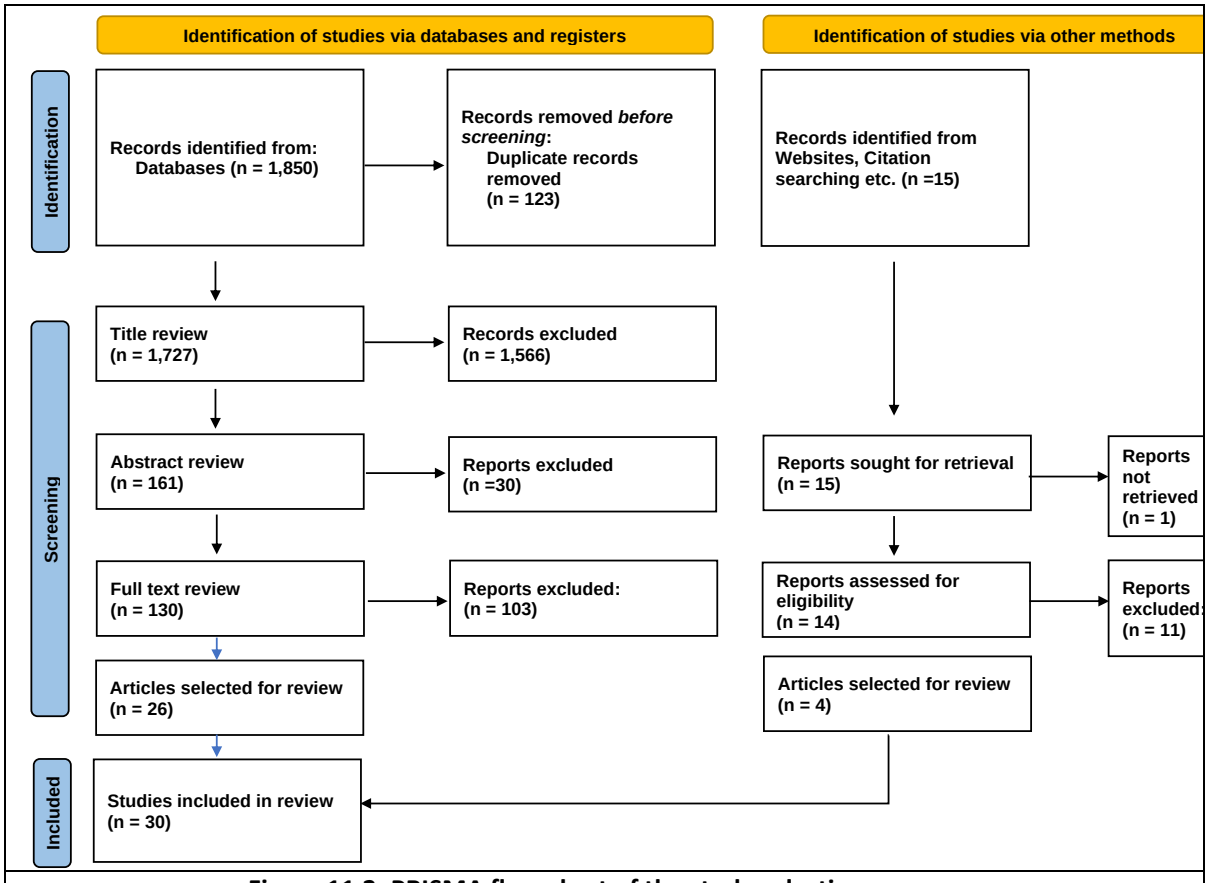


Figure 11.2: PRISMA flow chart of the study selection process

A systematic search of electronic data bases yielded 1,850 studies and other searches yielded 15 articles. After removal of duplicates, and title and abstract search, 1,153 articles were excluded, one article could not be retrieved, and 144 articles were subjected to full text review. Of these, 30 studies were selected to be included in the systematic review (Table 11.1). The studies were published between 2001 and 2021 and contained data from 1994/95 as the costing year to 2019.

Out of the thirty studies, four studies focused on health anxiety (Seivewright 2008, Barrett 2012, Tyrer 2014, Tyrer 2017 I), one on severe health anxiety (Morriss 2019), four on medically unexplained symptoms (Reid 2002, Reid 2003, Gathogo & Benjamin, 2013, Rohricht 2015) and one each on somatisation (Bermingham 2010) and non-cardiac chest pain (Tyrer 2017 II).

Nine studies focused on IBS (Akehurst 2002, Robinson 2006, Stamuli 2012, Soubieres 2015, Canavan 2016), including one on IBS with constipation (Tack 2019) and three on severe/refractory IBS (Creed 2003, Creed 2001, Everitt 2019).

Ten studies focused on Chronic Fatigue (Chisholm 2001, Sabes-Figuera 2010, Sabes-Figuera 2012, McCrone 2012) / Chronic Fatigue Syndrome (Clark 2021) / Chronic Fatigue and Chronic Fatigue Syndrome (McCrone 2003) / CFS/ME (O-Dowd 2006, Collin 2011, Richardson 2013) and one on Fibromyalgia (Soni 2020).

Of the thirty studies included, 14 were cost of illness studies. Sixteen were trials and thirteen of these trials included some form of cost-effectiveness analysis, one was a cost-consequence analysis, and two analysed cost reduction. Of the sixteen trials, baseline cost

data for participants were extracted from nine studies and costs of participants in the treatment as usual arm were extracted from seven studies.

11.4.1 SUMMARY OF MAIN CHARACTERISTICS OF INCLUDED STUDIES

The main characteristics of the selected studies are presented below, for three categories separately: Part 1) Medically unexplained symptoms, health anxiety and similar issues; Part 2) Irritable Bowel Syndrome and related illness ; 3) Chronic fatigue and related illness.

Table 11.1: Included studies: summary of main characteristics					
Part I. Medically unexplained symptoms, health anxiety, somatisation and related issues					
Author, Year	**Condition**	**Perspective**	**Study type**	**Economic analysis**	**Reference**
Reid 2002	Medically Unexplained Symptoms	NHS	Cohort study	Cost of illness study	Reid, S., Wessely, S., Crayford, T., Hotopf, M. 2002. Frequent attenders with medically unexplained symptoms: service use and costs in secondary care, *British Journal of Psychiatry.* 180, 248-253.
Reid 2003	Medically Unexplained Symptoms	NHS and societal	Cohort study	Cost of illness study	Reid, S., Crayford, T., Patel, A., Wessely, S., Hotopf, M. 2003. Frequent attenders in secondary care: a 3-year follow-up study of patients with medically unexplained symptoms, *Psychological Medicine*. 33:519-524
Seivewright 2008	Health Anxiety	NHS	RCT	Cost effectiveness analysis	Seivewright, H., Green, J., Salkovskis, P., Barrett, B., Nur, U., Tyrer, P. 2008. Cognitive–behavioural therapy for health anxiety in a genitourinary medicine clinic: randomised controlled trial. BJP. 193: 332-337
Bermingham 2010	Somatisation	NHS and societal	Collation of data	Cost of illness study	Bermingham, S.L., Cohen, A., Hague, J., Parsonage, M. 2010. The cost of somatisation among the working-age population in England for the year 2008-2009. *Mental Health in Family Medicine. 7: 71-84*
Barrett 2012	Health Anxiety	Health and social services	Cohort study	Cost of illness study	Barrett, B., Tyrer, P., Tyrer, H., Cooper, S. et al. 2012. An examination of factors that influence costs in medical patients with health anxiety. *Journal of Psychosomatic Research* 73:59–62
Gathogo 2013	Medically Unexplained Symptoms	NHS	Cohort study	Cost of illness study	Gathogo, E., Benjamin, C. 2013. Pilot of enhanced GP management of patients with MUS. https://dxrevisionwatch.files.wordpress.com/2013/06/esther-gathogo-charlotte-benjamin-pilot-enhanced-gp-management-medically-unexplained-sympthoms-kingsfund-may12.pdf

Tyrer, 2014	Health Anxiety	NHS	RCT	Cost effectiveness analysis	Tyrer, P., Cooper, S., Salkovskis, P., Tyrer, H. et al. 2014. Clinical and cost-effectiveness of cognitive behaviour therapy for health anxiety in medical patients: a multi-centre randomised controlled trial. *Lancet.* 383: 219-25
Rohricht, 2015	Medically Unexplained Symptoms	NHS	Clinical trial (not RCT)	Cost reduction analysis	Rohricht, F., Papadopoulos, N. 2015. Innovative and integrative care pathway for patients with MUS conditions. Available at https://www.health.org.uk/improvement-projects/integrative-care-pathway-for-patients-with-medically-unexplained-symptoms .
Tyrer 2017 I	Health Anxiety	NHS and societal	RCT	Cost effectiveness analysis	Tyrer, P., Salkovskis, P., Tyrer, H., Wang D. et al. 2017. Cognitive-behaviour therapy for health anxiety in medical patients (CHAMP): a randomised controlled trial with outcomes to 5 years. *Health Technology Assessment*. 21(50).
Tyrer, 2017 II	Non cardiac chest pain	NHS	RCT	Cost effectiveness analysis	Tyrer, P., Tyrer, H., Morriss, R., Crawford, M. et al. 2017. Clinical and cost-effectiveness of adapted cognitive behaviour therapy for non-cardiac chest pain: a multicentre, randomised controlled trial. *Open Heart* 4:e000582.
Morriss 2019	Severe health anxiety	NHS and societal	RCT	Cost effectiveness analysis	Morriss, R., Patel, S., Malins, S., Guo B et al. 2019. Clinical and economic outcomes of remotely delivered cognitive behaviour therapy versus treatment as usual for repeat unscheduled care users with severe health anxiety: a multicenter randomised controlled trial. *BMC Medicine*, 7:16
Part II. Irritable Bowel Syndrome and related illness					
Author, Year	**Condition**	**Perspective**	**Study type**	**Economic analysis**	**Reference**
Creed 2001	Severe, refractory IBS	NHS	Cross sectional survey	Cost of illness study	Creed, F., Ratcliffe, J., Fernandez, L., Tomenson, B. et al. 2001. Health-related quality of life and healthcare costs in severe, refractory irritable bowel syndrome. *Annals of Internal Medicine.* 134 (9Pt 2): 860-8

Akehurst, 2002	IBS	NHS	Case control study	Cost of illness study	Akehurst, R.L., Brazier, J.E., Mathers, N., O'Keefe, C. et al. 2002. Health-Related Quality of Life and Cost Impact of Irritable Bowel Syndrome in a UK Primary Care Setting. *Pharmacoeconomics.* 20 (7): 455-462
Creed 2003	Severe IBS	NHS	RCT	Cost effectiveness analysis	Creed, F., Fernandes, L., Guthrie, E., Palmer, S. et al. 2003. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology.* 124:303-317
Robinson 2006	IBS	NHS	RCT	Cost reduction analysis	Robinson, A., Lee, V., Kennedy, A., Middleton, L., et al. 2006. A randomised controlled trial of self-help interventions in patients with a primary care diagnosis of irritable bowel syndrome. *Gut.* 55:643-348
Stamuli, 2012	IBS	NHS	RCT	Cost effectiveness analysis	Stamuli, E., Bloor, K., Macpherson, H., Tilbrook, H. et al. 2012. Cost-effectiveness of acupuncture for irritable bowel syndrome: findings from an economic evaluation conducted alongside a pragmatic randomised controlled trial in primary care. *BMC Gastroenterology*. 12:149.
Soubieres, 2015	IBS	NHS	Cohort study	Cost of illness study	Soubieres, A., Wilson, P., Poullis, A., Wilkins, J., Rance, M. 2015. Burden of irritable bowel syndrome in an increasingly cost-aware National Health Service. *Frontline Gastroenterology.* 6: 246-251.
Canavan 2016	IBS	NHS	Cohort study	Cost of illness study	Canavan, C., West, J., Card, T. 2016. Calculating Total health service utilisation and costs from routinely collected electronic health records using the example of patients with irritable bowel syndrome before and after their first gastroenterology appointment. Pharmacoeconomics. 34:181-194
Everitt 2019	Refractory IBS	NHS and societal	RCT	Cost effectiveness analysis	Everitt, H., Landau, S., Little, P., Bishop, F.L. et al. 2019. Therapist telephone-delivered CBT and web-based CBT compared with treatment as usual in refractory irritable bowel syndrome: the ACTIB three-arm RCT. Health Technology Assessment. 23(17).

Tack, 2019	IBS-C	NHS	Cohort study	Cost of illness study	Tack, J., Stanghellini, V., Mearin, F., Yiannakou, Y. et al. 2019. Economic burden of moderate to severe irritable bowel syndrome with constipation in six European countries. *BMC Gastroenterology 19: 69.*
Part III. Chronic fatigue, Myalgic Encephalitis, and related illness					
Author, Year	**Condition**	**Perspective**	**Study type**	**Economic analysis**	**Reference**
Chisholm 2001	Chronic fatigue	NHS and societal	Trial	Cost-Consequence analysis	Chisholm, D., Godfrey, E., Ridsdale, L., Chalder, T. et al. 2001. *British Journal of General Practice.* 51:15-18
McCrone, 2003	Chronic fatigue and Chronic Fatigue Syndrome	NHS and societal	Cohort study	Cost of illness study	McCrone, P., Darbishire, L., Ridsdale, L., Seed, P. 2003. The economic cost of chronic fatigue and chronic fatigue syndrome in UK primary care. *Psychological Medicine.* 33: 253-261
O'Dowd 2006	CFS/ME	NHS	RCT	Cost effectiveness analysis	O'Dowd, H., Gladwell, P., Rogers, C.A., Hollinghurst, S., Gregory, A. 2006. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. *Health Technology Assessment.* 10: 37
Sabes-Figuera 2010	Chronic fatigue	NHS and societal	Cohort study	Cost of illness study	Sabes-Figuera, R., McCrone, P., Hurley, M., King, M., Donaldson, A.N., Ridsdale, L. 2010. The hidden cost of chronic fatigue to patients and their families. *BMC Health Services Research*. *10:56*
Collin 2011	CFS/ME	Societal	Cross sectional study	Cost of illness study	Collin, S.M., Crawley, E., May, M.T., Sterne, J.A.C. et al. 2011. The impact of CFS/ME on employment and productivity in the UK: a cross-sectional study based on the CFS/ME national outcomes database. *BMC Health Services Research. 11:217*
McCrone, 2012	Chronic fatigue	NHS and societal	RCT	Cost effectiveness analysis	McCrone, P., Sharpe, M., Chalder, T., Knapp, M. et al. 2012. Adaptive pacing, Cognitive behaviour therapy, Graded exercise and specialist medical care for chronic fatigue

					syndrome: a cost-effectiveness analysis. *PLoS ONE* 7(8): e40808.
Sabes-Figuera 2012	Chronic fatigue	NHS	RCT	Cost effectiveness analysis	Sabes-Figuera, R., McCrone, P., Hurley, M., King, M., Donaldson, A.N., Ridsdale, L. 2012. Cost-effectiveness of counseling, graded-exercise and usual care for chronic fatigue: evidence from a randomised trial in primary care. *BMC Health Services Research*. 12:264
Richardson 2013	CFS/ME	NHS and societal	RCT	Cost effectiveness analysis	Richardson, G., Epstein, D., Chew-Graham, C., Dowrick, C., Bentall, R.P. et al. (2013). Cost-effectiveness of supported self-management for CFS/ME patients in primary care. *BMC Family Practice.* 14:12
Soni 2020	Fibromyalgia	NHS	Cohort study	Cost of illness study	Soni, A., Santos-Paulo, S., Segerdahl, A., Javaid, M.K., et al. 2020. Hospitalization in fibromyalgia: a cohort-level observational study of in-patient procedures, costs and geographical variation in England. *Rheumatology*. 59: 2074-84.
Clark 2021	CFS	NHS and social care (**not** societal costs)	RCT	Cost effectiveness analysis	Clark, L.V., McCrone, P., Pesola, F., Vergara-Williamson, M. White, P.D. 2021. Guided graded exercise self-help for chronic fatigue syndrome: Long term follow up and cost-effectiveness following the GETSET trial. *Journal of Psychosomatic Research.* 146: 110484.

11.4.2 METHODOLOGICAL CHARACTERISTICS OF INCLUDED STUDIES

Illness definitions:

Health anxiety: The studies on severe / health anxiety used the Health Anxiety Inventory (HAI) score >20 (Seivewright 2008), the Structured Clinical Interview for the DSM-IV Axis I disorders (Barrett 2012), both the HAI and the SCI (Tyrer 2014), the Severe Health Anxiety Inventory (SHAI) score >18 (Morriss 2019) and GP/specialist diagnosis to define illness.

Medically unexplained symptoms: Patients with MUS were identified through medical record examination defined as patients presenting with physical symptoms, where investigations and clinical examination showed no/trivial/incidental abnormalities (Reid 2002, Reid 2003) and through GP assessment of patients presenting with physical symptoms not explained by organic pathology (Gathogo & Benjamin, 2013, Rohricht 2015).

Somatisation: Measured according to DSM criteria (Bermingham 2010).

IBS: Two studies used Rome I criteria to define illness (Akehurst 2002, Tack 2019); others used IBS specific ICD-10 codes (Soubieres 2015), IBS specific Read Codes (Canavan 2016) and GP/specialist diagnosis (Robinson 2006, Stamuli 2012). Severe/refractory IBS, patients with severe IBS not responding to usual treatment (Creed 2001), was defined using Rome I criteria along with prolonged symptom duration and lack of response to usual treatment (Creed 2003), and Rome III criteria with an IBS symptom severity score >75 (Everitt 2019).

Epidemiological approach: All 30 studies were prevalence-based studies assessing the costs of the illness for all cases during the time period, rather than for new cases during the period alone as would be done in an incidence-based study.

Cost Perspective: Of the 30 studies included, 17 reported from the NHS perspective alone, one from the societal perspective alone, and one from a NHS and social care perspective. The remaining 11 reported costs from both the NHS and Societal perspective.

Types of costs: All studies calculated patient costs based on direct costs: primary care visits, medication, other community costs, diagnostic tests and hospitalisations. The thirteen studies which reported on societal costs as well included studies that reported on indirect healthcare costs such as informal care (Chisholm 2001, Sabes-Figuera 2010, McCrone 2012, Richardson 2013, Morriss 2019) and on productivity costs (Reid 2003, Bermingham 2010, Sabes-Figuera 2010, Collin 2011, McCrone 2012, Richardson 2013, Everitt 2019). The type of costs included were primarily consultations, prescriptions, investigations, inpatient and outpatient care costs.

Methodological approach to costing: One study alone (Bermingham 2010) took a top-down approach to cost estimation – all others took a bottom-up approach (costing methodology described in Chapter 11.2).

Valuing unit costs: The unit costs were valued using PSSRU data for England.

11.4.3 QUALITY ASSESSMENT

The quality assessment questions were adapted from the Stuhldreher checklist (2012) as modified by Christensen et al (2020) and reported on if the criteria were met (Y), partially met (P) or not met (N) (Table 11.2). Where a question was not applicable (e.g. discounting was not applicable for studies less than 1 year), NA (not applicable) was reported. All the studies were of reasonable quality, with the majority of criteria at least partially met,

therefore there were no exclusions on quality grounds in these papers, since after careful assessment, it was decided that the methodological shortcomings were not severe enough to affect the accuracy of the cost calculations.

Table 11.2: Study quality assessment															
Author, Year	1. Study objective reported	2. Disease and diagnostic criteria (ICD/DSM etc) reported	3. Characteristics of disease group reported (sample size, age, gender)	4. Perspective of analysis reported	5. Sources (epidemiological data, health care use and unit costs) reported	6. Currency reference year	7. Costing methods reported in detail	8. Units of reported measures stated (e.g. mean annual / total costs)	9. Results discussed in relation to other studies if available	10. Limitations discussed	11. Discounting done where relevant and discount rate reported	12. Missing data proportion and imputation method described if applied	13. Sensitivity analysis carried out	14. Uncertainty estimates (SD / uncertainty estimates)	15. Conclusions allowing for uncertainty inherent in the results
Akehurst 2002	Y	Y	Y	P	P	Y	P	Y	Y	Y	NA	N	N	Y	P
Barrett 2012	Y	Y	Y	Y	P	Y	P	Y	P	Y	NA	N	N	P	P
Bermingham 2010	Y	P	P	Y	Y	P	P	Y	Y	Y	NA	NA	Y	N	P
Canavan 2016	Y	Y	Y	Y	P	Y	P	Y	Y	Y	NA	Y	Y	Y	Y
Chisholm 2001	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	NA	NA	Y	Y	Y
Clark 2021	Y	Y	Y	Y	P	Y	N	P	N	Y	N	Y	Y	Y	Y
Collin 2011	Y	Y	Y	Y	Y	P	P	Y	Y	Y	NA	N	P	P	Y
Creed 2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Creed 2003	Y	Y	Y	Y	Y	Y	P	P	Y	Y	NA	Y	Y	Y	Y
Everitt 2019	Y	Y	Y	Y	P	Y	P	P	Y	Y	NA	Y	Y	Y	Y
Gathogo 2013	Y	N	Y	Y	P	Y	P	Y	Y	N	NA	N	N	N	Y
McCrone, 2003	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	NA	N	Y	Y	Y
McCrone, 2012	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	NA	P	Y	Y	Y
Morriss 2019	Y	Y	Y	Y	Y	P	P	Y	Y	Y	NA	Y	Y	Y	Y
O'Dowd 2006	Y	P	Y	P	P	P	P	P	P	P	NA	Y	P	Y	Y
Reid 2002	Y	Y	Y	P	Y	Y	Y	P	Y	Y	NA	P	NA	Y	Y
Reid 2003	Y	Y	P	Y	Y	Y	P	P	Y	Y	NA	P	N	Y	Y
Richardson 2013	Y	P	N	Y	Y	Y	Y	P	Y	Y	NA	Y	Y	Y	Y
Robinson 2006	Y	P	Y	Y	P	P	P	P	P	Y	NA	Y	P	Y	Y
Rohricht 2015	Y	Y	Y	P	P	P	P	P	Y	Y	NA	N	N	Y	Y
Sabes-Figuera 2012	Y	Y	Y	Y	P	Y	P	Y	Y	Y	NA	Y	Y	Y	Y
Sabes-Figuera 2010	Y	Y	Y	P	Y	Y	P	Y	Y	Y	NA	N	Y	Y	Y

Seivewright 2008	Y	Y	P	Y	P	Y	P	P	Y	Y	NA	Y	Y	Y	Y
Soni 2020	Y	Y	P	Y	Y	Y	N	P	Y	Y	NA	Y	Y	Y	Y
Soubieres, 2015	Y	Y	P	P	Y	P	Y	Y	Y	Y	NA	NA	NA	NA	NA
Stamuli, 2012	Y	P	P	Y	Y	P	Y	Y	Y	Y	NA	Y	Y	Y	Y
Tack, 2019	Y	Y	P	Y	Y	P	Y	Y	Y	Y	NA	Y	Y	Y	Y
Tyrer, 2014	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	NA	Y	Y	Y	Y
Tyrer 2017 I	Y	Y	P	Y	P	Y	P	P	Y	Y	Y	Y	Y	Y	Y
Tyrer, 2017 II	Y	Y	Y	Y	P	P	N	Y	Y	Y	NA	N	Y	Y	Y

11.4.4 COSTS REPORTED

Part 1: Medically unexplained symptoms, health anxiety and other

Three cost of illness studies reported on the costs of Medically Unexplained Symptoms, as did one trial with a cost reduction analysis (Table 11.3). The Reid 2003 study was the most comprehensive cost of illness study reporting mean annual cost per patient of GBP336 in Primary care, GBP438 in Secondary care, with a total cost of GBP774 to the NHS based on 1999/2000 costing year data. They calculated lost productivity costs of GBP1,708, resulting in total NHS + Societal costs of GBP2,482. The Gathogo 2013 study, which is the most recent available cost of illness study estimated annual cost per MUS patient to the NHS at GBP1,535 in 2011/2012 costs, however, this was a very small study of only 10 patients. The most recent available costs of MUS are reported from the Rohricht 2015 trial and cost reduction analysis, where annual per patient cost was estimated at GBP2,300 using 2014 costing data.

For health anxiety, the reported costs in the only cost of illness study, Barrett 2012, are much higher, annual per patient costs of GBP1,752 in primary care, GBP3,766 in secondary care, resulting in a total annual cost to the NHS of GBP5,280 per patient using 2009/2010 costing data. They reported other costs of GBP312 per patient, but did not estimate costs of lost productivity. The most recent trial reporting on severe health anxiety, Morriss 2019, reported mean annual cost per patient to primary care of GBP2,066, to secondary care of GBP986 and a total annual cost to the NHS of GBP3,052 to the NHS using 2017 costing data. In one of the rare studies on costs of non-cardiac chest pain, mean annual cost per patient to secondary care was estimated at GBP3,448 using 2013/14 costing data (Tyrer 2017 II).

Lastly, the only top-down study to estimate overall costs of MUS in England, the Bermingham 2010 study reported annual healthcare costs for the working age population of GBP2.892bn, output losses of GBP5.235bn and QALYs lost of GBP9.348bn, reporting a total cost burden of GBP17.475bn based on 2008/2009 costing data.

Part 2: Irritable Bowel Syndrome and related conditions

The early studies reported relatively lower mean annual cost per patient of GBP316 (Akehurst 2002), GBP211 (Robinson 2006), as shown in Table 11.4. The Soubières 2015 study investigated IBS costs in secondary care using IBS specific ICD-10 codes and Symptom codes suggestive of IBS, using Hospital Episode Statistics (HES) data and 2012-2013 costing data. The number of patients who had symptom codes suggestive of IBS recorded far exceeded those with diagnosis codes for IBS, both as outpatients (28,849 vs 1,982) and as admitted patients (112,790 vs 918). For those with symptom codes and diagnosis codes respectively, average cost per outpatient for the year was GBP381 / 410 and per admitted patient GBP824 / 792.

For the same costing year 2012/2013, the Canavan 2016 study estimated mean annual cost per patient to primary care at GBP2,063, to secondary care at GBP588, at a total cost of GBP2,651 to the NHS.

Severe/Refractory IBS was reported to be costlier, at around GBP1000 per patient per year to the NHS (Creed 2001, 2003). The most recent study on refractory IBS, Everitt 2019, estimated GBP1,403 per patient, per year cost to the NHS, alongside other costs of GBP1,815 and GBP992 of lost productivity costs, resulting in total NHS + Societal costs of GBP4,210, based on 2015/16 costing data.

Part 3: Chronic Fatigue, CFS, CFS/ME and related conditions

The costs of Chronic fatigue, CFS and related conditions have been comprehensively reported since early 2000's with reported mean annual cost per patient to the NHS steadily increasing from GBP480 in 1998 (Chisholm 2001) to GBP1,012 by 2010 (Sabes Figuera 2010) and GBP1,392 in 2016/2017 (Clark 2021) (Table 11.5). The annual mean lost productivity cost estimates are divergent ranging from GBP8,970 (Richardson 2013) to GBP15,697 (McCrone 2012) for 2008/2009/2010, the most recent years for which they are reported. Total NHS/ Societal costs have been estimated at a range of GBP17,875 (Richardson 2013) to GBP 23,332 (McCrone, 2012).

Productivity costs / societal costs have been examined only sporadically for MUS and IBS; estimates for NHS + Societal costs for chronic fatigue / CFS range from GBP7,628 in 2000 (McCrone, 2003) to GBP23,332 in 2009 (McCrone, 2012).

11.4.5. EVOLUTION OF COSTS OVER TIME

For MUS, the mean annual cost to the NHS had increased from GBP774 in 1999/2000 (Reid 2003) to GBP2,300 by 2014 (Rohricht et al, 2015). In health anxiety, the mean annual cost to the NHS rose from GBP634 in 2004/2005 (Seivewright, 2008) to GBP3,052 in 2017 (Morriss et al, 2019). The cost of IBS to the NHS has increased from a low of GBP211 in 2002 to GBP2,651 reported for 2012/2013 (Canavan 2016), but a later estimate for 2014 brought it down to GBP1,753 (Tack 2019). Indicating the disparities in cost estimates, the costs for severe/refractory IBS, which was around five times the cost for IBS in 2003 at GBP1,065 was estimated at GBP1,403 for 2015 (Everitt, 2019), which is lower than the cost estimates for

IBS. The mean annual cost of chronic fatigue and chronic fatigue syndrome, estimated at GBP708 for 2000 (McCrone, 2003) had increased to GBP1,492 by 2009 (McCrone, 2012), but was reported at a slightly lower level for Chronic Fatigue Syndrome in 2021 at GBP1,392 (Clark, 2021). It is possible that this finding of higher costs are an artefact of the focus on incidence.

Table 11.3: Reported costs of Medically unexplained symptoms, health anxiety, somatisation and other (*Trial data in italics*)											
Author, Year	**Condition**	**Study type**	**Sample size**	**Age range or mean**	**Costing year**	**Mean annual cost per patient (GBP)**					
						Iry care	**IIry care**	**Costs to NHS**	**Indirect costs**	**Productivity costs**	**NHS+Societal costs**
Reid 2002	Medically Unexplained Symptoms	Cohort/cost of illness	61	18-65 years	**1994/ 1995**		318				
Reid 2003	Medically Unexplained Symptoms	Cohort/cost of illness	61	18-65 years	**1999/ 2000**	336	438	774		1,708	2,482
Gathogo 2013	Medically Unexplained Symptoms	Cohort/cost of illness	10	44 years median	**2011/ 2012**	72	1,463	1,535			
Rohricht, 2015	*Medically Unexplained Symptoms*	*Trial/cost reduction analysis*	*93*	*21-75 years*	***2014***	*1,464*	*836*	*2,300*			
Seivewright 2008	*Health Anxiety*	*RCT / cost effectiveness analysis*	*26*	*16-65 years*	***2004/ 2005***			*634*			
Tyrer, 2014	*Health Anxiety*	*RCT*	*170*	*47 years*	***2008/ 2009***	*1,752*	*2,112*	*3,864*			
Tyrer 2017 I	*Health Anxiety*	*RCT*	*170*	*47 years*	***2009/ 2010 5-year follow up***			*2,667*			
Barrett 2012	Health Anxiety	Cohort/cost of illness	444	49 years	**2009/ 2010**	1,514	3,766	5,280	312		
Morriss 2019	*Severe health anxiety*	*RCT / cost effectiveness analysis*	*26*	*18-64 years*	***2017***	*2,066*	*986*	*3,052*	*209*		

Tyrer, 2017 II	*Non cardiac chest pain*	*RCT / cost effectiveness analysis*	*25*	*48.7 years*	***2013/ 2014***		*3,448*		*284*		
Total cost of somatisation in working age population in England (GBP)								**Health care costs**	**Output losses**	**QALYs lost**	**Total burden**
Bermingham 2010	Somatisation	Data collation/Cost of illness	NA	18-65 years	**2008/ 2009**			2.892bn	5.235 bn	9.348bn	17.475bn

Table 11.4: Reported costs of Irritable Bowel Syndrome and related conditions (*Trial data in italics*)

Author, Year	**Condition**	**Study type**	**Age range/ mean**	**Sample size**	**Costing year**	**Mean annual cost per patient (GBP)**					
						Primary care	**IIry care**	**Costs to NHS**	**Other costs**	**Produc-tivity costs**	**NHS + Societal costs**
Akehurst, 2002	IBS	Case control study/cost of illness	47 years	161	**1997/1998**	109	207	316			
Robinson 2006	*IBS*	*RCT / cost reduction analysis*	*40 years*	*420*	***2002/2003*** *(Estimated)*	*169*	*42*	*211*			
Stamuli, 2012	*IBS*	*RCT / CEA*	*Not given*	*97*	***2010***			*574*			

Soubieres, 2015	IBS	Cohort study / cost of illness	Not given	Outpatients: Diagnosed IBS: 1,982;	**2012-2013**		410				
				IBS-related symptoms: 28,849			381				
				Inpatients: Diagnosed IBS: 918			792				
				IBS-related symptoms" 112,790			824				
Canavan 2016	IBS	Cohort study / cost of illness	30-75 years	2,076	**2012**	2,063	588	2,651			
Tack, 2019	IBS-C	Cohort study / cost of illness	46 years	104	**2014**			1,753	3,407		
Creed 2001	Severe, refract. IBS	Survey / cost of illness	Not given	257	**1998-1999** (Estimated)			1,065			
Creed 2003	*Severe IBS*	*RCT / CEA*	*18-65 years*	*86*	***1997/1998***			*1,039*			
Everitt 2019	*Refractory IBS*	*RCT / CEA*	*43.1 years*	*187*	***2015/2016***			*1,403*	*1,815*	*992*	*4,210*

Table 11.5: Reported costs of Chronic Fatigue, CFS, CFS/ME and related conditions (*Trial data in italics*)											
Author, Year	**Condition**	**Study type**	**Age range or mean**	**Sample size**	**Costing year**	**Mean annual cost per patient (GBP)**					
						Iry care	**IIry care**	**Cost to NHS**	**Other costs**	**Producti-vity costs**	**Costs: NHS + Societal**
Chisholm 2001	*Chronic fatigue*	*Trial / cost consequence analysis*	*16-75 years*	*129*	***1998***	*164*	*316*	*480*	*1,936*	*1,176*	*3,592*
McCrone, 2003	Chronic fatigue and CFS	Cohort study/ cost of illness	16 - 75 years	141	**2000/ 2001**			708	5,816	1,104	7,628
O'Dowd 2006	*CFS/ME*	*RCT / CEA*	*41.1 years*	*51*	***2003***	*161*	*294*	*455*			
Sabes-Figuera 2010	Chronic fatigue	Survey / cost of illness	16 - 75 years	222	**2006/ 2007**			1,012	2,044	4,700	7,756
Sabes-Figuera 2012	*Chronic fatigue*	*RCT / CEA*	*41 years*	*54*	***2006/ 2007***			*852*			
McCrone, 2012	*Chronic fatigue*	*RCT / CEA*	*38 years*	*640*	***2009/ 2010***	*1,402*	*90*	*1,492*	*6,142*	*15,697*	*23,332*
Richardson 2013	*CFS/ME*	*RCT / CEA*	*Not given*	*92*	***2008/ 2009***	*1,011*	*910*	*1,921*	*6,984*	*8,970*	*17,875*
Clark 2021	*CFS*	*RCT / CEA*	*38 years*	*158*	***2016/ 2017***	*1,268*	*124*	*1,392*	*6,888*		
Soni 2020	Fibromyalgia	Cohort study / COI	Peak 45-55 years	24,295	**2019** (Estimate)	Per episode cost of hospitalisation: Fibromyalgia Cost of 24,295 inpatient admissions in 4 years					£ 832 £20 million
Collin 2011	CFS/ME	Cross section/ COI	18-64 years	2,170	**2006-2010**	Loss of productivity per person per annum Total loss of productivity for 2,170 patients					£ 22,684 £49 million

11.5 Discussion

This study attempted to comprehensively report on the costs of medically unexplained symptoms in England. When considering MUS/Health Anxiety, IBS and Fatigue related conditions separately, the number of studies were limited: c.9/10 studies for each condition spread out over 20 years, which made a meaningful comparison difficult. Converting to a single year currency value was not carried out in an attempt to examine how the costs had evolved over the twenty-one years of the study period. Table 11.6, which summarises the most recent available data on the costs of MUS for England, indicates the wide disparity in the reported costs.

Table 11.6: Summary of most recent estimated costs of Medically Unexplained Symptoms, health anxiety and symptom syndromes to the NHS

Condition	Study Author and Year	Costing year	Cost to the NHS
MUS	Rohricht 2015	2014	2,300
Health Anxiety	Tyrer 2017 I (5-year follow-up) Morris 2019 (Severe health anxiety)	2009 – 2013 2017	2,667 3,052
IBS	Canavan 2016 Tack 2019 (IBS-C) Everitt 2019 (Refractory IBS)	2012 2014 2015	2,651 1,753 1,403
Chronic Fatigue / Chronic Fatigue Syndrome	McCrone 2012 Richardson 2013 Clark 2021	2009 2008 2016	1,492 1,921 1,392

For each of the three types of illness considered, there was wide variation in the reported costs, indicating the wide variation in how MUS is defined and operationalised and the lack of consensus on costing and cost calculation methodology. Although most studies reported similar cost categories in primary and secondary care (consultations, prescriptions, investigations, inpatient and outpatient care costs), the reported costs vary widely, indicating both lack of comprehensive data and agreement on what costs should be

included. For example, the Gathogo 2013 study reported GBP72 as mean annual cost per MUS patient in primary care (2011/2012 data) whereas the Rohricht study reported GBP1,464 as the mean annual cost per MUS patient (2014 data). The difference is too large to be explained by the different number of average contacts per patient per year in the studies (12 vs 14.5), and may be due to the different methods of costing – the Gathogo study costs the GP time based on GBP171.67 per registered patient for GMS contract whereas the Rohricht study uses unit cost of GP contact at GBP46.80. The Gathogo study cost for GP time appears quite understated even against the comparator the study itself reports – the NHS commissioning support Unit 2008/2009 MUS Pilot, which reports GBP1,352 mean cost per patient per year as the cost of GP time, using an estimated cost of GBP34 per GP contact.

The cost variation is significant in the reported costs of IBS: the Canavan 2016 study reports that the cost of prescriptions account for around two-thirds of the total costs to the NHS, at c. GBP1,731 per patient per year, whereas the Everitt 2019 study reported medication costs of merely GBP23 – 36 per patient per year.

Cost estimates reported in trials also appear to vary according to the time frame of the trial as well: for example, the Tyrer 2014 study reports total mean cost per patient with health anxiety per year to the NHS of GBP3,864 using 2008/2009 costing data, where the RCT assessed cost data for 2 years. When the same patients' costs are assessed in a five-year follow-up reported in the Tyrer 2017 I study, the mean annual cost declined to GBP2,667 per patient.

It has been previously noted in conditions such as anxiety disorders that the cost estimates derived in clinical trials can be overestimations since the patients recruited for trials are usually not representative of the total population with the illness condition; this is due to the inclusion of patients currently in contact with the healthcare system in trials resulting in a proportionately higher number of sick/sicker individuals being included in the trial (Konnopka & Konig, 2019). This situation can be seen in the cost estimates of three studies on Chronic Fatigue related conditions around the same time period: Sabes-Figuera 2010, a survey that reports on the cost of illness, estimates annual per CFS/ME patient cost to the NHS at GBP1,012 based on 2006/2007 costing data. Using 2009/2010 data in a clinical trial, McCrone 2012 report annual per person costs to the NHS at GBP1,492 and Richardson 2013 report on an RCT using 2008/2009 data at GBP1,921, costs that are respectively 50% and almost 100% higher than the costs reported in the survey. Such differences are also possible where recall bias affects self-reported healthcare utilisation measures (Franklin & Thorn, 2019; Leggett et al, 2016).

Strengths, limitations and comparisons with other studies: This is the only review that has assessed the costs of medically unexplained symptoms for a single country over time. The only previous systematic review on costs of medically unexplained symptoms (Konnopka, 2012) did not focus on a particular country. The strength and importance of this review is that the focus on a single country over a period of twenty-one years displayed the disparities in the reported numbers, allowed assessment of how costs have changed over time, and the cost differentials reported between different categories of illnesses under the common umbrella of MUS. The study found that reported numbers vary significantly based

on study design and methodological approach. For example, mean costs tend to be lower as the duration of the study increases, a case in point being the Tyrer 2014 study (mean annual cost of GBP3,864 on a 12-month timeframe) and the Tyrer 2017 I study, a five-year follow up of the same patients, reporting a mean annual cost of GBP2,667. The study showcased the differential between cost estimates based on population studies using surveys, and estimates generated from trials and consulting populations (for example in the three reports on chronic fatigue syndrome). The reported costs of refractory IBS is lower than the cost of what is reported as IBS within a similar timeframe, indicating how different costing methodologies, timeframes, cost inclusions lead to distorted results. Such differences would not be demonstrated but for a comprehensive review of this nature.

Limitations of the review include the lack of clarity on methodology in some of the studies, and the difficulty in understanding if there was under / over estimation of costs, given the lack of detail on costs included, for example, some studies include costs of comorbidities such as depression / anxiety, which can significantly alter cost estimates. These problems are not unique to costs of MUS studies but common in research related to other conditions such as back pain and depression (Luppa et al, 2020; Costa et al, 2012).

Implications and recommendations:

The dire need for research based on commonly agreed, clearly defined criteria and standardised research methodology so that studies can be replicated and results are comparable is evident from this research. Building on from a recently published systematic review of cost of illness studies on back pain (Zemedikun et al, 2021), recommendations for good practice based on the review findings include:

- Guidelines and standardisation of methodologies for use in both cost of illness studies and cost effectiveness studies related to MUS is a critical need.
- Given the significant diversity in cases and the lack of consensus, a clearly defined, detailed, bottom-up approach to cost estimation is preferable to a top-down approach.
- Use of electronic health records for case selection, cost estimation, and follow up for longer time periods can help to estimate resource use and costs in these patients.

11.6 Conclusions and next steps

In summary, illness definitions, cost definitions, cost components and other methodological differences result in a wide disparity in reported costs of MUS studies. Awareness of the scale of this disparity in cost reporting is important as these widely varying cost data has been used to assess cost-effectiveness of both pharmacological and non-pharmacological interventions for management of MUS patients; such wide variation in cost data may well impact the results of the cost-effectiveness analyses. MUS diagnosis should be based on clearly defined, agreed upon criteria during cost assessments and further research is necessary to reach consensus on cost assessments for MUS and related conditions, which can improve the study quality and reporting analysis of cost of illness and cost effectiveness analyses.

Further research is necessary to reach consensus on cost assessments for MUS and related conditions.

CHAPTER 12
ESTIMATING THE COSTS OF MUS IN PRIMARY CARE IN ENGLAND

12.1 Introduction

As discussed previously following the systematic review of costs of MUS in England in Chapter 12, the data on the costs of patients with MUS to the NHS is inconclusive, although the literature often states that the costs of these patients to the healthcare system are excessive. Therefore, it was decided to assess the actual real-life costs to the NHS of MUS patients by collating their actual service use and published average costs of these services in a consulting population in primary care in England using routinely recorded EHR data.

12.2 Objectives

- To calculate the mean cost per patient per year to the NHS for each of the two specific groups of MUS patients: GP-diagnosed MUS patients and EHR-defined MUS patients.
- To compare the total and component cost per patient for these two patient groups and identify the factors driving the costs.
- To estimate total costs to the NHS for existing and newly diagnosed MUS patients.

12.3. Methods

12.3.1. STUDY POPULATION

The study examined the service use of two groups of patients separately: the 667 GP-diagnosed MUS patients (patients for whom a GP had recorded a MUS specific Read code as

described in Chapter 8) and the 2,044 EHR-defined MUS patients (patients who did not receive a GP diagnosis of MUS but had MUS-related symptom codes recorded, and met other criteria indicating presence of MUS, young age, frequent consultations, absence of organic disease, as detailed in Chapter 9).

12.3.2. SERVICE USE

As is typically measured in cost of illness studies (Sabes-Figuera et al, 2010; Collin et al, 2011), service use was measured for each individual patient annually for consultations, investigations and referrals recorded on the primary care electronic health record database per patient, per year for five years, starting with the Index year (Year 1) as described in detail in Chapter 8.3.2.

Consultations: The number of consultations per patient per year.

Investigations: Number of times each of the list of 650 investigation related Read codes developed in Chapter 7 (Appendix 7.4, detailed in Chapter 7.4.1) were recorded for each patient for five years.

Referrals: Number of times each of the list of Referral related Read codes used in the primary care database found in Chapter 7 (Appendix 7.5, detailed in Chapter 7.4.2) was recorded per patient per year.

Prescriptions: The database provides the job category of the person in the NHS who generated the consultation code. Consultation codes associated with an appointment with a consultant, a general medical practitioner, an associate practitioner, specialty nurse

practitioner, nurse or community practitioner, who are all authorised to prescribe medication, were considered as giving rise to a prescription.

12.3.3. SERVICE COSTS

Unit costs per consultation and out-patient visits were sourced primarily from the Personal Social Services Research Unit (PSSRU) data (https://www.pssru.ac.uk/project-pages/unit-costs/) and supplemented by NHS costing data (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) for each year 2007-2014 (Summary data in Table 12.1, detailed data on the relevant Read codes and associated costs in Appendix 12.1, cost for each Read code for investigations in Appendix 7.4, for Read codes related to referrals in Appendix 7.5). Read codes used in the primary care database were aligned with the most relevant costing data available from the PSSRU data by the researcher and verified by the lead supervisor.

Table 12.1: Summary of unit costs of healthcare

GBP	2007	2008	2009	2010	2011	2012	2013	2014
Primary care								
Mean cost - GP consultation (surgery, clinic, telephone)	35	32	32	33	31	37	38	39
Mean cost - non-GP consultation practitioners (nurse, associate)	10	11	12	14	19	18	18	18
Mean prescription cost per consultation	44	45	44	43	43	46	45	44
Weighted mean of community based follow-up attendances	118	111	111	117	132	135	125	113
Secondary care								
A&E	98	111	110	114	127	129	133	137
Day service / out-patient	137	140	164	152	147	139	135	139
In-patient - per finished consultant episode	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873

Consultations: The mean cost per surgery, clinic or telephone consultation was used as the mean cost of a GP consultation. The mean cost per consultation for nurse practitioners and specialist nurse practitioners were used to calculate the mean cost for practitioners other than GPs. Where the data was not available for a particular type of cost in a given year, the mean of the two adjacent years' costs was used, and where it was not available for two consecutive years, the HCHS price inflator for other costs given in PSSRU data was used to extrapolate the closest available year's data. Where costs were given in the form of per hour of client contact, a consultation was considered to last 15 minutes, using the mean of the times spent by a GP in surgery, clinic, or telephone consultation. Home visits were excluded since they account for less than 1% of consultations (Hobbs et al, 2016).

Referrals: As detailed in Appendix 7.5, PSSRU data provide mean costs per A&E visit, outpatient attendance, and for inpatients – per finished consultant episode. Read codes for admissions and inpatient stays were costed at the inpatient-per finished consultant episode for each year regardless of the number of inpatient days, due to the lack of further detailed data on utilisation and costs. All codes linked to referrals to hospital clinics / clinicians were costed at the cost per outpatient attendance for each year. Referrals to community care, mental health facilities were costed at the PSSRU rates provided.

Investigations: National average unit cost for each different type of investigation was sourced from NHS Reference costs available at https://webarchive.nationalarchives.gov.uk/ukgwa/20130104223439/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_082571. Weblinks to Reference costs for each year can be seen at

https://www.gov.uk/government/news/reference-cost-guidance--2 . The costs are available separately for Primary Care Trusts, for NHS Trusts and Foundation Trusts or as combined data. Primary care trust data was used where available; where it was not combined mean cost data was used. The cost of all Read codes related to investigations in Appendix 7.4 were estimated at the closest relevant national average unit cost in the year these costs were incurred.

Prescriptions: PSSRU data provides the mean prescription cost per consultation on an annual basis and this data, given in Appendix 11.1, was used to calculate the cost of prescriptions per patient per year. Although prescription data for individual patients were available from the primary care database, studying a sample from this data for costing indicated that there was no significant incremental benefit to calculating prescription costs individually for all patients rather than using mean prescription cost per consultation.

12.3.4. ANALYSIS

The number of consultations in the index year, and the mean over five years was calculated for each patient, for GP-diagnosed MUS and EHR-defined MUS patient groups separately, and per index year sub-group of patients for each of the index years 2007 – 2010 (i.e., all patients diagnosed by a GP in 2007; all patients first defined as MUS by the EHR search mechanism in 2007, and so on).

The costs of consultations, prescriptions, investigations and referrals were also compared similarly, and combined to arrive at the total costs per patient for the index year; the mean cost per patient per year for the index year and over five years of the study were calculated.

The mean costs and their components for each patient group were analysed to identify the factors driving the costs.

Statistical analysis was carried out to establish if there was a statistically significant difference between the mean costs incurred by GP-diagnosed MUS patients and EHR-defined MUS patients. The Mann-Whitney U test can be used to test whether two sample means are equal or not when the assumptions of the t-test are not met, as in this case, where neither patient group showed a normal distribution.

To estimate the total cost of illness for MUS in England, the mean cost per patient per year calculated from this study is combined with published NHS data on the total number of patients consulting for MUS in England annually (Davies & Drummond 1994). Secondly, the incidence rate and the mean cost per new MUS patient calculated in this study is combined with published data on consultation frequency to calculate the number of new MUS patients annually and to estimate the costs to the NHS of new MUS patients each year.

12.4 Results

Service use data was taken for 667 GP-diagnosed MUS patients and 2,044 EHR-defined MUS patients (details of these patients in Chapters 8 and 9 respectively).

12.4.1 Healthcare utilisation

The key data on healthcare utilisation in these patient groups is reproduced below from the detailed data in chapter 10.1.3 on – investigations / referrals and 10.1.4 on consultations.

12.4.1.1 Consultations:

Consultation frequency is higher by 78% in the index year and 35% in the 5-year mean in the EHR-defined patient group than in the GP-diagnosed group. The detailed data per index-year based sub-group of patients is given in Appendix 10.1.

Table 12.2: Resource utilisation in five years of study period – consultations

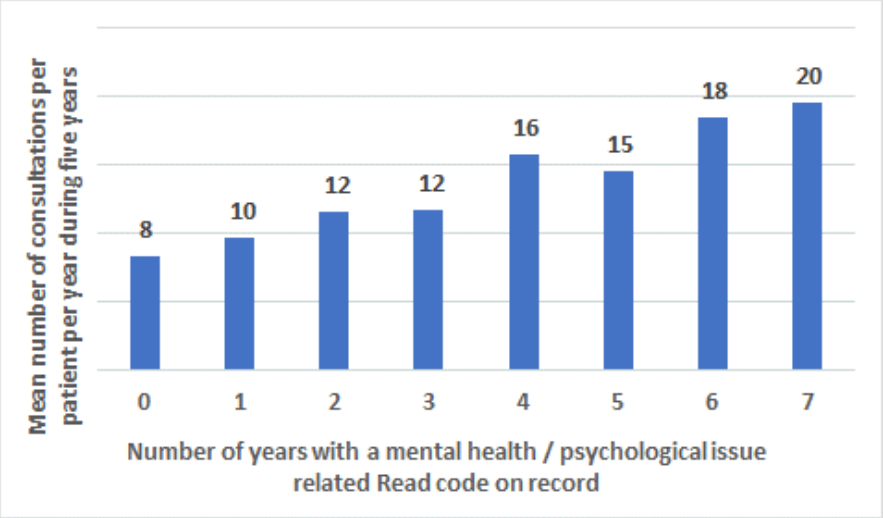
Mean number of consultations for all patients / (No. of patients in group)						**5-year mean**
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	
GP-diagnosed MUS patients (667)	12	11	10	11	12	11
EHR-defined MUS patients (2,044)	22	15	14	13	13	15
Difference	**78%**	**37%**	**31%**	**18%**	**9%**	**35%**

The mean consultation rate for both patient groups (11 and 15) are well above the age specific consultation rate for England of 3.1 (Hobbs et al, 2016), but well below the consultation frequency of the top 10% of most frequent attenders in the consulting population of England of 36.7 (Kontopantelis et al, 2021).

Table 12.3: Mean no. of consultations per patient per year compared for GP-diagnosed and EHR-defined MUS patients against the mean data for England

	England, age 18-55 years (2007 – 2014)	England, top 10% of most frequent consulters	GP-diagnosed MUS patients		EHR-defined MUS patients	
			Index year	Five-year mean	Index year	Five-year mean
Male	2.1		9	7	22	14
Female	4.1		13	13	22	15
Total	3.1	36.7	12	11	22	15

The consultation rate increases as the presence of mental health / psychological issues increase in a patient.



Mean annual Consultation rate during five years for patients:

a) with a mental health code: 13

b) without a mental health code: 8

Figure 12.1: GP-diagnosed MUS patients - mean number of consultations per patient per year according to duration of mental health / psychological issue related Read code recorded

12.4.1.2 Investigations and referrals

The GP-diagnosed MUS patients had less frequent investigations and referrals (39% and 42% respectively) compared to EHR-defined MUS patients (61% and 65%, Table 12.4). More patients in the GP-diagnosed MUS patient group had no investigations (17% cf.10% in EHR-defined group) and no referrals (21% cf.12% in EHR-defined group) carried out at all during the five years of the study. Data for patient sub-groups is found in Appendix 10.2.

Table 12.4: Investigations and referrals carried out for GP-diagnosed and EHR-defined MUS patients

Percentage of patients who had Investigations or referrals - for all patients / (No. of patients in group)						**No referrals / investigations for 5 years**
Investigations	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	
GP-diagnosed MUS patients (667)	42%	36%	38%	37%	42%	17%
EHR-defined MUS patients (2,044)	65%	43%	42%	43%	44%	10%
Referrals						
GP-diagnosed MUS patients (667)	39%	36%	29%	30%	32%	21%
EHR-defined MUS patients (2,044)	61%	41%	37%	37%	35%	12%

Prescriptions are costed based on the number of consultations with a GP, nurse or associate practitioner.

12.4.2 Costs per patient per year

The mean total cost per EHR-defined MUS patient in the Index year was GBP1,045, 70% higher than that of a GP-diagnosed MUS patient at GBP615 (Table 12.5). The five-year mean cost of GBP781 for an EHR-defined patients is 26% higher than the five-year mean of GBP618 for GP-diagnosed patients. The annual weighted mean cost of a new MUS patient is GBP939 in the index year and GBP741 over five years.

Table 12.5. Mean cost per patient per annum of consultations, prescriptions, referrals and investigations during the five years of the study period (GBP)

Total cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Mean**
GP-diagnosed MUS patients (n=667)	615	561	550	644	721	618
EHR-defined MUS patients (n=2,044)	1,045	709	686	720	747	781
Difference	***70%***	***26%***	***25%***	***12%***	***4%***	***26%***
Cost per MUS patient-weighted mean	**939**					**741**
Cost of consultations						
GP-diagnosed MUS patients (n=667)	232	218	229	270	302	250
EHR-defined MUS patients (n=2,044)	421	299	292	299	315	325
Difference	*81%*	*37%*	*28%*	*11%*	*4%*	*30%*
Cost of Prescriptions						
GP-diagnosed MUS patients (n=667)	216	206	211	242	263	227
EHR-defined MUS patients (n=2,044)	304	221	220	227	234	241
Difference	*41%*	*7%*	*5%*	*-6%*	*-11%*	*6%*
Costs of Referrals						
GP-diagnosed MUS patients (n=667)	111	97	79	99	100	97
EHR-defined MUS patients (n=2,044)	241	139	132	153	149	163
Difference	*117%*	*43%*	*68%*	*54%*	*50%*	*67%*
Cost of Investigations						
GP-diagnosed MUS patients (n=667)	55	40	32	32	56	43
EHR-defined MUS patients (n=2,044)	79	51	41	42	49	52
Difference	*43%*	*28%*	*27%*	*28%*	*-12%*	*21%*

Consultations accounted for the highest proportion of the total cost of both patient groups at 38% and 40% respectively; prescriptions had the second largest share at 35% and 29% in the two groups (Figure 12.2).

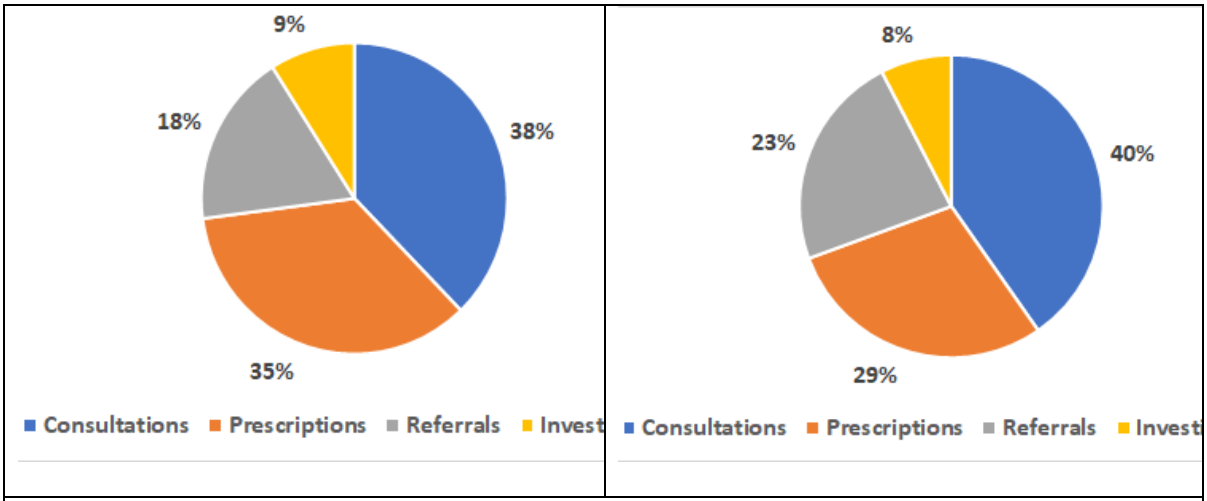


Figure 12.2. Composition of mean total cost per patient per year for GP-diagnosed (LHS) and EHR-defined MUS patients (RHS)

The mean cost of consultations was 81% higher for an EHR-defined patient at GBP421 per patient per year during the index year than for a GP-diagnosed MUS patient (GBP232), and the five-year mean 30% higher (GBP325 cf. GBP250).

The cost of referrals showed the largest difference between the two groups in the Index year, with the EHR-defined MUS patient group costing 117% over the GP-diagnosed group (GBP241 cf. GBP111) and the five-year mean was 67% higher in the EHR-defined MUS patient group (GBP163 cf. GBP67).

Charting the mean cost per patient per year shows that the cost is highest in the index year, declines until year 3 and rises thereafter, in both patient groups, and that the mean number of consultations per year follows the same trend (Figure 12.3).

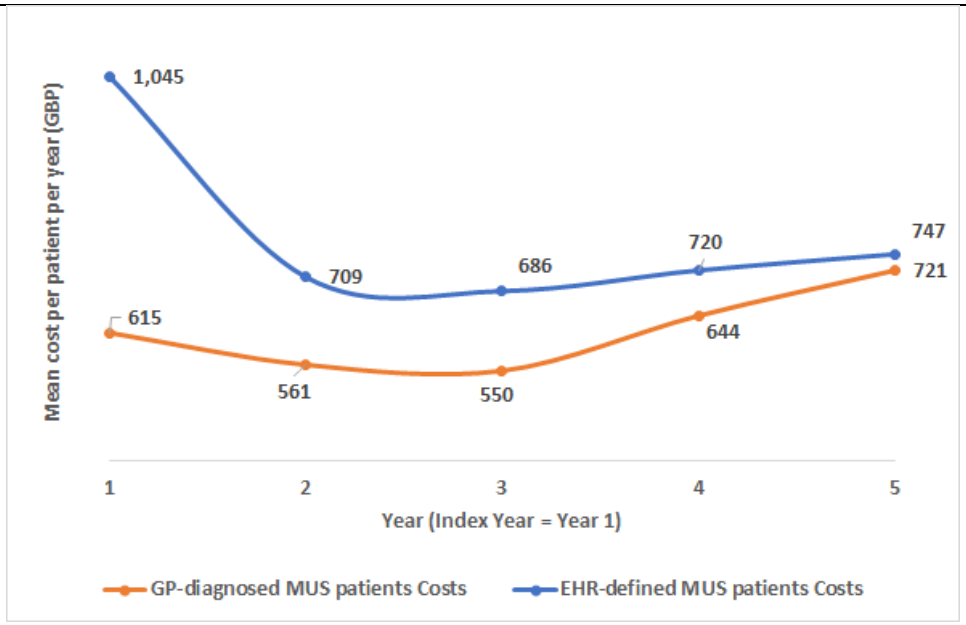


Figure 12.3. Mean cost per patient per year for GP-diagnosed / EHR-defined MUS patients

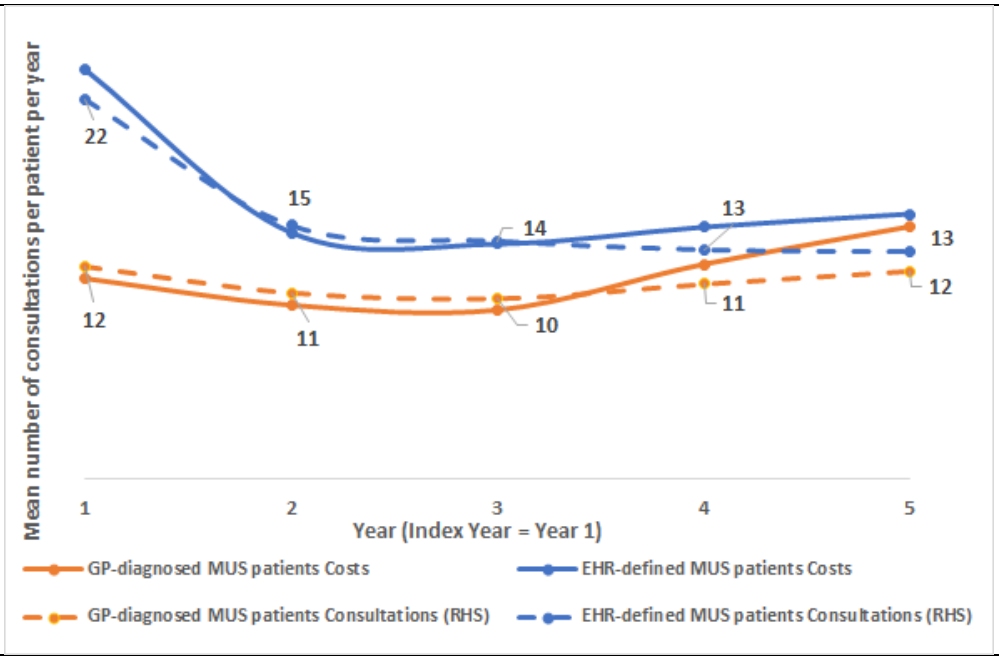


Figure 12.4. Mean number of consultations per patient per year for GP-diagnosed and EHR-defined MUS patients (alongside the mean cost per patient per year from the figure above)

The decline in sharper in the EHR-defined MUS patients group and even though there is some increase in the later years, it stays wells below the Index year costs. Costs for the GP-

diagnosed MUS patient group, on the other hand, is lower in the Index year, declines gradually until year 3 and then rises in the next two years, so that in the fifth year, there is only a 4% difference in the mean annual cost per patient between the two groups. The two histograms in Figure 12.5 show the distribution of mean annual costs in the two patient groups.

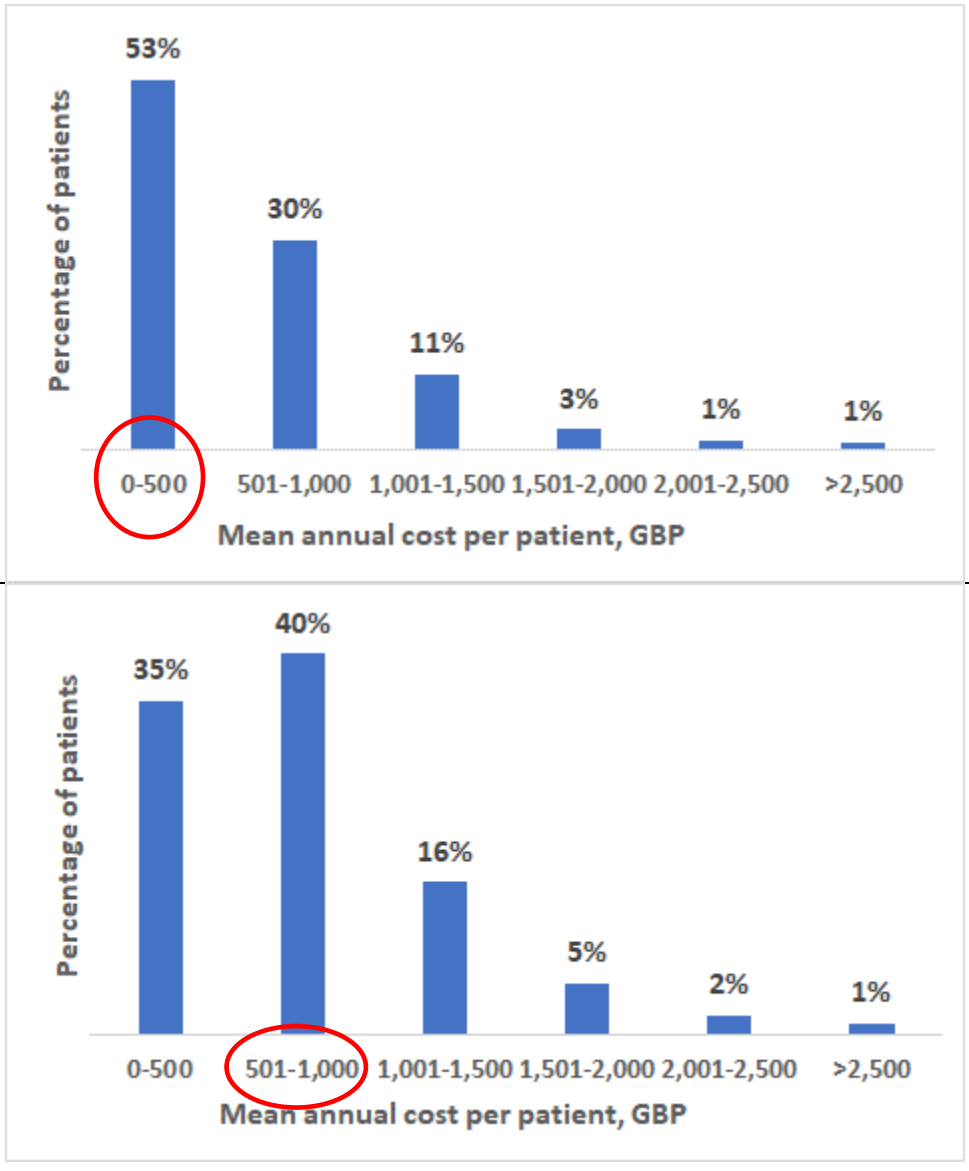


Figure 12.5: Mean annual cost of GP-diagnosed (above) and EHR-defined (below) patients

The majority of GP-diagnosed MUS patients (53%) were found to have a mean annual cost less than GBP500, 30% between GBP500-1000. However, only 35% of the EHR-defined MUS patients had a mean annual cost less than GBP500, and 40% had an annual cost between GBP500-1000;. In both groups, 2%-3% of the patients had a mean annual cost over GBP2,000.

Statistical analysis of difference between the mean costs for the two groups: Using the Mann-Whitney U test for the GP-diagnosed and EHR-defined patient groups (medians of 425 and 835, mean values of 615 and 1,045) for the mean cost per patient per year during the Index year of the study, and for the mean cost per patient per year over the five years of the study, both resulted in a p value of less than 0.01, indicating that there is a statistically significant difference between the mean annual costs of the two groups of patients at the 95% confidence level.

12.4.2 Total cost of patients with MUS to the NHS

Table 12.6 below presents the calculation of the total cost of patients with MUS to the NHS. NHS England estimates indicated 288m consultations annually between 2007-2010 and 311m consultations in 2021. Previous research indicated that 18% of consecutive attenders in England had an MUS (Taylor et al, 2011). The total number of consultations for MUS of 52m and 56m is derived from this data. The mean annual consultations per MUS patient was 13, estimated in this study. The total number patients consulting for MUS can therefore be calculated at 4.0m in 2007-2010 and 4.3m in 2021. This study estimated an annual mean cost per patient of MUS GBP939 in the first year of MUS complaints, weighted at 25% : 75%

diagnosed with MUS vs undiagnosed patients. Combining these data points gives a total annual cost of MUS to the NHS of GBP3.75 billion in 2007-2010.

Table 12.6: Estimating total cost of patients with MUS to the NHS 2007-10 and 2021			
Number of patients	**2007 - 2010**	**2021**	
Total consultations in England (m)	288	311	NHS estimates
Percentage of consultations for MUS	18%	18%	Taylor et al, 2012 for England
No. of consultations for MUS (m)	52	56	288 * 18% ; 311 * 18%
Mean consultations per MUS patient	13	13	Five-year mean
Number of MUS patients (m)	4.0	4.3	52/13 ; 56/13
Cost per patient			
Weighted mean cost in year of diagnosis (GBP)	939	1,067	(NHS Inflation data estimate)
Total cost to the NHS			
	2007-2010		**2021**
At mean cost per patient of GBP	939		1,067
Total annual cost to the NHS (GBP m)	**3,745**		**4,600**

Source for consultation data: https://digital.nhs.uk/data-and-information/publications/statistical/appointments-in-general-practice/march-2021 presented in https://www.bma.org.uk/advice-and-support/nhs-delivery-and-workforce/pressures/pressures-in-general-practice-data-analysis

The cost data for 2007-2010 was converted to 2021 costs using NHS inflation data estimates. This results in 2021 mean annual cost of a MUS patient of GBP1,067. The total cost of MUS to the NHS in 2021 can be estimated at GBP4.6 billion.

The cost of each new cohort of MUS patients was calculated using the total consulting population aged 18-50 years of 23.3 million in England and the calculated incidence rate of new patients of 1.8% (Table 12.7). This equates to around 420,000 new MUS patients per year, resulting in an annual cost to the NHS of GBP452 million.

Table 12.7: Cost for each cohort of new MUS patients	
18-50 population in England 2021 (m)	23.3
Incidence of MUS	1.8%
Number of new MUS patients per year (m)	0.42
Mean cost per new MUS patient in 2021 (GBP)	1,067
Total cost to the NHS per new MUS patient cohort (GBP m)	**452**

12.5. Discussion

12.5.1 PRINICIPAL FINDINGS

This study estimated the total annual cost to the NHS in 2021 at GBP4.6 billion and the annual cost of new patients at GBP450 million. For 2007-2010, the total cost was GBP3.74 billion. The mean cost per patient is GBP615 and GBP1,045 in the index year, the first year of consultation for MUS, for GP-diagnosed and EHR-defined MUS patient groups respectively and the five-year mean for the two groups is GBP618 and GBP781.

The number of consultations, primarily in the index year, is the key driver of these costs; MUS patients' mean consultation rates were nearly four times higher at 11 in the GP-diagnosed patient group, and five times higher at 15 for the EHR-defined patient group, than the age-group specific mean consultation rate for 18-55 years of 3.1 per patient per year for England (Hobbs et al, 2016).

12.5.2 STRENGTHS, LIMITATIONS AND COMPARISON WITH OTHER STUDIES

This is the first study in the last decade in England to use a bottom-up approach to estimate the total cost of MUS to the NHS over a five-year period, to analyse the component costs and driving factors underlying the increase in cost.

It is however limited by the lack of detailed data on prevalence of MUS in England, estimates from 2012 were used in the study. The failure to include the costs of treatment due to the lack of sufficient data in the electronic health records is a significant weakness.

The total annual cost estimate for the years 2007 to 2010 of GBP3.7 billion is 28% higher than the most recent cost estimates for MUS in the working population in England of GBP2.89 billion for 2008/2009 (Bermingham et al, 2010).

12.6 Conclusions and next steps

This study was undertaken to assess the real-life costs of MUS to the NHS, using real-life recorded data from a primary care database. The findings were that patients with MUS cost even more to the NHS than assessed previously. There appears to be an association between the costs, time to diagnosis and mental health issues, with the two latter factors appearing to drive up costs, although it is not possible to suggest these as causative factors. It does however suggest that costs may be reduced by measures such as effectively managing the patients' need for a diagnosis and by treating comorbid mental health issues.

This concludes the empirical research carried out to identify the real-life information on the issues affecting patients with MUS and their doctors. The next step is to consider the moral principles relevant to these issues.

CHAPTER 13
MORAL PRINCIPLES RELEVANT TO MUS RELATED CONCERNS

This section examines the moral principles that are related to the values and facts extracted from empirical data. The focus is on the factors necessary for treating a patient ethically; it is not a guideline for the clinical or therapeutic management of these patients. The key elements necessary for such ethical management that emerged as empirical research findings are considered in the light of established ethical principles.

Examining the values expressed by stakeholders (Chapter 4) indicate that the key concerns of physicians are related to the ethical principles of non-maleficence, beneficence and justice, in the form of fair distribution of limited resources. Patient concerns centre primarily around the principle of autonomy, specifically related to the loss of their autonomy, and it is intertwined with other moral concerns such as the loss of dignity and stigma, as indicated by the value patients placed on the need for a culture of respect.

These key principles roughly correspond to moral virtues: autonomy to the virtue of respect, non-maleficence to the virtue of non-malevolence, beneficence to the virtue of benevolence (Beauchamp and Childress, 2001, p.39). The principle of justice impacts both doctors and patients mainly regarding resource allocation and the doctors' role as a resource gatekeeper, but also in the form of the epistemic injustice MUS patients can suffer. However, these principles alone are not sufficient to discuss the complexity of the issues of concern and it is necessary to incorporate other important principles into the

ethical analysis. Rendtorff and Kemp (2000) proposed to add the principles of respect for dignity, integrity, and, vulnerability in to the discussion around ethical management of patients. Furthermore, the concepts of power imbalance and mutual respect appear to be relevant to the values expressed by stakeholders in the empirical research. In addition to these factors which are primarily related to how doctors treat patients, the concept of the virtuous patient, which considers the virtues a patient should possess in order to achieve optimal management of their conditions is discussed in relation to patients with MUS. Lastly, the concept of a stronger therapeutic alliance between doctors and patients, which was the higher order theme that was generated from the qualitative research synthesis, is considered.

This chapter examines these principles and concepts and discusses the existing literature in the context of issues related to patients with MUS.

13.1 AUTONOMY

The concept of autonomy is usually interpreted with reference to the negative obligation to not to obstruct an autonomous person from exercising his/her free will; however, autonomy can also be interpreted in a broader sense as the capacity a person has to 'create ideas and goals for life, for rational decision and action without coercion, for self-legislation and privacy' (Rendtorff and Kemp, 2000: 25). The concerns emerging from MUS patients' experiences can be related to the frustration and identity crisis they feel at the loss of this broader version of autonomy: frustration at self for being unable to recover (*Led to feel.. quite shamed… that I was contributing to my condition,* Nielsen et al, 2020*)*, for being

viewed as faking illness (*'you're just playing the system'* Pryma, 2017*)*, and being disbelieved (*biggest frustration was being [ignored] about your own symptoms,* Sibelli, 2018*)*.

Qualitative research among doctors gives evidence of lack of respect, disbelief and prejudice against patients with MUS among some doctors (*they don't diagnose it, and they don't treat it; they think it is a type of hysteria, a neurosis*; *I have to admit that it comes down to my own prejudice,* Briones, 2018), whereas other doctors acknowledge the patients' suffering and recognise the patients' stigma and problems (*they have the feeling that they are stigmatized; they fear that the doctors are going to say: 'ah, another hypocrite*; Briones, 2018) and accord respect for the epistemic privilege of patients (*I accepted and believed that he experienced the symptoms,* Aamland, 2014). Thus, empirical data indicates that respecting autonomy requires refraining from prejudice against and stigmatising patients, protecting their dignity, as well as showing respect for their epistemic privilege.

Showing respect for autonomy also includes enhancing and defending the right of the person to make choices (Beauchamp and Childress, 2001), linked to the idea John Stuart Mill describes as 'ensuring that people are free to act according to their personal values and beliefs,' as long as that does not harm anyone (Campbell, 2013). Mill's Harm Principle suggests that autonomy is paramount when he states that preventing harm to others is the only good reason to interfere with the choice of the person and that 'over himself, over his own body and mind, the individual is sovereign' (Mill, 2017 edition).

This, however, also needs to be considered within the context of two other principles:

a. Beneficence – the doctor's opinion on available and suitable treatment options. In England, this prevails over the patients' autonomy and the patient has no legal right to demand a treatment (or further investigations / referrals) if the doctor does not believe it is clinically indicated and it is in the best interests of the patient to have that treatment (England Department of Health Guide to consent for examination or treatment, 2009).

b. Justice – considering the fair division of limited resources. Even though the patient may wish to have multiple investigations, referrals and consultations, such wishes need to be considered against the needs of the entire patient population, particularly when considered with regard to the utility of acceding to such requests.

13.2 NON-MALEFICENCE AND BENEFICENCE

The principle of non-maleficence requires that one must not cause physical or mental harm to other people, beneficence requires not only removing harm, but actively promoting the well-being of patients; these two concepts are closely related and where there is conflict, the possible benefit from an action should be weighed against the possible harm from it, to decide on the action (Beauchamp and Childress, 2001). Since the well-being of patients is a primary aim of the practice of medicine, the failure to act beneficently towards a patient could be considered a 'betrayal of the trust which patients place in the good intentions of health professionals,' however this must be balanced against the risk of being paternalistic, which involves treating people even against their wishes 'for their own good' (Campbell, 2013, p. 45).

When considering the values indicated by stakeholders regarding non-maleficence and beneficence, doctors specified the need to balance the risk of harm if an organic disease is misdiagnosed as MUS against the risk of iatrogenic harm by repeating investigations (Brownell, 2016; Harsh,2016; Rask, 2021; Warner, 2017). Repeated investigations and referrals also need to be considered from the perspective of avoiding unnecessary use of limited resources, since the costs of investigations and referrals constitute a large proportion of the total cost incurred in the management of patients with MUS as discussed in Chapter 12.

This is further complicated by the risk of harming a patient merely by giving a diagnosis of MUS; MUS is a psychiatric diagnosis, and it has been pointed out that a psychiatric diagnosis can cause harm to the patient, even when it is accurately given due to the 'entrenched social attitudes towards mental illness (Shackle, 1985: 132). In the case of MUS, this harm can be worsened since MUS may be conflated with the psychiatric diagnosis; a doctor is not required to give any reason for the shift from 'we don't know why you are ill', which is diagnostic uncertainty, to 'you are ill because you have a psychiatric condition that is called MUS' (Bjorkman,2016; Brownell, 2016; Lian, 2017). This is why it is important to consider MUS as a working hypothesis, and to revise the hypothesis as necessary when new evidence is available (Olde Hartman, 2018).

Patients, however, emphasise the importance of receiving a diagnosis, as detailed in Chapter 4, since they find that a diagnosis legitimises their illness and gives them access to treatment. Although patients viewed receiving a diagnosis as a beneficent act which gave them both reassurance and a first step in finding an effective treatment, some doctors

considered it an act of beneficence to not give / delay giving a diagnosis of MUS because of these problems of diagnostic uncertainty, and to avoid harm to the patient, due not only to the stigma of mental illness but also because of a relaxation of clinical vigilance once a diagnosis of MUS is given, and because it can act as a self-fulling prophecy where the patient's condition deteriorates (Bayliss, 2016; Pohontsch, 2018).

Beauchamp defines the operative concept of the Beneficence model developed by Pellegrino and Thomasma (1987) as 'Beneficence in trust', meaning that 'physicians and patients hold in trust the goal of acting in the best interests of one another in the relationship (Pellegrino and Thomasma, 1987, quoted in Beauchamp, 2001). It is the lack of trust that the doctor is acting in her best interest that leads the patient to seek repeated reassurance, demand multiple, repeated investigations and referrals, non-compliance with treatment modules undertaken and to some extent, reject the psychosocial model of illness the doctor proposes. Similarly, it is when doctors lack trust in their patient that they tend to engage in defensive medicine, over investigating and colluding with patients to preserve the relationship, which is ultimately harmful to the patient. Therefore, developing trust in one another would be beneficial to both parties. While recognising that such 'beneficence in trust' is an ideal, that is not easily achieved, it needs to be pointed out as a worthy, and pragmatic target to aim to achieve.

The beneficence model necessitates the virtues of benevolence and trustworthiness in doctors (Pellegrino and Thomasma, 1988); Beauchamp explains that it is the 'morally good person with the right motives who is more likely to discern what should be done, to be

motivated to do it, and to do it' (Beauchamp, 2001). A doctor who simply follows rules and lacks moral character is less likely to act in the best interests of his patient.

Beneficence is linked in the minds of many to the benign, paternalistic doctor who takes on the entire responsibility for decision making for his patient, and will carry out actions in the patient's best interest, even if the patient does not agree (Pellegrino, 1987). It is therefore clarified that this thesis does not advocate paternalism. It aims to find the best solutions for resolving the tensions between the need to balance the values of ensuring the best interests of the patient, respecting the patient's autonomy by involving the patient in medical decision making, whilst not engaging in blind service to patient autonomy, and recognises that all this needs to be done within the ten minutes consultation time available.

The six features of the Pellegrino and Thomasma's beneficence model are described below.

1) The aim of medicine should be beneficent: the patient's needs should take priority (with rare exceptions), avoid harm, the doctors' obligation to act beneficently supersedes autonomy and paternalism.

2) Primacy of the existential condition of the patient: The existential condition of the patient, for example, if she can take rational decisions, nature of the illness.

3) No automatic ranking of values: Models such as paternalism and autonomy emphasise a single value over others, e.g. that promoting autonomy is paramount. In the beneficence model ethical primacy is given to patient benefit, and there is no further ranking.

4) Consensus: It is necessary to discuss and achieve consensus with the patient about her care, since the target in the beneficence model is to not to impose values on another. This is

obviously easier said than done, and takes up time and effort, and good communication. However, such time and effort invested in establishing consensus early on with the patient, and updating it as the situation evolves, can pay off in the form of better compliance, and a more positive relationship and patient management process overall in the long term.

5) Prudential moral object: In simple terms, this means that a dilemma should be resolved while preserving as many values of both the physician and the patient as possible (and not take a shortcut that is contrary to key values).

6) Axioms: These are the key moral rules that should guide decision making under a beneficence model. Firstly, that the doctor and the patient are free to make informed decisions and act fully as moral agents. This requires reaching consensus without coercion and deception from either party, without using one another for selfish ends, or without imposing the values of one on the other. Adhering to this principle would help avoid situations of for example, stigma and stereotyping patients. At the same time, this model imposes a duty on the patient to be trustworthy, to not abuse the system, nor use it for selfish secondary gains.

Secondly, the greater responsibility in the relationship is on the doctor since the power and information imbalance works in their favour. This places the onus on the doctor to not abuse the power imbalance and to work towards remedying that imbalance, for example by providing relevant information to the patient.

The third requirement is for moral integrity as a characteristic of the doctor. Since the basis of the beneficence model is for the patient's benefit to be given primacy, it is necessary that

the doctor can be trusted to keep to this aim. This requirement is critically important in the case of MUS patients, where there is much ambiguity around the diagnosis, the condition and the management. In such complex situations, rules and guidelines have little meaning since each case is different, and loopholes can be found, if necessary, therefore the moral integrity of the doctor is the cornerstone on which patient benefit can be sustained.

The final requirement states that 'physicians must respect and comprehend moral ambiguity yet not abandon the search for what is right and good in each decision'. (Pellegrino and Thomasma, 1987: 44).

13.3 JUSTICE, FROM THE PERSPECTIVE OF RESOURCE CONSTRAINTS

Justice is centred around the moral obligation to decide fairly between competing claims; however, it is more than equality or fairness alone (Campbell, 2003). Horizontal equity (where equals are treated equally), and vertical equity (treat unequals unequally in proportion to the morally relevant inequalities) date back to Aristotle but there is still no resolution on what such morally relevant inequalities are (Gillon, 1985). Gillon states that in practical terms justice comprises distributive justice (distribution of limited resources fairly), rights-based justice (respect for people's rights) and legal justice (respect for morally acceptable laws). Justice also requires 'specific provisions for protecting the vulnerable and to the furtherance of equality' (Campbell, 2003).

Resource constraints in the NHS force a role of resource gatekeeper on doctors. This means they are obliged to impose some level of control over which patient gets access to for example, investigations and referrals. Allocating resources fairly requires adjudicating fairly

between several competing moral claims: the ideal would be to provide sufficient healthcare for all those who need it, however, if there are more demands than the amount available, then it may be necessary to distribute available resources, but there is no final conclusion on which criteria (medical need, welfare maximisation or medical success for example), such decisions are to be made (Gillon, 1985).

Justice incorporates recognising an 'enforceable right to a decent minimum of healthcare within a framework of allocation that incorporates both utilitarian and egalitarian standards' (Beauchamp and Childress, 2001: 272). The reasoning behind this need to ensure that healthcare is distributed fairly, presupposes that there is something special about healthcare that makes it necessary to do so. Daniels states that everyone should have enough to ensure 'normal species functioning' because 'impairment of normal species functioning reduces the range of opportunities we have to construct life plans' (Daniels, 2001: 319).

MUS patients are seen as high users of resources; some of it is necessary to exclude organic illness, some of it may be unnecessary repeated tests and referrals. The actual situation was examined in this study using real-life, routinely recorded primary care data on the consultations, investigations and referrals of MUS patients (chapters 5-10). This showed that the number of consultations per year were indeed much higher in patients with MUS than those without, but also that 40%-60% of patients received no referrals or diagnostic tests within the first year of complaint and that around 10%-20% of patients had no referrals and diagnoses within the first five years of complaining about MUS. The data also showed that annual consultation rates appeared to be reduced when the patient is given a

diagnosis, and that the annual consultation rate increased if a patient had mental health issues recorded in addition to the complaints about MUS. Although causation cannot be established given the multiple factors acting on the issue, the data also showed that the total cost of a patient with diagnosed MUS was lower (GBP 615 in index year) than the cost of one who did not receive a diagnosis (GBP1,045 in index year).

Health care costs can indeed be high for MUS patients (Chapter 12) and a gatekeeper role may indeed be necessary for cost control. However, ensuring that these patients receive their fair share of healthcare resources to manage their illness, with greater weight accruing towards patient benefit, rather than towards financial concerns in healthcare decision making, may also be pragmatic since empirical data appears to show that efficient investigation, diagnosis and effective management could reduce total costs in the long run.

The next section discusses the ethical concepts around empirical findings – factors that were raised by the stakeholders in the qualitative research.

13.4 MUTUAL RESPECT BETWEEN DOCTOR AND THE MUS PATIENT

Mutual respect between patients and physicians incorporates the principles of respect for dignity and the respect for integrity. Marmot discusses three relevant aspects of dignity: firstly, that respect for human dignity should be unconditional, based on Kant, 'human dignity is an unconditional and incalculable value, admitting no trade-offs', secondly, that human dignity is affected by the way a person is treated, and thirdly, he links social inequalities to the loss of dignity in people who are disadvantaged, as they are deprived of the opportunities to exercise autonomy and control (Marmot, 2004). Integrity is related to

treating people fairly, avoiding blame, not stereotyping patients as malingerers, not putting an unfair burden on others.

The values expressed by stakeholders include the positive obligation to respect dignity, and the negative obligations to avoid blame, stigma, stereotyping, collusion, and placing the onus of getting well on the patient (as discussed in detail in Chapter 4). Empirical data from the CiPCA study countermands the stereotype that MUS patients exaggerate symptoms to obtain financial support from the government (benefit cheats). Such benefit payments are usually paid to the those in the lowest socio-economic strata. The third quartile of the Deprivation index, where the majority of MUS patients are located, is much less likely to include people on benefits (being the second least deprived group), whereas the first quartile, with the lowest socio-economic status, had a relatively lower percentage of MUS patients than the total population of the database, indicating that this stereotyping is unfair to the majority of MUS patients.

Stigma, stereotyping, discrimination is not unique to MUS, it is common to people with mental health issues, with consequences extending from social exclusion to reduced access to health care, to increased unemployment and premature mortality (Liu et al, 2017). Stigma has been described as having a more negative impact than the condition itself, but there is emerging evidence that stigma can be reduced with specifically targeted interventions (Thornicroft et al, 2016).

13.5 THE VIRTUOUS PATIENT

The empirical data indicated that some patients recognised that they too had obligations towards doctors in a successful doctor-patient relationship (Chen, 2020; Lian, 2017; Osborn, 2020; Rask, 2021). Although virtue theory in bioethics primarily focuses on doctors' virtues, there has been some research, both empirical and theoretical, on what constitutes patient virtues (Lebacqz, 1985; Pellegrino and Thomasma, 1988; Campbell and Swift, 2002; Dekkers et al, 2005; Gauthier, 2005; Miles, 2019). Reasons that have been put forward against an emphasis on patient virtues and duties of patients include that it may impact patient care and that it imposes requirements on vulnerable or weaker people; however it has also been pointed out that it is paternalistic to assume that a patient is incapable of moral considerations and actions simply due to illness ((Draper and Sorrell, 2002; Miles, 2019). What constitutes these patient virtues has been examined from the point of the role of the patient, identifying truthfulness and compliance as patient virtues necessary for healing, whereas tolerance and trust were identified as required for enhancing the doctor-patient relationship (Lebacqz, 1985; Pellegrino and Thomasma, 1988). However, this has been criticised for being a top-down approach that places the responsibility for healing on the doctor (Miles, 2019).

Both self-regarding virtues (self-respect, being realistic) and virtues related to others (maintaining good relationships, being courageous) were the virtues that patients named as important in qualitative research by Campbell and Swift (1988). In a later study, the virtues of courage, prudence, gratitude and self-worth were identified as patient virtues (Swift et al, 2002).

Duty-based strategies to identify patient duties towards doctors also indicated truthfulness and compliance as the key duties of a patient, whereas moral responsibility, the need to think of the impact of one's choices on others, has also been recognised as a necessity, since a virtuous patient would not take up more than their fair share of the resources resulting in resources not being available for others (Gauthier, 2005; Miles, 2019).

13.6 THE CONCEPT OF A THERAPEUTIC ALLIANCE

The term therapeutic alliance was first used by Freud to describe a specific aspect of the therapeutic relationship, that is 'collaborative, reality-based, and rooted in empathy' (Husain et al, 2016:196), and although rooted in psychotherapy and psychiatry, it is a concept that can be embraced by all healthcare professionals willing to work towards a common goal with their patients.

A therapeutic alliance can be conceptualised in many different ways but it is mostly agreed that the key elements of an alliance are aligned with Bordin's definition of the composition of the therapeutic alliance:

"1. Bonds: the reciprocal positive feelings the patient and health professional share with each other. These include mutual trust, regard, and confidence.

2. Goals: a set of targets or outcomes for the interaction endorsed, shared, and valued by the patient and health professional.

3. Tasks: both the health professional and patient must share beliefs and a commitment to undertake the tasks required of them as part of the therapeutic journey." (Bordin, 1979, reproduced in Husain et al, 2016).

The ability to form a strong therapeutic alliance has consistently been shown to be a very powerful predictor of outcomes, particularly the patients' estimate of the quality of the therapeutic alliance (Hatcher et al, 1996; Martin et al, 2000). Therapeutic alliance has been shown to be important in CBT, psychotherapy, pharmacotherapy and in placebo groups (Horvath & Simmonds, 1991; Castonguay et al, 1996). Even more importantly, improved treatment adherence has been linked to a strong therapeutic alliance (Frank and Gunderson, 1990; Mitchell & Selmes, 2007).

Both patients and doctors considered forming a therapeutic alliance based on empathy, compassion, good communication and shared decision making as a potential solution for better management of patients with MUS (Aamland,2014; Brownell, 2016; Chen, 2020; Harsh, 2016; Harvey, 2018; Lian, 2017; Maatz, 2016; Osborn, 2020; Rask, 2021; Warner,2017). How to build a good therapeutic alliance is not the focus of this thesis (but has been described extensively elsewhere (Husain et al, 2016; Stubbe, 2018, for example).

The evidence synthesis indicated several critical components of the therapeutic alliance, that could lead to more effective clinical / therapeutic management of MUS patients.

Positive communication was suggested as a most important element of a therapeutic alliance (Aamland,2014; Brownell, 2016; Harsh, 2016). Open, honest communication is the only way to establish a good therapeutic alliance, and to maintain it, although the onus of establishing good communication is on the doctor (Rosen, 2014). Improved communication can lead to shared decision making which was also cited as a key component of a therapeutic alliance (Chen, 2020; Lian, 2017; Harvey, 2018; Rask,2021).

Patients saw improved quality of patient contact as conducive to a therapeutic alliance, and saw empathy and compassion as critical components of a high-quality patient contact (Brownell, 2016; Den Boeft, 2016; Warner, 2017). Empathy, sympathy, compassion are inter-related, with some overlap, and are also related to the concept of patient-centred care. The term compassion mostly refers to suffering alongside the person actually undergoing the pain or hardship, but what differentiates therapeutic empathy from compassion is that therapeutic empathy requires action, whereas the other concepts do not (Howick et al, 2018). Therapeutic empathy has been defined as requiring understanding what a disease means to the patient, communicating that understanding to the patient and acting on that share understanding (Mercer et al, 2002).

Although viewed as a soft skill that is secondary to technical skills, empathy has been shown to be a critical component of therapeutic success (Halpern, 2003, Pedersen, 2008), and patients have been shown to have better outcomes when patients considered their relationship with the doctor to be empathic (Hojat et al, 2011; Derksen et al, 2013). Doctors too have been found to benefit from empathy, feeling greater job satisfaction (Larson et al, 2005). However, despite this importance, empathy has been found to be declining among doctors (Pedersen, 2010). Empathy training has been found to be effective in some studies (Riess et al, 2012) but for empathy to be effective, it is necessary for most stakeholders of healthcare to achieve a shift in perspective to acknowledge the critical role of empathy in successfully managing patient problems and to be committed to deeply integrate empathy into clinical practice (Howick et al, 2018).

13.7 CONCLUSION

This chapter considered the key elements necessary for ethical management of MUS patients that emerged as empirical research findings in the light of established ethical principles. The next chapter considers these ethical principles alongside the values expressed by stakeholders using qualitative research and the data extracted from real-life electronic healthcare records to develop boundary principles that form a framework that is an initial hypothesis of how patients with MUS could be managed more ethically.

CHAPTER 14
DERIVING BOUNDARY PRINCIPLES

14.1 Introduction

Dworkin (1978) helps clarify how to decide if an issue is indeed an ethical issue: to state that something is ethically wrong, and is an ethical concern, i) it should be morally wrong, and not just a personal preference or prejudice; ii) the reasons as to why it is a moral wrong, must meet the minimum standards of evidence and argument and must not be based on prejudice, alleged facts that may be false or implausible or on personal emotional reactions; iii) such reasons should presuppose a general moral principle or theory.

The evidence synthesis in Chapter 4 led to the extraction of values of stakeholders and findings from the real-life, routinely recorded data (Chapter 10 of the MUS in Primary care study, and the costs of MUS study in Chapter 12), provided further real-life information related to these values. The systematic derivation of this data from empirical sources indicates that these concerns are not merely personal preferences or prejudices but an extensive problem that could be a moral wrong.

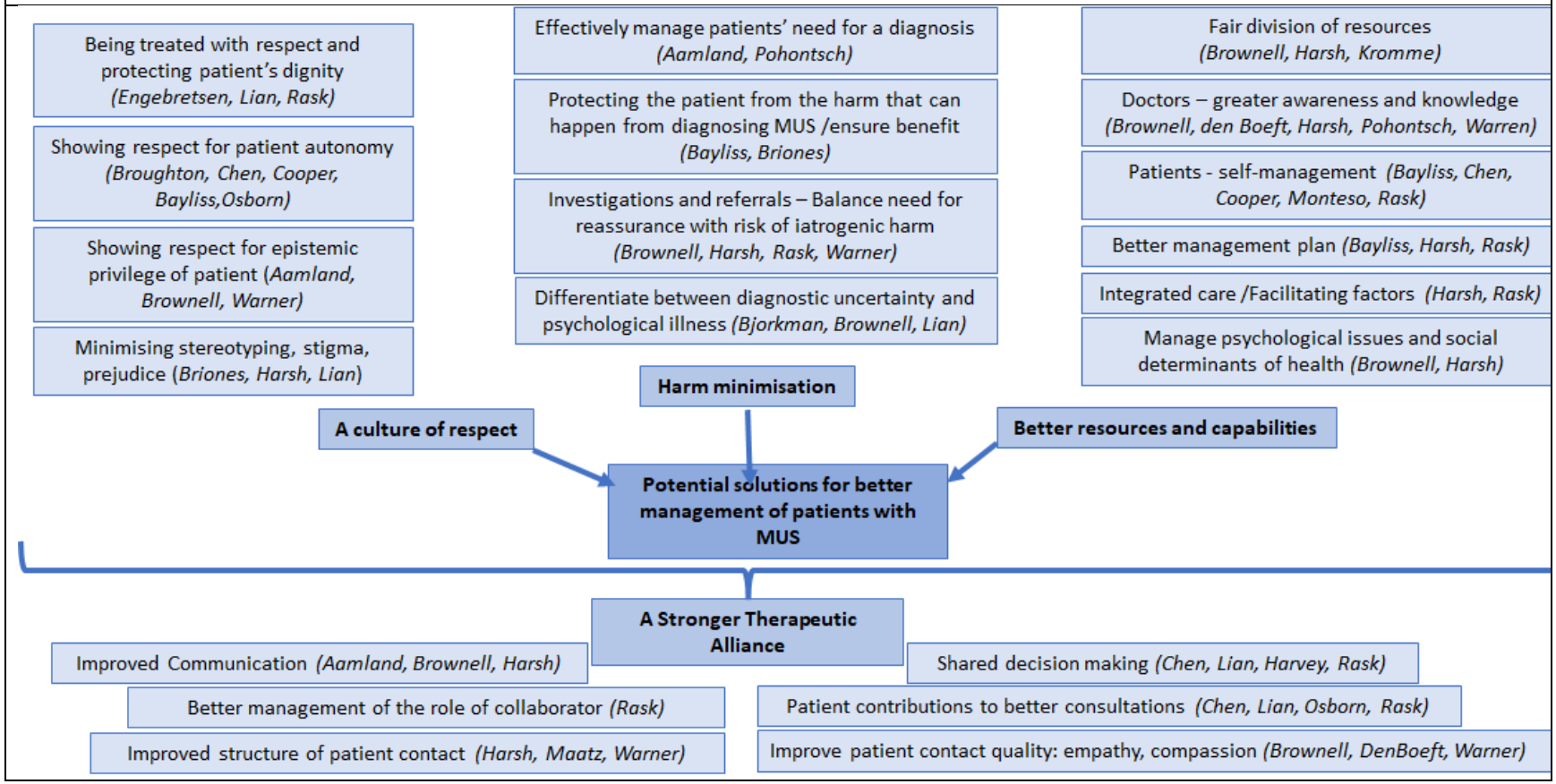
In this chapter, the values and facts extracted are summarised, the moral principles related to these concerns are discussed, and based on these, boundary principles are generated, forming a framework that is an initial hypothesis of how patients with MUS could be managed more ethically. The process of extracting the relevant boundary principles, the 'central and overriding values that inform the stakeholders' thinking about the problem', was through extensive empirical research from the perspectives of stakeholders, including

qualitative, quantitative and economic research, rather than from the point of view of the researcher. 'Justification is a matter of mutual support of many considerations, of everything fitting together into one coherent view.' (Rawls, 1999, p. 579). Coherence requires logical consistency and each component needs to reinforce / be reinforced by the other components, and the outcome is a process where ethical theory, the concerns and views of stakeholders, the needs and priorities of policy and the views of the 'thinker' are considered, resulting in a coherent, and therefore justifiable, 'equilibrium'. (Ives et al, 2017:304).

14. 2 Values expressed by stakeholders in primary research

Figure 14.1 below summarises the values of stakeholders extracted from qualitative research using direct quotes from participants to ensure that the views expressed are directly related to the stakeholders themselves (as described in detail in Chapter 4).

Figure 14.1: Value propositions emerging from empirical data



14. 3 Facts related to stakeholder values from empirical data

Table 14.1 summarises MUS-related facts sourced from the studies in Chapters 5-12.

<table>
<tr><th colspan="2">Table 14.1: Factual data related to issues of diagnosing and managing MUS patients</th></tr>
<tr><th>Values expressed by stakeholders extracted from primary research</th><th>Facts that operate on the issues of diagnosing and managing patients with MUS</th></tr>
<tr><td rowspan="2">A culture of respect
Respect for patients' autonomy (Broughton, Chen, Cooper, Bayliss, Osborn)
Respect for epistemic privilege of patient (Aamland, Brownell, Warner)
Protecting patients' dignity (Engebretsen, Lian)
Minimising stereotyping, stigma, prejudice (Briones, Harsh, Lian)</td><td>Deprivation – Majority of patients in 2nd/3rd quartile
• GP-diagnosed pts – 52% / 25%
• EHR-defined pts – 38% / 39%
• 23%-27% in 1st (most deprived) quartile
Illness perpetuation & delayed diagnosis:
MUS related complaint 5 years after first complaint:
• In EHR-defined MUS patients: 55%
• In GP-diagnosed patients: 13%
Subsequent diagnosis of MUS by GP out of the EHR defined patients : 11%</td></tr>
<tr><td>Harm minimisation
Balance need for reassurance vs risk of iatrogenic harm in investigations and referrals (Brownell, Harsh, Rask, Warner)
Effectively manage patients' need for diagnosis (Aamland, Pohontsch)
Differentiate diagnostic uncertainty and psychol. issues (Bjorkman, Brownell, Lian)</td><td>Percentage of patients with no investigations / referrals:
During index year
• GP-diagnosed pts – 58% / 61%
• EHR-defined pts – 35%/39%
At any time over 5 years
• GP-diagnosed pts – 17% / 21%
• EHR-defined pts – 10%/12%</td></tr>
<tr><td rowspan="2">Better resources and capabilities
Improved awareness and knowledge of MUS (Brownell, den Boeft, Harsh, Pohontsch, Warren)
Improved self-management capacity in patients (Bayliss, Chen, Cooper, Monteso, Rask)
Integrated care (Harsh, Rask)
Better management plan (Bayliss, Harsh, Rask)
Facilitating factors (Bayliss, Harsh, Rask)
Manage psychological issues and social determinants of health (Brownell, Harsh)</td><td>MUS Incidence rate per 1,000 registered population aged 18-50 years
• GP-diagnosed – 4.4 ; EHR-defined – 13.6
Mean no. of consultations per year in MUS patients cf. age 18-55yrs population mean for England of 3.1 :
Index year: GP-diagnosed – 12; EHR-defined – 22
5-year mean: GP-diagnosed – 11; EHR-defined - 15
No. of consultations in MUS patients with/without record of mental health issues: 13 / 8 (5-year mean)
Percentage of patients with MH issues increases with duration of MUS:
Duration of MUS : percentage of pts with MH issues
1 year - 58% 2 years - 64%
3 years - 70% 4 years - 74%</td></tr>
<tr><td>Estimated costs per patient with MUS:
GBP Index year 5-year mean
GP-diagnosed: 615 618
EHR-defined: 1,045 781
Estimated total cost to NHS: GBP4.6bn (2021)</td></tr>
</table>

It is clarified here that this data may only be applicable specifically to this patient population since the study limited patients selected to adults aged 18-50 years and excluded all patients who had co-morbid physical conditions. Furthermore, it is clarified that that any relationships between factors studied in the research are associations alone and are not implied to be causative, since there has been no research in to causative factors.

The evidence from real-life data from EHR showed the following in the patient population studied:

1) although there is a perception that patients with MUS falsely report or exaggerate illness in order to gain financial benefit, the majority of patients (77%) were in the 2nd or 3rd quartile in the Deprivation index. Only 23%-27% of the total patient cohort were placed in the most deprived first quartile, where they were more likely to receive financial benefits from the government.

2) the number of patients for whom doctors recorded a diagnosis of MUS (667 GP-diagnosed MUS patients out of 37,661 total in the age-group in the database), is much lower than the number of patients meeting the conditions that suggest they suffer from MUS potentially, but are not recorded with a diagnosis of MUS from their doctor (2,044 EHR-defined MUS patients out of 37,661), over a four-year period.

3) 55% of these EHR-defined MUS patients, i.e., 55% of all patients presenting with symptoms that suggest MUS, continued to have a record of a MUS-related symptom code even in the fifth year after the first complaint; 11% received a MUS diagnosis by a GP within five years of the first consultation for medically unexplained symptoms.

4) In the GP-diagnosed MUS patient group, 13% of patients continued to have a record of a MUS specific Read code even in the fifth year suggesting their conditions were unresolved.

5) In the GP-diagnosed patient group, 58% had no investigations done in the index year and 61% had no record of a referral. In the EHR-defined patient group, this percentage was 35% and 39% respectively. Moreover, 17% and 21% of the GP-diagnosed patients, and 10% / 12% of the EHR-defined patients had no investigations or referrals in the five years including the first year of their complaint.

6) The EHR data also showed that the consultation frequency is 78% higher in the first year in patients who do not receive a diagnosis (22 consultations in Year 1 and five-year mean of 15 per year) than those who do receive a diagnosis (12 consultations in Year 1 and five-year mean of 11 per year).

7) The number of consultations per year in MUS patients is higher in patients with a record of mental health issues (5-year mean: 13) than in patients without such a record (5-year mean: 8).

8) The percentage of patients with mental health issues increases with the duration of MUS. Among the patients with MUS recorded for one year alone, the percentage of those with a mental health issue on record was 58%. As the duration of MUS increased to 2,3 and 4 years, the percentage of patients with a mental health issue increased to 64%, 70% and 74% respectively.

9) The study on costs showed that the cost of undiagnosed MUS, i.e, the cost per EHR-defined MUS patient, is 70% higher in the first year than for GP-diagnosed MUS patients

(GBP1,045 per year cf. GBP615 per year) and 26% higher over five years (GBP781 per year cf. GBP618 per year).

It is clarified that these are factual data points that are applicable to the investigated population – and that no conclusions of causation can be drawn regarding any of the associations seen between any two or more factors without further investigation. No normative conclusions are drawn from this data.

14.4 BOUNDARY PRINCIPLES

The key information from empirical data and the prima facie key ethical principles are used to draw up the boundary principles that form tentative normative recommendations to manage MUS patients ethically, as shown in Table 14.2 below. Balancing the boundary principles and resolving the tensions between them would then produce definitive conclusions – however this thesis does not proceed to that stage of RBL, that would be carried out at a later stage.

Based on the value propositions derived from the analysis of empirical data and the theoretical literature, the boundary principles were developed, as a series of normative statements that describe how the ethical concern should be characterized and responded to. These statements, though formulated as normative statements, are to be treated as though they were true and justified only so that they can form the starting point for ethical enquiry. For these statements to be fully justified, they need to be 'supported by and supportive of' the rest of the principles that together form a coherent system (Ives, 2014, p.308).

Table 14.2: Boundary principles	
Value proposition from empirical data	**Boundary Principle**
Patients value being treated with respect as an individual and protecting their dignity.	It is important to protect the dignity of patients and treat them with respect as individuals.
Patients value respect shown for their autonomy.	Respecting patient autonomy could help engender a culture of respect in healthcare.
Doctors believe it is important to ensure the benefit of patients, which may sometimes be against what the patient wants.	Ensuring benefit to patients in an important value that should be observed.
Patients find it important that doctors believe what they say about their illness.	Respecting the epistemic privilege of patients is important.
Patients are distressed when facing stigma, prejudice and stereotyping.	It is important to prevent patients with MUS facing unwarranted stigma, prejudice and stereotyping.
Patients value receiving a diagnosis, a name for their illness.	It is important to provide a diagnosis without delay when clinically feasible.
Doctors believe it is necessary to protect the patient from the harm that can happen due to an MUS diagnosis.	Protecting the patient from the harm that could occur from an MUS diagnosis is important.
Patients and doctors believe it is important to differentiate between the uncertainty in diagnosis and psychological illness.	It is important to differentiate between diagnostic uncertainty and psychological illness.
Patients (and sometime their doctors) find it important to have multiple investigations and referrals for reassurance.	Providing reassurance by way of multiple investigations and referrals is important.
Doctors believe it is necessary to prevent the patient being harmed by excessive investigations and referrals.	It is important to prevent the iatrogenic harm to patients that can result from excessive investigations and referrals.
Patients value having access to healthcare resources as required.	It is important to ensure access to healthcare resources as patients require.
Doctors and patients value the fair division of available healthcare resources among all those who require it.	Fair division of healthcare resources is important.

Patients value greater awareness and knowledge of MUS on the part of doctors.	Ensuring that doctors have good awareness and knowledge of MUS is important.
Improving self-management practices can be beneficial to patients.	Ensuring that patients improve self-management practices is beneficial.
Patients and doctors value integrating care measures from allied healthcare personnel and facilitating factors for good management.	Integrating care from allied health personnel is beneficial.
Doctors believe managing psychological issues and addressing social determinants of health lead to better MUS management.	It is important to better manage psychological issues of patients to address concerns around social determinants of health for MUS patients
Patients value good communication with doctors.	It is important to improve communication with patients.
Patients value shared decision making.	Shared decision making is important.
Patients value empathy and compassion in doctors.	It is important to indicate empathy and compassion towards patients.
Patients believe that their contributions can improve consultations.	It is important to ensure that patients make active positive contributions towards better consultations.
Patients and doctors value a well-structured consultation.	It is important to improve the structure of the patient consultation.
Doctors believe the role of being a collaborator should be carefully managed.	It is important to manage the role of collaborator with the patient so that the patient is not harmed.

14.5 Conclusion

This section brought together the value propositions from qualitative research, factual data from electronic health records and the related ethical principles and finished by generating boundary principles.

CHAPTER 15
DISCUSSION AND CONCLUSION

15.1 Summary of key findings and discussion

This study examined the patient and physician concerns related to MUS comprehensively, filling an important and urgent need to discuss and address the ethical issues around MUS. The study employed a research strategy of empirical bioethics with reflexive bioethics as the methodology, modified the method of reflexive balancing to meet the requirements of this study, and developed boundary principles that form an initial hypothesis of how MUS patients could be managed more ethically. The final stage of reflexive balancing, resolving tensions between these boundary principles, and determining how these can operate together resulting in a fully balanced framework that generates normative solutions to the problem, is not within the scope of this thesis (and would be carried out at a later stage).

Identifying the problem, the first stage of reflexive balancing, carried out through a horizon review of the literature, indicated that the key concerns of patients and doctors centred around diagnostic uncertainty, delayed diagnosis, difficulty in managing a condition with an unpredictable and chaotic illness narrative, resource constraints, stigma, stereotyping and discrimination patients face, and the frustration of both patients and doctors.

As the second stage of reflexive balancing, disciplinary naïve enquiry in to the problem was carried out. Moving away from the more traditional process of seeking in-depth information from stakeholders (usually via interviews) used in reflexive balancing, this research modified the method to incorporate three different studies to investigate the problem.

1) <u>A systematic evidence synthesis of the qualitative research on patient and clinician experiences in recognising and managing MUS.</u>

This in-depth analysis elicited stakeholder values around diagnosing and managing patients with MUS, indicating the potential solutions for better management of patients with MUS: i) a culture of respect, ii) harm minimization, and iii) improving resources and capabilities. These would form the basis for a stronger therapeutic alliance between the doctor and the patient based on improved communication, shared decision-making, improved structure and quality of patient contact with empathy and compassion as key values. A stronger alliance would also require better management of the doctors' role as a collaborator, and a shift in attitude on the part of the patient could contribute to more effective consultations.

2) <u>An in-depth analysis of real-life routinely recorded electronic healthcare records (EHR) of consultations by MUS patients in a primary care data base.</u>

The following are the key findings of this 'MUS in primary care' study around the patient concerns that emerged from the qualitative evidence synthesis.

- Patient concerns around delayed diagnosis were mirrored in the real-life data: the study found 667 patients with a recorded diagnosis of MUS, and 2,044 undiagnosed patients who met the criteria for MUS (younger age group, consulting for MUS-related symptoms and high consultation frequency), over a four-year period 2007 – 2010, in a primary care database of c.37,661 patients.
- Of these patients, 74% - 77% were female.

- The socio-economic status of the patients was estimated using the English Deprivation indices and this showed 77% of the patients were located in the 2nd and 3rd Quartiles of the Deprivation index. This was contrary to the stereotype of viewing MUS patients as those who were exaggerating / falsifying symptoms to qualify for financial support from the government, as those qualifying for benefits would normally be within the most deprived quartile, Q1.
- In the GP-diagnosed MUS patient group, only 42% had some form of investigation carried out in the year of diagnosis, and only 39% had a referral of some form. In this group, 17% -21% of patients had no investigations or referrals over the entire five-year period. Although there is not sufficient data to arrive at a conclusion, this raises the concern whether these patients were given a diagnosis of MUS without adequately investigating their complaint.
- Among these patients, 68% of GP-diagnosed female patients and 72% of undiagnosed female patients had a record of a mental health/psychological issue over the seven years of the study. Of the male GP-diagnosed patients, 52% had such a record whereas 68% of the male undiagnosed MUS patients had a record of a mental health/psychological issue. Depression and anxiety were the most frequently recorded mental health issue (45%-65%).
- The consultation rates are much higher than the age-group specific mean consultation rate for 18-55 years of 3.1 per patient per year for England (Hobbs et al, 2016).

- Although causation cannot be proved due to the complexity of the relationship between mental health issues and MUS and confounding factors which may be present, delayed diagnosis of MUS appears to be associated with higher consultation rates and disease perpetuation: consultation rates in patients without a diagnosis were 78% higher in the index year (22 consultations per year compared to 12 in diagnosed MUS patients) and 35% higher over 5 years; 55% of patients without a diagnosis continued to consult for MUS-related symptoms even in Year 5, cf. only 13% of diagnosed MUS patients consulting for MUS in the Year 5.
- The consultation rate continued to be high in diagnosed patients too even though 63% of diagnosed MUS patients consulted for MUS only in the index year (but they continued to have a high consultation frequency in the following years for other reasons). The mean consultation rate increases with the increase in duration of mental health/psychological issues; diagnosed MUS patients with a mental health/psychological issue had a five-year mean consultation rate ranging from 10 - 20 consultations per year, compared to 8 consultations per year for those without such a mental health issue recorded. The percentage of patients with mental health issues also increases as the duration of MUS is prolonged. This indicates an association between the high consultation frequency of MUS patients and comorbid mental health issues, though not necessarily causation.

3) <u>Investigated the costs of MUS – through a systematic review and a cost of illness study.</u>

The systematic review of costs of MUS in England revealed a wide range of costs, for various reasons such as the widely varying definitions of MUS, type of patients involved, types of

cost included. A cost of illness study incorporating the resource utilisation data (consultations, prescriptions, investigations and referrals) from the MUS in primary care study and publicly available unit cost data was therefore carried out and found that

- The mean cost per patient per year was GBP1,045 in the first year in undiagnosed MUS patients, 70% higher when compared to GBP615 for GP-diagnosed Mus patients. Costs for undiagnosed patients were 26% higher over five-years.

- The higher number of consultations and associated prescription costs were the largest contributor to the higher costs in undiagnosed MUS patients.

- Total annual cost to the NHS of MUS patients was estimated at GBP3.7bn in the years 2007 – 2010 and at GBP4.6bn in 2021.

- Based on the estimate that around 420,000 patients newly consult for MUS in each year, the cost of each new cohort of MUS patients to the NHS in each year was estimated at GBP452 million.

It is necessary to clarify here that this increase in costs in patients who have not received a diagnosis of MUS is an associative factor and that the lack of diagnosis cannot be considered a cause for the increase in costs, without further clearer evidence.

The next step was to consider the moral principles related to these concerns; in addition to the usual four principles, this study also considered moral principles related to mutual respect, power imbalance, and the concept of the virtuous patient.

Based on these empirical findings of the facts and values that operate on the problem, and incorporating related moral principles, the study developed a framework of boundary

principles that focuses on the problem of better and more ethical management of patients with MUS, as shown in Table 14.2.

15.2 Strengths and limitations

This is the first study to use an empirical bioethics approach to investigate and to provide a theoretical underpinning for the ethical concerns related to MUS. It aimed to retain methodological rigour in the empirical research to give validity to the empirical findings.
This is the first research in England to use quantitative real-life data from routinely recorded data in a large, consulting primary care population to investigate the extent and intensity of issues related to the diagnosis and management of MUS patients described in qualitative research. This is one of the most comprehensive studies on MUS as it incorporates MUS in all its forms, ranging from transient, mild illness to symptom syndromes, and one of the largest, analysing data for over 188,000 person years (37,600 average patients x 5 years). Its value also lies in the analysis of 'real-world' data, as opposed to trial data, which can be skewed based on patient selection, methodology and other choices. A key strength of the study is the methodological rigour employed.
Based on the empirical findings it developed a statement of boundary principles around the ethical management of patients with MUS, that could at a next stage be used to develop a framework of normative recommendations to manage MUS ethically; this has never been attempted before and is important since the empirical findings provide the basis for such normative recommendations to have 'real-life purchase', rather than being based on ethical theories alone (Ives et al, 2017: ix).

The limitations of the study may relate to the methodological innovations; scrutiny by experts in empirical bioethics could help further streamline this approach. Regarding the EHR study, the research used the best possible methodologies after systematic review of available research on methodologies, however, it is possible that it did not capture all the relevant data on MUS patients as it aimed for greater specificity.

Furthermore, since the patient population of the EHR study was limited to those aged between 18-50 years and to those without co-existing medical conditions, these findings only apply to this specific subset of patients. Since the MUS patient population on the whole is highly heterogeneous, the numerical findings may not be applicable to the entire MUS patient population.

15.3 Implications and recommendations of the study

The research findings helped develop evidence that there are ethical concerns around the way that patients with MUS are currently diagnosed and managed. In the subset of MUS patients studied, there is an association between a delay in giving a diagnosis to patients, higher consultation levels and resulting costs. An association is also seen between the presence of mental health issues and the consultation frequency, although as clarified earlier, the study has not searched for evidence of causation. Therefore, managing potential mental health issues in these patients proactively is indicated, not only as an ethical issue, but also as a pragmatic measure that could help manage consultation frequency.

The doctor patient relationship in these patients has frequently been described as contentious, and patients and doctors suggestions on potential solutions for better

management of these patients includes taking an approach of building a therapeutic alliance with the patient, built on empathy, compassion, a culture of respect and improved resources and capabilities.

15.4 Conclusion

Some of the findings and recommendations are well known to patients and physicians; what this study provides is a comprehensive analysis of the issues from multiple perspectives and the theoretical underpinning for a move towards action in managing these patients effectively and ethically.

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APPENDICES

Appendices for Chapter 4

APPENDIX 4.1 SEARCH STRATEGY

EBSCO Search Strategy

(somatoform disorders or somatization disorders or medically unexplained symptoms) OR ('hypochondriasis' or 'hypochondriac' or 'hypochondria' or 'illness anxiety disorder' or 'health anxiety' or 'somatic symptom disorder') OR functional somatic symptoms OR functional somatic disorders OR functional somatic syndrome OR "multiple unexplained symptoms" OR "persistent physical symptoms" OR "psychosomatic symptoms" OR "psychophysiologic disorders" OR "bodily distress disorder" OR (ibs or irritable bowel syndrome or irritable bowel syndrome constipation or irritable bowel syndrome diarrhea) OR (chronic fatigue syndrome or myalgic encephalomyelitis or me/cfs) OR (chronic fatigue syndrome or exhaustion disorder) OR (fibromyalgia or fibromyalgia syndrome or fms or fm) OR non cardiac chest pain OR post viral fatigue syndrome OR (premenstrual syndrome or pms) OR temporomandibular joint dysfunction syndrome

AND

('qualitative research' or 'qualitative study' or 'qualitative methods' or interview or 'focus group') OR (qualitative research or qualitative study or qualitative methods or interview or ethnographic or phenomenological or case study)

APPENDIX 4.2 QUALITY APPRAISAL FRAMEWORK

Adapted from Critical Appraisal Skills Programme – CASP 2018

1. Was there a clear statement of the aims of the research?
2. Is a qualitative methodology appropriate?
3. Was the research design appropriate to address the aims of the research?
4. Was the recruitment strategy appropriate to the aims of the research?
5. Were the data collected in a way that addressed the research issue?
6. Has the relationship between researcher and participants been adequately considered?
7. Have ethical issues been taken into consideration?
8. Was the data analysis sufficiently rigorous?
9. Is there a clear statement of findings?
10. How valuable is the research?
11. Overall assessment

APPENDIX 4.3 STUDIES INCLUDED IN THE REVIEW

	Short name given	Reference
1	Aamland 2017	Aamland, A., Malterud, K. and Werner, E.L. (2014). Patients with persistent medically unexplained physical symptoms: a descriptive study from Norwegian general practice. *BMC Family Practice*, 15(1).
2	Bayliss 2016	Bayliss, K., Riste,L., Band, R., Peters, S. et al. (2016). Implementing resources to support the diagnosis and management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) in primary care: A qualitative study. *BMC Family Practice* 17:66: DOI 10.1186/s12875-016-0453-8
3	Bjorkman 2016	Bjorkman, I., Simren, M., Ringstrom, G., Ung, E.J. (2016). Patients' experiences of healthcare encounters in severe irritable bowel syndrome: an analysis based on narrative and feminist theory. *Journal of Clinical Nursing*, 25, 2967–2978
4	Briones-Vozmediano 2018	Briones-Vozmediano, E., Ohman, A., Goicolea, I., Cases, C. (2018) "The complaining women": health professionals' perceptions on patients with fibromyalgia in Spain, *Disability and Rehabilitation* 40:14, 1679-1685, DOI: 10.1080/09638288.2017.1306759
5	Broughton 2017	Broughton, J., Harris, S., Beasant, L., Crawley, E., Collin, S.M. (2017) Adult patients' experiences of NHS specialist services for chronic fatigue syndrome (CFS/ME): a qualitative study in England. BMC Health Services Research (2017) 17:384; DOI 10.1186/s12913-017-2337-6
6	Brownell 2016	Brownell, A.K.W., Atkins, C., Whiteley, A., et al. Clinical practitioners' views on the management of patients with medically unexplained physical symptoms (MUPS): a qualitative study. *BMJ Open* 2016;6:e012379. doi:10.1136/bmjopen-2016- 012379"
7	Chen 2020	Chen, A.T., Swaminathan, A. (2020). Factors in the Building of Effective Patient–Provider Relationships in the Context of Fibromyalgia. *Pain Medicine*, 21(1), 2020, 138–149; doi: 10.1093/pm/pnz054
8	Cooper 2017	Cooper, S., Gilbert, L. (2017). An exploratory study of the experience of fibromyalgia diagnosis in South Africa. Health 2017, Vol. 21(3) 337–353. DOI: 10.1177/1363459316677623
9	den Boeft 2016	den Boeft, M., Huisman, D., van der Wouden, J.C., Numans, M.E., van der Horst, H.E., Lucassen, P.L. and olde Hartman, T.C. (2016). Recognition of patients with medically unexplained physical symptoms by family physicians: results of a focus group study. *BMC Family Practice*, 17(1).
10	Engebretsen 2019	Engebretsen, K.M., Bjorbaekmo, W.S. (2019). Naked in the eyes of the public: A phenomenological study of the lived experience of suffering from burnout while waiting for recognition to be ill. J Eval Clin Pract. 2019;25:1017–1026. DOI: 10.1111/jep.13244

11	Harsh 2016	Harsh, J., Hodgson, J., White, M.B., Lamson, A.L., Irons, T.G. (2016). Medical Residents' Experiences With Medically Unexplained Illness and Medically Unexplained Symptoms. *Qualitative Health Research* 26(8):1091–1101; DOI: 10.1177/1049732315578400
12	Harvey 2018	Harvey, J.M., Sibelli, A., Chalder, T., Everitt, H. et al. (2018). Desperately seeking a cure: Treatment seeking and appraisal in irritable bowel syndrome. British Journal of Health Psychology (2018), 23, 561–579. DOI:10.1111/bjhp.12304
13	Houwen 2019	Houwen, J., Lucassen, P.L.B.J., Verwiel, A., Stappers, H.W., Assendelft, W.J.J., olde Hartman, T.C. and van Dulmen, S. (2019). Which difficulties do GPs experience in consultations with patients with unexplained symptoms: a qualitative study. *BMC Family Practice*, 20(1).
14	Kromme 2018	Kromme NMH, Ahaus KTB, Gans ROB, van de Wiel HBM (2018) Internists' dilemmas in their interactions with chronically ill patients; A comparison of their interaction strategies and dilemmas in two different medical contexts. PLoS ONE 13(5): e0194133. https://doi.org/10.1371/ journal.pone.0194133
15	Lian & Robson 2017	Lian, O.S. and Robson, C. (2017). 'It´s incredible how much I´ve had to fight.' Negotiating medical uncertainty in clinical encounters. *International Journal of Qualitative Studies on Health and Well-being*, 12(sup2).
16	Loewenberger 2021	Loewenberger, A., Davies, K., Agrawal, N., Poole, N., Cope, S.R. (2021). What do patients prefer their functional seizures to be called, and what are their experiences of diagnosis? – A mixed methods investigation. Epilepsy & Behavior 117 (2021) 107817
17	Maatz 2016	Maatz, A., Wainwright, M., Russell, A.J., Macnaughton, J., Yiannakou, Y. (2016) *J Psychosom Res*; 90:1-9. doi: 10.1016/j.jpsychores.2016.09.005;
18	Madden 2016	Madden, S., Sim, J. (2016). Acquiring a diagnosis of fibromyalgia syndrome: The sociology of diagnosis. *Social Theory & Health* (2016) 14, 88–108. doi:10.1057/sth.2015.7
19	Mohebbi 2019	Mohebbi Z, Sharif F, Peyrovi H, Rakhshan M, Naini MA, Zarshenas L. Experience Lived by Iranian Patients with Irritable Bowel Syndrome: Transitory Crisis and Liberation. Invest. Educ. Enferm. 2019; 37(3):e10. DOI: 10.17533/udea.iee.v37n3e10
20	Montesó 2018	Monteso-Curto P, Garcıa-Martinez M, Romaguera S, et al. Problems and solutions for patients with fibromyalgia: Building new helping relationships. J Adv Nurs. 2018;74:339–349. https://doi.org/10.1111/jan.13412
21	Muraleetharan 2018	Muraleetharan, D., Fadich, A., Stephenson, C., Garney, W. (2018). Understanding the Impact of Fibromyalgia on Men: Findings From a Nationwide Survey. *American Journal of Men's Health*. 12(4) 952–960
22	Nielsen 2020	Nielsen, G., Buszewicz, M., Edwards, M.J., Stevenson, f. (2020) A qualitative study of the experiences and perceptions of patients with functional motor disorder. *Disability and Rehabilitation*, 42:14, 2043-2048, DOI: 10.1080/09638288.2018.1550685

23	Osborn 2020	Osborn, E., Wittkowski, A., Brooks, J., Briggs, P.E., O'Brien, P.M.S. (2020). Women's experiences of receiving a diagnosis of premenstrual dysphoric disorder: a qualitative investigation. *BMC Women's Health.* 20:242 https://doi.org/10.1186/s12905-020-01100-8
24	Pohontsch 2018	Pohontsch, N.J., Zimmermann, T., Jonas, C., Lehmann, M. et al. (2018) Coding of medically unexplained symptoms and somatoform disorders by general practitioners – an exploratory focus group study *BMC Family Practice* (2018) 19:129; https://doi.org/10.1186/s12875-018-0812-8
25	Pryma 2017	Pryma, J. (2017). "Even my sister says I'm acting like a crazy to get a check": Race, gender, and moral boundary-work in women's claims of disabling chronic pain. *Social Science & Medicine* 181 (2017) 66e73 http://dx.doi.org/10.1016/j.socscimed.2017.03.048
26	Rask 2021	Rask, M.T., Jakobsen, P.R., Clemensen, J., Rosendal, M., Frostholm, L. (2021) . Development of an eHealth programme for self-management of persistent physical symptoms: a qualitative study on user needs in general practice. BMC Family Practice. 22:33. https://doi.org/10.1186/s12875-021-01380-5
27	Sallinen 2019	Sallinen, M., Mengshoel, A. M. (2019). "I just want my life back!" - Men's narratives about living with fibromyalgia. Disability and Rehabilitation: 41 (4): 422–429 https://doi.org/10.1080/09638288.2017.1395085
28	Sibelli 2018	Sibelli, A., Moss-Morris, R., Chalder, T., Bishop, F.L.et al. (2018). Patients' perspectives on GP interactions after cognitive behavioural therapy for refractory IBS: a qualitative study in UK primary and secondary care. British Journal of General Practice:e654
29	Warner 2017	Warner, A., Walters, K., Lamahewa, K., Buszewicz, M. (2017) How do hospital doctors manage patients with medically unexplained symptoms: a qualitative study of physicians. Journal of the Royal Society of Medicine; 2017, Vol. 110(2) 65–72; DOI: 10.1177/0141076816686348
30	Williams 2019	Williams, A.M., Christopher, G., Jenkinson, E. (2019). The psychological impact of dependency in adults with chronic fatigue syndrome/myalgic encephalomyelitis: A qualitative exploration. Journal of Health Psychology 2019, Vol. 24(2) 264–275. https://doi.org/10.1177/1359105316643376

APPENDIX 4.4 18 STUDIES WITH PATIENT VIEWS INCLUDED IN THE EVIDENCE SYNTHESIS

First author and Year of Publication	Title	Country	Setting - Iry/ IIry Care	Type of MUS of concern	Sample size	Sampling method	Data collection methods	Data analysis methods
Bjorkman 2016	Patients' experiences of healthcare encounters in severe IBS: an analysis based on narrative and feminist theory.	Sweden	Other	IBS	10 patients	Purposive / theoretical sampling	Semi-structured interview	Narrative and feminist theory based analysis
Madden 2016	Acquiring a diagnosis of fibromyalgia syndrome: sociology of diagnosis.	UK	Other	CFS/ME/FMS	17 patients aged 25-55 years	Convenience sampling	Interviews	Inductive thematic analysis
Broughton 2017	Adult patients' experiences of NHS specialist services for CFS/ME: a qualitative study in England.	UK	IIry	CFS/ME/FMS	16 adult patients with CFS/ME	Purposive sampling	Semi-structured interview	Thematic analysis
Cooper 2017	An exploratory study of the experience of fibromyalgia diagnosis in South Africa.	South Africa	Other	CFS/ME/FMS	14 Adults - 13 with FM diagnosis/2 with self-diagnosis of FM	Purposive and snowball sampling	Semi-structured interview	Thematic analysis
Lian & Robson 2017	"It´s incredible how much I´ve had to fight." Negotiating medical uncertainty in clinical encounters	Norway	Other	CFS/ME/FMS	256 participants; members of the Norwegian ME association	Convenience sampling	Written submissions	Qualitative thematic analysis

Pryma 2017	"Even my sister says I'm acting like a crazy to get a check": Race, gender, and moral boundary-work in women's claims of disabling chronicpain	USA	Other	CFS/ME/FMS	24 fibromyalgia sufferers recruited via fibromyalgia self-help organisations	Purposive sampling	Interviews	Qualitative analysis
Harvey 2018	Desperately seeking a cure: Treatment seeking and appraisal in irritable bowel syndrome.	UK	Other	IBS	52 IBS patients	Convenience sampling	Semi-structured interview	Inductive thematic analysis
Montesó 2018	Problems and solutions for patients with fibromyalgia: Building new helping relationships.	Spain	IIry	CFS/ME/FMS	44 patients with FM	Convenience sampling	Interview	Inductive thematic analysis
Muraleetharan 2018	Understanding the Impact of FM on Men: Findings From a Nationwide Survey.	USA	Other	CFS/ME/FMS	1,163 male patients self-reported as diagnosed with FM	Purposive sampling	Qualitative Survey	Thematic analysis
Sibelli 2018	Patients' perspectives on GP interactions after cognitive behavioural therapy for refractory IBS: a qualitative study in UK.	UK	Other	IBS	52 patients	Purposive sampling	Semi-structured interview	Inductive thematic analysis
Engebretsen 2019	Naked in the eyes of the public: A phenomenological study of the lived experience of suffering from	Norway	Other	MUS and other (Exhaustion disorder)	8 patients	Purposive sampling	Interview	Phenomenological approach

	burnout while waiting for recognition to be ill							
Mohebbi 2019	Experience Lived by Iranian Patients with Irritable Bowel Syndrome: Transitory Crisis and Liberation.	Iran	Primary	IBS	15 patients; age 21-73 years. 10 F / 5 M; IBS duration 1.5 - 30 years	Purposive sampling	Semi-structured interview	Thematic analysis
Sallinen 2019	"I just want my life back!" - Men's narratives about living with fibromyalgia.	Finland	Primary	CFS/ME/FMS	5 men with FM aged 24-51 years; FM over 3-23 years	Convenience sampling	Interview	Narrative analysis
Williams 2019	The psychological impact of dependency in adults with CFS/ME: A qualitative exploration.	UK	Other	CFS/ME/FMS	10 patients with CFS/ME 9F/1M aged 25 - 60 years; 4-20 years since diagnosis	Convenience sampling	Semi-structured interview	Thematic analysis
Chen 2020	Factors in the Building of Effective Patient–Provider Relationships in the Context of Fibromyalgia	USA	Other	CFS/ME/FMS	23 patients with FM 22F/1M aged 21 - 79 years; 1-58 years since diagnosis	Purposive sampling	Interview	Interpretative Phenomenological analysis and constructivist ground theory
Osborn 2020	Women's experiences of receiving a diagnosis of premenstrual dysphoric disorder: a qualitative investigation	UK	IIry	MUS and other (Premenstrual dysphoric disorder)	17 female patients; > 18 years with Premenstrual Dysphoric disorder	Convenience sampling	Interview	Reflexive thematic analysis

Nielsen 2020	A qualitative study of the experiences and perceptions of patients with functional motor disorder	UK	IIry	MUS and other (functional motor disorder	11 patients with Functional Motor Disorder; 9F/2M aged 21-67 years	Purposive sampling	Semi-structured interview	Thematic analysis
Loewenberger 2021	What do patients prefer their functional seizures to be called, and what are their experiences of diagnosis ? – A mixed methods investigation	UK	IIry	MUS and other (Functional seizures)	13 patients with Functional Seizures; 11F/2M aged 18-46+ years	Convenience sampling	Semi-structured interview	Thematic analysis

APPENDIX 4.5 10 STUDIES WITH DOCTOR VIEWS AMONG 30 STUDIES INCLUDED IN THE EVIDENCE SYNTHESIS

First author and Year of Publication	Title	Country	Setting	Type of MUS of concern	Sample size	Sampling method	Data collection methods	Data analysis methods
Brownell 2016	Clinical practitioners' views on the management of patients with medically unexplained physical symptoms (MUPS): a qualitative study	Canada	Other	MUS and other	12 Family Physicians and 18 Specialist Physicians	Purposive sampling	Interviews	Phenomenological analysis
den Boeft 2016	Recognition of patients with MUS by family physicians.	Netherlands	Primary	MUS and other	29 Family physicians	Purposive sampling	Focus group discussions	Constant thematic comparative analysis
Harsh 2016	Medical Residents' Experiences With Medically Unexplained Illness and Medically Unexplained Symptoms	USA	IIry	MUS and other	10 Medical Residents	Purposive sampling	Interviews	Phenomenological analysis
Maatz 2016	What's difficult: A multistage qualitative analysis of specialists experience with MUS	UK	IIry	MUS and other	17 senior clinicians	Purposive sampling	Semi-structured interview	Content analysis
Aamland 2017	Helpful strategies for GPs seeing patients with MUPS: a focus group study	Norway	Primary	MUS and other	24 GPs	Purposive sampling	Focus Group Discussion	Systematic text condensation

Warner 2017	How do hospital doctors manage patients with medically unexplained symptoms: a qualitative study of physicians	UK	IIry	MUS and other	20 Consultants and Training-grade Physicians	Purposive sampling	Interviews	Framework approach
Briones-Vozmediano 2018	"The complaining women": health professionals' perceptions on FM patients in Spain	Spain	Primary	CFS/ME/ FMS	12 doctors - GP, rheumatologist, psychologist, psychiatrist, physiotherapist	Convenience sampling	Interview	Content analysis
Kromme 2018	Internists' dilemmas in their interactions with chronically ill patients.	Netherlands	IIry	MUS and other	20 interns	Not given	Interview	Discourse analysis
Pohontsch 2018	Coding of MUS and Somatoform disorders by GPs - an exploratory focus group study.	Germany	Primary	MUS and other	20 GPs	Purposive sampling	Focus group discussions	Qualitative content analysis
Houwen 2019	Which difficulties do GPs experience in consultations with patients with unexplained symptoms: a qualitative study.	Netherlands	Primary	MUS and other	18 GPs	Not given	Interview	Constant comparative analysis

APPENDIX 4.6 2 STUDIES WITH BOTH PATIENT AND DOCTOR VIEWS OF 30 STUDIES INCLUDED IN THE EVIDENCE SYNTHESIS

First author and Year of Publication	Title	Country	Setting - Primary / Secondary Care	Type of MUS of concern	Sample size	Sampling method	Data collection methods	Data analysis methods
Bayliss 2016	Implementing resources to support the diagnosis and management of CFS/ME in Iry care.	UK	Primary	CFS/ME/FMS	11 patients and 8 GPs	Purposive sampling	Semi-structured interview	Inductive thematic analysis
Rask 2021	Development of an eHealth programme for self-management of persistent physical symptoms: a qualitative study on user needs in general practice.	Denmark	Primary	MUS and other	5 GPs from 4 practices; 14 patients	Purposive sampling	Interview	Thematic analysis guided by Braun & Clarke 5 step framework

APPENDIX 4.7 ASSESSMENT OF METHODOLOGICAL LIMITATIONS IN PRIMARY STUDIES

First author and Year of Publication	Was there a clear statement of the aims of the research?	Is a qualitative methodology appropriate?	Was the research design appropriate to address the aims of the research?	Was the recruitment strategy appropriate to the aims of the research?	Were the data collected in a way that addressed the research issue?	Has the relationship between researcher and participants been adequately considered?	Have ethical issues been taken into consideration?	Was the data analysis sufficiently rigorous?	Is there a clear statement of findings?	Does the research add value?	Overall assessment
Bayliss 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Bjorkman 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Brownell 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
den Boeft 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Harsh 2016	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	No concerns
Maatz 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Madden 2016	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Mild concerns
Aamland 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Broughton 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Cooper 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns

Lian & Robson 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Pryma 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Warner 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Briones-Vozmediano 2018	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Mild concerns
Harvey 2018	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Mild concerns
Kromme 2018	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Mild concerns
Montesó 2018	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Mild concerns
Muraleetharan 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Pohontsch 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Sibelli 2018	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Mild concerns
Engebretsen 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Houwen 2019	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Mild concerns
Mohebbi 2019	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Mild concerns
Sallinen 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Williams 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns

Chen 2020	Yes	Yes	Yes	Unclear	Yes	No	Yes	Yes	Yes	Yes	Moderate concerns
Nielsen 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Osborn 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No concerns
Loewenberger 2021	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Mild concerns
Rask 2021	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate concerns

APPENDIX 4.8 ASSESSMENT OF CONFIDENCE IN THE FINDINGS OF STUDIES INCLUDED IN THE EVIDENCE SYNTHESIS

First author and Year of Publication	**Overall methodological quality**	**Coherence**	**Relevance**	**GRADE-CERQual assessment of confidence in the evidence**
Bayliss 2016	No concerns	No concerns	No concerns	High confidence
Bjorkman 2016	No concerns	No concerns	No concerns	High confidence
Brownell 2016	Mild concerns	No concerns	No concerns	High confidence
den Boeft 2016	No concerns	No concerns	No concerns	High confidence
Harsh 2016	No concerns	No concerns	No concerns	High confidence
Maatz 2016	No concerns	No concerns	No concerns	High confidence
Madden 2016	Mild concerns	No concerns	No concerns	High confidence
Aamland 2017	No concerns	No concerns	No concerns	High confidence
Broughton 2017	No concerns	No concerns	No concerns	High confidence
Cooper 2017	No concerns	No concerns	No concerns	High confidence
Lian & Robson 2017	No concerns	No concerns	No concerns	High confidence

Pryma 2017	No concerns	No concerns	No concerns	High confidence
Warner 2017	No concerns	No concerns	No concerns	High confidence
Briones-Vozmediano 2018	Mild concerns	No concerns	No concerns	High confidence
Harvey 2018	Mild concerns	No concerns	No concerns	High confidence
Kromme 2018	Mild concerns	No concerns	No concerns	Moderate confidence
Montesó 2018	Mild concerns	No concerns	No concerns	High confidence
Muraleetharan 2018	Mild concerns	No concerns	No concerns	High confidence
Pohontsch 2018	No concerns	No concerns	No concerns	High confidence
Sibelli 2018	Moderate concerns	No concerns	No concerns	Low confidence
Engebretsen 2019	No concerns	No concerns	No concerns	High confidence
Houwen 2019	Mild concerns	No concerns	No concerns	Moderate confidence
Mohebbi 2019	Mild concerns	No concerns	No concerns	Moderate confidence
Sallinen 2019	No concerns	No concerns	No concerns	High confidence
Williams 2019	No concerns	No concerns	No concerns	High confidence
Chen 2020	Mild concerns	No concerns	No concerns	Moderate confidence
Nielsen 2020	No concerns	No concerns	No concerns	High confidence
Osborn 2020	No concerns	No concerns	No concerns	High confidence
Loewenberger 2021	Mild concerns	No concerns	No concerns	High confidence
Rask 2021	Moderate concerns	No concerns	No concerns	Moderate confidence

APPENDIX 4.9 LINE BY LINE CODING OF DIRECT QUOTATIONS FROM PARTICIPANTS – DOCTORS' EXPERIENCES

Code	Direct quote from participant
Biomedical reassurance via tests to deal with uncertainty (Rask)	*refer the patient to further tests at the hospital even though you have a clear expectation that everything is normal. But when blood tests and a scan confirm this, the patient is reassured to a higher extent*
Fear of missing severe illness (Rask)	*we have to hedge our bets because we are so afraid of missing severe illness*
GPs as collaborators (Rask)	*we are afraid of how the message will be received by the patient and whether we will get dismissed by him or her;*
	none of us dare say that we don't expect a physical explanation for their symptoms. Instead, the patients become more and more nervous as we all keep searching for an answer that isn't there
Collaboration among doctors to manage MUS beneficial	*The more we [healthcare professionals] act in compliance with each other, the more reassured the patient gets, and the safer we feel as physicians*
Lack of resources – mx options (Rask)	*I omit patients with PPS because we have only few options to help;* *I cannot do much for these patients. Currently, I don't have any proper service to offer them*
Lack of resources -time (Rask)	*I have neither the time, nor the tools to help them sufficiently*
Self help programmes useful (Rask)	*a self-help programme would be welcome; to let the patient know that he or she is expected to interact with the programme as part of the treatment*
Thorough psychosocial exploration (Houwen)	*I could have spent a bit more time on the anxiety and emotions, I feel I didn't ask her enough about why she's so worried about the nausea*
Being more person centred (Houwen)	*I could have asked, "What do you want to do? How do you feel about that?"*
Improve structure of consultation (Houwen)	*I could have summarised things. And I could have been more explicit about the stages, saying OK, this is the moment to ask questions and then I'll be doing the physical examination.*
	I'd have preferred to do that the other way round: first give the summary, then the conclusion, then the course of action. Now everything's a bit mixed together so that makes it rather chaotic
Improve quality of contact (Houwen)	*maintain contact with the patient rather than looking at the computer. I can imagine now that he might say the doctor showed a lack of interest in that last part. [...] I don't see any genuine interaction in the entire last part*
	I don't give her much space to sort out her own problems
Need to take control (Kromme)	*I steer much more with people who come to the clinic with a whole set of unrecognized symptoms.*
Dr feels pt wasting his time (Kromme)	*I do not have the entire morning, you have to do everything within the allotted time slot . . .) and one does not have three hours for that;*
	Sometimes I ignore it on purpose...I think I will get very many stories that I do not want at that moment
Need to provide reassurance to patient and GP	*they and their GP . . .) need reassurance that still nothing is wrong'*

Demanding patients are difficult	*most difficult is the demanding patient ..That is more troublesome This is actually the most important reason for my appointments running late*
Restrained coding to avoid stigmatising diagnoses (Pohontsch)	*F-category diagnoses are very stigmatising and related to several significant disadvantages*
Tentative diagnoses preferred (Pohontsch)	*Why should I do that? Why? I know what the patient's problem is, I documented it, I look for a somewhat fitting diagnoses and am happy if I find one quickly and am done*
Patients like a diagnosis	*It is a relief for them to know 'Someone labelled me. I feel taken seriously*
Coding for reimbursement (Pohontsch)	*F-category diagnoses are very stigmatising and related to several significant disadvantages*
Restrained coding – mental/behavioral codes only if necessary for referrals for MH care (Pohontsch)	*if I don't refer a patient to psychosomatic therapy or psychotherapy, I don't see the necessity in coding a F-category diagnosis; for short-term psychotherapy I definitely have to code an F-category diagnosis*
Coding wrong due to insufficient knowledge (Pohontsch)	*"I don't know the criteria*
FM pt prototype – the complaining woman (Briones)	*They have a lot of complaints ; their way of life is a continual complaint ;*
Demanding patients	*these people are also very, well very demanding*
Feeling of prejudice towards MUS patients	*I have to admit that it comes down to my own prejudice. I hold it against this sort of patient to a certain degree they're soft, you have to put pressure on them so that they will liven up their act/… /I think that in cases of women with fibromyalgia you're conditioned to think twice about granting them work leave*
	They are patients that … towards whom I feel rejection , I have to admit it
Drs' attitude towards pts: false / exaggerated symptoms to get benefits (Briones)	*there are many people, professional people, and doctors who do not believe in fibromyalgia, so they don't diagnose it, and they don't treat it; they think it is a type of hysteria, a neurosis*
Drs recognize patients' stigma and problems	*they have the feeling that they are stigmatized; they fear that the doctors are going to say: 'ah, another hypocrite; some people prefer not to use this diagnosis, because it will stigmatize the patient*
Issues based on patient's gender / race (Briones)	*They have a profile of complaining which, figuratively speaking, is more readily accepted by society in women than in men; it's really not so bad, nor would it justify sick leave. It's not the same when a woman in that condition asks to be let off work as it is for a man ; A woman who has spent her whole life as a housewife and has not paid into the social security system, and yet suffers enormously from fibromyalgia… but of course, there are problems with recognizing the disease*
Drs' feeling of desperation towards MUS patients	*When you get a patient with fibromyalgia you know that things are probably not going to go well, no matter what you do, no matter what treatment you apply, whatever approach you use*
Drs' attitude towards pts - acknowledge suffering; Aware of lack of social recognition of FM and possible psychological origin of FM (Briones)	*They feel mentally like no one understands them; that wherever they go no one pays attention;*
	"I know she is not putting me on now/ … /I'm not saying that she is not telling the truth, the feeling that she has is real

MUS challenging as it doesn't fit medical mould (Warner)	*Challenging perhaps because it doesn't fit the medical mould*
Some Drs – MUS a positive challenge (Warner)	*I like them (MUS patients). I think it's a challenge actually ... managing them over quite a long period of time you can, you feel as if you're achieving something*
Negative aspects of multiple investigations (Warner)	*at some stage be quite firm and say, 'I don't think I want to do any more tests. I think they are unnecessary. I think potentially they're dangerous*
Rationale for Ix – standard tests for all (Warner)	*Everybody gets a full panel of blood tests as standard. And then brain imaging, depending on what we're looking for...EEG ... and so on*
Rationale for Ix/Referrals - providing reassurance (Warner)	*I see my main function in the heart clinic as reassuring; Taking the patient seriously and facilitating further management';*
	whether or not you do a test on a patient, to a small degree, is driven by how much a patient needs the reassurance.
Rationale for Ix - / concern of missing org. pathology (Warner)	*you do every test you can think of to make sure you're not missing anything, and I'm very worried that I'm just missing something*
Rationale for Ix - threat of litigation (Warner)	*...I think if we were in an era where the lawyers weren't so prominent..then I probably wouldn't be so defensive.*
Importance of having a good relationship with patients (Warner)	*the key is to have a trusting relationship with the patient, that they're confident, they're happy that you have their best interests at heart. That you're looking at and believing them.*
Lack of training on MUS	*Nobody's ever taught me this. it's unstructured and it's pretty much what I've learnt as I've gone along*
Potential solutions to better managing MUS patients (Warner)	*To treat them properly you need to give them more time than anybody else. You need to develop a relationship with them*
	I think the key is to have a trusting relationship with the patient *they're happy that you have their best interests at heart.*
	That you're looking at and believing them
Barriers to effective MX – time pressure, lack of continuity – limited Mx options (Warner)	*I will not have a longstanding relationship with this patient, which is extremely unfortunate; These patients take time*
Comprehensive history as basis of discussion (Aamland)	*I try to be very systematic when I write the summary.. I feel this as a strength when I can tell the patient that we have done this and that..I sometimes browse through the summary to memorise what we actually have done*
Importance of diagnosis to a patient (Aamland)	*I have experienced, from my work with a lot of patients with MUPS, that a diagnosis actually has been of crucial importance*
Potential solutions to better managing MUS patients - showing that the patient is taken seriously through a thorough examination (Aamland)	*I do more regular examinations; touch the belly, listen, and examine. I do not expect to find anything, but then I come a bit further in getting good contact with the patient*

Potential solutions to better managing MUS patients - relationship of trust (Aamland)	*"Oh yeah, I trust you!" This makes me feel that we have been through something together that enables me to soothe her;*
Potential solutions to better managing MUS patients - good communication (Aamland)	*communicative dialogue between me and my patients with MUPS is far more important than what I actually do with them*
Potential solutions to better managing MUS patients - epistemic justice towards patient helps maintain therapeutic alliance (Aamland)	*I accepted and believed that he experienced the symptoms … If I had rejected him and told him that his symptoms didn't fit with any medical condition, that I didn't believe him, then I guess he would have found a new GP In this way, we have kept the alliance ;*
	if it is not too far away from my medical knowledge, I would go for it … If the patients have a narrative they believe in, instead of being rejected by "nothing is wrong with your tests" … I have seen how that has been really useful for several of my patients
Drs difficult emotions on pts – unrewarding – frustrating – guilty feeling at being unable to help (Maatz)	*very difficult to necessarily help*
	very difficult because the patient consciously or otherwise doesn't want it to change, I suspect difficult group of patients, not easy to deal with unfortunately lack of time;
	the classic orthopaedic approach … is 'they're mad'.
	angry people and it's pretty unrewarding and I mean I'm sure they find me unrewarding and I find dealing with them unrewarding
	I think it is frustrating … because you like to be able to help people
	we don't know what the diagnosis is we can't do anything and that is frustrating for me
	frustrated that they are not responding to any of the treatments
	you just feel really, really upset
Difficult identities – medical culture and professional identity issues (Maatz)	*group of patients who it's difficult to get surgeons and physicians interested in because it is not sexy and it is not perceived that there is an awful lot that you can do for them*
Diagnosis difficult (Maatz)	*I think it is quite difficult because it's not like all, you know, cancer or other sorts of common conditions that you can actually say 'yes, this patient has got this', which is a lot easier from a diagnostic point of view than someone with functional symptoms.*
Difficult service structures (Maatz)	*lack of support services …*
Drs and Pts have difficulty understanding their condition (Maatz)	*they may find it at first difficult to understand that this is an illness for which we have no diagnostic tests, for which we have no proper treatment, for which we have no proper understanding;*
	because all it is really saying is probably we don't really understand what is going on it's difficult to get across that there is no real diagnosis
Not that difficult – MUS pts as a positive challenge – helping them rewarding (Maatz)	*I don't think I find them as difficult as some people do; , they are an individual person I'm just honest with them ; it can sometimes be quite rewarding.*
	I think they can be perceived as difficult, but I don't think they are

	A proportion make me feel quite positive and good because I actually do feel able to explain the situation to them and they are taking it on board and you know, I think that they have actually benefitted from the consultation
Communication difficult (Maatz)	*when they are proving to be difficult patients and not answering your questions;*
Pts have difficult lives – bodily issues – social issues (Maatz)	*difficulty opening their bowels; 'difficult to have a social life' ; 'difficult childhoods and difficult relationships'*
Management difficult (Maatz)	*difficult to treat because most of these patients have gone to a few or a reasonable number of doctors before they end up in a speciality gastroenterology clinic*
Difficult pts– time wasters who can't be helped (Maatz)	*it is a difficult group … patients were time wasters who we can't help who are difficult to get throug*
Potential solutions to better managing MUS patients (Maatz)	*I think you have got to give people extra time when they are proving to be difficult patients ..got to be persistent and manage to break down the barriers to find out why*
Lack of education on MUS (Harsh)	*our medical education is not doing a very good job of teaching us to treat patients with medically unexplained illness; side of medicine that we don't learn in textbooks*
Integrated care a solution – involve therapist – care/social worker (Harsh)	*having a psychologist or psychiatrist or somebody to whom I could say 'How would you . . . kind of, deal with this with the patient?' to kind of help me out along the way"*
	"multidisciplinary approach"
	"stems from the fact that I have some resources available to me in my clinic,"
	"partner up and help these patients,"
	"having available a behavioral health component is enormously helpful
Potential solutions - biomedical therapies combined with psychosocial support	*provide social support, maybe doing less medically and more socially and more psychosocially."*
	"combined approach (biomedical therapies + psychosocial treatments)
Differentiate between diagnostic uncertainty and pyschosocial etiology	*not just quickly say, 'Oh it's just from stress and depression or something else that's going on*
	"appropriate medical evaluation' prior to assuming symptoms stem from psychosocial etiology
	a haphazard chicken or egg situation where you don't know whether it is the symptoms that are causing you to be depressed and frustrated or whether this is a manifestation of something else."
Acknowledgement of patient concerns - Pt frustrated (Harsh)	*frustrating" for patients*
Pts scared (Harsh)	*obviously scary*
Acknowledgement of patient dissatisfaction (Harsh)	*perhaps with an appropriate chip on their shoulder toward the health care system that has failed them so far*
Pts confused (Harsh)	*feel confused*
Pts find it expensive (Harsh)	*a very expensive process for the patient*

MUS diagnoses given when symptoms cannot be explained	*We almost just hang these on people when they have pain we can't explain or belly pain we can't explain*
Patients are demanding	*more demanding," "needy,"*
Patients are high utilisers of the medical system	*high utilizers" of the medical system*
Patient refusal to accept MUS diagnosis	*resistant about opening up and accepting that maybe these are somatic complaints*
MUS as a positive challenge	*can be kind of fun at times, like a challenge, like, 'Okay can I help them somehow?'*
Benefits from – discussion of symptom relief – and management vs a cure (Harsh)	*"a little bit of progress" The longer I can get them to stay out of the ED the better," "patch a few holes here and there"*
Dr frustration - Rx and outcome expectation difference (Harsh)	*From a physician standpoint it [MUI/S] can be very frustrating;*
	MUI/S "throws a huge monkey wrench in that [the diagnosis and treatment process] and [when] it doesn't work out so well, it becomes frustrating."
	annoying" and the "really challenging part of medicine
Wastebasket diagnoses – when Drs don't know what is going on (Harsh)	*"irritable bowel syndrome, fibromyalgia, and chronic pain that become these 'wastebasket diagnoses'*
Drs' ability to deal with diagnostic uncertainty	*sometimes we don't find a diagnosis for everything" vs "there's definitely a diagnosis for everything*
	"instead of saying 'have you thought about every possible thing on the differential' . . 'you know sometimes we just don't know
	learning how to be more comfortable in my own skin
	when do we stop digging"
	"how much harm we can do and how much worse we can make these situations a lot of times" in a "well-intentioned" effort to help patients
Potential solutions - good communication	*As long as we are paying the patient attention, we are not going to go wrong* *If you are listening to them and try to answer their question*
	more present with them . . . not as rushed
	to "sit down and really talk for 30 or 60 minutes" with the patient.
Potential solutions - regular patient contact	*I try to see her regularly because it seems to be one of the few things that will actually keep her out of the ED*
Potential solutions - awareness of own bias	*recognize my own bias toward the patients more readily."*
Potential solutions - be more empathetic	*"far more empathic"*
	Being patient
	probably the hardest thing is not being frustrated with them
Potential solutions - reassurance	*I'm going to do an evaluation to make sure that the things I know how to treat or the things I know are going to kill you—I look for them and make sure that they're not there*
Gaps in biomedical knowledge (Harsh)	*Especially when you get down to the biochemical level, there are things that we don't fully understand*

	Look back on what medicine didn't know a 100 years ago and what we know now. I think it's arrogant to think that we're at some place in medicine where we know everything
Chaotic consultations (den Boeft)	*When I think within 2 min "I do not have a clue of what is going on here", then I start to think "This can be MUPS".*
	with MUPS patients, what I usually notice is that the discussion does not go so well and you switch between phases
	with everything together, it just does not make sense.
	A long history…Without any serious diseases. With many referrals for additional examinations or to specialists
Dr negative feelings towards patients (den Boeft)	*I often use it as a diagnostic tool for MUPS, that I get irritated by patients.*
	many doctors have the same basic feeling about these patients - exhaustion, the desperation of the doctor and the way they easily get into a fight with these patients.
	feeling of irritability in the doctor
Dr feels powerless (den Boeft)	*It makes me feel powerless, because I do not get a way in*
Pts unable to cope (den Boeft)	*They do not have the coping strategies to get over it*
What helps better patient relationship (den Boeft)	*if you know more about the context, you can better empathise*
	When you have more experience or when you have a longer relationship
Gaps in biomedical knowledge (den Boeft)	*we cannot give an explanation with our current knowledge*
	certain things still unexplainable now, but maybe not in another 100 years. Lyme is always a good example
Subgroups of MUS patients (den Boeft)Anxious – unhappy – passive – distressed – puzzling	*anxious patients- tend to give a catastrophizing explanation*
	some patients with MUPS their mood can be low due to their symptoms. In the consultation room they can be apathetic
	They hand the problem over to you and you should have the solution - They want it all, but not coming from them
	some patients where there is absolutely no explanation at al
Managing resource constraints (Brownell)	*I don't feel at all that I'm the policeman for the system*
Drs negative feeling about patients (Brownell)	*patients can burn you out for the rest of the day*
Vicious cycle the desire for certainty can create (Brownell)	*some patients who always want another test to the point that you begin to worry they're going to glow in the dark*
	I think a lot of the patients tend to keep looking for an answer and they keep going doctor to doctor to doctor […] And a lot of times you have to say, "Look. you know, we don't have the answer for everything. We don't have the tests for everything.
	many of the primary care physicians are able to do is sort of recognize that—that this is a person that's going to be pushing for more investigations that aren't good for them
	What we are doing is by not acknowledging uncertainty we are creating overly anxious people who want certainty in […]every encounter

	Because we don't know what to do, You and I don't know what to do. We don't know what to tell these folks
Diagnosis necessary for doctor / admin purposes (Brownell)	*the pressure to come up with a diagnosis is often an administrative one rather than a professional one*
	But sometimes the patients don't need a diagnosis and the doctor is the one that needs the diagnosis for their own mental comfort.
Importance of communication (Brownell)	*We may not have an answer but we're both working towards the answer or we're at this point where we know we don't have an answer but we're willing to say, "Okay, fair enough, but I'll continue to try and help solve*
Social determinants of health – diet exercise stress management (Brownell)	*some exercise, and consider your social circumstances and address those*
	A lot of people that I see they're overweight, they have terrible lifestyles, they smoke too much, drink too much, don't eat the right food, they get no exercise. … I'll talk a lot about stress relief, because I think the chronic stress response plays a central role
Role of depression and its management in MUS patients (Brownell)	*there's something here that made me think of depression, and I think we should look at that today*
	a good thing to refer them to a psychiatrist,
Epistemic justice to the patient (Brownell)	*To confront the patient with, "Well there is no neurological evidence that could possibly explain this," is not a helpful explanation [….] This is actually hurtful to some patients because they might assume that you're saying that they're lying, or that they're crazy*
	you have to have the trust that what they are experiencing is what they are experiencing
Gaps in biomedical knowledge/awareness of limits of medicine (Brownell)	*medical science just hasn't figured out yet"*
Importance of relationships (Brownell)	*it is really important with establishing the right sort of relationship*
Empathy – compassion related to empathy (Brownell)	*You hope to establish some sort of rapport with that person*
	you actually do feel a sense of sort of empathy for the situation they are in
Lack of engagement - scepticism, complexity of Mx and working with pt/family (Bayliss)	*"not all doctors believe that there is Chronic Fatigue Syndrome and they just think it's in the patient's head.*
Lack of commitment – small no of pts – time pressure – not a priority not in QOF (Bayliss)	*It doesn't feel like there's a big win for the doctor, I think the level of commitment required to manage patients over the longer term is too much for a primary care professional; it's just a workload issue; It's not top of anyone's agenda ; the amount of importance you can give it isn't that much;*
	It's constantly very busy… there are new QOF things to do
Not always coded as MUS – stigmatising – lack of clarity around diagnosis (Bayliss)	*I used to be very reluctant to make the diagnosis, because I thought it was quite stigmatising*
Limited referral options (Bayliss)	*what's the point of learning all these skills for picking up cues and eliciting people's psychological problems, if you haven't got a counsellor to refer them to*
	I guess the one thing that worries me about [managing CFS/ME] in primary care, is being able to have that detailed knowledge about other resources and where to refer

Need to develop a Mx plan (Bayliss)	*[I have] a more clear idea in my own mind of how to manage it, as opposed to how to treat it, then I can follow up with saying; and this is what it means, and this is what we're going to do, and this what's likely to happen*
Need reliable info source online (Bayliss)	*what I'd like is that you had all that information on the website and I can give people the address… I can say to patients, look, this is…I know this is a good website and the information, I believe is up to date;*
	I'm all for patients being able to access reliable information
Need backup resources (Bayliss)	*I'd like to know the specific details, in terms of the waiting time for an assessment, and the referral criteria.*
	there need to be enough GPs to have the option to do 15 or 20 minute consultations, or half an hour appointments, when it's complicated
	I think you need more backup; oh, you need graded exercise, you need a bit of physio, and you think; well, where the bloody hell are you going to get it?

APPENDIX 4.10 LINE BY LINE CODING OF DIRECT QUOTATIONS FROM PATIENTS

Personal experiences of patients	
Code	Direct quote from participant
Abused/ ill-treated	*Mistreated by my husband (Monteso);*
	Son doesn't treat me well (Monteso);
	Suffered abuse when little (Monteso)
Anger	*Angry (Loewenberger)*
	Anger issues (Muralee)
Anxiety	*I couldn't cope with the anxiety (Osborn)*
	I get anxious (Monteso)
Confused	*At least understand what the problem is.. Lot of confusion (Chen)*
	nothing explained (Sibelli)
	Most people who go to the GP can't understand what's happening to them (Bayliss)
Depressed	*It does get me down quite a lot (Nielsen)*
	Depression (Muralee)
	Heavy heartedness (Sallinen)
	feeling just, very low, very hopeless, very tearful (Osborn)
Desperate	*When you're desperate.. You'll try.. I'll give it a go (Harvey)*
	I just can't hang on (Madden)
	I have lost everything (Bjorkman)
Distressed	*War and fracas in the body (Mohebbi)*
	never made the grief, I kept it in a box (Monteso)
Frightened	*Scary (Loewenberger)*
Frustrated	*Frustrating (Loewenberger)*
	Very frustrating.. No clear answers (Chen)
	biggest frustration was being [ignored] about your own symptoms (Sibelli)
	very frustrating (Bayliss)
	[if you don't know what you're treating, and the doctors don't know .. it can be so very, very frustrating (Madden)
Guilty	*Feeling of guilt (Rask)*

	I feel guilty (Williams)
Isolated, lonely and helpless	*Feel helpless; Feel very alone (Monteso)*
	if the doctor can't get it right — what hope have I got (Sibelli)
	Feel isolated..friends have gone and never come back (Muralee)
	I feel helpless (Bjorkman)
	loneliness and helplessness (Lian)
	Friends, … I've cut a lot of them off (Nielsen)
Lack of control	*I could not control the situation (Mohebbi)*
	Every test came back normal.. Something's going wrong with my brain and I don't really know what's happening to it (Madden)
Loss of sense of self	*I am like a completely different person (Osborn)*
	My need to escape reality ; Reality has become lost to me (Engebretsen)
	You are not the same person (Monteso)
	you begin to think is it all in my mind … you think you're going crazy (Madden)
Memory issues/Brain Fog	*my mind was not clear .. my thinking was clumsy (Sallinen)*
	Memory problems (Monteso)
Negative self-worth	*I just thought that I was horrible (Osborn)*
	You are just 'a nobody' then (Engebretsen)
	I just want my life back", You have to adjust everything to match the illness (Sallinen)
	I do not think I am important, even to myself (Monteso)
	it feels a bit like feeling sorry for yourself (Williams)
	Negative outlook of living (Muralee)
Shamed	*Led to feel.. Quite shamed… that I was contributing to my condition.. Without anyone actually saying that .. (Nielsen)*
	Quite shamed… that I was contributing to my condition.. Without anyone actually saying that .. (Nielsen)
	Led to feel ashamed that I need the help (Williams)
Stigmatised	*Carries a bad stigma (Muralee)*
Suicidal	*I felt like there was no point in living; I didn't want to live. I just wanted to be dead (Osborn)*
	I would have killed myself (Engebretsen)
	stressful job for 12 years… planning to hit the railroad track (Monteso)
	There are many days and hours that I wish I could die (Williams)

Unable to cope	*The pain was extremely debilitating (Cooper)*
Unachieved potential	*I had so many hopes for my life that I'm never going to be able to do (Osborn)*
	I could not fulfill my own expectations .. 2nd class citizen (Sallinen)
	I continually mourn the person that I used to be (Williams)
	Completely changed my life as I cannot function at a level even close to pre-FM levels (Muralee)
Uncertainty	*Rheumatologist knew right away what this was..uncertainty and confusion ended (Sallinen)t knowing whether you are going to get better or not (Nielsen)*
	Not knowing whether you are going to get better or not (Nielsen)

Not believed	
	It's incredible how much I've had to fight to be believed a long battle to be believed and taken seriously (Lian)
	met with great scepticism about my illness and zero knowledge about it (Lian)
	they look at me, and they think I'm not ill; and this illness doesn't look like I'm sick. But I am (Pryma)
	[Doctor] concluded that I was a hypochondriac (Lian)
	a strong scepticism (Engebretsen)
	he said that there was no such thing (Broughton)
	Some doctors didn't believe in ME (Lian)
	[this is complicated by] the fact that there are no diagnostic tests (Cooper)
	some people think it's still in your head and things and it's a bit patronizing (Broughton)
	nothing worse is there than when you feel that everyone thinks you are lying (Osborn)
	I'm experiencing what it means not to be believed (Engebretsen)
	It is not a real thing just all in my head (Muralee)
	invisible illness' nothing I can do to prove to you that I have this condition (Williams)
	People think I'm faking it (Loewenberger)
Not listened to and misunderstood	
	They stop listening to you (Loewenberger)
	don't listen to the patient at all (Lian)
	and zero understanding (Lian)
	not being understood (Lian)

Felt disrespect and dismissive attitude	
Dismissive	*doctors that are very dismissive...who don't like it when you ask questions (Chen)*
	dismissed all my symptoms and just said I just need to learn to live with it (Sibelli)
	My doctor is not bothered about my illness (Monteso)
Lack of respect	*I don't feel that he respects me (Engebretsen)*
	I don't feel that he (Dr) respects me (Sibelli)
Not treated as an individual	*they don't look at you as an individual (Sibelli)*
	they don't look at you as an individual (Harvey)
Treated rudely and badly	*I was treated extremely badly and disdainfully.. [Dr] called it a bunch of crazy people (Lian)*
	how rude they are (Lian)
	The doctor told me that my pain was not going to kill me. I feel very angry about how she treated me (Monteso)
	I was shouted at [by neurologist] (Lian)
Lack of empathy	*the medical profession is not a particularly empathetic profession (Cooper)*
Ridiculed	*first GP…actually ridiculed ME (Lian)*
	Doctor.. just laughed at me and said he couldn't be bothered to waste time on people like me (Lian)
	I have had doctors at the hospital who laugh at me (Lian)
Lack of support	*my GP.. that she couldn't help me 'we don't know what to do with you' (Lian)*
	zero help (Lian)
	no help, no guidance, no follow-up (Lian)
Prejudiced	*extreme prejudice (Lian)*
Onus on patients to get better	
	can't you just pull yourself together (Engebretsen)
	[Dr] thinks I brought this on myself' (Bjorkman)
	Men are expected to 'suck it up and tough it out' (Muralee)
	my own fault that I was ill!' (Lian)
	they put pressure on patients to 'pull themselves together' ..or to undergo treatment that makes patients worse (Lian)
	it's your fault (Pryma)
Importance of receiving a diagnosis	

	I still didn't think that was right at all not to tell me what he thought my problem was (Chen)
	[A] doctor's diagnosis has authority (Bjorkman)
	to actually know that it has been recognised, that somebody is there supporting you… is completely brilliant (Osborn)
	Over the moon-had actual diagnosis (Loewenberger)
	if you can put a name to something, sometimes there is usually something that can be done to help' (Madden)
	[with diagnosis] sort of idea of legitimacy and validation.. kind of a psychological benefit (Bayliss)
Problems worsened by race/gender	
	People aren't nearly as sympathetic toward men with FM (Muralee)
	[Dr said] I will never give fibromyalgia diagnosis to a man (Sallinen)
	I think as a Black woman,.. I will probably have a harder time getting disability for fibromyalgia than a white woman would (Pryma)
	your pain is not as bad as her pain (talking about the white woman), and everybody knows that Blacks and Hispanics have addictive personalities (Pryma)
	I believe if I had been a white woman, he would have gone, and, you know, done things quicker (Pryma)
Adversarial relationship with doctors	
	Fight to get treatment (Loewenberger)
	every single door was just being closed (Osborn)
	You're fighting everything and everyone (Osborn)
	With regard to my doctor it is a continuous battle (Engebretsen)
Lack of confidence in doctors	
Perception of lack of knowledge	
	how little knowledge the health services have about ME (Lian)
	primary health service knows little about fatigue-related conditions (Lian)
Dissatisfied with referrals and investigations	
	keep on thinking about whether the gynaecologist was thorough enough (Rask)
	need some more physical investigations to be sure that nothing severe is wrong with me (Rask)
	none of (medication) really helped so I didn't.. really like any of them (Harvey)
Feeling that health services failed the patient	
	because they totally failed me for many years (Lian)

Perception of misdiagnosis	
	diagnosed with bipolar disorder, ME, chronic fatigue, depression.. and given medication for all of those different things (Osborn)
	other GP, he just kept knocking me back time and time again—you are depressed, you're depressed, you're depressed (Osborn)
	being passed around' .. 'being on a merry-go-round' (Bjorkman)
Unwilling to accept Dr's diagnosis	
Not prepared to accept diagnosis	
	When the lived experience and understanding of one's own situation differs from the GP's understanding to such a degree - the GP's diagnosis is difficult to accept (Engebretsen)
	I don't think that I would have been prepared to accept it (Rask)
	have stress, we all have anxiety ..But I'm not sure that's relevant to me (Nielsen)
	I didn't want to accept that I had IBS (Sibelli)
Perception that MUS diagnosis given as the easy option	
	It's so easy for them to say that it is all psychological (Bjorkman)
	Health personnel.. all too easily utter the sentence: 'It is probably something mental' when there is something they can't explain (Lian)
	It is all too easy to blame psychological factors. It is often easy to do that when there is a lack of medical knowledge.. (Lian)
	I think it's a trial and error (Sibelli)
MUS diagnosis given when doctors can't find cause of illness	
	They can't put their finger on what's wrong so they tell you in a roundabout way that it's imaginary and it's all in your mind (Madden)
	because they don't understand the condition it doesn't really feel like they care very much and they've got other patients to deal with (Broughton)
	they think it is mental and that we are being quarrelsome if we don't admit that and get well with cognitive therapy (Lian)
	I just thought… you can't find anything specifically wrong with me…. Because we can't find anything else wrong with you (Nielsen)
	doctors can't find anything else wrong with you, so what they put on your results is IBS (Sibelli)
	think that's just a term they use when they haven't got any other diagnosis (Sibelli)

	It is not really a medical diagnosis at all; it's only based on symptoms, like psychiatric diagnoses (Bjorkman)
Accepting psychological diagnosis implies acceptance of faking illness	
	psychological feels like it should mean, it's literally you are making it up. It's all in your head … nothing wrong with you at all (Nielsen)
Difficult to get tests and referrals	
	..what I would like to see is that the GP will refer you. (Bayliss)
	Refer me on .. Do something (Nielsen)
Lack of time	
	I think the GPs are too busy (Bayliss)
	I don't believe GPs have enough time (Sibelli)
	I don't think anybody's got that time (Bayliss)
	they don't have time (Broughton)
Expensive	
	keep laying out money and, in the end, you're no different (Harvey)
	Incredibly expensive on every level Physically, emotionally.. psychologically (Cooper)
Accused of feigning illness for financial benefit	
	'acting like a crazy so I can get a check.' (Pryma)
	you're just playing the system (Pryma)
	always applying for disability they're not really disabled (Pryma)
Positive relationships	
Caring, understanding and supportive	
	I had the opportunity to work with some very caring physicians (Cooper)
	refreshing to meet someone who understands it and who really cares you know they really believe what you experience (Broughton)
	The rheumatologist of a specialized service and another that we witness in a proven way perfectly understands us (Monteso)
	really nice to feel that um I was being treated by expert professionals who understood the condition and were sympathetic to it and were really committed to helping (Broughton)
	I've got a very good doctor – very supportive (Nielsen)

	Most recent GP was very good and she was very sympathetic (Sibelli)
	… I went back to my GP who I'm fortunate is very supportive indeed (Broughton)
	I am really happy with her (GP). (Rask)
Takes patients seriously and has a good relationship with patients	
	I'd built up quite a solid relationship with him …I just felt that he was very engaging and it felt … [as if] he took me seriously (Cooper)
	[GP] she was fantastic because she said no no no we'll take this seriously' (Broughton)
	She relates to me. She doesn't just try to push medicine on me (Broughton)
Spends time and resources on patients	
	[FP] She takes her time with me (Rask)
	I never feel like she's rushing. I never feel like she has not got time for me (Chen)
	Makes sure that I get to see a specialist if she finds it relevant (Rask)
Explains and shares information	
	She's just been a really wonderful source, and she educates me (Chen)
	she was a brilliant doctor.. she explained to me why she was prescribing it (Harvey)
	I really appreciate people who give me information, give me options, and then let me decide for myself (Chen)
Expressed needs – what Patients want from doctors	
Need to be taken seriously	
	He [Specialist] was the first person that actually took my symptoms seriously (Osborn)
	I need them to make me feel that they are treating it seriously (Bayliss)
Need to be treated as an individual	
	I can expect my GP to listen to what I have to say and respect me as a person (Lian)
	each individual needs a different therapy (Monteso)
	You have to do what works for you (Monteso)
Need for information and guidance	
	I don't want to be with someone who's just going to throw pills at me (Chen)
	the 10% that I didn't know that he's been able to help me learn is priceless (Chen)
	Not clear what I'm supposed to be attentive to (Rask)
	GP .. To tell me visit this webpage (Rask)

Need for peer support	
	Get a feeling of not being alone by talking or seeing others in the same situation and see how they manage their symptoms (Rask)
	Attend and participate in society with other patients (Monteso)
	contact with people who have experienced the same stressful situations (Monteso)
	see other people going through exactly the same thing.. know it's not just me because of being lazy (Bayliss)
Need for support beyond medical treatment alone	
	GP could have helped me if she had asked how I was actually doing instead of only focusing on the symptoms from my stomach (Rask)
	I wish that I could visit my GP every two weeks, without any specific purpose besides having a deep and meaningful conversation (Rask)
	in my opinion they should carry on doing the tests until they find out exactly what is causing the problem (Madden)
	..get a sort of homework in an online programme and then your GP would follow-up on whether you have done it or not" (Rask)
	I can go to my GP if I feel distressed. Then I just sit there and cry (Rask)
	.. Relief to have presented all symptoms to GP .. Now it is up to him.. I have done my part.. (Rask)
Patient contributions to effective dr-pt relationships	
	as a patient, I need to go in clear and concise, not wandering (Chen)
	I don't have ridiculous expectations of what they can do for me (Chen)
	Change one's state of mind. Accept that you cannot achieve everything (Monteso)
	… I sort of accepted that maybe this is … psychological (Cooper)
	if it's a psychological thing, then it's a matter of me deciding how to … live with it, or how to manage it. (Cooper)
	[I visit] less frequently.. it's just easier to accept.. I've got [CFS/ME] instead of trying to look for something in each symptom (Bayliss)

Appendices for Chapter 6

APPENDIX 6.1 SEARCH STRATEGY

Appendix 6.1: Search strategy	
1	exp Medical Records/
2	exp Medical Records Systems, Computerized/
3	exp Electronic Health Records/
4	"electronic medical record*".ti,ab,kw.
5	"electronic health record*".ti,ab,kw.
6	"electronic record*".ti,ab,kw.
7	"computerised medical record*".ti,ab,kw.
8	"computerised health record*".ti,ab,kw.
9	"computerised record*".ti,ab,kw.
10	"electronic record*".ti,ab,kw.
11	"health record*".ti,ab,kw.
12	"administrative data".ti,ab,kw.
13	"electronic data".ti,ab,kw.
14	"health data".ti,ab,kw.
15	"primary care data".ti,ab,kw.
16	"GP data".ti,ab,kw.
17	"GP record*".ti,ab,kw.
18	EHR.ti,ab,kw.
19	EMR.ti,ab,kw.
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp Somatoform Disorders/ -
22	medically unexplained symptoms/ -
23	Psychophysiologic Disorders/
24	Fibromyalgia/
25	Fatigue Syndrome, Chronic/ -
26	Irritable Bowel Syndrome/-
27	somatisation.ti,ab,kw.
28	"somati*".ti,ab,kw.
29	somatoform.ti,ab,kw.
30	"psychosomatic dis*".ti,ab,kw.
31	"psychogen*".ti,ab,kw.
32	"functional somatic syndrome".ti,ab,kw.
33	"functional somatic symptom*".ti,ab,kw.
34	"functional syndrome*".ti,ab,kw.
35	"functional symptom*".ti,ab,kw.
36	"medically unexplained".ti,ab,kw.
37	"multiple unexplained symptom*".ti,ab,kw.
38	"multiple unexplained physical symptom*".ti,ab,kw.
39	"multiple physical symptom*".ti,ab,kw.
40	"medically unexplained physical symptom*".ti,ab,kw.
41	"persistent physical symptom*".ti,ab,kw.
42	"health anxiety".ti,ab,kw.
43	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44	20 and 44

APPENDIX 6.2 LIST OF ARTICLES FOR FULL TEXT REVIEW

		Author	Year	In review	Reason for rejection if rejected
1	The diagnostic challenges presented by patients with medically unexplained symptoms in general practice.	Aiarzaguena	2008	No	Does not use electronic medical records.
2	Chronic somatic complaints in adolescents: prevalence, predictive validity of the parent reports, and associations with social class, health status, and psychosocial distress.	Barkmann	2011	No	Study on adolescents alone - not a study of adults.
3	Distinctive patterns of medical care utilization in patients who somatise.	Barsky	2006	No	Does not use EMR to identify MUS patients.
4	A new questionnaire to identify bodily distress in primary care: The BDS checklists.	Budtz-Lilly	2015	No	Not relevant.
5	**Identifying patients with medically unexplained physical symptoms in electronic medical records in primary care: a validation study.**	**den Boeft**	**2014**	**Yes**	**1**
6	Patients with persistent medically unexplained symptoms in general practice: characteristics and quality of care.	Dirkzwager	2007	No	Does not compare selection criteria for identifying MUS from EMR against a different reference standard to confirm criteria validity.
7	Whether unexplained or not 3 or more concurrent somatic symptoms predict psychopathology and service use in community populations.	Escobar	2010	No	Does not use electronic medical records.
8	The combination of health anxiety and somatic symptoms: a prospective predictor of healthcare usage in primary care.	Fergus	2018	No	Study examined if health anxiety and somatic symptom severity predicted primary care service utilisation.
9	Is frequent attendance in primary care disease specific?	Foster	2006	No	Not relevant.
10	Mental disorders among frequent attenders in primary care: a comparison with routine attenders.	Gili	2011	No	Not relevant.
11	Administrative data used to identify patients with irritable bowel syndrome.	Goff	2008	No	Identified only IBS.

12	Using Read codes to identify patients with Irritable Bowel Syndrome in General Practice: a database study.	Harkness	2013	No	IBS only. Does not compare EMR record search criteria to a reference standard.
13	High utilizers of medical care: a crucial subgroup among somatising patients.	Hiller	2004	No	Not relevant.
14	Identifying persistent somatic symptoms in electronic health records: exploring multiple theory-driven methods of identification.	Kitselaar	2021	No	Does not compare EMR record search criteria to a reference standard
15	The course of newly presented unexplained complaints in general practice patients: a prospective cohort study.	Koch	2009	No	Not relevant.
16	Analysis of diagnoses extracted from electronic health records in a large mental health case register.	Kovalchuk	2017	No	Not relevant.
17	The resource utilisation of medically unexplained physical symptoms.	Lee	2016	No	Not relevant.
18	Patients with somatoform disorders: More frequent attendance and higher utilization in primary Out-of-Hours care?	Leutgeb	2018	No	Not relevant.
19	Identifying patients with chronic widespread pain in primary care.	Mansfield	2017	No	Identify chronic pain alone. Does not compare selection criteria for identifying chronic pain from EMR against a different standard measurement to confirm validity.
20	Costly patients with unexplained medical symptoms: A high-risk population.	Margalit	2008	No	Not relevant.
21	**Estimating the prevalence of medically unexplained symptoms from primary care records.**	**Morriss**	**2012**	**Yes**	**2**
22	Association Between Patient Review of Systems Score and Somatization.	Okland	2013	No	Limited to MUS in otolaryngology.
23	Medically unexplained physical symptoms (MUS) among adults in Canada: Comorbidity, health care use and employment.	Park	2017	No	Not relevant.
24	Clinical characteristics of persistent frequent attenders in primary care: case-control study.	Patel	2015	No	Removed as it is a case control study.

25	Diagnosis of somatoform disorders in primary care: diagnostic agreement, predictors, and comparisons with depression and anxiety.	Piontek	2018	No	Does not use electronic medical records.
26	Diagnosing somatisation disorder (P75) in routine general practice using the International Classification of Primary Care.	Schaefert	2010	No	Concerns the recording of MUS using ICPC code P75 and ICD codes.
27	**Screening for high utilizing somatizing patients using a prediction rule derived from the management information system of an HMO: a preliminary study.**	**Smith**	**2001**	**Yes**	**3**
28	**A method for rating charts to identify and classify patients with medically unexplained symptoms.**	**Smith**	**2004**	**Yes**	**4**
29	**The diagnostic accuracy of predicting somatisation from patients ICD-9 diagnoses.**	**Smith**	**2009**	**Yes**	**5**
30	The identification in primary care of patients who have been repeatedly referred to hospital for medically unexplained symptoms: a pilot study.	Benjamin Smith	2009	No	Does not compare EMR record search criteria to a reference test.
31	Somatization and health anxiety as predictors of health care use.	Tomenson	2012	No	Does not validate identification method against an established reference test.
32	Using electronic health records data to identify patients with chronic pain in a primary care setting.	Tian	2013	No	Focuses on chronic pain alone.
33	Diagnosis of Munchausen's syndrome by an electronic health record search.	Van Dinter	2009	No	Case study.
34	Identification of patients with mild or moderate MUS in primary care with a five year follow up.	Van Westrienen	2016	No	Congress presentation summary; assesses validity of criteria for MUS identification by checking for MUS during 5 year follow up.
35	Identification of patients with moderate MUS in primary care with a five years follow up.	Van Westrienen	2019	No	Prognostic study - not diagnostic.
36	Persistent presentation of medically unexplained symptoms in general practice.	Verhaak	2006	No	Not structured as an index test of identification compared against a reference test.

APPENDIX 6.3 DETAILS OF INDEX & REFERENCE TESTS AND RESULTS FOR SELECTED STUDIES

6.3.1 SMITH 2001 STUDY

Study setting and participant selection: All high-frequency users (without excluding those with organic disease) based on age and number of visits were considered for the study, out of 15,505 registered patients of a health management organisation (HMO) in Michigan, USA. Of this, 883 patients were selected for the study, and two-thirds of these patients (588) were randomly selected as the 'derivation set' - to derive the model, and the remaining one-third used to validate the model.

Index test:

- Hypothesis: Patients screen positive for MUS based on two criteria i) Higher consultation frequency ii) Higher somatisation potential.
- Somatisation potential assessed to be higher if the percentage of visits for the ICD-9 diagnosis code categories in the following body systems: nervous (320-389), gastro-intestinal (520-579), musculo-skeletal (710-739) and ill-defined body systems (780-799), were higher (than the percentage of visits for other ICD-9 diagnostic categories).
- Data of patients in derivation set analysed using logistic regression. Steps followed:
    1. Univariable models based on data available from the management information system – no. of visits, demographic data, somatisation potential based on ICD-9 diagnostic categories.
    2. All variables with a P<0.15 relationship with somatisation in the univariable analysis included in the initial multivariate model – age, gender, number of visits,

somatisation potential, employer, co-pay, relationship to subscriber (the latter three relevant in the insurance-based US medical care payment system).

3. Variables with strong independent association with somatisation ($P<0.05$) - Gender, number of visits and somatisation potential were included in the final model.

- The model's goodness-of- fit (Hosmer-Lemeshow Test) and the pseudo-R^2, indicating the proportion of explained variation compared to the maximum value of R^2, were calculated.

Reference test: The ability of the model to accurately identify somatisers was assessed by comparing the model results with a physician's diagnosis of somatisation based on patient chart review and the reason for the largest number of visits during the year. The physician was blinded to the hypothesis and predictors. Somatisation was diagnosed based on >1 physical symptom of ≥6 months duration after definitive testing and consultative evaluation did not indicate organic disease. Patients without investigations (blood tests, x-rays/scans) or referrals were not rated as somatisers.

Results:

Of the 883 patients with a mean age of 40.3 years (range 21-55 years), 67% women, and 10.7 mean number of visits, 122 were somatisers. Based on the logistic regression model, the probability of somatisation in a given patient was calculated using the following final model:

Figure 6.3.1 Smith 2001 – Logistic Regression model for somatisation status (N = 588)

Log { P / (1 – P) } = -7.420 + 1.146 X Gender + 0.166 X No. of Visits + 0.057 Somatisation potential

Gender = 1 if female

	β	χ2	P
Intercept	-7.420	117.160	<0.0001
Female gender	1.146	9.660	0.0019
Number of visits	0.166	42.390	<0.0001
Somatisation potential	0.057	66.030	<0.0001
c-statistic			
Derivation	0.90		
Validation	0.78		
Maximum R^2	0.45		
Hosmer-Lemeshow Test - P value	0.25		

Considering MUS prevalence of 14% and a cut-off point of 4% probability of patient having MUS:

Sensitivity: 97.5% Specificity: 54% Positive predictive value: 25.7% Negative predictive value: 99.2%

Considering MUS prevalence of 14% and a cut-off point of 40% probability of patient having MUS:

Sensitivity: 49.4% Specificity: 95.9% Positive predictive value: 66.1% Negative predictive value: 92.1%

The probability of somatisation in a patient was computed and the sensitivities and specificities given by the model at different probability cut-off values were determined. Positive predictive values (PPV - 'likelihood of somatisation when the screening test i.e., the index test, was positive') and negative predictive values (NPV - likelihood of not being a somatiser when the screening test was negative) were calculated based on the 14% somatisation prevalence rate seen in the patient population. The receiver operating curve (ROC curve) was plotted to assess the relationship between the proportion of true positives

(sensitivity) and the proportion of false positives (1 minus specificity) – a higher c-statistic indicates greater power of the model to differentiate between patients with MUS from those without.

Using a cut-off point of 0.04, i.e., where a patient is considered a somatiser if the model indicates a probability of somatisation of least 4%, the sensitivity of the model was 97.5% and the specificity was 54%. PPV was 25.7% whereas the NPV was 99.2%. A 4% probability of being a somatiser, and a PPV of 25.7% are very low values, due to the index test model picking up too many non-cases. When a 40% probability was considered, sensitivity fell to 49.4%, and the specificity rose to 95.9%. PPV rose to 66.1% and NPV to 92.1%.

The logistic model was then prospectively validated in the remaining one-third of patients. At the same 0.04 probability cut-off, the model correctly identified 39 of 43 somatisers (sensitivity 91%), and 129 of 252 non-somatisers (specificity 51%). At the same prevalence rate of 14%, PPV was 23% and NPV was 97%, with a 0.78 c-statistic.

6.3.2 SMITH 2009 STUDY

This study updated and tested the database screener developed in the Smith 2001 study.

Study setting and participant selection: Same participants as the Smith 2001 were considered with the eligible age range expanded to 18-65 years, number of visits increased to at least 8 visits per year in the two years prior to the study in order to ensure selecting a high-utilising patient group for the study where somatisation is more prevalent. Of 1,646 patients, after eliminations due to organic disease and incomplete records, 1,364 patients were selected; two-thirds, 901 patients, as the derivation set for logistic regression and 463 as the validation set.

Index test:

- Hypothesis: Somatising patients can be identified by screening administrative databases for i) female gender ii) age iii) increasing number of visits and iv) somatisation potential – defined as high % of visits recorded with ICD-9 diagnosis codes in nervous (320-389), gastro-intestinal (520-579), musculo-skeletal (710-739) and ill-defined body systems (780-799).
- Somatisation defined as 'no documented organic disease to explain one or more symptoms of at least six months,' changed from 2001 study that needed definitive testing/evaluation.
- Logistic regression model developed for somatisation status using four variables above

Reference test:

- Ability of model to accurately identify somatising patients assessed by comparing result from the model with a physician's diagnosis of somatisation based on patient chart review and the problem generating the most visits during 1 year. The physician was blinded to the hypothesis and predictors.

Results: Of the 1,364 patients with a mean age of 47.1 years (range 21-55 years), 71.6% women, and 12.8 mean number of visits, 319, i.e. 19.4%, met the criteria for somatisation.

Figure 6.3.2: Smith 2009– Logistic Regression model for somatisation status (N = 901)
Log { P / (1 – P) } = -5.327 + 0.134 X Age - 0.002 X Age^2 + 0.308 X Gender + 0.044 X No. of Visits + 0.026 Somatisation potential Considering MUS prevalence of 19.4% and a cut-off point of 0.3: Sensitivity: 46.5% Specificity: 82.5% Positive predictive value: 38.9% Negative predictive value: 86.5%

The c-statistic for the validation set was at 0.72 whereas 0.7 – 0.75 is usually considered acceptable discriminative ability. When the logistic regression model was applied to the validation set – the c-statistic was smaller at 0.68. Using a cut-off of 0.3 for the model – i.e. where a patient is considered a somatiser if the model indicates a probability of somatisation of 30%, the sensitivity of the model was 46.5% and the specificity was 82.5%; positive predictive value was 38.9% and negative predictive value 86.5%.

6.3.3 MORRISS 2012 STUDY

Study setting and Participant selection: 828 consecutive consulters in 8 GP practices in England; only eligibility criterion was for participants to be at least 18 years old.

Index test: Previous 2 years' EHR were analysed to find univariable associations of 38 demographic and healthcare use variables associated with MUS (from a literature review). Backward stepwise multilevel logistic regression, clustered by GP, was carried out to create a final model to estimate the probability of a patient having MUS (Figure 6.3.3). A similar model was built to assess the probability of a patient having severe MUS.

Figure 6.3.3: Variables associated with MUS in literature analysed in Morriss 2012 study

Univariate association of Variables with MUS		Not associated with MUS	
	P value	harmful alcohol use	chronic physical illness
Age	<0.01	past anxiety	high antibiotic use
Female gender	<0.01	counselling	excessive sweating
Antidepressants in last 2 years	<0.01	past eating disorder	hysterectomy
Multiple pain	<0.01	number of somatic symptoms	repeat urinary tract infection
Depression	<0.01	poor subjective health	bacterial gastroenteritis
Life stress	0.01	sleep problems	negative autoantibody test
Opiates	0.02	sexual problems	negative rheumatoid factor
Anxiety	0.02	obesity	negative ESR test
Chronic Fatigue	0.03	low exercise	dry skin
Asthma	0.09	psychiatric referrals	swollen neck glands
Referrals (number in last 2 years)	0.09	past depression	current smoking
		education	past smoking
		number of consultations per year	

Reference test:

- Seventeen trained GPs in eight GP practices rated 828 consecutive consulters as 1) definitely / probably MUS 2) possibly MUS 3) unsure 4) unlikely to be MUS 5) definitely not MUS and rated the severity of MUS as severe, moderate, mild, trivial, or as not relevant. Patients in first two categories were considered MUS patients.

Results:

Observed MUS prevalence according to the GP rating of patients was 19%. The study reported that at an optimal cut-off of predicted risk of 24%, estimated MUS prevalence according to the regression model was 18.4%, and thus close to what the authors considered was the gold standard assessment. At 24% cut-off, the sensitivity was only 40%.

Figure 6.3.4: Morriss 2012 – Logistic Regression models	
Probability value P for the **presence of MUS** in a patient $P = 1 / (1 + e^{-z})$ where z = -1.2862 – 0.0184 (per year of age) + 0.8489 (presence of prescription for opiates) + 0.5352 (presence of multiple pain sites) + 1.7151 (presence of chronic fatigue) + 1.1111 (presence of prescription for antidepressants), *During the previous 2 years* and e = 2.71828 c statistic in MUS model = 0.70 (95% CI 0.65 – 0.74)	Probability value P for the **presence of severe MUS** in a patient $P = 1 / (1 + e^{-z})$ where z = -2.3524 – 0.0164 (age in years) + 0.7173 (presence of prescription for opiates) + 0.7168 (presence of multiple pain sites) + 1.9456 (presence of chronic fatigue) + 1.2552 (presence of prescription for antidepressants) + 1.7151 (presence of negative erythrocyte sedimentation rate test) + 0.7709 (presence of life stress) - 0.5965 (presence of obesity) *During the previous 2 years*

Considering MUS prevalence rates at 18-20%, severe MUS at 3% and a cut-off point of 0.24 **Sensitivity: 40% Specificity: 86% ; Positive predictive value: 34% Negative predictive value: 89%**	A cut-off for P of 0.35 gives: **Sensitivity: 16.4% Specificity: 98.9%; Positive predictive value: 60% Negative predictive value: 92.5%**

6.3.4 SMITH 2004 STUDY

The Smith 2004 study developed a numerical method for chart rating to identify and classify MUS.

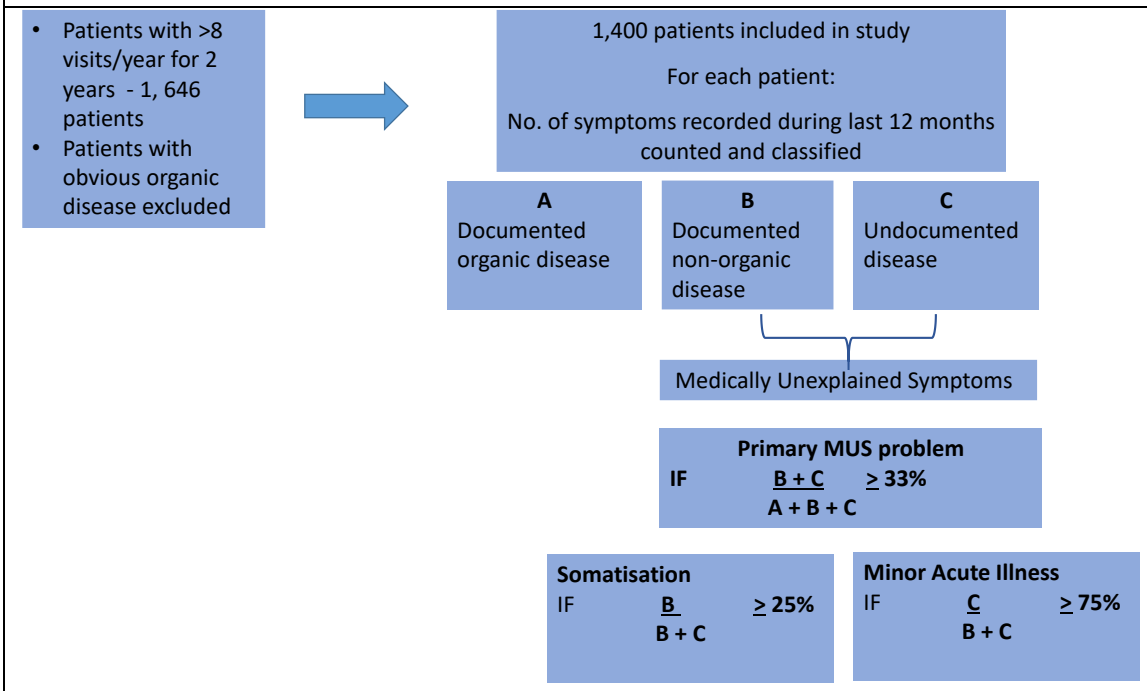
Study setting and participant selection: 1,400 adult, primary care patients without organic disease and with ≥ 8 consultations per year over two previous years; out of 28,000 adult patients in a US HMO.

Index test: A trained rater examined all the medical care provided to each of the 1,400 selected patients and classified each recorded symptom in to one of three categories as shown in Figure 6.3.5 below:

Figure 6.3.5: Smith 2004 study – patient symptom categorisation		
Definitive testing done: e.g. MRI/CT for low back pain, MRI/CT for headaches, laparoscopy for pelvic pain, endoscopy for inflammatory bowel disease		**Little / no laboratory or other objective diagnostic workup**
Documented organic disease	**Documented non-organic disease**	**Undocumented disease**
Definite diagnostic abnormalities on laboratory, diagnostic testing	Consultant's opinion / Definitive testing found little/no organic disease	

The total number of symptoms falling under each of the three categories above for all primary care visits over the year were counted. Documented non-organic disease and undocumented disease categories were collectively considered Medically Unexplained Symptoms. Researchers defined a patient's condition as a 'Primary MUS problem' when the combined total of documented non-organic disease symptoms (B in Figure 6.3.6) and undocumented disease symptoms (C in Figure 6.3.6 below) is ≥33% of the total number of symptoms recorded for each patient (A + B + C).

Figure 6.3.6: Smith 2004 study – Index test – Numerical method for chart rating



All patients designated as having a Primary MUS problem were then categorised in to two groups. Where the number of documented non-organic disease symptoms, B, was ≥ 25% of the total number of non-organic and undocumented disease symptoms, B / (B + C), this was considered Somatisation, or "bona fide MUS". When the number of undocumented disease symptoms (C) was ≥ 75% of total non-organic and undocumented disease symptoms, this

was considered Minor Acute Illness, not MUS. The authors stated that the proportion of 33% for a case to be considered primarily a MUS problem was set intentionally low to be as inclusive as possible, accepting that a high false-positive rate was likely.

Reference test: Diagnostic accuracy of the index test was determined by comparing index test results to the results of an independent, detailed review of the patient charts by a physician – with the study authors considering patient clinical chart rating by a physician as the gold standard for MUS diagnosis.

Results:

The authors state that of the 1,025 patients identified as having MUS by the index test, 319 were indicated as having an organic disease when using the gold standard physician rating (Fig 6.3.7). The study does not mention any false negatives. The observed prevalence of MUS is 50.4% in this high-utilising population of 1,400 patients, and 2.5% when considering the entire adult population of 28,000 patients.

Figure 6.3.7: Smith 2004 Study – comparison of Index test and Reference test calculated

		Reference test		
		Positive	Negative	
Index test	Test Positive	706	319	1025
	Test Negative	0	375	375
		706	694	1400

Sensitivity	100%
Specificity	54.0%
Positive predictive value	68.9%
Negative predictive value	100%

** Assuming There are no False Negatives as there is no mention of false negatives in the stu

The calculated sensitivity rate is high (100%) as shown above, whereas the specificity is only 54%. Positive predictive value is calculated to be 68.9% and the false positive rate was 31% (319/1025).

6.3.5 DEN BOEFT STUDY:

This study focused on validating an electronic health record screening method to identify MUS patients using PHQ-15 as a reference test.

Study setting and participant selection: Patients aged ≥ 18 years with five or more consultations during last 12 months who completed a PHQ-15 between 2005-2007 were selected from the Utrecht Health Project, Netherlands database ; those with Chronic Obstructive Pulmonary Disease (COPD), Hypertension (HT), Diabetes or an established psychiatric diagnosis were excluded.

Index test:

- An EHR screening method analysed consultation data in 12 months preceding a PHQ-15 assessment.
- Step 1 – all patients ≥18 years with ≥5 consultations over the past 12 months preceding the completion of a PHQ-15 assessment during 2005 – 2007; those with established chronic diseases such as COPD, HT, Diabetes and those with psychiatric diagnoses were excluded.
- Step 2: Two sub-groups of patients identified:

  1) Syndrome-based confirmed MUS - patients with >=1 consultation for a MUS symptom syndrome – IBS, Fibromyalgia or Chronic Fatigue Syndrome (ICPC codes D93, L18.01 and A04.01).

2) High-Risk MUS group - patients with ≥3 consultations for >=1 of 104 ICPC codes suggestive of MUS.

Reference test:

- PHQ -15, a validated diagnostic instrument found to be a moderately reliable questionnaire to detect MUS (Kroenke et al, 2002; van Ravesteijn et al, 2009), was used and PHQ-15 score cut-offs of >=5 and >= 10 were used as the reference test to identify MUS patients.
- The number of patients identified using the EHR screening method compared to number of patients identified as having MUS using PHQ-15 scores of (i) >=5 and (ii) >=10.

Results:

- Of the 1,223 participants in the study 756 (61.8%) were female and the mean age was 38.8 years.
- EHR screening identified 131 patients including 21 Syndrome-based confirmed patients and 126 High Risk MUS patients; most patients with Syndrome-based confirmed MUS also had >=1 ICPC code suggestive of MUS and were included in both sub-groups. This indicated an estimated MUS prevalence of 10.7%.
- Using a PHQ-15 score of ≥10 as the determinant of MUS, the reference test identified 176 MUS patients; observed MUS prevalence of 14.4%. With PHQ-15 >=5 as the cut-off, the number of MUS patients were 609, an observed MUS prevalence of 49.8%. Specificity was 93 – 95% and sensitivity was 17-30%.

Figure 6.3.8: den Boeft Study – reported comparison of index test against reference test PHQ-15

No. of MUS patients identified by Index and Reference Tests

	Reference test - PHQ-15		
No. of patients	**PHQ-15 <5**	**PHQ-15 5>=(PHQ-15)>10**	**PHQ-15 >=10**
Index test "MUS +"	29	49	53
Index test " No MUS "	585	384	123
Total = 1,223 patients	614	433	176

Total MUS patients identified		
by Index test	131	10.7%
by Reference test PHQ-15 >=10	176	14.4%
by Reference test PHQ-15 >=5	609	49.8%

Index test data a/to PHQ-15 cut-offs	**PHQ-15 >=5**	**PHQ-15 >=10**
Sensitivity	0.17	0.30
Specificity	0.95	0.93
Positive Predictive Value	0.78	0.40
Negative Predictive Value	0.54	0.89

APPENDIX 6.4 APPLICABLE FACTORS IN ASSESSING RISK OF BIAS IN QUADAS-2

1. Patient Selection	Describe methods of participant selection: Describe included patients (prior testing, presentation, intended use of index test and setting).
Signalling Questions	Was a consecutive or random sample of patients enrolled?
	Was a case-control design avoided?
	Did the study avoid inappropriate exclusions?
Risk of Bias	Could the selection of participants have introduced bias?
Applicability	Describe included patients (prior testing, presentation, intended use of index test and setting).
	Are there concerns that the included participants do not match the review question?
2. Index Test	Describe the index test and how it was conducted and interpreted.
	Were the index test results interpreted without knowledge of the results of the reference test?
	If a threshold was used, was it specified?
Risk of Bias (High/Low/Unclear)	Could the conduct or interpretation of the index test have introduced bias?
Applicability	Concerns that the index test, its conduct or interpretation differ from the review question.

3. Reference test	Describe the reference test, and how it was conducted and interpreted.
	Is the reference test likely to correctly classify the target condition?
	Were the reference test results interpreted without knowledge of the results of the index test?
Risk of Bias	Could the reference test, its conduct or its interpretation have introduced bias?
Applicability	Is there a concern that the target condition as defined by the reference test does not match the review question?
4. Flow and timing	Describe any patients who did not receive the index tests(s) and /or reference standard or who were excluded from the 2x2 table (refer to flow diagram)
	Describe the time interval and interventions between index test(s) and reference standard.
	Was there an appropriate interval between index test(s) and reference standard?
	Did all patients receive a reference standard?
	Were all patients included in the analysis?
Risk of Bias	Could the patient flow have introduced bias?

Appendices for Chapter 7

APPENDIX 7.1. SEARCH STRATEGY FOR EVIDENCE SUMMARY OF CODE LISTS OF DIAGNOSED MUS

Appendix 7.1. Search strategy for evidence summary of code lists of diagnosed MUS

EBSCO Search Strategy

(somatoform disorders or somatization disorders or medically unexplained symptoms) OR ('hypochondriasis' or 'hypochondriac' or 'hypochondria' or 'illness anxiety disorder' or 'health anxiety' or 'somatic symptom disorder') OR functional somatic symptoms OR functional somatic disorders OR functional somatic syndrome OR "multiple unexplained symptoms" OR "persistent physical symptoms" OR "psychosomatic symptoms" OR "psychophysiologic disorders" OR "bodily distress disorder" OR (ibs or irritable bowel syndrome or irritable bowel syndrome constipation or irritable bowel syndrome diarrhoea) OR (chronic fatigue syndrome or myalgic encephalomyelitis or me/cfs) OR (chronic fatigue syndrome or exhaustion disorder) OR (fibromyalgia or fibromyalgia syndrome or fms or fm) OR non cardiac chest pain OR post viral fatigue syndrome OR (premenstrual syndrome or pms) OR temporomandibular joint dysfunction syndrome

AND

("Read code") OR ("ICPC code") OR ("ICD code")

APPENDIX 7.2: MUS SPECIFIC READ CODE LIST

As described in Chapter 7.3.3

Appendix 7.2: MUS Specific Read code list - List of Read codes to record diagnosed MUS that were used in primary care –

Diagnostic codes referring to specific MUS Symptom Syndromes		**Codes referring to specific psychogenic, functional or pseudo conditions**		**Codes that refer to a general condition of "medically unexplained" or other related term**	
E2016-2	Globus hystericus	E2277	Psychogenic dyspareunia	E2016	Other conversion disorders
E2781	Tension headache	E2613	Psychogenic hyperventilation	E207	Hypochondriasis
Eu455	[X]Globus pharyngeus	E2644	Psychogenic dyspepsia	E26z	Psychosomatic disorder NOS
Eu45y-2	[X]Globus hystericus	E2651	Psychogenic vaginismus	Eu44	[X]Dissociative [conversion] disorders
F286	Chronic fatigue syndrome	E2757	Psychogenic polydipsia	Eu44-2	[X]Conversion reaction
F286-1	CFS - Chronic fatigue syndrome	Eu444-2	[X]Psychogenic dysphonia	Eu450	[X]Somatization disorder
F286-6	ME - Myalgic encephalomyelitis	Eu445-1	[X]Pseudoseizures	Eu452	[X]Hypochondriacal disorder
F302	Atypical face pain	Eu522-3	[X]Psychogenic impotence	Eu452-1	[X]Body dysmorphic disorder
J0464	Temporomandibular joint-pain- dysfunction syndrome	F2461-2	Neurogenic bladder	R0907	[D]Hypochondrial pain
J521	Irritable colon - Irritable bowel syndrome	J52	Functional GI tract disorders NEC	R2yz-1	God only knows
J5210	Irritable bowel syndrome with diarrhoea	J520	Constipation - functional	ZV655-1	[V]"Worried well"
J5211	Irritable bowel syndrome characterised by constipation	J525	Functional diarrhoea	*16H*	*Unexplained symptoms continue**
J521-1	Irritable bowel syndrome	K16y8-1	Functional voiding disorder	*16T*	*Medically unexplained symptoms**
K584	Premenstrual tension syndrome	*16F0*	*Functional urinary and faecal incontinence**	*2J4*	*Worried well**
N239	Fibromyalgia	*246M*	*White coat hypertension**	*8CC*	*TLC - tender loving care**
N239-1	Myofascial pain syndrome				
N248	Fibromyalgia				
N2480	Myofascial pain syndrome				
R065B	[D]Non cardiac chest pain				
R065B-4	[D]Non-cardiac chest pain				
1828	*Atypical chest pain**				

**Seven symptom codes (i.e. not diagnosis codes, in italics) were also included in this MUS Specific Read codes list as they referred to the diagnosis of MUS, rather than to symptoms.*

APPENDIX 7.3 MUS RELATED SYMPTOM CODE LISTS

The creation of this list is described in Chapter 7.3.

a. Gastrointestinal symptoms

Appendix 7.3.1: MUS related Symptom codes - Gastrointestinal system related symptom codes					
19B	Flatulence/wind	R077	[D]Abnormal faeces	197A	Generalised abdominal pain
19B2	Excessive flatulence	R0771	[D] Stools loose	197B	Upper abdominal pain
19B5	Excessive flatus	R121	[D]Stool contents abnormal	197C	Lower abdominal pain
19B-5	Wind symptom	1925	Excessive salivation	197D	Right upper quadrant pain
R073	Flatulence, eructation and gas pain	1929	Tongue symptoms	J16y4	Dyspepsia
R0730	Flatulence	192A	Bad taste in mouth	J16y4-1	Flatulent dyspepsia
R073z-1	[D]Wind	192Z	Mouth symptom NOS	19EC	Painful defaecation
19B-1	Belching symptom	194	Swallowing symptoms	J096	Glossodynia
19B3	Excessive belching	194-1	Dysphagia	J096-2	Painful tongue
R0731	[D]Eructation	194Z	Swallowing symptom NOS	J5747	Anal pain
19B-2	Bloating symptom	R072	[D]Dysphagia	J5748	Rectal pain
19A2	Abdomen feels bloated	R0720	[D]Difficulty in swallowing	J574F	Anorectal pain
19A3	Abdomen feels distended	R072z	[D]Dysphagia NOS	R073z	[D]Flatulence, eructation and gas pain NOS
19A4	Abdomen feels swollen	ZV416-2	[V]Problems with swallowing	R079	[D] Defaecation painful
19AZ	Abd. distension symptom NOS	195	Indigestion symptoms	M180-2	Sore bottom
R0733	[D]Abdominal distension, gaseous	1954	Indigestion	R090	[D]Abdominal pain
R0734	[D]Bloating	195Z	Indigestion symptom NOS	R0905	[D]Epigastric pain

19C	Constipation	J16y4-2	Indigestion NOS	R0909	[D]Pain in right iliac fossa
19C-1	Constipation symptom	1955	Heartburn	R090A	[D]Pain in left iliac fossa
19C2	Constipated	1955-1	Heartburn symptom	R090E	[D]Recurrent acute abdominal pain
19CZ	Constipation NOS	R071	[D]Heartburn	R090H	[D]Upper abdominal pain
J5204	Chronic constipation	R0711	[D]Waterbrash	R090J	[D]Right upper quadrant pain
J520z	Constipation NOS	R071z	[D]Heartburn NOS	R090K	[D]Left upper quadrant pain
J52y1	Difficulty in ability to defaecate	1968	Abdominal discomfort	R090N	[D]Nonspecific abdominal pain
19EA	Change in bowel habit	1984	Upset stomach	R090y	[D]Other specified abdominal pain
19EA-1	Altered bowel habit	1984-1	Upset tummy	R090z	[D]Abdominal pain NOS
19EB	Frequency of defaecation	J08zz-1	Discomfort in mouth	Ryu11	[X]Other and unspecified abdominal pain
19EE	Increased frequency of defaecation	J52z-1	Bowel dysfunction	198	Nausea
R078	[D]Change in bowel habit	1969	Abdominal pain	198-1	C/O - nausea
19F	Diarrhoea symptoms	19690	Abdominal wall pain	R0700	[D]Nausea
19F-1	Diarrhoea	1971	Central abdominal pain	J10y	Other oesophageal disorders
19F2	Diarrhoea	1973	Left subcostal pain	J574z	Other rectal and anal disorders NOS
19F-2	Loose stools	1974	Right subcostal pain	R07	[D]Digestive system symptoms
19FZ	Diarrhoea symptom NOS	1975	Left flank pain	J151	Chronic gastritis
J4-3	Noninfective diarrhoea	1976	Right flank pain	J155	Gastritis unspecified
J43z-1	Chronic diarrhoea	1977	Right iliac fossa pain	Jyu13	[X]Other gastritis
J4z-1	Presumed non-infectious diarrhoea	1978	Left iliac fossa pain		
J4zz-1	Diarrhoea - presumed non-infectious	197-1	Flank pain		

b. Cardiac/Respiratory systems

Appendix 7.3.2: MUS related Symptom codes – Cardiac/Respiratory system related symptom codes					
17	Respiratory symptoms	R060A	[D]Dyspnoea	R0650	[D]Chest pain, unspecified
R06	[D]Respiratory system and chest symptoms	R060D	[D]Breathlessness	R0656	[D]Chest discomfort
R0600	[D]Respiratory symptom, unspecified	181	Palpitations	R0658	[D]Chest tightness
173	Breathlessness	1812	Palpitations	R065A	[D]Musculoskeletal chest pain
1732	Breathless - moderate exertion	1814	Fluttering of heart	R065D	[D]Central chest pain
1733	Breathless - mild exertion	181-1	Awareness of heartbeat	R065z	[D]Chest pain NOS
1734	Breathless - at rest	181-2	Fluttering of heart	Ryu04	[X]Other chest pain
1738	Difficulty breathing	181Z	Palpitations NOS	186	C/O cold extremities
1739	Shortness of breath	R050-1	[D]Rapid heartbeat	1860	C/O cold hands
173-1	Breathlessness symptom	R051	[D]Palpitations	1861	C/O cold feet
173-2	Dyspnoea - symptom	R0510	[D]Awareness of heartbeat	186-1	C/O cold peripheries
173-3	Shortness of breath symptom	R051z	[D]Palpitations NOS	186z	C/O cold extremities NOS
173C	Short of breath on exertion	182	Chest pain	1C5	Sneezing symptoms
173C-1	Dyspnoea on exertion	1822	Central chest pain	R04z3	[D]Sneezing
173C-2	SOBOE	1824	Anterior chest wall pain	1C8Z	Nasal symptom NOS
173Z	Breathlessness NOS	182B	Rib pain	1C93	Persistent sore throat
232A	O/E - hyperventilating	182B0	Costal margin chest pain	1D22	Symptom: chest wall
232C	Noisy breathing	182C	Chest wall pain	1D22-1	C/O - a chest wall symptom
R0601	[D]Hyperventilation	182Z	Chest pain NOS	R04z2	[D]Mouth breathing
R0608	[D]Shortness of breath	R065	[D]Chest pain		

c. Genito-urinary system

Appendix 7.3.3: MUS related Symptom codes – Genito-urinary system related symptom codes					
1A	Genitourinary symptoms	R0830	[D]Enuresis NOS	1AE	Vaginal discomfort
R08	[D]Urinary system symptoms	R0842	[D]Nocturia	K42y6	Vulvodynia
1A1	Micturition frequency	1A42	Urine looks dark	K58y0	Other pelvic pain - female
1A1-1	Frequency of micturition	1D25	Symptom: genital area	1A59	C/O pelvic pain
1A1-2	Polyuria	R086z	[D]Urination abnormality NOS	R090G-1	[D] Pelvic pain
1A1-3	Urinary frequency	K16V1	Overactive bladder	1A5A	C/O perineal pain
1A12	Frequency of micturition	K16y4	Irritable bladder	R090G-2	[D] Perineal pain
R084	[D]Micturition frequency and polyuria	K16y4-2	Unstable bladder	R090G	[D]Pelvic and perineal pain
R0840	[D]Frequency of micturition, unspecified	1A53	Lumbar ache - renal	1A5B	Pain in penis
R0841	[D]Polyuria	1A53-1	C/O - loin pain	1A5C	Pain in scrotum
R084z	[D]Frequency of micturition or polyuria NOS	R090C	[D]Loin pain	1A5D	Urethral pain
1A25	Urgency	1A53-2	C/O - lumbar pain	R081	[D]Dysuria
1A25-1	Urgency of micturition	1A53-3	C/O - renal pain	R081z	[D]Dysuria NOS
R0862	[D] Urgency of micturition	1A580	Vaginal pain	R090B	[D]Groin pain
1A220	Nocturnal enuresis	1A581	Vulval pain	R0908	[D]Suprapubic pain
1A	Genitourinary symptoms	R0830	[D]Enuresis NOS	1AE	Vaginal discomfort

d. Neurological symptoms

Appendix 7.3.4: MUS related Symptom codes – Neurological symptom codes					
1B4	Sensory symptoms	F222-1	Left sided weakness	1B52-1	Feels off balance
1BZ2	Transient neurological symptoms	F223-1	Right sided weakness	1B53	Dizziness present
6663	Neurological symptom changes	R2y2	[D]Nervousness	1B5-3	Unsteady symptom
1B1G	Headache	R2y2-2	[D]Nervous tension	1B55	Dizziness on standing up

1B1G-1	C/O - a headache	R2y3	[D]Debility, unspecified	1B6-1	Faint symptom
1B1G-2	Cephalgia	R0072-1	[D]General weakness	1B68	Felt faint
1BA3	Unilateral headache	1B41	Has pins and needles	R0021	[D]Fainting
1BA5	Frontal headache	1B43	Has tingling sensation	R004	[D]Dizziness and giddiness
1BA6	Occipital headache	R0203	[D]Tingling of skin	R0040	[D]Dizziness
1BA8	Temporal headache	1B44	Has numbness	R0041	[D]Giddiness
1BB1	Aching headache	1B442	Numbness of limbs	R0042	[D]Light-headedness
E2781	Tension headache	1B49	Sensory disturbance in limb	R004z	[D]Dizziness and giddiness NOS
E2781-1	Muscular headache	R0206	[D]Numbness	1BR	Reduced concentration
F2620	Cluster headache	1B46	C/O paraesthesia	1BW	Poor concentration
F2626	[X]Tension type headache	1B47	Transient paraesthesia	Eu900	[X]Disturbance of activity and attention
F262B	Chronic tension-type headache	R0207	[D]Paraesthesia	1C	Ear/nose/throat symptoms
Fyu5D	[X]Cervicogenic headache	1B48	Burning feet	1C15	Popping sensation in ear
Fyu5E	[X]Chronic headache disorder	C2623	Burning feet syndrome	1C22	Buzzing in ear
R040	[D]Headache	29B50	O/E - paraesthesia in hands	2BJ6	O/E - twitching eyes
R040z	[D]Pain in head NOS	2G2D	Numbness of hand	Eu953	[X]Involuntary excessive blinking
1B22-2	Shaking	R020	[D]Skin sensation disturbance	F13z2	Restless legs syndrome
R0103	[D]Tremor NOS	R020z	[D]Skin sensation disturbance NOS	J046	Temporomandibular joint disorders

1B3-2	Weakness symptoms	R0201	[D]Burning of skin	J046z	Temporomandibular joint disorder NOS
1B320	Weakness of arm	R0204	[D]Hyperaesthesia	R0032-1	[D]Fit (in non epileptic) NOS
1B321	Weakness of leg	R0205	[D] Hypoaesthesia	R003z	[D]Convulsion NOS
1B323	Facial weakness	1B5-1	Dizziness symptom	R003z-1	[D]Seizure NOS
E205	Neurasthenia - nervous debility	1B52	Unsteadiness present	N2420	Neuralgia unspecified
F22-1	Hemiparesis			N2421	Neuritis unspecified

e. Fatigue

Appendix 7.3.5: MUS related Symptom codes – Fatigue related symptom codes

168	Tiredness symptom	168-1	Fatigue - symptom	R007	[D]Malaise and fatigue
1682	Fatigue	168-2	Lethargy - symptom	R0070	[D]Malaise
1683	Tired all the time	168-3	Malaise - symptom	R0071	[D]Fatigue
1684	Malaise/lethargy	1683-1	C/O - "tired all the time"	R0073	[D]Lethargy
1688	Exhaustion	168Z	Tiredness symptom NOS	R0075	[D]Tiredness
		E205-2	Tired all the time	R007z	[D]Malaise and fatigue NOS

f. Musculoskeletal system

Appendix 7.3.6: MUS related Symptom codes: Musculoskeletal system related symptom codes					
14G3-1	H/O: knee problem	1D13-2	C/O - an ache	N0946	Arthralgia of the lower leg
1M10	Knee pain	1D13-1	Pain	N0947	Arthralgia of the ankle and foot
1M12	Anterior knee pain	1DC1	Burning pain	N2452	Pain in leg
N0946-1	Knee joint pain	1DC2	Aching pain	N2452-1	Aching leg syndrome
N094M	Arthralgia of knee	1DC6	Tightening pain	N245-6	Leg pain
N094W	Anterior knee pain	1DC8	Generalised pain [symptom]	N245-8	Thigh pain
N0956-1	Knee stiff	1DC9	Shooting pain	N245-9	Pain in buttock
ZV49z-1	[V] Problem knee	1M	Pain	N2454	Calf pain
14G4	H/O: back problem	8BAO	Pain and symptom management	N0947-1	Ankle joint pain
16C	Backache symptom	Eu62y-1	[X]Chronic pain personality syndrome	N094P	Arthralgia of ankle
16C2	Backache	F369	Complex regional pain syndrome	N245-1	Ankle pain
16C6	Back pain without radiation NOS	F369-1	Chronic regional pain syndrome	1M11	Foot pain
16CZ	Backache symptom NOS	N094z	Arthralgia NOS	N2451	Foot pain
N142-4	Lumbago	N096-2	Musculoskeletal pain - joints	N245-3	Foot pain
N145	Backache, unspecified	N0945	Arthralgia of the pelvic region and thigh	ZV49z-2	[V] Foot problem
N145-2	Back pain, unspecified	N0969	Other joint symptoms of multiple sites	1D28-2	C/O - foot symptom
N14z	Back disorders NOS	R00z2	[D]Pain, generalized	1D130	C/O - pain in toes
N141	Pain in thoracic spine	R00z2-1	[D]General aches and pains	N2451-1	Toe pain
16C7	C/O - upper back ache	R00zz	[D]Other general symptoms NOS	ZV49z-3	[V] Toe problem
16C5	C/O - low back pain	R01z2	[D]Musculoskeletal pain	N094T	Arthralgia of 1st MTP joint
16C9	Chronic low back pain	R01	[D]Nervous and musculoskeletal symptoms	N245-5	Heel pain
16CA	Mechanical low back pain	R01-1	[D]Musculoskeletal symptoms	N2456	Tender heel pad
N142	Pain in lumbar spine	Ryu70	[X]Other chronic pain	1M3	Pain in face
N142-1	Low back pain	N094K	Arthralgia of hip	26BF	Persistent mastalgia

N1472-1	Pain in coccyx
16A	Stiff neck symptom
16A2	Stiff neck
16A3	Wry neck/torticollis
16A3-1	Torticollis - symptom
16A3-2	Wry neck symptom
1D21-2	C/O - a neck symptom
N13z	Cervical and neck disorders NOS
N131	Cervicalgia - pain in neck
N131-1	Pain in cervical spine
N135	Torticollis unspecified
N135z	Torticollis NOS
N135z-1	Stiff neck NOS
N135z-2	Wry neck
N138	Cervicalgia
1DCC	Aching muscles
N20-1	Polymyalgia
N23y4	Spasm of muscle
N23yE	Spasm of back muscles
N2410	Myalgia unspecified
N2410-1	Intercostal myalgia
N2410-2	Muscle pain
1D12	C/O: stiffness
N095	Joint stiffness NEC
N0959	Multiple stiff joints
N095z	Joint stiffness NEC, NOS
1D13	C/O: a pain
N094K-2	Hip pain
N094L	Arthralgia of sacro-iliac joint
N0945-2	Hip joint pain
1M0	Pain in upper limb
N245-2	Arm pain
N2453	Pain in arm
N0942	Arthralgia of the upper arm
1M00	Pain in elbow
1M00-1	Elbow pain
N0942-1	Elbow joint pain
N094D	Arthralgia of elbow
N0943	Arthralgia of the forearm
N0943-1	Wrist joint pain
N094F	Arthralgia of wrist
N094F-1	Wrist pain
N0944	Arthralgia of the hand
N0964	Other joint symptoms of the hand
N2450	Hand pain
N245-4	Hand pain
N0944-1	Hand joint pain
N094G	Arthralgia of MCP joint
N094H	Arthralgia of PIP joint of finger
N095W	Stiff finger
N2172	Metatarsalgia NOS
N2450-1	Thumb pain
N2450-2	Finger pain
1M1	Pain in lower limb
R0400	[D]Facial pain
R0400-1	[D]Face ache
R040z-1	[D]Jaw pain
N094	Pain in joint - arthralgia
N0940	Arthralgia of unspecified site
N094-1	Ache in joint
N0949	Arthralgia of multiple joints
N0941	Arthralgia of the shoulder region
N0941-1	Shoulder joint pain
N094A	Arthralgia of shoulder
N094B	Arthralgia of sternoclavicular joint
N094C	Arthralgia of acromioclavicular joint
N2457	Shoulder pain
N245-7	Shoulder pain
N2455	Axillary pain
N245	Pain in limb
N247	Other musculoskeletal limb symptoms
N247z	Musculoskeletal limb symptoms NOS
ZV49-1	[V]Limb problems
ZV493	[V]Sensory limb problems
N096-1	Joint crepitus
N0990	Clicking shoulder
N0999	Clicking hip
N099A	Multiple clicking joints
N099C	Clicking knee
N099E	Clicking ankle
N097	Difficulty in walking

g. Miscellaneous symptom codes

Appendix 7.3.7: MUS related Symptom codes: Miscellaneous symptom codes					
16	General symptoms	R0260-1	[D]Pale	R0054	[D]Hypersomnia NOS
16-1	Polysymptomatic	1686	Heavy legs	1D15	C/O: itching
16-2	Symptoms vague	16E	Feels unwell	M18z	Pruritus NOS
16ZZ	General symptom NOS	1B1B	Cannot sleep - insomnia	M18z-2	Itch
R00	[D]General symptoms	1B1B0	Initial insomnia	Myu2D	[X]Pruritus, unspecified
R0z	[D]Symptoms NOS	1B1B-1	C/O - insomnia	Mz-1	Sore skin
R2-3	[D]Uncertain diagnosis	1B1Q	Poor sleep pattern	1N03	C/O: dry skin
168-4	C/O "Muzzy head"	1BX0	Delayed onset of sleep	28G	Forgetful
1B6A	Muzzy headed	1BX1	Excessive sleep	2I19	Discomfort
1B6D	Funny turn	1BX2	Sleeping pattern	E2Cy0	Breath holder
1D21	Symptom: head/neck	1C7	Snoring symptoms	R09	[D]Other abdominal and pelvic symptoms
R0701-1	[D] Sickness	1C72	Snores	R09z	[D]Other abdominal or pelvic symptom
ZV655	[V]Person with feared complaint, no diagnosis made	1C7Z	Snoring symptom NOS	R09zz	[D]Abdominal or pelvic symptom NOS
ZV655-3	[V]No problem, feared complaint unfounded	E274	Non-organic sleep disorders	171-2	Sputum - symptom
1612	Appetite loss - anorexia	E2741	Transient insomnia	1CB3	Throat pain
1613	Appetite increased	E2741-1	Insomnia NOS	1CB5	Throat irritation
1615	Reduced appetite	E2742	Persistent insomnia	R041	[D]Throat pain
1612-2	Loss of appetite - symptom	E2748	Night terrors	R041-1	[D]Throat discomfort
161Z	Appetite symptom NOS	E2749	Nightmares	1CB4	Feeling of lump in throat
R0300	[D]Appetite loss	E274D-1	Restless sleep	R042z-1	[D]Lump throat

16-3	Multiple symptoms	E274y-1	Dreams	1CB2	Choking sensation
1652	Feels hot/feverish	Eu515	[X]Nightmares	R04z0	[D]Choking sensation
166	Sweating symptom	Fy0	Sleep disorders	1CBZ	Throat symptom NOS
166Z	Sweating symptom NOS	1B67-1	Drowsiness - symptom	Ryu52	[X]Other and unspecified disturbances of smell and taste
R0081	[D]Excessive sweating	R0000	[D]Drowsiness	R011	[D]Smell and taste disorder
1672-1	Flushes - symptom	R0001	[D]Somnolence	R011z	[D]Smell or taste disorder NOS
R0261	[D]Flushing	R005	[D]Sleep disturbances	ZV415	[V]Problem with smell or taste
R0262	[D]Excessive blushing	R0050	[D]Sleep disturbance, unspecified	ZV415-1	[V]Problems with smell
1674	Pale colour	R005-1	[D]Insomnia - symptom	ZV415-2	[V]Problems with taste
R0260	[D]Pallor	R0052	[D]Insomnia NOS		

APPENDIX 7.4 READ CODES AND COSTS: RECORDS OF INVESTIGATIONS FOR PATIENTS IN PRIMARY CARE DATABASE

Description of creation of this Read Code list is given in Chapter 7.4.1 and the method of derivation of costs is given in Chapter 12.

Costs sourced from PSSRU data and NHS costing data.

Cost of each of 650 investigation codes recorded in IDMUS/UNIDMUS patients

Read code	Description	2007	2008	2009	2010	2011	2012	2013	2014
32	Electrocardiography	£37	£34	£36	£38	£40	£42	£44	£47
42	Haematology	£3	£3	£1	£3	£3	£3	£3	£3
43	Immunology	£23	£8	£10	£8	£8	£5	£5	£29
46	Urine examination	£6	£1	£1	£1	£1	£1	£1	£1
321	ECG - general	£37	£34	£36	£38	£40	£42	£44	£47
423	Haemoglobin estimation	£3	£3	£1	£3	£3	£3	£3	£3
424	Full blood count - FBC	£3	£3	£1	£3	£3	£3	£3	£3
442	Thyroid hormone tests	£6	£1	£1	£1	£1	£1	£1	£1
461	Urine exam. - general	£6	£1	£1	£1	£1	£1	£1	£1
524	Plain X-ray skull	£26	£28	£29	£29	£30	£28	£30	£30
527	Plain X-ray pelvis	£26	£28	£29	£29	£30	£28	£30	£30
529	Plain X-ray hand	£26	£28	£29	£29	£30	£28	£30	£30
535	Standard chest X-ray	£26	£28	£29	£29	£30	£28	£30	£30
547	Barium swallow	£423	£446	£469	£442	£436	£415	£423	£428
554	Coronary arteriogr.-general	£37	£34	£36	£38	£40	£42	£44	£47
567	Computerised axial tomography	£131	£134	£141	£125	£117	£111	£115	£115
569	Nuclear magnetic resonance	£257	£271	£366	£367	£369	£296	£338	£355
585	Other diagnostic ultrasound	£71	£66	£61	£77	£98	£93	£75	£73
3118	Diagnostic lumbar puncture	£419	£441	£465	£489	£515	£542	£570	£600
3148	Sleep studies	£749	£738	£824	£759	£657	£605	£508	£423
3155	Tilt table test (ECG)	£37	£34	£36	£38	£40	£42	£44	£47

3166	Breath test	£84	£88	£150	£206	£106	£266	£136	£143
3168	Defaecating proctogram	£521	£548	£577	£559	£606	£594	£616	£628
3211	ECG requested	£37	£34	£36	£38	£40	£42	£44	£47
3212	Standard ECG	£37	£34	£36	£38	£40	£42	£44	£47
3213	Exercise ECG	£86	£68	£103	£90	£61	£64	£67	£88
3214	Ambulatory ECG	£34	£57	£47	£59	£62	£65	£68	£72
3216	ECG normal	£37	£34	£36	£38	£40	£42	£44	£47
3217	ECG abnormal	£37	£34	£36	£38	£40	£42	£44	£47
3219	ECG equivocal	£37	£34	£36	£38	£40	£42	£44	£47
3241	ECG: no LVH	£37	£34	£36	£38	£40	£42	£44	£47
3242	ECG: shows LVH	£37	£34	£36	£38	£40	£42	£44	£47
3262	ECG: extrasystole	£37	£34	£36	£38	£40	£42	£44	£47
3263	ECG: ventricular ectopics	£37	£34	£36	£38	£40	£42	£44	£47
3264	ECG: atrial ectopics	£37	£34	£36	£38	£40	£42	£44	£47
3272	ECG: atrial fibrillation	£37	£34	£36	£38	£40	£42	£44	£47
3299	ECG: right bundle branch block	£37	£34	£36	£38	£40	£42	£44	£47
3374	Lung function testing abnormal	£43	£46	£78	£28	£30	£31	£33	£34
3377	Lung function restrictive	£43	£46	£78	£28	£30	£31	£33	£34
3395	Peak exp. flow rate: PEFR/PFR	£43	£46	£78	£28	£30	£31	£33	£34
3511	Surgical biopsy taken	£515	£542	£570	£600	£632	£665	£700	£737
3614	Endoscopy normal	£423	£446	£469	£442	£436	£415	£423	£428
3617	Colonoscopy normal	£517	£544	£573	£533	£528	£489	£509	£519
3618	Colonoscopy abnormal	£517	£544	£573	£533	£528	£489	£509	£519
4131	Blood test requested	£3	£3	£1	£3	£3	£3	£3	£3
4145	Blood sample -> Lab NOS	£3	£3	£1	£3	£3	£3	£3	£3
4146	Urine sample sent to Lab	£16	£9	£6	£9	£9	£8	£8	£8
4147	Swab sent to Lab	£11	£7	£5	£8	£8	£7	£7	£7
4219	Haematology result abnormal	£3	£3	£1	£3	£3	£3	£3	£3
4235	Haemoglobin low	£3	£3	£1	£3	£3	£3	£3	£3
4239	Haemoglobin high	£3	£3	£1	£3	£3	£3	£3	£3
4258	Haematocrit	£3	£3	£1	£3	£3	£3	£3	£3

4392	Rubella antibody absent	£23	£8	£10	£8	£8	£5	£5	£29
4393	Rubella antib. present -immune	£23	£8	£10	£8	£8	£5	£5	£29
4421	Thyroid hormone tests normal	£6	£1	£1	£1	£1	£1	£1	£1
4427	Free T4 level	£6	£1	£1	£1	£1	£1	£1	£1
4435	Prolactin level	£6	£1	£1	£1	£1	£1	£1	£1
4512	Renal function tests abnormal	£6	£1	£1	£1	£1	£1	£1	£1
4612	Urinalysis requested	£16	£9	£6	£9	£9	£8	£8	£8
4613	Urinalysis = no abnormality	£16	£9	£6	£9	£9	£8	£8	£8
4614	Urinalysis = abnormal	£16	£9	£6	£9	£9	£8	£8	£8
4615	MSU sent to lab.	£11	£7	£5	£8	£8	£7	£7	£7
4616	MSU = no abnormality	£11	£7	£5	£8	£8	£7	£7	£7
4617	MSU = abnormal	£11	£7	£5	£8	£8	£7	£7	£7
4618	Urine dipstick test	£6	£1	£1	£1	£1	£1	£1	£1
4619	MSU = no growth	£11	£7	£5	£8	£8	£7	£7	£7
4622	Urine: dark/concentrated	£6	£1	£1	£1	£1	£1	£1	£1
4662	Urine glucose test negative	£6	£1	£1	£1	£1	£1	£1	£1
4663	Urine glucose test = trace	£6	£1	£1	£1	£1	£1	£1	£1
4664	Urine glucose test = +	£6	£1	£1	£1	£1	£1	£1	£1
4665	Urine glucose test = ++	£6	£1	£1	£1	£1	£1	£1	£1
4666	Urine glucose test = +++	£6	£1	£1	£1	£1	£1	£1	£1
4668	Glycosuria	£6	£1	£1	£1	£1	£1	£1	£1
4672	Urine protein test negative	£6	£1	£1	£1	£1	£1	£1	£1
4673	Urine protein test = trace	£6	£1	£1	£1	£1	£1	£1	£1
4674	Urine protein test = +	£6	£1	£1	£1	£1	£1	£1	£1
4675	Urine protein test = ++	£6	£1	£1	£1	£1	£1	£1	£1
4693	Urine: trace non-haemol. blood	£6	£1	£1	£1	£1	£1	£1	£1
4695	Urine blood test = +	£6	£1	£1	£1	£1	£1	£1	£1
4697	Urine blood test = +++	£6	£1	£1	£1	£1	£1	£1	£1
4698	Urine dipstick for blood	£6	£1	£1	£1	£1	£1	£1	£1
4918	Semen exam: normal	£3	£4	£5	£10	£6	£4	£8	£7
5211	Plain X-ray requested	£26	£28	£29	£29	£30	£28	£30	£30

5241	Plain X-ray skull normal	£26	£28	£29	£29	£30	£28	£30	£30
5244	Plain X-ray frontal sinuses	£26	£28	£29	£29	£30	£28	£30	£30
5245	Plain X-ray maxillary sinuses	£26	£28	£29	£29	£30	£28	£30	£30
5246	Plain X-ray orbit	£26	£28	£29	£29	£30	£28	£30	£30
5251	Plain X-ray spine normal	£26	£28	£29	£29	£30	£28	£30	£30
5254	Plain X-ray cervical spine	£26	£28	£29	£29	£30	£28	£30	£30
5255	Plain X-ray thoracic spine	£26	£28	£29	£29	£30	£28	£30	£30
5256	Plain X-ray lumbar spine	£26	£28	£29	£29	£30	£28	£30	£30
5257	Plain X-ray lumbar/sacral spine	£26	£28	£29	£29	£30	£28	£30	£30
5271	Plain X-ray pelvis normal	£26	£28	£29	£29	£30	£28	£30	£30
5272	Plain X-ray pelvis abnormal	£26	£28	£29	£29	£30	£28	£30	£30
5283	Plain X-ray shoulder joint	£26	£28	£29	£29	£30	£28	£30	£30
5287	Plain X-ray elbow	£26	£28	£29	£29	£30	£28	£30	£30
5289	Plain X-ray of wrist	£26	£28	£29	£29	£30	£28	£30	£30
5291	Plain X-ray hand normal	£26	£28	£29	£29	£30	£28	£30	£30
5292	Plain X-ray hand abnormal	£26	£28	£29	£29	£30	£28	£30	£30
5295	X-ray phalanges of fingers	£26	£28	£29	£29	£30	£28	£30	£30
5351	Standard chest X-ray requested	£26	£28	£29	£29	£30	£28	£30	£30
5352	Standard chest X-ray normal	£26	£28	£29	£29	£30	£28	£30	£30
5353	Standard chest X-ray abnormal	£26	£28	£29	£29	£30	£28	£30	£30
5371	Mammography requested	£26	£28	£29	£29	£30	£28	£30	£30
5372	Mammography normal	£26	£28	£29	£29	£30	£28	£30	£30
5373	Mammography abnormal	£26	£28	£29	£29	£30	£28	£30	£30
5472	Barium swallow normal	£423	£446	£469	£442	£436	£415	£423	£428
5482	Barium meal normal	£423	£446	£469	£442	£436	£415	£423	£428
5542	Coronary arteriography normal	£37	£34	£36	£38	£40	£42	£44	£47
5671	CAT scan requested	£131	£134	£141	£125	£117	£111	£115	£115
5672	CAT scan normal	£131	£134	£141	£125	£117	£111	£115	£115
5673	CAT scan abnormal	£131	£134	£141	£125	£117	£111	£115	£115
5674	CAT scan - skull	£131	£134	£141	£125	£117	£111	£115	£115
5675	CAT scan - brain	£131	£134	£141	£125	£117	£111	£115	£115

5677	CAT scan - neck	£131	£134	£141	£125	£117	£111	£115	£115
5678	CAT scan - thorax	£131	£134	£141	£125	£117	£111	£115	£115
5679	CAT scan - abdomen	£131	£134	£141	£125	£117	£111	£115	£115
5692	Nuclear magn reson normal	£257	£271	£366	£367	£369	£296	£338	£355
5694	Magnetic resonance imaging of brain abnormal	£278	£249	£178	£243	£207	£189	£191	£185
5697	Magnetic resonance imaging of lumbar spine abnormal	£278	£249	£178	£243	£207	£189	£191	£185
5699	Magnetic resonance imaging of cervical spine abnormal	£278	£249	£178	£243	£207	£189	£191	£185
5853	U-S heart scan	£71	£66	£61	£77	£98	£93	£75	£73
5676	CAT scan - face	£131	£134	£141	£125	£117	£111	£115	£115
5856	U-S pelvic scan	£71	£66	£61	£77	£98	£93	£75	£73
5857	U-S skeletal scan	£71	£66	£61	£77	£98	£93	£75	£73
5858	Doppler studies (ultrasound)	£71	£66	£61	£77	£98	£93	£75	£73
5859	U-S gallbladder scan	£71	£66	£61	£77	£98	£93	£75	£73
5882	Spirometry	£43	£46	£78	£28	£30	£31	£33	£34
7135	Biopsy of breast	£283	£298	£314	£330	£348	£366	£385	£406
7415	FESS - diagnostic endoscopy of nose and sinus	£1,059	£1,115	£1,174	£1,119	£1,058	£1,317	£1,109	£1,138
7418	Diagnostic nasendoscopy	£1,059	£1,115	£1,174	£1,119	£1,058	£1,317	£1,109	£1,138
31130	EEG normal	£188	£96	£135	£273	£158	£143	£139	£150
31140	EEG abnormal	£188	£96	£135	£273	£158	£143	£139	£150
31170	EMG - Electromyography normal	£188	£96	£135	£273	£158	£143	£139	£150
31340	Audiogram bilateral abnormality	77	115	137	76	56	70	104	67.8
32130	Exercise ECG normal	£86	£68	£103	£90	£61	£64	£67	£88
32140	Ambulatory ECG normal	£34	£57	£47	£59	£62	£65	£68	£72
36140	Gastroscopy normal	£423	£446	£469	£442	£436	£415	£423	£428
36141	Bronchoscopy normal	£1,059	£1,115	£1,174	£1,119	£1,058	£1,317	£1,109	£1,138
36150	Gastroscopy abnormal	£423	£446	£469	£442	£436	£415	£423	£428
44340	FSH level normal	£6	£1	£1	£1	£1	£1	£1	£1
44341	FSH level abnormal	£6	£1	£1	£1	£1	£1	£1	£1
44351	Prolactin level raised	£6	£1	£1	£1	£1	£1	£1	£1
52540	Plain X-ray cervical spine normal	£26	£28	£29	£29	£30	£28	£30	£30
52541	Plain X-ray cervical spine abnormal	£26	£28	£29	£29	£30	£28	£30	£30

52550	Plain X-ray thoracic spine normal	£26	£28	£29	£29	£30	£28	£30	£30
52551	Plain X-ray thoracic spine abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52560	Plain X-ray lumbar spine normal	£26	£28	£29	£29	£30	£28	£30	£30
52561	Plain X-ray lumbar spine abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52570	Plain X-ray lumbar/sacral spine normal	£26	£28	£29	£29	£30	£28	£30	£30
52571	Plain X-ray lumbar/sacral spine abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52580	Plain X-ray sacrum normal	£26	£28	£29	£29	£30	£28	£30	£30
52630	Plain X-ray clavicle normal	£26	£28	£29	£29	£30	£28	£30	£30
52830	Plain X-ray shoulder joint normal	£26	£28	£29	£29	£30	£28	£30	£30
52831	Plain X-ray shoulder joint abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52840	Plain X-ray scapula normal	£26	£28	£29	£29	£30	£28	£30	£30
52870	Plain X-ray elbow normal	£26	£28	£29	£29	£30	£28	£30	£30
52880	Plain X-ray of radius/ulna normal	£26	£28	£29	£29	£30	£28	£30	£30
52890	Plain X-ray of wrist normal	£26	£28	£29	£29	£30	£28	£30	£30
52932	Plain X-ray scaphoid normal	£26	£28	£29	£29	£30	£28	£30	£30
52950	X-ray phalanges of fingers normal	£26	£28	£29	£29	£30	£28	£30	£30
52960	X-ray of thumb normal	£26	£28	£29	£29	£30	£28	£30	£30
56790	CT (computed tomography) of abdomen and pelvis	£131	£134	£141	£125	£117	£111	£115	£115
56811	Bone densimetry normal	£71	£75	£78	£72	£67	£62	£69	£59
58530	Echocardiogram normal	£63	£59	£46	£84	£84	£75	£72	£84
58531	Echocardiogram abnormal	£63	£59	£46	£84	£84	£75	£72	£84
58551	Ultrasound scan of upper abdomen	£71	£66	£61	£77	£98	£93	£75	£73
58580	Doppler studies normal	£71	£66	£61	£77	£98	£93	£75	£73
58581	Doppler studies abnormal	£71	£66	£61	£77	£98	£93	£75	£73
70650	Electroencephalography	£188	£96	£135	£273	£158	£143	£139	£150
70652	Nerve conduction studies	£92	£97	£102	£107	£113	£98	£65	£150
70658	Sleep studies	749	738	824	759	657	605	508	423.72
71353	Stereotactically guided core needle biopsy of breast	£283	£298	£314	£330	£348	£366	£385	£406
74252	Diagnostic endoscopic examination of nasopharynx NEC	£1,059	£1,115	£1,174	£1,119	£1,058	£1,317	£1,109	£1,138
74363	Diagnostic fibreoptic endoscopic exam of pharynx + larynx	£543	£572	£602	£583	£613	£639	£658	£640

75220	Biopsy of lesion of tongue	£247	£260	£274	£288	£303	£319	£336	£354
75270	Biopsy of lesion of tongue	£247	£260	£274	£288	£303	£319	£336	£354
3133-1	Hearing test normal	77	115	137	76	56	70	104	67.8
3133-2	Audiogram normal	77	115	137	76	56	70	104	67.8
313B	Audiogram	77	115	137	76	56	70	104	67.8
315B	Ambulatory blood pressure recording	£34	£57	£47	£59	£62	£65	£68	£72
316A	Hydrogen breath test	£84	£88	£150	£206	£106	£266	£136	£143
317-2	Urodynamic studies	£569	£599	£210	£192	£168	£173	£164	£153
3173-1	Urodynamic studies normal	£569	£599	£210	£192	£168	£173	£164	£153
3174-1	Urodynamic studies abnormal	£569	£599	£210	£192	£168	£173	£164	£153
321B	12 lead ECG	£37	£34	£36	£38	£40	£42	£44	£47
321C	ECG sinus rhythm	£37	£34	£36	£38	£40	£42	£44	£47
321Z	ECG - general - NOS	£37	£34	£36	£38	£40	£42	£44	£47
32-2	ECG	£37	£34	£36	£38	£40	£42	£44	£47
329A	ECG: left bundle branch block	£37	£34	£36	£38	£40	£42	£44	£47
32K3	ECG: Q-T interval prolonged	£37	£34	£36	£38	£40	£42	£44	£47
32M	24 Hour ECG	£34	£57	£47	£59	£62	£65	£68	£72
336Z	Allergy testing NOS	£23	£8	£10	£8	£8	£5	£5	£29
337-2	Pulmonary function tests	£43	£46	£78	£28	£30	£31	£33	£34
3395-1	PEFR - peak exp. flow rate	£43	£46	£78	£28	£30	£31	£33	£34
3395-3	Peak flow rate	£43	£46	£78	£28	£30	£31	£33	£34
339M	FEV1/FVC ratio	£43	£46	£78	£28	£30	£31	£33	£34
33B9	Exercise tolerance test	£86	£68	£103	£90	£61	£64	£67	£88
33B91	Exercise tolerance test done	£86	£68	£103	£90	£61	£64	£67	£88
33B93	Exercise tolerance test normal	£86	£68	£103	£90	£61	£64	£67	£88
33B94	Exercise toler test equivocal	£86	£68	£103	£90	£61	£64	£67	£88
33BA	Impaired left ventricular function	£63	£59	£46	£84	£84	£75	£72	£84
33BD	Echocardiogram requested	£63	£59	£46	£84	£84	£75	£72	£84
33G0	Spirometry reversibility negative	£43	£46	£78	£28	£30	£31	£33	£34
33G1	Spirometry reversibility positive	£43	£46	£78	£28	£30	£31	£33	£34
33H	Salbutamol reversibility	£43	£46	£78	£28	£30	£31	£33	£34

33H0	Negative reversibility test to salbutamol	£43	£46	£78	£28	£30	£31	£33	£34
33H1	Positive reversibility test to salbutamol	£43	£46	£78	£28	£30	£31	£33	£34
361A	Sigmoidoscopy normal	£315	£331	£349	£316	£304	£282	£286	£285
3B1	Biopsy result normal	£515	£542	£570	£600	£632	£665	£700	£737
3B2	Biopsy result abnormal	£515	£542	£570	£600	£632	£665	£700	£737
41D0	Blood sample taken	£3	£2	£3	£3	£3	£4	£3	£3
41D1	Urine sample obtained	£16	£9	£6	£9	£9	£8	£8	£8
42A	Mean corpuscular volume (MCV)	£3	£3	£1	£3	£3	£3	£3	£3
42A3	MCV - raised	£3	£3	£1	£3	£3	£3	£3	£3
42A4	MCV - low	£3	£3	£1	£3	£3	£3	£3	£3
42B6	Erythrocyte sedimentation rate	£3	£3	£1	£3	£3	£3	£3	£3
42B62	ESR normal	£3	£3	£1	£3	£3	£3	£3	£3
42B63	ESR raised	£3	£3	£1	£3	£3	£3	£3	£3
42H	Total white cell count	£3	£3	£1	£3	£3	£3	£3	£3
42h0	Clotting screening test	£3	£3	£1	£3	£3	£3	£3	£3
42H-2	White cell count	£3	£3	£1	£3	£3	£3	£3	£3
42H3	Leucocytosis -high white count	£3	£3	£1	£3	£3	£3	£3	£3
42H5	White cell count abnormal	£3	£3	£1	£3	£3	£3	£3	£3
42J	Neutrophil count	£3	£3	£1	£3	£3	£3	£3	£3
42J2	Neutropenia	£3	£3	£1	£3	£3	£3	£3	£3
42J3	Neutrophilia	£3	£3	£1	£3	£3	£3	£3	£3
42J4	Neutrophil count abnormal	£3	£3	£1	£3	£3	£3	£3	£3
42M	Lymphocyte count	£3	£3	£1	£3	£3	£3	£3	£3
42M5	Lymphocyte count abnormal	£3	£3	£1	£3	£3	£3	£3	£3
42P	Platelet count	£3	£3	£1	£3	£3	£3	£3	£3
42P2	Thrombocytopenia	£3	£3	£1	£3	£3	£3	£3	£3
42P3	Thrombocythaemia	£3	£3	£1	£3	£3	£3	£3	£3
42P4	Platelet count abnormal	£3	£3	£1	£3	£3	£3	£3	£3
42Q	Coagulation/bleeding tests	£3	£3	£1	£3	£3	£3	£3	£3
42Qe	Factor V Leiden genotype	£3	£3	£1	£3	£3	£3	£3	£3
42QE1	INR - international normal ratio abnormal	£3	£3	£1	£3	£3	£3	£3	£3

42Qf	DDimer level	£3	£3	£1	£3	£3	£3	£3	£3
42Qu	Activated partial thromboplastin time ratio	£3	£3	£1	£3	£3	£3	£3	£3
42R4	Serum ferritin	£3	£3	£1	£3	£3	£3	£3	£3
42R41	Ferritin level low	£3	£3	£1	£3	£3	£3	£3	£3
42T	Serum vitamin B12	£3	£3	£1	£3	£3	£3	£3	£3
42T2	Serum vitamin B12 low	£3	£3	£1	£3	£3	£3	£3	£3
42T3	Serum vit B12 borderline	£3	£3	£1	£3	£3	£3	£3	£3
42U2	Serum folate low	£3	£3	£1	£3	£3	£3	£3	£3
42U5	Serum folate	£3	£3	£1	£3	£3	£3	£3	£3
42W4	HbA1c level (DCCT aligned)	£3	£3	£1	£3	£3	£3	£3	£3
42W5	Haemoglobin A1c level - IFCC standardised	£3	£3	£1	£3	£3	£3	£3	£3
43B2	Hepatitis B immune	£23	£8	£10	£8	£8	£5	£5	£29
43B4	Hepatitis B surface antig +ve	£23	£8	£10	£8	£8	£5	£5	£29
43B6	Hepatitis B non immune	£23	£8	£10	£8	£8	£5	£5	£29
43C2-1	HIV negative	£11	£7	£5	£8	£8	£7	£7	£7
43C3-1	HIV positive	£11	£7	£5	£8	£8	£7	£7	£7
43dB	Hepatitis B core antibody level	£23	£8	£10	£8	£8	£5	£5	£29
43F1	Rheumatoid factor positive	£23	£8	£10	£8	£8	£5	£5	£29
43G41	Parietal cell antibodies positive	£23	£8	£10	£8	£8	£5	£5	£29
43G5	Thyroid autoantibodies	£23	£8	£10	£8	£8	£5	£5	£29
43GE	Lupus anticoagulant screen	£23	£8	£10	£8	£8	£5	£5	£29
43J4	IgM	£23	£8	£10	£8	£8	£5	£5	£29
43J7	IgE	£23	£8	£10	£8	£8	£5	£5	£29
43jK	Chlamydia deoxyribonucleic acid detection	£23	£8	£10	£8	£8	£5	£5	£29
43k7	Helicobacter pylori antigen test	£23	£8	£10	£8	£8	£5	£5	£29
43QU	House dust mite RAST test	£23	£8	£10	£8	£8	£5	£5	£29
43U	Chlamydia antigen test	£23	£8	£10	£8	£8	£5	£5	£29
43U1	Chlamydia antigen ELISA positive	£23	£8	£10	£8	£8	£5	£5	£29
43U2	Chlamydia antigen ELISA negative	£23	£8	£10	£8	£8	£5	£5	£29
43U6	Chlamydia test negative	£23	£8	£10	£8	£8	£5	£5	£29
43X3	Hepatitis C antibody test positive	£23	£8	£10	£8	£8	£5	£5	£29

442-2	TSH level	£6	£1	£1	£1	£1	£1	£1	£1
442-3	Thyroid function tests	£6	£1	£1	£1	£1	£1	£1	£1
442A	TSH - thyroid stim. hormone	£6	£1	£1	£1	£1	£1	£1	£1
442A1	Serum TSH level abnormal	£6	£1	£1	£1	£1	£1	£1	£1
442C	Thyroid horm tests borderline	£6	£1	£1	£1	£1	£1	£1	£1
442H	Thyroid function tests normal	£6	£1	£1	£1	£1	£1	£1	£1
442I	Thyroid function tests abnormal	£6	£1	£1	£1	£1	£1	£1	£1
442J	Thyroid function test	£6	£1	£1	£1	£1	£1	£1	£1
442V	Serum free T4 level	£6	£1	£1	£1	£1	£1	£1	£1
442W	Serum TSH level	£6	£1	£1	£1	£1	£1	£1	£1
443j	Serum prolactin level	£6	£1	£1	£1	£1	£1	£1	£1
448s	Dexamethasone suppression test	£6	£1	£1	£1	£1	£1	£1	£1
44A	Blood hormone levels NOS	£6	£1	£1	£1	£1	£1	£1	£1
44A1	Serum parathyroid hormone	£6	£1	£1	£1	£1	£1	£1	£1
44AJ	Plasma parathyroid hormone level	£6	£1	£1	£1	£1	£1	£1	£1
44CC	Plasma C reactive protein	£6	£1	£1	£1	£1	£1	£1	£1
44CC1	C reactive protein abnormal	£6	£1	£1	£1	£1	£1	£1	£1
44CN	Serum amylase level	£6	£1	£1	£1	£1	£1	£1	£1
44D	Liver function tests - general	£6	£1	£1	£1	£1	£1	£1	£1
44D1	Liver function tests normal	£6	£1	£1	£1	£1	£1	£1	£1
44D-1	Liver function tests	£6	£1	£1	£1	£1	£1	£1	£1
44D2	Liver function tests abnormal	£6	£1	£1	£1	£1	£1	£1	£1
44D6	Liver function test	£6	£1	£1	£1	£1	£1	£1	£1
44DZ	Liver function tests NOS	£6	£1	£1	£1	£1	£1	£1	£1
44E	Serum bilirubin level	£6	£1	£1	£1	£1	£1	£1	£1
44EC	Serum total bilirubin level	£6	£1	£1	£1	£1	£1	£1	£1
44F	Serum alkaline phosphatase	£6	£1	£1	£1	£1	£1	£1	£1
44f1	Serum fasting glucose level	£6	£1	£1	£1	£1	£1	£1	£1
44G	Liver enzymes	£6	£1	£1	£1	£1	£1	£1	£1
44g0	Plasma random glucose level	£6	£1	£1	£1	£1	£1	£1	£1
44g1	Plasma fasting glucose level	£6	£1	£1	£1	£1	£1	£1	£1

44G-1	ALT - blood level	£6	£1	£1	£1	£1	£1	£1	£1
44G3	ALT/SGPT serum level	£6	£1	£1	£1	£1	£1	£1	£1
44G30	ALT/SGPT level normal	£6	£1	£1	£1	£1	£1	£1	£1
44G31	ALT/SGPT level abnormal	£6	£1	£1	£1	£1	£1	£1	£1
44G4	Gamma - G.T. level	£6	£1	£1	£1	£1	£1	£1	£1
44G9	Serum gamma-glutamyl transferase level	£6	£1	£1	£1	£1	£1	£1	£1
44H4	CK - creatine kinase level	£6	£1	£1	£1	£1	£1	£1	£1
44I4	Serum potassium	£6	£1	£1	£1	£1	£1	£1	£1
44I42	Low serum potassium level	£6	£1	£1	£1	£1	£1	£1	£1
44I5	Serum sodium	£6	£1	£1	£1	£1	£1	£1	£1
44I51	Serum sodium level abnormal	£6	£1	£1	£1	£1	£1	£1	£1
44I8	Serum calcium	£6	£1	£1	£1	£1	£1	£1	£1
44I81	Raised serum calcium level	£6	£1	£1	£1	£1	£1	£1	£1
44IC	Corrected serum calcium level	£6	£1	£1	£1	£1	£1	£1	£1
44J-2	Urea and electrolytes	£6	£1	£1	£1	£1	£1	£1	£1
44J3	Serum creatinine	£6	£1	£1	£1	£1	£1	£1	£1
44J9	Serum urea level	£6	£1	£1	£1	£1	£1	£1	£1
44JB	Urea and electrolytes	£6	£1	£1	£1	£1	£1	£1	£1
44K5	Serum urate level	£6	£1	£1	£1	£1	£1	£1	£1
44LA	Serum vitamin D	£6	£1	£1	£1	£1	£1	£1	£1
44M4	Serum albumin	£6	£1	£1	£1	£1	£1	£1	£1
44MC	Serum troponin T level	£6	£1	£1	£1	£1	£1	£1	£1
44O4	Serum lipids high	£6	£1	£1	£1	£1	£1	£1	£1
44p	Biochemical test	£6	£1	£1	£1	£1	£1	£1	£1
44P3	Serum cholesterol raised	£6	£1	£1	£1	£1	£1	£1	£1
44P5	Serum HDL cholesterol level	£6	£1	£1	£1	£1	£1	£1	£1
44q	Biochemical screening test	£6	£1	£1	£1	£1	£1	£1	£1
44Q3	Serum triglycerides raised	£6	£1	£1	£1	£1	£1	£1	£1
44q8	Hyperlipidaemia screening test	£6	£1	£1	£1	£1	£1	£1	£1
44T1	Random blood sugar	£6	£1	£1	£1	£1	£1	£1	£1

44T12	Random blood sugar raised	£6	£1	£1	£1	£1	£1	£1	£1
44T2	Fasting blood sugar	£6	£1	£1	£1	£1	£1	£1	£1
44T9	Glucometer blood sugar	£6	£1	£1	£1	£1	£1	£1	£1
44TK	Fasting blood glucose level	£6	£1	£1	£1	£1	£1	£1	£1
44U	Blood glucose result	£6	£1	£1	£1	£1	£1	£1	£1
44U4	Blood glucose 5-6.9 mmol/L	£6	£1	£1	£1	£1	£1	£1	£1
44U9	Blood glucose abnormal	£6	£1	£1	£1	£1	£1	£1	£1
44Uz	Blood glucose raised NOS	£6	£1	£1	£1	£1	£1	£1	£1
44V	Glucose tolerance test	£6	£1	£1	£1	£1	£1	£1	£1
44V1	Glucose tolerance test normal	£6	£1	£1	£1	£1	£1	£1	£1
44W8	Serum lithium level	£6	£1	£1	£1	£1	£1	£1	£1
44W80	Lithium level therapeutic	£6	£1	£1	£1	£1	£1	£1	£1
4543-1	Synacthen test	£6	£1	£1	£1	£1	£1	£1	£1
4547-1	Short synacthen test	£6	£1	£1	£1	£1	£1	£1	£1
46-1	Urine tests	£16	£9	£6	£9	£9	£8	£8	£8
461-2	Urinalysis - general	£16	£9	£6	£9	£9	£8	£8	£8
461A	MSU = equivocal	£11	£7	£5	£8	£8	£7	£7	£7
464Z	Urine smell NOS	£11	£7	£5	£8	£8	£7	£7	£7
467A	24 hour urine protein output	£6	£1	£1	£1	£1	£1	£1	£1
469-1	Blood in urine test	£6	£1	£1	£1	£1	£1	£1	£1
46f2	Urine leucocyte test = +	£6	£1	£1	£1	£1	£1	£1	£1
46f3	Urine leucocyte test = ++	£6	£1	£1	£1	£1	£1	£1	£1
46f4	Urine leucocyte test = +++	£6	£1	£1	£1	£1	£1	£1	£1
46G4	Urine micr.:leucocytes present	£6	£1	£1	£1	£1	£1	£1	£1
46G4-1	Leucocytes in urine	£6	£1	£1	£1	£1	£1	£1	£1
46G4-2	Sterile pyuria	£11	£7	£5	£8	£8	£7	£7	£7
46G7	Urine microscopy: pus cells	£11	£7	£5	£8	£8	£7	£7	£7
46J1	Urine HCG titre	£11	£7	£5	£8	£8	£7	£7	£7
46TC	Urine albumin:creatinine ratio	£6	£1	£1	£1	£1	£1	£1	£1
46U	Urine culture	£11	£7	£5	£8	£8	£7	£7	£7
46U3	Urine culture - E. coli	£11	£7	£5	£8	£8	£7	£7	£7

46W	Urine microalbumin	£6	£1	£1	£1	£1	£1	£1	£1
46W1	Urine microalbumin negative	£6	£1	£1	£1	£1	£1	£1	£1
46X0	Urine nitrite positive	£6	£1	£1	£1	£1	£1	£1	£1
46Z	Urine test NOS	£16	£9	£6	£9	£9	£8	£8	£8
46Z1	Urine microscopy	£11	£7	£5	£8	£8	£7	£7	£7
49-1	Semen analysis	£16	£9	£6	£9	£9	£8	£8	£8
4I2D0	Wound swab culture positive	£11	£7	£5	£8	£8	£7	£7	£7
4I2D-1	Wound swab	£11	£7	£5	£8	£8	£7	£7	£7
4J13-1	Stool sample culture negative	£11	£7	£5	£8	£8	£7	£7	£7
4Ja0	Helicobacter pylori stool test positive	£11	£7	£5	£8	£8	£7	£7	£7
4JD20	Clostridium difficile toxin A detected	£11	£7	£5	£8	£8	£7	£7	£7
4JD6	Helicobacter serology positive	£11	£7	£5	£8	£8	£7	£7	£7
4JF1	Ear swab taken	£11	£7	£5	£8	£8	£7	£7	£7
4JF2	Nasal swab taken	£11	£7	£5	£8	£8	£7	£7	£7
4JF4	Throat swab taken	£11	£7	£5	£8	£8	£7	£7	£7
4JF5	Sputum sent for C/S	£11	£7	£5	£8	£8	£7	£7	£7
4JG4	Skin wound swab taken	£11	£7	£5	£8	£8	£7	£7	£7
4JH4	Stool sample for C/S	£11	£7	£5	£8	£8	£7	£7	£7
4JH40	Stool culture cryptosporidium positive	£11	£7	£5	£8	£8	£7	£7	£7
4JH42	Stool culture positive	£11	£7	£5	£8	£8	£7	£7	£7
4JI4	Blood culture	£3	£3	£1	£3	£3	£3	£3	£3
4JJ	Urine sample for organism	£11	£7	£5	£8	£8	£7	£7	£7
4JJ1	MSU sent for C/S	£11	£7	£5	£8	£8	£7	£7	£7
4JJ2	MSU sent for bacteriology	£11	£7	£5	£8	£8	£7	£7	£7
4JJ-2	Mid-stream urine sample	£11	£7	£5	£8	£8	£7	£7	£7
4JJ-3	Urine for culture	£11	£7	£5	£8	£8	£7	£7	£7
4JJ-4	Early morning urine	£6	£1	£1	£1	£1	£1	£1	£1
4JK-1	Vaginal swab taken	£11	£7	£5	£8	£8	£7	£7	£7
4JK2	High vaginal swab taken	£60	£26	£21	£21	£18	£17	£8	£7
4JK20	High vaginal swab culture positive	£60	£26	£21	£21	£18	£17	£8	£7
4JK21	High vaginal swab culture negative	£60	£26	£21	£21	£18	£17	£8	£7

4JK3	Low vaginal swab taken	£11	£7	£5	£8	£8	£7	£7	£7
4JK5	Cervical swab taken	£60	£26	£21	£21	£18	£17	£8	£7
4JK9	Endocervical chlamydia swab	£11	£7	£5	£8	£8	£7	£7	£7
4JO0	CLO test positive	£6	£1	£1	£1	£1	£1	£1	£1
4JO1	CLO test negative	£6	£1	£1	£1	£1	£1	£1	£1
4JQB	Helicobacter pylori test positive	£6	£1	£1	£1	£1	£1	£1	£1
4JRA	Methicillin resistant staphylococcus aureus screening test	£11	£7	£5	£8	£8	£7	£7	£7
4JS8	Cryptosporidium microscopy	£11	£7	£5	£8	£8	£7	£7	£7
4K1	Histology	£60	£26	£30	£34	£31	£39	£41	£29
4K12	Specimen sent for histology	£60	£26	£30	£34	£31	£39	£41	£29
4K13	Histology normal	£60	£26	£30	£34	£31	£39	£41	£29
4K14	Histology abnormal	£60	£26	£30	£34	£31	£39	£41	£29
4K1D	Histology laboratory test	£60	£26	£30	£34	£31	£39	£41	£29
4K1Z	Histology NOS	£60	£26	£30	£34	£31	£39	£41	£29
4K2	Cervical smear result	£60	£26	£30	£34	£31	£39	£41	£29
4K21	Cervical smear:inadequate spec	£60	£26	£30	£34	£31	£39	£41	£29
4K2-1	Dyskaryosis on cervical smear	£60	£26	£30	£34	£31	£39	£41	£29
4K22	Cervical smear: negative	£60	£26	£30	£34	£31	£39	£41	£29
4K23	Cerv.smear: mild dyskaryosis	£60	£26	£30	£34	£31	£39	£41	£29
4K23-1	CIN I - mild dyskaryosis	£60	£26	£30	£34	£31	£39	£41	£29
4K24	Cerv.smear: severe dyskaryosis	£60	£26	£30	£34	£31	£39	£41	£29
4K24-1	CIN III - severe dyskaryosis	£60	£26	£30	£34	£31	£39	£41	£29
4K28	Cerv.smear: mod.dyskaryosis	£60	£26	£30	£34	£31	£39	£41	£29
4K28-1	CIN II - moderate dyskaryosis	£60	£26	£30	£34	£31	£39	£41	£29
4K29	Cerv.smear: borderline changes	£60	£26	£30	£34	£31	£39	£41	£29
4K2D	Cervical smear transformation zone cells present	£60	£26	£30	£34	£31	£39	£41	£29
4K2Z	Cervical smear result NOS	£60	£26	£30	£34	£31	£39	£41	£29
4K34	Cervical smear - candida	£60	£26	£30	£34	£31	£39	£41	£29
4K38	Cervical smear - actinomyces	£60	£26	£30	£34	£31	£39	£41	£29
4K3D	HPV - Human papillomavirus test positive	£11	£7	£5	£8	£8	£7	£7	£7
4K45	Cx. smear: repeat 6 months	£60	£26	£30	£34	£31	£39	£41	£29

4K47	Cx. smear: repeat 12 months	£60	£26	£30	£34	£31	£39	£41	£29
4K5	Cytology - general	£60	£26	£21	£21	£18	£17	£8	£7
4K54	Cytology laboratory test	£60	£26	£21	£21	£18	£17	£8	£7
4K55	Cervical cytology test	£60	£26	£21	£21	£18	£17	£8	£7
4KAZ	Vaginal vault smear NOS	£60	£26	£21	£21	£18	£17	£8	£7
4KD	Urine cytology	£60	£26	£21	£21	£18	£17	£8	£7
4KD0	Urine cytology normal	£60	£26	£21	£21	£18	£17	£8	£7
4L3	DNA studies	£60	£26	£21	£21	£18	£17	£8	£7
4L46	BRCA2 gene mutation positive	£60	£26	£21	£21	£18	£17	£8	£7
52-1	Plain X-rays	£26	£28	£29	£29	£30	£28	£30	£30
524A	Facial bones X-ray	£26	£28	£29	£29	£30	£28	£30	£30
525-2	Lumbar spine X-ray	£26	£28	£29	£29	£30	£28	£30	£30
5254-1	Cervical spine X-ray	£26	£28	£29	£29	£30	£28	£30	£30
525A	Plain X-ray thoracolumbar spine	£26	£28	£29	£29	£30	£28	£30	£30
528-1	Arm X-ray	£26	£28	£29	£29	£30	£28	£30	£30
528-2	Humerus X-ray	£26	£28	£29	£29	£30	£28	£30	£30
528-4	Shoulder X-ray	£26	£28	£29	£29	£30	£28	£30	£30
529-1	Hand X-ray	£26	£28	£29	£29	£30	£28	£30	£30
5295-1	Finger X-ray	£26	£28	£29	£29	£30	£28	£30	£30
5296-1	Thumb X-ray	£26	£28	£29	£29	£30	£28	£30	£30
52A	Plain X-ray hip/leg	£26	£28	£29	£29	£30	£28	£30	£30
52A1	Plain X-ray hip/leg normal	£26	£28	£29	£29	£30	£28	£30	£30
52A-2	Hip X-ray	£26	£28	£29	£29	£30	£28	£30	£30
52A3	Plain X-ray hip joint	£26	£28	£29	£29	£30	£28	£30	£30
52A-3	Knee X-ray	£26	£28	£29	£29	£30	£28	£30	£30
52A30	Plain X-ray hip joint normal	£26	£28	£29	£29	£30	£28	£30	£30
52A31	Plain X-ray hip joint abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52A7	Plain X-ray knee	£26	£28	£29	£29	£30	£28	£30	£30
52A70	Plain X-ray knee normal	£26	£28	£29	£29	£30	£28	£30	£30
52A71	Plain X-ray knee abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52A9	X-ray shaft of tibia/fibula	£26	£28	£29	£29	£30	£28	£30	£30

52A90	X-ray of tibia/fibula normal	£26	£28	£29	£29	£30	£28	£30	£30
52AA	Plain X-ray ankle joint	£26	£28	£29	£29	£30	£28	£30	£30
52AA0	Plain X-ray ankle joint normal	£26	£28	£29	£29	£30	£28	£30	£30
52AA1	Plain X-ray ankle joint abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52AA-1	Ankle X-ray	£26	£28	£29	£29	£30	£28	£30	£30
52B	Plain X-ray foot	£26	£28	£29	£29	£30	£28	£30	£30
52B1	Plain X-ray foot normal	£26	£28	£29	£29	£30	£28	£30	£30
52B-1	Foot X-ray	£26	£28	£29	£29	£30	£28	£30	£30
52B2	Plain X-ray foot abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52B5-1	Toe X-ray	£26	£28	£29	£29	£30	£28	£30	£30
52B70	Calcaneum X-ray normal	£26	£28	£29	£29	£30	£28	£30	£30
52B71	Calcaneum X-ray abnormal	£26	£28	£29	£29	£30	£28	£30	£30
52B8	Forefoot X-ray	£26	£28	£29	£29	£30	£28	£30	£30
52D	Plain X-ray abdomen	£26	£28	£29	£29	£30	£28	£30	£30
52D0	Plain X-ray abdomen normal	£26	£28	£29	£29	£30	£28	£30	£30
535-1	Chest X-ray - routine	£26	£28	£29	£29	£30	£28	£30	£30
5352-1	Chest X-ray normal	£26	£28	£29	£29	£30	£28	£30	£30
535Z	Standard chest X-ray NOS	£26	£28	£29	£29	£30	£28	£30	£30
537-1	Mammography - X-ray	£26	£28	£29	£29	£30	£28	£30	£30
538-2	Abdominal X-ray	£26	£28	£29	£29	£30	£28	£30	£30
5382-1	Abdominal X-ray normal	£26	£28	£29	£29	£30	£28	£30	£30
53B-2	Kids.,urets, bladder abdo xray	£26	£28	£29	£29	£30	£28	£30	£30
53G	Abdominal X-ray	£26	£28	£29	£29	£30	£28	£30	£30
54A-1	Barium enema	£521	£548	£577	£559	£606	£594	£616	£628
54A2	Barium enema normal	£521	£548	£577	£559	£606	£594	£616	£628
54C-2	Intravenous urogram	£569	£599	£210	£192	£168	£173	£164	£153
54P8	Hip arthrogram	£144	£151	£159	£168	£176	£186	£195	£206
55-2	Angiogram	£37	£34	£36	£38	£40	£42	£44	£47
554-1	Coronary arteriography	£37	£34	£36	£38	£40	£42	£44	£47
554Z	Coronary arteriog-general NOS	£37	£34	£36	£38	£40	£42	£44	£47
55Z	Cardiovascular angiography NOS	£37	£34	£36	£38	£40	£42	£44	£47

567-1	CAT scan	£131	£134	£141	£125	£117	£111	£115	£115
567-3	Computerised tomograph scan	£131	£134	£141	£125	£117	£111	£115	£115
56780-1	CT of thorax and abdomen	£131	£134	£141	£125	£117	£111	£115	£115
567A	CAT scan - pelvis	£131	£134	£141	£125	£117	£111	£115	£115
567C	CAT scan brain - abnormal	£131	£134	£141	£125	£117	£111	£115	£115
567F	Computed tomography of urinary tract	£131	£134	£141	£125	£117	£111	£115	£115
567F-1	CT urogram	£131	£134	£141	£125	£117	£111	£115	£115
569-2	Magnetic resonance imaging	£278	£249	£178	£243	£207	£189	£191	£185
5692-1	MRI scan normal	£278	£249	£178	£243	£207	£189	£191	£185
5693-1	MRI scan abnormal	£278	£249	£178	£243	£207	£189	£191	£185
569B	Magnetic resonance imaging of lumbar spine normal	£278	£249	£178	£243	£207	£189	£191	£185
569E	Magnetic resonance imaging of cervical spine normal	£278	£249	£178	£243	£207	£189	£191	£185
569F	Magnetic resonance imaging of brain normal	£278	£249	£178	£243	£207	£189	£191	£185
569H	Magnetic resonance imaging of shoulder	£278	£249	£178	£243	£207	£189	£191	£185
569H-1	MRI of shoulder	£278	£249	£178	£243	£207	£189	£191	£185
569K0	Magnetic resonance imaging of brain	£278	£249	£178	£243	£207	£189	£191	£185
569K-1	MRI of head	£278	£249	£178	£243	£207	£189	£191	£185
569L	Magnetic resonance imaging of knee	£278	£249	£178	£243	£207	£189	£191	£185
569L-1	MRI of knee	£278	£249	£178	£243	£207	£189	£191	£185
569M	Magnetic resonance imaging of cervical spine	£278	£249	£178	£243	£207	£189	£191	£185
569M-1	MRI of cervical spine	£278	£249	£178	£243	£207	£189	£191	£185
569P	Magnetic resonance imaging of lumbar spine	£278	£249	£178	£243	£207	£189	£191	£185
569P-1	MRI of lumbar spine	£278	£249	£178	£243	£207	£189	£191	£185
56G	Computed tomography angiography	£131	£134	£141	£125	£117	£111	£115	£115
573F-1	Isotope bone scan	£71	£75	£78	£72	£67	£62	£69	£59
574A	VQ - Ventilation perfusion scan	£166	£175	£184	£194	£204	£215	£226	£238
5853-1	Echocardiogram	£63	£59	£46	£84	£84	£75	£72	£84
5858-2	Doppler ultrasound	£71	£66	£61	£77	£98	£93	£75	£73
585B	U-S kidneys	£71	£66	£61	£77	£98	£93	£75	£73
585B-1	Renal ultrasound	£71	£66	£61	£77	£98	£93	£75	£73
585C	US scan of breast	£71	£66	£61	£77	£98	£93	£75	£73

585D	US scan of scrotum	£71	£66	£61	£77	£98	£93	£75	£73
585E	US scan of bladder	£71	£66	£61	£77	£98	£93	£75	£73
585G	Ultrasound scan of thyroid	£71	£66	£61	£77	£98	£93	£75	£73
585h	US scan of soft tissue mass	£71	£66	£61	£77	£98	£93	£75	£73
585H1	Renal ultrasound normal	£71	£66	£61	£77	£98	£93	£75	£73
585i	US scan of neck	£71	£66	£61	£77	£98	£93	£75	£73
585j	US scan of shoulder joint	£71	£66	£61	£77	£98	£93	£75	£73
585j-1	US scan of shoulder	£71	£66	£61	£77	£98	£93	£75	£73
585k	Echocardiogram shows normal left ventricular function	£63	£59	£46	£84	£84	£75	£72	£84
585m	Ultrasound scan of abdomen and pelvis	£71	£66	£61	£77	£98	£93	£75	£73
5861-1	Mammogram-thermographic	£26	£28	£29	£29	£30	£28	£30	£30
58D	Ultrasound scan	£71	£66	£61	£77	£98	£93	£75	£73
58D0	Duplex scan performed	£71	£66	£61	£77	£98	£93	£75	£73
58D1	US scan of hip	£71	£66	£61	£77	£98	£93	£75	£73
58D2	Ultrasound scan requested	£71	£66	£61	£77	£98	£93	£75	£73
58D3	Transvaginal ultrasound scan	£71	£66	£61	£77	£98	£93	£75	£73
58DD	Ultrasound scan of hand	£71	£66	£61	£77	£98	£93	£75	£73
58DE	Ultrasound scan of wrist	£71	£66	£61	£77	£98	£93	£75	£73
58DP	Ultrasound scan of Achilles tendon	£71	£66	£61	£77	£98	£93	£75	£73
58EF	Hip DXA scan result normal	£71	£75	£78	£72	£67	£62	£69	£59
58EH	Hip DXA scan result osteopenic	£71	£75	£78	£72	£67	£62	£69	£59
58EM	Lumbar DXA scan result osteoporotic	£71	£75	£78	£72	£67	£62	£69	£59
58EN	Lumbar DXA scan result osteopenic	£71	£75	£78	£72	£67	£62	£69	£59
58ET	Femoral neck DEXA scan result normal	£71	£75	£78	£72	£67	£62	£69	£59
58EW	Femoral neck DEXA scan result osteopenic	£71	£75	£78	£72	£67	£62	£69	£59
58F	Bone density scan	£71	£75	£78	£72	£67	£62	£69	£59
5C00	CT scan brain - normal	£131	£134	£141	£125	£117	£111	£115	£115
5C01	Carotid artery doppler normal	£71	£66	£61	£77	£98	£93	£75	£73
5C12	Computerised tomography brain scan abnormal	£131	£134	£141	£125	£117	£111	£115	£115
5C12-1	CT brain scan abnormal	£131	£134	£141	£125	£117	£111	£115	£115
6831-1	TB - Tuberculosis screening	£11	£7	£5	£8	£8	£7	£7	£7

683C	Chlamydia trachomatis screening	£11	£7	£5	£8	£8	£7	£7	£7
684Z	Infection screening NOS	£11	£7	£5	£8	£8	£7	£7	£7
685-2	Cervical smear screen	£60	£26	£21	£21	£18	£17	£8	£7
685R	Liquid based cervical cytology screening	£60	£26	£21	£21	£18	£17	£8	£7
6862-1	Mammography - screening	£26	£28	£29	£29	£30	£28	£30	£30
6879-1	Cholesterol screen	£6	£1	£1	£1	£1	£1	£1	£1
688-1	Anaemia screen	£6	£1	£1	£1	£1	£1	£1	£1
68C1	Screening chest X-ray	£26	£28	£29	£29	£30	£28	£30	£30
68C1-1	CXR - screening	£26	£28	£29	£29	£30	£28	£30	£30
68K	Urine screening	£16	£9	£6	£9	£9	£8	£8	£8
68K5	Urine screen normal	£37	£35	£34	£37	£38	£35	£36	£37
68K6	Urine screen abnormal	£16	£9	£6	£9	£9	£8	£8	£8
68K7	Urine screen for chlamydia	£16	£9	£6	£9	£9	£8	£8	£8
68M	Spirometry screening	£43	£46	£78	£28	£30	£31	£33	£34
7047-1	Diagnostic lumbar puncture	£419	£441	£465	£489	£515	£542	£570	£600
71350-1	Needle guided breast biopsy	£283	£298	£314	£330	£348	£366	£385	£406
7425-1	Diagnostic pharyngoscopy	£1,059	£1,115	£1,174	£1,119	£1,058	£1,317	£1,109	£1,138
744Bz	Rigid diagnostic bronchoscopy NOS	£1,575	£1,658	£1,745	£1,654	£1,502	£1,995	£1,559	£1,637
744H0	Fibreoptic bronchoscopy and biopsy	£543	£572	£602	£583	£613	£639	£658	£640
74542-1	Open biopsy of lung	£546	£574	£605	£637	£670	£705	£742	£782
7457z-1	Cervical mediastinoscopy NEC	£403	£425	£447	£471	£495	£521	£549	£578
745D4	Post bronchodilator spirometry	£43	£46	£78	£28	£30	£31	£33	£34
761F	Diagnostic fibreoptic endoscopic exam of upper GI tract	£423	£446	£469	£442	£436	£415	£423	£428
761F0	Diagnostic fibreoptic endoscopy & biopsy of upper GI tract	£441	£465	£489	£469	£454	£434	£447	£469
761F1	Diagnostic gastroscopy NEC	£423	£446	£469	£442	£436	£415	£423	£428
761F-1	Diagnostic fibreoptic gastroscopy	£423	£446	£469	£442	£436	£415	£423	£428
761Fz	Diagnostic fibreoptic endoscopic exam upper GI tract NOS	£423	£446	£469	£442	£436	£415	£423	£428
771J	Diagnostic endoscopic examination on colon	£517	£544	£573	£533	£528	£489	£509	£519
771J0	Diagnostic fibreoptic endoscopic exam & biopsy colon lesion	£527	£555	£584	£562	£572	£489	£509	£604
771J1	Check colonoscopy	£517	£544	£573	£533	£528	£489	£509	£519
771J-1	Diagnostic colonoscopy	£517	£544	£573	£533	£528	£489	£509	£519

771M	Diagnostic fibreoptic sigmoidoscopic examination lower bowel	£418	£440	£463	£432	£412	£374	£385	£285
771M0	Diagnostic fibreoptic sigmoidoscopic exam/biopsy lower bowel lesion	£425	£447	£471	£470	£467	£451	£385	£285
771M1	Sigmoidoscopy NEC	£315	£331	£349	£316	£304	£282	£286	£285
771Mz	Diagnostic fibreoptic sigmoidoscopic exam of lower bowel NOS	£418	£440	£463	£432	£412	£374	£385	£285
771Mz-1	Fibreoptic sigmoidoscopy NEC	£418	£440	£463	£432	£412	£374	£385	£285
771Q-1	Diagnostic rigid sigmoidoscopic examination of rectum	£211	£222	£234	£199	£196	£189	£186	£285
771Qz-1	Sigmoidoscopy NEC	£315	£331	£349	£316	£304	£282	£286	£285
772A	Diagnostic proctoscopy	£521	£548	£577	£559	£606	£594	£616	£628
780B0	Biopsy of liver NEC	£967	£1,018	£1,072	£1,128	£1,188	£1,250	£1,316	£1,385
7B1B0	Endoscopic retrograde pyelography - unspecified	£314	£330	£347	£366	£385	£345	£293	£278
7B2A	Diagnostic cystoscopy	£314	£330	£347	£366	£385	£345	£293	£278
7B2A6	Diagnostic cystoscopy using flexible instrument	£314	£330	£347	£366	£385	£345	£293	£278
7B2A8	Check cystoscopy using flexible instrument	£314	£330	£347	£366	£385	£345	£293	£278
7B2Az	Diagnostic cystoscopy NOS	£314	£330	£347	£366	£385	£345	£293	£278
7D030-1	Biopsy of vulva	£121	£128	£135	£142	£149	£157	£165	£174
7D055	Biopsy of vulva	£121	£128	£135	£142	£149	£157	£165	£174
7D1C2	Colposcopy NEC	£217	£228	£240	£245	£214	£191	£188	£174
7E0E1	Diagnostic hysteroscopy and endometrial biopsy	£504	£531	£559	£547	£531	£558	£519	£508
7E0E-1	Diagnostic hysteroscopy	£504	£531	£559	£547	£531	£453	£443	£423
7E0Ez-1	Hysteroscopy NEC	£504	£531	£559	£547	£531	£453	£443	£423
7E0F1-1	Endometrial biopsy	£355	£373	£393	£414	£436	£458	£483	£508
7E0F8	Endometrial biopsy	£355	£373	£393	£414	£436	£458	£483	£508
7E0F9	Endometrial sampling using pipelle	£355	£373	£393	£414	£436	£458	£483	£508
7E2A2-1	Cervical smear NEC	£60	£26	£21	£21	£18	£17	£8	£7
7G0A	Punch biopsy of skin	£515	£542	£570	£600	£632	£665	£700	£737
7G0A1	Punch biopsy of lesion of skin NEC	£515	£542	£570	£600	£632	£665	£700	£737
7G0C	Other biopsy of skin	£515	£542	£570	£600	£632	£665	£700	£737
7G0C1	Biopsy of lesion of skin NEC	£515	£542	£570	£600	£632	£665	£700	£737
7G0C3	Incision biopsy of skin	£515	£542	£570	£600	£632	£665	£700	£737

7H292	Diagnostic laparoscopy of female pelvis	£671	£1,185	£956	£944	£1,244	£1,297	£1,314	£1,341
7H29-3	Diagnostic laparoscopy	£671	£1,185	£956	£944	£1,244	£1,297	£1,314	£1,341
7H55	Biopsy of muscle	£1,014	£1,068	£1,124	£1,183	£1,245	£1,311	£1,380	£1,453
7H629-1	Sentinel lymph node biopsy	£1,064	£1,120	£1,179	£1,241	£1,306	£1,375	£1,447	£1,524
7H62z	Excision or biopsy of lymph node NOS	£1,064	£1,120	£1,179	£1,241	£1,306	£1,375	£1,447	£1,524
7H680	Biopsy of sentinel lymph node	£1,064	£1,120	£1,179	£1,241	£1,306	£1,375	£1,447	£1,524
7K1W4	Bone marrow trephine biopsy NEC	£781	£822	£865	£911	£959	£1,009	£1,062	£1,118
7K36	Diagnostic arthroscopy of knee	£144	£151	£159	£168	£176	£186	£195	£206
7K36z	Diagnostic arthroscopy of knee NOS	£144	£151	£159	£168	£176	£186	£195	£206
7K46	Diagnostic arthroscopy of shoulder joint	£144	£151	£159	£168	£176	£186	£195	£206
7K6Y-1	Diagnostic arthroscopy of other joint	£144	£151	£159	£168	£176	£186	£195	£206
7K6Yz-1	Arthroscopy NEC	£144	£151	£159	£168	£176	£186	£195	£206
7M0E5	Fine needle aspiration NOC	£197	£207	£218	£229	£241	£254	£267	£281
7M0F1	Fine needle aspiration biopsy for cytology NOC	£197	£207	£218	£229	£241	£254	£267	£281
7P030	Computed tomography of sinuses	£131	£134	£141	£125	£117	£111	£115	£115
7P032	Ultrasound of thyroid gland	£71	£66	£61	£77	£98	£93	£75	£73
7P040	Computed tomography of chest	£131	£134	£141	£125	£117	£111	£115	£115
7P042	Plain x-ray of chest	£26	£28	£29	£29	£30	£28	£30	£30
7P051	Ultrasound of abdomen	£71	£66	£61	£77	£98	£93	£75	£73
7P061	Ultrasound of pelvis	£34	£36	£38	£40	£42	£44	£47	£0
7P072	Cardiac magnetic resonance imaging	£278	£249	£178	£243	£207	£189	£191	£185
7P085	D-Dimer assay	£3	£3	£1	£3	£3	£3	£3	£3
7P092	Ultrasound of testes	£71	£66	£61	£77	£98	£93	£75	£73
7P0A0	Bone densitometry	£71	£75	£78	£72	£67	£62	£69	£59
7P0A8	Plain X-ray of bone	£26	£28	£29	£29	£30	£28	£30	£30
7P0D2	Magnetic resonance cholangiopancreatography	£278	£249	£178	£243	£207	£189	£191	£185
7P0F	Diagnostic imaging of breast	£26	£28	£29	£29	£30	£28	£30	£30
7P0H	Diagnostic echocardiography	£63	£59	£46	£84	£84	£75	£72	£84
7P0Hz	Diagnostic echocardiography NOS	£63	£59	£46	£84	£84	£75	£72	£84
7P10	Neuropsychology tests	£343	£361	£380	£400	£307	£413	£379	£448
7P121	Balance assessment	£77	£81	£85	£89	£94	£99	£110	£114

7P132	Hydrogen breath test	£84	£88	£150	£206	£106	£266	£136	£143
7P142	Test strip urinalysis	£6	£1	£1	£1	£1	£1	£1	£1
7P172	Glucose tolerance test	£6	£1	£1	£1	£1	£1	£1	£1
7P176	Short synacthen test	£6	£1	£1	£1	£1	£1	£1	£1
7P1A	Diagnostic blood tests	£3	£3	£1	£3	£3	£3	£3	£3
7P1Az	Diagnostic blood tests NOS	£3	£3	£1	£3	£3	£3	£3	£3
9N7D	Phlebotomy generated from secondary care done by practice	£3	£2	£3	£3	£3	£4	£3	£3
9ND1	Haematology report received	£3	£3	£1	£3	£3	£3	£3	£3
9ND2	Clin chemistry report received	£6	£1	£1	£1	£1	£1	£1	£1
9ND3	Microbiology report received	£11	£7	£5	£8	£8	£7	£7	£7
9ND4	X-ray report received	£26	£28	£29	£29	£30	£28	£30	£30
9ND7	Histopathology report received	£60	£26	£30	£34	£31	£39	£41	£29
9NDC	Ultrasound scan report received	£71	£66	£61	£77	£98	£93	£75	£73

APPENDIX 7.5. READ CODES AND COSTS RELATED TO REFERRALS RECORDED IN THE PRIMARY CARE DATABASE

The collation of this list is described in Chapter 7.4.2, and the method of deriving the costs in Chapter 11.3.3. Source: PSSRU data

Appendix 7.5 Read codes related to referrals recorded for patients in primary care database and their costs

Read Code	Read Code Description	Costs of referrals sourced from PSSRU data							
		2007	2008	2009	2010	2011	2012	2013	2014
8H1	Admit to intensive care unit	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H2	Emergency hospital admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H21	Admit medical emergency unsp.	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H22	Admit surgical emergency unsp.	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H23	Admit psychiatric emergency	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H26	Admit gynaecological emergency	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H29	Admit ENT emergency	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H2B	Admit ophthalmological emerg.	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H2E	Admit neurology emergency	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H2F	Admit urology emergency	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H2Q	Admit cardiology emergency	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H3	Non-urgent hospital admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H35	Admitted to alcohol detoxification centre	213	219	231	142	147	150	152	152
8H36	Non-urgent medical admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H37	Non-urgent surgical admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H38	Non-urgent psychiatric admission.	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H3G	Non-urgent ophthalmological admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H3H	Non-urgent rheumatology admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H3J	Non-urgent neurology admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H3K	Non-urgent urology admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H3U	Non-urgent oral surg. admission	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H3Z	Other hospital admission NOS	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873

8HB31	Postoperative visit	137	140	164	152	147	139	135	109
8Hd	Admission to hospital	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8HJA-1	Casualty self-referral	98	111	110	114	127	129	133	137
8HN1	In-patient stay 1 day	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8HN2	In-patient stay 2 days	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8HN3	In-patient stay 3 days	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8HN4	In-patient stay 4 days	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8H	Referral for further care	137	140	164	152	147	139	135	109
8H4	Referral to physician	137	140	164	152	147	139	135	109
8H41	General medical referral	137	140	164	152	147	139	135	109
8H43	Dermatological referral	137	140	164	152	147	139	135	109
8H44	Cardiological referral	137	140	164	152	147	139	135	109
8H45	Immunological referral	137	140	164	152	147	139	135	109
8H46	Neurological referral	137	140	164	152	147	139	135	109
8H48	Gastroenterological referral	137	140	164	152	147	139	135	109
8H49	Psychiatric referral	131	130	126	136	143	146	100	122.5
8H4a	Referral to renal physician	137	140	164	152	147	139	135	109
8H4A-1	Referred to genito urinary physician	137	140	164	152	147	139	135	109
8H4B	Referred to rheumatologist	137	140	164	152	147	139	135	109
8H4C	Referred to chest physician	137	140	164	152	147	139	135	109
8H4D	Referral to psychogeriatrician	137	140	164	152	147	139	135	109
8H4E	Referral to oncologist	137	140	164	152	147	139	135	109
8H4g	Referral to respiratory physician	137	140	164	152	147	139	135	109
8H4h	Referral to neurologist	137	140	164	152	147	139	135	109
8H4I	Refer to geneticist	137	140	164	152	147	139	135	109
8H4J	Referred to anaesthetist	137	140	164	152	147	139	135	109
8H4K	Referred to endocrinologist	137	140	164	152	147	139	135	109
8H4L	Referred to nephrologist	137	140	164	152	147	139	135	109

8H4m	Referral to minor surgery special interest GP	35	32	32	33	31	37	38	39
8H4S	Referral to dermatology special interest GP	35	32	32	33	31	37	38	39
8H5	Referral to surgeon	137	140	164	152	147	139	135	109
8H51	General surgical referral	137	140	164	152	147	139	135	109
8H52	Ophthalmological referral	137	140	164	152	147	139	135	109
8H53	ENT referral	137	140	164	152	147	139	135	109
8H54	Orthopaedic referral	137	140	164	152	147	139	135	109
8H55	Neurosurgical referral	137	140	164	152	147	139	135	109
8H58	Gynaecological referral	137	140	164	152	147	139	135	109
8H580	Referral for female sterilisation	137	140	164	152	147	139	135	109
8H5A	Referral to oral surgeon	137	140	164	152	147	139	135	109
8H5B	Referred to urologist	137	140	164	152	147	139	135	109
8H5D	Referred to vascular surgeon	137	140	164	152	147	139	135	109
8H5F	Refer to maxillofacial surgeon	137	140	164	152	147	139	135	109
8H5J	Referral to colorectal surgeon	137	140	164	152	147	139	135	109
8H5K	Referral to upper gastrointestinal surgeon	137	140	164	152	147	139	135	109
8H5L	Referral to hand surgeon	137	140	164	152	147	139	135	109
8H5M	Referral to breast surgeon	137	140	164	152	147	139	135	109
8H5N	Referral to bariatric surgeon	137	140	164	152	147	139	135	109
8H5Q	Referral to orthopaedic surgeon	137	140	164	152	147	139	135	109
8H5W	Referral to spinal surgeon	137	140	164	152	147	139	135	109
8H6	Referral to other doctor	137	140	164	152	147	139	135	109
8H62	Referral to G.P.	35	32	32	33	31	37	38	39
8H68	Referral to haematologist	137	140	164	152	147	139	135	109
8H69	Refer to pain clinic	137	140	164	152	147	139	135	109
8H6Z	Refer to other doctor NOS	35	32	32	33	31	37	38	39
8H7	Other referral	137	140	164	152	147	139	135	109
8H7l	Referral to hospital-based podiatry service	18	23	23	22	31	31	30	30

8H7A	Refer to mental health worker	41	44	46	48	65	67	65	47
8H7h	Urgent referral	137	140	164	152	147	139	135	109
8H7N	Refer for colposcopy	137	140	164	152	147	139	135	109
8H7n	Referral to retinal screener	137	140	164	152	147	139	135	109
8H7o	Fast track referral	137	140	164	152	147	139	135	109
8H90	Telephone contact by consultant	137	140	164	152	147	139	135	109
8HB	Other follow-up	137	140	164	152	147	139	135	109
8HBA	Follow up in outpatient clinic	137	140	164	152	147	139	135	109
8HBJ	Stroke / transient ischaemic attack referral	137	140	164	152	147	139	135	109
8HC1	Refer to A. & E. department	98	111	110	114	127	129	133	137
8He	Referral to intermediate care	137	140	164	152	147	139	135	109
8HJ	Self-referral to hospital	137	140	164	152	147	139	135	109
8HJA	Trauma self-referral	137	140	164	152	147	139	135	109
8Hn0	Fast track referral for suspected skin cancer	137	140	164	152	147	139	135	109
8Hn1	Fast track referral for suspected gynaecological cancer	137	140	164	152	147	139	135	109
8Hn2	Fast track referral for suspected breast cancer	137	140	164	152	147	139	135	109
8Hn4	Fast track referral for suspected colorectal cancer	137	140	164	152	147	139	135	109
8Hn5	Fast track referral for suspected urological cancer	137	140	164	152	147	139	135	109
8Hn7	Fast track referral for suspected lung cancer	137	140	164	152	147	139	135	109
8Hn9	Fast track referral for suspected upper GI cancer	137	140	164	152	147	139	135	109
8HnB	Fast track referral for suspected head and neck cancer	137	140	164	152	147	139	135	109
8HTB	Referral to fertility clinic	137	140	164	152	147	139	135	109
8HTI	Referral to breast clinic	137	140	164	152	147	139	135	109
8HTJ	Referral to rapid access chest pain clinic	137	140	164	152	147	139	135	109
8HTP	Referral to musculoskeletal clinic	137	140	164	152	147	139	135	109
8HTY	Referral to memory clinic	137	140	164	152	147	139	135	109
8H72	Refer to district nurse	55	60	63	64	64	62	60	57
8H73	Refer to health visitor	32	83	86	88	53	62	51	65

8H76	Refer to dietitian	28	30	31	29	31	31	31	33
8H77	Refer to physiotherapist	35	38	39	37	31	31	30	32
8H78	Refer to counsellor	61	64	67	71	60	60	63	50
8H7g	Referral to palliative care service	119	123	127	131	136	185	189	168
8H7J	Refer to occupational therap.	36	38	40	38	31	31	30	32
8H7k	Referral to community-based podiatry service	18	23	23	22	31	31	30	30
8H7p	Referral to community alcohol team	100	109	106	117	132	131	135	139
8H7R	Refer to chiropodist	18	23	23	22	31	31	30	30
8H7V	Refer to audiologist	137	140	164	152	147	139	135	109
8H7w	Referral to continence nurse	66	73	75	77	44	43	42	64
8H7X	Refer to podiatry	18	23	23	22	31	31	30	30
8HBF-1	Podiatry follow-up	18	23	23	22	31	31	30	30
8HBR	NHS Health Check follow up	137	140	164	152	147	139	135	109
8Hk7	Referred for health coaching	137	140	164	152	147	139	135	109
8HT2	Referral to hearing aid clinic	137	140	164	152	147	139	135	109
8HT3	Referral to audiology clinic	41	44	46	48	65	67	65	47
8H7B	Refer to community psych. nurse	41	44	46	48	65	67	65	47
8H7B-1	Refer to CPN	41	44	46	48	65	67	65	47
8H7i	Referral to smoking cessation advisor	118	111	125	117	132	135	153	139
8HB8	Mental therapy follow-up	72	70	72	70	39	38	36	37
8HBP	Smoking cessation 12 week follow-up	118	111	125	117	132	135	153	139
8Hc	Referral to mental health team	72	70	72	70	39	38	36	37
8Hc0	Referral to community mental health team	72	70	72	70	39	38	36	37
8HH5	Refer to domiciliary physiotherapy	35	38	39	37	31	31	30	32
8Hq	Admission to substance misuse detoxification centre	213	219	231	142	147	150	152	152
8HTK	Referral to stop-smoking clinic	118	111	125	117	132	135	153	139
8H7M	Refer to stoma nurse	66	73	75	77	44	43	42	64
8H7q	Referral for exercise therapy	33	36	37	35	32	32	32	33

8H7S	Refer to orthotist	36	38	40	38	32	32	32	33
8H7T	Refer to psychologist	67	72	77	81	135	135	134	134
8H7Z	Refer to other health worker	61	64	67	71	60	60	63	50
8Hc2	Referral to primary care mental health team	72	70	72	70	39	38	36	37
8HHA	Refer to community physiotherapist	35	38	39	37	31	31	30	32
8HHe	Referral to community drug and alcohol team	100	109	106	117	132	131	135	139
8HHH	Refer to weight management programme	118	111	111	117	132	135	125	112
8HHH0	Referral to local authority weight management programme	118	111	111	117	132	135	125	112
8HHJ	Referral to respiratory nurse specialist	66	73	75	77	44	43	42	64
8HHK	Referral to bereavement counsellor	61	64	67	71	60	60	63	50
8HHQ	Referral to walk in centre	118	111	111	117	132	135	125	112
8HHt	Fast track cancer referral	137	140	164	152	147	139	135	109
8HJE	Neurology self-referral	137	140	164	152	147	139	135	109
8HJJ	Self-referral to accident and emergency department	98	111	110	114	127	129	133	137
8Hk	Referred to service	137	140	164	152	147	139	135	109
8HkF	Referral to substance misuse service	107	101	101	87	157	94	103.5	113
8HkG	Referral to specialist alcohol treatment service	107	101	101	87	157	94	103.5	113
8HkJ	Referral to alcohol brief intervention service	107	101	101	87	157	94	103.5	113
8HkK	Referral to improving access to psychological therapies prog	61	64	67	71	60	60	63	50
8HkM	Referral to hepatobiliary and pancreatic surgery service	137	140	164	152	147	139	135	109
8Hkp	Referral to community ear, nose and throat service	118	111	111	117	132	135	125	112
8Hkq	Referral to community dermatology service	118	111	111	117	132	135	125	112
8Hku	Referral to community gynaecology service	118	111	111	117	132	135	125	112
8Hkw	Referral to COPD community nursing team	118	111	111	117	132	135	125	112
8HkX	Referral to exercise on referral programme	118	111	111	117	132	135	125	112
8Hld	Referral to clinical allergy service	118	111	111	117	132	135	125	112
8Hlf	Referral to slimming club	118	111	111	117	132	135	125	112
8Hlq	Referral to community musculoskeletal service	118	111	111	117	132	135	125	112

8Hn6	Fast track referral for suspected haematology malignancy	137	140	164	152	147	139	135	109
8Hn8	Fast track referral for suspected sarcoma	137	140	164	152	147	139	135	109
8HnA	Fast track referral for suspected brain tumour	137	140	164	152	147	139	135	109
8HND	In-patient stay 13 days	1,971	1,917	1,972	2,055	2,186	2,357	2,536	2,873
8HT	Referral to clinic	137	140	164	152	147	139	135	109
8HTa	Referral to genitourinary clinic	137	140	164	152	147	139	135	109
8HTc	Referral to psychosexual clinic	137	140	164	152	147	139	135	109
8HTG	Referred to acute chest pain clinic	137	140	164	152	147	139	135	109
8HTH	Referral to back pain clinic	137	140	164	152	147	139	135	109
8HTn	Referral to sleep clinic	137	140	164	152	147	139	135	109
8HTX	Referral to incontinence clinic	137	140	164	152	147	139	135	109

APPENDIX 7.6. CHRONIC ORGANIC DISEASE RELATED READ CODES RECORDED IN THE PRIMARY CARE DATABASE.

The details of deriving this Read code list is described in Chapter 7.4.3.

Appendix 7.6: Chronic organic disease related Read codes recorded in primary care database					
1Z1	Chronic renal impairment	BB5j2	[M]Endometrioid carcinoma	G340	Coronary atherosclerosis
1Z10	Chronic kidney disease stage 1	BB5M0	[M]Tubular adenoma NOS	G3400	Single coronary vessel disease
1Z11	Chronic kidney disease stage 2	BB5R0	[M]Carcinoid tumour NOS	G340-1	Triple vessel disease of the heart
1Z12	Chronic kidney disease stage 3	BB5R9	[M]Neuroendocrine carcinoma	G340-2	Coronary artery disease
1Z13	Chronic kidney disease stage 4	BB5U0	[M]Villous adenoma NOS	G343	Ischaemic cardiomyopathy
1Z14	Chronic kidney disease stage 5	BB5U3	[M]Tubulovillous adenoma	G3z	Ischaemic heart disease NOS
1Z15	Chronic kidney disease stage 3A	BB5y4	[M]Prolactinoma	G580	Congestive heart failure
1Z16	Chronic kidney disease stage 3B	BB690	[M]Sebaceous adenoma	G5800	Acute congestive heart failure
1Z19-1	CKD stage 2 with proteinuria	BB81C	[M]Mucinous cystadenoma NOS	G5801	Chronic congestive heart failure
1Z1A	Chronic kidney disease stage 2 without proteinuria	BB91-1	[M]Duct carcinoma NOS	G580-1	Congestive cardiac failure
1Z1B	Chronic kidney disease stage 3 with proteinuria	BBbB	[M]Astrocytoma NOS	G5802	Decompensated cardiac failure
1Z1B-1	CKD stage 3 with proteinuria	BBbL	[M]Glioblastoma NOS	G580-2	Right heart failure
1Z1C	Chronic kidney disease stage 3 without proteinuria	BBbL-1	[M]Glioblastoma multiforme	G580-3	Right ventricular failure
1Z1C-1	CKD stage 3 without proteinuria	BBd0	[M]Meningioma NOS	G580-4	Biventricular failure
1Z1E	Chronic kidney disease stage 3A without proteinuria	BBE1	[M]Malignant melanoma NOS	G581	Left ventricular failure
1Z1E-1	CKD stage 3A without proteinuria	BBe1	[M]Malignant melanoma NOS	G58-1	Cardiac failure
1Z1F-1	CKD stage 3B with proteinuria	BBE1-2	[M]Melanoma NOS	G6	Cerebrovascular disease
1Z1G	Chronic kidney disease stage 3B without proteinuria	BBE2	[M]Nodular melanoma	G61-1	CVA - cerebrovascular accident due to intracerebral haemorrhage
1Z1H	Chronic kidney disease stage 4 with proteinuria	BBe5-3	[M]Schwannoma NOS	G61-2	Stroke due to intracerebral haemorrhage
1Z1H-1	CKD stage 4 with proteinuria	BBe8	[M]Neuroma NOS	G66	Stroke and cerebrovascular accident unspecified

1Z1J	Chronic kidney disease stage 4 without proteinuria	BBEF-1	[M]Lentigo maligna	G66-1	CVA unspecified
1Z1K	Chronic kidney disease stage 5 with proteinuria	BBF1	[M]Sarcoma NOS	G66-2	Stroke unspecified
1Z1L	Chronic kidney disease stage 5 without proteinuria	BBG0	[M]Fibroma NOS	G66-3	CVA - Cerebrovascular accident unspecified
B01	Malignant neoplasm of tongue	BBg1-1	[M]Lymphoma NOS	G667	Left sided CVA
B060	Malignant neoplasm of tonsil	BBg2-1	[M]Non-Hodgkins lymphoma	G668	Right sided CVA
B10	Malignant neoplasm of oesophagus	BBGD	[M]Fibrous histiocytoma NOS	G671	Generalised ischaemic cerebrovascular disease NOS
B105	Malignant neoplasm of lower third of oesophagus	BBGK	[M]Dermatofibroma NOS	G6711	Chronic cerebral ischaemia
B10z	Malignant neoplasm of oesophagus NOS	BBGK-2	[M]Histiocytoma NOS	G673	Cerebral aneurysm, non-ruptured
B10z-1	Oesophageal cancer	BBJB0	[M]Angiomyolipoma	G679	Small vessel cerebrovascular disease
B11	Malignant neoplasm of stomach	BBK00	[M]Leiomyoma NOS	G6z	Cerebrovascular disease NOS
B110	Malignant neoplasm of cardia of stomach	BBK00-1	[M]Fibroid uterus	G70y	Other specified artery atheroma
B13	Malignant neoplasm of colon	BBL3	[M]Pleomorphic adenoma	G70y0	Carotid artery atherosclerosis
B131	Malignant neoplasm of transverse colon	BBm7	[M] Monoclonal gammopathy	G70y0-1	Carotid artery disease
B133	Malignant neoplasm of sigmoid colon	BBMz	[M]Fibroepithelial neoplasm NOS	H31	Chronic bronchitis
B134	Malignant neoplasm of caecum	BBN0	[M]Synovioma, benign	H3-1	Chronic obstructive airways disease
B134-1	Carcinoma of caecum	BBn0-2	[M]Myeloma NOS	H3120	Chronic asthmatic bronchitis
B136	Malignant neoplasm of ascending colon	BBP1	[M]Mesothelioma, malignant	H3122	Acute exacerbation of chronic obstructive airways disease
B13z	Malignant neoplasm of colon NOS	BBQ8	[M]Dermoid cyst	H32	Emphysema
B13z-1	Colonic cancer	BBT2	[M]Cavernous haemangioma	H322	Centrilobular emphysema
B140	Malignant neoplasm of rectosigmoid junction	BBTB	[M]Angiokeratoma	H32z	Emphysema NOS
B141	Malignant neoplasm of rectum	BBW0	[M]Osteochondroma	H33	Asthma

B141-1	Carcinoma of rectum	BBW2-1	[M]Enchondroma	H330	Extrinsic (atopic) asthma
B141-2	Rectal carcinoma	C10	Diabetes mellitus	H3300-1	Hay fever with asthma
B1503	Hepatocellular carcinoma	C1000-1	Insulin dependent diabetes mellitus	H330-1	Allergic asthma
B152	Malignant neoplasm of liver unspecified	C101	Diabetes mellitus with ketoacidosis	H330-2	Childhood asthma
B160	Malignant neoplasm of gallbladder	C104-1	Diabetic nephropathy	H330-3	Hay fever with asthma
B17	Malignant neoplasm of pancreas	C106	Diabetes mellitus with neurological manifestation	H33-1	Bronchial asthma
B170	Malignant neoplasm of head of pancreas	C108	Insulin dependent diabetes mellitus	H331-1	Late onset asthma
B17z	Malignant neoplasm of pancreas NOS	C109	Non-insulin dependent diabetes mellitus	H333	Acute exacerbation of asthma
B1z0-1	Cancer of bowel	C109-2	Type 2 diabetes mellitus	H33z	Asthma unspecified
B21	Malignant neoplasm of larynx	C10E	Type 1 diabetes mellitus	H33z1	Asthma attack
B211	Malignant neoplasm of supraglottis	C10E-1	Type I diabetes mellitus	H33zz	Asthma NOS
B22	Malignant neoplasm of trachea, bronchus and lung	C10E-2	Insulin dependent diabetes mellitus	H33zz-1	Exercise induced asthma
B226	Mesothelioma	C10EM	Type 1 diabetes mellitus with ketoacidosis	H33zz-2	Allergic asthma NEC
B22z	Malignant neoplasm of bronchus or lung NOS	C10EQ	Type 1 diabetes mellitus with gastroparesis	H36	Mild chronic obstructive pulmonary disease
B22z-1	Lung cancer	C10F	Type 2 diabetes mellitus	H37	Moderate chronic obstructive pulmonary disease
B232	Mesothelioma of pleura	C10F-1	Type II diabetes mellitus	H38	Severe chronic obstructive pulmonary disease
B32	Malignant melanoma of skin	C10F7	Type 2 diabetes mellitus - poor control	H3y1	Chron obstruct pulmonary dis wth acute exacerbation, unspecified
B3257	Malignant melanoma of back	C10FJ	Insulin treated Type 2 diabetes mellitus	H3z	Chronic obstructive airways disease NOS
B33	Other malignant neoplasm of skin	C10FM	Type 2 diabetes mellitus with persistent microalbuminuria	J11	Gastric ulcer - (GU)

B33-1	Basal cell carcinoma	C1A0	Metabolic syndrome	J11z	Gastric ulcer NOS
B33-2	Epithelioma	C320	Pure hypercholesterolaemia	J11z-1	Gastric erosions
B333	Malignant neoplasm skin of other and unspecified parts face	C3200	Familial hypercholesterolaemia	J12	Duodenal ulcer - (DU)
B33-3	Rodent ulcer	C320-1	Familial hypercholesterolaemia	J1202	Acute duodenal ulcer with perforation
B3334	Malignant neoplasm of skin of nose (external)	C320z	Pure hypercholesterolaemia NOS	J123	Duodenal erosion
B33-6	Epithelioma basal cell	C3210	Hypertriglyceridaemia	J12z	Duodenal ulcer NOS
B338	Squamous cell carcinoma of skin	C322	Mixed hyperlipidaemia	J13	Peptic ulcer - (PU) site unspecified
B33z	Malignant neoplasm of skin NOS	C324	Hyperlipidaemia NOS	J13z	Peptic ulcer NOS
B34	Malignant neoplasm of female breast	C328	Dyslipidaemia	J40-1	Crohn's disease
B34-1	Ca female breast	C329	Hypercholesterolaemia	J401z-1	Crohn's colitis
B34z	Malignant neoplasm of female breast NOS	F110	Alzheimer's disease	J4-1	Colitis - noninfective
B41	Malignant neoplasm of cervix uteri	F1100	Alzheimer's disease with early onset	J410	Ulcerative proctocolitis
B41z	Malignant neoplasm of cervix uteri NOS	F12	Parkinson's disease	J4101	Ulcerative colitis
B4302	Malignant neoplasm of endometrium of corpus uteri	F12X	Secondary parkinsonism, unspecified	J4103	Ulcerative proctitis
B440	Malignant neoplasm of ovary	F152	Motor neurone disease	J4-2	Inflammatory bowel disease
B440-1	Cancer of ovary	F20	Multiple sclerosis	J42z0	Ischaemic colitis NOS
B454	Malignant neoplasm of vulva unspecified	F203	Exacerbation of multiple sclerosis	J43	Other non-infective inflammatory gastroenteritis and colitis
B46	Malignant neoplasm of prostate	F207	Relapsing and remitting multiple sclerosis	J436	Microscopic colitis
B47	Malignant neoplasm of testis	F21z	Central nervous system demyelination NOS	J4360	Collagenous colitis
B47z-1	Seminoma of testis	F23	Congenital cerebral palsy	J4361	Lymphocytic colitis

B483	Malignant neoplasm of penis, part unspecified	F25	Epilepsy	J437	Colitis
B49	Malignant neoplasm of urinary bladder	F2510	Grand mal (major) epilepsy	J4z3	Non-infective colitis NOS
B49z	Malignant neoplasm of urinary bladder NOS	F2514	Epileptic seizures - tonic	J690	Coeliac disease
B4A	Malig neop of kidney and other unspecified urinary organs	F2515	Tonic-clonic epilepsy	J690z	Coeliac disease NOS
B4A0	Malignant neoplasm of kidney parenchyma	F2516	Grand mal seizure	K05	Chronic renal failure
B4A-1	Renal malignant neoplasm	F253-1	Status epilepticus	K050	End stage renal failure
B4Az	Malignant neoplasm of kidney or urinary organs NOS	F2540	Temporal lobe epilepsy	K05-2	End stage renal failure
B51	Malignant neoplasm of brain	F2545	Complex partial epileptic seizure	K053	Chronic kidney disease stage 3
B53	Malignant neoplasm of thyroid gland	F2550-1	Focal epilepsy	N010-1	Septic arthritis
B56-1	Lymph node metastases	F258	Post-ictal state	N023	Gouty arthritis
B570	Secondary malignant neoplasm of lung	F25H	Generalised seizure	N0237	Gouty arthritis of the ankle and foot
B577	Secondary malignant neoplasm of liver	F25z	Epilepsy NOS	N0238	Gouty arthritis of toe
B577-1	Liver metastases	F25z-1	Fit (in known epileptic) NOS	N040	Rheumatoid arthritis
B58	Secondary malignant neoplasm of other specified sites	F372	Polyneuropathy in diabetes	N040P	Seronegative rheumatoid arthritis
B5830	Secondary malignant neoplasm of brain	F3720	Acute painful diabetic neuropathy	N040T	Flare of rheumatoid arthritis
B5832	Cerebral metastasis	F3721	Chronic painful diabetic neuropathy	N045	Other juvenile arthritis
B585	Secondary malignant neoplasm of bone and bone marrow	F372-2	Diabetic neuropathy	N047	Seropositive erosive rheumatoid arthritis
B590	Disseminated malignancy NOS	F420	Diabetic retinopathy	N04X	Seropositive rheumatoid arthritis, unspecified
B590-1	Carcinomatosis	F4200	Background diabetic retinopathy	N04y1	Sero negative arthritis
B61	Hodgkin's disease	F4201	Proliferative diabetic retinopathy	N05	Osteoarthritis and allied disorders

B627	Non - Hodgkin's lymphoma	F4202	Pre-proliferative diabetic retinopathy	N050	Generalised osteoarthritis - OA
B627C-1	Follicular lymphoma NOS	F4204	Diabetic maculopathy	N0501	Generalised osteoarthritis of the hand
B627E	Diffuse large B-cell lymphoma	F4206	Non proliferative diabetic retinopathy	N0502	Generalised osteoarthritis of multiple sites
B627W	Unspecified B-cell non-Hodgkin's lymphoma	F421	Other background retinopathy	N050z	Generalised osteoarthritis NOS
B630	Multiple myeloma	F4210	Unspecified background retinopathy	N05-1	Osteoarthritis
B641	Chronic lymphoid leukaemia	F4213	Hypertensive retinopathy	N051E	Localised, primary osteoarthritis of toe
B641-1	Chronic lymphatic leukaemia	F4250	Unspecified senile macular degeneration	N051G	Osteoarthritis of spinal facet joint
B650	Acute myeloid leukaemia	F4251	Dry senile macular degeneration	N0534	Localised osteoarthritis, unspecified, of the hand
B6y0	Myeloproliferative disorder	F425-1	Senile macular degeneration	N0535-2	Hip osteoarthritis NOS
B78	Uterine leiomyoma - fibroids	F4252	Wet senile macular degeneration	N0536-1	Patellofemoral osteoarthritis
B781	Intramural uterine leiomyoma	F4276	Retinitis pigmentosa	N05z	Osteoarthritis NOS
B78-1	Fibroids	F45	Glaucoma	N05z1	Osteoarthritis NOS, of shoulder region
B781-1	Mural fibroids	F4501	Open angle glaucoma with borderline intraocular pressure	N05z2-1	Elbow osteoarthritis NOS
B7A1	Dermoid cyst	F4504	Ocular hypertension	N05z3-1	Wrist osteoarthritis NOS
B7A-1	Dermoid cyst of ovary	F4504-1	Raised intra-ocular pressure	N05z4	Osteoarthritis NOS, of the hand
B7A2	Benign teratoma of ovary	F451	Open-angle glaucoma	N05z4-1	Finger osteoarthritis NOS
B7F10	Acoustic neuroma	F4510	Unspecified open-angle glaucoma	N05z4-2	Thumb osteoarthritis NOS
B7F20	Cerebral meningioma	F4511	Primary open-angle glaucoma	N05z5	Osteoarthritis NOS, pelvic region/thigh
B7H2-1	Pituitary adenoma	F4512	Low tension glaucoma	N05z5-1	Hip osteoarthritis NOS
B8-1	Bowen's disease	F4512-1	Normal pressure glaucoma	N05z6	Osteoarthritis NOS, of the lower leg
B82	Carcinoma in situ of skin	F4513-1	Pigment dispersion syndrome	N05z6-1	Knee osteoarthritis NOS
B828W	Melanoma in situ, unspecified	F452	Primary angle-closure glaucoma	N05z7	Osteoarthritis NOS, of ankle and foot

B830	Carcinoma in situ of breast	F4522	Acute primary angle-closure glaucoma	N05z7-1	Ankle osteoarthritis NOS
B8301	Intraductal carcinoma in situ of breast	F4566-1	Rubeotic glaucoma	N05z7-2	Foot osteoarthritis NOS
B8333-1	Vulval intraepithelial neoplasia	F45z	Glaucoma NOS	N05z7-3	Toe osteoarthritis NOS
B834	Carcinoma in situ of prostate	F46	Cataract	N05z8	Osteoarthritis NOS, other specified site
B917	Neoplasm of uncertain behaviour of bladder	F4605	Cortical cataract	N05z9	Osteoarthritis NOS, of shoulder
B91z1	Neoplasm of uncertain behaviour of kidney	F4607	Nuclear cataract	N05zB	Osteoarthritis NOS, of acromioclavicular joint
B927	Neurofibromatosis - Von Recklinghausen's disease	F4655	Posterior capsule opacification	N05zC	Osteoarthritis NOS, of elbow
B934	Polycythaemia vera	F466	Bilateral cataracts	N05zE	Osteoarthritis NOS, of wrist
B934-1	Polycythaemia rubra vera	F46z	Cataract NOS	N05zF	Osteoarthritis NOS, of MCP joint
B934-2	Primary polycythaemia	G2	Hypertensive disease	N05zH	Osteoarthritis NOS, of DIP joint of finger
B9374	Essential (haemorrhagic) thrombocythaemia	G20	Essential hypertension	N05zJ	Osteoarthritis NOS, of hip
B937-4	Myelodysplasia	G200	Malignant essential hypertension	N05zL	Osteoarthritis NOS, of knee
B937W	Myelodysplastic syndrome, unspecified	G20-1	High blood pressure	N05zN	Osteoarthritis NOS, of ankle
BB03	[M]Neoplasm, metastatic	G202	Systolic hypertension	N05zS	Osteoarthritis NOS, of 1st MTP joint
BB12	[M]Carcinoma NOS	G20z	Essential hypertension NOS	N05zz	Osteoarthritis NOS
BB13	[M]Carcinoma, metastatic, NOS	G20z-1	Hypertension NOS	N065	Unspecified polyarthropathy or polyarthritis
BB1J	[M]Small cell carcinoma NOS	G21	Hypertensive heart disease	N065A	Generalised arthritis
BB22	[M]Papillary carcinoma NOS	G24	Secondary hypertension	N065z-1	Polyarthritis
BB2-2	[M]Squamous cell neoplasms	G25	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)	N066	Unspecified monoarthritis
BB25	[M]Squamous cell papilloma	G250	Stage 1 hyperten (NICE 2011) without evidnce end organ damge	N0667	Unspecified monoarthritis of the ankle and foot
BB25-3	[M]Keratotic papilloma	G25-1	Stage 1 hypertension	N06z-1	Arthritis

BB29	[M]Squamous cell carcinoma in situ NOS	G2z	Hypertensive disease NOS	N06z1-1	Shoulder arthritis NOS
BB29-2	[M]Intraepidermal carcinoma NOS	G3	Ischaemic heart disease	N06z3-1	Wrist arthritis NOS
BB2A	[M]Squamous cell carcinoma NOS	G30	Acute myocardial infarction	N06z4-1	Hand arthritis NOS
BB2B	[M]Squamous cell carcinoma, metastatic NOS	G300	Acute anterolateral infarction	N06z5-1	Hip arthritis NOS
BB2L	[M]Bowen's disease	G301z	Anterior myocardial infarction NOS	N06z6-1	Knee arthritis NOS
BB31	[M]Basal cell carcinoma NOS	G30-5	MI - acute myocardial infarction	N06z7-1	Ankle arthritis NOS
BB3B	[M]Pilomatrixoma	G3071	Acute non-ST segment elevation myocardial infarction	N06z7-2	Foot arthritis NOS
BB3C	[M]Superficial basal cell carcinoma	G308	Inferior myocardial infarction NOS	N06zA	Acute arthritis
BB3D	[M]Basal cell carcinoma, nodular	G30X0	Acute ST segment elevation myocardial infarction	N11D	Osteoarthritis of spine
BB4	[M]Transitional cell papillomas and carcinomas	G30z	Acute myocardial infarction NOS	N11D0	Osteoarthritis of cervical spine
BB43	[M]Transitional cell carcinoma NOS	G3111	Unstable angina	N11D1	Osteoarthritis of thoracic spine
BB50	[M]Adenoma NOS	G311-3	Unstable angina	N11D2	Osteoarthritis of lumbar spine
BB51	[M]Adenocarcinoma in situ	G3114	Worsening angina	N11z-1	Osteoarthritis spine
BB52	[M]Adenocarcinoma NOS	G3115	Acute coronary syndrome	N330	Osteoporosis
BB53	[M]Adenocarcinoma, metastatic, NOS	G32	Old myocardial infarction	N3300	Osteoporosis, unspecified
BB57	[M]Adenocarcinoma, intestinal type	G3-2	Atherosclerotic heart disease	N3302	Postmenopausal osteoporosis
BB5a0	[M]Renal cell carcinoma	G33	Angina pectoris	N330B	Vertebral osteoporosis
BB5cz	[M]Parathyroid adenoma or adenocarcinoma NOS	G3-3	IHD - Ischaemic heart disease	N330z	Osteoporosis NOS
BB5D1	[M]Cholangiocarcinoma	G33z	Angina pectoris NOS	N331-4	Osteoporotic vertebral collapse
BB5f1-1	[M]Follicular carcinoma	G33z7	Stable angina	N3319	Osteoporosis + pathological fracture thoracic vertebrae
BB5h0	[M]Adrenal cortical adenoma NOS	G33zz	Angina pectoris NOS		

APPENDIX 7.7. MENTAL HEALTH / PSYCHOLOGICAL ISSUES RELATED READ CODES RECORDED IN THE PRIMARY CARE DATABASE

(Used to record comorbid conditions of mental health issues along with Medically Unexplained Symptoms. The process of deriving this Read code list is given in Chapter 7.4.4).

Appendix 7.7: 1,102 Mental Health related Read codes recorded in primary care database					
28	Mild cognitive impairment	E214	Compulsive personality disorders	Eu311	[X]Bipolar affect disorder cur epi manic wout psychotic symp
146	H/O: psychiatric disorder	E2140	Anankastic personality	Eu31-1	[X]Manic-depressive illness
280	Moderate cognitive impairment	E2141	Obsessional personality	Eu312	[X]Bipolar affect disorder cur epi manic with psychotic symp
1465	H/O: depression	E2151	Munchausen's syndrome	Eu31-2	[X]Manic-depressive psychosis
1466	H/O: anxiety state	E2152	Emotionally unstable personality	Eu313	[X]Bipolar affect disorder cur epi mild or moderate depressn
1467	H/O: anorexia nervosa	E216	Inadequate personality disorder	Eu314	[X]Bipolar affective disorder, current episode severe depression without psychotic symptoms
1469	H/O: behaviour problem	E217	Antisocial or sociopathic personality disorder	Eu315	[X]Bipolar affective disorder, current episode severe depression with psychotic symptoms
1612	Appetite loss - anorexia	E21y	Other personality disorders	Eu316	[X]Bipolar affective disorder, current episode mixed
2232	O/E - mentally confused	E21y0	Narcissistic personality disorder	Eu317	[X]Bipolar affective disorder, currently in remission
2253	O/E - distressed	E21y1	Avoidant personality disorder	Eu319	[X]Bipolar affective disorder type II
2258	O/E - anxious	E21y2	Borderline personality disorder	Eu319-1	[X]Bipolar II disorder
2800	Severe cognitive impairment	E21y7	Psychoneurotic personality disorder	Eu31y-1	[X]Bipolar II disorder
6655	Psych. drug side effects	E21yz	Other personality disorder NOS	Eu31z	[X]Bipolar affective disorder, unspecified

6657	On lithium	E21z	Personality disorder NOS	Eu32	[X]Depressive episode
6779	Psychological counselling	E224-1	Flasher	Eu320	[X]Mild depressive episode
28000	Cognitive impairment	E225	Trans-sexualism	Eu321	[X]Moderate depressive episode
13HT1	Stress at home	E227	Psychosexual dysfunction	Eu322	[X]Severe depressive episode without psychotic symptoms
13HT2	Unable to cope	E2270	Unspecified psychosexual dysfunction	Eu323	[X]Severe depressive episode with psychotic symptoms
13Z80	Social adjustment problem	E2271	Inhibited sexual desire	Eu323-3	[X]Single episode of psychotic depression
146A	H/O: attempted suicide	E227-1	Lack of libido	Eu324	[X]Mild depression
146B	H/O: deliberate self harm	E2273	Impotence	Eu325	[X]Major depression, mild
146D	H/O: manic depressive disorder	E2273-1	Erectile dysfunction	Eu326	[X]Major depression, moderately severe
146G	H/O: agoraphobia	E2274	Inhibited female orgasm	Eu327	[X]Major depression, severe without psychotic symptoms
146H	H/O: psychosis	E2275	Inhibited male orgasm	Eu328	[X]Major depression, severe with psychotic symptoms
146J	H/O: low self-esteem	E2276	Premature ejaculation	Eu329	Single major depressive episode, severe, with psychosis, psychosis in remission
146Z	H/O: psychiatric disorder NOS	E2277	Psychogenic dyspareunia	Eu32A	Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
14Od	At risk of dementia	E227z	Psychosexual dysfunction NOS	Eu32y	[X]Other depressive episodes
14X7	Victim of emotional abuse	E227z-1	Fear of ejaculation	Eu32z	[X]Depressive episode, unspecified
16ZB1	Feeling low or worried	E22y1	Voyeurism	Eu32z-1	[X]Depression NOS
1B12-2	Tension - nervous	E22y4	Gender role disorder of adolescent or adult	Eu32z-2	[X]Depressive disorder NOS
1B13	Anxiousness	E22z	Psychosexual disorder NOS	Eu32z-4	[X] Reactive depression NOS
1B13-1	Anxiousness - symptom	E23	Alcohol dependence syndrome	Eu32z-500	[X]Depressive episode

1B13-2	Anxious	E230	Acute alcoholic intoxication in alcoholism	Eu33	[X]Recurrent depressive disorder
1B14	Tenseness	E2300	Acute alcoholic intoxication, unspecified, in alcoholism	Eu330	[X]Recurrent depressive disorder, current episode mild
1B14-1	Tenseness - symptom	E231	Chronic alcoholism	Eu331	[X]Recurrent depressive disorder, current episode moderate
1B16	Agitated	E23-1	Alcoholism	Eu332	[X]Recurr depress disorder cur epi severe without psyc sympt
1B17	Depressed	E2311	Continuous chronic alcoholism	Eu333	[X]Recurrent depress disorder cur epi severe with psyc symp
1B17-1	C/O - feeling depressed	E2312	Episodic chronic alcoholism	Eu333-1	[X]Endogenous depression with psychotic symptoms
1B17-2	C/O - feeling unhappy	E2313	Chronic alcoholism in remission	Eu333-5	[X]Recurrent severe episodes of psychotic depression
1B19	Suicidal	E231z	Chronic alcoholism NOS	Eu334	[X]Recurrent depressive disorder, currently in remission
1B19-1	Suicidal - symptom	E23-2	Alcohol problem drinking	Eu33-5	[X]SAD - Seasonal affective disorder
1B1A-1	Amnesia symptom	E23z	Alcohol dependence syndrome NOS	Eu33y	[X]Other recurrent depressive disorders
1B1I	Crying, excessive	E23z-500	Alcohol dependence syndrome NOS	Eu33z	[X]Recurrent depressive disorder, unspecified
1B1I1-1	C/O weepiness	E24	Drug dependence	Eu34	[X]Persistent mood affective disorders
1B1L	Stress related problem	E240	Opioid type drug dependence	Eu340	[X]Cyclothymia
1B1L-500	Acute reaction to stress	E2400	Unspecified opioid dependence	Eu340-3	[X]Cyclothymic personality
1B1O	Restless	E2401	Continuous opioid dependence	Eu341	[X]Dysthymia
1B1P	Crying	E240-1	Heroin dependence	Eu341-3	[X]Neurotic depression
1B1T	Feeling stressed	E2402	Episodic opioid dependence	Eu341-4	[X]Persistant anxiety depression
1B1U	Symptoms of depression	E240-2	Methadone dependence	Eu34y	[X]Other persistent mood affective disorders
1B1V	C/O - panic attack	E240-3	Morphine dependence	Eu34z	[X]Persistent mood affective disorder, unspecified

1B1X	Behavioural problem	E240-4	Opium dependence	Eu3y	[X]Other mood affective disorders
1B6	Disturbance of consciousness	E240z	Opioid drug dependence NOS	Eu3y1	[X]Other recurrent mood affective disorders
1Ba0	Obsessional thoughts	E241	Hypnotic or anxiolytic dependence	Eu3y2	[X]Premenstrual dysphoric disorder
1BC	Morbid jealousy	E24-1	Drug addiction	Eu3z	[X]Unspecified mood affective disorder
1BD	Harmful thoughts	E2410	Hypnotic or anxiolytic dependence, unspecified	Eu4	[X]Neurotic, stress - related and somoform disorders
1BD1	Suicidal ideation	E2411	Hypnotic or anxiolytic dependence, continuous	Eu40	[X]Phobic anxiety disorders
1BD2	Morbid thoughts	E241-1	Anxiolytic dependence	Eu400	[X]Agoraphobia
1BD3	Suicidal plans	E2412	Hypnotic or anxiolytic dependence, episodic	Eu400-1	[X]Agoraphobia without history of panic disorder
1BD4	Suicide risk	E241-3	Benzodiazepine dependence	Eu400-2	[X]Panic disorder with agoraphobia
1BD5	High suicide risk	E241-4	Diazepam dependence	Eu401	[X]Social phobias
1BD6	Moderate suicide risk	E241-6	Sedative dependence	Eu401-2	[X]Social neurosis
1BD8	At risk of DSH - deliberate self harm	E241z	Hypnotic or anxiolytic dependence NOS	Eu402	[X]Specific (isolated) phobias
1BDA	Thoughts of deliberate self harm	E242	Cocaine type drug dependence	Eu402-2	[X]Animal phobias
1BH	Delusions	E2420	Cocaine dependence, unspecified	Eu402-3	[X]Claustrophobia
1BH0	Delusion of persecution	E2422	Cocaine dependence, episodic	Eu402-4	[X]Simple phobia
1BH-1	Delusion	E242z	Cocaine drug dependence NOS	Eu403	[X]Needle phobia
1BH3	Paranoid ideation	E243	Cannabis type drug dependence	Eu40y	[X]Other phobic anxiety disorders
1BN	Wandering	E2430	Cannabis dependence, unspecified	Eu40z	[X]Phobic anxiety disorder, unspecified
1BT	Depressed mood	E2431	Cannabis dependence, continuous	Eu40z-1	[X]Phobia NOS
1BT-1	Low mood	E2432	Cannabis dependence, episodic	Eu41	[X]Other anxiety disorders
1BT-2	Sad mood	E2433	Cannabis dependence in remission	Eu410	[X]Panic disorder [episodic paroxysmal anxiety]
1BY	Elevated mood	E243z	Cannabis drug dependence NOS	Eu410-1	[X]Panic attack
1G2-1	Poor body image	E244	Amphetamine or other psychostimulant dependence	Eu410-2	[X]Panic state

1JA2	Suspected dementia	E2440	Amphetamine or psychostimulant dependence, unspecified	Eu411	[X]Generalized anxiety disorder
1JJ	Suspected depression	E2441	Amphetamine or psychostimulant dependence, continuous	Eu411-1	[X]Anxiety neurosis
1P00	Hyperactive behaviour	E244z	Amphetamine or psychostimulant dependence NOS	Eu411-2	[X]Anxiety reaction
1P04	C/O - akathisia	E247	Other specified drug dependence	Eu411-3	[X]Anxiety state
1P3	Compulsive behaviour	E2470	Other specified drug dependence, unspecified	Eu412	[X]Mixed anxiety and depressive disorder
1S4	Mood observations	E2472	Other specified drug dependence, episodic	Eu412-1	[X]Mild anxiety depression
1S40	Dysphoric mood	E247z	Other specified drug dependence NOS	Eu413	[X]Other mixed anxiety disorders
1S42	Manic mood	E249	Combined drug dependence, excluding opioids	Eu41y	[X]Other specified anxiety disorders
212S	Depression resolved	E24A	Ecstasy type drug dependence	Eu41y-1	[X]Anxiety hysteria
212T	Psychosis, schizophrenia + bipolar affective disord resolved	E24z	Drug dependence NOS	Eu41z	[X]Anxiety disorder, unspecified
212W	Schizophrenia resolved	E25	Nondependent abuse of drugs	Eu41z-1	[X]Anxiety NOS
212X	Psychosis resolved	E250	Nondependent alcohol abuse	Eu42	[X]Obsessive - compulsive disorder
225E	O/E - paranoid delusions	E2500	Nondependent alcohol abuse, unspecified	Eu420	[X]Predominantly obsessional thoughts or ruminations
225J	O/E - panic attack	E2501	Nondependent alcohol abuse, continuous	Eu421	[X]Predominantly compulsive acts [obsessional rituals]
28E	Cognitive decline	E250-1	Drunkenness NOS	Eu422	[X]Mixed obsessional thoughts and acts
28H	Mentally vague	E2502	Nondependent alcohol abuse, episodic	Eu42-2	[X]Obsessive-compulsive neurosis
2JR	Lack mental capacity make decision Mental Capacity Act 2005	E250-2	Hangover (alcohol)	Eu42y	[X]Other obsessive-compulsive disorders

3AB1	Mildy abnormal behaviour	E2503	Nondependent alcohol abuse in remission	Eu42z	[X]Obsessive-compulsive disorder, unspecified
3AB3	Change in behaviour	E250-4	Intoxication - alcohol	Eu43	[X]Reaction to severe stress, and adjustment disorders
62T1	Puerperal depression	E250z	Nondependent alcohol abuse NOS	Eu430	[X]Acute stress reaction
665A	Psych.treatment stopped	E251	Tobacco dependence	Eu430-1	[X]Acute crisis reaction
66h	Dementia monitoring	E252	Nondependent cannabis abuse	Eu430-2	[X]Acute reaction to stress
7L1a	Cognitive behavioural therapy	E2520	Nondependent cannabis abuse, unspecified	Eu430-4	[X]Crisis state
8BA7	Relaxation therapy	E2521	Nondependent cannabis abuse, continuous	Eu431	[X]Post - traumatic stress disorder
8BM0	Mental health medication review	E2522	Nondependent cannabis abuse, episodic	Eu432	[X]Adjustment disorders
8BM02	Dementia medication review	E252z	Nondependent cannabis abuse NOS	Eu432-2	[X]Grief reaction
8CAh	Advice regarding symptoms on discontinuation of SSRI	E255	Nondependent opioid abuse	Eu433	[X]Acute post-traumatic stress disorder following military combat
8CM2	Psychiatry care plan	E255z	Nondependent opioid abuse NOS	Eu434	[X]Chronic post-traumatic stress disorder following military combat
8CM9	Mental health care programme approach contingency plan	E256	Nondependent cocaine abuse	Eu435	[X]Delayed post-traumatic stress disorder following military combat
8CMe0	Dementia advance care plan	E2562	Nondependent cocaine abuse, episodic	Eu43y	[X]Other reactions to severe stress
8CMG1	Review of mental health care plan	E257	Nondependent amphetamine or other psychostimulant abuse	Eu43z	[X]Reaction to severe stress, unspecified
8CMZ	Dementia care plan	E2570	Nondependent amphetamine/psychostimulant abuse, unspecified	Eu45y-5	[X]Teeth-grinding
8CMZ1	Dementia care plan reviewed	E257-2	Stimulant abuse	Eu46	[X]Other neurotic disorders
8CQ	Mental health crisis plan	E257z-1	Nondependent amfetamine or psychostimulant abuse NOS	Eu460	[X]Neurasthenia

8CQ1-1	Mental health CPA crisis plan available	E259	Nondependent mixed drug abuse	Eu461	[X]Depersonalization - derealization syndrome
8CR7	Mental health personal health plan	E2590	Nondependent mixed drug abuse, unspecified	Eu46y	[X]Other specified neurotic disorders
8CSA	Dementia advance care plan agreed	E2594	Misuse of prescription only drugs	Eu46y-3	[X]Occupational neurosis, including writer's cramp
8CV3	Psychological therapy started	E25y0	Nondependent other drug abuse, unspecified	Eu46z	[X]Neurotic disorder, unspecified
8CY	Mental Health Care Programme Approach	E25y-1	Analgesic abuse	Eu46z-1	[X]Neurosis NOS
8G	Psychotherapy/sociotherapy	E25y-2	Laxative abuse	Eu50	[X]Eating disorders
8G1	General psychotherapy	E25y-3	Steroid abuse	Eu500	[X]Anorexia nervosa
8G-1	Psychotherapy	E25yz	Nondependent other drug abuse NOS	Eu501	[X]Atypical anorexia nervosa
8G10	Psychotherapy - behavioural	E25z	Misuse of drugs NOS	Eu502	[X]Bulimia nervosa
8G11	Psychotherapy - cognitive	E2620	Cardiac neurosis	Eu502-1	[X]Bulimia NOS
8G12	Psychotherapy - psychodynamic	E26y0	Bruxism (teeth grinding)	Eu504	[X]Overeating associated with other psychological disturbncs
8G13	Cognitive-behaviour therapy	E270	Stammering or stuttering	Eu505	[X]Vomiting associated with other psychological disturbances
8G15	Computerised cognitive behavioural therapy	E270-1	Stammering	Eu50y	[X]Other eating disorders
8G43	Disabling psych.problem rehab.	E270-2	Stuttering	Eu50y-1	[X]Pica in adults
8G51	Group psychotherapy	E271	Anorexia nervosa	Eu50y-2	Eating disorder related code (code not found)
8G8Z	Therapeutic hypnosis NOS	E272	Tics	Eu50z	[X]Eating disorder, unspecified
8G91	Therapeutic psychology	E2720	Tic disorder unspecified	Eu510	[X]Nonorganic insomnia
8G94	Anxiety management training	E2721	Transient childhood tic	Eu513	[X]Sleepwalking
8G96	Problem solving therapy	E2722	Chronic motor tic disorder	Eu515	[X]Nightmares
8H23	Admit psychiatric emergency	E2723	Gilles de la Tourette's disorder	Eu52	[X]Sex dysfunction not caused by organic disorder or disease
8H230	Emerg psychiatric admiss MHA	E272z	Tic NOS	Eu520	[X]Lack or loss of sexual desire

8H38	Non-urgent psychiatric admisn.	E2731	Head-banging	Eu520-2	[X]Hypoactive sexual desire disorder
8H49	Psychiatric referral	E2732	Spasmus nutans - nodding spasm	Eu520-3	[X] Lack of libido
8H4D	Referral to psychogeriatrician	E274	Non-organic sleep disorders	Eu521-1	[X]Anhedonia sexual
8H7B	Refer to community psych.nurse	E2740	Unspecified non-organic sleep disorder	Eu522	[X]Failure of genital response
8H7B-1	Refer to CPN	E2741	Transient insomnia	Eu522-1	[X]Female sexual arousal disorder
8H7T	Refer to psychologist	E2741-1	Insomnia NOS	Eu522-2	[X]Male erectile disorder
8HB8	Mental therapy follow-up	E2742	Persistent insomnia	Eu522-3	[X]Psychogenic impotence
8HC	Referral to mental health team	E2743-1	Hypersomnia NOS	Eu523	[X]Orgasmic dysfunction
8Hc0	Referral to community mental health team	E2745	Jet lag syndrome	Eu523-2	[X]Psychogenic anorgasmy
8Hg9	Discharged from community mental health service	E2746	Shifting sleep-work schedule	Eu524	[X]Premature ejaculation
8HHs	Referral to psychosis early intervention service	E2747	Somnambulism - sleep walking	Eu526	[X]Nonorganic dyspareunia
8HkK	Referral to improving access to psychological therapies prog	E2748	Night terrors	Eu527	[X]Excessive sexual drive
8HL9	Psychiatry D.V. done	E2749	Nightmares	Eu52y	[X]Oth sex dysfunction, not caused by organic disordr/dsease
8HLC	Psychogeriatric D.V. done	E274B	Repeated rapid eye movement sleep interruptions	Eu53	[X]Mental and behav disorders assoc with the puerperium NEC
8HlK	Referral for cognitive behavioural therapy	E274C	Other sleep stage or arousal dysfunction	Eu530	[X]Mild mental/behav disorder assoc with the puerperium NEC
8HTc	Referral to psychosexual clinic	E274D-1	Restless sleep	Eu530-1	[X]Postnatal depression NOS
8HVS	Private referral to psychogeriatrician	E274F	Inversion of sleep rhythm	Eu530-2	[X]Postpartum depression NOS
8I3l	Cognitive behaviour therapy declined	E274y-1	Dreams	Eu531-1	[X]Puerperal psychosis NOS
8I3y	Psychological therapy declined	E274z	Non-organic sleep disorder NOS	Eu531-1	[X]Puerperal psychosis NOS
8IA1	Patient health questionnaire (PHQ-9) declined	E2750	Unspecified non-organic eating disorder	Eu55-3	[X]Abuse of steroids or hormones

9bA	Psychiatry	E2751	Bulimia (non-organic overeating)	Eu55-5	[X]Laxative habit
9bA2	Child and adolescent psychiatry	E2752	Pica	Eu6	[X]Disorders of adult personality and behaviour
9bA4	Psychotherapy (specialty)	E2756	Non-organic loss of appetite	Eu60	[X]Specific personality disorders
9H-1	Patient "sectioned"	E2758	Specific food craving	Eu600	[X]Paranoid personality disorder
9H7	Removed from severe mental illness register	E275y	Other specified non-organic eating disorder	Eu602	[X]Dissocial personality disorder
9H8	On severe mental illness register	E276	Non-organic enuresis	Eu602-2	[X]Antisocial personality disorder
9H90	Depression annual review	E2760	Non-organic primary enuresis	Eu602-3	Personality disorder related code (code not found)
9H91	Depression medication review	E2761	Non-organic secondary enuresis	Eu602-4	Personality disorder related code (code not found)
9H92	Depression interim review	E27z0	Hair plucking	Eu602-5	Personality disorder related code (code not found)
9HA0	On depression register	E27z2	Lisping	Eu603	[X]Emotionally unstable personality disorder
9N1T	Seen in psychiatry clinic	E27z3	Masturbation	Eu603-1	[X]Aggressive personality disorder
9N2a	Seen by community psychiatric nurse	E27z4	Nail-biting	Eu603-2	[X]Borderline personality disorder
9N2W	Seen by psychologist	E27z5	Thumb-sucking	Eu605	[X]Anankastic personality disorder
9N2W2	Seen by child and adolescent psychologist	E28	Acute reaction to stress	Eu605-2	[X]Obsessional personality disorder
9N2z	Seen by child and adolescent mental health service	E280	Acute panic state due to acute stress reaction	Eu605-3	[X]Obsessive-compulsive personality disorder
9Ngp	On drug ther ADHD (attention deficit hyperactivity disorder)	E281	Acute fugue state due to acute stress reaction	Eu606	[X]Anxious [avoidant] personality disorder
9Nk6	Seen in mental health clinic	E283	Other acute stress reactions	Eu607	[X]Dependent personality disorder
9Nla	Seen by psychiatrist	E2830	Acute situational disturbance	Eu608	[X]Addictive personality
9Nla0	Seen by child and adolescent psychiatrist	E2831	Acute posttrauma stress state	Eu60y	[X]Other specific personality disorders
9NlG	Seen by forensic psychiatrist	E283z	Other acute stress reaction NOS	Eu60z	[X]Personality disorder, unspecified

9NlK	Seen by psychotherapist	E284	Stress reaction causing mixed disturbance of emotion/conduct	Eu61	[X]Mixed and other personality disorders
9NN5	Under care of psychiatrist	E28z	Acute stress reaction NOS	Eu62y-1	[X]Chronic pain personality syndrome
9NN7	Under care of mental health team	E28z-1	Examination fear	Eu63	[X]Habit and impulse disorders
9NNE	Under the care of psychologist	E28z-2	Flying phobia	Eu630	[X]Pathological gambling
9NNM-1	Under care of CPN	E29	Adjustment reaction	Eu630-1	[X]Compulsive gambling
E	Mental disorders	E290	Brief depressive reaction	Eu633	[X]Trichotillomania
E0	Organic psychotic conditions	E2900	Grief reaction	Eu63y	[X]Other habit and impulse disorders
E00	Senile and presenile organic psychotic conditions	E2900-1	Bereavement reaction	Eu63z	[X]Habit and impulse disorder, unspecified
E000	Uncomplicated senile dementia	E290z	Brief depressive reaction NOS	Eu64	[X]Gender identity disorders
E001	Presenile dementia	E291	Prolonged depressive reaction	Eu640	[X]Transsexualism
E00-1	Senile dementia	E292	Adjustment reaction, predominant disturbance other emotions	Eu642	[X]Gender identity disorder of childhood
E001z	Presenile dementia NOS	E2920	Separation anxiety disorder	Eu64z	[X]Gender identity disorder, unspecified
E002	Senile dementia with depressive or paranoid features	E2923	Specific academic or work inhibition	Eu64z-1	[X]Gender-role disorder NOS
E00-2	Senile/presenile dementia	E2923-2	Specific work inhibition	Eu65	[X]Disorders of sexual preference
E0020	Senile dementia with paranoia	E2924	Adjustment reaction with anxious mood	Eu65z	[X]Disorder of sexual preference, unspecified
E0021	Senile dementia with depression	E292y	Adjustment reaction with mixed disturbance of emotion	Eu662	[X]Sexual relationship disorder
E003	Senile dementia with delirium	E292z	Adjustment reaction with disturbance of other emotion NOS	Eu6y	[X]Other disorders of adult personality and behaviour
E004	Arteriosclerotic dementia	E2930	Adjustment reaction with aggression	Eu6yy	[X]Other specified disorders of adult personality/behaviour
E004-1	Multi infarct dementia	E293z	Adjustment reaction with predominant disturbance conduct NOS	Eu70	[X]Mild mental retardation

E004z	Arteriosclerotic dementia NOS	E294	Adjustment reaction with disturbance emotion and conduct	Eu71	[X]Moderate mental retardation
E00y	Other senile psychoses	E29y1	Other post-traumatic stress disorder	Eu72	[X]Severe mental retardation
E00z	Senile or presenile psychoses NOS	E29y3	Elective mutism due to an adjustment reaction	Eu7z	[X]Unspecified mental retardation
E01	Alcoholic psychoses	E29y5	Other adjustment reaction with withdrawal	Eu80	[X]Specific developmental disorders of speech and language
E010	Alcohol withdrawal delirium	E29z	Adjustment reaction NOS	Eu800	[X]Specific speech articulation disorder
E010-1	DTs - delirium tremens	E2A0	Frontal lobe syndrome	Eu800-1	[X]Developmental phonological disorder
E010-2	Delirium tremens	E2A1	Organic personality syndrome	Eu800-2	[X]Developmental speech articulation disorder
E011	Alcohol amnestic syndrome	E2A10	Mild memory disturbance	Eu801	[X]Expressive language disorder
E0110	Korsakov's alcoholic psychosis	E2A11	Organic memory impairment	Eu801-1	[X]Developmental dysphasia, expressive type
E0112	Wernicke-Korsakov syndrome	E2A12	Change in personality	Eu801-2	[X]Developmental aphasia, expressive type
E012	Other alcoholic dementia	E2A2	Post-concussion syndrome	Eu802-2	[X]Developmental dysphasia, receptive type
E013	Alcohol withdrawal hallucinosis	E2B	Depressive disorder NEC	Eu805	[X]Semantic-pragmatic disorder
E014	Pathological alcohol intoxication	E2B1	Chronic depression	Eu806	[X]Auditory processing disorder
E015	Alcoholic paranoia	E2C	Disturbance of conduct NEC	Eu80y	[X]Other developmental disorders of speech and language
E01y	Other alcoholic psychosis	E2C0	Aggressive unsocial conduct disorder	Eu80y-1	[X]Lisping
E01y0	Alcohol withdrawal syndrome	E2C00	Aggressive outburst	Eu80z	[X]Developmental disorder of speech and language unspecified
E01z	Alcoholic psychosis NOS	E2C01	Anger reaction	Eu80z-1	[X]Language development disorder NOS
E02	Drug psychoses	E2C0z	Aggressive unsocial conduct disorder NOS	Eu810	[X]Specific reading disorder
E020	Drug withdrawal syndrome	E2C-1	Behaviour disorder	Eu810-2	[X]Developmental dyslexia

E021	Drug-induced paranoia or hallucinatory states	E2C10-1	School refusal	Eu814	[X]Moderate learning disability
E0210	Drug-induced paranoid state	E2C11	Solitary stealing	Eu815	[X]Severe learning disability
E0211	Drug-induced hallucinosis	E2C11-1	Shop lifting	Eu816	[X]Mild learning disability
E021z	Drug-induced paranoia or hallucinatory state NOS	E2C12	Tantrums	Eu81y-1	[X]Developmental expressive writing disorder
E022	Pathological drug intoxication	E2C31	Pathological gambling	Eu81z	[X]Developmental disorder of scholastic skills, unspecified
E023	Nicotine withdrawal	E2C32	Kleptomania	Eu81z-1	[X]Learning disability NOS
E02yz	Other drug psychoses NOS	E2C4z	Mixed disturbance of conduct and emotion NOS	Eu81z-2	[X]Learning disorder NOS
E02z	Drug psychosis NOS	E2Cy0	Breath holder	Eu82	[X]Specific developmental disorder of motor function
E03	Transient organic psychoses	E2Cz	Unspecified disturbance of conduct	Eu82-1	[X]Clumsy child syndrome
E030	Acute confusional state	E2Czz	Disturbance of conduct NOS	Eu82-2	[X]Developmental co - ordination disorder
E0301	Acute confusional state, of infective origin	E2D	Disturbance of emotion specific to childhood and adolescence	Eu82-3	[X]Developmental dyspraxia
E030-2	Toxic confusional state	E2D0	Disturbance of anxiety and fearfulness in childhood and adolescence	Eu84	[X]Pervasive developmental disorders
E0304	Acute confusional state, of cerebrovascular origin	E2D00	Childhood and adolescent overanxiousness disturbance	Eu840	[X]Childhood autism
E030z	Acute confusional state NOS	E2D01	Childhood and adolescent fearfulness disturbance	Eu840-1	[X]Autistic disorder
E031	Subacute confusional state	E2D0z	Disturbance anxiety and fearfulness childhood/adolescent NOS	Eu845	[X]Asperger's syndrome
E031z	Subacute confusional state NOS	E2D1	Childhood and adolescence disturbance of unhappiness	Eu84y	[X]Other pervasive developmental disorders
E03y0	Organic delusional syndrome	E2D-1	Adolescent - emotional problem	Eu84z	[X]Pervasive developmental disorder, unspecified

E03y3	Unspecified puerperal psychosis	E2D1-2	Unhappiness of childhood or adolescence	Eu84z-1	[X]Autistic spectrum disorder
E03yz	Other transient organic psychoses NOS	E2D-2	Disturbance of emotion specific to childhood and adolescence	Eu85	[X]Global developmental delay
E040	Non-alcoholic amnestic syndrome	E2D2z	Childhood and adolescent sensitivity disturbance NOS	Eu9	[X]Behavioural/emotional disords onset childhood/adolescence
E040-1	Korsakoff's non-alcoholic psychosis	E2D2z-1	School refusal	Eu90	[X]Hyperkinetic disorders
E041	Dementia in conditions EC	E2D3	Childhood and adolescent relationship problem	Eu900	[X]Disturbance of activity and attention
E042	Chronic confusional state	E2D3z	Childhood and adolescent relationship problem NOS	Eu900-1	[X]Attention deficit hyperactivity disorder
E0z	Organic psychoses NOS	E2Dy	Other childhood and adolescent emotional problems	Eu900-1-500	[X]Attention deficit disorder
E1	Non-organic psychoses	E2Dy0	Childhood and adolescent oppositional disorder	Eu90z	[X]Hyperkinetic disorder, unspecified
E10	Schizophrenic disorders	E2Dyz	Other childhood and adolescent emotional problems NOS	Eu91	[X]Conduct disorders
E1000	Unspecified schizophrenia	E2Dz	Childhood and adolescent emotion disorder NOS	Eu911	[X]Unsocialized conduct disorder
E1002	Chronic schizophrenic	E2Dz-2	Constantly crying baby	Eu912-5	[X]Truancy from school
E1004	Acute exacerbation of chronic schizophrenia	E2E	Childhood hyperkinetic syndrome	Eu913	[X]Oppositional defiant disorder
E1005	Schizophrenia in remission	E2E0	Child attention deficit disorder	Eu91z	[X]Conduct disorder, unspecified
E101	Hebephrenic schizophrenia	E2E01	Attention deficit with hyperactivity	Eu91z-1	[X]Childhood behavioural disorder NOS
E102	Catatonic schizophrenia	E2E0z	Child attention deficit disorder NOS	Eu91z-2	[X]Childhood conduct disorder NOS
E103	Paranoid schizophrenia	E2E2	Hyperkinetic conduct disorder	Eu92	[X]Mixed disorders of conduct and emotions
E1032	Chronic paranoid schizophrenia	E2Ez	Hyperkinetic syndrome NOS	Eu920	[X]Depressive conduct disorder
E1034	Acute exacerbation of chronic paranoid schizophrenia	E2F	Specific delays in development	Eu92-1	[X]Emotional behavioural problems

E103z	Paranoid schizophrenia NOS	E2F02	Developmental dyslexia	Eu92z	[X]Mixed disorder of conduct and emotions, unspecified
E104	Acute schizophrenic episode	E2F03	Specific spelling difficulty	Eu930	[X]Separation anxiety disorder of childhood
E106	Residual schizophrenia	E2F1	Dyscalculia	Eu931	[X]Phobic anxiety disorder of childhood
E107	Schizo-affective schizophrenia	E2F2	Other specific learning difficulty	Eu932	[X]Social anxiety disorder of childhood
E10z	Schizophrenia NOS	E2F3	Speech or language developmental disorder	Eu93z	[X]Childhood emotional disorder, unspecified
E11	Affective psychoses	E2F3-2	Speech development disorder	Eu940	[X]Elective mutism
E110	Manic disorder, single episode	E2F3z	Speech or language developmental disorder NOS	Eu940-1	[X]Selective mutism
E1100	Single manic episode, unspecified	E2F4	Coordination disorder (dyspraxia)	Eu941	[X]Reactive attachment disorder of childhood
E110-1	Hypomanic psychoses	E2F4-1	Clumsiness syndrome	Eu942	[X]Disinhibited attachment disorder of childhood
E1104	Single manic episode, severe, with psychosis	E2F4-2	Dyspraxia syndrome	Eu95	[X]Tic disorders
E111	Recurrent manic episodes	E2F5	Mixed development disorder	Eu951	[X]Chronic motor or vocal tic disorder
E11-1	Bipolar psychoses	E2F5-1	Global delay	Eu952	[X]Comb vocal multiple motor tic disorder - de la Tourette
E111z	Recurrent manic episode NOS	E2Fy	Other development delays	Eu953	[X]Involuntary excessive blinking
E112	Single major depressive episode	E2Fz	Developmental disorder NOS	Eu95z	[X]Tic disorder, unspecified
E11-2	Depressive psychoses	E3	Mental retardation	Eu9y0	[X]Nonorganic enuresis
E1120	Single major depressive episode, unspecified	E30	Mild mental retardation, IQ in range 50-70	Eu9y2	[X]Feeding disorder of infancy and childhood
E1121	Single major depressive episode, mild	E310	Moderate mental retardation, IQ in range 35-49	Eu9y3	[X]Pica of infancy and childhood
E112-1	Agitated depression	E311	Severe mental retardation, IQ in range 20-34	Eu9y5	[X]Stuttering [stammering]

E1122	Single major depressive episode, moderate	Eu	[X]Mental and behavioural disorders	Eu9y7	[X]Attention deficit disorder
E112-2	Endogenous depression first episode	Eu0	[X]Organic, including symptomatic, mental disorders	Euz	[X]Mental disorder, not otherwise specified
E1123	Single major depressive episode, severe, without psychosis	Eu00	[X]Dementia in Alzheimer's disease	Euz-1	[X]Mental illness NOS
E1124	Single major depressive episode, severe, with psychosis	Eu000	[X]Dementia in Alzheimer's disease with early onset	Ez	Mental disorders NOS
E112-4	Endogenous depression	Eu001	[X]Dementia in Alzheimer's disease with late onset	F110	Alzheimer's disease
E112z	Single major depressive episode NOS	Eu001-2	[X]Senile dementia,Alzheimer's type	F111	Pick's disease
E113	Recurrent major depressive episode	Eu002	[X]Dementia in Alzheimer's dis, atypical or mixed type	F116	Lewy body disease
E11-3	Manic psychoses	Eu00z	[X]Dementia in Alzheimer's disease, unspecified	F12X	Secondary parkinsonism, unspecified
E1130	Recurrent major depressive episodes, unspecified	Eu00z-1	[X]Alzheimer's dementia unspec	F12z	Parkinson's disease NOS
E113-1	Endogenous depression - recurrent	Eu01	[X]Vascular dementia	F21y2	Binswanger's disease
E1132	Recurrent major depressive episodes, moderate	Eu011	[X]Multi-infarct dementia	F4817	Photophobia
E1133	Recurrent major depressive episodes, severe, no psychosis	Eu012	[X]Subcortical vascular dementia	F4Jy-2	Convergence disorders
E1134	Recurrent major depressive episodes, severe, with psychosis	Eu013	[X]Mixed cortical and subcortical vascular dementia	Fyu30	[X]Other Alzheimer's disease
E1137	Recurrent depression	Eu01y	[X]Other vascular dementia	G655	Transient global amnesia
E114	Bipolar affective disorder, currently manic	Eu01z	[X]Vascular dementia, unspecified	R0013	[D]Hallucinations, tactile
E1140	Bipolar affective disorder, currently manic, unspecified	Eu02	[X]Dementia in other diseases classified elsewhere	R0090	[D]Toxic confusional state

E1144	Bipolar affect disord, currently manic,severe with psychosis	Eu022	[X]Dementia in Huntington's disease	R009-1	[D] Senile confusion
E115	Bipolar affective disorder, currently depressed	Eu023	[X]Dementia in Parkinson's disease	R00z0	[D]Amnesia (retrograde)
E1150	Bipolar affective disorder, currently depressed, unspecified	Eu025	[X]Lewy body dementia	R00zX	[D]Disorientation, unspecified
E1154	Bipolar affect disord, now depressed, severe with psychosis	Eu02y	[X]Dementia in other specified diseases classif elsewhere	R0463	[D]Dyslexia
E1156	Bipolar affective disorder, now depressed, in full remission	Eu02z	[X] Unspecified dementia	R2y2-2	[D]Nervous tension
E116	Mixed bipolar affective disorder	Eu02z-4	[X] Senile dementia NOS	Ryu5	[X]Symptoms/signs inv cognit, percept, emotion state & behav
E1160	Mixed bipolar affective disorder, unspecified	Eu02z-5	[X] Senile psychosis NOS	Ryu55	[X]Other symptoms and signs involving emotional state
E116z	Mixed bipolar affective disorder, NOS	Eu041	[X]Delirium superimposed on dementia	TK	Suicide and selfinflicted injury
E117	Unspecified bipolar affective disorder	Eu04y	[X]Other delirium	TK0	Suicide + selfinflicted poisoning by solid/liquid substances
E1170	Unspecified bipolar affective disorder, unspecified	Eu04z	[X]Delirium, unspecified	TK00	Suicide + selfinflicted poisoning by analgesic/antipyretic
E1176	Unspecified bipolar affective disorder, in full remission	Eu05	[X]Oth mental disorder brain damag/dysfunction/physical disr	TK02	Suicide + selfinflicted poisoning by oth sedatives/hypnotics
E118	Seasonal affective disorder	Eu050	[X]Organic hallucinosis	TK03	Suicide + selfinflicted poisoning tranquilliser/psychotropic
E11y	Other and unspecified manic-depressive psychoses	Eu052	[X]Organic delusional [schizophrenia-like] disorder	TK04	Suicide + selfinflicted poisoning by other drugs/medicines
E11y0	Unspecified manic-depressive psychoses	Eu053	[X]Organic mood [affective] disorders	TK05	Suicide + selfinflicted poisoning by drug or medicine NOS
E11y1	Atypical manic disorder	Eu054	[X]Organic anxiety disorder	TK20	Suicide + selfinflicted poisoning by motor veh exhaust gas
E11y3	Other mixed manic-depressive psychoses	Eu055	[X]Organic dissociative disorder	TK21	Suicide and selfinflicted poisoning by other carbon monoxide

E11yz	Other and unspecified manic-depressive psychoses NOS	Eu057	[X]Mild cognitive disorder	TK3	Suicide + selfinflicted injury by hang/strangulate/suffocate
E11z1	Rebound mood swings	Eu05z	[X]Unspec mental disorder brain damag/dysfunction/physcal dr	TK-3	Poisoning - self-inflicted
E11z2	Masked depression	Eu06	[X]Personality and behav disorder brain dis dam and dysfunct	TK30	Suicide and selfinflicted injury by hanging
E11zz	Other affective psychosis NOS	Eu060	[X]Organic personality disorder	TK3y	Suicide + selfinflicted inj oth mean hang/strangle/suffocate
E12	Paranoid states	Eu061	[X]Postencephalitic syndrome	TK3z	Suicide + selfinflicted inj by hang/strangle/suffocate NOS
E120	Simple paranoid state	Eu062	[X]Postconcussional syndrome	TK-4	Suicide and self harm
E121	Chronic paranoid psychosis	Eu0z-1	[X]Organic psychosis NOS	TK5	Suicide and selfinflicted injury by firearms and explosives
E122	Paraphrenia	Eu1	[X]Mental and behavioural disorders due to psychoactive subs	TK-5	Attempted suicide
E12y	Other paranoid states	Eu10	[X]Mental and behavioural disorders due to use of alcohol	TK60	Suicide and selfinflicted injury by cutting
E12yz	Other paranoid states NOS	Eu100-1	[X]Acute alcoholic drunkenness	TK601	Self inflicted lacerations to wrist
E12z	Paranoid psychosis NOS	Eu101	[X]Mental and behav dis due to use of alcohol: harmful use	TK61	Suicide and selfinflicted injury by stabbing
E13	Other non organic psychoses	Eu102	[X]Mental and behav dis due to use alcohol: dependence syndr	TK6z	Suicide and selfinflicted injury by cutting and stabbing NOS
E130	Reactive depressive psychosis	Eu102-1	[X]Alcohol addiction	TK7	Suicide and selfinflicted injury by jumping from high place
E130-1	Psychotic reactive depression	Eu103	[X]Mental and behav dis due to use alcohol: withdrawal state	TK-7	Para-suicide
E133	Acute paranoid reaction	Eu104-1	[X]Delirium tremens, alcohol induced	TK7z	Suicide+selfinflicted injury-jump from high place NOS
E135	Agitated depression	Eu105-1	[X]Alcoholic hallucinosis	TKx1	Suicide and selfinflicted injury by burns or fire
E13z	Nonorganic psychosis NOS	Eu105-4	[X]Alcoholic psychosis NOS	TKz	Suicide and selfinflicted injury NOS

E13z-1	Psychotic episode NOS	Eu107-1	[X]Alcoholic dementia NOS	U2	[X]Intentional self-harm
E140-2	Autism	Eu108	[X]Alcohol withdrawal-induced seizure	U20	[X]Intentional self poisoning/exposure to noxious substances
E140-3	Childhood autism	Eu11	[X]Mental and behavioural disorders due to use of opioids	U200-1	[X]Overdose - paracetamol
E140z	Infantile autism NOS	Eu112	[X]Mental and behav dis due to use opioids: dependence syndr	U200z	[X]Intent self poison nonopioid analgesic unspecif place
E1y	Other specified non-organic psychoses	Eu112-1	[X]Drug addiction - opioids	U2020	[X]Int self poison/exposure to sedative hypnotic at home
E1z	Non-organic psychosis NOS	Eu112-2	[X]Heroin addiction	U2040	[X]Int self poison/exposure to psychotropic drug at home
E2	Neurotic, personality and other nonpsychotic disorders	Eu113	[X]Mental and behav dis due to use opioids: withdrawal state	U204-1	[X]Overdose - antidepressant
E20	Neurotic disorders	Eu11z	[X]Ment & behav dis due use opioids: unsp ment & behav dis	U2050	[X]Int self poison/exposure to narcotic drug at home
E200	Anxiety states	Eu12	[X]Mental and behavioural disorders due to use cannabinoids	U208	[X]Int self poison/exposure to other/unspec drug/medicament
E2000	Anxiety state unspecified	Eu122	[X]Mental and behav dis due to cannabinoids: dependence synd	U2084	[X]Intent self pois oth/unsp drug/medic in street/highway
E2001	Panic disorder	Eu122-1	[X]Drug addiction - cannabis	U209	[X]Intent self poison/exposure to alcohol
E2001-1	Panic attack	Eu12y	[X]Men/behav dis due to use cannabinoids: oth men/behav disd	U20A	[X]Intentional self poison organ solvent,halogen hydrocarb
E2002	Generalised anxiety disorder	Eu132	[X]Mental and behav dis due to seds/hypntcs: dependence synd	U20B0	[X]Int self poison/exposure to other gas/vapour at home
E2003	Anxiety with depression	Eu132-1	[X]Drug addiction- sedative / hypnotics	U20yy	[X]Int self poison unspecif chemical other spec place
E2004	Chronic anxiety	Eu142-1	[X]Drug addiction - cocaine	U2-1	[X]Self inflicted injury
E2005	Recurrent anxiety	Eu180	[X]Mental & behav dis due vol solvents: acute intoxication	U210	[X]Intent self harm by hanging strangulat/suffocat occ home
E200z	Anxiety state NOS	Eu182-1	[X]Drug addiction - solvent	U21y	[X]Intent self harm by hangng strangul/suffoct oth spec plce

E2019	Multiple personality	Eu19	[X]Men & behav disorder multiple drug use/psychoactive subst	U2-2	[X]Injury - self-inflicted
E201A	Dissociative reaction unspecified	Eu192-1	[X]Drug addiction NOS	U2-3	[X]Suicide
E202	Phobic disorders	Eu20	[X]Schizophrenia	U2-4	[X]Attempted suicide
E2020	Phobia unspecified	Eu200	[X]Paranoid schizophrenia	U2-5	[X]Para-suicide
E2021	Agoraphobia with panic attacks	Eu200-1	[X]Paraphrenic schizophrenia	U27	[X]Intentional self harm by smoke, fire and flames
E202-1	Social phobic disorders	Eu202-1	[X]Catatonic stupor	U272	[X]Intent self harm by smoke fire/flame sch/ins/pub adm area
E2022	Agoraphobia without mention of panic attacks	Eu20y-3	[X]Schizophrenifrm psychos NOS	U28	[X]Intentional self harm by steam hot vapours / hot objects
E202-2	Phobic anxiety	Eu20z	[X]Schizophrenia, unspecified	U280	[X]Intent self harm by steam hot vapour/hot obj occ at home
E2023	Social phobia, fear of eating in public	Eu21	[X]Schizotypal disorder	U29	[X]Intentional self harm by sharp object
E2024	Social phobia, fear of public speaking	Eu22	[X]Persistent delusional disorders	U290	[X]Intentional self harm by sharp object occurrence at home
E2026	Acrophobia	Eu220	[X]Delusional disorder	U291	[X]Intent self harm by sharp object occ resident instit'n
E2027	Animal phobia	Eu220-1	[X]Paranoid psychosis	U29z	[X]Intentional self harm by sharp object occ unspecif place
E2028	Claustrophobia	Eu220-2	[X]Paranoid state	U2A	[X]Intentional self harm by blunt object
E2029	Fear of crowds	Eu220-5	[X]Paranoia	U2B	[X]Intentional self harm by jumping from a high place
E202A	Fear of flying	Eu221-1	[X]Capgras syndrome	U2D	[X]Intentional self harm by crashing of motor vehicle
E202B	Cancer phobia	Eu223	[X]Paranoid state in remission	U2E	[X]Self mutilation
E202C	Dental phobia	Eu22z	[X]Persistent delusional disorder, unspecified	U2y	[X]Intentional self harm by other specified means
E202D	Fear of death	Eu23	[X]Acute and transient psychotic disorders	U2y0	[X]Intentionl self harm by oth specif means occurrn at home

E202E	Fear of pregnancy	Eu230	[X]Acute polymorphic psychot disord without symp of schizoph	U2y2	[X]Intent self harm oth specif mean occ sch/ins/pub adm area
E202z	Phobic disorder NOS	Eu231	[X]Acute polymorphic psychot disord with symp of schizophren	U2y4	[X]Intent self harm by oth specif means occ street/highway
E202z-1	Weight fixation	Eu233	[X]Other acute predominantly delusional psychotic disorders	U2yy	[X]Intent self harm oth specif means occ oth specif place
E203	Obsessive-compulsive disorders	Eu23y	[X]Other acute and transient psychotic disorders	U2yz	[X]Intent self harm by oth specif means occ unspecif place
E2030	Compulsive neurosis	Eu23z	[X]Acute and transient psychotic disorder, unspecified	U2z	[X]Intentional self harm by unspecified means
E2031	Obsessional neurosis	Eu23z-1	[X]Brief reactive psychosis NOS	U2z0	[X]Intentional self harm by unspecif means occurrn at home
E203z	Obsessive-compulsive disorder NOS	Eu25	[X]Schizoaffective disorders	U2z7	[X]Intentional self harm by unspecif means occurrn on farm
E204	Neurotic depression reactive type	Eu251	[X]Schizoaffective disorder, depressive type	U2zz	[X]Intent self harm by unspecif means occ at unspecif place
E204-1	Postnatal depression	Eu25z	[X]Schizoaffective disorder, unspecified	ZV070	[V]Isolation
E205	Neurasthenia - nervous debility	Eu26	[X]Nonorganic psychosis in remission	ZV11y	[V]Personal history of other specified mental disorder
E205-1	Nervous exhaustion	Eu2y	[X]Other nonorganic psychotic disorders	ZV1B2	[V]Personal history of self-harm
E206	Depersonalisation syndrome	Eu2z	[X]Unspecified nonorganic psychosis	ZV40	[V]Mental and behavioural problems
E20z	Neurotic disorder NOS	Eu2z-1	[X]Psychosis NOS	ZV400	[V]Problems with learning
E20z-1	Nervous breakdown	Eu3	[X]Mood - affective disorders	ZV40-1	[V]Behavioural problems
E21	Personality disorders	Eu30	[X]Manic episode	ZV40-2	[V]Mental problems
E210	Paranoid personality disorder	Eu300	[X]Hypomania	ZV403	[V]Other behavioural problems
E2111	Hypomanic personality disorder	Eu301	[X]Mania without psychotic symptoms	ZV40-3	[V]Psychological problems
E2112	Depressive personality disorder	Eu30-1	[X]Bipolar disorder, single manic episode	ZV40z	[V]Unspecified mental or behavioural problem

E2113	Cyclothymic personality disorder	Eu302	[X]Mania with psychotic symptoms	ZV57D	[V]Psychotherapy, not elsewhere classified
E211z	Affective personality disorder NOS	Eu30z	[X]Manic episode, unspecified	ZV62	[V]Other psychosocial circumstances
E212	Schizoid personality disorder	Eu30z-1	[X]Mania NOS	ZV624	[V]Social maladjustment
E2120	Unspecified schizoid personality disorder	Eu31	[X]Bipolar affective disorder	ZV62A	[V] Gender dysphoria
E212z	Schizoid personality disorder NOS	Eu310	[X]Bipolar affective disorder, current episode hypomanic	ZV69	[V]Psychiatric paitient admission details
E213-1	Aggressive personality				

APPENDIX 7.8. VULNERABILITY: READ CODES INDICATING HISTORY OF CHILDHOOD, DOMESTIC OR SEXUAL ABUSE RECORDED IN PRIMARY CARE DATABASE.

(The process of deriving this code list is given in Chapter 7.4.5).

Appendix 7.8: 145 Read codes related to vulnerability recorded in primary care database					
1338	Fostered	14K1	Intentional overdose of prescription only medication	67Ia	Advice about domestic violence
1463	H/O: drug dependency	14X	History of abuse	8B23	Drug addiction therapy
1468	H/O: psychological trauma	14X0	History of physical abuse	8B23-3	Drug dependence therapy
133P	Vulnerable adult	14X1	History of sexual abuse	8B2N	Drug addiction detoxification therapy - methadone
13c	Drug user	14X2	History of emotional abuse	8B2P	Drug addiction maintenance therapy - methadone
13c0	Injecting drug user	14X3	History of domestic violence	8B2Q	Drug addiction maintenance therapy - buprenorphine
13c1	Intravenous drug user	14X5	Victim of physical abuse	8B2R	Drug addiction detoxification therapy - buprenorphine
13cH	Persistent substance misuse	14X6	Victim of sexual abuse	8CM5	Child in need plan
13cM	Substance misuse	14X8	Victim of domestic violence	8CMB	Vulnerable adult care plan
13D1	Homeless family	14XD	History of domestic abuse	8CMH	Looked after child health action plan completed
13D-1	Homeless	14XG	Victim of domestic abuse	8GE7	Foster care

13D2	Homeless single person	14XH	Victim of child sexual exploitation	9F2	Child at risk-case conference
13D4	Illegal migrant	1J1	Suspected drug abuse	9F2Z	Child at risk case conf NOS
13DZ	Housing lack NOS	1J3	Suspected child abuse	9N0Z	Seen in drug rehabilitation centre
13E	Inadequate housing	1J30	Suspected sexual abuse of child	TK601-1	Slashed wrists self inflicted
13EH	Housing problems	1J31	Suspected non-accidental injury to child	TL	Homicide and injury purposely inflicted by other persons
13FL	Living rough	1T	History of substance misuse	TL0	Homicide and assault by fight, brawl and rape
13HA	Battered wife - history	1T0	H/O heroin misuse	TL01	Homicide or assault by rape
13HD	Violent spouse	1T00	H/O daily heroin misuse	TL01-1	Sexual assault
13Id	On child protection register	1T01	H/O weekly heroin misuse	U200	[X]Intent self poison/exposure to nonopioid analgesic
13IF	Child at risk	1T02	Previous history of heroin misuse	U2000	[X]Int self poison/exposure to nonopioid analgesic at home
13If	Child is cause for concern	1T13	Previous history of methadone misuse	U201	[X]Intent self poison/exposure to antiepileptic
13IF-1	Vulnerable child	1T22	H/O infrequent ecstasy misuse	U202	[X]Intent self poison/exposure to sedative hypnotic
13Ig	Family member on child protection register	1T3	H/O benzodiazepine misuse	U202-1	[X]Overdose - sleeping tabs

13Ii	Subject to care order under Children Act 1989	1T4	H/O amphetamine misuse	U202-2	[X]Overdose - diazepam
13Ii0	Subject to care order under section 20 of Children Act 1989	1T43	Previous history of amphetamine misuse	U202-3	[X]Overdose - temazepam
13Ii3	Subject to care order under section 31 of Children Act 1989	1T5	H/O cocaine misuse	U202-5	[X]Overdose - nitrazepam
13Ij	Subject to interim care order under Children Act 1989	1T51	H/O weekly cocaine misuse	U202-6	[X]Overdose - benzodiazepine
13Ij0	Sub to interim care order under section 38 Children Act 1989	1T53	Previous history of cocaine misuse	U204	[X]Intent self poison/exposure to psychotropic drug
13Iv	Subject to child protection plan	1T6	H/O crack cocaine misuse	U204-2	[X]Overdose - amitriptyline
13IV	Looked after child - Children (Scotland) Act 1995	1T60	H/O daily crack cocaine misuse	U204-3	[X]Overdose - SSRI
13Iw	No longer subject to child protection plan	1T62	H/O infrequent crack cocaine misuse	U205	[X]Intent self poison/exposure to narcotic drug
13VF	At risk violence in the home	1T8	H/O cannabis misuse	U205-1	[X]Overdose - heroin
13VX	At risk of sexual exploitation	1T80	H/O daily cannabis misuse	U2080	[X]Int self poison/exposure to oth/unsp drug/medicam home
13W40	Child/parent violence	1T82	H/O infrequent cannabis misuse	U20A0	[X]Intent self pois organ solvent,halogen hydrocarb, home

13Wd	Domestic abuse victim in household	1T83	Previous history of cannabis misuse	U20B-1	[X]Self carbon monoxide poisoning
13WT	Child protection observation	1T9	H/O solvent misuse	U21	[X]Intent self harm by hanging strangulation / suffocation
13WT1	Child protection category emotional	1TD	H/O opiate misuse	U720	[X]Sequelae of intentional self-harm
13WT2	Child protection category physical	1TD3	Previous history of opiate misuse	U721	[X]Sequelae of assault
13WT4	Child protection category neglect	1TE	Uses heroin on top of substitution therapy	ZV114	[V]Personal history of psychoactive substance abuse
13WX	Child is cause for safeguarding concern	1V	Drug misuse behaviour	ZV4F9	[V]Probs rel alleg sex abuse child by pers out prim sup grp
13Za	Victim of bullying when not in school	1V64	Illicit drug use	ZV4G4	[V]Problem relatd/alleg sex abuse cld by person prim sup grp
13ZB	Refugee	1V65	Heroin misuse	ZV4G5	[V]Problems related to alleged physical abuse of child
13Zd	Failed asylum seeker	1V66	Ecstasy misuse	ZV4G7	[V] Bullying of child
13ZF	Bullied at school	38C0	Child in care health assessment	ZV4H3	[V]Emotional neglect of child
13ZN	Asylum seeker	38C00	Looked after child initial health assessment	ZV4J8	[V]Victim of torture

146F	H/O: drug abuse	38C01	Looked after child health assessment 6-month review	ZV612	[V]Child abuse
14K0	H/O: repeated overdose	38C02	Looked after child health assessment annual review	ZV612-2	[V]Child neglect

Appendices for Chapter 10

APPENDIX 10.1 CONSULTATION FREQUENCY OVER FIVE YEARS

Appendix 10.1. Resource utilisation in five years of study period – consultations						
Mean number of consultations for all patients / (No. of patients in group)						**5-year mean**
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	
GP-diagnosed MUS patients (667)	12	11	10	11	12	11
EHR-defined MUS patients (2,044)	22	15	14	13	13	15
Difference	**78%**	**37%**	**31%**	**18%**	**9%**	**35%**
Mean no. of consultations in each Index year based on patient sub-group						
Patient sub-group Index year / (No. of patients in sub-group)	*Mean number of consultations per patient per year*					
Index year 2007 patients						
GP-diagnosed MUS patients (168)	12	11	11	11	12	
EHR-defined MUS patients (593)	21	15	14	14	14	
Index year 2008 patients						
GP-diagnosed MUS patients (158)	12	12	11	12	14	
EHR-defined MUS patients (557)	22	15	12	11	11	
Index year 2009 patients						
GP-diagnosed MUS patients (161)	13	11	10	11	11	
EHR-defined MUS patients (471)	23	15	15	14	14	
Index year 2010 patients						
GP-diagnosed MUS patients (180)	11	9	9	10	11	
EHR-defined MUS patients (423)	21	14	13	14	13	

APPENDIX 10.2- INVESTIGATIONS AND REFERRALS OVER FIVE YEARS

Appendix 10.2. Resource utilisation in five years of study period – investigations and referrals						
Percentage of patients who had Investigations or referrals - for all patients / (No. of patients in group)						**No referrals / investigations for 5 years**
Investigations	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	
GP-diagnosed MUS patients (667)	42%	36%	38%	37%	42%	17%
EHR-defined MUS patients (2,044)	65%	43%	42%	43%	44%	10%
Referrals						
GP-diagnosed MUS patients (667)	39%	36%	29%	30%	32%	21%
EHR-defined MUS patients (2,044)	61%	41%	37%	37%	35%	12%
Investigations for each Index-year based patient sub-group						
Patient sub-group Index year / (No. of patients in sub-group)	*Percentage of patients who had Investigations each year*					*For 5 years no Investigations*
Index year 2007 patients						
GP-diagnosed MUS patients (168)	42%	38%	40%	39%	41%	16%
EHR-defined MUS patients (593)	60%	40%	43%	40%	44%	12%
Index year 2008 patients						
GP-diagnosed MUS patients (158)	37%	40%	32%	30%	39%	20%
EHR-defined MUS patients (557)	66%	42%	37%	38%	36%	12%
Index year 2009 patients						
GP-diagnosed MUS patients (161)	47%	35%	39%	42%	47%	14%
EHR-defined MUS patients (471)	67%	46%	45%	47%	50%	7%
Index year 2010 patients						
GP-diagnosed MUS patients (180)	42%	32%	42%	37%	42%	18%
EHR-defined MUS patients (423)	65%	42%	41%	49%	47%	9%
Referrals for each Index-year based patient sub-group						
Patient group Index year / (No. of patients in sub-group)	*Percentage of patients who had Investigations each year*					*For 5 years no referrals*
Index year 2007 patients						
GP-diagnosed MUS patients (168)	35%	33%	33%	35%	37%	23%
EHR-defined MUS patients (593)	58%	42%	44%	42%	38%	10%
Index year 2008 patients						
GP-diagnosed MUS patients (158)	34%	40%	32%	30%	33%	15%
EHR-defined MUS patients (557)	58%	40%	33%	30%	31%	14%
Index year 2009 patients						
GP-diagnosed MUS patients (161)	44%	38%	29%	29%	21%	26%
EHR-defined MUS patients (471)	63%	41%	38%	39%	34%	11%
Index year 2010 patients						
GP-diagnosed MUS patients (180)	44%	34%	26%	26%	39%	22%
EHR-defined MUS patients (423)	65%	40%	35%	36%	35%	12%

Appendices for Chapter 11

APPENDIX 11.1 COST OF ILLNESS STUDY – QUALITY ASSESSMENT CHECKLIST

Cost of illness study – quality assessment checklist
1. Study objective reported
2. Disease and diagnostic criteria (ICD/DSM etc) reported
3.Characteristics of disease group reported (sample size, age, gender)
4. Perspective of analysis reported
5. Sources (epidemiological data, healthcare use and unit costs) reported
6. Currency and reference year reported
7. Costing methods reported in detail
8. Units of reported measures stated (e.g. mean annual / total costs)
9. Results discussed in relation to other studies if available
10. Limitations discussed
11. Discounting done where relevant and discount rate reported
12. Missing data proportion reported and imputation method described if applied
13. Sensitivity analysis carried out
14. Uncertainty estimates (SD / uncertainty estimates)
15. Conclusions allowing for uncertainty inherent in the results

Appendices for Chapter 12

APPENDIX 12.1. PSSRU DATA ON UNIT COSTS OF HEALTHCARE

PSSRU data on unit costs of healthcare(GBP)

GP	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Per surgery consultation of 11.7 minutes	34	31	31	32	30	36	37	38
Per clinic consultation of 17.2 minutes	50	46	45	47	44	53	55	56
Per telephone consultation 7.1 minutes	21	19	19	19	18	22	23	23
Home visit (lasting 23.4 minutes)	55	50	103	106	99	92	95	98
Mean cost of GP consultation (surgery, clinic, telephone)	**35**	**32**	**32**	**33**	**31**	**37**	**38**	**39**
Nurse practitioner / Associate practitioner	8	9	10	14	14	14	14	14
Specialist Nurse practitioner	12	13	14	14	23	22	22	22
Mean cost for non-GP practitioners	**10**	**11**	**12**	**14**	**19**	**18**	**18**	**18**
Prescription costs per consultation	**44**	**45**	**44**	**43**	**43**	**46**	**45**	**44**
Cost per patient contact in primary care								
Community nurse (per hour with patient contact)	55	60	63	64	64	62	60	57
Mental health nurse (per hour of patient contact)	41	44	46	48	65	67	65	47
Health visitor (per hour of client contact /patient related work)	32	83	86	88	53	62	51	65
Community nurse specialist (per hour of patient related work)	66	73	75	77	44	43	42	64
Clinical support worker - community (per hour spent with patient)	21	23	23	23	24	24	25	20
GP practice nurse (per consultation)	8	9	10	14	14	14	14	14
Clinical nurse specialist (per hour of client contact)	52	54	55	57	82	81	80	80
Clinical nurse specialist (per consultation)	12	13	14	14	23	22	22	22
Community mental health team (per hour per team member)	72	70	72	70	39	38	36	37
Hospital physiotherapist (per hour of client contact)	33	36	37	35	32	32	32	33

Hospital occupational therapist (per hour of client contact)	36	38	40	38	32	32	32	33
Hospital speech and language therapist (per hour of client contact)	36	38	40	37	31	31	32	33
Dietitian (per hour of client contact)	28	30	31	29	31	31	31	33
Community physiotherapist (per hour of client contact)	35	38	39	37	31	31	30	32
Community occupational therapist (per hour of client contact)	36	38	40	38	31	31	30	32
Community speech & language therapist	35	38	39	37	31	31	30	30
Community chiropodist / podiatrist (per hour)	18	23	23	22	31	31	30	30
Clinical psychologist (per hour of client contact)	67	72	77	81	135	135	134	134
Counseling services (per surgery consultation)	61	64	67	71	60	60	63	50
Palliative care service	119	123	127	131	136	185	189	168
Secondary care	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
A&E	98	111	110	114	127	129	133	137
Day service / outpatient attendance (non-consultant-led)	137	140	164	152	147	139	135	139
In patient - per finished consultant episode	1,971	1917	1,972	2,055	2,186	2357	2,536	2873
Day cases (HRG data)	600	619	638	637	686	680	697	701
Mental health services								
Intensive care	500	532	560	585	630	654	674	694
In patient care	259	272	289	299	319	338	430	497
Outpatient attendance	131	130	126	136	143	146	100	123
Community follow up	118	111	125	117	132	135	153	139
Outpatient - Drugs and alcohol services - adult	107	101	101	87	157	94	104	113
Community drug and alcohol services - adult	100	109	106	117	132	131	135	139
Weighted average of all community based follow-up attendances	118	111	111	117	132	135	125	113
Admission to alcohol detox centre (per day)	213	219	231	142	147	150	152	152
Dentist (per hour of patient contact)								82