Investigating comorbid mood disorders in people with inflammatory rheumatological conditions: a mixed methods study

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Tables

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List of Abbreviations

ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
AIMS	Arthritis Impact Measurement Scale
AS	Ankylosing Spondylitis
BAI	Beck's Anxiety Inventory
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BDI	Beck's Depression Inventory
BMI	Body Mass Index
BNF	British National Formulary
BSR	British Society of Rheumatology
CBT	Cognitive Behavioural Therapy
CC	Collaborative Care
CCM	Chronic Care Model
CG	Clinical Guideline
CHD	Coronary Heart Disease
CiPCA	Consultations in Primary Care Archive
CMD	Common Mental Disorders
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CRN	Clinical Research Network
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DAS28	Disease Activity Score in 28 Joints
DIP	Distal Interphalangeal
DM	Diabetes Mellitus
DMARD	Disease Modifying Anti-Rheumatic Drug
EQ-5D-5L	EuroQol 5-Dimension Scale
EULAR	European League Against Rheumatism
ESR	Erythrocyte Sedimentation Rate
FACIT	Functional Assessment of Chronic Illness Therapy

GAD	Generalised Anxiety Disorder
GCA	Giant Cell Arteritis
GHQ	General Health Questionnaire
GP	General Practitioner
GRADE	Modified Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Anxiety Rating Scale
HAQ	Health Assessment Questionnaire
HF	Heart Failure
HLA	Human Leucocyte Antigen
HRQoL	Health-Related Quality of Life
HTN	Hypertension
IAPT	Improving Access to Psychological Therapies
IHD	Ischaemic Heart Disease
IL	Interleukin
IMD	Index of Multiple Deprivation
IRC	Inflammatory Rheumatological Condition
LAI	Lansbury's Activity Index
LSI	Life Satisfaction Index
LTC	Long-term Condition
MCS	Mental Component Summary
MDT	Multidisciplinary Team
MHAQ	Modified Health Assessment Questionnaire
MRI	Magnetic Resonance Imaging
NHP	Nottingham Health Profile
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NOS	Newcastle Ottawa Scale
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

OA	Osteoarthritis
PCS	Physical Component Summary
PHQ	Patient Health Questionnaire
PIER	Patient Information and Educational Resources
PIS	Patient Information Sheet
PMR	Polymyalgia Rheumatica
PN	Practice Nurse
PPIE	Patient and Public Involvement and Engagement
PsA	Psoriatic Arthritis
PtGA	Patient Global Assessment of Health
PVD	Peripheral Vascular Disease
NSAID	Non-Steroidal Anti-Inflammatory Drugs
QOF	Quality and Outcomes Framework
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomised Control Trial
RCGP	Royal College of General Practitioners
RF	Rheumatoid Factor
RUG	Research User Group
SC-90-R	Symptom Checklist-90-Revised
SFB	Scientific Foundation Board
SF-36	Short-Form 36
SJC	Swollen Joint Count
SMI	Self-Management Intervention
SPCR	School for Primary Care Research
STAI	Speilberger State and Trait Anxiety Inventory
TJC	Tender Joint Count
TNF	Tumour necrosis factor
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale (**+/- GH** (global health))
WHOQoL-BREF	World Health Organisation Quality of Life-BREF

Statistical Terminology

r	Pearson's correlation coefficient
b	Multiple regression coefficient
CI	Confidence interval
HR	Hazard ratio
IR	Incidence rate
IRR	Incidence rate ratio
IQR	Interquartile range
OR	Odds ratio
PH	Proportional hazards
SD	Standard deviation
n.s.	Non-significant
P	p value
χ^2	Chi-squared

Abstract

Background

Mood problems in people with rheumatoid arthritis (RA) are under-recognised and treated, contributing to increased mortality. Comorbid depression is associated with increased disease activity and reduced quality of life (QoL), though the impact of anxiety is unclear. Understanding patients' preferences regarding case-finding for mood problems and determining the impact of anxiety in RA, could support the development of an intervention to improve the management of comorbid mood problems. There is a lack of literature reporting the prevalence of mood problems in other inflammatory rheumatological conditions (IRCs).

Methods

Using mixed methods, I have conducted a qualitative study, to explore RA patients' perspectives of comorbid mood problems and a systematic review, to determine the impact of anxiety in RA. Through a cohort study, using Read codes from primary care data, I have established the incidence and prevalence of mood problems in different IRCs. I have also analysed patients' responses to case-finding questions for mood problems within questionnaires, to determine the proportion with IRCs who self-report mood symptoms.

Results

People with RA feel able to disclose mood symptoms within a nurse-led review. Anxiety is associated with worse QoL and increased disease activity in RA. Self-reported symptoms of mood problems are common in different IRCs, though they are less

frequently recorded in primary care records, suggesting potential under-recognition of mood problems in people with IRCs.

Conclusions

Comorbid mood problems in people with IRCs are common, yet under-recognised, and can negatively impact on outcomes, supporting the requirement for case-finding within a nurse-led review.

Declarations

I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where stated otherwise by reference or acknowledgment, the work presented is entirely my own.

Acknowledgements

The work presented in this thesis would not have been possible without the support of a multitude of patients, clinicians, researchers and ultimately my family! Firstly, I would like to thank the National Institute for Health Research for providing my funding for an Academic Clinical Fellowship post whilst working as a General Practice (GP) Registrar between 2015-2017. Furthermore, I would like to extend my gratitude to the School of Primary Care Research, who awarded me a GP Progression Fellowship, providing 18 months part-time funding between August 2017 and January 2019, in addition to the Haywood Foundation, who provided a further 6 months part-time funding between February 2019 and July 2019, enabling me to complete my PhD.

In addition, I would like to thank the Scientific Foundation Board (SFB) of the Royal College of General Practitioners (RCGP), who have awarded me two separate practitioner grants, each of approximately £1000. These grants have supported patient and public involvement and engagement (PPIE) in all of my studies, whilst also funding interview transcription costs.

PPIE has been integral throughout my PhD, hence I would like to extend my gratitude to all the members of the public who gave their time to contribute to my research, by advising on the focus of my studies, helping to develop patient-facing documents, providing alternative perspectives on my analysis and advising on dissemination. In particular, I would like to thank June Brammar, who facilitated patient collaboration in the development of an information leaflet, to help share my research outcomes with patients and the public. I am particularly grateful to the Keele Research User Group (RUG), Haywood User Group and Stoke National Rheumatoid Arthritis

Society, who all provided me with rewarding opportunities to share my work with patients and the public, and to obtain feedback.

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Most of all I would like to extend my gratitude to my supervisors. Professor Carolyn Chew-Graham and Dr Samantha Hider have supported me from the start of my PhD, helping to shape and develop my research ideas throughout this thesis. Their dedication to academia is inspiring and they have encouraged me to aspire to the highest standards. In particular, they have been instrumental in helping me to obtain funding to complete my studies, whilst always providing support and encouragement at conference presentations and celebrating my successes on being awarded research prizes. Furthermore, I am grateful for the help I have received in the final two years of

my PhD from Dr Milica Blagojevic-Bucknall. She has helped to prepare my data for analysis and has provided invaluable advice on the conduct of my cohort study, systematic review meta-analysis and the analysis of questionnaire data within the INCLUDE study.

Finally, this huge amount of work would not have been possible without the endless support of my loving family.

The Author

I had a wonderful childhood growing up in the Staffordshire Moorlands with my Mum, Dad and older brother, Byron. My brother and I were lucky to have loving and supportive parents who helped us to make many happy childhood memories. I often spent time with my Dad, walking, fishing and birdwatching in the Peak District, whilst my Mum encouraged my love of learning. I was always competitive and loved to succeed in school and through a variety of extra-curricular interests I developed, from playing the violin, to drawing and painting. On family holidays to Greece I also grew a passion for classical history, exploring homeric palaces and temples.

I particularly enjoyed playing in the local and county orchestras and was successful in my violin examinations, to an extent that I contemplated applying to music school. However, I was also fascinated by the natural world and biology became one of my favourite subjects. Meanwhile, I enjoyed learning more about ancient history in my spare time and joined a young archeologists' club. Reflecting my diversity of interests, I studied five A-levels; biology, chemistry, maths, classical history and music. It was my fascination with the complexity of the human body and the challenges of diagnostics that led me to study medicine.

I was delighted to be accepted to the local medical school at Keele University. On the basis of my A-level results, I obtained a grant to support my studies, whilst to pay for the running costs of my car, I played my violin at weddings and celebrations during the weekends, which provided a welcome break from studying. A highlight of my training was the chance to join the Buxton Mountain Rescue team on call-outs during my elective period. I also found the opportunity to conduct a research project using

stem cells fascinating. I succeeded in my medical examinations and graduated as overall prize winner in my cohort.

I worked as a junior doctor through various rotations at the local hospital, but missed the academic elements of my training. My favourite placement was in general practice. I found the opportunity to follow-up the progress of patients and their families over time particularly rewarding, and the experience helped me to fully appreciate the value of a holistic approach to care.

At the time I was planning to apply for general practice, I saw an advertisement for an academic general practitioner (GP) training position and knew this would be the perfect challenge I was looking for. My application was successful and soon I was invited into the world of academic general practice. I completed a range of modules in preparation for my research, from statistics and epidemiology to research methods and medical ethics. I found my first conference in Oxford inspiring and enthusiastically embarked on my studies. I enjoyed using some artistic flair in my presentations and was awarded several prizes for oral and poster presentations of my research (appendix 1). I was also proud to have my research accepted for publication (appendix 2 and 3). I gained further insight into the regulations governing research as a co-investigator on a pilot trial, whilst I was also able to share my knowledge and experiences with several medical students who I began to mentor, as a personal development tutor. On completing my training, I was able to overcome several hurdles to securing funding, which enabled me to complete this thesis, alongside my work as a GP.

Over the past 2 years I have embraced the dual challenge of working as a newly qualified GP and academic. Meeting deadlines has led me to sacrifice many evenings and weekends, so on completing my thesis I am looking forward to spending time with

my family and exploring more fascinating parts of ancient Greece. I am immensely proud to work for the National Health Service and am sure I will return to academia, which is integral to the advancement of clinical practice.

CHAPTER 1

Introduction

1.0 INTRODUCTION

1.1 Overview

Within my thesis I have investigated comorbid mood problems in people with inflammatory rheumatological conditions (IRCs). Through four interconnected studies, I have aimed to improve our understanding of the identification, incidence, prevalence and potential impact of mood problems in different IRCs. In the following section, I will discuss my rationale for performing these studies and outline the content of each chapter.

1.2 Rationale for Studies

The relationship between the mind and body has been debated by philosophers for centuries. In 400 BC, the ancient Greek physician Hippocrates developed the concept that the life of the whole patient should be considered as part of any disease process (Kleisiaris, Sfakianakis & Papathanasiou, 2014). Hippocrates advocated treatments to improve both physical and mental health, believing them to be intrinsically connected. Six hundred years later, Galen built on the early theories of Hippocrates, hypothesising that bodily fluids such as *yellow* and *black bile*, *blood* and *phlegm* were linked to different moods, including feeling melancholy, listless, angry or optimistic (Kagan, 1998). Hippocrates and Galen were amongst the earliest physicians to recognise the interactions that occur between biological and psychological factors, which led them to develop a holistic approach to care, taking account of a persons' physical, mental and emotional health.

Over 2,000 years later, the benefits of holistic care are now being rediscovered. However, many of the complex interactions between physical and mental health

problems are still poorly understood and frequently care is fragmented (Kvamme, Olesen & Samuelsson, 2001). Understanding the interactions of long-term physical health problems with common mental disorders, such as anxiety and depression, could support the development of interventions to improve patient outcomes. Therefore, within this thesis I have aimed to improve the understanding of comorbid mood problems in people with long-term physical health problems, specifically, IRCs.

IRCs encompass a range of conditions which can cause joint pain, swelling and stiffness. Rheumatoid arthritis (RA), one of the commonest IRCs, is frequently associated with anxiety and depression (Covic et al., 2012; Matcham et al., 2013). However, these mood problems are often not recognised or treated (Cepoiu et al., 2007), which can lead to increased morbidity and mortality (Ang et al., 2005). Therefore, improved recognition and management of mood problems in RA should be a healthcare priority.

As past research into IRCs and mood problems has focussed on RA and depression, there is a lack of understanding of the impact of anxiety in people with RA. Anxiety frequently exists in isolation from depression (Kaufman & Charney, 2000) and can be managed differently (NICE, 2011; NICE, 2009a). Anxiety can also be associated with altered help-seeking behaviour (Fine et al., 2008). Therefore, it is important that the impact of anxiety is understood, to facilitate appropriate treatment. Meanwhile, the burden of mood problems in other IRCs, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), polymyalgia rheumatica (PMR) and giant cell arteritis (GCA), is poorly understood. Consequently, there is a potential health need which is not being addressed in people living with AS, PsA, PMR and GCA, that needs to be characterised.

In chapter 2, I will discuss our current understanding of mood problems in different IRCs, including their incidence and prevalence, potential interactions with

physical health problems and impact on quality of life (QoL) and disease activity. In addition, I will summarise current recommendations for the identification and management of comorbid mood problems in people with IRCs. As I will outline in chapter 3, my overall aim has been to improve the recognition and management of anxiety and depression in people with different IRCs. In chapter 4 I will discuss my rationale for taking a pragmatic approach, using a mixed methods multiphase design.

Through chapters 5-8, I will discuss the four main studies I have conducted. For each, I will describe my methods, present my results, consider the implications of my findings and reflect on the contributions of patient and public involvement and engagement (PPIE). The four study chapters will comprise of a qualitative study (chapter 5) exploring the perspectives of people with RA on comorbid mood problems, a systematic review (chapter 6), to determine the impact of anxiety on QoL and disease activity in people with RA, and a cohort study (chapter 7) to determine the incidence and prevalence of anxiety and depression in different IRCs. Lastly, in chapter 8, I will discuss INCLUDE (INtegrating and improving Care for patients with infLammatory rheUmatological DisordErs in the community), a pilot feasibility trial, for which I am a co-investigator. Within my thesis, I will present my analysis of baseline questionnaire data collected as part of the INCLUDE study, with a focus on comorbid mood problems in people with IRCs.

In chapter 9 I will review the overall findings of my PhD, drawing comparisons between the results of different studies in the context of the existing background literature. After concluding my investigation of comorbid mood problems in people with IRCs, I will consider the wider implications of my results for patients and practitioners, and will make recommendations for future research.

I will also reflect on my own personal journey, a process that has highlighted to me the many challenges and rewards of being an academic general practitioner (GP). Completing a PhD has opened my understanding to the world of academia and strengthened my resolve to be the best possible GP, who acknowledges the whole person and keeps alive the founding principles of medicine, established by the great physicians of ancient Greece.

CHAPTER 2
Background

2.0 BACKGROUND

2.1 The National Health Service

The National Health Service (NHS) was founded in 1948 on the ideal that good healthcare should be available to all. Remaining free at the point of delivery, the NHS delivers care for more than 64 million people in the United Kingdom (UK), treating over 1 million patients every 36 hours (NHS Confederation, 2017).

Health care services can be defined as primary, secondary or tertiary. Primary care services are often the first point of contact in the healthcare system and include general practice, community pharmacy, optometry and dental services. Primary care professionals focus on preventing illness, whilst also diagnosing and managing a broad range of physical and mental health problems. Patients may be referred by a primary care professional, such as a general practitioner (GP), to secondary care for review by a specialist, with expertise in a particular health problem. Secondary care delivers planned and emergency care and is often hospital based, though some clinics are based within the community. Tertiary care is provided in specialist regional centres, where there may be access to more specialised equipment or expertise, for the investigation and management of particular health problems.

Following the 70th anniversary of the NHS, the NHS Long Term Plan was published (NHS, 2019). This plan has outlined changes to support staff, relieve workforce pressures, enhance the quality of care provided, prevent illnesses, upgrade technology, improve sustainability and join together care for patients. The long-term plan aims to create more integrated teams of GPs, community health and social care staff. Primary Care Networks, which were announced as part of the 2019 GP contract,

serve communities of 30,000 to 50,000 people. Since the 1st July 2019, these networks have been funded to employ a clinical pharmacist and social prescribing link worker, who can take a holistic approach to peoples' health and wellbeing and connect them to community groups and services for practical and emotional support (NHS England, 2019a) Over the next few years, further funding will be provided to employ physiotherapists, physician associates and paramedics.

Within the 2019 GP contract, changes to the Quality and Outcomes Framework (QOF) were also announced. The QOF is an annual reward and incentive programme based on the achievement of certain targets by GP practices (NHS England, 2019b). These targets have been amended to support more individualised, patient-centred, evidence-based care.

2.2 Inflammatory rheumatological conditions

Rheumatological conditions affect the joints, bones, cartilage, ligaments and muscles. Inflammation of these areas can cause swelling, stiffness, pain and a reduced movement range, which can impact on an individual's ability to function in their work, family and social lives. The presence of inflammation can also contribute to debilitating systemic symptoms, such as fatigue (Abhishek et al., 2017).

The inflammatory rheumatological conditions (IRCs) discussed within this thesis include rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). My initial two studies have focused on people with RA, due to this being one of the most common and frequently researched IRCs in the literature. Consequently, this initial focus has enabled me to build on a foundation of existing research. Following on from the suggestions of a patient and

public involvement and engagement (PPIE) group and due to the relative lack of literature reporting the burden of mood problems in other inflammatory conditions, I have subsequently widened my focus to other IRCs.

These other IRCs (AS, PsA, PMR and GCA) were chosen due to them being amongst the most frequent IRCs (section 2.1.1- 2.1.5). In addition, from the small amount of literature available, some of these conditions were reported to potentially be associated with mood problems (section 2.9). Later in this chapter, I will discuss the limited evidence reported on comorbid mood problems in people with IRCs, though firstly, I have provided an overview of each IRC.

2.2.1 Rheumatoid arthritis

RA is a long-term condition (LTC) characterised by synovial joint inflammation, that affects 0.67% of the adult population (Abhishek et al., 2017). It is multifactorial, with a genetic susceptibility linked to human leukocyte antigen (HLA) DR1 and DR4 (Silman and Pearson, 2002). Women are approximately 3 times more likely to develop RA than men, with the commonest age of onset being between 70 to 80 years (Abhishek et al., 2017).

Typically, people with RA present with a symmetrical polyarthritis affecting the small joints of the hands and feet. They often describe persistent joint pain, swelling, heat and early morning stiffness lasting more than 30 minutes, sometimes associated with systemic symptoms of fever, sweats, malaise, and weight loss. In more advanced disease, people can present with loss of function due to joint damage. The American College of Rheumatology (ACR) European League Against Rheumatism (EULAR) have

produced diagnostic criteria for RA, which are based on the degree of joint involvement, serological test results, acute phase reactants and symptom duration (appendix 4).

RA can have a variety of extra-articular features, involving the eyes, lungs and cardiovascular system (Gullick and Scott, 2011), and can contribute to increased morbidity and mortality (Ang et al., 2005; Dadoun et al., 2013; Abhishek et al., 2018). Therefore, prompt referral of patients with suspected RA is recommended to enable early treatment with drugs to prevent inflammation, improving long-term outcomes (NICE, 2018).

In people with newly diagnosed RA, first line treatment is with a conventional disease-modifying anti-rheumatic drug (cDMARD), with the option of short-term bridging treatment with glucocorticoids. RA activity is subsequently monitored using composite scores, such as the Disease Activity Score in 28 joints (DAS28), until the disease is controlled. If remission or low disease activity are not achieved despite escalation of the cDMARD dose, an additional cDMARD can be commenced. For individuals with severe disease that doesn't respond to a combination of cDMARDs, biological (b)DMARDs can be used. These genetically engineered drugs target proteins within the immune system, to help reduce inflammation.

In the longer term, RA can have major implications on peoples' relationships, work, self-image and social roles (Coventry et al., 2011). People who sustain joint damage or develop extra-articular complications may require the input of multiple professionals to support their daily functioning, hence guidelines by the National Institute for Health and Care Excellence (NICE) recommend that people with RA should be supported by a multidisciplinary team (MDT) (NICE, 2018). Alongside rheumatologists and nurse specialists, physiotherapists, occupational therapists,

podiatrists and orthotics can provide support with non-pharmacological treatments, with one person taking responsibility for coordination of care. Referral to other specialities can be arranged, for example, to help manage comorbid mood problems or offer advice about potential joint replacements.

GPs also have an integral role in the management of people with RA. They are required to promptly refer patients with suspected RA to secondary care to enable early treatment, whilst also assessing for comorbidities (NICE, 2018). However, in a qualitative study exploring barriers to integrated care for people with RA, only a minority of GPs reported regularly reviewing their patients with RA. After arranging a patients' initial referral, they felt only marginally involved in ongoing care (Pollard et al., 2011). Some GPs felt the priority given to RA patients in primary care had fallen due to a lack of QOF incentives (Pollard et al., 2011).

QOF incentives to perform an annual review for people with RA, including an assessment of fracture and cardiovascular disease (CVD) risk, were introduced in 2013. However, the incentives to assess fracture and CVD risk were retired only a year later (NHS Employers, 2015). Since then, the incentive has been to perform an annual review for people with RA (NHS England, 2019b), though the content of this has not been specified, hence important aspects of comorbidity assessment could be missed.

In 2015, a national GP survey was performed to determine the content of primary care RA annual reviews. Despite NICE advocating a holistic annual review for people with RA, primary care reviews were often found to focus on previous QOF domains, such as CVD and fracture risk screening (Hider et al., 2015), whilst assessments of disease activity and questions to identify potential mood problems were neglected. Therefore, possible opportunities for intervention were missed.

People with RA also have an important role to play in the management of their condition, with NICE Quality standards for the management of RA (QS33), recommending that people are offered support to self-manage their condition and encouraged to participate in treatment decisions (NICE, 2018). Self-management of LTCs is a type of self care. The Department of Health (2005, p1), defines self-care as "the actions people take to...maintain good physical and mental health; prevent illness or accidents; care for minor ailments and LTCs; and maintain health or wellbeing after an acute illness or discharge from hospital." Educational, behavioural and cognitive strategies to support self-management of LTCs have been developed (Iversen, Hammond & Betteridge, 2010).

A self-management programme developed for people with RA, has been found to improve mood and QoL. Participants attended six weekly meetings, during which they were educated about how to manage pain, fatigue and the psychological impact of their condition (Vermaak et al., 2015). Cognitive behavioural therapy (CBT) techniques were used to help people to understand how their thoughts and feelings affected their behaviour and to teach them coping skills, whilst goal setting techniques were also used to assist with behavioural change. Improvements in fatigue, depression and mental quality of life (QoL) were noted immediately after the intervention, with improvements in mood and QoL maintained at 12-months follow-up. As this study used a single group repeated measures design, there was no control group for comparison. Consequently, ongoing medical management was an important confounding factor that was not controlled for. In addition, as follow-up was only for a year, the longer term effects are also unclear. Therefore, to further assess the effectiveness of the self-management programme, a randomised control trial (RCT) would be needed.

Online support tools have also been found to improve the ability of people with RA to manage everyday stresses linked to their condition, though qualitative interviews with people who used the tool found that long-term engagement depended on the personality traits of participants and their existing social networks (Kostova, Caiata-Zufferey & Schulz, 2015). Consequently, the tool may be most useful if targeted towards people with RA who lack social support. However, as participants volunteered to be interviewed, it is possible there was a selection bias, with people who were more willing to discuss their experiences coming forward, leaving less opportunities to explore the views of more reticent patients.

Social support can strengthen self-esteem and improve self-management, whilst also buffering the negative impact of low health literacy (Lee, Arozullah & Cho, 2004). A cross-sectional study involving Greek patients with RA, found that the social support, assessed using the quality of social support scale, predicted QoL far beyond disease activity and demographic factors (Pitsilka, Kafetsios & Niakas, 2015). However, as this study was conducted in a region of Greece, it may not be generalisable to other populations, where cultural differences could impact on the extent to which people rely on social support networks to manage their LTCs.

2.2.2 Ankylosing spondylitis

AS is an IRC with a prevalence of between 0.1% and 2% (Gran & Husby, 1993). A principal symptom of AS is low back pain. Persistent inflammation at the junction of the intervertebral spinal ligaments and vertebrae, can eventually lead to fusion from fibrosis and calcification (ankylosis). Inflammation can also occur where tendons and ligaments attach to bone (enthesitis), where cartilage joins the ribs (costochondritis) and at the

sacroiliac joints, causing buttock pain (Elyan & Khan, 2006). Over time, progressive involvement of the lumbar, thoracic and cervical spine can lead to a fixed, flexed posture.

AS is 3 times more common in men than women, and usually begins between 20 to 30 years of age (Sieper, 2012). AS is thought to be caused by a combination of genetic and environmental factors, being more common in people with the HLA-B27 gene (Khan, 2002).

When suspected, a prompt referral of the patient by their GP to rheumatology is advised (NICE, 2013a). On review, a rheumatologist may consider blood tests for HLA-B27 to support their diagnosis, x-rays of the sacroiliac joints and spine which can be diagnostic in well established AS, or Magnetic Resonance Imaging (MRI) which can detect early changes in the sacroiliac joints (Elyan & Khan, 2006).

Alongside regular physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs) can reduce joint pain and stiffness, whilst glucocoritcoid injections may also be used to manage inflamed joints, enthesitis or sacroiliitis (NICE, 2013a). Inadequately controlled disease can be managed with biologics such as anti-tumour necrosis factor (TNF) agents (Zochling, 2006).

2.2.3 Psoriatic arthritis

Psoriasis is an autoimmune-mediated chronic, inflammatory disease characterised by scaly skin lesions (Menter et al., 2008). The prevalence of psoriasis in the general population is estimated at 2-3%. Approximately 5-25% of patients with psoriasis develop PsA (Gladman, 2005). PsA affects men and women equally and is most common between the ages of 30 and 55 years (NICE, 2012).

Symptoms of PsA include joint pain, swelling and stiffness, swollen fingers or toes (dactylitis), enthesitis, nail pitting, discolouration, or onycholysis (detachment) and fatigue (Gladman et al., 2005). Some people present with a symmetrical polyarthritis predominantly affecting their wrists, hands, ankles and feet, whilst others may develop lone distal interphalangeal (DIP) disease, involving only the terminal phalanx (finger bone) and nail. Arthritis mutilans is a rare variation of DIP disease, involving resorption of the terminal phalanx (Gladman et al., 2005).

Due to the variable presentation of psoriatic arthritis, an individualised treatment approach is recommended (Gossec et al., 2015). Initial management options include physiotherapy, NSAIDs and DMARDs, progressing to biological agents such as TNF-alpha or interleukin (IL)-17 inhibitors (Coates et al., 2014; Van den Bosch & Coates, 2018), whilst in advanced disease, joint surgery may be indicated (Michet et al., 2005).

2.2.4 Polymyalgia rheumatica

PMR is an inflammatory condition of unknown cause, with an average age at onset of 70 years (Mitchet & Matteson, 2008). PMR is characterised by pain and morning stiffness in the neck, shoulders, and pelvic girdle (Salvarani et al., 2002). The annual incidence of PMR is 84 per 100,000 (Smeeth et al., 2006), with a lifetime risk of 1.7% for men and 2.4% for women (Crowson et al., 2011).

PMR should be suspected in a person over 50 years of age, presenting with at least 2 weeks of bilateral shoulder and/or pelvic girdle pain and stiffness lasting for at least 45 minutes after waking or periods of rest (Dasgupta et al., 2009). Additional features include a low-grade fever, fatigue, anorexia, weight loss, and depression. GCA (described in section 2.1.5), is an associated condition which can be complicated by a

loss of sight. Therefore, this should always be excluded on the assessment of a patient with suspected PMR.

When PMR is suspected, blood tests should be performed to check for raised inflammatory markers, which can support the diagnosis. Differential diagnoses such as infection or cancer should be excluded. People with atypical features of PMR, such as weight loss, night pain, chronic symptom onset or low/ very high inflammatory markers should be referred for further investigations.

If PMR is the most likely diagnosis, a trial of treatment with oral prednisolone should be prescribed, and follow-up arranged after one week to assess the clinical response. If the patient reports a global improvement in their symptoms of 70% or more within a week, a working diagnosis of PMR can be made. If there is a lesser response, the diagnosis should be reconsidered and a referral made to a specialist (Dasgupta et al., 2009; NICE, 2013b).

For those with a working diagnosis of PMR, the dose of prednisolone should be reduced slowly once symptoms are fully controlled. Patients should be reviewed regularly for side-effects of treatment and signs of relapse. Treatment is usually required for 1 to 3 years (Dasgupta et al., 2009; NICE, 2013b).

2.2.5 Giant cell arteritis

GCA is a type of chronic vasculitis characterised by inflammation in the walls of medium and large arteries. The extracranial branches of the carotid artery and branches of the ophthalmic artery are preferentially involved, although the aorta and its' major branches may also be affected (Warrington & Matteson, 2007; Dasgupta et al., 2010).

GCA often occurs in association with PMR, though its' cause is unknown (Dasgupta et al., 2010). The annual incidence of GCA in the UK is 20 per 100,000 people

(Smeeth et al., 2006). It is three times more common in women than in men (Dasgupta et al., 2010) and the average age of onset is 70 years (Gonzalez-Gay, 2004).

GCA should be suspected if a person aged over 50 years presents with a temporal headache, with or without temporal tenderness. Almost half of people with GCA report jaw claudication (Hunder et al., 1990), whilst up to 40% may also present with symptoms of PMR (Dasgupta et al., 2010). Patients should be asked about visual symptoms, due to a risk of partial or complete visual loss. High inflammatory markers support a diagnosis of GCA, though they may be normal (Dasgupta et al., 2010).

All people with suspected GCA should be referred for an urgent rheumatology review and consideration of investigations such as temporal artery ultrasound and/or biopsy (Dasgupta et al, 2010). Same day ophthalmology review should be requested for any patient with visual symptoms (Dasgupta & Hassan, 2007), as intravenous glucocorticoids may be required. Otherwise, treatment is with oral prednisolone. Treatment response should be reviewed after 48 hours, and if this is poor, differential diagnoses should be considered, such as herpes zoster, migraine, glaucoma, sinus disease, ear problems, cervical spondylosis and temporomandibular joint pain (Dasgupta et al., 2010; NICE, 2014).

A good response to treatment within the first two days supports a diagnosis of GCA. A specialist can confirm the diagnosis, after which shared care between GPs and specialists is recommended. The dose of prednisolone is reduced slowly over several months and treatment is often required for 1 to 2 years, though some people may require low doses of prednisolone for several years (Dasgupta et al., 2010). Regular follow-up is required to monitor for relapses and adverse treatment effects.

2.2.6 Burden of inflammatory rheumatological conditions

IRCs, including RA, AS, PsA, PMR and GCA have wide-ranging impacts. Comorbidities such as anxiety and depression are common in people with RA (Gullick and Scott, 2011; Matcham et al, 2013; Covic et al., 2012), but are often under-recognised and under-treated (Cepoiu et al., 2007), which can contribute to increased morbidity and mortality (Marrie et al., 2018a; Ang et al., 2005). However, less data exists to define the burden of mood problems in people with other IRCs.

Therefore, in my thesis I aim to determine the incidence, prevalence and impact of anxiety and depression in different IRCs, whilst through interviews I have explored patients' preferences for the identification and management of comorbid mood problems. In the following sections I will define anxiety and depression, discuss current evidence for how these mood problems should be identified and treated and more specifically, the management of comorbid anxiety and depression in people with LTCs. Finally, I will discuss the limited literature that reports on the prevalence, identification and management of mood problems in IRCs, highlighting the lack of data available for certain conditions.

2.3 Mental Health Problems in Primary Care

It is estimated that 300 million consultations are undertaken each year in general practice (NHS England, 2017a). A significant proportion of these consultations relate to psychological problems, with up to 30% of people presenting to their GP having a mental health component to their illness (Royal College of General Practitioners, 2016). 90% of all mental health problems are managed entirely within primary care, with the most common psychiatric presentations including generalised anxiety disorder (GAD),

depression, panic disorder and alcohol or drug dependence (Royal College of General Practitioners, 2016).

Mood can be defined as a persons' emotional state of mind (American Psychiatric Association, 2000). In people with mood problems, their emotional state can interfere with their ability to function. Within this thesis I have focussed on the two commonest mood problems; anxiety and depression.

2.4 Anxiety and Depression

The 2014 Adult Psychiatric Morbidity Survey reported a 7.8% prevalence of mixed anxiety and depression amongst the English adult population over the preceding week. 5.9% had a GAD, whilst 3.3% reported suffering from a depressive disorder (NatCen Social Research, 2016).

GAD is characterised by persistent tension and excessive worry about a range of events (NICE, 2011a). To meet the diagnostic criteria for GAD, which are listed in figure 2.1 (p 20), there must be 3 or more associated symptoms of anxiety that have been present for at least 6 months and contribute to impaired functioning. GAD is one of range of anxiety disorders which include post-traumatic stress disorder, obsessive-compulsive disorder and specific phobias. Such anxiety disorders can exist in isolation, but are commonly associated with other anxiety or depressive disorders (NICE, 2011a).

Central to the diagnosis of depression is a persistent low mood and a loss of interest or pleasure in most activities persisting for more than two weeks. Associated symptoms include a change in weight of more than 5% or an altered appetite, a change in sleep or activity, fatigue, poor concentration and suicidal thoughts. The degree of depression is determined by the number and severity of associated symptoms, in

addition to any associated functional impairment (NICE, 2009a). The diagnostic criteria for depression are listed in figure 2.2 (p 21).

Figure 2.1- *Diagnostic criteria for Generalised Anxiety Disorder (American Psychiatric Association, 2000)*

Generalised Anxiety Disorder- Diagnostic Criteria	
A	Excessive anxiety and worry, occurring frequently for at least 6 months, about a number of events or activities (such as work or school performance)
B	The person finds it difficult to control the worry
C	The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not over the past 6 months); 1. restlessness or feeling on edge 2. being easily fatigued 3. difficulty concentrating 4. irritability 5. muscle tension 6. sleep disturbance
D	The focus of anxiety is not about; - having a panic attack (panic disorder) - being embarrassed in public (social phobia) - being contaminated (obsessive-compulsive disorder) - being away from home or close relatives (separation anxiety disorder) - gaining weight (anorexia nervosa) - having multiple physical complaints (somatisation disorder) - having a serious illness (hypochondriasis) In addition, the anxiety does not occur exclusively in association with post-traumatic stress disorder.
E	The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
F	The disturbance is not due to the direct physiological effects of a substance or general medical condition, and does not occur exclusively during a mood disorder, psychotic disorder or pervasive developmental disorder.

Figure 2.2- *Diagnostic criteria for depression (American Psychiatric Association, 2000).*

<table>
<tr><th colspan="2">Depressive Episode Criteria</th></tr>
<tr><td>A
Depressed mood
Loss of interest in usual activities
Reduced energy and decreased activity</td><td>B
Reduced self-esteem and confidence
Ideas of guilt and unworthiness
Pessimistic thoughts
Disturbed sleep
Diminished appetite
Ideas of self-harm</td></tr>
<tr><td colspan="2">Severity of Depressive Episode;
Mild: > 1 from column A plus 1-2 from column B, or 5-6 total symptoms, but mild in severity and functional impairment.
Moderate: > 1 from column A plus 2-3 from column B, or 7 – 8 total symptoms, but moderate functional impairment.
Severe: All 3 from column A plus > 3 from column B. Or fewer symptoms but any of these including severe functional impairment, psychotic symptoms, a recent suicide attempt, or active suicidal ideation.</td></tr>
</table>

The literature suggests that depressive symptoms are not recognised in approximately half of patients attending general practice with these disorders (Gilbody, 2003). In addition, the rates of diagnosis and treatment of anxiety are much lower than expected, given their high prevalence within the general population (Lecrubier, 2007). Multiple barriers to the recognition of anxiety and depression in primary care patients have been identified. Mood problems may be normalised as an understandable response to the losses associated with a LTC, or patients may struggle to describe how they are feeling (Coventry et al., 2011). Some may fear the stigma associated with a

diagnosis of mental illness, or may present with associated somatic symptoms, possibly believing them to be more medically legitimate (Alderson, Foy & House, 2015).

Doctors may lack appropriate training to recognise symptoms, or may be reluctant to openly inquire about depression (Richards et al., 2004). Some could attribute symptoms to physical illness requiring further investigation, whilst other health problems such as alcohol dependence could obscure the diagnosis (Buszewicz & Chew-Graham, 2011). Further potential barriers include financial constraints, a lack of time and poor continuity of care (Docherty, 1997).

2.5 Management of people with anxiety and depression

NICE has produced clinical guidelines (CG) for the management of GAD (CG 113), depression (CG 90) and depression in people with chronic physical health problems (CG 91). Guidelines for GAD and depression outline a stepped-care model to guide practitioners to identify the most effective and least intrusive interventions (NICE, 2011a; NICE, 2009a). If a person declines or does not benefit from a treatment they are offered an appropriate intervention from the next step. The stepped care models are summarised in figures 2.3 (p23) and 2.4 (p24).

GPs can help to diagnose and educate patients, signposting to online and self-help resources, or referring onto social prescribing services (discussed in section 2.1). Social prescribing has been suggested to work for a range of people, including those living with LTCs, people who are lonely or have complex social needs and those who require mental health support (NHS England, 2017b). GPs can refer people to psychological therapies or specialist care for more intensive management. People can

also self-refer to Improving Access to Psychological Therapies (IAPT) services (NHS England, 2018a), who will communicate the outcome of psychological treatments with GPs.

Figure 2.3- *The stepped-care model for Generalised Anxiety Disorder (NICE, 2011a).*

Step	Focus of the intervention	Nature of the intervention
STEP 1	All known and suspected presentations of GAD.	Identification and assessment; education about GAD and treatment options; active monitoring.
STEP 2	Diagnosed GAD that has not improved after education and active monitoring in primary care.	Low-intensity psychological interventions: individual non-facilitated self-help, individual guided self-help and psychoeducational groups.
STEP 3	GAD with an inadequate response to step 2 interventions or marked functional impairment.	Choice of a high-intensity psychological intervention (cognitive behavioural therapy/ applied relaxation) or a drug treatment.
STEP 4	Complex treatment-refractory GAD and very marked functional impairment, such as self-neglect or a high risk of self-harm.	Highly specialist treatment, such as complex drug and/or psychological treatment regimens; input from multi-agency teams, crisis services, day hospitals or inpatient care.

Figure 2.4- *The stepped-care model for depression (NICE, 2009a).*

Step	Focus of the intervention	Nature of the intervention
STEP 1	All known and suspected presentations of depression.	Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions.
STEP 2	Persistent subthreshold depressive symptoms; mild to moderate depression.	Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions.
STEP 3	Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression.	Medication, high-intensity psychological interventions, combined treatments, collaborative care and referral for further assessment and interventions.
STEP 4	Severe and complex depression; risk to life; severe self-neglect.	Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional and inpatient care.

For step 1 of the stepped care model, GPs have a role in providing information and educating people about anxiety or depression and ensuring they are closely followed up to assess for any deterioration in their mood. For people who are persistently symptomatic, step 2 consists of low intensity interventions. For anxiety, these include self-help and educational groups, whilst people with depression can be offered guided self-help or CBT, which aims to explore and change how people think about their lives, to help free them from unhelpful patterns of behaviour (NHS England,

2018b). For depression that persists despite these measures, further management options include medication or group CBT.

If these treatments prove ineffective, people can be offered high-intensity interventions, as part of step three of the care model. For anxiety, these include medication prescribed by a persons' GP, applied relaxation or CBT through IAPT services. People with depression can be offered antidepressants by their GP, or psychological therapies, including CBT, interpersonal therapy or behavioural activation. Interpersonal therapy is a talking treatment that helps people with depression to identify and address problems in their relationships with family, friends and partners, whilst behavioural activation helps depressed people take practical steps towards enjoying life again (NHS England, 2018b). If these treatments prove ineffective, patients can be stepped up to a specialist step 4 service, where they may be offered more intensive psychological therapy, combinations of medication or inpatient support.

In the following sections, I will discuss the burden of mood problems in LTCs (section 2.6), evidence for how anxiety and depression should be identified and managed in LTCs (section 2.7) and patient and practitioner perspectives of mood problems in LTCs (section 2.8). Afterwards, I will specifically focus on anxiety and depression in people with IRCs.

2.6 Anxiety and depression in people with long-term conditions

An estimated 15 million people in the UK suffer from LTCs (Naylor et al., 2012). These encompass a range of illnesses that can be managed, but not cured. Examples include diabetes mellitus (DM), asthma, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD) and RA. Mood problems are more prevalent in people

with LTCs compared to those without. Approximately 20% of have depression, whilst anxiety is 2 to 3 times more common (Naylor et al., 2012). In comparison, the adult psychiatric morbidity survey of UK adults, conducted in 2014, reported 5.9% of the general population to have symptoms of a GAD, and 3.3% to have symptoms of a depressive disorder, in the preceding week (NatCen Social Research, 2016)

Considering specific LTCs, 14% of people with DM have been reported to have anxiety (Grigsby et al., 2002), whilst approximately 20% have depression (Salinero-Fort et al., 2018). Depression is also 2 to 3 times more common amongst people with CHD, whilst 24% are estimated to suffer from anxiety (Bankier, Januzzi & Littman, 2004). People with COPD are three times more likely to have a mental health problem (Naylor et al., 2012), with panic disorders being ten times more prevalent in people with COPD when compared to the general population (Livermore et al., 2010).

Whilst physical illness can lead people to be at high risk of depression or anxiety, mood disorders may also lead to physical illness, amplify physical symptoms or potentially increase the chance of complications from physical illness (Chew-Graham et al., 2014). For instance, depression has been linked to an increase in the production of pro-inflammatory cytokines (Dowlati et al., 2010), influencing the pathogenesis of a range of LTCs including CHD, type 2 DM and IRCs (Kiecolt & Glaser, 2002).

For example, depression has been found to be a risk factor for incident CHD in women (O'Neil et al., 2016). A prospective longitudinal study involving 860 Australian women randomly selected from electoral rolls, found that depression predicted the 18-year incidence of CHD following adjustment for typical risk factors (odds ratio (OR)= 3.22, 95% CI, 1.45-6.93). However, as baseline depression diagnosis was determined

using retrospective reports by participants during structured clinical interviews, recall bias could have affected the associations observed (O'Neil et al., 2016).

Comorbid mood disorders have been linked to higher morbidity and mortality rates in people with different LTCs (Lin et al., 2009). A large prospective study involving over 4,000 people with type 2 DM, recruited from primary care, examined the association between depression (baseline Patient Health Questionnaire (PHQ)-9≥ 10) and mortality. After adjustment for baseline demographic and clinical characteristics, depression in people with DM was significantly associated with all cause mortality (hazard ratio (HR) 1.52, 95% confidence interval (CI), 1.19- 1.95) (Lin et al., 2009).

Comorbid depression has also been found to be associated with increased cardiac morbidity and mortality in people CHD (Carney et al., 2002). The question of whether there is a direct causal link between depression and poor CHD outcomes has proven more difficult to answer, with several theories having been proposed. For instance, adverse cardiac outcomes in depression could relate to behavioural factors such as inactivity, smoking and poorer compliance with medications (Carney & Freedland, 2017). However, biological factors could also mediate the relationship between depression and poor cardiac outcomes through autonomic dysregulation and inflammation (Carney & Freedland, 2017). Alternatively, as those with the most severe CHD generally have the worst physical health and functional ability, they could be more likely to develop depression. Due to the severity of their underlying CHD, this subset of patients would inherently have higher morbidity and mortality rates (Katon, 2011).

Anxiety has also been found to be associated with increased mortality in people with LTCs, including CHD (Watkins et al., 2013). A cohort of 934 people with CHD who were enrolled at a UK medical centre for cardiac catheterisation, were followed up for

3 years. Anxiety, defined as a Hospital anxiety and depression score for anxiety (HADS-A) ≥8, was associated with significantly increased mortality (HR (95% CI) = 2.18 (1.47, 3.22) (Watkins et al., 2013). However, attending hospital for an emergency procedure, may have increased baseline anxiety, whilst the association between anxiety and mortality may have been affected by an increased number of deaths from the catheterisation procedure.

Depression in DM negatively impacts on QoL (Goldney et al., 2004), can lead to poorer concordance with medical management and may adversely affect diet, exercise and smoking behaviour (de Groot et al., 2001). Poor concentration, social isolation and feelings of hopelessness related to depression can also reduce a patients' motivation to self-manage, contributing to higher morbidity and mortality in people with DM (Mut-Vitcu et al., 2016). In addition, an association has been found between depressive symptoms in people with DM and higher cholesterol levels, potentially contributing to worse physical health outcomes (Gary et al., 2000). However, as this was a cross-sectional study, inferences about causality must be made cautiously. Although depression could worsen metabolic control, poor diabetic control could also lead to depression. In addition, patients self-reported a diagnosis of depression, so results could have been biased by individuals under-reporting symptoms or incorrectly assigning themselves a diagnosis of depression. In addition, three times as many women, compared to men, participated in the study, meaning potential selection bias could have influenced the cross-sectional associations observed.

An association between depression and increased use of emergency care has also been identified in people with LTCs. A prospective study involving 355 patients from 6 GP practices, examined the association between COPD and emergency hospital

admissions over a 12-month follow-up period (Blakemore et al., 2019). Depression was assessed by questionnaire using the HADS Score for depression (HADS-D). Validated cut off scores for anxiety and depression on the HADS are as follows; 8-10 mild, 11-14 moderate, 15-21 severe symptoms (Zigmond & Snaith, 1983; Bjelland et al., 2002). In this study, depression, defined as a HADS-D score ≥8, was independently associated with 4.8 times increased odds of emergency hospital attendance and admission, whilst even subthreshold depressive symptoms (HADS-D score 4-7) were associated with a 2.8 times increased odds of emergency hospital admission (Blakemore et al., 2019). Only 50% responded to questionnaires, introducing potential bias, though the authors found no significant differences between the rates of mental health problems in the group who returned their questionnaires, to overall rates recorded using the QOF database.

Mood problems in people with LTCs have also been linked to the length of hospital admissions (Ng et al., 2017). In a prospective cohort study, 376 people with COPD who were hospitalised for an acute exacerbation, were followed up for a year. After adjustment, comorbid anxiety and depression were found to be associated with increased mortality, length of hospital stay and reduced QoL. However, data on hospitalisation and length of stay were based on self-report, hence associations could have been affected by recall bias (Ng et al., 2017).

2.7 Identification and management of anxiety and depression in people with long-term conditions

Depression is often under-recognised and under-treated in people with LTCs (Memel et al., 2000; Cepoiu et al., 2007). A systematic literature review and meta-analysis found the accuracy of depression recognition by non-psychiatric physicians to

be low (Cepoiu et al., 2007). However, potentially relevant literature could have been missed, as only articles written in French and English were included. In addition, many studies classed patients with sub-threshold symptoms as missed depression diagnoses. Sub-threshold depression is often transient and in this category of depression (Jackson et al., 1998), treatment and placebo have similarly high rates of remission (Barrett et al., 2001), hence recognition and treatment may not have offered any benefit in these cases.

GPs have been found to under-recognise anxiety and depression in people with osteoarthritis (OA) (Memel et al., 2000). At two UK practices, where patients had a good continuity of care with the same GP, 200 people with OA, who had seen their usual GP in the previous week, were identified using electronic records. These patients were sent a questionnaire to complete, which included the HADS, whilst their GP was also asked to complete a questionnaire, which included a three-point scale to assess for anxiety or depression. There was a moderate prevalence of depression and anxiety identified, though these mood problems, particularly anxiety, were often not recognised by the GP. For example, 8.3% of patients reported symptoms of depression, though GPs only identified symptoms of low mood in 6% of participants. Meanwhile, 24.4% of patients reported anxiety symptoms, which were only recognised by 11.9% of GPs (Memel et al., 2000). However, this study was dependent on the frequency of consultation by participants and the familiarity of different GPs with their patients.

In recognition of the links between mood disorders and higher morbidity and mortality in LTCs, guidelines have been written on how depression should be identified and treated in adults with chronic physical health problems (NICE, 2009b). However, no similar guideline has been published to assist the recognition and management of

anxiety in LTCs. This is despite anxiety being under-recognised and associated with increased morbidity and mortality in people with LTCs (Watkins et al., 2013).

The General Health Questionnaire (GHQ)-28, PHQ-9 and PHQ-2 (also referred to as the two stem questions), have been found to be most sensitive at detecting depression in people with a chronic physical illness (Meader et al., 2011). The PHQ-2 questions ask about the frequency of depressed mood and anhedonia over the past 2 weeks, scoring each as 0 ("not at all") to 3 ("nearly every day") (Kroenke, Spitzer and Williams, 2003). The PHQ-2 questions overlap with the two-question instrument (Whooley et al., 1997), which asks about depression symptoms over the preceding month, rather than the past 2 weeks, and has the option of a “yes” or “no” response, rather than 4 potential responses, numbered 0-3 (Whooley et al., 1997). The PHQ-2 questions are often favoured due to their ease of application and efficiency (Meader et al., 2011), though the two-question instrument also has a high sensitivity and moderate specificity for the detection of depression (Bosanquet et al., 2015). The PHQ-2 questions and two-question instrument are outlined in figure 2.5 (p 32).

A meta-analysis examining the utility of PHQ-9 and the PHQ-2 for screening and case finding revealed that both tools had high negative predictive values of 98.6% and 94.1% respectively. This would imply that the PHQ-2 or PHQ-9 could be used to rule out those without depression, with few false negatives. Although the PHQ-2 was found to be useful as a screening test, lower positive predictive values for case-finding on comparison to the PHQ-9, suggested it would not be optimal for the confirmation of a diagnosis of depression. Therefore, the PHQ-2 has been suggested to be most useful as an initial screening tool for depression, to be followed by the PHQ-9 in those scoring positively (Mitchell et al., 2016).

Figure 2.5- *The PHQ-2 (Kroenke, Spitzer & Williams, 2003) and the two-question instrument (Whooley et al., 1997)*

Tool	**PHQ-2** *(Two-stem questions)*	**Two-question instrument** *(Whooley questions)*
Prompt	Over the last 2 weeks, how often have you been bothered by any of the following problems:	During the past month, have you been bothered by:
Symptoms	1. Feeling down, depressed or hopeless? 2. Having little interest or pleasure in doing things?	
Responses	0= Not at all 1= Several days 2= More than half the days 3= Nearly every day	0= No 1= Yes
Score Range	0 to 6	0 to 2

A more recent meta-analysis analysed the accuracy of the PHQ-9 using individual data from 17,357 people, who participated in 58 studies (Levis et al., 2019). Again the PHQ-9 was found to be sensitive at detecting depression. Participants without a prior diagnosis of depression completed the PHQ-9, then underwent diagnostic interviews after 2 weeks. A PHQ-9 score of ≥10 maximised combined sensitivity (0.88 (95% CI= 0.82-0.88) and specificity (0.85 (95% CI= 0.82-0.88) in the 29 studies using semi-structed interviews as a reference. However, there was significant heterogeneity across studies. Some subgroup analysis on the age and gender of participants was performed, though a lack of data on comorbidities meant this couldn't be analysed.

Although the literature suggests that the PHQ-2 questions are sensitive to depression, the way in which the questions are posed could lead to systematic under-detection of depression (Maxwell et al., 2013). In a qualitative study exploring the experiences of primary care practitioners involved in the identification of depression in

patients with DM and CHD, Maxwell and colleagues reported that practitioners struggled to incorporate the PHQ-2 questions into a consultation. Some nurses described lacking the skills required to provide patients with adequate support at the point of use (Maxwell et al., 2013), suggesting an unmet training need. In addition, several practitioners described the assessment as too mechanistic or reported finding the process uncomfortable. Consequently, a more individualised approach has been recommended, with less time pressures to facilitate the development of rapport. However, due to increasing demands on their time, practitioners may struggle to achieve this (Maxwell et al., 2013). As study participants were self-selecting, people with an interest in research or depression management could have been more likely to volunteer, potentially reducing the diversity of perspectives gained. In addition, data for this study was gathered through focus groups, some of which were small or did not include a mix of different professionals. This could have reduced the diversity in perspectives shared, particularly if there were more dominant participants who could have discouraged others from disclosing opposing views.

A qualitative study explored the experiences of nurses in recognising depression, in older people with multimorbidity (Waterworth et al., 2015). Overall, nurses reported a lack of confidence in discussing low mood with patients, with many believing this was not their responsibility, further supporting a requirement for training to improve the recognition and management of mood problems in people with LTCs. However, as this study involved nurses working in New Zealand, the results may not be generalisable to other countries, where nurses could have received different training.

A qualitative study involving interviews with patients and their GPs, revealed different perceptions of depression assessment using tools, incentivised by the QOF.

GPs considered their clinical judgement to be more important than objective assessments, and felt the use of structured questions could compromise the doctor-patient relationship by interfering with the consultation process. However, patients perceived the use of incentivised tools as an efficient way to supplement medical decisions and as evidence of their GP taking their problems seriously (Leydon et al., 2011). Interviews were conducted until data saturation was reached, to help ensure a full diversity of perspectives were considered. However, as participants volunteered, those who agreed to be interviewed could have had more negative views of depression assessment tools, compared to the norm. Patients were recruited to the study by their GP, who may have selected people to be interviewed who would be likely to share more positive views of their experiences consulting their GP (Leydon et al., 2011).

Consequently, self-reported measures to identify mood problems can be easy to apply, whilst facilitating comparisons between studies. However, some practitioners can struggle to integrate structured questions within consultations, prefering an individualized approach that facilitates the development of rapport to encourage disclosure of concerns, rather than socially desirable responses.

The GAD-7 scale is used to assess the severity of anxiety (Spitzer et al., 2006). A systematic review of the accuracy of the GAD-7 tool, involving 5223 participants from 12 studies, found an acceptable pooled sensitivity (0.83 (95% CI 0.71, 0.91) and specificity (0.84 (95% CI 0.70, 0.92) of the GAD-7 tool for identifying anxiety (Plummer et al., 2016). An abbreviated version, GAD-2, which includes the first two questions of GAD-7, has been recommended as a case-finding tool for anxiety in primary care, having 90% sensitivity for GAD (Ballenger et al., 2001). The GAD-2 questions are listed in figure 2.6 (p35).

Figure 2.6- *GAD-2 (Spitzer et al., 2006).*

GAD-2	
Prompt	Over the last 2 weeks, how often have you been bothered by any of the following problems:
Symptoms	1. Feeling nervous, anxious or on edge? 2. Being unable to stop or control worrying?
Responses	0= Not at all 1= Several days 2= More than half the days 3= Nearly every day
Score Range	0 to 6

QOF incentives to ask case-finding questions for depression in CHD and DM were retired in 2013 (NHS Employers, 2015). A study exploring the impact of these incentives found that whilst these QOF indicators were in place there was a significant increase in new depression-related diagnoses. However, as there were no control practices the influence of emerging national and local guidelines on this outcome could not be excluded (McLintock et al., 2014). It is possible that the use of structured tools could have led to some screening bias, with positive responses to questions being more likely to be recorded.

A systematic review aimed to determine the impact of routinely assessing depression severity using structured tools in primary care, as incentivised by the QOF (Shaw et al., 2013). From 8 studies that met the eligibility criteria, no evidence was found on whether a structured assessment of depression severity and subsequent treatment based on the assessment, led to improved QoL or depression remission. Increased depression severity at diagnosis, determined by GP judgement or use of a structured

tool, was associated with higher treatment and referral rates, though this was based on low quality evidence, hence further research would be required to determine the impact of using structured case-finding questions for depression on outcomes.

It is possible that the retirement of the QOF indicators for use of tools to identify depression, could have led to fewer patients with LTCs being asked the case-finding questions, hence reduced recognition of comorbid mood problems. However, QOF targets could also have contributed to a performance managed and time-limited primary care environment, which could have led to less patient-centred discussions about mood. In fact, a qualitative study of barriers to managing depression in people with LTCs found evidence to suggest that consultations under the terms of the QOF could encourage reductionist approaches to case-finding for depression in people with CHD and DM, with discussion of depression being pushed into the margins of annual physical health check-ups, creating barriers to a patient-centered approach to the recognition and management of mood problems (Coventry et al., 2011).

To improve the management of comorbid mental health problems in people with LTCs, an expansion of IAPT services focusing on people with LTCs has been planned, as outlined within the Five Year Forward View for Mental Health (NHS England, 2016). Psychological therapy will be integrated into existing services, either within primary or secondary care, meaning physical and mental health care provision will be co-located.

Older people could particularly benefit from this expansion of IAPT services, as multimorbidity, the presence of 2 or more LTCs, is more prevalent in people aged over 65 years (Barnett et al., 2012). Multimorbidity is associated with an increased risk of developing comorbid anxiety (Vancampfort et al., 2017) and depression (Read et al., 2017). Evidence suggests that older people are under-represented in those accessing

IAPT services (Pettit et al., 2017), with fewer referred, despite a greater proportion of older adults completing their treatment and sometimes having better outcomes, compared to those of working age.

NICE CG91 on the management of depression in adults with a chronic physical health problem, highlights the role of collaborative care (CC) as a model to improve the liaison between physical and mental health services, in addition to primary and specialist care (NICE, 2009b). NICE CG123 on the identification of common mental health disorders and pathways to care, also outlines how clinicians, managers and commissioners should work together to design local care pathways that provide an integrated programme of care across primary and secondary care services (NICE, 2011b).

Key components of CC include a MDT approach to care, structured management plans, scheduled follow-ups and enhanced inter-professional communication (Gunn et al., 2006). CC is particularly advocated for people with moderate to severe depression associated with a LTC that has failed to respond to high-intensity psychological interventions and pharmacological treatment (NICE, 2009b). The foundations of CC were set by the Chronic Care Model (CCM), which aimed to transform the care of people with chronic illnesses from acute and reactive to proactive, and planned. In people with LTCs, team-based delivery of care, improved use of information symptoms and patient education and support, as advocated by the CCM, have been found to improve overall outcomes (Coleman et al., 2009).

A Cochrane systematic review published in 2012 aimed to assess the effectiveness of CC for people with anxiety and depression (Archer et al., 2012). Following review of 79 RCTs involving 24,308 participants, a significant improvement in

mood outcomes for adults treated with the CCM was found for up to two years, though not beyond this time. Heterogeneity in terms of participants, interventions, comparisons and outcome measures was noted. Some limitations, such as the blinding of participants and clinicians, reflected the reality of conducting intervention trials in practice.

The Collaborative Interventions for Circulation and Depression (COINCIDE) trial was designed to test whether depression in LTCs could be improved by integrating low-intensity psychological interventions within the routine primary care management of LTCs (Coventry et al., 2015). CC delivered in partnership with practice nurses was found to reduce mood problems and improve self management of chronic disease in people with mental and physical multimorbidity. Again, a lack of blinding of participants and researchers could have introduced bias. In addition, the treatment effects were only small, though the population studied were deprived with high levels of multimorbidity (Coventry et al., 2015).

A nested qualitative study within the COINCIDE trial found that CC between physical and mental health specialists facilitated access to depression care for patients with LTCs (Knowles et al., 2015). However, some participants reported preferring their mental and physical health to be managed by recognised 'experts', not their primary care nurse, whilst several felt that having a separate space to review their mental health liberated discussion of concerns (Knowles et al., 2015). Therefore, models of integrated care would need to be flexible to the needs of patients who may view their depression and LTC as separate problems (Knowles et al., 2015). The majority interviewed were older patients, so although this would represent the population most likely to be seeking help, it may not reflect the views of younger patients.

Building on the requirement for integrated treatment of LTCs and mood problems, the ENHANCE (Healey et al., 2015) study, evaluated the feasibility and acceptability of a nurse-led LTC review for identifying and managing osteoarthritis (OA)-related joint pain and mood problems within primary care LTC reviews. Preliminary results showed that some of the practice nurses had difficulty managing a combination of joint pain alongside mood problems within one consultation. However, there was some evidence of good integration, and the consultation was reported to be acceptable to patients (Jinks et al., 2015). Therefore, incorporating case-finding for anxiety and depression within primary care nurse-led LTC reviews could potentially improve the recognition and management of mood problems in people with LTCs.

Having discussed the burden of mood problems in people with LTCs and evidence for how comorbid anxiety and depression should be managed in this population, in the next section, I will discuss the perspectives of patients and practitioners on mood problems in people with LTCs.

2.8 Patient and practitioner perspectives of mood problems in people with long-term conditions

In a systematic review of the beliefs held by people with depressive symptoms, particularly in the presence of a LTC, multiple causes for low mood were reported, from negative life events to stress and physical illness (Alderson et al., 2012). Whilst some perceived their symptoms to be part of normal life, hence preferred to not be told they had depression, others gleaned comfort from their diagnosis by knowing that treatment would be available (Alderson et al., 2012). Several felt that a diagnosis of depression gave them a new identity, which for the majority was unwelcome, with some fearing

that they would be perceived as unable to cope or that their judgement would not be trusted, jeopardising potential friendships or employment prospects (Alderson et al., 2012). Limiting this review to primary care-based studies written in the English language, could have led to potentially relevant studies being excluded, though this did increase the relevance of the review to the management of depression in primary care, particularly to inform case-finding for depression.

A qualitative meta-synthesis of the experiences of patients with a LTC and comorbid mood problems, found that most perceived their LTC to have caused their anxiety or depression (DeJean, 2013). Alternatively, some perceived their mood problems to have caused their LTC, attributing high blood sugars to constant worry, or heart disease to depression having caused a "heavy heart". Others perceived their LTC and mood to be inter-related, with the two conditions exacerbating each other, whist some perceived no connection between their LTC and mood. A greater range of perspectives may have been captured if the review had focused on broader psychological responses to living with a chronic disease, rather than the experiences of people with LTCs of being diagnosed with comorbid anxiety or depression. However, the focus of this review ensured that the authors' objectives were met, whilst a second stage of analysis involving a comparison of findings across studies, helped to highlight exceptions for development into new themes, facilitating a greater depth of understanding.

As part of a study aiming to develop a community-based intervention for older people living with anxiety and depression, older adults were interviewed to determine their perspectives of mood problems (Kingstone et al., 2017). Participants reported multiple forms of loss after developing a LTC, which they perceived to have caused

mood problems. For example, participants reported reduced mobility, the loss of significant relationships, changes in their ability to participate in hobbies and a loss of independence as a consequence of ageing with a LTC, to negatively impact on their mood. Despite the researchers attempting to recruit a broad range of people to interview, a lack of male or housebound people participated, meaning some perspectives may have been missed.

A mixed methods study aimed to determine whether people with heart disease and comorbid depression had different causal beliefs about their depression, when compared to people in routine care for depression (Magaard et al., 2018). Beliefs about depression were measured using the Brief-Illness Perception Questionnaire and categorised using qualitative methods. Compared to people in routine care for depression, those with heart disease and comorbid depression more often attributed their depression to physical illness (48% vs. 16%), and less often to problems at work (25% vs. 35%) or negative life events (19% vs. 25%). However, a significant limitation of this study was that the presence of other LTCs was not accounted for. The group with cardiac diseases were older, hence were more likely to have other LTCs, which could have affected their causal beliefs, whilst the characteristics of the depression group were not described, hence they could have had other LTCs that influenced their beliefs.

A study exploring the views of older people on the relationship between depression and CHD, found that treatment for depression could be more acceptable if discussed in terms of its' effects on overall CVD risk. Therefore, highlighting the negative impact of poorly managed mental health problems on physical comorbidities, could make patients more willing to acknowledge and treat their mood disorders (Bogner et al., 2008). As this study focused on the views of people over 65 years, who were all from

the same geographical area, alternative perspectives may have been gained from a more diverse or younger population.

In a qualitative study exploring patients' experiences of living with depression and CHD, participants perceived strong links between their LTC and depression, with some men feeling emasculated by their CHD and others feeling depressed by the "medicalization" of their lives (Simmonds et al., 2013). Participants were ambivalent about accessing primary care interventions for depression, due to feeling their GP would not be able to help with their complex health and social needs. Most cited a preference for talking therapies and interventions providing opportunities for social interaction rather than medication. After 30 interviews, data saturation was reached, though as participants were mainly from deprived areas, alternative perspectives may have been gained from a more diverse population.

A further qualitative study exploring the perspectives of people with depression and CHD or DM, found that participants feared stigmatization for having depression or taking medication, whilst some felt responsible for independently overcoming their depression (Alderson et al., 2014). More diverse perspectives may have been gained if the interviewer had not disclosed their identity as a GP and if the sample had included more females and ethnic minorities. Overall, results suggest that to engage patients in the detection and management of depression, their beliefs about comorbid mental illness and treatment need to be explored.

A related Q-methodology study aimed to identify patients' views about depression in CHD or DM and understand how these could influence clinical practice (Alderson, Foy & House, 2015). Participants were asked to rank 57 statements about their understanding of depression in chronic physical illness from +5 (strongly agree), to

-5 (strongly disagree) on a grid. A researcher was present who interviewed participants afterwards, to explore their reasons for the placing of statements. Five different accounts about depression in LTCs were identified, which varied in terms of the role chronic illness had in depression, the role of medical interventions and the importance given to supportive networks. Based on these accounts, different management approaches were recommended, highlighting the need for clinicians to explore patients' perspectives of mood problems and develop an individualised approach to the detection and treatment of comorbid depression. Although participants varied in age, they were mainly white British and from the same geographical area, potentially limiting generalisability. When using Q-methodology, participants may not have understood the meaning of some statements hence they could have randomly placed some cards. However, a researcher was present who explored the reasons behind the ranking of statements. It is still possible that some perspectives on mood problems could have been missed, though the statements used were informed by a systematic review and qualitative interview study. Identifying socially shared viewpoints through Q-methodology enabled different management approaches to be suggested, to improve provision of individualised care and concordance with treatment.

A further qualitative study explored the perceptions of patients and practice nurses (PNs) of depression in people with DM and CHD screened for subthreshold depression (Pols et al., 2018). Interviewing both PNs and patients facilitated deeper insights. In particular, PNs often perceived patients to not be depressed and to have a minimal need for specific care, whilst most patients interviewed perceived themselves to be at least mildly depressed (Pols et al., 2018). This could have been due to an overlap between the symptoms of a patients' LTC and mood problems, making it difficult for the

PN or patient to recognise anxiety or depression as separate problems (DeJean, 2013). This could also have reflected normalisation of mood problems by patients and their practitioners, who could have conceptualised depression as a frequent and understandable response to the losses associated with a LTC (Coventry et al., 2011). Furthermore, practitioners may have lacked certainty on how to negotiate labels for depression in people with LTCs, in a way that facilitated shared understanding and management (Coventry et al., 2011).

As identified in other qualitative studies (Simmonds et al., 2013), patients expressed a preference for self-help advice and talking therapies to manage their depression (Pols et al., 2018). An individuals' perceived need for care did not always match their help-seeking behavior, often due to a lack of awareness of depression and its' management, suggesting an educational need (Pols et al., 2018). Stigmatization was a further barrier to help-seeking (Pols et al., 2018), as identified in other studies (Alderson et al., 2014). A limitation was that six of the nine PNs interviewed were psychosocial PNs, who may have had different perspectives from PNs without specialist training, limiting the generalisability of findings.

In another qualitative study, GPs were interviewed regarding their role in the detection and management of comorbid mood problems in people with chronic physical illnesses. GPs cited time constraints, a lack of confidence in diagnostic acumen and a perception that patients don't wish to discuss emotional problems as barriers to the identification of anxiety and depression in LTCs (Chew-Graham & Hogg, 2002). To enable the implications for GP training to be discussed, all GPs interviewed were involved in undergraduate teaching. It is possible that different perspectives may have been gained from a wider sample of GPs. However, interviewing this subset of GPs helped to

highlight potential training requirements, to facilitate the empowerment of patients to disclose mood problems and engage with management plans. Findings would support the need for collaborative management strategies for depression in people with LTCs, as discussed in section 2.6 (Gunn et al., 2006).

A nested qualitative evaluation within a service development pilot aimed to determine the feasibility of training PNs to deliver a psychosocial intervention within a CC framework for people with depression and LTCs (Webster et al., 2016). Patients and a purposive sample of professionals taking part in the intervention were interviewed. Patients valued a PN being available to listen to their mood concerns. However, a perceived scarcity of time and resources, in addition to a lack engagement by the whole practice team in a model of CC, exacerbated pressures perceived by PNs. A need for formal supervision of PNs was identified, to support them in undertaking the role of a case manager for people with depression and LTCs. Only three patients participated in interviews, despite the offer of reimbursement for participation, hence alternative perspectives could have been missed, though the study findings were strengthened by the analysis of clinicians' and patients' perspectives.

A mixed methods study aimed to determine patients' readiness to receive psychosocial care during nurse-led DM consultations in primary care (van Dijk-de Vries et al., 2016). In depth patient interviews were followed by questionnaires designed to explore findings within a larger group of patients. Although patients supported an integrated approach, they often did not expect a discussion about psychosocial problems within their DM consultation. Younger patients were generally more open to discussing psychosocial problems with the PN compared to people aged over 65 years.

This would suggest a requirement for patients to be informed about the changing role of PNs.

Having discussed the prevalence, impact, identification and management of anxiety and depression in people with LTCs, in addition to the perspectives of patients and practitioners on comorbid mood problems in this population, I will now focus on mood problems in people with IRCs.

2.9 Anxiety and depression in people with IRCs

The majority of literature on comorbid mood problems in IRCs is focused on RA. Therefore, the first two parts of this section are about anxiety and depression in people with RA (section 2.9.1), in addition to patients' and practitioners' perspectives on the identification and management of mood problems in people with RA (section 2.9.2). The final section summarises the relative lack of literature on anxiety and depression in other IRCs (2.9.3).

2.9.1 Anxiety and depression in people with rheumatoid arthritis

In common with other physical LTCs, there is an increased prevalence of both depression and anxiety in people with RA. A meta-analysis reported the prevalence of depression in RA to be 38.8%, with 16.8% suffering from a major depressive disorder (Matcham et al., 2013). However, a limited number of studies within the review used a psychiatric assessment supported by diagnostic criteria to confirm a depression diagnosis, meaning the reported prevalence could have been overestimated. The high prevalence of depression could also have been affected by an overlap between symptoms of RA and somatic symptoms of depression, such as poor sleep or fatigue.

One study estimated that up to 20% of people with RA have anxiety (VanDyke et

al., 2004), though anxiety was identified using screening questionnaires without any diagnostic evaluation, hence this prevalence could have been overestimated. A study using potentially more accurate psychiatric assessments to diagnose anxiety in people with RA, reported a lower prevalence of 13% (Isik et al., 2006), whilst a later study using questionnaires to assess for anxiety reported a prevalence of 14% (Covic et al., 2012). This still suggests that the prevalence of anxiety in RA is much higher than the general population of England, where a survey an estimated 5.9% to have had symptoms of a GAD in the preceding week (NatCen Social Research, 2016).

The literature also suggests that the incidence of mood problems in people with RA is increased (Marrie et al., 2018b). A Canadian cohort study estimated the incidence of depression and anxiety in people with RA, using population-based administrative health data. 10,206 incident cases of RA identified between 1989 and 2012, were matched to 50,960 controls. The incidence of depression (incidence rate ratio (IRR) (95% CI) 1.46 (1.35, 1.58)) and anxiety (IRR (95%CI) 1.24 (1.15, 1.34)) was significantly higher in the RA cohort, when compared to the control group over the study period. However, medical comorbidities were not evaluated or controlled for, which could have confounded the associations observed. The use of administrative data may also have limited the accuracy of diagnostic codes reported. Conversely, strengths of the study included its' size and general population approach.

A recent quantitative meta-analysis aimed to evaluate the relationship between RA and incident anxiety. This included 10 studies, involving 139,875 participants, with follow-up varying between 1 to 9.2 years (Qui et al., 2019). The incidence of anxiety was significantly increased in people with, compared to those without RA (OR 1.20, 95% CI 1.03-1.39). There were high levels of heterogeneity between studies, potentially

attributable to study design, geographical area and follow-up duration. However, studies included were of high quality and individual studies were found to have little influence on the overall results in the sensitivity analysis.

Comorbid depression in people with RA has been found to be associated with increased RA-related hospitalization and overall healthcare costs (Joyce et al., 2009). However, as this study was conducted in the United States of America (USA), the cost of a potential admission could have been a deterrant to attending hospital when ill. Consequently, it is possible that a stronger association would be seen in a UK population, where there are no financial barriers to accessing care.

The literature also suggests that depression in people with RA is a risk factor for increased mortality (Ang et al., 2005). A cohort of people with RA were followed-up at clinic appointments over 18 years. The primary independent variable was the mean Arthritis Impact Measurement Scale (AIMS) depression score during the first 4 years of entry into the clinic cohort. After adjusting for covariates, the hazard ratio for each unit increase in the average 4-year AIMS depression score on mortality, was 1.14 ($p<0.0001$), suggesting that depression in RA was associated with increased mortality. The generalisability of this data could be questioned as it all originated from a single arthritis centre, though the prevalence of depression and mortality rate in this sample were similar to other settings. As the relationship between depression and mortality in the RA cohort may have been confounded by comorbid medical disorders, sensitivity analyses were performed, and deaths within the first two years of the study were excluded. In addition, a combination of the Health Assessment Questionnaire (HAQ) score, erythrocyte sedimentation rate (ESR) and grip strength were used to help control for the confounding effect of higher disease activity.

It has been suggested that the causal pathways between RA and depression are bidirectional, with possible explanations including biological, psychological and behavioural processes (Rathbun, Reed & Harrold., 2013). In terms of biological processes, depression has been linked to a rise in pro-inflammatory cytokines (Maes et al., 1995). A small study has also suggested that anti-TNF could interact with serotonin transmission, potentially affecting mood, though further research would be needed to confirm this association (Cavanagh et al., 2010). As cytokine dysregulation is pivotal in the pathogenesis of RA, pro-inflammatory cytokines produced in RA could potentially precipitate or exacerbate depression and vice-versa.

In terms of psychological processes, negative thoughts in people with depression could influence how symptoms of RA are perceived, whilst depression could also affect behaviour, potentially causing a decrease in exercise, deconditioning, reduced endorphin release and increased pain (Covic et al., 2003). When clinical and psychological measures were collected from 157 patients with RA over a 12-month period, helplessness and passive coping were found to significantly mediate the relationship between physical disability in people with RA, and future depression and pain. When specific passive coping strategies were identified, catastrophising was a particularly detrimental factor associated with increased pain and low mood (Covic et al., 2003). Consequently, interventions that focus on improving coping strategies, such as CBT, could potentially reduce future depression and pain severity in people with RA.

A recent cohort study found evidence supporting a bidirectional association between RA and depression (Lu et al., 2016). The incidence of depression was higher in the RA cohort, when compared to those without RA (15.69 vs. 8.95 per 1,000 person-years). However, the incidence of RA was also found to be higher amongst those with

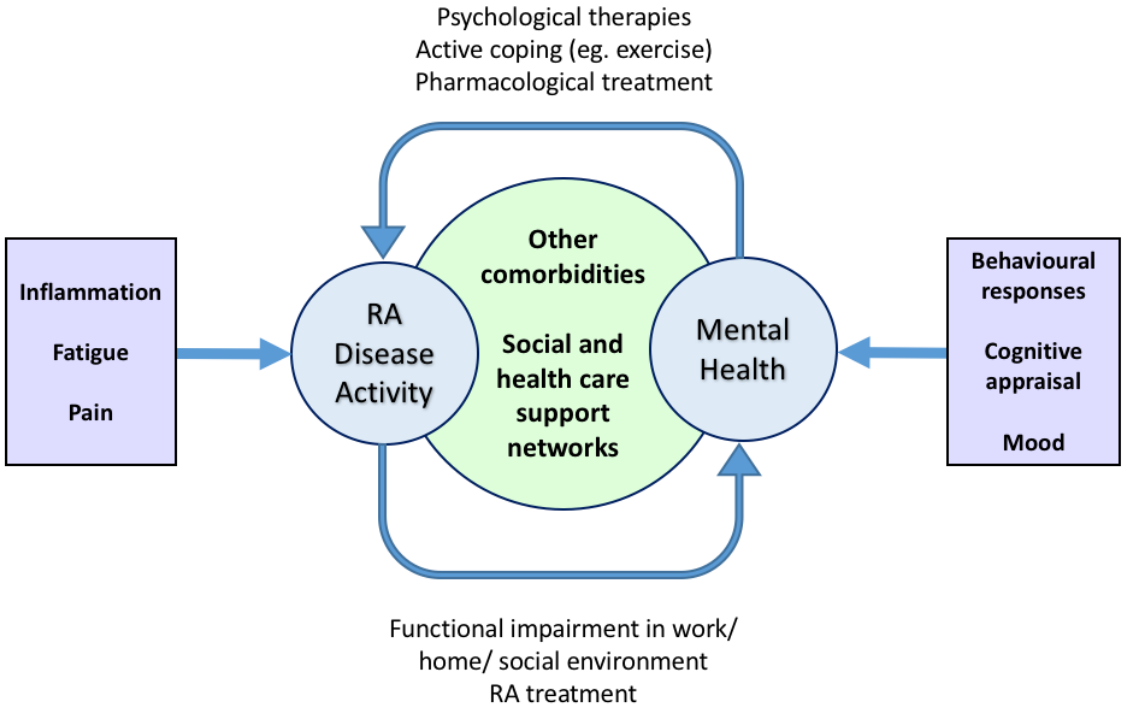
depression compared to those without (2.07 vs. 1.21 per 1,000 person years), athough there may have been some residual confounding as there was no data on educational level and social networks to enable adjustments to be made.

A large cohort study aimed to determine predictors of psychological health (using the mental component summary (MCS) score of the short form (SF)-36) in people with RA. A total of 15,282 participants were recruited from a Swiss and an American cohort. Pain was found to be the most important predictor of psychosocial health in people with RA, followed by disease activity and functional disability (Courvoisier et al*.,* 2012). As participants had to complete at least two SF-36 scores, they may have been more compliant with treatment and had a higher QoL than the general RA population. However, the use of large cohorts from different geographical areas enhanced the generalisability of findings.

The interactions between mental health and RA have been conceptualised in model by Sturgeon et al. (2016), which I have adapted, as shown in figure 2.7 (p51). The figure highlights the bidirectional association between disease activity and mental health. Increased disease activity in people with RA, associated with inflammation, pain and fatigue, can lead to functional impairment, which can negatively influence mental health. Changes in cognitive appraisal (a patients' interpretation of their disease activity), behavioural response (eg. catastrophising) and mood, can affect a persons' mental health, which is further mediated by psychological or pharmacological treatments and active coping, again impacting on disease activity. I have added a dimension, a central circle, to highlight the influence of other comorbidities, MDT support and social networks on mental health and disease activity in people with RA. Beyond this are general socio-economic, cultural and environmental conditions that can

affect the complex relationship between physical and mental health, as summarised in Dahlgren and Whitehead's Rainbow model (1991). In particular, poor living and working conditions, which may relate to lack of employment opportunities, poor housing, or lack of basic requirements such as food, water or sanitation, can negatively impact on mental health and disease activity.

Figure 2.7- *Interactions between RA disease activity and mood, adapted from Sturgeon et al., 2016.*



Most literature examining the impact of mood problems in RA has focused on depression, not anxiety. Several studies have found a significant association between depression in people with RA and a reduced QoL. For example, an Italian study involving 92 RA patients examined the impact of comorbid depression on QoL (Bazzichi et al., 2005). Depressive symptoms contributed to a significant reduction in QoL, even after controlling for functional status, duration of illness and demographic characteristics, though other potential confounding factors such as comorbidities were not controlled for, which could also have affected this association. A further study based in Colombia

examined the relationship between depression and QoL in 103 RA patients compared to 73 controls. RA patients had much higher rates of depression and a lower QoL than controls and a significant negative correlation was found between depression and all QoL subscales, assessed using SF-36 (Senra et al., 2017). However, the small size of this study, limited to a specific geographical area, would limit generalisability.

Several studies have also found depression in people with RA to impact on treatment response. A systematic review examined the relationship between depression, disease activity and treatment response in RA (Rathbun, Reed & Harrold, 2013). Depression was found to decrease the efficacy of pharmacological and some non-pharmacological treatments, such as CBT. Overall results suggested that depression may increase disease activity in RA. However, only English-language articles were included and a search of the grey literature was not performed, meaning the review only included 7 studies. These were of variable quality, with several using convenience sampling which could have led to selection bias, reducing generalisability. Sample sizes were often small, hence when no association was observed this may have been due to a lack of statistical power. In addition, there was a lack of adjustment for potential confounders, hence the observed results could have been due to factors other than depression.

A UK study investigated how mood changed when people with RA were exposed to anti-TNF drugs (Hider et al., 2009). People starting an anti-TNF drug were assessed for depression using the HADS-D, then changes in mood and disease activity (using DAS28) were reviewed at interval over the following year. People with depression had higher DAS28 scores at all time points. In people with persistent depression, smaller reductions in DAS28 scores were also noted in response to anti-TNF therapy. Data were collected at a time when anti-TNF drugs were first introduced to the UK, hence a

severely affected group of historical non-responders to DMARDs were included. Due to having more severe RA and a higher burden of depression, they may not have responded as well, due to having irreversible joint damage from their RA, influencing their mood. However, results suggest that improved identification and management of comorbid depression in people with RA could potentially improve their response to anti-TNF drugs.

A further study examined the relationship between depression and treatment response in 18,421 people with RA receiving biologic treatment, using data from the British Society for Rheumatology Biologics Register (Matcham et al., 2018). Patients who were experiencing symptoms of depression when started on biologic treatment had a 20-40% reduced odds of achieving a good treatment response at 1 year. This poorer response to treatment was maintained beyond 1 year of follow-up. However, this study was limited by the lack of validated tools or diagnostic interviews used to ascertain the diagnosis of depression. Within the database used for this study, three measures of depression were available; any self-reported history of depression upon enrolment to the database; a threshold of ≤40 on the normed mental health subscale of the SF-36; one item specific to mental health on the EuroQol 5-Dimension Scale (EQ-5D). Therefore, there may have been some misclassification of depression, athough the size of the study adds to the likely precision of the estimates.

Another study explored factors influencing disease remission in people with inflammatory polyarthritis. Depression was found to predict a lower disease remission (OR (95% CI) 0.74 (0.55, 1.00)) (Cook et al., 2016). As comorbidities including depression were self-reported, patients could have incorrectly self-diagnosed depression, which could have reduced the observed effect of depression on remission rates.

When the impact of anxiety in people with RA has been examined, this has often been in combination with depression. However, at least 40% of people with anxiety in the general population do not have comorbid depression (Kaufman and Charney, 2000). A study involving a secondary analysis of clinical trial data aimed to determine whether depression and anxiety would predict physical disability, disease activity and treatment response in 379 people with RA (Matcham et al., 2016b). Baseline depression and anxiety symptoms were associated with increased DAS28 and tender joint counts (TJC), whilst persistent mood symptoms were associated with a higher DAS28, TJC, patient global assessment (PtGA) and HAQ scores, indicating increased disease activity and worse physical functioning. Baseline depression and anxiety were also associated with reduced odds of clinical remission and a 50% reduction in response to prednisolone treatment. However, adjustments were not made for the socioeconomic status of participants, which was not recorded, hence it is not possible to establish the extent to which these results reflect patients of low socioeconomic status, or the wider RA population. Therefore, future studies would benefit from taking account of the socioeconomic status of participants and controlling for this within any analysis. In addition, the EQ-5D was used to identify people with RA who had comorbid anxiety and depression. Validated tools containing more detailed questions, such as GAD-7 and PHQ-9, could have more accurately identified people with anxiety and depression, though the proportion of people reporting mood problems within this study was similar to prevalence estimates, improving confidence in the results.

A study in China considered the impact of anxiety and depression on QoL in people with RA (Mok et al., 2012). 200 people with RA were interviewed by a physician, who determined a diagnosis of anxiety and depression. After adjustment for covariates,

anxiety and depression were found to be associated with reduced QoL, measured using the SF-36. Study participants did not include those on biological drugs, who often have more severe RA. Therefore, the QoL of the overall RA population with comorbid mood problems may be worse than reported in this study.

Mental health problems in people with RA have also been found to affect how disease activity is self-reported. For example, a cross-sectional study involving 101 people with RA recruited from a tertiary rheumatology department, evaluated the difference between patient and physician reported global assessments of disease activity (Duarte et al., 2015). People with RA were found to rate their disease activity higher than their physicians. This difference was strongly correlated with increased patient anxiety ($r=0.551$, $p<0.001$) and depression ($r=0.464$, $p<0.001$). In another study, 195 people with RA completed a global assessment of disease activity, which was compared to an assessment by a physician. Anxiety and depression were associated with greater discordance between the patient and physician global assessments of disease activity (Liu, Bathon & Giles, 2015). Both studies used validated tools to diagnose a mood disorder, had moderate sample sizes and considered other potential covariates such as fatigue, functional status and QoL, though almost half of the disconcordance between physician and patient global assessments remained unexplained. This suggests that there are other covariates that have not been considered, that are influencing the differences observed between patient and physician global assessments of disease activity.

A cross-sectional study involving 322 people with RA awaiting biologic treatment, found that when assessing disease activity using DAS28, patient-reported measures such as the visual analogue scale (VAS), which forms part of the DAS28 score,

were more strongly influenced by psychological variables (Cordingley et al., 2014). Therefore, separate reporting of the different components of DAS28 alongside an assessment of mood could help to guide patient management.

Acknowledging the links between mental and physical health in people with RA, a recent systematic review and meta-analysis of 57 trials aimed to determine the impact of RA treatment on mental health problems (Matcham et al., 2019). Following treatment with biologic DMARDs, a small but significant improvement in the mental health of people with RA was noted, when assessed using the SF-36. However, the impact of RA treatment on the MCS score of the SF-36 was approximately half the effect seen on the SF-36 physical component summary (PCS) score. This suggests that mental health problems are unlikely to resolve by just controlling disease activity in people with RA, supporting the need for integrated mental health care within routine practice.

In recognition of the links between mood problems in people with RA, reduced QoL and treatment response, and increased morbidity and mortality, NICE has created Quality Standards for the management of RA (QS33), to facilitate early recognition of comorbid mood problems (NICE, 2013c). Within this Quality Standard, NICE recommends that clinicians should regularly reassess mood within the context of an annual review clinic (NICE, 2013c). This recommendation is also supported by NICE guidelines for the management RA in adults, which recommend that people with RA are offered psychological interventions as part of multidisciplinary care (NICE, 2018).

Recognition and treatment of depression in people with RA can have multiple benefits. For instance, a meta-analysis of 27 RCTs, testing the efficacy of psychological interventions to manage pain, found that people with RA receiving a psychological treatment, reported significantly less pain compared to control groups. Improvements

in secondary outcomes, such as anxiety, depression and self-efficacy were also noted in response to psychological interventions (Dixon et al., 2007). The review was limited by heterogeneity between studies due to the use of different psychological interventions, including CBT, hypnosis and stress management, whilst outcome measures for pain also varied. However, the large number of RCTs included in the meta-analysis increased the overall strength of evidence.

In addition to CBT, affective interventions such as mindfulness meditation have been found to reduce depression in people with RA (Zautra et al, 2008). In a study involving 144 people with RA, participants were randomly assigned to one of three treatments; CBT for pain, mindfulness meditation or an education only group. People with RA who had recurrent depression benefited most from mindfulness meditation, which led to improvements in mood and a reduced TJC. However, the diagnosis of depression was determined using 6 yes/ no questions about mood, not a validated tool, reducing the reliability of results. In addition, although NICE guidelines recommend mindfulness as a way to prevent depression, in people who have had 3 or more episodes of low mood in the past, they do not recommend mindfulness for treatment of active depression, due to a lack of evidence.

An RCT aiming to determine the impact of a self-help intervention on mood problems, involved 82 people with rheumatic disease being allocated to an intervention group, who received an internet-based cognitive behavioural self-help programme, or a control group (Garnefski et al., 2013). When participants were followed up after 2 months, the self-help programme had significantly reduced anxiety and depression symptoms, measured using the HADS. However, participants were recruited online and only included a small number of men, limiting generalisability. In addition, differences

seen between the intervention and control groups could have been due to the additional attention given to the intervention group, rather than the actual self-help programme delivered.

A systematic review and meta-analysis of interventions for depression and anxiety in people with RA, found no RCTs reporting on interventions for anxiety, and eight reporting on interventions for depression (Fiest et al., 2017). From six pharmacological interventions, three were found to improve depression in people with RA. A further RCT reporting the proportion who achieved a 50% reduction in RA symptoms, in response to two different pharmacological treatments, found no significant treatment effect (Bird & Broggini, 2000), whilst one reported psychological intervention did not lead to any significant improvement in depression (Evers et al., 2002). Due to the small number of trials available and the risk of bias within these trials, the level of evidence was only low to moderate, hence further studies would be required to make more definitive conclusions about the most effective treatments to recommend for anxiety and depression in people with RA.

A more recent pilot study aimed to determine whether treatment with antidepressants altered how 128 people with RA and comorbid anxiety and depression responded to DMARD or biologic drug treatment (Abramkin et al., 2018). Over five years, people treated with DMARDs and antidepressants achieved remission significantly more often than those taking DMARDs alone ($p=0.02$), highlighting the potential benefits of integrated treatment of RA and comorbid mood problems, which could improve overall outcomes.

A further study explored the efficacy of a combined pharmacologic and cognitive-behavioural approach to the management of major depression in RA (Parker

et al., 2003). The use of antidepressant medication alone was found to be as effective as a combination of medication and psychological treatment. In addition to improving depression, antidepressants were found to improve the self-efficacy, social interaction and coping skills of participants, whilst reducing anxiety, stress and fatigue. Antidepressant treatment did not impact on pain or disease activity measures, though the small sample size in this study could have led to minor differences between the treatment groups not being recognised. In addition, as the study was only focussed on those with severe depression, different responses to psychological therapies may have been observed in those with mild or moderate depression.

Three hours of low impact aerobic exercise per week, has also been found to positively impact on depression in people with RA. In an RCT involving 220 people with RA, participants were randomised to class or home exercises, or a control group. Exercises did not involve any running or jumping movements and one foot always had to remain on the ground (Neuberger et al., 2007). After 12 weeks of exercise, there had been a significant reduction in pain, fatigue and depression symptoms in the class exercise compared to the control group. This trend was not observed in the home exercise group, potentially due to participants exercising less intensively at home. Through use of a convenience sample, potential selection bias could have affected results, whilst a large number dropped out the study before baseline measures were taken, meaning the remaining participants may have been more motivated to engage with an exercise programme than the general population living with RA.

Despite the benefits of treating comorbid anxiety and depression in people with RA, a national GP survey performed in 2015 found that primary care reviews for people with RA frequently focus on previous QOF domains such as CVD and fracture risk

screening (Hider et al., 2015), whilst questions to identify potential mood problems are often not included. The literature also suggests that most rheumatologists do not routinely screen for depression in people with RA, due to time constraints, a lack of confidence in dealing with mental health issues, or a belief that it is not their responsibility (Nicassio, 2008; Sleath et al., 2008).

A secondary analysis of baseline data from an RCT aimed to determine how rheumatologists and people with RA who had symptoms of depression communicated about their low mood during appointments (Sleath et al., 2008). Audio-recorded consultations of rheumatologists with people with RA were reviewed. From 21 patients who were scored as having moderately severe to severe symptoms of depression (PHQ-9 score >15), only 4 discussed depression during their medical visits, and each time the discussion was initiated by the patient. During 200 audio-recorded consultations, none of the rheumatologists raised the topic of mood problems. The small sample size was a potential limitation of this study, though the study findings highlight the need to improve case-finding for comorbid anxiety and depression in people with RA. No data was obtained on the barriers and facilitators to the discussion of depression during the clinic appointments, which would have provided greater insights as to how care could be improved.

2.9.2 Patient and practitioner perspectives on the identification and management of anxiety and depression in people with rheumatoid arthritis

There is a lack of literature reporting patient and practitioner perspectives on the identification and management of mood problems in people with RA. A study exploring the perspectives of Hispanic patients with RA and depression, reported that

antidepressants were often perceived as unnecessary, or associated with side-effects. Many believed depression was linked to a weakness of character, so perceived that a positive attitude and personal strength would be most important in overcoming depression. However, 80% reported they would be open to seeing a therapist if necessary. The majority felt that support groups providing information about depression and facilitating dialogue between patients would be beneficial (Withers et al., 2015).

The potential stigma associated with a diagnosis of depression could have been a barrier to disclosure or discussion of depression in interviews. Study participants also reported seeing rheumatology clinics as an opportunity to discuss physical, not mental health. The applicability of these results to people with RA, living in the UK, could be questioned, as the majority of Hispanic patients interviewed were of low socioeconomic status, with many being uninsured hence unable to afford treatment. Therefore, they could have expressed a preference for self-management due to the potential expense of psychological therapies or antidepressants. They may also have lacked awareness of alternative management options. Outcomes could also have been influenced by selection bias, as those invited to take part had to be in regular attendance at a rheumatology clinic in Los Angeles. This would have excluded those unable to afford hospital care, newly diagnosed patients or those not motivated to regularly attend the clinic. As a more motivated subset may have been interviewed, the propensity to self-manage depression may have been over-represented. As 89% of participants were female, male views could also have been under-represented.

A survey sent to rheumatology units at 143 acute trusts in England explored the provision of psychological support for people with inflammatory arthritis (Dures et al.,

2014). Nurses from 73 rheumatology units (51%) responded. From these, 73% rated their units' psychological support provision as inadequate, despite most acknowledging that it was within their remit to offer support. Up to 42% reported that they had referred patients requiring psychological support to other services, whilst 26% cited using CBT approaches as part of their consultations. Barriers to the provision of psychological support included a lack of training and sufficient time, difficulty obtaining funding, an emphasis on addressing physical rather than mental health problems and a concern that there was no-one to refer the patient to if problems were identified. Recommendations to improve provision included to address clinicians' training needs and to integrate psychological support into care pathways. Of note, almost half of surveys were not returned in this study. It is possible that the units who didn't respond were systematically different from those who did complete the survey. Some may not have responded due to a lack of knowledge about local services or due to a fear of disclosing negative views about their rheumatology unit, leading to potential under-estimation of the gap in service provision. Alternatively, some may have been motivated to respond by poor local services, to publicise their need for support. It is also possible that some questionnaire responses were influenced by discussion with colleagues, rather than reflecting participants' own perceptions. Respondents may also have lacked sufficient knowledge about local psychological support provision to provide accurate responses.

To explore patients' preferences for psychological support in inflammatory arthritis, a questionnaire was mailed to 1,200 randomly selected people with RA from an arthritis charity database, whilst questionnaires were also consecutively handed out to 1,080 patients attending 6 regional hospitals (Dures et al., 2016a). From these, 53% of patients completed the questionnaire. Overall, demand for psychotherapy was high.

Whilst 66% of patients reported that they would use a self-management clinic, 48% felt they would also benefit from peer support groups. Whilst 46% expressed a desire for counselling, 34% wanted support with managing the impact of their depression. Three quarters identified the rheumatology nurse as one of their ideal sources of support, whilst 50% selected their GP. Less than a third also named a psychologist or counsellor, suggesting fewer patients perceived a need to access specialist psychological support (Dures et al., 2016a). This would mirror a stepped care approach in which patients start with the lowest appropriate treatment and step up to more intensive services as needed (NICE, 2011a; NICE, 2009a). Further preferred sources of support included family and friends, patient support groups and occupational therapists.

It could be argued that the preferences expressed in this study would depend on the individual experiences of patients and their perceptions of different care providers' roles and accessibility (Dures et al., 2016a). With improved access and exposure patients could come to prefer individualised psychological interventions. In addition, the preference of patients in this study to have psychological support delivered by their LTC team contrasts with a nested interview study in the COINCIDE trial, in which patients expressed a preference for a separate space to discuss their mental health concerns (Knowles et al., 2015). Nevertheless, the questionnaire's findings support other research that has found rheumatology team involvement can help patients to improve their sense of disease control and psychological wellbeing (Avidsson et al., 2006). Self-management advice from clinical teams often focusses on biomedical aspects of rheumatic disease. Exploring biopsychosocial factors and empowering patients with CBT techniques could potentially enhance self-management (Dures and Hewlett, 2012). However, this would be dependent on patients taking some responsibility for self-

management and having a degree of cognitive and emotional self-awareness. In addition, clinicians would require training to teach basic CBT techniques and in a time-pressured environment, they could struggle to deliver such interventions effectively.

Responses to the open-ended questions from the study questionnaires provided further insights into the perceptions of patients about the psychological impact of inflammatory arthritis (Dures et al., 2016b). Psychological distress was often attributed to pain and fatigue. Patients reflected on the challenges of an altered life course, including strained relationships, loneliness and fears about the future. Many recounted experiences of feeling unheard or struggling to ask for help and a need to be understood and supported by others, from family and friends, to clinicians. Participants also commented on how they had developed ways to cope with the impact of their arthritis.

Strengths of this study included the large and diverse sample size. However, the closed questions which preceded subsequent open ended questions might have influenced responses and imposed constraints on what participants perceived to be relevant. Compared with qualitative data collected through face-to-face semi-structured interviews, there was no opportunity to encourage participants to clarify responses. However, questionnaire data might have been less affected by social desirability, leading participants to be more open in their responses.

2.9.3 Anxiety and depression in people with ankylosing spondylitis, psoriatic arthritis, polymyalgia rheumatica and giant cell arteritis

As past research exploring mood problems in people with IRCs has mainly focused on one of the commonest conditions, RA, the scale and burden of anxiety and depression in other IRCs, particularly PMR and GCA, has not been studied as extensively.

The main reported literature for AS, PsA, PMR and GCA is summarised in sections 2.9.3.1 to 2.9.3.4.

2.9.3.1 Ankylosing Spondylitis

In AS, estimates of the prevalence of depression vary. A systematic review to determine the prevalence of depression in AS included 17 studies, involving 3187 participants (Hopkins & Moulton, 2016). Within these studies, 6 different diagnostic tools were reported, with prevalence estimates for depression ranging between 4.9-55.5%. In studies using HADS-D to screen for depression, 37.7% had mild depression, (HADS-D ≥8) and 8.2% had moderate depression (HADS-D ≥11). Significant correlations were noted between depression, disease activity and CRP. However, the review was limited by heterogeneity between studies due to the use of different diagnostic tools and thresholds for a diagnosis of depression. Consequently, the prevalence of depression could have been over-estimated due to the lower thresholds required for a depression diagnosis in some studies.

A more recent systematic review aiming to determine the prevalence of depression in AS included 14 studies (Zhao et al., 2018). The pooled prevalence of depression, according to a HADS-D score of ≥11, was 18% (95% CI 3-36%). Almost all of the studies included in the review involved hospital cohorts, who would potentially have had more severe disease than a primary care cohort. However, the included studies were generally of high quality with a low risk of publication bias.

A population-based cohort study based in Sweden aimed to determine the risk of depression in people with AS, relying on depression diagnoses made by a doctor (Meesters et al., 2014). The prevalence of depression in the AS cohort of 1,738 patients

was 10%. Compared to the general population seeking care, there was an 80% increase in depression diagnosed by a doctor in women with AS, and a 50% increase in men. Although adjustments were made for the age and gender of participants, adjustments were not made for other potential confounders. In addition, data was only obtained from individuals who consulted their doctor. Therefore, it is possible the prevalence of depression was under-estimated as some individuals with depression may not have consulted their doctor, due normalising mood symptoms, attributing them to a physical health problem, or potentially lacking motivation to seek help. However, relying on depression diagnoses made by a doctor helped to ensure the validity of diagnoses made.

A population-based cohort study using data from 2 large healthcare organisations in the USA examined the risk of depression in people with AS (Wu et al., 2017). Patients with AS were frequency matched (1:4) with a general population cohort. The adjusted IRR of depression was 1.34 (95% CI 1.23, 1.47). However, patients with a prior diagnosis of depression were not excluded, which could have biased results.

Nonetheless, a retrospective cohort study examining the risk of psychiatric disorders following a diagnosis of AS supported an association between AS and mood problems (Shen et al, 2016). Using the Taiwan National Health Insurance Research Database, the records of 2331 patients with AS were compared to an age and gender matched cohort of 9324 patients without AS. The overall adjusted HR for depressive disorders was 1.72 (95% CI 1.30, 2.27) and for anxiety, 1.85 (95% CI 1.37, 2.50), suggesting that AS is associated with an increased risk of both depression and anxiety. The risk of depression was significantly elevated within a year of diagnosis, though the risk of anxiety only increased beyond a year after diagnosis with AS. The risk of anxiety and depression remained significantly increased over 5 years after diagnosis. Certain

confounding factors could not be controlled for due to a lack of information in the research database, including excessive alcohol consumption, tobacco use and a high body mass index (BMI), all potential risk factors for anxiety or depression. However, it is possible that the prevalence of mood problems was underestimated in this study, as all those included had to have sought medical review. It is possible that individuals with mild symptoms may not have mentioned them, lacking candidacy for care, whilst more severe mood symptoms could have been a barrier to help-seeking. However, AS and psychiatric diagnoses were validated by specialists, whilst a further strength of this study was the large sample size.

Another study aimed to describe the association between disease activity and psychological status in AS. Participants were recruited from an AS review group based at a regional UK hospital and assessed at 6 monthly intervals, up to 4 times (Martindale et al., 2006). From 110 participants, 89 completed all 4 assessments, which included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and HADS. The estimated prevalence of anxiety in AS was 25%, and depression, 10%. Increased BASDAI scores had a significant positive correlation with anxiety and depression. However, it is possible that the characteristics of people attending the AS review group were different from the general population living with AS, reducing the generalisability of findings.

A qualitative study aimed to explore the impact of AS on the daily lives of young men (Primholdt et al., 2017). Semi-structured interviews were conducted with 5 men recruited from a rheumatology hospital in Denmark. For analysis, the natural meaning units in interview texts were identified, then summarised into short statements, before being developed into themes, following discussion by the research team. A main theme was daily living and psychological reactions. Within this theme, one participant reflected

on their experience of being diagnosed with depression after developing AS. They reported being offered antidepressant medication, which they declined in favour of psychological therapy due to already taking several medications. Another participant reported having rarely opened up about their feelings, though the reasons for this were not explored further. Several described how they perceived stress to trigger periods of inflammation and pain. A significant limitation of this study was the small sample size, only consisting of young men. Further patient perspectives could have been gained from a more diverse sample. However, it does suggest that comorbid depression has a significant impact on young men with AS. There is a preference for psychological therapy to manage mood problems, rather than pharmacological treatment, which supports findings in people with RA (Withers et al., 2015; Pols et al., 2018). There are potential barriers to the disclosure of mood problems in this population, which require further exploration.

2.9.3.2 Psoriatic Arthritis

In a systematic review aiming to determine the point prevalence of anxiety and depression in people with PsA, and the impact of PsA treatment on mood, 3 studies met the inclusion criteria (Kamalaraj et al., 2019). The prevalence of depression in people with PsA ranged between 9-22%, whilst the prevalence of anxiety was between 15-30%. One study found that treatment for PsA with etanercept for 24 weeks, led to a reduction in the prevalence of depression and anxiety (Gniadecki et al., 2012), though insufficient reporting of sampling, response rates and methods of analysis increased the risk of bias. The search was kept broad to ensure eligible studies were included, though due to the systematic review only including 3 studies, heterogeneity was high, with variation in

sample populations and the method of anxiety or depression assessment, limiting the strength of findings (Kamakaraj et al., 2019).

A systematic review assessing the incidence and prevalence of anxiety and depression in people with PsA, found 10 studies meeting the inclusion criteria (Zusman et al., 2018). Mood problems were assessed using the HADS, PHQ-9 and the International Classification of Diseases 9th Revision Codes. The pooled prevalence of anxiety, based on 4 studies involving 15,878 people with PsA, was 27% (95% CI=12%, 43%) whilst the pooled prevalence of depression from 6 studies, involving 22,163 people with PsA, was 20% (95% CI= 15%, 25%). The incidence of depression was reported in 3 studies, with meta-analysis yielding a pooled IRR of 1.34 (95% CI= 1.20, 1.49), though the incidence of anxiety was not reported. The quality of included studies varied, increasing the risk of potential bias. In particular, the cut off scores for diagnosis of anxiety or depression within individual studies varied, with some including mild mood symptoms, potentially leading to the pooled prevalences of anxiety and depression being overestimated within this review.

A Canadian study involving 611 people with PsA reported the prevalence of anxiety and depression to be 20.7%. However, as participants were asked to self-report their diagnosis, the accuracy of this estimate would be limited. For instance, some participants may not have recognised they had symptoms of a mood disorder, whilst others may have misdiagnosed themselves with anxiety or depression (Husted et al., 2011).

A cross-sectional study involving 495 patients with PsA determined the prevalence of comorbid anxiety and depression, either by attributing a diagnosis to individuals receiving pharmacological treatment for a mood disorder or by using a score

of ≥11 on the HADS. Whilst 29.7% had symptoms of anxiety, 17.6% were found to have depression (Freire et al., 2011). The study was strengthened by the use of a validated outcome measure, and by being conducted across 75 Spanish hospitals to help ensure a more diverse and representative sample of people with PsA. The higher prevalence of anxiety compared to depression in PsA was supported in a more recent study, where 603 consecutive patients attending a rheumatology outpatient appointment were assessed for anxiety and depression using the HADS (McDonough et al., 2014). However, in this study the threshold for diagnosis was lower, with a HADS score of ≥8 indicating anxiety and depression. Therefore, the overall prevalence of mood disorders was higher in the second study, due to the inclusion of individuals with mild symptoms (HADS score of 8-10), with 36.6% suffering from anxiety and 22.2% depression (McDonough et al., 2014).

A US population-based cohort study examined the risk of depression in 5138 people with PsA, who were frequency matched with a general population cohort (Wu et al., 2017). There was an increased risk of depression in the PsA cohort compared to the general population, with an adjusted IRR of 1.22 (95% CI 1.16, 1.29). However, as patients with a preceding history of depression were not excluded the incidence rate could have been overestimated.

Data from the Clinical Practice Research Datalink (CPRD) was used to examine the incidence rate of treated depression in 7,643 patients with PsA (Hagberg et al., 2016). People with PsA had higher rates of treated depression compared to people without PsA (IRR (95% CI) = 1.38 (1.27, 1.49). The incidence rate of treated depression was even higher in people with PsA who were on systemic therapy, such as a DMARD, to treat their arthritis (IRR (95% CI) = 1.59 (1.35, 1.86). It is possible that the people with

PsA on systemic therapy had more severe PsA, hence potentially more joint pain and functional limitation, which could have impacted negatively on their mood.

A study in Greece aimed to determine the association between psychological factors and Health-Related QoL (HRQoL) in people with PsA and RA (Kotsis et al., 2012). Consecutive patients with PsA attending a follow-up clinic at a rheumatology hospital were recruited (n=83), and compared to patients with RA (n=199) attending the same department. Patients were reviewed by a rheumatologist and asked to complete self-reported questionnaires, which included the PHQ-9 questions and the World Health Organisation QoL instrument (WHOQoL-BREF). In addition, the validated Greek version of the Symptom Checklist-90-Revised (SC-90-R) was used to assess for psychological problems, including anxiety and depression. From 83 patients with PsA, 21.7% had moderate or severe depression, compared to 25.1% with RA, determined by a PHQ-9 score of ≥10. Although the proportions with anxiety were not reported, multiple regression analysis found anxiety and depression, when assessed using the SC-90-R, to be associated with reduced physical HRQoL. However, this association was only statistically significant for anxiety (standardized (ß) regression coefficient= -0.28, $p<0.01$). Due to the small sample size of patients with PsA, the generalisability of these findings would be limited. It is possible that the association between PsA and depression could also have reached statistical significance with a larger sample size.

A systematic review and thematic synthesis of patients' experiences of psoriasis and PsA included 56 studies involving 337 individuals with PsA (Sumpton et al., 2019). The majority of data related to people with psoriasis. However, people with PsA reported a sense of life disruption and fear of deterioration, with anxiety provoked by the unpredictability of joint flares. Some reported poor recognition of their distress by

medical professionals or expressed hopelessness and suicidal thoughts due to the burden of their symptoms. Preliminary findings suggest that through validation of the burden of PsA and a holistic approach to care, the recognition of mood symptoms in this population could be improved. Initially though, further research is required to determine the prevalence of anxiety in people with PsA.

2.9.3.3 Polymyalgia Rheumatica

A study exploring the clinical characteristics of people with PMR found the prevalence of depression to be 2% (Kimura et al., 2009). However, this study only involved 123 patients who were all treated at one community hospital, limiting generalisability. In addition, the diagnosis of depression was determined by medical record review, without using a validated measurement tool, hence it is likely that some people with depression were missed.

A study using the MCS of the SF-36 to ascertain depression, found that people with PMR had significantly lower mean MCS scores at presentation, than population norms within the same age range (65-74 years) (MCS scores 38.9 versus 53.2) (Hutchings et al., 2007). This would indicate that the emotional QoL or mental health of people with PMR, was worse than in people without PMR. However, the MCS had improved significantly after 12 months, suggesting that depression improved following treatment for PMR.

A recent cross-sectional study aimed to determine the prevalence of depression in PMR (Vivekanatham et al., 2018). Questionnaires were sent to older adults from 150 general practices with a first Read code for PMR in their medical records within the preceding 3 years. Depression was measured using the PHQ-8, with current depression defined as a PHQ-8 score of ≥10. From 550 respondents, 15% reported symptoms of

depression. Depression was significantly associated with female gender and PMR symptoms. People aged over 80 years were less likely to report depressive symptoms than younger people aged 50-59 years. Due to the complexity of diagnosing PMR, it is possible that some diagnoses made by GPs were inaccurate. However, the majority of PMR diagnoses are made in primary care and rheumatologists are likely to see individuals with a different disease spectrum, who are unlikely to represent the general population living with PMR, hence using a primary care population increased generalisability.

For a cohort study aiming to characterise people with incident PMR in primary care, people with newly diagnosed PMR were mailed baseline questionnaires to complete (Muller et al., 2016). These included the GAD-7 and PHQ-8 questions for anxiety and depression, with a score of ≥10 indicating moderate to severe mood problems. From 739 individuals mailed a questionnaire, 654 responded, of whom 13% had moderate to severe anxiety and 22% had moderate to severe depression. This study was strengthened by a large sample size including participants from across the UK, increasing generalisability.

A qualitative study explored peoples' experiences of living with PMR (Twohig et al., 2015). A total of 22 semi-structured interviews were analysed thematically using constant comparison, with 5 key themes emerging, including the psychological impact of PMR. Participants described the impact of disability on their mood and reported feeling fearful about their future prognosis. Many reported feeling relieved after being diagnosed with PMR, as they had both a label to validate their experiences and knew they could have an effective treatment to relieve their symptoms. Following diagnosis, several reported feeling anxious about potential medication side-effects and their

future disease trajectory. Results suggest PMR has a profound psychological impact, particularly prior to a diagnosis being made, hence acknowledging and helping patients to manage their anxiety could lead to improved outcomes. Of note, GPs conducted interviews, which could have affected the way participants discussed their experiences. However, the setting of interviews which were conducted in a naturalistic style helped to mitigate against this. The study was strengthened by the recruitment of participants from primary care, where the majority of PMR is managed, to help ensure transferability of findings.

2.9.3.4 Giant Cell Arteritis

A UK cohort study examined the association between GCA, vascular disease and other comorbidities in people with GCA compared to non-vasculitis patients (Li, Neogi and Jick, 2017). Within the CPRD database, 9,778 people with GCA were identified. Each individual was matched by age, gender and practice, to 10 people without vasculitis. Individuals with GCA were more likely to have a history of depression (17.6% Vs 13.8%, $p<0.0001$), whilst the risk of developing depression in people with GCA was also significantly increased (HR (95% CI) = 1.32 (1.25, 1.39). Limitations included the potential misclassification of GCA cases and a risk of detection bias, whereby people with GCA may have had more clinical contacts leading to an increased number of comorbidities being recognised and coded in the clinical record. However, a strength of this study was the large national database utilised, which increased the generalisability of results.

A qualitative study explored the perspectives of individuals with GCA on the impact of their condition (Liddle et al., 2017). A total of 24 patients with GCA participated in semi-structured telephone interviews and an inductive thematic analysis

of transcripts was performed. GCA was noted to have a substantial impact on patients' bodies and minds, with themes including fear and anxiety, loss of confidence, and changes in mood and sleep. Body changes secondary to glucocorticoid therapy and fear of potential visual loss contributed to the psychological symptoms reported by patients. It is possible that face-to-face interviews could have facilitated further development of rapport and subsequent disclosure of more thoughts and experiences by participants, enabling deeper insights. In addition, the sample included a lack of individuals from ethnic minorities. However, analysis was supported by brief field notes, and interviews were conducted until data saturation was reached.

There is a lack of literature on the incidence and prevalence of anxiety in GCA, though comorbid mood problems are likely to be a significant burden in this condition which require further investigation.

2.10 Summary

RA is an inflammatory joint disease that affects 0.67% of the population (Ahbishek et al., 2017). In common with other LTCs, the prevalence of mood disorders in people with RA is high, with approximately 20% having anxiety and 38.8% depression (VanDyke et al., 2004; Matcham et al., 2013). Links have been identified between anxiety and depression in LTCs such as RA, and increased morbidity and mortality (Ang et al., 2005; Abhishek et al., 2018). Therefore, recognition and treatment of mood disorders in LTC's should be a health care priority. Despite this, QOF incentives to ask case-finding questions in CHD and diabetes have recently been retired, and although the QOF incentivises an annual review of RA this doesn't specify mood assessment (NHS Employers, 2015). NICE does recommend a regular reassessment of mood within an RA

annual review clinic (NICE, 2013c) though this guidance doesn't extend to patients with other IRCs such as AS, PsA, PMR and GCA.

There is some evidence to suggest that comorbid mood problems are also common in other IRCs, though further research is required, particularly to determine the prevalence of anxiety and depression in people with PMR and GCA.

NICE has created guidelines on the identification and mangement of depression in adults with chronic physical health problems (NICE, 2009b), though guidelines for anxiety have been relatively neglected. The literature suggests that the two stem questions are sensitive at detecting depression and also preferred due to their ease of application (Meader et al., 2011; Whooley et al., 1997), though the way in which these questions are posed could lead to systematic under-detection of depression (Maxwell et al., 2013).

SMIs to support people with RA to self-manage their condition (Vermaak et al., 2015), in addition to psychological interventions (Dixon et al., 2007), can reduce anxiety, depression and pain. Antidepressants can also reduce low mood and fatigue, whilst helping to improve the self-efficacy of people with RA (Parker et al., 2003). Despite a high demand for psychological therapies in people with RA (Dures et al., 2016a), a recent survey suggested that provision of support in UK rheumatology units is largely inadequate (Dures et al., 2014). There is a lack of evidence about how comorbid mood problems in other IRCs should be managed.

2.11 Rationale for studies reported in this thesis

In people with RA, comorbid mood problems are often not recognised or treated and can lead to increased morbidity and mortality. Understanding patients' preferences

regarding case-finding for anxiety and depression in RA could inform the development of an intervention to improve the recognition and management of comorbid mood problems, potentially improving overall outcomes.

Past research into comorbid mood problems in IRCs has mainly focused on the prevalence and impact of depression in RA. When the impact of anxiety in RA has been examined, this has often been in combination with depression, despite at least 40% of individuals with anxiety in the general population not having associated depression. Anxiety has also been linked to different help-seeking behaviour and can be managed differently from depression. Understanding the impact of anxiety on the QoL and disease activity of people with RA could provide evidence to support the recognition and appropriate management of this frequent comorbidity, and suggest areas for future implementation studies to improve outcomes.

As prior research has focused on RA, there is a lack of literature reporting the prevalence of mood problems in people with other IRCs, such as AS, PsA, PMR and GCA. Determining the proportion of people living with IRCs who have recognised mood problems and comparing this to the number who self-report mood symptoms when asked to respond to case-finding questions, could help to determine whether many people with IRCs have unrecognised mood problems.

Although NICE recommends that people with RA should have a holistic annual review including an assessment of mood, there is no similar guideline for people with other IRCs. Improving our understanding of comorbid mood problems in different IRCs could help to inform the development of a primary care nurse-led annual review for people with IRCs, to improve the recognition and management of anxiety and depression, which could potentially reduce associated morbidity and mortality.

CHAPTER 3

Aims and Objectives

3.0 AIMS AND OBJECTIVES

3.1 Research questions

1. What are the preferences of people with rheumatoid arthritis (RA) for the identification and management of comorbid anxiety and depression?

2. What is the association between anxiety in people with RA, and disease activity and quality of life (QoL)?

3. What is the incidence and prevalence of anxiety alone, in addition to anxiety and/ or depression, in people with different inflammatory rheumatological conditions (IRCs), including RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA), polymyalgia rheumatica (PMR) and giant cell arteritis (GCA)?

4. What is the prevalence of anxiety and depression, when determined using the case-finding questions for mood problems, in people with different IRCs (RA, AS, PsA, PMR and GCA)?

3.2 Aims and objectives

My overall aim within this thesis, has been to investigate comorbid mood disorders in people with IRCs.

My specific aims have been as follows;

1. To explore the experiences of people with RA of help-seeking for comorbid anxiety and depression and to understand their preferences for the identification and management of comorbid mood problems.

2. To understand the impact of anxiety on the QoL and disease activity of people with

RA.

3. (a) To determine the proportion of people with different IRCs who have mood problems which have been recognised and treated.

(b) To establish whether the risk of a person developing a mood problem is increased after they are diagnosed with an IRC.

4. To determine the proportion of people with IRCs who have active mood problems, which may not have been recognised or recorded using Read codes in their primary care records.

My specific objectives have been as follows;

1. Interview people with RA to explore their perspectives of comorbid anxiety and depression and their preferences for the identification and management of comorbid mood problems.

2. Review the literature reporting the association between anxiety in people with RA, and disease activity and QoL.

3. (a) Determine the proportion of people with IRCs who have a current mood problem that has been identified and recorded in their primary care records.

(b) Retrospectively examine the number of people who have developed a mood problem after being diagnosed with an IRC, which has been identified and recorded in their primary care records.

4. Send people with IRCs a questionnaire to complete which includes case-finding questions to identify potential anxiety and depression, then analyse their responses to determine the prevalence of self-reported mood symptoms.

3.3 Studies performed to respond to the research questions

In order to respond to my specific research questions, I have used mixed methods to complete four main studies, as outlined below. These include a qualitative study, a systematic review, a cohort study and an analysis of baseline questionnaire data collected as part of the INCLUDE (INtegrating and improving Care for patients with infLammatory rheUmatological DisordErs in the community: A pilot randomised controlled trial) study (Hider et al., 2018). INCLUDE is a pilot trial, aiming to determine the feasibility and acceptability of a nurse-led annual review based in primary care, for people with IRCs.

1. Qualitative Study (Chapter 5)

To explore the perspectives of people with RA of comorbid mood problems, I have interviewed people with RA who attended a nurse-led integrated review at a community rheumatology hospital.

2. Systematic Review and meta-analysis (Chapter 6)

To determine the association between anxiety in people with RA, and QoL and disease activity, I have performed a narrative synthesis, then meta-analysis of primary outcome measures for QoL and disease activity**.**

3. Cohort Study (Chapter 7)

Using primary care data, I have investigated the prevalence of, and factors associated with (a) anxiety alone and (b) anxiety and/ or depression, in people with IRCs and have investigated whether there is an association between the diagnosis of an IRC (RA, PsA,

AS, PMR, GCA) and subsequent consultation for (a) anxiety alone or (b) anxiety and/ or depression.

4. INCLUDE Study (Chapter 8):

I have analysed responses to baseline patient questionnaires, completed by INCLUDE study participants, to determine the prevalence of anxiety and depression in people with IRCs (RA, AS, PsA, PMR, GCA) and covariates associated with mood problems.

CHAPTER 4
Methodologies

4.0 METHODOLOGIES

4.1 Overview

Within this chapter I will review my overall aims which have guided my research methodologies. Considering my ontology and epistemology, I will justify my decision to take a pragmatic approach (section 4.3), using mixed methods (section 4.4). In particular, I will discuss my use of a multiphase mixed methods design (section 4.5), which has enabled me to address a broad range of sequential research questions. Finally, in response to each research question, I will justify my methodological approach to data collection and analysis (section 4.6). I have described my methods in further detail within each study chapter (5-8).

4.2 Overall study aims

Overall, I aim to investigate comorbid mood problems in people with inflammatory rheumatological conditions (IRCs). As discussed in chapter 3, my specific aims are as follows;

1. To explore the experiences of people with rheumatoid arthritis (RA) of help-seeking for comorbid anxiety and depression and to understand their preferences for the identification and management of comorbid mood problems.
2. To understand the impact of anxiety on the quality of life (QoL) and disease activity of people with RA.
3. To determine the proportion of people with different IRCs who have mood

problems which have been recognised and treated, and to establish whether the risk of a person developing a mood problem is increased after they are diagnosed with an IRC.

4. To determine the proportion of people with IRCs who have active mood problems, which may not have been recognised or recorded in their primary care records.

4.3 Theoretical Approach

Ontology is a word derived from the Greek, ontos (means) and logos (reason), meaning the study of being. Ontology is concerned with understanding existence and what constitutes reality. Epistemology, from the Greek, episteme (knowledge) and logos (reason), means the theory of knowledge (Grix, 2010). Epistemology builds on the desire to know about being and reality, by determining how we understand the world, what constitutes valid knowledge and how it can be obtained (Grix, 2010).

My first research question aimed to explore the perspectives of people with RA on case-finding for comorbid mood problems. Therefore, my understanding of what it meant to be human and what constituted human experience was essential. I needed to gain insight to the meaning people drew from their interactions with the world. I did not want to merely explain how people behaved when seeking help for mood problems, but to understand the reasons why they behaved in a certain way, so that I could suggest ways in which the recognition of mood problems in people with RA could be improved.

Consequently, when approaching my first research question, my ontology, or understanding of what constituted reality, was a world in which existence became meaningful in the minds of humans through their interactions with the world.

Therefore, when approaching my first study I referred to a method of inquiry in philosophy known as phenomenology, which is based on the premise that reality consists of objects and events (phenomena) as they are perceived in the human consciousness (Kaufer & Chemero, 2015). In particular, I was influenced by phenomenologists such as Edmund Husserl (1859-1938) and Maurice Merleau-Ponty (1908-1961), who studied the meaning of human consciousness and awareness. Husserl (1970) argued that people and objects in the world were interdependent, hence could not be described in isolation, whilst Merleau-Ponty (1945) suggested that all human experiences were formed by an interaction between the body, mind and world.

Therefore, in order to obtain deep insights, I needed to explore peoples' interactions with the world and how they interpreted their experiences of seeking help for mood problems. From my review of the background literature, I understood that mood problems in people with RA had complex biological, behavioural and psychosocial interactions, hence could not be considered in isolation of the world. Peoples' perspectives would differ based on their experiences and interpretations, hence I was not seeking an objective truth, rather an understanding of multiple truths observed through the eyes of individuals. In depth insight into these perspectives would not have been possible through structured questionnaires, but rather through exploratory questioning.

Building on this understanding of what constitutes reality, my epistemology, or theory of knowledge, was based on constructing meaning from peoples' interactions with the world. This is known as a constructivist epistemology (Crotty, 1998). Constructivists believe that individuals develop varied subjective views of their experiences, formed through interactions with others, but also, through historical and

social norms that operate in individuals' lives. Constructivist researchers aim to interpret the views others have about the world to generate theories. I determined that an inductive approach, constructing theories from the data, would enable me to incorporate different perspectives and be open to new insights, to facilitate understanding about mood problems in people with RA.

This approach contrasts with positivism, a theoretical perspective drawn from an objectivist epistemology. Positivists believe knowledge is based on natural phenomena and assume there is a stable reality where phenomena exist whether we observe or understand them. They believe knowledge is based on natural phenomena, which researchers derive information about through sensory experiences, then interpret using reason and logic (Green & Thorogood, 2009). A positivist approach would have been too inflexible to address my initial research question and would not have facilitated the depth of understanding of social processes that I aimed to achieve. Whilst a positivist approach would have helped me to explain the behaviour of participants, a constructivist approach enabled me to understand it, through exploration of peoples' perspectives of their experiences.

Positivists advocate "value-free" enquiry. To enable scientific enquiry to be true for all places and times, positivists believe research should not be influenced by a researchers' political or emotional views (Green & Thorogood, 2009). However, it could be argued that truth varies according to the time and place. Throughout history our understanding of the world has developed and widely held truths have evolved. In order to obtain deep insights into phenomena, we also need to acknowledge their context in peoples' lives and in the wider political environment. With depth of understanding then

comes the ability to suggest outcomes that can be applied in the real world to have a meaningful impact.

A “value-free” approach to understanding patients’ perspectives of mood problems in RA would not have been possible. In order to obtain deep insights, I had to closely interact with participants, during which time my role as an interviewer and furthermore, a general practitioner (GP), potentially influenced patients’ perspectives. Denscombe described the "interviewer effect", whereby an individuals’ perception of their interviewer influences their response to questions (Sim & Wright, 2000, p109), with social differences such as nationality, race, class, age, gender and socioeconomic status all potentially affecting the establishment of rapport. When GPs participating in qualitative studies were interviewed by a peer, rather than a researcher from another discipline, richer and more personal accounts of attitudes and behaviour were obtained from participants, when they knew their interviewer was a clinican (Chew-Graham, May & Perry, 2002). However, the GP interviewer was also identified as an expert and judge of clinical decision making and moral judgements. This could have led participants to be reluctant to disclose negative views of clinicians, or to be afraid of saying something clinically inaccurate, possibly making interviews less insightful.

Therefore, I determined a “value-bound” approach to my first research question would be most appropriate. This acknowledges the researcher as part of what is being studied that cannot be separated (Sim & Wright, 2000). However, if a researcher is not open about their preconceptions and how these influence their research, this could affect the reliability of a study. Consequently, Lincoln and Guba (1985), have described the importance of reflexivity, which entails a researcher being aware of their influence on the process and outcomes of research. Through reflexivity, researchers acknowledge

how the research process has bought about changes in themselves, but also how these changes have affected the research process.

Lincoln and Guba (1985), have suggested that researchers could make regular diary entries during a research project, to facilitate reflexivity. However, researchers could keep these diary entries private and not critically reflect on their content or openly acknowledge their own influence on the interpretation of results. Alternatively, researchers could discuss their interpretations of phenomena with colleagues, to help acknowledge their personal impact on a study. However, the success of this approach would depend upon colleagues feeling able to challenge each others' beliefs and would be less effective if researchers were selective about who they discussed their research with, for example, if they approached people with similar world viewpoints. Consequently, having multiple investigators contributing to a study could help to promote dialogue and reveal hidden beliefs or perspectives, which could lead to the development of complementary as well as divergent understandings of a study (Barry et al., 1999). Reporting the influence of preconceptions and values on a research project within publications could also help individuals to more accurately interpret research outcomes, through awareness of a researchers' viewpoint.

Alternatively, postpositivism represents the thinking after positivism, recognising that all observation has error, and theories are revisable (Philips & Burbules, 2000). Whilst positivists emphasize independence between the researcher and the object of research, postpositivists accept that the values of the researcher can influence what is observed. In addition, whilst positivists believe science aims to uncover the truth, postpositivists believe an absolute truth can never be found, hence they indicate

a failure to reject a hypothesis, rather than stating they have proven a hypothesis to be correct or incorrect (Creswell, 2014).

Whilst postpositivists acknowledge that researchers and the object of their research (eg. a person being interviewed) are not independent, a postpostivisit approach would still have required me to test a hypothesis, be objective and examine my methods and conclusions for bias (Creswell, 2014). Drawing on my experiences as a GP and the background literature on comorbid mood problems in long-term conditions (LTCs), I had some pre-existing ideas which I could have used to develop a hypothesis. However, in response to my first research question, I wanted to maintain an open and exploratory approach, to ensure that I considered all potential perspectives. Therefore, I determined a constructivist approach would be most appropriate, to enable me to discover the meaning participants attached to their experiences and also to react to unexpected findings and broaden my enquiry when necessary.

Although my initial study was underpinned by a constructivist epistemology, my approach had to change in response to my subsequent research questions. To provide further insight into mood problems in people with IRCs, I had to utilise quantitative methods, guided by an objectivist epistemology.

For example, by performing a cohort study, and through analysis of baseline questionnaire data within the INCLUDE study, I aimed to test a hypothesis, that mood problems were more common in people with IRCs. I aimed to uncover objective truths, not to understand patients' perspectives or to generate theories. Taking a "value-bound" approach underpinned by a constructivist epistemology could have biased my results, as I aimed to conduct a "value-free" enquiry, avoiding any potential emotional, subjective or political influence on my results.

In addition, to determine the impact of anxiety in people with RA, I aimed to test a theory that anxiety was associated with increased disease activity and a reduced QoL. Consequently, I again needed to undertake value-free enquiry, underpinned by an objectivist epistemology. However, I was also open to identifying any patterns in the data and generating new potential theories when analysing data found through the review.

Systematic reviews can be described as aggregative or configurative in nature. Whilst aggregative reviews have a positivist foundation, aiming to test a theory using a priori methods to draw together all available evidence, configurative reviews have an idealist philosophy, aiming to generate theories by exploring available evidence (Gough et al., 2012). Therefore, although my review had a realist foundation, underpinned by an objectivist epistemology, I was open to generating new theories on performing my analysis, taking a constructivist approach. Therefore, my theoretical foundation for this review included different philosophical viewpoints. Consequently, in order to respond to all of my research questions, I decided that I needed to take a more pragmatic approach.

A pragmatic worldview emphasizes using all approaches available to understand a research problem (Creswell, 2014). Charles Pierce (1839-1914) developed the pragmatic maxim, which functions to guide the conduct of thought toward its' purpose. Pierce sought to clarify the meaning of different intellectual concepts by tracing their practical consequences, whilst later twentieth century contributors, William James (1845-1910) and John Dewey (1839-1914), emphasized the importance of the consequences of actions based upon particular conceptions (Cherryholmes, 1992). Therefore, Pierce, along with James and Dewy, sought to move the focus of research

from theories and descriptions to future practical applications, with research being driven by anticipated consequences (Haack & Lane, 2006: p.18-26). This suggests that they were keen for research to have a practical application, rather than being performed to build on existing theories and descriptions, without any meaningful change being implemented. Morgan (2007) later highlighted the importance of a pragmatic approach, to focus attention on a research problem and enable the use of a combination of approaches to derive further knowledge about a problem. The use of different philosophical approaches with a combination of methods, was recognised to enable more complex research questions to be answered, with the focus being maintained on problem solving to reach a practical application or meaningful consequence.

Pragmatism is not committed to one system of philosophy. Truth is not based on a duality between reality within the mind or independent of the mind. Instead, pragmatists see truth as what works at the time. Therefore, rather than subscribing to a single approach (eg. qualitative or quantitative), pragmatists use different methods to collect and analyse data, to gain the best possible understanding of the research problem (Creswell, 2014). Taking a pragmatic approach, enabled me to conduct a qualitative study underpinned by a constructivist epistemology, then subsequently take an objectivist approach to my quantitative research on the incidence and prevalence of mood problems. A pragmatic approach also enabled me to conduct a systematic review underpinned by positivist foundations, but to consider a theory generating approach when analysing the overall evidence found, to help explain patterns in the results. Consequently, a pragmatic approach enabled me to use a range methods underpinned by different epistemologies, in order to gain a greater understanding of my overall research question.

4.4 Mixed Methods Design

In this section I will provide a background to mixed methods designs and how they can be classified. Subsequently, in section 4.5, I will discuss my methodological approach to each of my studies, before justifying my use of a multiphase mixed methods design (section 4.6), to address my research questions.

4.4.1 Overview

Methodology refers to the principles underlying the research approach taken and applies to data collection and analysis (Britten, 2011). I have taken a mixed methods approach to maximise my potential to understand the detection, incidence, prevalence and impact of mood problems in people with IRCs.

Mixed methods research involves the generation, analysis and mixing of both quantitative and qualitative data in response to research questions or hypotheses (Johnson, Onwuegbuzie & Turner, 2007). Data can be collected in a single study or a series of studies, concurrently, whereby different sets of data are obtained simultaneously and are independent of each other, or sequentially, whereby data are collected in different phases, through which the data are connected (Creswell & Plano Clark, 2007).

Mixed methods research emerged as a concept during the 1950s, and has since gone through several stages of development which include the Formative Period, Paradigm Debate Period, Procedural Development Period, Advocacy and Expansion Period and the Reflective Period (Creswell, 2011).

During the Formative Period, researchers first began using more than one method within a study. For example, Campbell and Fiske (1959), introduced the use of

multiple quantitative methods within a single study, to enable better validation of diagnostic measures. Later, Cook and Reichardt (1979) discussed ways to combine both qualitative and quantitative data, arguing that both of these approaches would be required to enable a comprehensive evaluation. For example, a medical screening test could have a high sensitivity and specificity on quantitative evaluation, though would need to be acceptable to patients on qualitative evaluation, to make it viable for use in screening.

Despite the benefits of comprehensive evaluation being recognised during the Formative Period of mixed methods development, researchers began to question whether it would be appropriate to integrate different philosophical perspectives within a mixed methods study, which led to the Paradigm Debate Period (Rossman & Wilson, 1985). Whilst people known as "purists" viewed qualitative and quantitative methods as mutually exclusive, others, known as "situationalists", argued that both methods were of equal value and that their use should be adapted to different circumstances. Meanwhile, "pragmatists" argued that different methods could be integrated together to provide a more workable solution to research questions (Rossman & Wilson, 1985).

A pragmatic approach, using mixed methods, aims to combine the strengths and offset the weaknesses of qualitative and quantitative studies. Qualitative studies can provide deep insights into peoples' lives and enable voices to be directly heard, though sample sizes are often small and lack generalisability. Meanwhile, although quantitative studies don't provide the same depth of understanding about individuals' lives, through the use of large, randomised samples, they can provide data which is more generalisable at a population level. Therefore, using a combination of methods can help to answer more complex questions and provide a more complete understanding of phenomena

(Gelo, Braakmann, & Benetka, 2008). Although the skills, time and resources required for mixed methods research can be challenging, particularly for a single researcher, taking this approach can provide useful opportunities for collaboration between qualitative and quantitative researchers, who can learn from each others' expertise, corroborate or elaborate on findings (Creswell, 2011).

Over time, quantitative and qualitative researchers began to reach agreement on some points of philosophical disagreement, acknowledging that observation was not a direct window into reality, but that observations were affected by peoples' prior experiences and knowledge (Tashakkori & Teddlie, 1998). However, some researchers continued to debate whether pragmatism could be embraced as a philosophical foundation for mixed methods research. For example, in 2004, Howe argued that mixed methods approaches could lead to the marginalisation of qualitative research. Subsequently, in 2006, Giddings argued that mixed methods would not necessarily produce the "best of both worlds" (p. 195) and could lead to reduced methodological diversity within qualitative and quantitative research. However, others argued that a team-based approach, involving both qualitative and quantitative researchers, would ensure equal representation of different methods and help to maintain methodological diversity within studies (Creswell, 2011).

Despite continued debate, researchers did begin to seek a greater understanding of how to conduct a mixed methods study. This led to the third phase of mixed methods development, known as the Procedural Development Period. Designs were developed that varied in terms of the priority given to qualitative and quantitative data and the sequence in which data were collected (Morgan, 1998). However, these designs did not consider different stages of data integration. Therefore, Tashakkori and Teddlie (1998)

proposed further mixed methods designs which included integration of methods at the data collection, analysis or interpretation stages. Another consideration raised during the Procedural Development Period was the need to take account of a researchers' perspective when commencing a study. All researchers have pre-existing assumptions based on their gender, culture and experiences that may influence their research, whilst social scientists can also view their enquiries through a formal lens, for example, from a feminist perspective. Therefore, researchers also suggested that a transformational value or action-orientated perspective would need to be considered within mixed methods designs (Greene & Caracelli, 1997).

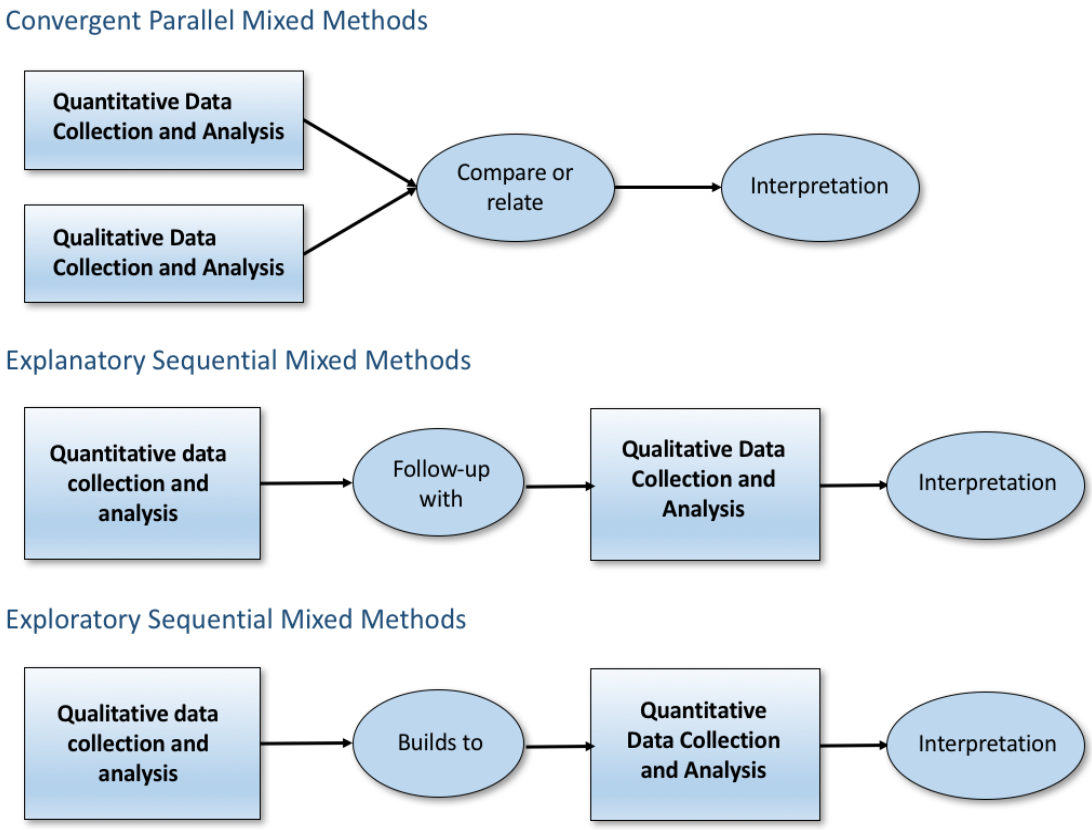
During the Advocacy and Expansion Period, mixed methods became recognised as a distinct discipline (Johnson & Onwugebuzie, 2004). Methodological pluralism facilitated the triangulation of data, using different methods or data sources to develop a comprehensive understanding of phenomena and to test the validity of results (Patton, 1999). Publications also highlighted the rationale and potential for mixing methods within research (Creswell, 2009). The final period of mixed methods development, the Reflective Period, has continued until the present day. Researchers are still discussing the priorities, issues and controversies surrounding mixed methods research (Creswell, 2011). A growing body of evidence suggests that merging different approaches to answer a specific research problem does not compromise methodological purity, but can enhance the rigour of a study. It is important that this debate continues, as more regular use and discussion of mixed methods will facilitate advancement of its' concepts. The multitude of mixed methods designs that were proposed during the Paradigm Debate Period have since been distilled into three basic and several advanced designs. These designs take account of the main factors that help

researchers to determine which mixed methods design to use, and are described in detail in section 4.4.2 (Creswell, 2014).

4.4.2 Classification of mixed methods designs

Creswell (2014) identified three basic mixed methods study designs, as outlined in figure 4.1 (p98). First, a convergent parallel approach involves the researcher collecting and analysing qualitative and quantitative data separately, for example through qualitative interviews and questionnaires on the same subject, then comparing the results to see if the findings confirm or refute each other. Secondly, an explanatory sequential design involves a first phase in which the researcher collects and analyses quantitative data. The results are then used to plan a second qualitative phase, which helps to explain the initial quantitative data in more detail. An example would be to collect and analyse survey data, then conduct qualitative interviews to help explain the survey findings. Thirdly, an exploratory sequential design involves a first phase during which qualitative data is collected and analysed, with the results informing the design of a second quantitative phase. For example, this could involve an initial focus group which informs the development of an instrument which can be tested on a sample of the population. These different designs help to highlight the benefits of mixed methods research, which can be used to gain deeper insights by comparing outcomes of different methods or to plan and inform different stages of research, helping to ensure plans are evidence-based and relevant to patients.

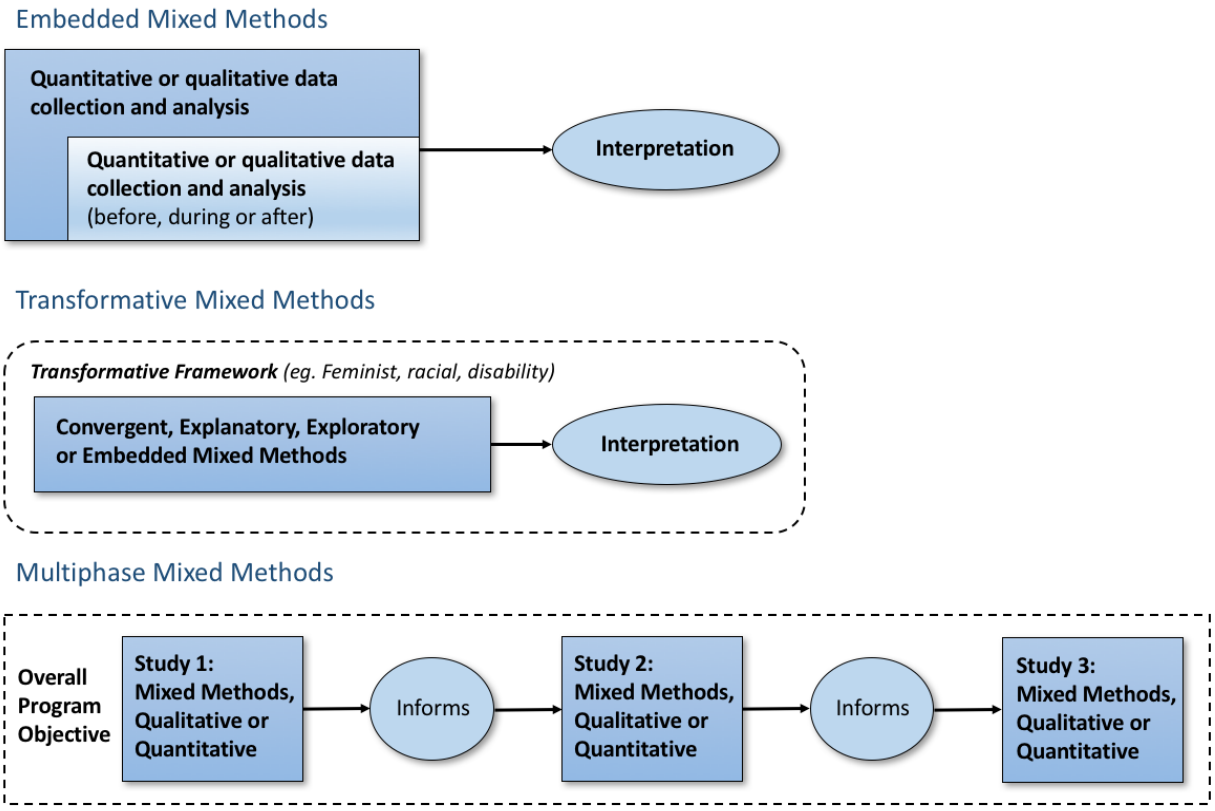
Figure 4.1- *Basic mixed methods designs. Figure adapted from Creswell, 2014, p220.*



As outlined in figure 4.2 (p99), Creswell (2014) also developed several advanced mixed methods designs, incorporating elements of the convergent, explanatory sequential and exploratory sequential approaches. Firstly, the embedded mixed methods design nests one or more forms of data (qualitative, quantitative or both) within a larger design (eg. a narrative study). Secondly, in transformative mixed methods, the researcher uses a social justice theory (eg. feminist) as a framework for a mixed methods study, with the theory framing aspects of the study from the research question to data collection, analysis and interpretation. Thirdly, in multiphase mixed methods, researchers conduct several projects in a longitudinal study, with each stage building on the last to address a common issue. This can include convergent and

sequential mixed methods approaches, or sometimes only qualitative or quantitative studies.

Figure 4.2- *Advanced mixed methods designs. Figure adapted from Creswell, 2014, p221.*



4.5 Methodological Approaches to Individual Studies

In the following sections, I will provide an overview of my main research questions, before justifying my methodological approach to each. Subsequently, in section 4.6, I will describe how these studies were linked within a multiphase mixed methods design and explain my reasons for this overall approach, referring back to my justifications for the methodological approach taken in each study.

4.5.1 Exploring the perspectives of people with RA of comorbid mood problems

4.5.1.1 Research question and overview of methodological approach

> What are the preferences of people with RA for the identification and management of comorbid anxiety and depression?

To address this first question, I conducted a qualitative study, aiming to explore the perspectives of people with RA of comorbid mood problems.

4.5.1.2 Justification for qualitative methods

Qualitative methods involve a process of enquiry to understand a social or human problem (Creswell, 2003). Qualitative methods aim to answer 'what', 'how' and 'why' questions (Green & Thorogood, 2009), to help us understand the meaning people draw from situations, to identify unknown phenomena, to gain insight into processes underlying social life and to develop an explanation for human activity and interaction (Sim & Wright, 2000). Therefore, I determined that a qualitative approach would be best to enable me to explore, understand and evaluate the impact of anxiety and depression in RA.

Exploratory research is flexible, allowing a change in the research process based on new insights. It is often used to approach problems on which little prior research has been performed, and can form the foundation of more conclusive research (Sim & Wright, 2000). Although I had read literature on comorbid mood problems in other LTCs, which could have enabled me to make a tentative hypothesis, I wanted to ensure I used a flexible design, to enable me to respond to any unexpected cues within interviews. Consequently, I took an exploratory approach.

Alternatively, I could have used a descriptive design. Descriptive designs are used to describe the characteristics of a population or phenomenon, and can be used as a basis for further research (Sim & Wright, 2000). For example, a survey of people with RA about comorbid mood problems, could identify a preference for talking treatments, after which exploratory interviews could be performed to understand the reasons behind this. However, descriptive designs do not answer questions about how, when or why certain characteristics are found or phenomena occur (Sim & Wright, 2000). Consequently, a descriptive design would have enabled me to describe the phenomenon surrounding anxiety and depression, but would not have facilitated the depth of insight potentially gained from an exploratory approach, to understand the reasons underlying a persons' preferences or behaviours.

Explanatory research is frequently used to test a hypothesis and to explain rather than describe phenomena being studied (Sim & Wright, 2000). An explanatory approach can be used to identify the extent and nature of cause and effect relationships. However, due to the potential impact of a range of factors on a relationship between two variables, causality can often be inferred, though not proven with a high level of certainty. Drawing on the findings of research into comorbid mood problems in other LTCs, I could have generated a hypothesis, and used an explanatory approach to test this, though this approach would not have been flexible enough to address my research question and explore emerging ideas, as supported by an exploratory approach.

Qualitative studies have already been used to explore patient perspectives of mood problems in LTCs (Coventry et al., 2011; Alderson et al., 2012; Simmonds et al., 2013; Alderson et al., 2014; Bogner et al., 2008). Therefore, I felt that a qualitative study design would be appropriate to add to the existing literature.

4.5.1.3 Qualitative methods

On deciding to conduct a qualitative study, I considered several methods to generate data, including semi-structured or unstructured interviews, focus groups, observation, content analysis of written materials and video or audio-recorded consultations (Bryman, 2016).

I chose to conduct semi-structured interviews. This method enabled me to pose specific questions to fulfil my research aims, whilst also leaving an opportunity for discussions to be extended into unexpected areas, helping to increase the depth and breadth of data (Green & Thorogood, 2009).

I could have analysed video or audio-recorded consultations of patients with a practitioner, where they were asked the case-finding questions for anxiety or depression. However, this approach would not have enabled as detailed insights into patient perspectives as a face-to-face interview. Although a video-recorded consultation would have enabled me to observe patients' responses to questions through their body language, I would not have been able to respond to cues or directly question patients to explore their personal perspectives more deeply. It is possible that the behaviour of participants would have been influenced by the knowledge that they were being recorded. In addition, this approach could have generated a lot of irrelevant data that would have been time consuming to process.

Ethnographic research, which involves observing society from the point of view of participants could have enabled the exploration of certain cultural phenomena surrounding anxiety and depression in RA (Green & Thorogood, 2009). However, this process would have been time consuming and generated a significant amount of data irrelevant to my research aims. Due to this method involving no direct communication

with participants, it would also have been difficult to obtain the required depth of insight into the specific topic of interest.

A focus group would have been an alternative method to explore a range of views. A focus group involves a small group of people meeting to discuss a particular topic under the direction of a facilitator, who has a list of topics to discuss (Krueger & Casey, 2000). Within a group, participants may have felt more confident to express negative opinions. However, some could have preferred to share personal accounts within the privacy of their home environment in a semi-structured interview, rather than in a public focus group. The breadth of data obtained through a focus group could also have been limited by the influence of dominant personalities, who may have prevented more reserved participants from expressing opposing views. In addition, a focus group could have been difficult to arrange when participants were geographically isolated.

Unstructured interviews, without any predetermined questions or answer categories, could have provided interesting insights (Minichiello, Aroni & Timewell, 1992). Participants could have directed the conversation further, potentially leading them to discuss new phenomena not previously considered. In addition, participants could have felt more at ease and able to open up about their true feelings leading to the generation of more valid data. However, with a lack of direction, participants could easily have diverged from the topic of interest, leading to a proportion of the data being irrelevant to the research aims, making the interview and subsequent analysis more time consuming. In addition, without questions to prompt particular discussion areas, certain topics could have been left unexplored.

4.5.1.4 Analysis

There were a broad range of potential approaches to qualitative research analysis that I considered. I discounted discourse and conversation analysis, as these would have been used to analyse the linguistic characteristics of data and I was not concerned with *how* language was used by participants to communicate, but rather the ideas and beliefs contained within responses (Bryman, 2016).

I aimed to explore and identify new patient perspectives on case-finding for mood problems, to inform future health care policies and guidelines for the optimal care of people with RA. Consequently, I decided to perform a thematic analysis, which involves examining and recording patterns of meaning (or "themes") within data. Stages of thematic analysis include initial familiarisation with the data, then identification of codes, which are often words or short phrases. Coding of the data is a way of indexing or categorising the text, to help establish a framework of ideas about it. Codes can be organised and linked together to develop themes, which are recurrent concepts used to summarise the range of beliefs voiced by participants (Braun & Clarke, 2006).

To help ensure recognition of the full range of perspectives, I used a cyclical process of data collection, analysis and provisional coding, followed by the use of codes to guide further sampling and analysis (Glaser & Strauss, 1967). This cyclical process was continued until a point of data saturation was met, when no new ideas emerged (Saunders et al., 2018). The constant movement between data and emerging theories meant that analysis was both inductive and deductive, with emerging data and analysis guiding further cases to investigate by 'theoretical sampling' (Charmaz, 2012). A process of constant comparison, through which cases within the same data set were compared,

helped the recognition of recurring ideas, whilst also highlighting exceptions, which could then be developed into new themes (Dye et al., 2000).

Thematic analysis was flexible, as I was able to adopt an inductive approach, in which the coding and theme development were directed by the content of the data, or a deductive approach, in which codes and theme development were directed by existing concepts. However, a thematic approach did not promote deeper analysis of the data to link the descriptions of participants' key beliefs to theories, for example, to explain why patients may prefer certain care settings or providers for assessment of their mood disorders in RA. Nonetheless, my main aim was not to develop theories to explain the data, but to understand and give meaning to the data (Braun & Clarke, 2006).

By using inductive analysis, I enabled my research to be *grounded* in the data, and for new emerging concepts to be recognised. In addition, I was able to use the background knowledge I had acquired through my review of the literature to enhance my analysis, by taking a deductive approach to test emerging ideas derived from the literature.

Data collection and analysis were performed simultaneously. This iterative process ensured I would have the opportunity to adapt my hypotheses and methodology in response to new emerging data (Bryman, 2016). However, recognising that this approach could lead to a loss of focus, I regularly consulted with my supervisors to discuss new data and maintain my focus on the research question through the process of analysis (Britten et al., 1995). In addition, these regular meetings with research colleagues provided an opportunity to develop my topic guide and themes within my analysis.

I also used 'memos', which can be defined as the written forms of our abstract thinking about data (Strauss, Corbin, & Corin, 2008), to assist my transition between coding and analysis of the data. Memos can include operational notes about data collection, whilst theoretical memos can also contain ideas about emerging hypotheses and the development of codes and themes. These can act as an intermediate step between coding and writing, helping researchers to categorise codes for analysis, identify gaps in the data and note where comparisons can be made (Charmaz, 2006).

Several concepts within a grounded theory approach overlap with thematic analysis. Grounded theory involves the generation of theory, *grounded* in the data, that has been systematically collected and analysed (Noble & Mitchell, 2016). Data collection and analysis occur simultaneously, with codes developed from the data, categories constructed inductively and memos used to assist the transition between coding and writing. However, I did not take a pure grounded theory approach, as this would have required me to possess no prior knowledge which could have influenced my research, which was not possible (Green & Thorogood, 2009). As a clinician, I was aware of the connections between LTCs and mood problems and had personal experiences of case-finding for mood problems. I had also developed my research question after reviewing existing literature. Therefore, some background knowledge was integral to my study, to ensure that my research enabled new insights and added to the literature on RA.

Alongside my thematic analysis, I applied a framework to improve my depth of understanding of the data obtained. Framework analysis was originally developed for use in healthcare research. It involves "summarising and classifying data within a thematic framework", to enable deep analysis of data, with a final stage of mapping and interpreting codes to promote the development of practical strategies as an endpoint

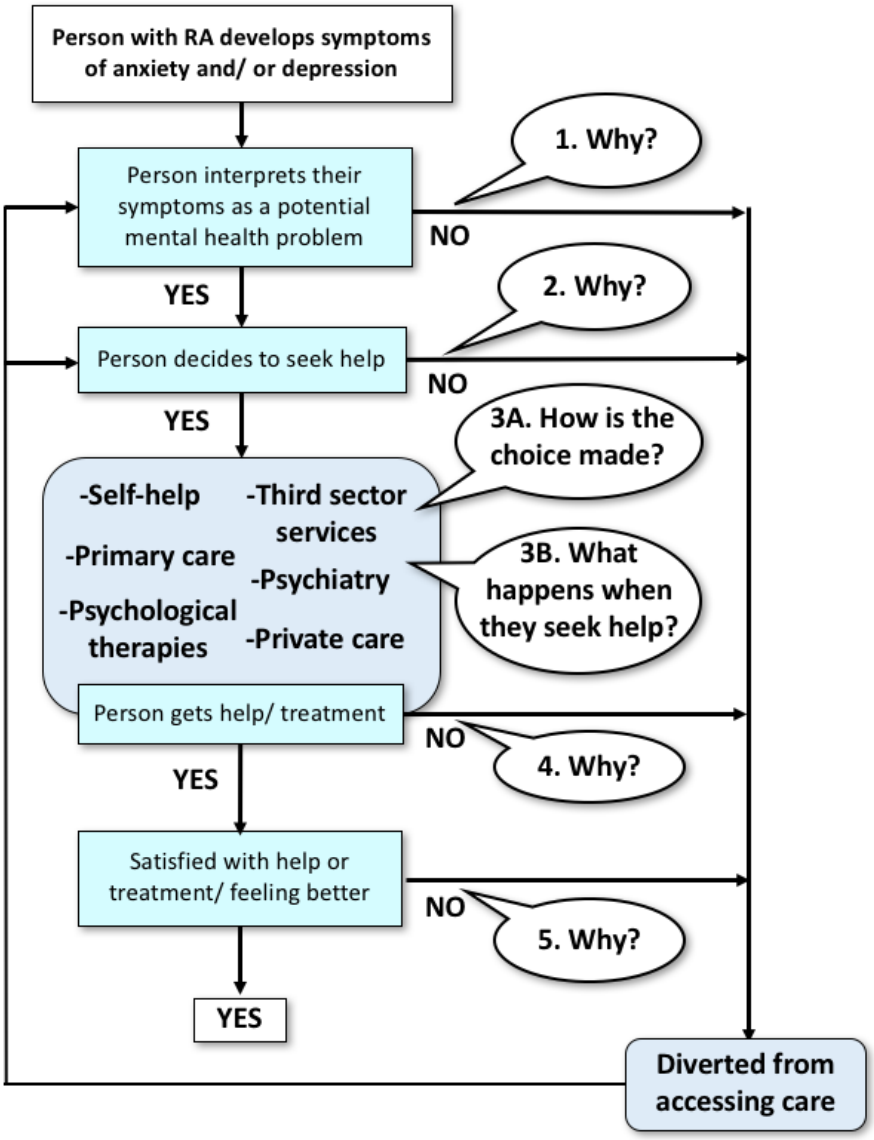
(Green & Thorogood, 2009, p218). As my study was exploratory, the use of a pre-determined framework for analysis could have led to unexpected themes and anomalies being overlooked within the analysis. However, I applied a framework later in my analysis when access to care had emerged as a predominant theme. I felt that this secondary analysis would lead to greater depth of insight into patients' perceptions, helping me to recognise patterns in the data, whilst also drawing attention to new potential themes (Gale et al., 2013).

For my analysis, I adapted an existing framework, which was developed to analyse potential barriers to accessing primary mental health care for people from hard to reach groups, including people with advanced cancer, medically unexplained symptoms and the elderly (Kovandžić et al., 2011). The original framework was reported to be fruitful in highlighting "fine grain" insights, increasing the impact of participants' and researchers' efforts (Kovandžić et al., 2011, p1). I adapted the framework to help analyse potential barriers to accessing mental health support within primary and secondary care for people with RA and comorbid anxiety or depression.

The original framework, and my adapted version, were informed by the work of Dixon-Woods (2006), who drew together key processes occurring before and at the point of entry into systems of care. In particular, three useful concepts relating to access to care were considered. The first concept, candidacy, refers to the process by which a person's eligibility to use a service is formulated through their interactions with health services. The second, concordance, indicates the importance of a match between a users' and practitioners' narrative and successful access to an intervention (Stevenson & Scambler, 2005). The third, recursivity refers to the influence of a users' previous

experiences of health services on their future help-seeking (Rogers, Hassell & Nicolaas, 1999).

Figure 4.3- *A framework for researching access to mental health care for individuals with RA and comorbid mood problems (adapted from Kovandžić et al., 2011: p5)***.**



This framework helped to draw together data at particular points where individuals with RA might have encountered barriers to accessing care for comorbid mood problems. However, I recognised that by using a framework for analysis, there

was a risk of data losing its' context, hence when I analysed interview extracts using the framework, I repeatedly referred back to the original context of the data.

4.5.1.5 Integration of qualitative and quantitative data

To understand the perspectives of people with RA about mood problems, I could have used quantitative methods. Quantitative research explains phenomena by collecting numerical data that are analysed using mathematically based methods, to answer 'how many' or 'how much' type questions (Sim & Wright, 2000). I could have used survey methods to ask a larger number of patients about how approachable they found their GP when help-seeking for mood problems, for example, using the General Practice Assessment Questionnaire, a patient survey used by GPs and their practices, which includes questions about the approachability of practitioners (Roland et al., 2013).

However, a purely quantitative approach would not have enabled me to fulfil my aim, to gain insight into patients' experiences by exploring their attitudes and beliefs in detail. I could have utilised open questions within a questionnaire, but patients may have not completed these due to a lack of understanding or time, or they may have been too embarrassed to record their mood concerns. In addition, a questionnaire would not have been able to record and respond to participants' body language, whilst patients may have misunderstood questions, or lacked the necessary hand dexterity or health literacy to answer questions. In addition, due to a lack of literature, I would not have known what questions would be important to ask, highlighting the importance of an open and exploratory approach.

However, I felt that by utilising some quantitative data I could enhance my research findings by providing a context to the patient population from which I drew my sample of patients to interview. Within chapter 5, I have described my methods in detail. In brief, interview participants were sampled from people who had attended an RA annual review clinic (section 5.6). Before the clinic, they had been asked to complete questionnaires that included the case-finding questions for mood problems. By analysing patients' responses to these case-finding questions within the annual review clinic questionnaire, I was able to provide a background to the prevalence of mood disorders in the local population with RA, helping to demonstrate the proportion who could benefit from case-finding for anxiety and depression and subsequent signposting for management. Performing a qualitative study that was linked to a pilot nurse-led annual review facilitated the sampling of patients for interviews, as questionnaire responses were used to identify patients who had potential anxiety or depression. This meant I was able to invite a sample of patients to be interviewed who had experience of living with a mood problem, increasing the potential breadth of experiences I was able to explore.

By integrating qualitative and quantitative data, I was able to triangulate findings to develop a comprehensive understanding of phenomena and to test the validity of results (Bryman, 2006). Patton described four forms of triangulation, including investigator triangulation, where multiple researchers are involved in an investigation, theory triangulation, where more than one theoretical scheme is used to interpret phenomena, data source triangulation, where data is collected at different times, places or by different people, and method triangulation, which involves more than one method being used to gather data. By using a form of method triangulation, using data from

interviews and questionnaires, I was able to use patient perspectives to help illustrate and explain findings generated from the case-finding questions within questionnaires. By exploring patient perspectives of the annual review consultation within my interviews, I also built on the quantitative data generated, improving the relevance and validity of my results (Bryman, 2006).

4.5.2 Determining the impact of anxiety in people with rheumatoid arthritis

4.5.2.1 Research question and overview of methodological approach

What is the association between anxiety in people with RA, and disease activity and QoL?

In response to this question, I have conducted a systematic review and meta-analysis.

4.5.2.2 Justification for performing a systematic review and meta-analysis

To determine the impact of anxiety in people with RA, I aimed to test a theory that anxiety was associated with increased disease activity and a reduced QoL, by aggregating all available evidence. To fulfil this aim, I performed a systematic review and meta-analysis. Performing a meticulous search of the literature and subsequent quality assessment of relevant articles enabled me to minimise bias and determine the magnitude of the association between anxiety and different outcomes in people with RA.

A systematic review involves the collation of evidence fitting pre-specified eligibility criteria to answer a specific research question. Systematic reviews have a reproducible methodology, involve a systematic search to identify all studies meeting the eligibility criteria, include an assessment of the validity of findings to reduce the risk

of bias and a synthesis of all relevant findings. Subsequent meta-analysis involves the use of statistical methods to combine the data from several studies into a single quantitative measure or summary effect size (Higgins and Green, 2011).

Alternatively, I could have performed a narrative review, though this would not have involved a systematic search of the literature, hence could have led to selection bias. In my review of the literature, I had identified that a systematic review had previously been performed to determine the impact of comorbid depression in people with RA (Rathbun, Reed & Harrold, 2013), so I felt this would be an appropriate design to help me to review and collate existing research evidence.

An exploratory design would not have been appropriate as I had a hypothesis about the impact of mood problems in people with IRCs. I knew that research had been performed on my topic of interest, though no systematic review had been performed to collate this evidence. Therefore, a descriptive approach enabled me to review and describe existing evidence.

4.5.3 Determining the incidence and prevalence of mood problems in different inflammatory rheumatological conditions

4.5.3.1 Research question and overview of methodological approach

What is the incidence and prevalence of anxiety alone, in addition to anxiety and/ or depression, in people with different IRCs?

I have conducted a cohort study using a regional primary care database to determine the incidence and prevalence of mood problems, in people with different IRCs.

4.5.3.2 Justification for performing a cohort study

To establish the incidence and prevalence of anxiety and depression in different IRCs, I aimed to test a hypothesis, that mood problems were more common in people with IRCs. I aimed to uncover objective truths, not to understand patients' perspectives or to generate theories. An exploratory design would not have been appropriate as I had a hypothesis about the relationship between IRCs and mood problems. Therefore, I wanted to have a predetermined design to keep my study focused on my research question and to minimise any potential bias. Alternatively, a descriptive design would have enabled me to describe the prevalence of mood problems cross-sectionally, though I would not have been able to analyse the association between IRCs and mood problems over time. Therefore, to enable me to determine the both the incidence and prevalence of anxiety and depression, I used an explanatory design. Specifically, I conducted a cohort study.

Performing a cohort study enabled me to retrospectively match a group of individuals with IRCs, to a group without IRCs, and compare how many developed mood problems over time. An alternative would have been a case-control study, though this would have required me to group participants based on the presence or absence of anxiety and/ or depression, then to make a retrospective comparison of variables that were possible causative factors. However, I just wanted to focus on the association between IRCs and mood problems. My primary objective was not want to determine the association between mood problems and other variables, so if I had used this design, a large proportion of individuals would not have been relevant to my analysis.

My study design was quasi-experimental. This design lacks the full control of an experimental design, either due to there not being a separate control group, or due to

subjects not being randomly assigned to the control group. For this study, I did have a control group, though group membership was determined by the presence or absence of an IRC, rather than individuals being randomised from a single pool of subjects.

4.5.4 Determining the prevalence of mood problems in people with IRCs using the case-finding questions for anxiety and depression

4.5.4.1 Research question and overview of methodological approach

What is the prevalence of anxiety and depression in people with different IRCs, when determined using the case-finding questions?

I have analysed baseline questionnaire data from a pilot feasibility study called INCLUDE (Hider et al., 2018), in which individuals with different IRCs were invited to a nurse-led review based in primary care. This review focused on identifying comorbidities including cardiovascular disease (CVD), osteoporosis and mood problems, and signposting patients for management of these.

Within the baseline questionnaire, people with different IRCs were asked to self-report known anxiety or depression and to answer the case-finding questions for mood problems. I was then able to analyse participants' responses.

4.5.4.2 Justification for analysing questionnaire data

As outlined in section 4.5.3.2, I had planned a cohort study to establish the incidence and prevalence of anxiety and depression in different IRCs, using a primary care dataset. However, knowing that mood problems were under-recognised and

under-treated in people with RA (Cepoiu et al., 2007), I hypothesised that mood problems in people with other IRCs were also likely to be under-recognised, hence not recorded within primary care records. Therefore, as a co-investigator on the INCLUDE study, I aimed to re-test the same hypothesis, that mood problems were more common in people with IRCs, but to do this by analysing patients' responses to the case-finding questions for anxiety and/ or depression.

By comparing the proportion of people with IRCs found to have anxiety and depression through the use of the case-finding questions, to the proportion with mood problems already coded in their primary care records, I determined I would be able to characterise the potential burden of unrecognised comorbid mood problems in people with IRCs.

I aimed to uncover objective truths, not to understand patients' perspectives or to generate theories. Therefore, an exploratory design would not have been appropriate as I had a predetermined hypothesis about a potential relationship between IRCs and mood problems that I wanted to test using different methods. Instead, I determined that a descriptive study would be more appropriate, to enable me to collect information on the psychological characteristics of individuals. However, my approach could also be described as explanatory, as I planned to analyse differences in the associations between variables.

The INCLUDE study team, guided by the suggestions of a patient and public involvement and engagement (PPIE) group and stakeholder group, attended by GPs, nurse practitioners and practice nurses (PNs), collaboratively decided on the content of the study questionnaires (section 8.6). To collect data on psychological characteristics, the INCLUDE questionnaires included the EuroQol 5-Dimension Scale (EQ-5D), the

Patient Health Questionnaire (PHQ)-8 and Generalised Anxiety Disorder (GAD)-7 questions. These closed-ended questions, with predetermined response options, provided me with quantitative data to analyse.

Alternatively, I could have performed structured interviews to collect responses to these questions. Structured interviews would have enabled individuals lacking the appropriate literacy to complete a questionnaire to respond. There could have been less omissions or errors in responses to questions, as through interviews, I could have probed for answers and provided people who I interviewed, the opportunity to clarify questions if needed. However, interviews would have been more time consuming, whilst responses could have been influenced by my body language or communication skills. A lack of anonymity, compared to a postal questionnaire, could also have influenced responses, as some people could have been reluctant to disclose symptoms of mood problems due to fear of stigmatisation. In addition, people of a working age may have been less likely to agree to participate in a structured interview compared to retired individuals who could have had more time available to participate. Using a questionnaire meant that data could be gathered from a large number of individuals, representative of the general population, over a shorter period of time (Sim and Wright, 2000).

4.6 A Multiphase Mixed Methods Design

In this section, I will discuss how I used an embedded mixed methods design in response to my first research question, and how this study was sequentially linked to subsequent studies within a multiphase mixed methods design.

4.6.1 Embedded mixed methods design in response to my first research question

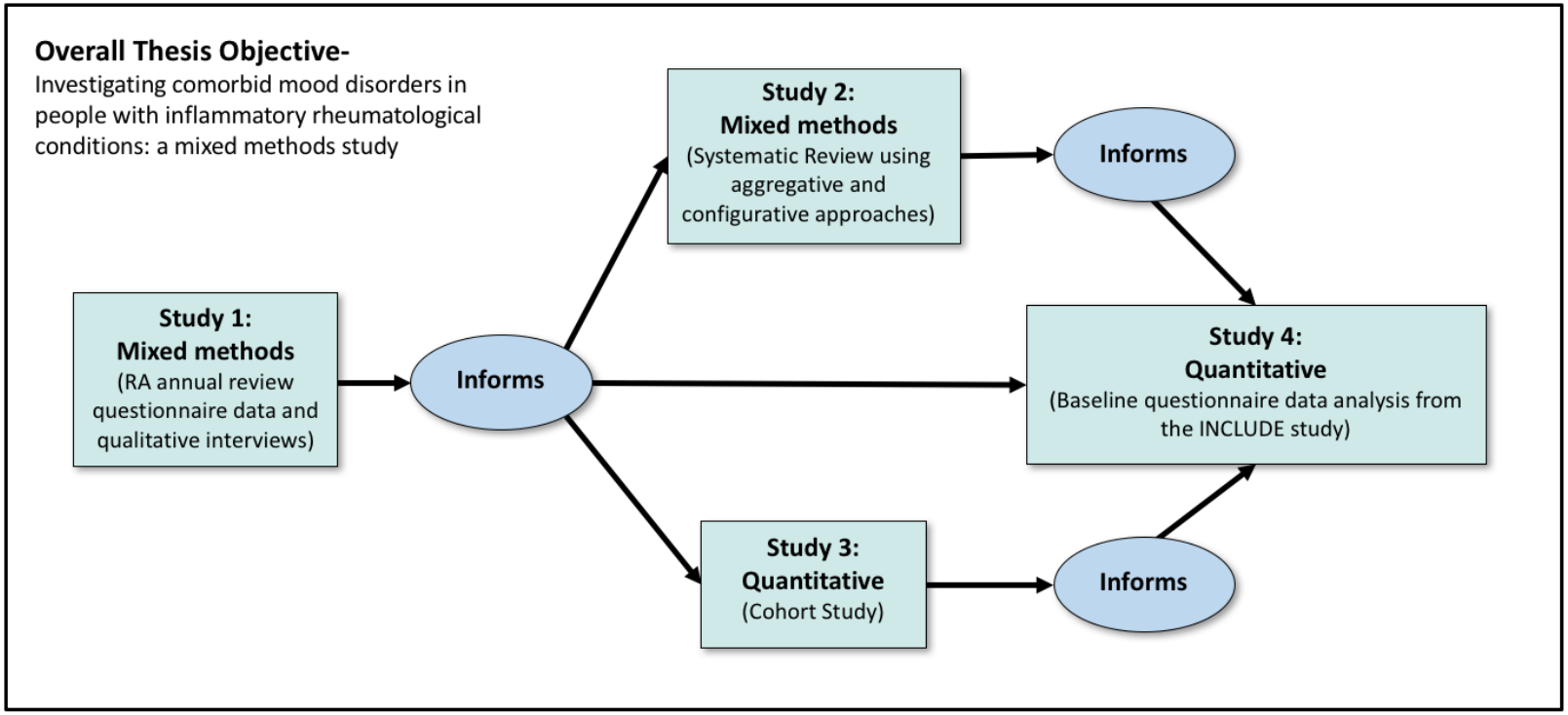
In section 4.5.1.5, I have discussed how I integrated qualitative and quantitative data for my qualitative study, and how triangulation of data helped to improve the validity of my results. Data yielded from interviews was integrated with quantitative data (PHQ-2 and GAD-2 scores) reported in questionnaires completed by people with RA attending a pilot nurse-led annual review. PHQ-2 and GAD-2 scores were used to provide a background to the prevalence of mood disorders in the local population with RA, whilst questionnaire responses also facilitated the sampling of people with RA and potential mood problems for interviews.

This approach of having concurrent qualitative and quantitative data collection, using quantitative data from questionnaires to sample patients, then using data from qualitative interviews to add meaning to findings from the clinic questionnaires, could be described as an embedded mixed methods design (Creswell, 2014).

4.6.2 Connection to a multiphase mixed methods design

My mixed methods design developed further as I progressed to answer my other research questions through a systematic review, cohort study and questionnaire data analysis. Therefore, the embedded mixed methods design became the first stage of a multiphase design, aiming to further understand the scale and impact of mood problems in people with IRCs. A multiphase mixed methods design involves a researcher or team examining a problem through a series of qualitative and quantitative studies, with each new approach building on what was learned previously to address an overall objective (Creswell, 2014). My final multiphase mixed methods design is outlined in figure 4.4, with a summary of each stage written below.

Figure 4.4- *A multiphase mixed methods design for my thesis. Adapted from Creswell, 2014, p221*



Study 1: Mixed Methods (Qualitative interview data supported by quantitative data from RA annual review questionnaires).

Study 2: Mixed Methods (Systematic review using an aggregative and configurative approach to determine the association between anxiety in people with RA, and disease activity and QoL).

Study 3: Quantitative (Cohort study to determine the incidence and prevalence of anxiety and depression in people with IRCs, recorded in primary care data).

Study 4: Quantitative (Analysis of baseline questionnaire data within the INCLUDE Study, to determine the proportion of people with IRCs and self-reported symptoms of anxiety and/ or depression, determined through use of the case-finding questions).

4.6.3 Justification for a multiphase mixed methods design

Prior to planning a multiphase study, I considered other mixed methods designs (Creswell, 2014). A convergent parallel mixed methods design would have required me to collect qualitative and quantitative data concurrently, then integrate this data when interpreting my results. However, my research was sequential, with my focus expanding from RA to other types of IRCs, following analysis of my initial qualitative data. Alternatively, an explanatory design would have required me to begin with a quantitative project, before conducting a qualitative study to provide greater meaning to the data. However, the initial focus of my study was to understand patient perspectives through a qualitative study, hence this approach would not have been suitable. With an exploratory sequential design, I could have built on my initial qualitative study findings by conducting a quantitative study. However, my qualitative study provided inspiration for further multi-staged work expanding on the original research focus, hence a two stage design process would not have been suitable.

Using a multiphase mixed methods design required more time, support and experience using qualitative and quantitative methods to implement, due to the expertise required in a variety of methods. However, this approach enabled me to address a broader range of research questions in which studies built on each other, providing a greater depth of understanding about mood problems in people with IRCs.

A multiphase mixed methods design is flexible enough to incorporate different design elements to address connected research questions as they arise through a study. Concurrent and sequential strands can be included over a period of time. For example, a team used this study design to develop evidence-based mental health practices for the school-aged population in Sri-Lanka (Nastasi et al., 2007). Whilst some qualitative

and quantitative studies were conducted independently, then data merged to obtain a greater understanding, at other times the methods were sequentially connected, with qualitative data being used to develop a psychological measure, then quantitative data being used to validate it (Natasi et al., 2007).

In contrast to this design (Natasi et al., 2007), my research has not aimed to develop or validate an intervention or measure, rather to improve our understanding of comorbid mood disorders in people with IRCs. However, there are similarities between my thesis design (figure 4.4) and Natasi's mixed methods design (2007), which have both included sequentially connected studies. For example, within my qualitative study, patient perspectives shared during interviews (discussed in chapter 5), led me to systematically review the literature on the impact of anxiety in people with RA, which I noted was under-reported in comparison to depression. Perspectives shared by PPIE participants within my qualitative study also informed my cohort study, by prompting me to analyse the impact of anxiety alone and widen the focus of my research to mood problems in other IRCs. Systematic review findings highlighted the impact of anxiety alone (discussed in chapter 6), whilst my cohort study demonstrated a variable burden of mood problems in different IRCs, with some potentially not being recognised or recorded in primary care records (chapter 7). These findings, along with perspectives shared by PPIE participants, all informed the INCLUDE study questionnaire analysis, by prompting a focus on case-finding for anxiety and/or depression in people with different IRCs (chapter 8). At the end of each individual chapter, I have described how data obtained has informed subsequent steps in my thesis (sections 5.12, 6.7 and 7.8).

CHAPTER 5
Qualitative Study

5.0 QUALITATIVE STUDY

The perspectives of people with rheumatoid arthritis about comorbid anxiety and depression

5.1 Overview

As part of the evaluation of a nurse-led rheumatoid arthritis (RA) annual review service at a community rheumatology hospital, I conducted a nested qualitative study to explore the perspectives of people with RA about comorbid mood problems. Within this chapter I have first explained the role of the annual review service, use of clinic questionnaires and how patients were recruited to be interviewed. Alongside my analysis, I have discussed the impact of patient and public involvement and engagement (PPIE) and how this study informed subsequent work within my thesis.

5.2 Rheumatoid Arthritis Annual Review Clinic

The National Institute for Health and Care Excellence (NICE) quality standards (2013c), suggest that people with RA should have an annual review of their condition, although guidelines do not specify where this should occur. The Haywood Foundation, a local charity supported a pilot annual annual review service for patients with RA in North Staffordshire.

Patients with RA attending two consultant rheumatology clinics, were invited by letter (appendix 5), to attend a nurse led annual review service instead of their usual consultant follow-up appointment. The service was delivered by a rheumatology nurse specialist who reviewed disease activity, quality of life (QoL), physical functioning and comorbidities such as hypertension (HTN), ischaemic heart disease (IHD), osteoporosis

and depression. The aim of the annual review clinic was to offer a holistic approach to disease management and to facilitate better exploration of the wider impact of RA, including on mental health.

5.3 Patient Completed Questionnaire

Prior to their appointment, patients were sent a short questionnaire to complete (appendix 6). The content and layout of the questionnaire was informed and refined with input from the Haywood User Group, comprising of patients and carers who met regularly at the local rheumatology hospital. The questionnaire captured patient demographics, RA disease activity (Visual Analogue Scale (VAS)), disease damage (Health Assessment Questionnaire (HAQ)), anxiety (Generalised Anxiety Disorder (GAD)-2) and depression (Patient Health Questionnaire (PHQ)-2), pain control, work status and self reported comorbidities. The questionnaire also assessed the requirement for patients to be informed and educated about their RA drug treatment. Further domains highlighted as good practice by NICE, such as a review of cardiovascular risk (QRisk2), bone health (with FRAX if appropriate), disease complications and the impact of RA on QoL and functioning were also assessed (NICE, 2018).

5.4 Two Phase Study

Phase 1: Data on patient demographics and responses to GAD-2 and PHQ-2 questions was extracted from the patient questionnaires.

Phase 2: A purposive sample of patients from phase 1 were invited to participate in a semi-structured interview to explore their views of the annual review clinic and their perspectives on comorbid mood problems in people with RA.

5.5 Ethical Considerations

Ethical approval was granted by the West of Scotland Research Ethics Service Committee (WoSRES/15/WS/0063), Project ID 170210 (appendix 7). Data for the study was handled in accordance with the 1998 Data Protection Act and its' amendment in 2003 (Information Commissioner's Office, 2011). Indentifiable patient data, including addresses, audio recordings of the interviews and transcripts were stored on a single computer protected with a firewall, up-to-date antivirus software and password access. All interviews and transcripts were anonymised.

5.6 Identification and Study Processes

5.6.1 Phase 1- Cross sectional patient questionnaire at annual review clinic

Questionnaires were reviewed and if necessary, completed during the nurse-led consultation. Following the nurse consultation, if required, patients were signposted for specialist advice from different multidisciplinary team (MDT) members, including podiatry, orthotics, physiotherapy, occupational therapy and orthopaedics. Through use of the GAD-2 and PHQ-2 case-finding questions, the clinic nurse was also able to identify and signpost patients with symptoms of anxiety and depression to appropriate community services, such as MIND, a mental health charity, or Improving Access to Psychological Therapies (IAPT) services, facilitating access to counselling or cognitive behavioural therapy (CBT). If required, General Practitioner (GP) review was also suggested for consideration of medication or secondary care involvement for the management of anxiety and depression.

During the clinic, the nurse was able to consult an overseeing rheumatology consultant for advice. GPs were informed of the clinic outcomes by letter, preventing unnecessary duplication of work.

Patients were asked to consent to their anonymised data being used for research purposes. To support later qualitative analysis of interviews, data was extracted on patient demographics and responses to the GAD-2 and PHQ-2 questions for anxiety and depression.

5.6.2 Phase 2- Interviews

A score of 3 or more out of a possible score of 6, on the PHQ-2 (Kroenke, Spitzer & Williams, 2003) or GAD-2 (Spitzer et al., 2006) questions (detailed in figures 2.5 and 2.6), indicated that a patient could have symptoms of anxiety or depression. Consequently, these individuals were given a patient information sheet (PIS) at the end of their annual review appointment by the clinic nurse (appendix 8), inviting them to take part in the qualitative interview phase of the study. Patients providing consent to future contact had their details securely emailed (via nhs.net) to the interviewer.

Patients were then invited to take part in a single face to face interview at a convenient time and place, such as their home, the local community rheumatology hospital or university. Consent to participate in the study and digitally record the interview was re-checked with each participant prior to their interview, and a consent form signed (appendix 9). Two copies of the consent form were completed, one for the patient and the other for the interviewer. Participants were given the opportunity to withdraw their consent at any point.

Each interview was digitally recorded. A topic guide was utilised (appendix 10), which had been developed from existing literature, and informed by discussion within the research team. After enquiring about participants' general health problems, the interviewer explored the perspectives of people with RA of comorbid anxiety and depression and their preferences for the management of mood problems. In addition, peoples' views of the annual review service were explored, including whether they felt it was an appropriate place to discuss their mood. Relevant areas were explored in depth until data saturation was achieved. The topic guide was refined during the course of the study, with the information that emerged in early interviews used to develop further questions for exploration in subsequent interviews.

The first interview was treated as a pilot, but as data collection was successful, it was included in the final dataset. All interviews were audio-recorded and lasted between 12-73 minutes, with an average length of 34 minutes. A total of 14 interviews were conducted until data saturation was reached.

Digital recordings and transcripts were stored on a password protected computer. In addition, two password protected excel documents were used to store data (appendices 11 and 12). The first of these contained the patients' name, ID number, telephone number, address and GP. A further column within this document was used to record circumstances when an interview was declined or cancelled. The second document contained the patients' ID number, gender, ethnicity, the first part of their postcode, employment status, GAD-2 and PHQ-2 scores. After the completion of each interview, the patients' name was removed from the first excel document and replaced by initials.

5.7 Data Analysis

5.7.1 Quantitative Analysis

A total of 179 questionnaires completed at the nurse-led review clinic were reviewed. An excel document was used to record patients' demographics (age and gender), in addition to their PHQ-2 and GAD-2 scores. The document was stored securely on a password protected computer. The proportion of patients responding positively to the case-finding questions for anxiety and depression was calculated, in addition to the number with low, moderate and high GAD-2 and PHQ-2 scores. Simple statistics were used to describe the data, including frequencies and percentages, in addition to the mean and range of data obtained (Stark, 2018).

5.7.2 Qualitative Analysis

The first 7 interviews were transcribed verbatim by the interviewer to increase familiarity with the data. An independent transcription company was subsequently used. Prior to analysis all transcripts were checked and anonymised by the interviewer. Analysis began as soon as the first transcript was available. Therefore, data collection and analysis were conducted concurrently, enabling modification of the topic guide to reflect emerging themes (appendix 10).

The researcher performing the interviews led analysis. Data were analysed using principles of constant comparison (Creswell, 2003). To generate conceptual themes, inductive coding of text segments, followed by re-coding and memo writing was used. Regular meetings took place between the study team members to agree overarching thematic interpretations.

Following analysis of the first 7 transcripts, access to care was noted to be a key emerging theme. Therefore, further analysis was conducted using a framework, as discussed in my methodology (section 4.5.1.4), and displayed in figure 4.3 (p108). This was adapted from an existing framework developed to analyse potential barriers to accessing primary mental health care for people from hard to reach groups (Kovandžić et al., 2011). On adapting the framework for my study, I was informed by the work of Dixon-Woods (2006a, 2006b), drawing together processes that occur before and at the point of entry into systems of care.

5.8 Quantitative Results

5.8.1 The annual review clinic

Once ethical and Human Research Authority approvals had been obtained, the annual review clinic was established in July 2015. Over the following 12 months until August 2016, 179 patients attending the nurse-led annual review clinic consented to be part of the research study and completed the clinic questionnaire. From these, 120 (67%) were female, reflecting the known higher prevalence of RA in women (Abhishek e al., 2017). The average age of patients attending the clinic was 67 years, with a range of 29-92 years. From the 179 people who attended the clinic, 38 (21%) scored ≥ 3 on the PHQ-2 questions, whilst 43 (24%) scored ≥ 3 on the GAD-2 questions, suggesting they might have anxiety or depression.

5.8.2 Interview participants

Between September 2015 and August 2016, 29 patients scoring ≥ 3 on the PHQ-2 and/or GAD-2 were invited to take part in a single face to face interview at a venue

convenient to them. Interviews lasted between 12-73 minutes, with an average length of 34 minutes. From the 29 patients invited to be interviewed, 14 agreed to participate. As detailed in appendix 11, from the 15 who did not participate, 5 were unable to be contacted, 2 declined, citing to poor physical health and 1 reported they were too busy. The remaining patients who declined to participate did not give a reason.

Table 5.1 (p130), summarises the characteristics of the 14 participants, who were all white British, reflecting the demographics of the local area. More females participated, reflecting both the higher prevalence of RA in women (Abhishek et al., 2017) and the proportion of females attending the clinic (67%). The majority of people interviewed were retired, with an average age of 63 years.

For each interview participant, an index of multiple deprivation (IMD) score was calculated. This is a measure of relative deprivation for neighbourhoods in England, expressed in deciles from 1 (most deprived) to 10 (least deprived). The score is based on a person's postcode (Department for Communities and Local Government, 2015). For my interview participants, the mean IMD was 5.9, with a range of 1-9, demonstrating that a range of socioeconomic statuses were represented within those patients I interviewed.

From the 14 individuals who consented to be interviewed, the burden of anxiety symptoms (mean GAD-2= 4.9, standard deviation (SD)= 1.1), was slightly higher than depression symptoms (mean PHQ-2= 4.6, SD=1.1). Whilst 5 people predominantly reported symptoms of anxiety, 2 mainly described symptoms of depression. The remaining 7 individuals had equal scores on both the PHQ-2 and GAD-2 questions.

Table 5.1- *Demographic Characteristics of participants (n=14).*

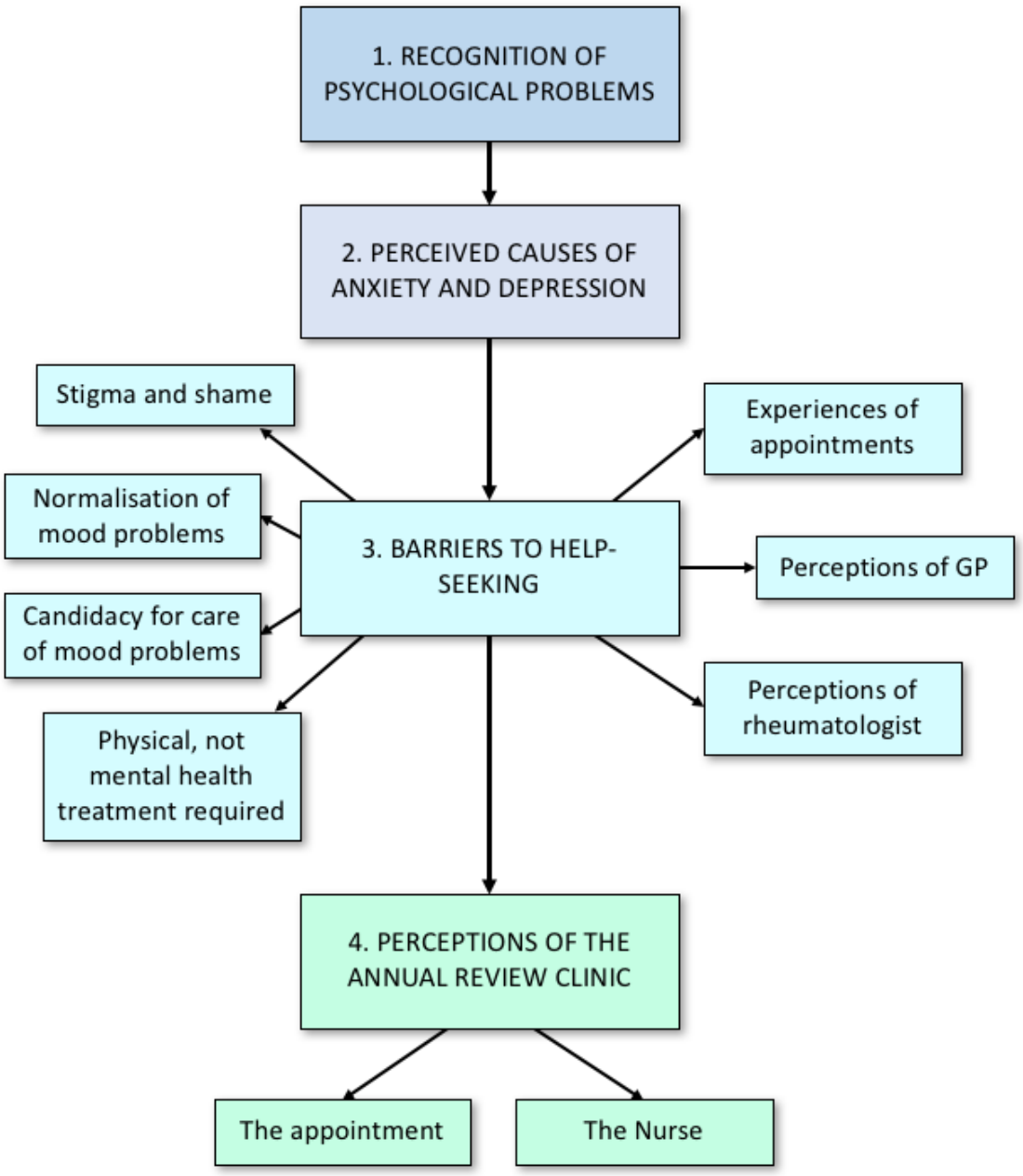
Gender	Female = 12 Male = 2
Ethnicity	White British = 14
Age	40-50 years = 1 50-60 years = 4 60-70 years = 7 >70 years = 2
Employment status	Employed = 3 Retired = 4 Retired through ill health = 6 Unemployed = 1
Index of Multiple Deprivation (IMD) [1]	Mean= 5.4 Standard Deviation= 2.8 Range= 1-9
PHQ-2 Score	Mean= 4.6 Standard Deviation= 1.1
GAD-2 Score	Mean= 4.9 Standard Deviation 1.1

[1] *Measure of relative deprivation for neighborhoods in England, expressed in deciles from 1 (most deprived) to 10 (least deprived)*

5.9 Qualitative Results

I have presented my qualitative data as a series of four connected themes, some with several sub-themes, as outlined in figure 5.1 (p131), For each theme, I will give illustrative data with participant identifiers, and discuss my interpretation.

Figure 5. 1- *Themes discussed within qualitative results*



5.9.1 Recognition of psychological problems

Participants described the processes through which they came to recognise that they were suffering from a mood problem. Some noted a change in their sense of self,

whilst others required time to reflect on their feelings before they recognised that they were anxious and/ or depressed.

"…the way I'm feeling now I could just cry at the drop of a hat. That's not me." (Participant 8, female, 62 years).

"… deep down I have noticed my mood change whilst I've been off, you know, and I think that's when you've got more time to think… I think those worries are always there but because you're so busy and your life's busy you haven't got time to think about them." (Participant 11, female, 53 years).

Several participants only recognised that they were suffering from anxiety or depression when a relative commented on their mood.

"I know I've been moody, I mean like I say, I think I've been alright, but until somebody tells you you've not been alright you don't know." (Participant 4, female, 58 years).

"I like joking. So for me to be like this is very unusual. It's getting worse, I suppose. I've actually got to the stage where my husband said to the kids, 'Don't tell mum anything that'd stress her out.'" (Participant 8, female, 62 years).

Some participants described how discussing their mood with the annual review clinic nurse helped them to recognise that they were suffering from anxiety or depression.

"She said, 'Do you get depressed?' and I said, 'Not a lot, no, not really,' but it's only until afterwards when you think about it and you think, 'Yes, you do really,' and it is connected to the arthritis." (Participant 8, female, 62 years).

"When she was saying it I was thinking, god, I feel like that, you know, it's so, it's so, like when somebody else said it, I thought, well I'm not on my own, somebody else must feel like that." (Participant 14, female, 71 years).

In summary, the recognition of anxiety and depression was facilitated by the personal reflections of participants and comments made by relatives. For some, direct questioning by the annual review clinic nurse also provided a forum for the acknowledgement of mood problems and encouraged participants to reflect on whether they had anxiety and/or depression.

5.9.2 Perceived causes of anxiety and/ or depression in people with RA

Participants variably perceived the interaction between their mood problems and RA. Most felt that joint pains, fatigue and loss of mobility related to their RA had led them to suffer from anxiety and/or depression.

"I felt I had a very low mood, because, well because it was really about the worst I'd ever felt, last time I went, because I'd had shoulder pain for weeks." (Participant 2, female, 56 years).

"It wears you down, it wears you down and you're fatigued at times quite badly and that can make you worn out, mentally and physically worn out, it has a physical side, has a mental effect on you…" (Participant 11, female, 53 years).

Several participants reported that their mood could vary in relation to flares of RA.

"Yeah, it does make you really miserable and grumpy and then some days can be okay." (Participant 13, female, 45 years).

"I mean when you have a flare, that's miserable, but it isn't just the flares, it's how I feel in myself as well...the depression, the anxiety, I get ever so anxious." (Participant 7, female, 61 years).

Other participants perceived their mood problems to have been provoked by a loss of independence and social isolation as a result of their RA. Some described the impact of reduced mobility on their personal relationships and how they had been forced to give up hobbies that they used to enjoy.

"…I get very, very frustrated. Because I used to love walking, and I'd do a lot of keep fit, and all of it, I can't do nothing like that. No… But it's like things like, I can't play with me grandson. You know what I mean, it's like, his other nanna takes him to the park and chases him around, whereas I can't do that, no." (Participant 14, female, 71 years).

" … I can't do what I want to do. It's nice having somebody here just to talk to, you know. I mean my daughter stops now and then, but she's working all day you know, and she comes round every night." (Participant 3, female, 64 years).

Several participants reported work-related stress and financial pressures due to their RA leading them to feel anxious and/ or depressed. For some, this was exacerbated by the loss of social connections at work.

"… I don't think the arthritis is helping at all, but without it I'd still be working, I'd still be at X (work), and I'd have all my friends, and I'd be doing what I enjoyed doing." (Participant 7, female, 61 years).

"It's depressing at times because you're thinking what would happen you know, how would I get money if I hadn't got a job, who would employ me with health problems and at 54, I'm nearly 54 would they like they'd probably put you under the pile." (Participant 11, female, 53 years).

One participant thought that their low mood had been precipitated by anaemia, which they had developed secondary to their RA.

"Some of it I think is linked to my arthritis because I tend to be anaemic quite a lot and I have to keep an eye on that and it's surprising how that affects you, if you don't sort it out really…You are more tired, but I think it also makes you feel low in yourself as well…" (Participant 12, female, 70 years).

Rather than RA triggering mental health problems, some participants perceived the reverse to be true, with stress, anxiety or low mood triggering flares of RA.

"Every time I've had severe stress come my way and I've not been feeling good that seems to have an effect on the rheumatoid…" (Participant 11, female, 53 years).

"I had my forms through from the DLA is it? And I'd got to fill them in, and for a couple of weeks of trying to do it, everything's churning, I made an appointment at the citizen's advice, to go and get them to sit and help me with it. So it's coming to the appointment, got a flare, can't go." (Participant 7, female, 61 years)

Several participants perceived other chronic physical health problems to have caused their mood symptoms, such as hypothyroidism, whilst one participant reported recurrent hospital admissions for the treatment of abscesses to have negatively impacted on their mental health.

"I had a bit of a weep, and she looked at my records and said that my thyroid was too low. So she upped my thyroid... I do feel a little better with my thyroxine being upped a bit." (Participant 4, female, 58 years).

"I always seem to be in hospital for one thing or another, you know. I had a bout last year. I went in hospital as many as four times and had operations, with the abscesses that I used to get, and that used to get me down, you know." (Participant 1, female, 54 years).

Some participants couldn't understand why they had developed mood problems. One suggested that their propensity to become anxious and depressed was related to their personality.

"I can always remember saying, 'but why am I depressed, I've got nothing to be depressed about!' You know, I'd got a fantastic husband, fantastic kids..." p7, line 30-31. "But that's down to, that's down to personality, you know what I mean? It's nothing to do with the arthritis that's just how I am." (Participant 7, female, 61 years).

"I get a bit grumpy maybe. I just can't help it. I go down a bit. I can't think of the reason why. I haven't actually got a reason to be down. Everything's fine, money-wise and everything, and yet I go down, and then I come out of it again." (Participant 10, female, 61 years).

Another participant perceived their low mood to be multifactorial, with their RA and chronic obstructive pulmonary disease (COPD) contributing.

"It's a combination of my arthritis and my lung condition, COPD, you know. The lung condition is percentage wise 70:30" (Participant 6, male, 70 years).

Others accounted their mood problems to social issues, such as domestic violence or bereavement.

"Nobody bothers. You feel worthless. It just all gets you down. I've had quite a rocky marriage. He used to be violent. That didn't help none. That was very bad." (Participant 9, female, 68 years).

"… I did feel quite low but I thought it was more to do with my mum passing away than so much with my arthritis, you know, because it was traumatic, because she'd been with me a long time as well, she was more like a partner really than my mum." (Participant 12, female, 70 years).

One participant also felt that their family history of depression and suicide strongly influenced their mental health.

"I had a brother what committed suicide, gassed himself in his car. My nephew tried hanging himself with a belt round his neck and he nearly died. It's one family problem after another." (Participant 9, female, 68 years).

Another participant perceived their anxiety and/ or depression to have developed before their RA, but to be negatively influenced by their arthritis.

"I suffer anxiety and depression, which I think have got worse, having the arthritis as well." (Participant 7, female, 61 years).

In summary, some participants perceived their RA and mood problems to be linked, though the direction of this link varied. Whereas several reported RA-related pain, loss of mobility and social isolation to precipitate their anxiety and depression, others described RA flares being triggered by low mood or anxiety. Others perceived their mood problems to be separate from their RA, related to other chronic physical health problems or social circumstances, whilst some acknowledged that their anxiety and depression were multifactorial.

5.9.3 Barriers to help-seeking

Candidacy is the process by which a person's eligibility to use a service is formulated through their local interactions with health services (Stevenson and Scambler, 2005). Participants perceived various barriers to help-seeking for anxiety and depression in RA, which led some to perceive they lacked candidacy for care.

Fear of stigmatisation and normalisation of mood problems prevented some participants from seeking help, whilst others described how past negative experiences of consulting their GP or rheumatologist had recursively affected their future help-seeking behaviours.

5.9.3.1 Stigma and shame

Several participants reported having felt too embarrassed to disclose their mental health concerns to their GP, with some perceiving their low mood as a sign of weakness.

> "It was particularly at first because I had been active and I suppose periodically, you might anyway, feel a bit low you know, when things get on top of you a bit…but certainly I did at first, I felt a bit inadequate and don't like to admit weakness and stuff like that…" (Participant 12, female, 70 years).

"…it's only in the last few weeks that I have mentioned about my anxiety and depression to my GP, because I find it very embarrassing. I feel ashamed of having it really, because I've got no reason to, well I have now, I've got the arthritis, but somehow it excuses it, it allows it." (Participant 7, female, 61 years).

One participant described their fear of appearing 'stupid' if they were to disclose their mood concerns to their rheumatology consultant, whilst another reported problems opening up to their GP due to medical students often being present during consultations, which further limited disclosure of mood problems.

"I never mentioned it to Dr X (consultant rheumatologist), because I think they'd think I'm being stupid." (Participant 5, female, 78 years).

"…there are students in there and when you try and tell him personal stuff and you look at the fellow sitting there and you think, 'My son is as old as you'. It's sort of embarrassing… that sort of stops me dead in my tracks…" (Participant 13, female, 45 years).

Thus, the perception of mental health problems as a sign of weakness and fear of stigmatization were significant barriers to help-seeking for mood problems. The presence of other witnesses, such as medical students, during consultations was perceived as a further source of potential embarrassment.

5.9.3.2 Normalisation of mood problems

Several participants did not formulate their experience of suffering into a mental health problem. Instead, they perceived their symptoms to be stress-related or part of a 'grumpy' personality.

"I'm always worried. I think a lot of it's stress. I worry about anything and nothing. I know it's nothing to worry about but I can't help myself. Everyday things I worry about." (Participant 5, female, 78 years).

"I have been dubbed grumpy by my family sometimes." (Participant 6, male, 70 years).

Others normalised mood problems as an expected "side-effect" of any long-term condition (LTC), which prevented them from seeking help for their mood problems.

"I think low mood is just a side-effect of any illness." (Participant 2, female, 56 years).

5.9.3.3 Candidacy for care of mood problems

Several participants perceived other people to have greater health needs, which led them to lack candidacy for care. This was a barrier to them them seeking help for their anxiety and depression.

"I tend to keep it to myself I think. I don't want to bother. I'd just rather be left alone and get on with it. I try not to be too much trouble, really." (Participant 10, male, 61 years).

"I mean I always think, some people are so much worse off so you just have to get on with it, that's my mother's adage as well." (Participant 12, female, 70 years).

Some participants described how their relatives influenced their perceived candidacy for care. For instance, several reported their relatives to be dismissive of their mental health concerns, which prevented them from seeking help.

"…they (relatives) keep saying don't be silly, you're alright. But it's ok for people saying don't worry if I can help it. Well I can't and I'm sure a lot of people can't." (Participant 5, female, 78 years).

However, others reported their relatives to prompt them to seek help for psychological concerns.

"I know I've been moody, I mean like I say, I think I've been alright, but until somebody (*husband*) tells you you've not been alright you don't know..." (Participant 4, female, 58 years).

In summary, several participants did not formulate their symptoms into a mental health problem, or normalised them as an expected consequence of any illness, which was a barrier to help-seeking for mood concerns. Some participants perceived others to have greater health needs, hence lacked candidacy for care. Several participants described how their feelings of candidacy were influenced by their relatives, which was often a barrier to accessing care, but could also facilitate help-seeking for anxiety and depression.

5.9.3.4 Physical, not mental health treatment required

Further barriers to help-seeking for anxiety and depression related to patients' perceptions of the interaction between their RA and mood problems. Some participants didn't raise their mood concerns during RA review appointments as they perceived that better physical, not mental health treatment would be required to improve their mood. For example, one participant perceived their low mood to be caused by joint pains, and another, anaemia, secondary to their RA.

"Some of it I think is linked to my arthritis because I tend to be anaemic quite a lot and I have to keep an eye on that and it's surprising how that affects you, if you don't sort it out really…" (Participant 12, female, 70 years).

"It's one (an injection) I went onto – a research one which was about 400 around the world from what I can gather…That's what I'm waiting for…as I'm sick of my arms and that aching and it'll take a bit away so I don't feel as depressed then..." (Participant 9, female, 68 years).

Consequently, perceptions of the treatment required for anxiety and depression in RA, influenced participants' help-seeking behaviour. As some felt that their mood problems were a consequence of a physical health problem, they focussed on seeking physical, not mental health treatment.

5.9.3.5 Experiences of appointments

Participants reported a lack of continuity of care and problems accessing appointments with their GP as barriers to the disclosure of mood problems.

"I phoned up. No, she wasn't available. She said we'd got two other doctors and I said no, I'd rather see the same doctor." (Participant 7, female, 61 years).

"I've been there years and years. I just find them a waste of time. You never get to see a doctor. You get palmed off with anybody. You're lucky if you see a doctor there, anybody. I don't feel they are bothered." (Participant 9, female, 68 years).

Participants recognised the pressure of restricted appointment times on GPs, but felt that provision of time during individual appointments and encouragement to attend follow-up would be integral to disclosure of psychological concerns.

> “I suppose it’s because they are so busy and as I’ve said, I do understand where they’re coming from, they have so many people to deal with…and they’ve only got a certain length of time, you know, they’re not, whilst there’s some brilliant doctors about and there undoubtedly is, GPs I mean, they do have a really tough job…” (Participant 12, female, 70 years).

> "He’s just very approachable. You just can talk to him about anything. I did go a few times and he said I must come back." (Participant 8, female, 62 years).

Consequently, system-level problems related to access to GPs, restricted time during appointments and a lack of continuity of care or adequate follow-up appointments were further barriers to help-seeking for anxiety and depression.

5.9.3.6 Perceptions of GP

Several participants described appointments with their GP as anxiety-provoking which recursively affected future help-seeking for mental health problems. Some admitted telling their doctor they were fine in order to finish their consultation quickly, meaning any underlying problems were not addressed.

> "I get ever so anxious. I'm not good with, when I have doctor's appointments or medical appointments. I tend to go in and say yeah I'm fine, just so I can get out again." (Participant 7, female, 61 years).

"I get all, I don't know, when I see the doctor. Although they are very good, don't get me wrong, they're marvellous. I forget half of it, then I come away and I don't know anything then…" (Participant 5, female, 78 years).

Some participants perceived their GP to prioritise physical above mental health concerns.

"…doctors are busy enough with physical complaints." (Participant 2, female, 56 years).

Several participants reported past negative experiences of help-seeking, when their GP had lacked time or been dismissive, which had prevented them from disclosing their mental health concerns.

"…they haven't got the time really. I think that's the only thing." (Participant 14, female, 71 years).

"There are a lot of people in that surgery and you go in, you sit down and you've got five or ten minutes and then you're coming back out again and you forget half the stuff you want to really talk about because I've only gone, usually, for my medication. It's just when he does actually say, 'How do you feel?' I just say, 'I feel really down' and he briefly asks me why and I don't feel like I have time to tell him before he's giving me the leaflet." (Participant 13, female, 45 years).

Other participants described their GP as intimidating, which had recursively affected their future help-seeking for psychological problems.

"And you go in and he just looks at you, you know, and I think to myself, well I'm not telling you how I feel, you know……God, well he just sits there and he's very stern

looking, and you go in, and he'll say 'what can I do for you?', and you think nothing, I'm out the door!" (Participant 14, female, 71 years).

Other participants described establishing positive relationships with their GP influenced by body language and rapport which helped to facilitate the disclosure of mental health concerns.

"I just think he'd got a really big heart and I think he was very, very understanding of how you might be feeling and very, very supportive indeed." (Participant 11, female, 53 years).

In summary, some participants perceived their GP prioritised physical above mental health concerns and reported their appointments to be anxiety-provoking, recursively affecting help-seeking. Lack of time and poor continuity of care were perceived to be further barriers to disclosure of mood problems. However, participants suggested that good communication and encouragement to attend follow-up would facilitate discussion of psychological concerns.

5.9.3.7 Perceptions of Rheumatologist

Participants perceived their rheumatologist to only be responsible for physical, not mental health care, which was a barrier to the disclosure of mood concerns during RA review appointments.

"I don't talk about mood and anxiety when I go for a consultant, no I don't. The only thing when I go, I just think about my body, my neck, my skeleton, my body basically." (Participant 7, female, 61 years).

Often participants perceived their consultant to lack the time required to discuss mood problems, which was a further barrier to disclosure. Several reported never being asked about their mood during review appointments.

> "I saw one once and he was very nice, but the others, they sort of want you in and out." (Participant 14, female, 71 years).

> "They're more concerned about the pain and if I was in any pain and what medication I was taking and, I suppose, if they could add another tablet. I don't recall being asked how my mood was at the time, no." (Participant 13, female, 45 years).

Some participants described appointments with their rheumatologist to be anxiety-provoking, which prevented disclosure of mental health concerns and detracted from an effective discussion of how well their RA was controlled.

> "I knew I've got to get this anxiety sorted, because it's stopping me actually telling the medical profession, ie. the consultants just what's going on, because the moment I get in there, my stomach starts churning…" (Participant 7, female, 61 years).

One participant described their fear of appearing 'stupid' if they were to disclose their mood concerns to their rheumatology consultant, whilst another reported having sufficient rapport to disclose psychological concerns.

> "I never mentioned it to Dr X (consultant rheumatologist), because I think they'd think I'm being stupid." (Participant 5, female, 78 years).

> "…Dr X (consultant rheumatologist) and everybody I've seen there to be honest with you, you feel comfortable with yeah, very, very laid back indeed, they've no, how

can I put it, I'm the doctor, there's none of that, I think they don't make you feel like that at all, they're amazing, absolutely." (Participant 11, female, 53 years).

In summary, participants generally perceived their rheumatologist to be responsible for physical, not mental health care, which was a barrier to the disclosure of mood concerns. Further barriers included a lack of time, fear of stigmatization and anxiety-provoking appointments. However, one participant reported feeling comfortable to discuss their anxiety and depression with their rheumatologist.

5.9.4 Perceptions of the annual review clinic

5.9.4.1 The appointment

The majority of patients perceived the annual review appointment to be more detailed than their usual consultant review, which was facilitated by the provision of time.

"…she covered everything. Yes, she really did, it's like me leg just sticks out. And, err, and she examined me and everything, whereas the doctors, they haven't got the time." (Participant 14, female, 71 years).

"I went for an interview with the nurse, into a separate room, and she went through, many things really, how things were, and how I was being affected by certain things, and it was quite useful…" (Participant 2, female, 56 years).

Some participants found it helpful to consult someone different, as it enabled them to retrace their history and amend any factors that had changed.

"It was a different person. Talking to her was like a fresh start, when you speak to somebody new. I could go over it again and add things or take things away or what's gone better, what's gone worse." (Participant 10, male, 61 years).

Participants recognised an emphasis on understanding the wider psychosocial impact of their RA within the clinic, which they often perceived to be poorly explored by their rheumatologist (as described above), who they felt, focused on joint swelling and pain.

"Well she wanted to know how it affected me like you've asked me, which the doctor doesn't go into that, it's more, how much pain, he looks at your joints you know, if they're more swollen, all those sort of things..." (Participant 12, female, 70 years).

Some participants expressed initial concerns about seeing a nurse instead of 'their doctor', though the majority reported their problems to have been addressed and consultant advice sought if required, for instance, regarding a change in RA medication.

So how did that make you feel, that you didn't see Dr X? "Initially relieved, and disappointed, because I know the flares are coming more. But X (clinic nurse) was very good. She spoke to, I think it was Dr X she spoke to and they have increased my medication. Which at the end of the day is what I was going to ask them to do." (Participant 7, female, 61 years).

Participants reported feeling involved in treatment decisions made at the RA annual review clinic.

"...there was two options with this new medication, and also they'd asked me to read both leaflets and decide which I thought was the better, and I don't know if it

was fortunate because I picked the right one, and that was the one they thought." (Participant 6, male, 70 years).

"She was on about injecting into me knees at first, and I said I'd got like, is it a titanium knee? So she said she wouldn't, she thought that wouldn't do. She said, 'so what do you think about a steroid injection'. I said, 'do you think that would help?', and she said 'yes, I think it would.' " (Participant 14, female, 71 years).

Participants perceived the case-finding questions, used to identify anxiety and depression during the clinic, to be acceptable. Some reported feeling better after being given the opportunity to discuss their mood.

So how did it make you feel when they asked you about your mood?

> "Well, in a way better, because I could explain to them how I was feeling, you know. I'm not the sort of person to get down, but I have been just lately" (Participant 5, female, 78 years).

Were you asked about your mood whilst you were at the clinic?

> "Yes, yes…"
>
> *And how did you feel about that?*
>
> "Alright, and I don't mind saying it because, you know, I felt I had a very low mood, because, well because it was really about the worst I'd ever felt, last time I went, because I'd had shoulder pain for weeks and I hadn't really been able to do anything at all." (Participant 2, female, 56 years).

Recently diagnosed patients described the annual review clinic as a learning process about potential complications of RA, including anxiety and depression. For one participant, learning that others with RA were affected by mood problems led them to realise they were not on their own, facilitating discussion of mood concerns.

> "…if you don't get prompted – if it's new to you, you wouldn't know to ask that question. Anything that's relative to arthritis needs to be put down and say, 'Have you got this, that, or the other?' And they can say, 'Ooh yes. I've got that.' Otherwise you wouldn't perhaps think about it. So it is helpful, yes" (Participant 10, male, 61 years).

> "Yes, and when she was saying it I was thinking, god, I feel like that, you know, it's so, it's so, like when somebody else said it, I thought, well I'm not on my own, somebody else must feel like that!" (Participant 14, female, 71 years).

In summary, participants perceived the annual review clinic to be useful and recognised the focus on the wider impact of their RA. Participants reported feeling involved in treatment decisions made and although some reported initial concerns about seeing a nurse instead of their doctor, the majority felt that their concerns were addressed. Participants perceived the case-finding questions to be acceptable, with several describing the clinic as a learning process, during which they were provided with a forum for the disclosure of mood concerns.

5.9.4.2 The nurse

One participant reported that they would need more time to build a rapport with the annual review nurse before disclosing their mood concerns, highlighting the importance of continuity of care.

"…I think with your health you've got to know somebody to, I don't know, to tell them how you're feeling..." (Participant 11, female, 53 years).

Some participants had previously seen the annual review nurse at their local rheumatology hospital, hence felt that their familiarity would facilitate disclosure of mood concerns. One participant also reported that the review nurses' experience in treating joint problems would enable her to understand their RA-related problems, such as low mood, better.

"I think I opened up to that nurse because I knew her. Whereas a counsellor, I don't know them." (Participant 4, female, 58 years).

"I think they understand more, the women at the X (rheumatology hospital), they know everything. I feel they're listening to me and trying to explain everything." (Participant 5, female, 78 years).

Another participant felt their rapport with the annual review nurse was affected by an unwelcome comment she made about her being obese.

"Yes, till she said I was obese! And I'm sat in there, I'm sitting there, and, and I'm thinking, oh my god…" (Participant 14, female, 71 years).

However, the annual review clinic nurse was largely perceived to facilitate disclosure of mood concerns. Participants described her as approachable, caring and understanding.

"…she seemed to understand. Again, I think it's probably a personality thing. It sounds snobbish to say it's because she wasn't a consultant, because that's my age coming into play. Doctors, they're up there. I don't know, she was just really nice, and really easy to talk to..." (Participant 7, female, 61 years).

"Yes, she was warm, she was friendly, you know, she was very approachable I would say." (Participant 12, female, 70 years).

In addition, participants perceived the clinic nurse to listen well to their concerns, a process which was facilitated by the adequate provision of time to talk about their mood.

"I did prefer talking to the nurse about everything… talking to the nurse I was one to one and could tell her a little bit more. She'd got the time to do it." (Participant 5, female, 78 years).

"Yeah, she was relaxed. She wasn't trying to shove me through the door. She'd just got time to listen." (Participant 13, female, 45 years).

Participants described feeling more relaxed during their nurse-led review than their consultant appointment, which facilitated disclosure of concerns they said that they might have forgotten on seeing their doctor.

"You always come out thinking, 'I should have said this. I should have said that'. That's why, sometimes, I do make an appointment and go and speak to the Rheumatology Nurse where she'll just answer the questions I have but it's nice." (Participant 13, female, 45 years).

"I suppose I did open up more to the nurse, because I get all, I don't know, when I see the doctor. Although they are very good, don't get me wrong, they're marvellous. I forget half of it, then I come away and I don't know anything then, whereas with the nurse, whether it's more time with them, and I can get back to them more if you know what I mean." (Participant 5, female, 78 years).

Therefore, although some participants felt they would need more time to build a rapport, the majority reported the clinic nurse to be approachable, caring and to listen well, all of which facilitated the disclosure of mood concerns.

5.10 Discussion

5.10.1 Summary of findings

The proportion of people with RA who reported symptoms suggestive of possible anxiety (24% scoring ≥ 3 on the GAD-2 questions) and depression (21% scoring ≥ 3 on the PHQ-2 questions) within the annual review questionnaires, exceeded one-week prevalence rates for GAD (5.9%) and depression (3.3%), determined by a survey of the general population of England (NatCen Social Research, 2016).

Whilst the proportion of people with RA who reported symptoms of possible depression was slightly lower than the prevalence of depression reported in the literature (Matcham et al., 2013), the proportion with symptoms of anxiety was higher than previously reported (Covic et al., 2012). The impact of anxiety, particularly on help-seeking for care of mood problems, emerged on analysis of the interview data.

The recognition of anxiety and depression was facilitated by the personal reflections of participants and comments made by their concerned relatives. For some, direct questioning by the annual review clinic nurse also provided a forum for the acknowledgement of mood problems. Some participants perceived their RA and mood problems to be linked, though the direction of this link varied. Whereas several reported RA-related pain, loss of mobility and social isolation to precipitate their anxiety and depression, others described RA flares being triggered by low mood or anxiety. Others

perceived their mood problems to be separate from their RA, often due to social circumstances.

Overall, there were multiple barriers to help-seeking for anxiety and depression in RA. Fear of stigmatization prevented some participants from discussing their mental health problems, whilst others normalised their symptoms of distress. Several participants lacked candidacy for care, perceiving others to have greater health needs, whilst others sought better management of their physical health, to improve their mental health.

Participants generally perceived their rheumatologist to be responsible for physical, not mental health care, which was a barrier to the discussion of mood concerns. Poor access to GP appointments was described as a barrier to the disclosure of mental health concerns and was perceived to negatively impact on continuity of care. GPs were perceived to lack time, whilst several participants described appointments as anxiety-provoking, recursively affecting help-seeking. Good communication and encouragement to attend follow-up were suggested as methods to facilitate disclosure of mood problems.

The case-finding questions were perceived to be acceptable, when asked in the context of the annual review clinic. Participants reported the annual review clinic to be useful and recognised a focus on the wider impact of their RA. Several described the clinic as a learning process, during which they were provided with a forum for the disclosure of mood concerns. Although some participants felt they would need more time to build a rapport, the majority reported the clinic nurse to be approachable, caring and to listen well, all of which facilitated the disclosure of mood concerns.

5.10.2 Strengths and limitations

Use of exploratory methods, followed by further analysis using a framework, enabled deeper insights into the barriers and facilitators to patients with RA accessing care for psychological problems. To help participants to feel at ease and not see the interview as an encounter with a stranger, telephone conversations with participants prior to the face-to-face interviews were used to establish rapport. Participants were not informed that their interviewer was a GP, as this could have been a barrier to them sharing negative opinions of clinicians. To facilitate reflexivity memo notes were kept and regular team meetings were held where the interpretation of data was discussed.

As only patients with a high PHQ-2 or GAD-2 score were interviewed, different views could have been articulated by individuals without mood problems. In addition, participants were predominantly white British and female, hence a greater range of perspectives may have been gained from a more diverse population. However, a range of different socioeconomic statuses were represented within the sample interviewed and attempts were made to purposively sample participants of different ages.

5.10.3 Patient and public involvement and engagement

The content and layout of the patient questionnaire was informed and refined with input from the local Haywood User Group, who offered anonymous feedback on its' layout and content. I gained funding from Royal College of General Practitioner's (RCGP) Scientific Foundation Board (SFB) to conduct a further PPIE meeting, to discuss the potential interpretation of ambiguous data extracts, in addition to strategies for dissemination of findings.

Initially, attempts were made to recruit PPIE group members from the Haywood User Group. A simple presentation of the research aims and the reasons for patient involvement was made to the group at one of their regular meetings, and although 9 volunteered to participate, only 2 had RA. Following discussion between research team members, it was agreed that as the research would impact on patients with RA, it would be best to just include this subset of patients, who would potentially benefit the most from their involvement and have personal experiences of living with inflammatory arthritis to draw upon. Therefore, to supplement the 2 patients with RA recruited from the Haywood User Group, a further 6 patients were invited from the Keele Research User Group (RUG). The Keele RUG includes over 130 members who have experience of living with a LTC, or are a carer or close relative of someone with a LTC (Keele University, 2019). One of the PPIE group participants had previously attended the annual review clinic.

During the PPIE meeting, various interview extracts were presented to the group. Although participants agreed with the interpretation of the majority, some offered alternative perspectives, enriching analysis. Participants agreed that anxiety and depression were common in people with chronic illness, but suggested that sometimes people don't recognise this, or feel that nothing can be done. In addition, participants suggested that people may feel more comfortable disclosing mood problems to a nurse rather than a consultant.

The PPIE group suggested that there was a need for patients with RA to be educated about mood problems and potential treatments. On discussing ways to publicise findings, patients suggested that leaflets could be given out at pharmacies or GP surgeries. The role of the patient information and educational resource (PIER) at the

local rheumatology hospital, as an information resource was also discussed. Participants suggested that disease-specific support groups and Arthritis Research United Kingdom (ARUK) would also be interested in the findings.

Feedback from the group was used to support future decisions regarding continuation of the pilot clinic. A leaflet was collaboratively produced with patients (appendix 13) to outline the links between RA and anxiety and depression, which included information on where patients could seek further help. The leaflet, which was approved by the RCGP SFB, was left for patients to access at the PIER. In addition, overall findings of the qualitative study were presented to the Haywood User Group.

5.11 Conclusion

A nurse-led annual review clinic provides a suitable forum for the discussion of comorbid anxiety and depression in patients with RA. There is need for education of people with RA about comorbid mood problems, hence patients have helped to collaboratively develop a leaflet, endorsed by the SFB, which is available for the public to access at a local rheumatology hospital educational resource.

The annual review clinic has been commissioned to continue in the longer-term, with the aim of improving the recognition and management of comorbidities such as anxiety and depression in RA.

5.12 Connection to subsequent studies

Within the next chapter I have aimed to build on the findings of my qualitative study, by determining the impact of anxiety in RA. I was led to focus on comorbid anxiety after hearing patients describe the multiple ways this had impacted on their help-

seeking behaviour, access to care and perceived response to RA treatments. From a review of the background literature, I had identified a lack of studies focusing on the impact of anxiety, with the majority reporting on the impact of depression in RA, hence I felt this would be an important area to investigate further.

CHAPTER 6
Systematic Review

6.0 SYSTEMATIC REVIEW

The association of anxiety with quality of life and disease activity in rheumatoid arthritis

6.1 Introduction

As discussed in the background chapter (section 2.9.1), the link between rheumatoid arthritis (RA) and mental health problems is well established. The estimated prevalence of anxiety in people with RA is 13-20% (VanDyke et al., 2004; Isik et al., 2006; Covic et al., 2012), whilst prevalence estimates for depression vary from 16.8% when assessed by diagnostic interview, to 38.8% when determined using the Patient Health Questionnaire (PHQ)-9 (Matcham et al., 2013). These estimates are substantially higher than in the general adult population of England, in which the one-week prevalence of generalised anxiety disorder (GAD) and depression determined by screening questions, is 5.9% and 3.3% respectively (NatCen Social Research, 2014). Despite their frequency, comorbid anxiety and depression in people with RA are often under-recognised and under-treated (Cepoiu et al., 2007), contributing to increased morbidity and mortality (Ang et al., 2005).

To date, most literature examining the impact of mood problems on quality of life (QoL) and disease activity in RA has focused on depression. As discussed in section 2.9.1, several studies have shown depressive symptoms in people with RA to be associated with a significant reduction in QoL (Bazzichi et al., 2005; Senra et al., 2017), whilst a systematic review examining the impact of mood problems on disease activity, found that depression may be associated with increased disease activity in RA (Rathbun,

Reed & Harrold, 2013). Baseline depressive symptoms have also been associated with a reduced response to RA treatment over time (Matcham et al., 2018; Hider et al., 2009) and a lower disease remission rate (Cook et al., 2016).

When the impact of anxiety in RA has been examined, this has often been in combination with depression (Matcham et al., 2016b). However, at least 40% of individuals with anxiety in the general population do *not* have comorbid depression (Kaufman & Charney, 2000). Anxiety has been linked to different help-seeking behavior when not associated with comorbid depression. A recent study found the severity of mood symptoms, determined using Becks' Anxiety Inventory (BAI) and Becks Depression Inventory (BDI), to predict help-seeking behavior in individuals with anxiety alone, but not in those with a combination of anxiety and depression (Fine et al., 2018). In addition, evidence suggests the direct effect of anxiety on pain, is higher than that of depression (Smith & Zautra, 2008). It is possible that anxiety leads to increased physical arousal, increasing pain sensitivity or the interpretation of sensations as painful (Clark & Watson, 1991). Meanwhile, depression, through the absence of pleasure, may increase vulnerability to pain at times of stress (Smith & Zautra, 2008). Therefore, it can not be assumed that anxiety interacts the same as depression with QoL and disease activity in people with RA.

In addition, although some options for the management of anxiety (Clinical Guideline (CG) 113) and depression (CG90) overlap, there are several key differences (NICE, 2011; NICE, 2009a). For example, the stepped care model for anxiety includes treatment options such as applied relaxation, and suggests a higher threshold for medication use than for depression. Consequently, it is important that anxiety is recognised, especially when it exists in isolation, to facilitate the provision of

appropriate treatment. Despite this, few studies have examined the impact of anxiety alone in people with RA.

6.2 Aims and Objectives

The aim of this study was to understand the impact of anxiety on the QoL and disease activity of people with RA. My objective was to perform a systematic review and meta-analysis, to determine the association between anxiety, and QoL and disease activity, in people with RA.

6.3 Methods

6.3.1 Systematic Review Protocol (PROSPERO)

A systematic review protocol was established a priori for this review and registered with the international prospective register of systematic reviews, PROSPERO (number CRD42017062580) (Machin, 2018). The protocol is detailed in appendix 14. This contains a background to the review, specific objectives, eligibility and exclusion criteria for studies, the search strategy and review methods utilised.

6.3.2 Search strategy and study eligibility

A search strategy was developed using comprehensive text word searching of the title, abstract or keywords and database Subject Headings, combining terms for anxiety ("anxiety", "anxiolytic agent", "anxiet* or anxious") and RA ("arthritis, rheumatoid" or "rheumat* adj3 (arthriti* or diseas* or condition* or nodule*)").

As it was anticipated that there would be a lack of eligible studies examining the primary outcome measures (section 6.3.3), the search was kept broad to capture as

many alternative descriptive terms for the outcomes of interest as possible, to be considered as additional outcome measures.

Systematic searches were conducted in five electronic databases (Web of Science, PsycINFO (EBSCO), CINAHL (EBSCO), Embase (Ovid), Medline (Ovid)) from inception to February 2019, using customised search terms for each database (appendix 15). In addition, a search for grey literature from across Europe was conducted using "www.opengrey.eu".

Grey literature is research that is either unpublished or has been published in a non-commercial form. Examples can include government reports, theses, dissertations, newsletters, policy statements and conference proceedings (Winters and Weir, 2017). Some grey literature sources such as doctoral theses can be more detailed than published articles, and often these can be available in advance of academic publications (Winters and Weir, 2017). Searching for grey literature helped to minimise potential publication bias. Publication bias occurs when the decision to publish or distribute research findings is based on the outcome of a study (Winters and Weir, 2017). Consequently, a grey literature search was included to facilitate a less biased, real world view of the interaction between anxiety and QoL or disease activity in RA.

After completion of the database searches and removal of duplicate articles in refworks, unique citations were imported into Covidence, a review management software. Titles, abstracts and full texts were screened by paired independent reviewers (Dr Annabelle Machin and either Dr Ian Scott or Dr Randula Haththotuwa (see acknowledgements)) using pre-specified selection criteria. Inter-rater disagreement was minimal, with any disagreements resolved through discussion, re-examination of the article, or by the independent vote of a third reviewer (Dr Opeyemi Babatunde).

The reference lists of key papers were hand-searched to identify other relevant studies that hadn't been found during the initial database searches. Citation tracking of index papers was also used to identify any relevant related studies.

All articles including adults (>18 years) with RA, which reported anxiety (separately from depression) and either QoL or disease activity outcome measures were included. Any study setting or design was included. The full inclusion and exclusion criteria are detailed in table 6.1.

Table 6.1- *Inclusion and Exclusion Criteria*

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Population aged ≥ 18 years with RA. • Exposure of anxiety. • People in the comparator/ control group (if any) aged ≥ 18 years with RA. • Primary outcome of short form (SF)-36 and/ or disease activity score in 28 joints (DAS28) and/ or additional validated outcome measures for QoL or disease activity.	• Any participants < 18 years. • Data not specific to anxiety and RA. • An interpreter could not be found for an article not written in the English Language. • Efforts to retrieve a full text were unsuccessful and the abstract contained insufficient data.

6.3.3 Outcome measures

6.3.3.1 Disease activity

The Disease Activity Score in 28 joints (DAS28) (Prevoo et al., 1995) was the primary outcome measure for disease activity, though other validated measures of disease activity were also included. DAS28 is a composite score comprising of biochemical measures (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), clinician assessment of disease activity via a 28 swollen joint count (SJC) and

tender joint count (TJC), and self-report via a visual analog scale (VAS), to determine a patients' perceived disease activity). The DAS28 score is used to monitor RA activity, gauge response to therapy and determine treatment pathways; particularly access to biologic treatment in the United Kingdom (UK). On commencing treatment with a disease modifying anti-rheumatic drug (DMARD), clinicians monitor DAS28 scores over time, aiming for remission (a DAS28 score <2.6), or low disease activity if remission is not possible despite appropriate escalation of treatment (DAS28 <3.2) (NICE, 2018).

DAS28 was chosen as the primary outcome as it is the most widely used and reported outcome measure for disease activity in RA. However, DAS28 has several disadvantages. For example, the 28 joint counts used as part of the DAS28 do not include the feet, meaning those with significant foot synovitis may have falsely low scores. However, individuals with significant foot involvement often have hand symptoms which are included in the score, whilst exclusion of the feet makes the score more efficient to complete. In addition, joint damage in the feet can often be a chronic problem, hence not indicative of ongoing disease activity, meaning examination of the feet is a less accurate way of assessing treatment response. A further potential disadvantage of DAS28 is that scores could be misleadingly low if an individuals' inflammatory markers don't rise significantly during a disease flare. Also, when it is unclear to a clinician whether a joint is swollen or tender, this could lead to significant variation in the score (Fransen & van Riel, 2009).

6.3.3.2 Quality of life

QoL is a multi-dimensional concept used to describe an individual's perceptions, satisfaction, and evaluation of different aspects of their lives, such as physical health, functioning, emotional wellbeing, social life and relationships. Health-related (HR)QoL

is important for measuring the impact of disease and subjective wellbeing (Carr et al., 2015).

The short form (SF)-36 was the primary outcome measure used for QoL in this review, though additional validated QoL outcome measures were included. SF-36 is a set of patient self-reported QoL measures (Ware & Sherbourne, 1992). The SF-36 assesses eight health concepts: 1) limitations in physical activities; 2) limitations in social activities; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality; and 8) general health perceptions. These eight scales can be aggregated into two summary measures, the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

The PCS and MCS scores are calculated by weighting, then summing the 8 original health domains. Weights are gained from factor analysis of datasets gained from general population surveys (Ware, Kosinski & Keller, 1994). Domain scores are weighted due to the 8 health domains being significantly intercorrelated, with changes to physical dimensions impacting on dimensions measuring mental health, and vice versa (Ware et al., 1995). Therefore, weighting the 8 health domains, helps to take account of how changes in a primarily physical domain impact on mental health, whilst conversely accounting for the impact of changes in a predominantly mental health domain on physical health.

The SF-36 was chosen due to it being acceptable to patients, having high internal validity and being more precise than the SF-12 and SF-8 health surveys (Brazier et al., 1992). However, as a consequence of being more detailed, SF-36 can take longer to complete, whilst it also contains no variable for sleep. An alternative would have been

the Nottingham Health Profile, though this can be less sensitive to lower levels of dysfunction (Jenkinson, Coulter and Wright, 1993), whilst EuroQol (EQ)-5D can be less sensitive to variations in health status, when compared to the SF-36 (Liao, Tan and Yang, 2016).

One study assessed the reliability and responsiveness of different QoL instruments used in people with RA. When the reliability of different QoL instruments was evaluated, by agreement and internal consistency, the RA-QoL scale was found to be more reliable than the SF-36 in people with RA. However, components of the SF-36 were more responsive to change (Linde et al., 2008). The SF-36 is widely used and reported in the literature as a measure of QoL, enabling comparison with different conditions, hence this was used as the primary outcome measure for QoL.

6.3.4 Data extraction

A customised and piloted data extraction tool was used to extract relevant data from the included articles. Extracted data included country of origin, study design, methodology, sample characteristics, main findings and relevant statistical measures. Data extraction was completed independently by AM and RH, and any disagreements resolved through discussion. Where only abstracts were available, or insufficient information was reported, authors were contacted via email for further details.

6.3.5 Study quality assessment

For this systematic review, a quality assessment tool for non-randomised studies was required, as eligible studies were anticipated to be either cohort or cross-sectional studies.

Deeks et al. (2003), systematically reviewed 182 tools for assessing the

methodological quality of non-randomised studies. From this, six tools were identified as potentially useful for systematic reviews. However, not all of these tools adequately reviewed how study participants were allocated into groups, hence did not assess the risk of selection bias. In addition, several of the tools were not suitable to use for different study designs. The two most useful tools identified were the Downs and Black instrument (Downs and Black, 1998) and the Newcastle Ottawa Scale (NOS) (Wells et al., 2019).

The Downs and Black checklist includes 27 questions and enables articles to be assigned a numeric score for study quality out of 30. Whilst detailed, when used, reviewers have reported it to be difficult to apply and time consuming to use (MacLehose et al., 2000).

The NOS comprises an eight-item scale, with versions for cohort, case-control and cross-sectional studies (Wells et al., 2019). Domains of selection, comparability and outcome or exposure are evaluated, with stars allocated for features of quality, up to a maximum of nine. Higher scores indicate an article has better methodological aspects. However, the ability of the NOS to distinguish between high and low quality studies has been questioned (Stang, 2010), whilst it has also been found to have low reliability between individual reviewers, meaning scores can vary considerably dependent on the reviewer (Hartling et al, 2013). However, it has been found to be simple to use and interpret, hence has been recommended by the Cochrane Collaboration (Higgins & Green, 2011).

An alternative would have been the RTI Item Bank on Risk of Bias and Precision of Observational Studies. Consisting of 29 multiple choice items within 11 domains, the RTI Item Bank can be applied to multiple study designs (Viswanathan & Berkman, 2012).

Although it can be useful at detecting variation in study quality, it has been described as more burdensome to use than the NOS (Margulis, 2014), whilst many aspects of the RTI item bank also overlap with the NOS.

Another option would have been the Critical Appraisal Skills Programme checklist, a set of eight tools designed to assess the quality of different study types (CASP, 2018). The tool for cohort studies includes 12 questions which encourage the reviewer to critically appraise the study under review. However, unlike the NOS, there is no tool adapted for use in cross-sectional studies.

Due to the advantages of the NOS above other tools, this was used to assess the quality of studies within this review. The quality assessment criteria for both cohort and cross-sectional studies are listed in table 6.2.

Table 6.2- *NOS cohort and cross-sectional study quality assessment criteria*

Newcastle Ottawa Scale Study Criteria	
Cohort study	**Cross-sectional study**
• Representativeness of the exposed cohort • Selection of the non-exposed cohort • Ascertainment of the exposure • Comparability of the cohorts • Assessment of the outcome • Length of follow-up • Adequacy of follow-up cohorts	• Representativeness of the sample • Sample size • Non-respondents • Ascertainment of the exposure • Controlling for confounding factors • Assessment of the outcome • Statistical analysis

6.3.6 Analysis

6.3.6.1 Meta-analysis

Meta-analysis is a method used to combine the results of different trials in order to obtain a quantified synthesis. As the size of individual studies can sometimes be too small to reliably detect an outcome, meta-analysis can be used to pool the results of studies and increase the power of statistical analyses (Borenstein et al. 2009). However, when combining the results from a group of studies, the individual studies need to be similar enough so that the combined study estimate provides a meaningful description of the set of studies. Some variation between studies due to chance is expected, though excessive variation, known as statistical heterogeneity needs to be assessed for (Borenstein et al., 2009).

A meta-analysis of quantitative data on the primary outcome measures was performed. Due to differences in the reporting of SF-36, for meta-analysis, correlation coefficients between anxiety and the PCS or "physical functioning" subscale scores were pooled to give an overall impression of the association between anxiety and physical QoL. Additionally, correlation coefficients between anxiety and the MCS or "mental health" subscale scores were pooled to give an overall value for the association between anxiety and mental QoL.

To pool the estimates of the correlation coefficient values, two methods were considered; a fixed effects and random effects model (DerSimonian & Laird, 1989). A fixed effects model accounts for within study variability using the inverse variance method. This gives more weight to studies that have small variances, using the reciprocals of study variances (standard error squared) as study weights. Therefore, the fixed effect model is used when there is little evidence of heterogeneity.

The random effects model accounts for variance both within and between individual studies, hence is used when a large degree of heterogeneity is noted. The method used within the random effects model is a variation of the inverse variance approach, with weight given to studies according to the reciprocals of the sum of within and between study variances.

As there was evidence of significant heterogeneity between the studies, a random effects model was used (DerSimonian & Laird, 1989). The χ^2 statistic was used to assess for the presence of heterogeneity. Due to the sampling distribution of correlation coefficients not being normally distributed, Fisher's z' transformation was used to calculate a confidence interval on the population value of Pearson's correlation.

Using *atanh* command in Stata (version 14.0), correlation coefficients (r) were converted to Fisher's z scores r(z') and an associated standard error calculated using the standard formula SE[r(z')]= √(1/(n-3)). The r(z') values were pooled using the *metan* command in Stata, and subsequently transformed back to obtain a pooled r-value using *tanh* command in Stata, then plotted together with study-specific estimates. The Cochran Q statistic was used to assess for the presence of heterogeneity. In addition, the I^2 statistic (DerSimonian & Laird, 1989; Higgins et al., 2003) was calculated to examine the proportion of total variation in study estimates which could be explained by heterogeneity.

As meta-analysis could only be used to synthesise the quantitative results for primary outcome measures, a narrative synthesis was utilised to summarise the overall study results, including additional outcome measures.

6.3.6.2 Narrative Synthesis

Narrative synthesis is an approach to the review and synthesis of findings from multiple studies. Words and text are used to explain the findings of included studies. A narrative synthesis approach was chosen as it was anticipated that there would be a variety of data including qualitative and quantitative findings to synthesise. In addition, this method was chosen as it was felt the search would yield a variety of additional outcome measures that could not be synthesised using a purely statistical meta-analysis.

A common criticism of narrative synthesis is that it is subject to author interpretation. Therefore, guidance funded by the Economic and Social Research Council of the UK was followed (Popay et al., 2006).

Extracted data were synthesised using a narrative synthesis framework in four stages:

1. An idea of how anxiety relates to QoL and disease activity was developed, to inform decisions about the review question, the types of studies to include, and to contribute to the interpretation of findings.
2. A preliminary synthesis of the findings of included studies was developed to organise findings. After a summary of all studies was tabulated, separate data analysis of primary and additional outcome measures for QoL and disease activity was performed.
3. Relationships between the studies were explored. Potential sources of heterogeneity were considered, that could explain differences in study findings.
4. The strength of evidence for drawing conclusions and generalising findings to different populations was assessed, considering the methodological quality of

included studies and the overall evidence in relation to each of the specified outcomes.

6.4 Results

A hypothesis that anxiety would be associated with reduced QoL and increased disease activity was developed. Due to an anticipated lack of literature, all study types were considered, with primary and additional validated outcome measures for each outcome analysed separately, as outlined below.

6.4.1 Summary of included studies

Figure 6.1 shows the flow of studies within the review (p174). A total of 20 final studies were identified for inclusion (Al-Fadl et al., 2014; Kojima et al., 2009b; Nas et al., 2011; Ozcetin et al., 2007; Alpi et al., 2017; Celiker & Borman, 2001; Grosso et al., 2015; Ichikawa et al., 1995; Karahan et al., 2016; Matcham et al., 2016a; Miwa et al., 2002; Mok, Lock & Cheung, 2012; Overman et al., 2012; Wan et al., 2015; Zulgerel & NandinErdene, 2014; Kuijper et al., 2018; Dyball et al., 2018; Sergeant et al., 2018; Ruhaila & Cheng, 2018; Fragoulis et al., 2018).

The characteristics of the 20 studies included in the final analysis are summarised in 3 tables. Table 6.3a (prospective cohort studies) (p175) and 6.3b (cross-sectional studies) (p176), contain studies reporting disease activity outcomes, whilst table 6.4 summarises the studies reporting QoL outcomes (p177-178), which are all cross-sectional. Significant results are highlighted in bold on the right of each table in the "findings" column, with the significance level indicated in the results column, using 1-3 asterix. In the footnotes below each table, abbreviations are given in full, quality assessment scores described and the interpretation of significance levels explained.

Figure 6.1- *Study Flow*

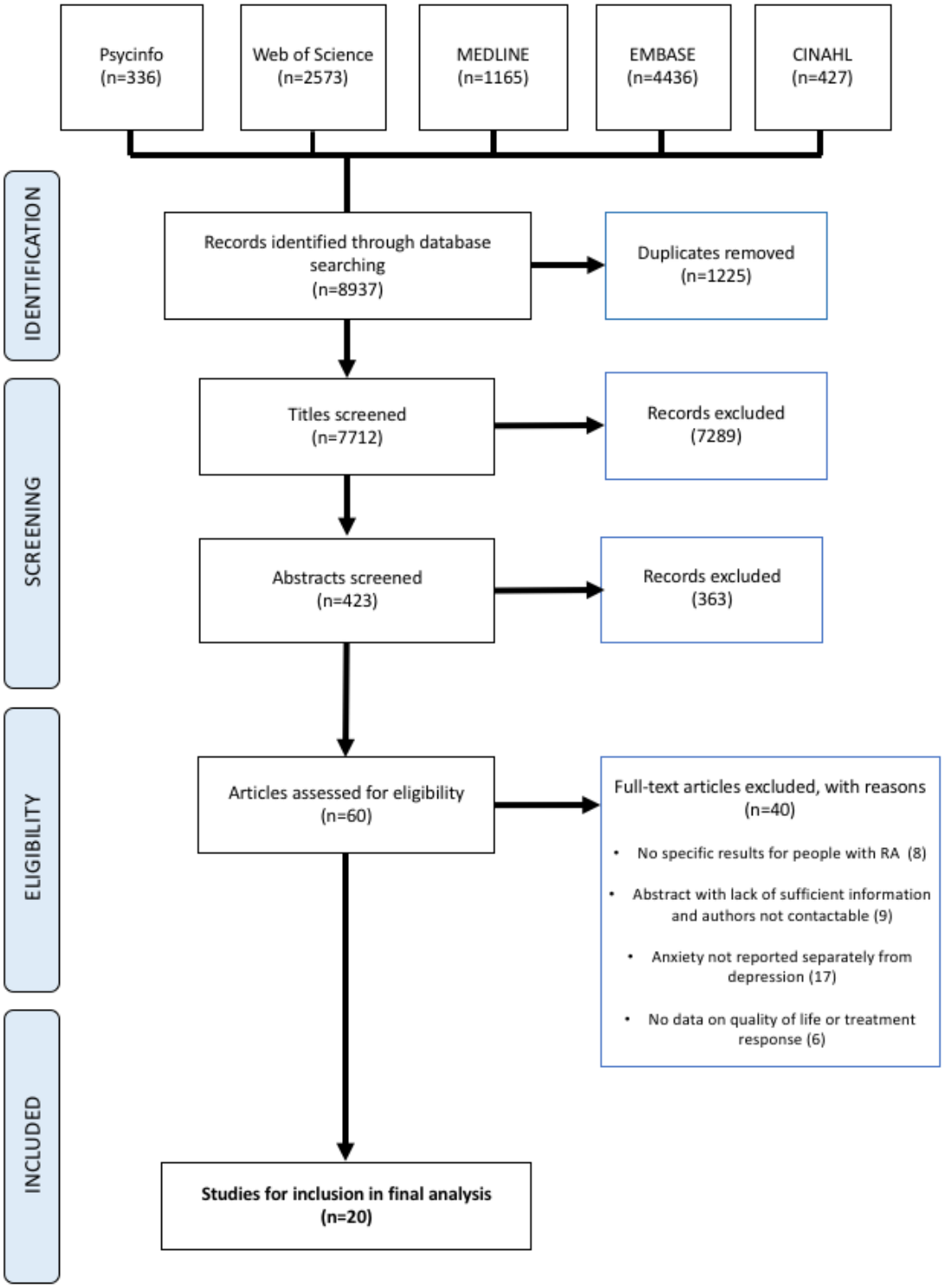


Table 6.3a- *Summary of characteristics of **prospective cohort studies** reporting disease activity outcome measures*

First Author/ Year/Country	Sample Size (male:female)	Mean Age	Ascertainment of anxiety	Outcome measures	Results	Study Quality [1]	Findings
Dyball, 2018. (Abstract) UK	2919 (701: 2218)	57.3	HADS-A	DAS28	Baseline HADS-A and change in DAS28 at 6 months. Adjusted b=0.01 (n.s.), 95% CI, -0.01, 0.04.	6	Baseline anxiety associated with smaller improvements in DAS28 at 6 months, not significant.
Fragoulis, 2018. (Abstract) UK	848 (gender not reported)	Not reported	HADS-A	DAS28	HADS-A and DAS 28 at: -baseline r=no value given*** -6 months r=0.230*** -12 months r=0.217***	4	Baseline anxiety correlated with disease activity at baseline, 6 and 12 months, **significant**.
Kuijper, 2018. Netherlands.	281 (91:190)	53.0	HADS-A	DAS28	HADS-A and DAS28 at: 3 months, b=0.043**, 95%CI, 0.013, 0.073 9 months, b=0.017(n.s.), 95%CI, 0.010,0.044 15 months, b=0.012(n.s.), 95%CI, -0.020, 0.043	7	Anxiety associated with increased disease activity, **significant at 3 months**, non-significant at 9 and 15 months.
Matcham, 2016a. UK	56 (12:44)	53.6	HADS-A	DAS28	Anxiety and DAS28 Baseline, r= 0.29 *	7	Anxiety correlated with increased disease activity at baseline, **significant**.
					Baseline anxiety and DAS28 at 1 year follow up, r= 0.33*		Baseline anxiety correlated with increased disease activity at 1 year, **significant**.
					unadjusted b= 0.04*. 95% CI, 0.00, 0.07. Adjusted b = 0.02 (n.s.), 95% CI, 0.00, 0.05.		Anxiety associated with disease activity at 1 year, non-significant when adjusted.
Overman, 2011. Netherlands	545 (168:377)	56.0	10 item anxiety scale	Thompson Articular Index	Anxiety and Thompson Articular Index b(SE)=55.1736 (21.0731) **	6	Anxiety is associated with more swollen, tender joints, **significant**.
				ESR	Anxiety and ESR b(SE) =0.2448 (0.0759) **		Anxiety is associated with increased inflammation, **significant**.
Sergeant, 2018. UK	1050 (343:707)	59.0	HADS-A	Non-response to treatment	HADS-A and non-response (improvement in DAS28 ≤0.6/ stopped due to inefficacy) at 6 months -Multivariable analysis OR (95%CI) =1.07 (1.03, 1.12)**	7	Higher baseline anxiety predicts non-response (reduced improvement in disease activity in response to treatment), **significant**.

r = pearsons correlation coefficient, b = multiple regression coefficient, CI= confidence interval, SE= standard error, OR= odds ratio, SD= standard deviation.
n.s.= not significant (p>0.05), *(p<0.05), ** (p<0.01), ***(p<0.001)
DAS28= Disease Activity Score in 28 Joints, **ESR**= Erythrocyte Sedimentation Rate, **HADS-A**= Hospital Anxiety and Depression Score, for anxiety.
[1] Quality rated out of 9 using Newcastle Ottawa Scale: 0–2 = low quality, 3–6 = medium quality and 7–9 = high quality

Table 6.3b- *Summary of characteristics of **cross-sectional studies** reporting disease activity outcome measures*

First Author/ Year/Country	Sample Size (male:female)	Mean Age	Ascertainment of anxiety	Outcome measures	Results	Study Quality[1]	Findings
Al-Fadl, 2014. Egypt	26 (8:18)	43.4	HAM-A	DAS28	HAM-A and DAS28 r= 0.47*	5	Anxiety correlated with increased disease activity, **significant**.
Grosso, 2015. (Abstract) Italy	200 (29:171)	62.4	HADS-A	DAS28	RA and Anxiety vs. RA and no mood problem. Mean DAS28(SD): 3.38(1.18) vs. 2.48(0.78) **	5	Patients with anxiety have increased disease activity compared to those without anxiety, **significant**.
Ichikawa, 1995. Japan	92 (16:76)	53.4	BAI	Pain VAS	Anxiety and Pain VAS r=0.432 ***	5	Anxiety correlated with increased pain, **significant**.
				LAI	Anxiety and LAI r=0.237 *		Anxiety correlated with increased disease activity, **significant**.
Karahan, 2016. Turkey	148 (32:116)	51.1	Zung's self rating anxiety scale	DAS28	BAI and DAS28 r=0.159, (n.s.)	5	Anxiety correlated with increased disease activity, non-significant.
Kojima, 2009b. Japan	120 (22:98)	57.7	HADS-A	SJC, TJC, CRP, Physicians' global assessment	HADS-A and disease activity (composite score of SJC, TJC, CRP, Physicians' global assessment) Factor loading -0.10 (n.s.)	6	Relationship between anxiety and disease activity non-significant.
Miwa, 2002. Japan	82 (20:62)	62.0	HADS-A	VAS	Anxiety and VAS (a) In group with mean activity <0.5, r=0.2935* (b) In group with mean activity >=0.5, r=-0.0269 (n.s.)	4	Anxiety correlated with increased pain. **Significant** in people with lower mean activity, non-significant in people with higher mean activity.
Ruhaila & Cheng, 2018. Malaysia	192 (22:167)	49.6	DASS	DAS28	DASS (21) and DAS28 r=0.233**	5	Anxiety correlated with increased disease activity, **significant**.
Zulgerel,2014 (Abstract) Russia	51 (2:49)	43.0	Spielberg Chennai Test	DAS28	Anxiety and DAS28 r=0.126 (n.s.)	1	Anxiety correlated with increased disease activity, non-significant.

r= pearsons correlation coefficient, SD= standard deviation, n.s.= not significant (p>0.05), *(p<0.05), ** (p<0.01), ***(p<0.001)
BAI= Beck's Anxiety Inventory, **CRP**= C-Reactive Protein, **DAS28**= Disease Activity Score in 28 Joints, **DASS**= Depression, Anxiety and Stress Scale, **LAI**= Lansbury's Articular Index, **HADS-A**= Hospital Anxiety and Depression Score (for anxiety), **HAM-A**= Hamilton's Anxiety Rating Scale, **SJC**= Swollen Joint Count, **TJC**= Tender Joint Count, **VAS**= Visual Analogue Scale
[1] Quality rated out of 9 using Newcastle Ottawa Scale: 0–2 = low quality, 3–6 = medium quality and 7–9 = high quality.

Table 6.4- *Summary of characteristics of studies reporting QoL outcome measures (all cross-sectional)*

First Author/ Year/Country	Sample Size (male: female)	Mean Age	Ascertainment of anxiety	Outcome measures	Results	Study Quality [1]	Study findings
Al-Fadl, 2014. Egypt	26 (8:18)	43.4	HAM-A	PCS/ MCS of SF-36	Anxiety and PCS, r= -0.38 * Anxiety and MCS, r= -0.34 *	5	Anxiety correlated with lower physical and mental QoL, **significant**.
Alpi, 2016. Colombia	62 (3:59)	59.7	HADS-A	QoL-RA scale	Anxiety and QoL-RA scale, r=-0.644 ** Anxiety and QoL-RA sub-scores; -Physical ability, r=-0.492 ** -Support, r=-0.454 ** -Pain, r=-0.489 *** -Tension, r=-0.581 ** -Health, r=-0.624 ** -Arthritis, r=-0.510 ** -Support, r=-0.593 ** -Mood, r=-0.674 **	5	Anxiety correlated with reduced QoL, **significant**.
					Anxiety and QOL-RA, adjusted b=-0.453 ***		Anxiety has a negative association with QoL, **significant**.
Celiker, 2001. Turkey	20 (0:20)	46.6	STAI	LSI	Anxiety and LSI. A- State (current anxiety), r=-0.5005 * A-Trait (long-standing anxiety), r=-0.5103 (n.s.)	3	Anxiety correlated with reduced life satisfaction, **significant for current anxiety**, non-significant in long-standing anxiety.
Karahan, 2016. Turkey	148 (32:116)	51.1	BAI	WHOQoL-BREF	BAI and WHOQol-BREF -Mild anxiety - (n.s.) -Moderate/ severe anxiety - *	5	Non-significant correlation between mild anxiety and worse QoL, **significant in moderate to severe anxiety.**
Kojima, 2009b. Japan	120 (22:98)	57.7	HADS-A	SF36 (PCS/ MCS)	HADS-A and PCS of SF-36, r= -0.25 ** HADS-A and MCS of SF-36, r= -0.51 ***	6	Anxiety correlated with lower physical and mental health QoL scores, **significant**.
Mok, 2012. China	200 (42:158)	51.4	Chinese Bilingual Structured Interview	SF-36	Anxiety vs no psychiatric disorders, mean (SD) SF36= 31.2 (12.9)*** vs. 56.6 (20)**	6	Anxiety group, reduced QoL compared to group without psychiatric disorders, **significant**.
Nas, 2011. Turkey	421 (72:349)	50.15 (at risk of anxiety group)	HADS-A	SF-36	Anxiety and SF-36 subscales. -Physical function, r=-0.28 *** -Vitality, r=-0.40 *** -Social function=-0.36 *** -General health, r=-0.29 *** -Physical role, r=-0.24 *** -Mental health, r=-0.48 *** -Emotional role, r=-0.23 *** -Bodily pain, r=-0.32 ***	6	Anxiety is correlated with reduced QoL for all SF-36 subscales, **significant**.

					Anxiety (n=166) vs. without anxiety (n=255). SF-36 subscales, adjusted OR (95% CI), **significant in bold.** **Physical function, 0.99 (0.98, 1.00),** Physical role, 0.99 (0.99, 1.00) Bodily pain, 0.99 (0.97, 1.00)**, General health, 0.99 (0.98, 1.00) Vitality, 0.972 (0.961, 0.984), Social functioning, 0.984 (0.975, 0.995) Mental health, 0.97 (0.95, 0.98), Emotional role, 0.99 (0.99, 1.00)**		The QoL of RA patients with, compared to patients without anxiety, is **significantly worse on most SF-36 subscales** apart from physical role and bodily pain.
				RA-QoL	Anxiety (n=166) vs. without anxiety (n=255). RA-QoL, OR (95% CI) = 1.060 (1.032,1.088)		The QoL of RA patients with, compared to without anxiety is worse, **significant**.
				NHP	Anxiety (n=166) vs. without anxiety (n=255), NHP subscales, OR (95% CI). **Significant in bold (all). Physical mobility, 1.017 (1.009, 1.025), Energy, 1.015 (1.009, 1.021) Social isolation, 1.017 (1.011, 1.023), Pain, 1.011 (1.004,1.018), Emotional reaction, 1.026 (1.019, 1.033), Sleep, 1.018 (1.011, 1.025)**		The QoL of RA patients with, compared to patients without anxiety, is worse on all NHP subscales, **significant**.
Ozcetin, 2007 Turkey	34 (8:26)	50.4	BAI	SF-36	Beck anxiety scores and SF-36 subscale scores Physical role, r= -0.451 **, Bodily pain, r= -0.583 *** General health, r= -0.706 ***, Vitality, r= -0.737 *** Social functioning, r= -0.718 ***, Mental health, r=- -0.655 *** Emotional role, r= -0.326 (n.s.)	6	Anxiety correlated with reduced QoL scores. **Statistically significant for most SF-36 subscales** except emotional role.
Wan, 2015 Singapore	108 (22:86)	56.4	HADS-A	HRQoL (EQ-5D)	Anxiety and HRQoL using EQ-5D, r=-0.58**	8	Anxiety is correlated with reduced QoL, **significant**.

r = Pearsons correlation coefficient, b = multiple regression coefficient, CI= confidence interval, SE= standard error, OR= odds ratio, SD= standard deviation, n.s.= not significant (p>0.05), *(p<0.05), ** (p<0.01), ***(p<0.001)

BAI= Beck's Anxiety Inventory, **EQ-5D**= EuroQol 5-Dimension Scale, **HADS-A**= Hospital Anxiety and Depression Score (anxiety scale), **HAM-A**= Hamilton Anxiety Rating Scale, **HRQoL**= Health related quality of life, **LSI**= Life Satisfaction Index, **MCS**= Mental Component Summary Score of SF-36, **NHP**= Nottingham Health Profile, **PCS**= Physical Component Summary Score of SF-36, **RA**= Rheumatoid arthritis, **STAI**= Spielberger State and Trait Anxiety Inventory, **SF-36**= Short Form 36, **WHOQoL-BREF**= World Health Organisation Quality of Life-BREF, **QoL-RA scale**= Quality of life rheumatoid arthritis scale.

[1] Quality rated out of 9 using Newcastle Ottawa Scale: 0–2 = low quality, 3–6 = medium quality and 7–9 = high quality

Included studies involved a total of 7,455 patients with a mean age of 53.5 years. The overall proportion of females was 80%. Sample sizes ranged from 20-2919 with a mean of 372. From the 20 studies, 16 were full text articles (Al-Fadl et al., 2014; Kojima et al., 2009b; Nas et al., 2011; Ozcetin et al., 2007; Alpi et al., 2017; Celiker & Borman, 2001; Ichikawa et al., 1995; Karahan et al., 2016; Matcham et al., 2016a; Miwa et al., 2002; Mok, Lok & Cheung, 2012; Overman et al., 2012; Wan et al., 2015; Kuijper et al., 2018; Sergeant et al., 2018; Ruhaila & Cheng, 2018), whilst 4 were conference abstracts (Grosso et al., 2015; Zulgerel & NandinErdene, 2014; Dyball et al., 2018; Fragoulis et al., 2018).

The majority, 14, were cross-sectional in design (Al-Fadl et al., 2014; Kojima et al., 2009b; Nas et al., 2011; Ozcetin et al., 2007; Alpi et al., 2017; Celiker & Borman, 2001; Grosso et al., 2015; Ichikawa et al., 1995; Karahan et al., 2016; Miwa et al., 2002; Mok, Lok & Cheung, 2012; Wan et al., 2015; Zulgerel et al., 2014; Ruhaila & Cheng, 2018), whilst 6 were prospective cohort studies (Matcham et al., 2016a; Overman et al., 2012; Kuijper et al., 2018; Dyball et al., 2018; Sergeant et al., 2018; Fragoulis et al., 2018).

In terms of outcomes, 11 of the studies assessed disease activity only (Grosso et al., 2015; Ichikawa et al., 1995; Matcham et al., 2016a; Miwa et al, 2002; Overman et al., 2012; Zulgerel & NandinErdene, 2014; Kuijper et al., 2018; Dyball et al., 2018; Sergeant et al., 2018; Rahaim et al., 2018; Fragoulis et al., 2018), 6 assessed QoL only (Nas et al., 2011; Ozcetin et al., 2007; Alpi et al., 2017; Celiker & Borman, 2001; Mok, Lok & Cheung, 2012; Wan et al., 2015) and 3 assessed both disease activity and QoL (Al-Fadl et al., 2014; Kojima et al., 2009b; Karahan et al., 2016). The Hospital Anxiety and Depression Scale (HADS) was the most frequently used tool to identify anxiety.

The primary outcome measure for disease activity, DAS28, was reported in 9 studies. Additional outcome measures for disease activity across 4 studies included the Lansbury Articular Index (LAI), Thompson Articular Index, Pain VAS and a composite score comprising of CRP, SJC, TJC and a Physician's global assessment.

The primary outcome measures for QoL, SF-36 or the PCS, MCS or subscale scores of SF-36, were reported in 5 studies. Other outcome measures for QoL reported in 5 studies, included Health Related QoL (HRQoL) using the EuroQol 5-Dimension Scale (EQ-5D), Life-Satisfaction Index (LSI), Nottingham Health Profile (NHP), QoL-RA scale and World Health Organisation QoL- BREF (WHOQoL-BREF).

6.4.2 Methodological Quality Assessment for included studies

Quality assessment using the NOS is presented in tables 6.3a (p175), 6.3b (p176) and 6.4 (p177), whilst additional details are reported in appendix 16.

Most articles were of moderate methodological quality. Many lacked detail on the representativeness of their RA sample (Al-Fadl et al., 2014; Celiker and Borman, 2001; Ichikawa et al., 1995; Karahan et al., 2016; Kojima et al., 2009b; Miwa et al., 2002; Zulgerel and NandinErdene, 2014), or on non-responders (Al-Fadl et al., 2014; Alpi et al., 2017; Celiker and Borman, 2001; Dyball et al., 2018; Fragoulis et al., 2018; Grosso et al., 2015; Ichikawa et al., 1995; Karahan et al., 2016; Kojima et al., 2009b; Kuijper et al.,.2018; Miwa et al., 2002; Mok, Lok & Cheung, 2012; Nas et al., 2011; Ozcetin et al., 2007; Sergeant et al., 2018; Zulgerel and NandinErdene, 2014), whilst several studies also had small sample sizes, of 20 (Celiker and Borman, 2001), 26 (Al-Fadl et al., 2014; Nas et al., 2011) and 34 participants (Ozcetin et al., 2007), which limited generalisability.

Most studies reported using validated tools to ascertain the exposure, anxiety. The HADS was most frequently used, whilst other tools used included Beck's Anxiety Inventory (BAI), the Spielberger State and Trait Anxiety Inventory (STAI), the Hamilton Anxiety Rating Scale (HAM-A) and Zung's self-rating anxiety scale. One study used the Speilberg Chennai test (Zulgerel and NandinErdene, 2014). This non-validated tool was not described, making it difficult to determine its' diagnostic accuracy and whether its' use could have introduced potential bias. Another study used the Chinese Bilingual Studied Interview (Mok, Lok & Cheung, 2012) to ascertain the exposure. Although this tool is not widely utilised, it involves an interview being conducted by a psychiatrist, hence is likely to have a high diagnostic accuracy.

Some studies did not report if they controlled for potential confounding factors, which could have introduced bias (Alpi et al., 2017; Fragoulis et al., 2018; Miwa et al., 2002; Zulgerel and NandinErdene, 2014). All cross-sectional studies apart from one, a conference abstract (Zulgerel and NandinErdene, 2014), included a description of their approach to statistical analysis, reporting confidence intervals and p-values as appropriate. Across the 6 included cohort studies, the length of follow-up ranged from 6 months to 5 years (Dyball et al., 2018; Fragoulis et al., 2018; Kuijper et al., 2018; Matcham et al., 2016a; Overman et al., 2012; Sergeant et al., 2018), sufficient time periods to determine the association between anxiety and disease activity.

6.4.3 Association between anxiety and disease activity in RA

6.4.3.1 Anxiety and DAS28

The overall findings of the 9 studies that reported the association between anxiety and DAS28, the primary outcome measure for disease activity, are summarised

in table 6.3a (p175) and 6.3b (p176). These included 5 cross-sectional (Al-Fadl et al., 2014; Grosso et al., 2015; Karahan et al., 2016; Ruhaila & Cheng, 2018; Zulgerel and NandinErdene, 2014) and 4 cohort studies (Dyball et al., 2018; Fragoulis et al., 2018; Kuijper et al. 2018; Matcham et al., 2016a), involving a total of 7,455 participants.

All 5 cross-sectional studies found anxiety to be associated with an increased DAS28 score, although this was only statistically significant in 3 studies (Al-Fadl et al, 2014; Grosso et al., 2015; Ruahila & Cheng, 2018). From the 4 cohort studies, 2 found a statistically significant association between baseline anxiety and increased DAS28 at 6 and 12 months' follow-up (Matcham et al., 2016a; Fragoulis et al., 2018). One study found a statistically significant association between baseline anxiety and increased DAS28 at 3 months, but not at 9 and 15 months (Kuijper et al., 2018), whilst another study found an association between anxiety and increased DAS28 at 6 month's follow-up, that was not statistically significant (Dyball et al., 2018).

One further study reported DAS28 in terms of non-response to treatment with methotrexate, being indicated as an improvement in DAS28 by ≤0.6 or treatment discontinuation due to inefficacy (Sergeant et al., 2018). On multivariable analysis, higher baseline anxiety was found to significantly predict non-response to treatment after 6 months, odds ratio (OR) (95% confidence interval (CI)) = 1.07 (1.03, 1.12).

In addition, 4 studies also reported the subcomponents of DAS28, including the Patient Global Assessment (PtGA) or Pain VAS, TJC, SJC and ESR or CRP (Grosso et al., 2015; Matcham et al., 2016a; Dyball et al., 2018; Ruhaila & Cheng, 2018). Further examination of these results found anxiety to be most significantly associated with the more subjective assessments of disease activity, such as the PtGA, Pain VAS and TJC. For example, one cohort study found anxiety to be positively correlated at baseline and at

1-year follow-up with the PtGA, TJC, SJC and ESR, though this correlation was only significant for the PtGA ($r=0.31$, $p<0.05$ at baseline, $r=0.43$, $p<0.01$ at 1-year follow-up) (Matcham et al., 2016a). On multiple regression analysis baseline anxiety was also significantly associated with PtGA and TJC at 1-year follow-up (Matcham et al., 2016a). In another study, Pain VAS and TJC measurements were significantly higher in people with anxiety compared to those without, though there was no significant difference in the ESR or SJC between groups (Grosso et al., 2015). A further study found anxiety to be significantly correlated with increased VAS pain ($r=0.341$, $p<0.001$) and TJC ($r=0.197$, $p=0.007$), but not SJC ($r=0.060$, $p=0.412$) (Ruhaila & Cheng, 2018). In addition, Dyball et al. (2018) found baseline anxiety to be associated with smaller improvements in PtGA at 6 months ($b=0.74$, 95% CI 0.32, 1.26, $p=0.001$).

6.4.3.2 Anxiety and additional disease activity outcomes

Additional disease activity outcome measures were reported in 4 studies, which are detailed in tables 6.3a and 6.3b. These included a cohort study (Overman et al., 2012) and 3 cross-sectional studies (Ichikawa et al., 1995; Kojima et al., 2009b; Miwa et al., 2002). Overall, anxiety was associated with increased pain, inflammatory markers and disease activity for the majority of additional outcome measures.

One study used the Thompson articular index, a weighted score including swollen and painful joints (Taal et al., 1998), and ESR, as additional disease activity outcome measures. A significant association was found between anxiety and an increased Thompson articular index and ESR, suggesting anxiety in people with RA is associated with increased disease activity (Overman et al., 2012). Another study (Ichikawa et al., 1995), assessed disease activity using Pain VAS and the LAI, which

consists of morning stiffness, ESR, grip strength and a painful joint count (Lansbury, 1956). A significant positive correlation was found between anxiety and Pain VAS, in addition to the LAI, suggesting anxiety in people with RA to be associated with increased pain and disease activity (Ichikawa et al., 1995). A further study analyzing the correlation between anxiety and VAS (reported as a measure of arthralgia) split participants into two subgroups with lower and higher mean activity levels (Miwa et al., 2002). In less active patients, anxiety was significantly correlated with higher VAS scores, though this correlation became non-significant in more active patients, suggesting anxiety only increases arthralgia in people with RA who are less active. One study found no association between anxiety and disease activity, when assessed using a combination of the physician's global assessment, TJC, SJC and CRP (Kojima et al., 2009b). This was potentially due to the physician completing the global assessment, rather than the patient, as with DAS28, since the physician may have reported lower disease activity on their global assessment than a patient with anxiety, who may have self-assessed their disease activity to be worse.

6.4.4 Association between anxiety and QoL in RA

6.4.4.1 Anxiety and SF-36

The findings of the 5 studies reporting SF-36 for QoL (Al-Fadl et al., 2014; Kojima et al., 2009b; Mok, Lok and Cheung, 2012; Nas et al., 2011; Ozcetin et al., 2007), are summarised in table 6.4 (p177). These were all cross-sectional studies, involving a total of 801 patients. Anxiety had a significant negative association with SF-36 and its' subscale scores in the majority of studies reporting this outcome, indicating worse QoL.

In particular, a significant negative correlation was reported between anxiety and SF-36 in one study (Mok, Lok and Cheung, 2012), in addition to the PCS and MCS of

SF-36 in 2 further studies (Al-Fadl et al., 2014; Kojima et al., 2009b). Another article found a significant negative correlation between anxiety and all SF-36 subscale scores apart from emotional role (Ozcetin et al., 2007). A further study reported a significant negative correlation between high risk anxiety (defined as a score ≥10 on the Turkish version of the HADS) and all SF-36 subscales (Nas et al., 2011). In addition, when people with RA, with and without anxiety were compared, all SF-36 subscale scores apart from physical role and bodily pain were significantly worse in the group with anxiety (Nas et al., 2011).

6.4.4.2 Anxiety and additional QoL outcome measures

Different QoL outcome measures were reported in 5 studies (Alpi et al., 2017; Celiker and Borman, 2001; Karahan et al., 2016; Nas et al., 2011; Wan et al., 2015), which are summarised in table 6.4 (p177). These were all cross-sectional studies, involving 759 participants. Anxiety was negatively associated with all additional QoL outcome measures. This finding was significant in the majority of studies.

In particular, a significant negative correlation was found between moderate or severe anxiety and the Turkish version of the WHOQoL-BREF score (Karahan et al., 2016), though this correlation was non-significant in mild anxiety. A significant negative correlation was also found between current anxiety and the LSI (Celiker et al., 2001), EQ-5D (Wan et al., 2015) and QoL-RA scale (Alpi et al., 2017). In addition, one study found a significant negative association between anxiety and the QoL-RA scale on multiple regression analysis, supporting a link between anxiety and worse QoL in people with RA (Alpi et al., 2017). Another study reported RA-QoL scores and NHP subscale scores to be significantly worse in people with RA and anxiety, compared to those without anxiety, supporting a link between anxiety and worse QoL (Nas et al., 2011).

6.4.5 Meta-analysis

On meta-analysis, anxiety was associated with increased disease activity using DAS28 scores. Meta-analysis of mental and physical QoL scores also found anxiety to be negatively correlated with QoL, as reported in table 6.5. Pooled r values showed the strongest association to be between anxiety and reduced QoL, in particular worse mental QoL.

Table 6.5- *Meta-analysis of correlation coefficients between anxiety and DAS28, physical QoL and mental QoL*

Meta-analysis	DAS28	Physical QoL	Mental QoL
Pooled r (CI)	0.23 (0.14, 0.31)	-0.39 (-0.58, -0.20)	-0.50 (-0.57, -0.43)
Q statistic	χ^2=3.85 (d.f.=4) p=0.43	χ^2=13.95 (d.f.=3) p<0.01	χ^2=3.35 (d.f.=3) p= 0.34
I^2	0.0%	78.5%	10.3%

r = pearsons correlation coefficient, CI= confidence interval, p= p value, χ^2= chi-squared, d.f.= degrees of freedom

There was only evidence of significant heterogeneity between studies for physical QoL (Q statistic= 13.95, p<0.01; I^2=78.5%). This could have been due to one study that was used in the physical QoL meta-analysis involving proportionately more participants (Nas et al. 2011). Alternatively, another study used in the physical QoL meta-analysis had a correlation coefficient value that was much lower, compared to the other reported values, which could have contributed to increased heterogeneity (Ozcetin et al., 2007).

In contrast, heterogeneity was 0% for the DAS28 meta-analysis. This was due to the studies reporting DAS28 being more homogeneous. Further, if we consider the calculation used to determine I^2 (I^2= 100% x (Q- degrees of freedom)/Q), as the Q statistic was 3.85 and the degrees of freedom 4, the I^2 value for DAS28 was negative. I^2 values are automatically set to 0 when the value is negative, so that the value falls between 0-100 (Higgins et al., 2003). Figures 6.2, 6.3 and 6.4 (p188), contain forest plots of the meta-analysis of DAS28, Physical QoL and Mental QoL outcomes for the original scale r. More detailed calculations are listed in appendix 17.

Figure 6.2- *Forest Plot displaying meta-analysis of correlation coefficients between anxiety and DAS28*

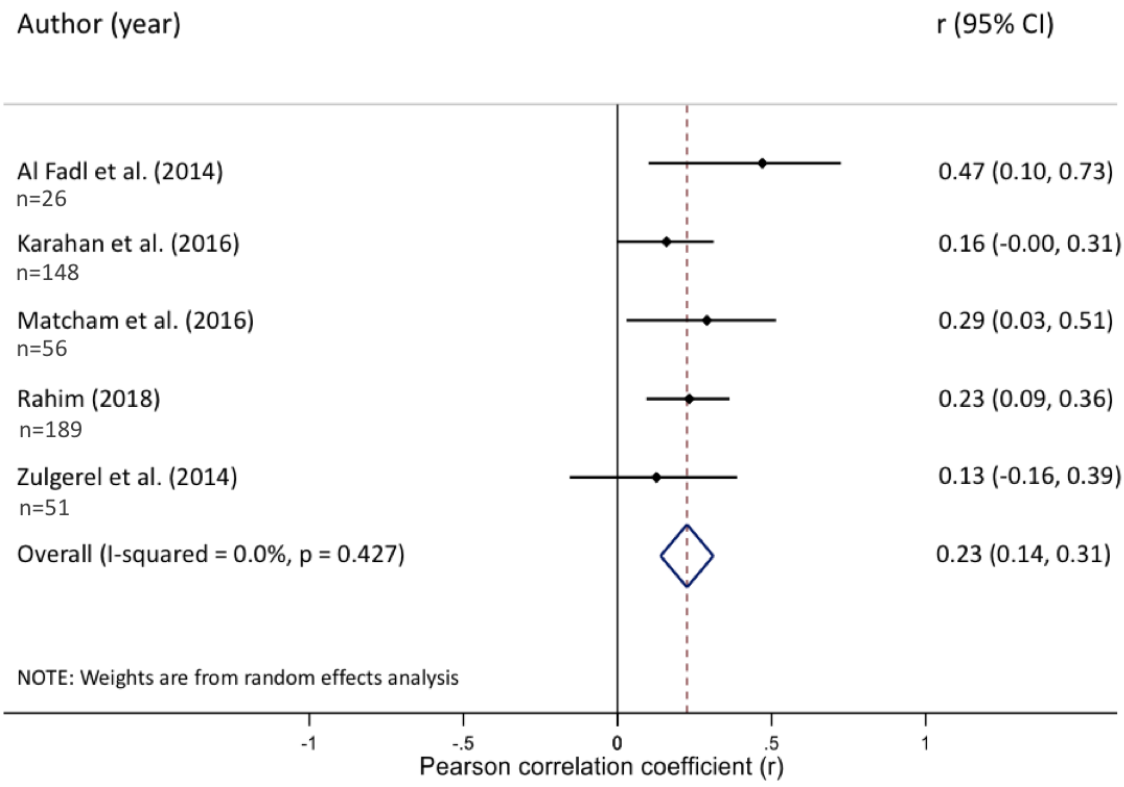


Figure 6.3- *Forest Plot displaying meta-analysis of correlation coefficients between anxiety and physical QoL*

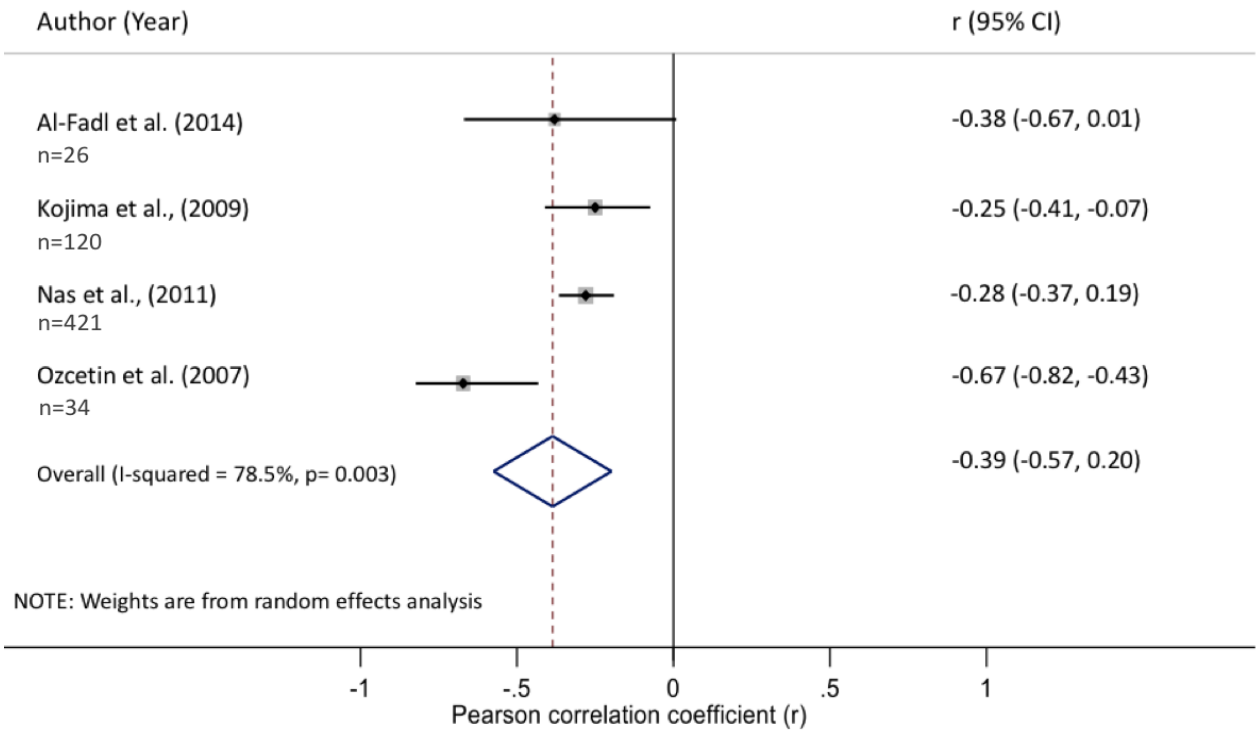
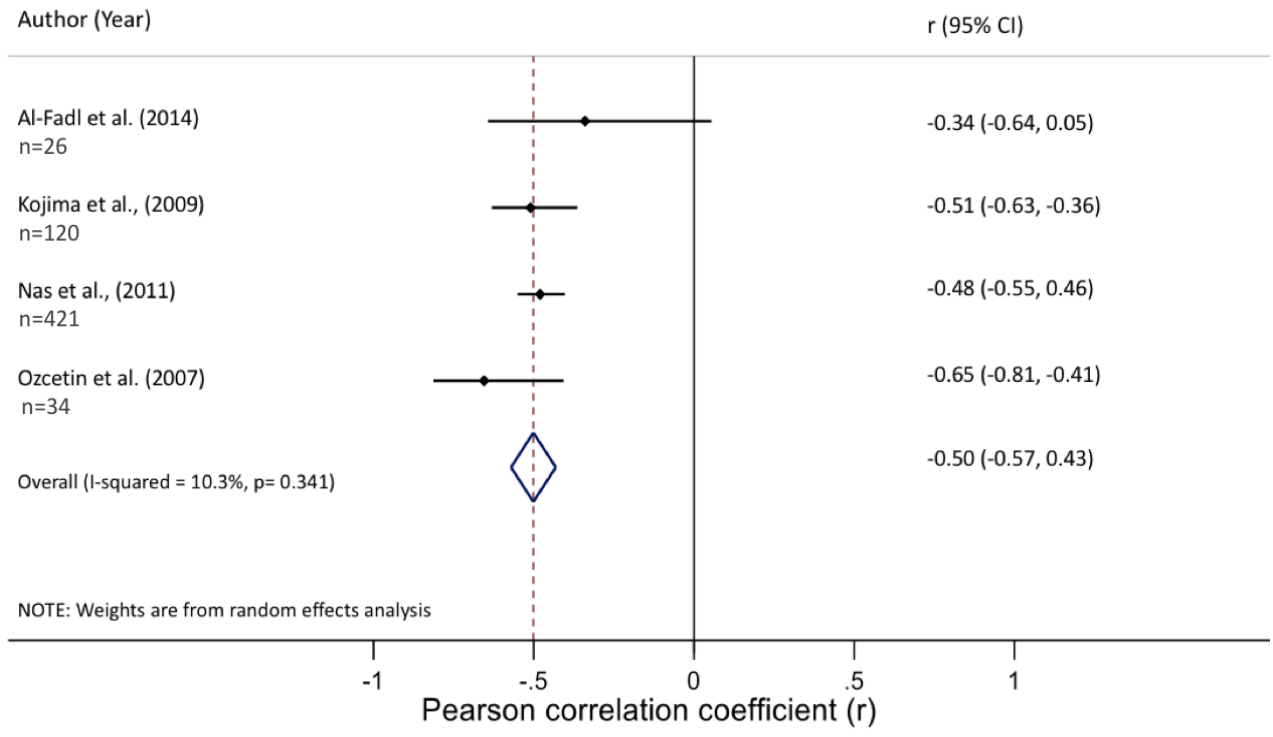


Figure 6.4- *Forest Plot displaying meta-analysis of correlation coefficients between anxiety and mental QoL*



6.4.6 Strength of Evidence

The overall strength of evidence for the association between anxiety in people with RA, and disease activity and QoL has been reviewed in table 6.6 (p190), using the Modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Schünemann et al., 2013). Most studies reporting disease activity outcomes had consistent effect sizes, moderate sample sizes and controlled for confounding factors, with low heterogeneity on meta-analysis of the correlation between anxiety and DAS28. Therefore, the strength of evidence for the association between anxiety and disease activity was felt to be moderate. Meanwhile, though effect sizes were relatively consistent for QoL outcomes, almost half of the studies had small sample sizes and there was significant heterogeneity on meta-analysis of mental QoL, meaning the overall strength of evidence for the association between anxiety and QoL was low. Details of how the GRADE score was calculated are in appendix 18.

Table 6.6- *Strength of evidence for association between anxiety in people with RA, and disease activity and QoL.*

Outcome	Evidence Base	Strength of Association	Strength of Evidence (GRADE) [a.b]	Comments
Disease Activity	14 studies n=6613 6 cohort (table 6.3a) 8 cross-sectional (table 6.3b)	**Meta-analysis** Anxiety correlation with DAS28 Pooled r (CI)= 0.23 (0.14, 0.31) **Narrative synthesis** Association between anxiety and increased disease activity - 2 studies significant baseline to 12 months - 1 study significant 3 months, non-significant 9 /15 months - 1 study non-significant 6 months Correlation between anxiety and increased disease activity - 7 studies significant, 3 studies non-significant	Moderate ⊕⊕⊕	Most studies had consistently small/ moderate effect sizes, a reasonable sample size and controlled for confounding factors. There was low heterogeneity in the meta-analysis.
Quality of Life	9 Studies n=1139 All cross-sectional (table 6.4)	**Meta-analysis** Anxiety correlation with Physical QoL Pooled r (CI)= -0.39 (-0.57, -0.20) Anxiety correlation with Mental QoL Pooled r (CI)= -0.50 (-0.57, -0.43) **Narrative synthesis** Correlation between anxiety and reduced QoL - 6 studies significant negative correlation - 1 study non-significant negative correlation with mild anxiety, but significant negative correlation with moderate/ severe anxiety - 1 study non-significant with long-standing anxiety but significant with current anxiety	Low ⊕⊕	Most studies had consistently small/ moderate effect sizes, though nearly half of the studies had small sample sizes and there was significant heterogeneity on meta-analysis of mental QoL, limiting the strength of evidence.

a. GRADE assessment included risk of bias, inconsistency, indirectness, imprecision, large effect (strength of association) and dose-response gradient (appendix 18).
b. Symbols for quality of evidence: ⊕⊕⊕⊕ High, further research is unlikely to change our confidence in the estimate of effect; ⊕⊕⊕ Moderate, further research is likely to have an important impact on our confidence in the estimate of effect and may change it; ⊕⊕ Low, further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; ⊕Very low, any estimate of effect is very uncertain.

6.5 Discussion

6.5.1 Summary of findings

This is the first systematic review to examine the relationship between anxiety in people with RA, and disease activity and QoL. Findings suggest that anxiety is associated with increased disease activity and reduced QoL.

This systematic review demonstrates that anxiety in people with RA is associated with increased disease activity, both cross-sectionally and at 3 months (Kuijper et al., 2018), 6 months (Fragoulis et al., 2018) and 12 months (Matcham et al., 2016a) follow-up. These findings complement previous research, showing that depression in people with RA is associated with increased disease activity (Rathbun, Reed & Harrold, 2013).

Whilst one study (involving 52 participants) found the impact of baseline anxiety on disease activity to increase between 6 and 12-month follow-up (Matcham et al., 2016a), two larger studies (involving 281 and 848 participants) found the impact of baseline anxiety to reduce over time (Kuijper et al., 2018; Fragoulis et al., 2018). The reasons for this observation are unclear, with Kuijper et al. (2018), hypothesising that in early RA, when treatment has not yet been optimised, anxiety could influence subjective components of DAS28, whilst once disease is better controlled, people may adapt to living with RA, leading to a reduction in anxiety.

Alternatively, this review, suggests the association between anxiety and increased disease activity may, in part, be due to people with anxiety reporting higher PtGA scores and other subjective measures of disease activity (Grosso et al., 2015; Matcham et al., 2016a; Dyball et al., 2018; Ruhaila & Cheng, 2018), rather than an objective increase in disease activity.

The strength of evidence for the association between anxiety and increased DAS28 was moderate, as although most studies had good sample sizes and all used validated tools to determine the exposure and outcome, there were several potential sources of bias and the reported effect sizes were only small to moderate.

Considering QoL outcomes, this systematic review also demonstrates that anxiety in people with RA is cross-sectionally associated with reduced QoL, complementing previous research showing that depression in RA is associated with poorer QoL (Bazzichi et al., 2005; Senra et al., 2017). On review of the SF-36 subscale effect sizes, the largest impact of anxiety was seen on vitality, social functioning and mental health scores (Ozcetin et al., 2007; Nas et al., 2011). Effect sizes for reduced social functioning and mental health scores could be interpreted as symptoms of anxiety as well as components of QoL. Meanwhile, larger effect sizes for the correlation between anxiety and vitality, could have been confounded by known associations between mood problems and fatigue in RA (Matcham et al., 2015), with fatigue having a further negative impact on QoL.

The strength of evidence for the association between anxiety and reduced QoL was low, as although all studies used validated tools to determine the exposure and outcome, and the majority controlled for confounding factors, there were several potential sources of bias, including small sample sizes and a lack of detail on sampling methods. Most effect sizes were only small to moderate, whilst on performing a meta-analysis, heterogeneity was high for physical QoL.

6.5.2 Strengths and limitations

A number of strengths and limitations need to be considered when interpreting the results. The search strategy was kept broad, to ensure that all available evidence on this topic was considered. A search for grey literature was also performed, though no additional studies meeting the inclusion criteria were found. In addition, there were some limitations as to which studies could be included. For example, nine potentially relevant studies could not be included as the published conference abstracts lacked sufficient data, and the authors did not respond to requests to provide additional data. Furthermore, twelve studies had to be excluded as anxiety was not reported separately from depression as an outcome. As anxiety frequently exists in isolation, future studies should consider reporting anxiety and depression separately, to enable their individual effects to be assessed.

Meta-analysis was limited by the small number of studies which provided suitable data to enable statistical pooling of results. Where pooled estimates of correlation were obtained, these, as well as the associated measures of the extent of heterogeneity, should be interpreted with caution. Potential sources of heterogeneity were differences in the source populations, sampling methods and adjustments made for confounding factors between studies. In the future, availability of suitable data may allow the impact of individual factors on the outcomes to be investigated using meta-regression analysis.

All available evidence regardless of the methodological study quality was incorporated within this review. Overall, the quality of the included studies was varied. Several potential sources of bias were identified in terms of the sampling methods, sample sizes, method of outcome measurement and loss of participants to follow-up.

Half of the studies had sample sizes of less than 100, suggesting results may be less generalisable. Qualitative studies may have provided a greater depth of understanding of how anxiety impacts on assessments of disease activity from the perspective of patients, whilst a randomised control trial (RCT) would have provided stronger evidence on the impact of anxiety on QoL and disease activity in people with RA.

6.5.3 Patient and Public Involvement

The results were discussed with a patient and public involvement and engagement (PPIE) group comprised largely of the members who met to discuss the prior qualitative study. On reviewing evidence from the systematic review, some PPIE attendees initially asked for clarification about the quality of individual articles and the size of the studies, hence the weight that could be applied to study findings. Attendees commented that the majority of articles found a strong link between anxiety and increased disease activity, particularly those reporting DAS28. Participants also agreed that the overall evidence on QoL outcomes, suggested that anxiety had a negative impact on QoL in people with RA.

The PPIE group also contributed to the dissemination plan. Attendees gave multiple suggestions, which included the use of social media, practice newsletters or summaries sent to patient participation groups at regional GP practices and the Haywood Foundation, a local organisation supporting arthritis research. These suggestions were used to develop a dissemination plan to help ensure results were shared with a wide clinical, academic and public audience. Details of presentations given to lay audiences are listed in appendix 27.

6.5.4 Implications

As recommended by the National Institute for Health and Care Excellence (NICE) (NG 100) (2018), GPs need to actively seek to identify and treat comorbid anxiety in people with RA to improve outcomes. Rheumatologists should consider reviewing the subcomponents of DAS28 scores in people who respond poorly to RA treatments, as disproportionately high subjective component scores (PtGA, TJC) compared to objective scores of disease activity (SJC, ESR), could indicate a deterioration in a patients' mental health rather than an increase in their disease activity. This would be supported by previous studies which have found people with RA and psychological comorbidities to rate their disease activity higher than their physicians (Liu, Bathon & Giles, 2015; Duarte et al., 2015), with patient-reported measures such as the VAS being more strongly influenced by psychological variables (Cordingley et al., 2014). Consequently, in this situation, managing any underlying anxiety or depression alongside joint inflammation, rather than purely focusing treatment on reducing the physical symptoms of RA, could lead to reduced disease activity and an improved QoL.

6.6 Conclusion

Anxiety in people with RA is associated with worse QoL and increased disease activity. Therefore, optimal management plans could involve pharmacological and/ or psychological approaches to manage comorbid anxiety, in addition to anti-inflammatory medications to reduce joint pain, swelling and stiffness. Better identification and management of comorbid anxiety by both patients and clinicians has the potential to improve outcomes for people with RA.

6.7 Connection with subsequent studies

This systematic review builds on the findings of my qualitative study by providing further evidence of the negative impact of anxiety in RA. It highlights the need for a focus on the identification and management of comorbid anxiety in addition to depression in individuals with RA.

Following on from the suggestions of my PPIE group detailed in chapter 5 (section 5.10.3), in chapter 7, I have widened my focus to other inflammatory rheumatological conditions (IRCs). This is due to past research mainly focusing on comorbid mood problems in RA, but not other IRCs, such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). Due to a lack of prior literature reporting the burden of mood problems, particularly anxiety, in this population (section 2.9.3), I aim to determine the incidence and prevalence of anxiety and depression in different IRCs.

CHAPTER 7
Cohort Study

7.0 COHORT STUDY

The incidence and prevalence of mood problems in IRCs

7.1 Introduction

Rheumatoid arthritis (RA) is a common inflammatory rheumatological condition (IRC), which is associated with an increased risk of comorbid anxiety and depression (section 2.9.1). Most research examining comorbid mood problems in IRCs has focussed on depression in people with RA, finding low mood to be associated with a reduced quality of life (QoL) and increased disease activity and mortality. Due to a lack of literature on the impact of anxiety in people with RA, a systematic review and meta-analysis were performed, as detailed in chapter 6. Anxiety was found to be correlated with both increased disease activity and reduced QoL in people with RA.

As discussed in chapter 2 (section 2.9.3), there is a lack of literature reporting the prevalence of anxiety and depression in people with different IRCs, particularly polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). Consequently, given the known links between RA, mood problems and increased morbidity and mortality, further research is needed to determine the incidence and prevalence of mood problems in people with different IRCs.

7.2 Aims and Objectives

Aims: To perform a matched retrospective cohort study to investigate the incidence and prevalence of (a) anxiety alone and (b) anxiety and/ or depression, in people with

RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA), PMR and GCA. The reasons for analysing anxiety, but not depression alone, are discussed in section 7.3.1.1.

Objectives:

1. Investigate the prevalence of, and factors associated with, anxiety in addition to anxiety and/ or depression among patients with IRCs.
2. Assess whether there is an association between the diagnosis of an IRC (RA, AS, PsA, PMR, GCA) and subsequent consultation for anxiety, in addition to anxiety and/ or depression.

7.3 Methods

7.3.1 Data source: CiPCA Database

The study was undertaken using the Consultations in Primary Care Archive (CiPCA), a well established database of anonymised medical record data from a set of 9 general practices in North Staffordshire, in the United Kingdom (UK) (Medical Record Data Research, 2014), dating from the year 2000. CiPCA is an extensively used on-going database of routinely collected primary care information, such as consultations, prescriptions, investigations and referrals on approximately 90,000 registered patients. General Pracitioners (GPs) enter the data using coding schemes such as Read codes and British National Formulary (BNF) codes. Read codes are the standard clinical terminology system used within general practice in the UK (Benson, 2011). They support electronic coding for patient phenomena, including clinical symptoms and signs, laboratory results, diagnoses and procedures.

The practices that contribute data to CiPCA undergo a regular Keele consultation

data training and validation programme, hence coded clinical activity is of a high standard (Porcheret et al., 2004). Therefore, the quality of data is comparable to larger national databases (Jordan et al., 2007). The application submitted to use data from the CiPCA database is in appendix 19.

7.3.1.1 Required Read codes

Read code lists were used to identify medical records relating to IRCs (RA, AS, PsA, PMR, GCA) and mood problems, as well as a range of comorbidities (chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus (DM), heart failure (HF), ischaemic heart disease (IHD), peripheral vascular disease (PVD), stroke and cancer) and lifestyle factors (obesity, alcohol consumption and smoking).

For RA, AS, PsA, PMR, depression, comorbidities and lifestyle factors, permission was sought to use established Read code lists derived using a rigorous consensus approach from the CiPCA data manager (Morbidity Definitions, 2014). Lists of all such codes used may be found in the morbidity section of the medical record data research repository at www.keele.ac.uk/mrr. For GCA, a Read code list from a prior CiPCA study was used (Petri et al., 2015), whilst for anxiety, a Read code list developed by a consensus group, including GPs and electronic health record researchers, was used. These Read code lists are in appendix 20.

Within the established Read code list for depression, is the code "anxiety with depression". This is frequently used by GPs when recording a consultation with an individual who has depression and associated anxiety symptoms. To determine the association between different IRCs and isolated depression, this Read code for "anxiety with depression" would have had to be removed from the list. However, this potentially would have led to a large number of depressed people being excluded from the analysis,

making the results inaccurate. Therefore, depression alone was not examined, though the established depression and anxiety Read code lists were combined to enable analysis of individuals with anxiety and/ or depression.

Having a second Read code list for anxiety alone was felt to be important, due to the lack of literature reporting the prevalence of anxiety in different IRCs, in addition to the findings of the systematic review discussed in chapter 7, which suggested that anxiety has a significant impact on QoL and disease activity in people with RA. The Read code list for anxiety did not include the code "anxiety with depression", meaning some individuals with anxiety could have been missed. However, from my clinical experience, when an individual consults their GP with predominantly anxiety symptoms, a Read code for anxiety is usually recorded, not "anxiety with depression".

7.3.2 Prevalence of anxiety and depression (objective 1)

This section outlines details pertaining to objective 1.

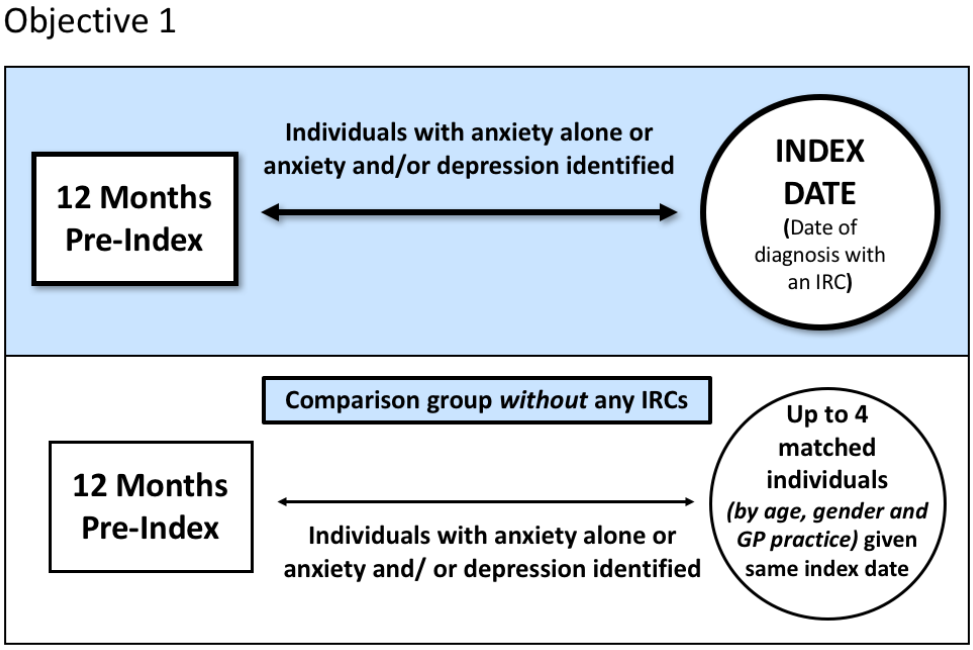
7.3.2.1 Study population

The cohort included men and women aged ≥18 years with a first ever Read code diagnosis of one of the IRCs of interest (RA, AS, PsA, AS, GCA) recorded between 1/1/2001 and 31/12/2015. The date of diagnosis with an IRC was defined as the index date.

A comparison group without any IRCs were drawn by assigning each individual with an IRC at their index date with up to 4 age (within 3 years), gender and general practice matched individuals. The comparison group had no record of an IRC up until the point of their matched case's index date and were alive and contributing medical record data at the time. Individuals in the comparison group were assigned the same

index date as their matched individuals with an IRC. All individuals were required to have at least 12 months' general practice registration history before the index date. Figure 7.1 shows how the study population for objective 1 was derived to determine the prevalence of mood problems in people with IRCs. The approach to statistical analysis is detailed in section 7.3.2.2.

Figure 7.1- *Objective 1: graphical representation*



7.3.2.2 Statistical analysis

The characteristics of individuals were summarised using frequencies and percentages, and compared between those with and without an IRC using chi square tests. The success of matching was also described.

Prevalence rates, and corresponding 95% confidence intervals (CIs), of anxiety, in addition to anxiety and/ or depression, in the 12 months prior to index date were calculated among those with an IRC, and among those without for comparison purposes. Logistic regression models were used to obtain estimates of association, in

terms of odds ratios (ORs) and associated 95% CIs, between IRCs and anxiety alone, in addition to anxiety and/ or depression. Estimates of unadjusted associations were obtained first, followed by adjustment for covariates.

For overall IRCs, logistic regression models were also used to analyse the association between covariates (age, gender, deprivation, COPD, asthma, DM, HF, IHD, PVD, stroke, cancer, obesity, alcohol consumption, smoking status) and anxiety, in addition to anxiety and/ or depression. The association between covariates and mood problems was also analysed for people with RA and PMR separately, to determine any condition-specific associations. There were too few individuals with AS, PsA or GCA and mood problems to enable separate analysis for these conditions. Adjustments were made for covariates that had a significant unadjusted association. This was to avoid overadjustment. Section 7.3.3.4 contains more details on the covariates and how they were established.

7.3.3 Incidence of anxiety and depression (objective 2)

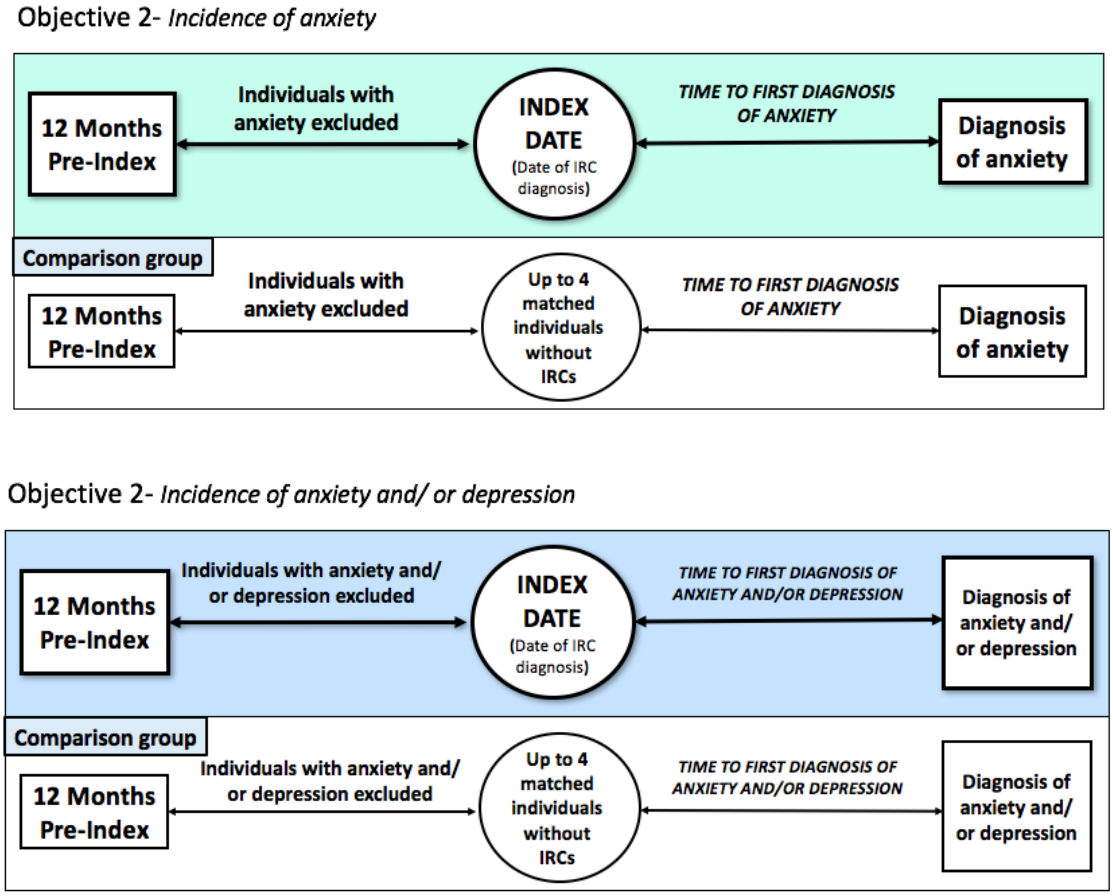
This section outlines details pertaining to objective 2.

7.3.3.1 Study population

Two separate datasets were constructed for incidence analyses, as represented graphically in figure 7.2 (p204).

1. Incidence of anxiety - study population as in section 7.3.2.1, excluding individuals with a record of anxiety during the 12-months pre-index date.
2. Incidence of anxiety and/ or depression - study population as in section 7.3.2.1, excluding individuals with a record of anxiety and/ or depression during the 12-months pre-index date.

Figure 7.2- *Objective 2: graphical representations.*



7.3.3.2 Exposure

The exposure was a Read code for one of the IRCs of interest being investigated (RA, AS, PsA, PMR, GCA).

7.3.3.3 Outcome

The outcome of interest was the time from the index date to the first diagnosis of anxiety, and the time to the first diagnosis of anxiety and/ or depression. Anxiety and/ or depression comprised of a combination of the Read code lists for anxiety and depression. The depression Read code list included the code "anxiety with depression", hence when the anxiety and depression Read code lists were combined, they included

people with anxiety or depression alone, and individuals with a combination of both mood problems.

7.3.3.4 Covariates

Covariates believed to potentially confound the relationship between IRCs and anxiety or depression were selected based on their previously established relationship with IRCs and anxiety and depression. These included age and gender (mostly accounted for through the matched study design), select comorbidities (COPD, asthma, DM, HF, IHD, PVD, stroke, cancer) (Naylor et al., 2012), obesity, smoking status and alcohol misuse/ dependence, determined by a clinical record of alcoholism or alcohol dependence (Velten et al., 2018). Read codes are listed in appendix 20.

Deprivation status was considered as a further covariate (Elliot, 2016). This was determined using the index of multiple deprivation (IMD), which is based on a persons' postcode. The IMD is commonly used as a measure of relative deprivation for neighbourhoods in England, expressed in deciles from 1 (most deprived) to 10 (least deprived) (Department for Communities and Local Government, 2015).

The total number of primary care contacts over 12-months pre-index, were also included as a covariate. This was to enable adjustments to be made for the frequency of consultation, to take account of the extra potential opportunities that individuals attending more primary care appointments would have for the discussion of mood concerns. The average member of the public consults their GP approximately six times per year, whilst the frequency of consultation is likely to be higher in people with LTCs, such as an IRC, compared to people without any long-term health problems (NHS Digital, 2009).

Multimorbidity (≥2 comorbidities), was considered as an additional covariate, due to its' known association with LTCs and mood problems (Vancampfort et al., 2017; Read et al., 2016). However, individuals with IRCs already have one morbidity, whilst people with IRCs and mood problems are multimorbid. Therefore, to take account of the association between mood problems in people with IRCs and the burden of further comorbidities, a variable titled, "one of more additional comorbidities" was included in analyses.

Potential confounders were identified via Read codes in the record at any time prior to the index date. For confounders that could change over time (obesity, alcohol misuse/ dependence and smoking), information recorded closest to the index date was used. To determine the number of primary care contacts, every entry on the primary care computer system, EMIS, counted as a single contact. If several blood test results were recorded on a single day, these were counted as a single contact.

The absence of Read codes for IRCs, anxiety, depression and covariates (with the exception of obesity, alcohol dependence and smoking) was assumed to indicate that people did not have the condition of interest and consequently that these data were not missing. Categories for missing data were defined for obesity, alcohol dependence and smoking status. Multiple imputation was not considered for these variables as previous studies using the Clinical Practice Research Datalink (CPRD) indicated that missing data on these variables was not missing at random (Clarson et al., 2015).

7.3.3.5 Analysis

Data were managed and analysed in SPSS (version 24) and STATA (version 14). The characteristics of individuals were summarised using frequencies and percentages,

and compared between those with and without an IRC using chi square tests. The success of matching was also described.

Cox proportional hazard regression models were used to obtain associations between IRCs and the time to occurrence of anxiety, in addition to anxiety and/or depression, in terms of Hazard Ratios (HR). Corresponding 95% CIs were based on robust standard errors to account for any possible clustering due to matching (Lin & Wei, 1989). Unadjusted HRs were obtained first, followed by adjustment for the covariates discussed in section 7.3.3.4. Proportionality of hazards assumption, the assumption that the effect of covariates is constant over time, was tested graphically and via Schoenfeld residuals. Where the assumption failed for any covariate, the interaction of that covariate with appropriate function(s) of time was included in the model. Right censoring was assumed to be non-informative and was taken as the earliest of date of death, end of registration at the practice, or the 31/08/2016.

The association between IRCs and anxiety alone, in addition to anxiety and/ or depression was primarily explored over the whole follow-up, but also specifically at one, two and five years post index date; stratified effect sizes were obtained, using the lincom command in STATA, which calculates appropriate linear combinations of coefficients and associated CIs.

7.4 Results

7.4.1 Prevalence of anxiety and depression (objective 1)

7.4.1.1 Cohort characteristics

The prevalence cohort comprised of 7425 individuals; 1485 with IRCs and 5940 without IRCs (exact 1:4 matching was possible). As detailed in table 7.1 (p208), the

majority of people with IRCs had RA (n=565) or PMR (n=679), whilst fewer had GCA (n=104), PsA (n=85) and AS (n=57). This would fit with population estimates, with the prevalence of RA being reported as approximately 0.67% (Abhishek et al., 2017) and PMR between 0.91-1.53% (Yates et al., 2016), compared to lower prevalence estimates of 0.13% for AS (Dean et al., 2016), 0.22% for PsA (Egeberg et al., 2017) and 0.25% for GCA (Yates et al., 2016). From the 1485 individuals with IRCs, 4 had Read codes for both PMR and GCA, whilst one had a combination of AS and PsA.

Table 7.1- *Individuals with and without IRCs*

<table>
<tr><th colspan="2">Individuals with and without IRCs in the prevalence cohort</th></tr>
<tr><td colspan="2">Total number of individuals in the cohort= 7425</td></tr>
<tr><td>1485 with IRCs
Rheumatoid Arthritis (RA)= 565
Ankylosing Spondylitis (AS)= 57
Psoriatic Arthritis (PsA)= 85
Polymyalgia Rheumatica (PMR)= 679
Giant Cell Arteritis (GCA)= 104</td><td>5940 without IRCs</td></tr>
</table>

Table 7.2 summarises the demographics, comorbidities, lifestyle factors and numbers of primary care contacts by people with and without IRCs (p209). To calculate associations between covariates and IRCs, overall and individual IRCs have been compared to people without IRCs. Significant associations between covariates and IRCs have been emphasized in bold and between 1 to 3 asterix have been used to indicate p-values for reported associations. Further details are given in the table footnotes. Anxiety and depression have not been included in the comorbidities listed in table 7.2, as they are reported separately in table 7.3 (p214), with more detailed analysis.

Table 7.2- *Demographics, comorbidities, lifestyle characteristics and primary care contacts by IRC status.*

Covariate [b]		**Condition** [a]						
		No IRC(n=5940)	**All IRCs**(n=1485)	**RA** (n=565)	**AS** (n=57)	**PsA** (n=85)	**PMR** (n=679)	**GCA** (n=104)
Age *Mean (SD)*		65.7 (15.5)	65.7 (15.5)	59.5 (13.1)	45.3 (14.5)	47.8 (13.4)	74.1 (9.5)	74.1 (10.4)
Age Group *Number (%)*	18-50 [1]	1068 (18.0)	257 (17.3)	**161 (28.5) ****	**36 (63.2) ****	**49 (57.7) ****	**9 (1.3) ****	**2 (1.9) ****
	51-65 [2]	1579 (26.6)	384 (25.8)	**196 (34.7) ****	17 (29.8)	27 (31.8)	**122 (17.9) ****	24 (23.1)
	66-75 [3]	1534 (25.8)	394 (26.5)	127 (22.5)	**1 (1.7) ****	**8 (9.4) ****	**233 (34.3) ****	27 (26.0)
	76-95 [4]	1759 (29.6)	451 (30.4)	**81 (14.3) ****	**3 (5.3) ****	**1 (1.1) ****	**316 (46.5) ****	**51 (49.0) ****
Female *(%)* [5]		3920 (66)	980 (66)	379 (67)	**15 (26) *****	**43 (51) *****	462 (68)	76 (73)
Deprivation Status *Number (%)*	Least	971 (16.4)	284 (19.9)	92 (16.3)	11 (19.3)	17 (20.0)	157 (23.1)	20 (19.2)
	Mid	3636 (61.6)	880 (59.3)	350 (61.9)	29 (50.9)	46 (54.1)	393 (57.9)	65 (62.5)
	Most [6]	1297 (22.0)	309 (20.8)	123 (21.8)	17 (29.8)	22 (25.9)	129 (19.0)	19 (18.3)
≥1 additional comorbidity N (%)[7]		2914 (49.1)	**804 (54.1) *****	290 (51.3)	**17 (29.8) ****	**22 (25.9) *****	**407 (59.7) *****	**69 (66.3) *****
Comorbidity *Number (%)*	HF [8]	183 (3.1)	57 (3.8)	17 (3.0)	1 (1.8)	0 (0)	**33 (4.9) ****	6 (5.8)
	IHD [9]	874 (14.7)	246 (16.6)	71 (12.6)	**3 (5.3) ***	**4 (4.7) ***	**144 (21.2) *****	**24 (23.1) ***
	DM [10]	681 (11.5)	176 (11.9)	62 (11.0)	4 (7.0)	4 (4.7)	87 (12.8)	**19 (18.3) ***
	PVD [11]	249 (4.2)	74 (5.0)	29 (5.1)	2 (3.5)	4 (4.7)	31 (4.6)	8 (7.7)
	COPD [12]	1176 (19.8)	**387 (26.1) *****	**157 (22.8) *****	9 (15.8)	**10 (11.8) ***	**181 (26.6) ****	30 (28.8)
	Asthma [13]	781 (13.1)	**270 (19.2) *****	**119 (21.1) *****	7 (12.3)	6 (7.1)	**118 (17.4) ***	**20 (19.2) ****
	Stroke [14]	488 (8.2)	125 (8.4)	**27 (4.8) ****	**0 (0) ***	**2 (2.4) ***	**77 (11.3) ***	**19 (18.3) *****
	Cancer [15]	924 (15.5)	230 (15.5)	72 (12.7)	**2 (3.5) ***	**6 (7.1) ****	**133 (19.6) ****	18 (17.3)
Smoking Status *Number (%)*	Current [16]	1421 (23.9)	**388 (26.1) *****	**184 (32.6) *****	21 (36.8)	26(30.6)	**135 (19.4) *****	22 (21.2)
	Non-smoker	2541 (42.8)	620 (41.8)	214 (37.9)	21 (36.8)	30 (35.3)	315 (46.4)	41 (39.4)
	Ex-smoker	1767 (29.7)	467 (31.4)	163 (28.8)	14 (24.6)	28 (32.9)	225 (33.0)	41 (39.4)
	Not known	211 (3.6)	10 (0.7)	4 (0.7)	1 (1.8)	1 (1.2)	4 (0.7)	0 (0)

Table 7.2- *Continued…*

Covariate			Condition [a]						
			No IRC(n=5940)	**All IRCs**(n=1485)	**RA** (n=565)	**AS** (n=57)	**PsA** (n=85)	**PMR** (n=679)	**GCA** (n=104)
Obesity *Number (%)* [17]			756 (12.7)	**224 (15.1) ***	**112 (19.8) *****	5 (8.8)	16 (18.8)	80 (11.8)	4 (3.8)
Alcohol dependence *N (%)* [18]			130 (2.2)	29 (2.0)	13 (2.3)	**1 (1.8) ***	**5 (5.9) ***	**6 (0.9) ***	4 (3.8)
Number of primary care contacts *(12M pre-index)*	Mean (SD)		13.0 (11.7)	21.0 (12.8)	20.9 (12.6)	14.4 (8.9)	16.6 (10.0)	21.8 (12.8)	23.8 (15.6)
	(n/10,000 people, 95% CI)	0-5	3016 (2957, 3075)	445 (436, 454)	442 (433,451)	1579 (1548,1610)	1294 (1269,1319)	279 (274,282)	192 (188,196)
		6-20	4972 (4875, 5059)	5186 (5079,5283)	5204 (5102,5306)	5965 (5848,6082)	5294 (5190,5398)	5103 (5003,5203)	5096 (4996,5196)
		21-50	1873 (1837, 1911)	3997 (3919, 4075)	4000 (3922,4078)	2456 (2408,2504)	3294 (3229,3339)	4221 (4138,4304)	3942 (3865,4019)
		>50 [19]	139 (135, 143)	**377 (369, 385) ****	**354 (347,361) ****	0 (0,0)	118 (116,120)	**397 (390,404) ****	**769 (754,784) *****

Abbreviations; HF (heart failure), IHD (ischaemic heart disease), DM (diabetes mellitus), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), RA (rheumatoid arthritis), AS (ankylosing spondylitis), PsA (psoriatic arthritis), PMR (polymyalgia rheumatica), GCA (giant cell arteritis), SD (standard deviation), n (number).

a All IRCs and individual IRCs are compared to people without IRCs. P-values for the association between different covariates and overall/ different IRCs are represented as *p<0.05, **p<0.01, ***p<0.001. Where no asterix is given, associations are not statistically significant.

b Reference categories for each covariate analysed are listed in footnotes 1-20 below.

[1] Aged 18-50 years Vs not aged 18-50 years, [2] Aged 51-65 years Vs not aged 51-65 years, [3] Aged 66-75 years Vs not aged 66-75 years, [4]Aged 76-95 years Vs not aged 76-95 years, [5] Female Vs male gender, [6] Most Deprived Vs less deprived, [7] 1 or more comorbidities in addition to IRC Vs no additional comorbidities, [8] HF Vs no HF, [9] IHD Vs no IHD, [10] DM Vs no DM, [11] PVD Vs No PVD, [12] COPD Vs no COPD, [13] Asthma Vs no asthma, [14] Stroke Vs no stroke, [15] Cancer Vs no cancer, [16] Current Smoker Vs non-smoker, [17] Obese Vs not obese, [18] Alcohol dependence Vs no alcohol dependence, [19] Primary Care Contacts >50 Vs Primary Care Contacts ≤50.

Approximately two thirds of the individuals with IRCs were female. In common with population epidemiology, more males had AS (Sieper, 2012) and more females had RA (Abhishek et al., 2017), PMR (Crowson et al., 2011) and GCA (Dasgupta et al., 2010). There were almost equal proportions of males and females with PsA, reflecting the gender ratio observed in general population (Gladman et al., 2005).

The age of individuals ranged between 18-95 years, with a mean of 66 years (standard deviation (SD)= 15.5). More individuals with RA, AS and PsA were aged 18-50 years, whilst more people with PMR and GCA were aged 76-95 years, compared to those without IRCs. These differences were all statistically significant. This would reflect age trends observed for these conditions within the general population (Sieper, 2012; Gladman, 2005; Michet & Matteson, 2008; Gonzalez-Gay, 2004). There were no significant differences between the deprivation status of people with and without IRCs, though the proportion of individuals in the "most deprived" group was highest in people with AS and PsA.

The proportion with one or more comorbidities (in addition to an IRC) was higher in people with IRCs, compared to those without IRCs (54.1% Vs 49.1%, $p<0.001$). Considering different IRCs, the proportion with one of more additional comorbidities was higher in people with RA (51.3% Vs 49.1%, $p<0.05$), PMR (59.9% Vs 49.1%, $p<0.001$) and GCA (66.3% Vs 49.1%, $p<0.001$), compared to those without IRCs. All of these differences were statistically significant.

All comorbidities apart from cancer were more prevalent in people with IRCs, compared to those without IRCs, but this difference was only statistically significant for COPD (26.1% Vs 19.8%, $p<0.001$) and asthma (19.2% Vs 13.1%, $p<0.001$). IHD and strokes were more frequent in people with GCA (IHD: 23.1% Vs 14.7%, $p<0.05$) (Stroke:

18.3% Vs 8.2%, p<0.001) and PMR (IHD: 21.2% Vs 14.7%, p<0.001) (Stroke: 11.3% Vs 8.2%, p<0.01), compared to those without IRCs. In addition, more individuals with PMR had comorbid HF (4.9% Vs 3.1%, p=0.01) and cancer (19.6% Vs 15.5%, p<0.01), whilst DM was more frequent in people with GCA (18.3% Vs 11.5%, p<0.05), compared to those without IRCs. COPD and asthma were more frequent in RA (COPD: 22.8% Vs 19.8%, p<0.001) (Asthma: 21.1% Vs 13.1%, p<0.001) and PMR (COPD: 26.6% Vs 19.8%, p<0.001) (Asthma: 17.4% Vs 13.1%, p<0.01), whilst more individuals with GCA also had asthma (19.2% Vs 13.1%, p=0.01), compared to those without IRCs. All of these differences were statistically significant. Meanwhile, less people with AS and PsA had a history of IHD and cancer, whilst fewer individuals with RA, AS and PsA had a background of stroke, compared to those without IRCs. These differences were all significant.

Considering lifestyle factors, a higher proportion of people with IRCs were current smokers (26.1% Vs 23.9%, p<0.001) or obese (15.1% Vs 12.7%, p<0.05), when compared to individuals without IRCs. Considering different IRCs, more people with RA were smokers (32.6% Vs 23.9%, p<0.001) and obese (19.8% Vs 12.7%, p<0.001), whilst less people with PMR were current smokers (19.4% Vs 23.9%, p<0.001), compared to those without IRCs. Although similar proportions of people with and without IRCs had a history of alcohol dependence, more people with PsA (5.9% Vs 2.2%, p<0.05), but less with AS (1.8% Vs 2.2%, p<0.05) and PMR (0.9% Vs 2.2%, p<0.05), had a history of alcohol dependence, compared to those without matched IRCs. These differences were all statistically significant.

The mean number of primary care contacts over 12 months before the index date, was higher in individuals with IRCs compared to those without IRCs (mean(SD)= 21.0 (12.8) Vs 13.0 (11.7)). More individuals with RA, PMR and particularly GCA, had

over 50 primary care contacts, compared to individuals without IRCs (RA: 354 Vs 139/ 10,000 people, p<0.01) (PMR: 397 Vs 139/ 10,000 people, p<0.01) (GCA: 769 Vs 139/ 10,000 people, p<0.001). These differences were statistically significant, though no significant differences were found between the number of primary care contacts by people with AS and PsA, compared to those without IRCs.

7.4.1.2 The association of anxiety alone, and anxiety and/ or depression with IRCs

The prevalence of anxiety alone, in addition to anxiety and/ or depression, in people with IRCs compared to those without IRCs, is reported in table 7.3 (p214). There was no difference in the prevalence of anxiety alone between those with and without IRCs (4.2% Vs 4.2%, p=0.98). Anxiety alone was more prevalent in individuals with RA (4.6% Vs 4.1%, p=0.61), AS (5.3% Vs 4.1%, p=0.87), PsA (9.4% Vs 4.1%, p=0.07) and GCA (7.7% vs 4.1%, p=0.08), compared to people without IRCs, though these differences were not statistically significant. In contrast, anxiety alone was less prevalent in individuals with PMR, when compared to those without IRCs (2.8% Vs 7.5%, p=0.09). Again, this difference was not statistically significant.

Anxiety and/or depression were more prevalent in people with IRCs compared to those without (8.3% Vs 7.5%, p=0.28). However, this difference was not statistically significant. Considering individual IRCs, anxiety and/ or depression were more prevalent in those with RA (8.7% Vs 7.5%, p=0.29), AS (12.3% Vs 7.5%, p=0.11), PsA (14.1% Vs 7.5%, p=0.02) and GCA (14.4% vs 7.5%, p<0.01), compared to people without IRCs. This difference was statistically significant in people with PsA and GCA. In contrast, anxiety and/ or or depression were less prevalent in individuals with PMR, compared to those without IRCs (6.0% Vs 7.5%, p=0.18). This difference was not statistically significant.

Table 7.3- *The prevalence, unadjusted and adjusted odds of anxiety and anxiety and/or depression in overall and individual IRCs*

Mood problem		Condition						
		No IRCs (n=5940)	**Overall IRCs** (n=1485)	**RA** (n=565)	**AS** (n=57)	**PsA** (n=85)	**PMR** (n=679)	**GCA** (n=104)
Anxiety	**Prevalence** *Number (%)*	247 (4.2)	62 (4.2)	26 (4.6)	3 (5.3)	8 (9.4)	19 (2.8)	8 (7.7)
	Unadjusted OR (95% CI), p-value [1]		1.00 (0.76, 1.34) p=0.98	1.11 (0.74, 1.88) p=0.61	1.12 (0.27, 4.67) p=0.87	2.07 (0.95, 4.53) p=0.07	0.66 (0.41, 1.07) p=0.09	1.92 (0.92, 4.00) p=0.08
	Adjusted OR (95% CI), p-value [1, 2]		0.98 (0.74, 1.30) p=0.88	1.04 (0.68, 1.58) p=0.86	1.37 (0.30, 6.20) p=0.69	1.75 (0.78, 3.93) p=0.18	0.68 (0.42, 1.09) p=0.11	1.76 (0.83, 3.70) p=0.14
Anxiety and/ or Depression	**Prevalence** *Number(%)*	443 (7.5)	123 (8.3)	49 (8.7)	7 (12.3)	12 (14.1)	41 (6.0)	15 (14.4)
	Unadjusted OR (95% CI), p-value[1]		1.12 (0.91, 1.38) p=0.28	1.18 (0.87, 1.61) p=0.29	2.01 (0.85, 4.80) p=0.11	**2.04 (1.10, 3.79) p=0.02**	0.80 (0.57, 1.11) p=0.18	**2.09 (1.20, 3.65) p<0.01**
	Adjusted OR (95% CI), p-value [1, 2]		1.09 (0.89, 1.35) p=0.34	1.02 (0.74, 1.40) p=0.90	1.69 (0.64, 4.47)	**1.90 (1.01, 3.57) p=0.04**	0.88 (0.63, 1.23) p=0.46	**2.15 (1.21, 3.79) p<0.01**

CI= confidence interval, OR= odds ratio

[1] Overall and individual IRCs have been compared to people without IRCs. Significant values are in bold.

[2] Adjusted for age, gender, smoking status (current smoker), obesity, alcohol dependence, comorbidities (HF, IHD, DM, PVD, COPD, Asthma, Stroke, Cancer) and primary care contacts.

The odds of anxiety alone, in addition to anxiety and/ or depression are also reported in table 7.3 (p214). The odds of anxiety in overall IRCs were marginally reduced after adjustment, compared to people without IRCs (odds ratio (OR) (95% confidence interval (CI) = 0.98 (0.74, 1.30)). Considering different IRCs, the adjusted odds of anxiety were increased in RA (OR (95% CI) = 1.04 (0.68, 1.58)), AS (OR (95% CI) = 1.37 (0.30, 6.20)), PsA (OR (95% CI) = 1.75 (0.78, 3.93)) and GCA (OR (95% CI) = 1.76 (0.83, 3.70)), though they were reduced in PMR (OR (95% CI) = 0.68 (0.42, 1.09)), compared to people without IRCs. None of these differences were significant.

The odds of anxiety and/or depression in overall IRCs were increased, compared to people without IRCs, though this increase was not significant, before or after adjustment (adjusted OR (95% CI) = 1.09 (0.89, 1.35)). Considering different IRCs, the adjusted odds of anxiety and/or depression were increased in RA (OR (95% CI) = 1.02 (0.74, 1.40)), AS (OR (95% CI) = 1.69 (0.64, 4.47)), PsA (OR (95% CI) = 1.90 (1.01, 3.57)) and GCA (OR (95% CI) = 2.15 (1.21, 3.79)), compared to people without IRCs. The increased odds of anxiety and /or depression were statistically significant in people with PsA and GCA. However, the adjusted odds of anxiety and/ or depression were reduced in PMR (OR (95% CI) = 0.88 (0.63, 1.23)), compared to people without IRCs.

In table 7.4 is an analysis of the association between different covariates and anxiety alone, and anxiety and/ or depression, in people with IRCs (p217). The odds of having a Read code for a mood problem varied dependent on age. The unadjusted odds of anxiety alone (OR (95% CI) = 0.46 (0.22, 0.94)), and anxiety and/ or depression (OR (95% CI) = 0.58 (0.36, 0.93)), were reduced in people aged 66-75 years, though statistical significance was lost after adjustment. Meanwhile, there was a statistically significant increase in the adjusted odds of people aged 18-50 years with IRCs having anxiety alone

(adjusted OR (95% CI) = 2.46 (1.33, 4.56)), or anxiety and/ or depression (adjusted OR (95% CI) = 2.69 (1.66, 4.36)).

In people with IRCs, there was also a statistically significant increase in the unadjusted odds of being a female and having anxiety alone (OR (95% CI) = 1.68 (1.10, 2.57)), though this association became non-significant after adjustment. No significant associations were found between deprivation status and mood problems. In addition, no significant associations were found between the comorbidities analysed and anxiety alone. Increased odds of anxiety and/ or depression in people with IRCs and asthma lost significance after adjustment, though there was a statistically significant increase in the adjusted odds of anxiety and/ or depression in people with IRCs and cancer (OR (95% CI) = 1.75 (1.07, 2.87)).

In people with IRCs and one or more additional comorbidities, the odds of having a mood problem were increased, though no statistically significant associations were found. However, in people with a high number of primary care contacts, there was a statistically significant increase in the adjusted odds of mood problems, particularly with over 50 primary care contacts per 10,000 people (over 12-months pre-index date) (Anxiety: OR (95% CI) = 18.30 (5.85, 57.28)) (Anxiety and/or depression: OR (95% CI) = 3.34 (2.21, 5.36)).

Considering lifestyle factors, a statistically significant association was found between alcohol dependence and anxiety and/ or depression in people with IRCs (adjusted OR (95% CI) = 4.82 (1.83, 12.73)). An association between obesity and anxiety and/ or depression lost significance after adjustment. No significant associations were found between smoking and mood problems in people with IRCs.

Table 7.4- *Association between covariates and anxiety, in addition to anxiety and/or depression, in people with IRCs*

Covariates		Anxiety		Anxiety and/ or depression	
		Unadjusted OR (95% CI) p value	Adjusted OR * (95% CI) p value	Unadjusted OR (95% CI) p value	Adjusted OR * (95% CI) p value
Age Group (years)	18-50	**2.02 (1.15, 3.57) p=0.01**	**2.46 (1.37, 4.56) p=0.01**	**2.14 (1.41, 3.24) p<0.001**	**2.90 (1.66, 4.36) p<0.001**
	51-65	1.09 (0.61, 1.93) p=0.77	1.37 (0.68, 2.76) p=0.38	1.16 (0.77, 2.74) p=0.49	0.74 (0.44, 1.26) p=0.27
	66-75	**0.46 (0.22, 0.94) p=0.03**	0.50 (0.23, 1.09) p=0.08	**0.58 (0.36, 0.93) p=0.03**	0.82 (0.54, 1.18) p=0.14
	76-95	0.94 (0.54, 1.64) p=0.82	0.73 (0.36, 1.47) p=0.38	0.72 (0.47, 1.11) p=0.14	0.55 (0.32, 1.27) p=0.12
Gender	Female	1.66 (0.92, 3.01) p=0.09	1.43 (0.77, 2.69) p=0.26	**1.68 (1.10, 2.57) p=0.02**	1.47 (0.93, 2.33) p=0.72
Deprivation Status	Low	0.67 (0.33, 1.38) p=0.28	0.79 (0.38, 1.64) p=0.52	0.67 (0.40, 1.12) p=0.13	0.95 (0.64, 1.43) p=0.82
	Mid	1.02 (0.61, 1.71) p=0.95	1.01 (0.59, 1.73) p=0.97	1.08 (0.74, 1.58) p=0.67	0.95 (0.64, 1.43) p=0.82
	High	1.34 (0.75, 2.41) p=0.32	1.19 (0.65, 2.18) p=0.58	1.25 (0.81, 1.93) p=0.31	1.29 (0.81, 2.06) p=0.29
Comorbidities	CVD [1]	0.92 (0.58, 1.47) p=0.72	0.71 (0.42, 1.22) p=0.21	0.79 (0.55, 1.13) p=0.20	0.76 (0.26, 1.12) p=0.54
	HF	1.78 (0.62, 5.10) p=0.28	1.44 (0.48, 4.35) p=0.52	1.87 (0.86, 4.03) p=0.11	1.12 (0.44, 2.86) p=0.81
	DM	0.50 (0.18, 1.40) p=0.19	0.44 (0.11, 1.58) p=0.33	0.79 (0.43, 1.47) p=0.46	0.68 (0.24, 1.67) p=0.52
	COPD	1.08 (0.61, 1.90) p=0.80	0.81 (0.44, 1.49) p=0.49	1.47 (0.99, 2.18) p=0.06	1.15 (0.57, 2.31) p=0.69
	Asthma	1.21 (0.64, 1.25) p=0.56	0.78 (0.40, 1.53) p=0.47	**1.66 (1.09, 2.55) p=0.02**	1.09 (0.68, 1.75) p=0.72
	Cancer	1.48 (0.79, 2.77) p=0.23	1.58 (0.81, 3.06) p=0.18	**1.61 (1.02, 2.53) p=0.04**	**1.75 (1.07, 2.87) p=0.03**
≥1 comorbidities in addition to IRC		1.18 (0.71, 1.98) p=0.52	1.02 (0.51, 1.64) p=0.76	1.31 (0.90, 1.91) p=0.16	1.08 (0.57, 1.39) p=0.44
Current Smoker		1.07 (0.61, 1.90) p=0.81	1.08 (0.79, 1.48) p=0.62	1.35 (0.91, 2.01) p=0.14	1.16 (0.75, 1.82) p=0.50
Obesity		1.69 (0.91, 3.11) p=0.10	1.53 (0.81, 2.89) p=0.19	**1.67 (1.06, 2.62) p=0.03**	1.38 (0.84, 2.26) p=0.21
Alcohol Dependence		1.73 (0.40, 7.42) p=0.47	1.76 (0.10, 5.99) p=0.47	**4.45 (1.93, 10.26) p<0.001**	**4.82 (1.83, 12.73) p=0.02**
Number of primary care contacts	0-5	0.09 (0.01, 1.27) p=0.12	0.42 (0.08, 1.34) p=0.18	0.16 (0.02, 1.19) p=0.07	0.33 (0.05, 2.47) p=0.28
	6-20	0.28 (0.05, 1.15) p=0.06	0.89 (0.12, 1.23) p=0.08	0.33 (0.04 1.25) p=0.08	0.87 (0.07, 3.75) p=0.35
	21-50	**3.03 (1.75, 5.24) p<0.001**	**4.58 (2.47, 8.44) p<0.001**	**2.60 (1.76, 3.84) p<0.001**	**15.20 (5.93, 39.00) p<0.001**
	>50	**6.58 (0.27, 18.27) p<0.001**	**18.30 (5.85, 57.28) p<0.001**	**7.34 (3.14, 17.17) p<0.001**	**3.34 (2.21, 5.36) p<0.001**

*Adjusted for significant unadjusted associations. Anxiety- adjusted for age 18-50 years and 66-75 years, number of primary care contacts 21-50 and 50+. Depression- adjusted for age 18-50 years, 66-75 years, asthma, cancer, obesity, alcohol dependence and number of primary care contacts 21-50 and >50.

[1] CVD (Cardiovascular disease) includes a history of stroke, IHD and PVD.

The association between covariates and mood problems was also analysed for individual IRCs. There were too few individuals with AS, PsA or GCA who had mood problems to enable associations to be determined (number of individuals reported in table 7.3), so analysis focussed on RA and PMR, to see if there were any differences in covariates associated with mood problems in these two main conditions. As the results were very similar to overall IRCs, the tables reporting these associations are in appendix 21.

There was a statistically significant increase in the adjusted odds of anxiety (OR (95%CI) = 2.70 (1.15, 6.32)), in addition to anxiety and/ or depression (OR (95% CI) = 2.07 (1.06, 4.04)), in people aged 18-50 years with RA, though no significant associations were found between age and mood problems in people with PMR. In people with RA and PMR, statistically significant adjusted associations were found between a high number of primary care contacts and mood problems, as was observed in overall IRCs. No significant unadjusted or adjusted associations were found between gender, deprivation status, smoking or obesity and mood problems, though analysis was limited by small sample sizes.

7.4.2 Incidence of anxiety alone, and anxiety and/or depression (objective 2)

In this section, characteristics of the cohorts used to assess the incidence of anxiety alone and incidence of anxiety and/ or depression will be described. Subsequently, I will assess and discuss the incidence of anxiety and median time to anxiety diagnosis, among those with and without IRCs, and make comparisons. This will be repeated for the outcome of anxiety and/ or depression.

I will further investigate the association between IRCs and anxiety, in addition to anxiety and/ or depression, at 0-1, 1-2, 2-5 and 5+ years post-index date.

7.4.2.1 *Incidence of anxiety*- Cohort Characteristics

As shown in table 7.5, the incidence of anxiety cohort comprised of 6879 individuals; 1423 with IRCs and 5456 without IRCs. The majority with IRCs had RA (n=539) or PMR (n=660), whilst fewer had GCA (n=96), PsA (n=78) and AS (n=54).

Table 7.5- *Number of individuals with and without IRCs in the anxiety incidence cohort and the diagnoses of those individuals with IRCs*

Diagnoses of individuals in the anxiety incidence cohort	
Total number of individuals= **6879**	
1423 with IRCs • Rheumatoid Arthritis (**RA**)= **539** • Ankylosing Spondylitis (**AS**)= **54** • Psoriatic Arthritis (**PsA**)= **78** • Polymyalgia Rheumatica (**PMR**)= **660** • Giant Cell Arteritis (**GCA**)= **96**	**5456** without IRCs

There was a ratio of 1:3.8 individuals with IRCs matched to individuals without IRCs by age, gender and GP practice. The ratio was less than 1:4 due to individuals with a diagnosis of anxiety pre-index date being excluded, as outlined in section 7.3.3.1. From the 1423 individuals with IRCs, 3 had Read codes for both PMR and GCA, whilst one had a combination of AS and PsA.

Table 7.6 (p221-222), summarises the demographics, lifestyle factors, comorbidities and number of primary care contacts by individuals with and without

IRCs. The mean age of individuals with IRCs was 65.9 (SD=15.4), whilst approximately two thirds were female.

Similar trends in age, gender, deprivation, comorbidities and lifestyle factors were observed in the anxiety incidence cohort, when compared to the prevalence cohort characteristics discussed in section 7.4.1.1. However, there were several differences. Although diabetes and asthma were more still more frequent in people with GCA, and smoking more frequent in people with RA, when compared to people without IRCs, these differences were not statistically significant. In contrast to the prevalence cohort, there was a statistically significant increase in both the number of current smokers with AS and the frequency of COPD in people with GCA, compared to those without IRCs. Although strokes remained less frequent in people with PsA and alcohol problems less frequent in people with AS, compared to those without IRCs, these differences were no longer statistically significant in the anxiety incidence cohort.

Table 7.6- ***Anxiety incidence cohort***- *Demographics, comorbidities, lifestyle characteristics and primary care contacts by IRC status.*

Covariate		Condition [a]						
		No IRC(n=5456)	**All IRCs**(n=1423)	**RA** (n=539)	**AS** (n=54)	**PsA** (n=78)	**PMR** (n=660)	**GCA** (n=96)
Age *Mean (SD)*		65.9 (15.4)	65.9 (15.4)	66.5 (15.3)	44.7 (14.1)	48.6 (13.5)	74.3 (9.2)	73.8 (10.6)
Age Range *(years)*	18-50 [1]	953 (17.5)	238 (16.7)	**133 (25.7) ****	**28 (66.7) ****	**34 (48.6) ****	**6 (0.9) ****	**0 (0) ****
	51-65 [2]	1438 (26.4)	367 (25.8)	**186 (35.9) ****	12 (28.5)	**29 (41.1) ****	**111 (17.1) ****	25 (25.8)
	66-75 [3]	1439 (26.4)	385 (27.1)	120 (23.1)	**1 (2.4) ****	**7 (10.0) ****	**227 (35.0) ****	28 (28.9)
	76-95 [4]	1622 (29.7)	433 (30.4)	**79 (15.3) ****	**1 (2.4) ****	**0 (0) ****	**305 (47.0) ****	**44 (45.3) ****
Female *(%)* [5]		4471 (65)	925 (65)	361 (67)	**14 (26) ****	**40 (51) ***	449 (68)	70 (73)
Deprivation Status *Number (%)*	Least	875 (16.2)	287 (19.9)	89 (16.5)	11 (20.4)	15 (19.3)	153 (23.2)	20 (20.9)
	Mid	3359 (61.9)	843 (59.2)	333 (61.8)	27 (50.0)	43 (55.1)	381 (57.7)	61 (63.5)
	Most [6]	1189 (21.9)	293 (20.6)	117 (21.7)	16 (29.6)	20 (25.6)	126 (19.1)	15 (15.6)
≥1 additional comorbidities *N(%)* [7]		2647 (48.5)	**768 (54.0) *****	278 (51.6)	**14 (25.9) *****	**19 (24.4) *****	**395 (59.8) *****	**62 (64.6) ****
Comorbidity *Number (%)*	HF [8]	170 (3.1)	53 (3.7)	16 (3.0)	0 (0)	0 (0)	**32 (4.8) ***	5 (5.2)
	IHD [9]	813 (14.9)	235 (16.5)	70 (13.0)	**2 (3.7) ***	**4 (5.1) ***	**137 (20.7) *****	**22 (22.9) ***
	DM [10]	633 (11.6)	172 (12.1)	62 (11.5)	4 (7.4)	4 (5.1)	85 (12.9)	17 (17.7)
	PVD [11]	296 (4.3)	73 (5.1)	25 (4.6)	2 (3.7)	3 (3.8)	31 (4.7)	8 (7.3)
	COPD [12]	1047 (19.2)	**370 (26.0) *****	**142 (26.3) *****	7 (13.0)	10 (12.8)	**175 (26.5) *****	**29 (30.2) ***
	Asthma [13]	690 (12.7)	**257 (18.1) *****	**106 (19.7) *****	5 (9.3)	6 (7.7)	**115 (17.4) ****	18 (18.8)
	Stroke [14]	446 (8.2)	120 (8.4)	**25 (4.6) ****	**0 (0) ***	2 (2.6)	**76 (11.5) ****	**17 (17.7) ****
	Cancer [15]	836 (15.3)	217 (15.3)	67 (12.4)	**2 (3.7) ***	**4 (5.1) ****	**128 (19.4) ****	16 (16.7)
Smoking Status *Number (%)*	Current [16]	1289 (23.6)	370 (26.0)	**174 (32.3) ****	**20 (37.0) ***	24 (30.8)	**131 (19.8) ****	22 (22.9)
	Non-smoker	2349 (43.1)	595 (41.8)	207 (38.4)	20 (37.0)	26 (33.3)	305 (46.1)	38 (39.6)
	Ex-smoker	1616 (29.6)	447 (31.4)	154 (28.6)	13 (24.1)	27 (34.6)	220 (33.3)	36 (37.5)
	Not known	202 (3.7)	11 (0.8)	4 (0.7)	1 (1.9)	1 (1.3)	5 (0.8)	0 (0)

Table 7.6- *Continued…*

Covariate			Condition [a]						
			No IRC(n=5456)	**All IRCs**(n=1423)	**RA** (n=539)	**AS** (n=54)	**PsA** (n=78)	**PMR** (n=660)	**GCA** (n=96)
Obesity *Number (%)* [17]			689 (12.6)	**210 (14.8) *****	**107 (19.9) *****	5 (9.3)	14 (17.9)	75 (11.3)	9 (9.4)
Alcohol dependence *N (%)* [18]			109 (1.9)	27 (1.9)	13 (2.4)	1 (1.9)	**4 (5.1) ***	**5 (0.8) ***	4 (4.2)
Number of primary care contacts (12 months pre-index)	Mean (SD)		31.1 (11.8)	20.6 (12.3)	20.4 (12.1)	13.8 (8.8)	16.0 (10.1)	21.3 (12.1)	23.6 (15.8)
	(n/10,000 people, 95% CI)	0-5	3070 (3010, 3130)	464 (455, 473)	464 (455, 465)	1667 (1634, 1700)	1410 (1382, 1438)	288 (282, 294)	208 (204, 212)
		6-20	4982 (4891, 5079)	5299 (5195, 5303)	5325 (5221, 5429)	6296 (6173, 6419)	5385 (5279, 5491)	5197 (5097, 5299)	5313 (5209, 5417)
		21-50	1822 (1786, 1858)	3893 (3817, 3969)	3915 (3838, 3992)	2037 (1097, 2077)	3077 (3017, 3137)	4152 (4071, 4233)	3646 (3574, 3691)
		>50 [19]	126 (123, 129)	**344*** (337, 351)**	**297* (291, 303)**	0 (0, 0)	128 (125, 131)	**364*** (357, 371)**	**1833*** (1797, 1869)**

Abbreviations; HF (heart failure), IHD (ischaemic heart disease), DM (diabetes mellitus), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), RA (rheumatoid arthritis), AS (ankylosing spondylitis), PsA (psoriatic arthritis), PMR (polymyalgia rheumatica), GCA (giant cell arteritis), SD (standard deviation), n (number).

a All IRCs and individual IRCs are compared to people without IRCs. P-values for the association between different covariates and overall/ different IRCs are represented as *p<0.05, **p<0.01, ***p<0.001. Where no asterix is given, associations are not statistically significant.

b Reference categories for each covariate analysed are listed in footnotes 1-20 below.

[1] Aged 18-50 years Vs not aged 18-50 years, [2] Aged 51-65 years Vs not aged 51-65 years, [3] Aged 66-75 years Vs not aged 66-75 years, [4]Aged 76-95 years Vs not aged 76-95 years, [5] Female Vs male gender, [6] Most Deprived Vs less deprived, [7] 1 or more comorbidities in addition to IRC Vs no additional comorbidities, [8] HF Vs no HF, [9] IHD Vs no IHD, [10] DM Vs no DM, [11] PVD Vs No PVD, [12] COPD Vs no COPD, [13] Asthma Vs no asthma, [14] Stroke Vs no stroke, [15] Cancer Vs no cancer, [16] Current Smoker Vs non-smoker, [17] Obese Vs not obese, [18] Alcohol dependence Vs no alcohol dependence, [19] Primary Care Contacts >50 Vs Primary Care Contacts ≤50.

7.4.2.2 *Incidence of anxiety and/or depression*- cohort characteristics

The incidence of anxiety and/or depression cohort comprised of 6417 individuals; 1363 with and 5054 without IRCs. As detailed in table 7.7, the majority with IRCs had RA (n=516) or PMR (n=639), whilst fewer had GCA (n=89), PsA (n=73) and AS (n=50). Three individuals had Read codes for both PMR and GCA, whilst one individual had both AS and PsA. There was a ratio of 1:3.7 individuals with IRCs matched to individuals without IRCs by age, gender and GP practice. The ratio was less than 1:4 due to individuals with a diagnosis of anxiety and/or depression pre-index being excluded.

Table 7.7- *Number of people with and without IRCs in the anxiety and/or depression incidence cohort and the diagnoses of those individuals with IRCs*

<table>
<tr><th colspan="2">Diagnoses of individuals in the anxiety and/or depression incidence cohort</th></tr>
<tr><td colspan="2">Total number of individuals in the cohort= 6417</td></tr>
<tr><td>1363 with IRCs
Rheumatoid Arthritis (RA)= 516
Ankylosing Spondylitis (AS)= 50
Psoriatic Arthritis (PsA)= 73
Polymyalgia Rheumatica (PMR)= 639
Giant Cell Arteritis (GCA)= 89</td><td>5054 without IRCs</td></tr>
</table>

Table 7.8 summarises the the demographics, lifestyle factors, comorbidities and number of primary care contacts by individuals with and without IRCs (p224). Similar trends in age, gender, comorbidities and lifestyle factors were observed in the anxiety and/or depression incidence cohort, when compared to the anxiety incidence cohort (section 7.4.2.1). However, there was a statistically significant reduction in the number of smokers with PsA and the number of people with AS who were in the most deprived category, compared to those without IRCs. Although HF was more frequent in PMR, IHD more frequent in GCA and alcohol dependence less frequent in PsA, when compared to those without IRCs, these differences were no longer statistically significant.

Table 7.8- *Anxiety and/or depression incidence cohort- Demographics, comorbidities, lifestyle characteristics and primary care contacts by IRC status.*

Covariate		Condition [a]						
		No IRC (n=5054)	**All IRCs** (n=1363)	**RA** (n=516)	**AS** (n=50)	**PsA** (n=73)	**PMR** (n=639)	**GCA** (n=89)
Age *Mean (SD)*		66.4 (15.2)	66.4 (15.2)	60.0 (14.4)	45.4 (12.8)	48.9 (13.8)	74.1 (9.5)	74.7 (10.3)
Age Range *(Years)*	18-50 [1]	842 (16.7)	221 (16.2)	**124 (25.0) ****	**24 (63.2) ****	**31 (47.0) ****	**7 (1.1) ****	**0 (0) ****
	51-65 [2]	1306 (258)	349 (25.6)	**177 (35.7) ****	12 (31.6)	**28 (42.4) ****	**108 (17.1) ****	20 (22.2)
	66-75 [3]	1362 (26.9)	372 (27.3)	118 (23.8)	**1 (2.6) ****	**7 (10.6) ****	**219 (34.8) ****	27 (30.0)
	76-95 [4]	1540 (30.6)	421 (30.9)	**77 (15.5) ****	**1 (2.6) ****	**0 (0) ****	**296 (47.0) ****	**43 (47.8) ****
Female *(%)* [5]		3285 (65)	886 (65)	341 (66)	**13 (26) *****	**36 (49) *****	**435 (68) ****	57 (64)
Deprivation Status *Number (%)*	Least	813 (16.2)	278 (20.4)	87 (16.9)	9 (18.0)	13 (20.5)	149 (23.3)	19 (21.3)
	Mid	3110 (61.9)	806 (59.1)	318 (61.6)	25 (50.0)	40 (54.8)	370 (57.9)	55 (61.8)
	Most [6]	1099 (21.9)	279 (20.5)	111 (21.5)	**16 (32.0) ***	18 (24.7)	120 (18.8)	15 (16.9)
≥1 additional comorbidity *N (%)* [7]		2459 (48.7)	**730 (53.6) ****	263 (51.0)	**14 (28.0) *****	**17 (23.3) *****	**379 (59.3) *****	**57 (64.0) *****
Comorbidity *Number (%)*	HF [8]	158 (3.1)	49 (3.6)	16 (3.1)	0 (0)	0 (0)	29 (4.5)	4 (4.5)
	IHD [9]	767 (15.2)	227 (16.7)	68 (13.2)	**2 (4.0) ***	**4 (5.5) ***	**113 (17.7) *****	20 (22.5)
	DM [10]	599 (11.6)	164 (12.0)	60 (11.6)	4 (8.0)	4 (5.5)	80 (12.6)	16 (18.0)
	PVD [11]	223 (4.4)	71 (5.2)	28 (5.4)	2 (4.0)	3 (4.1)	30 (4.7)	8 (9.0)
	COPD [12]	964 (19.1)	**346 (25.4) *****	**139 (26.9) *****	7 (14.0)	**8 (11.0) ***	**165 (25.8) *****	**27 (30.3) ***
	Asthma [13]	636 (12.6)	**238 (17.5) *****	**104 (20.2) *****	5 (10.0)	5 (6.8)	**107 (16.7) ***	17 (19.1)
	Stroke [14]	426 (8.4)	118 (8.7)	**25 (4.8) ****	**0 (0) ***	2 (2.7)	**74 (11.6) ****	**17 (19.1) *****
	Cancer [15]	775 (15.3)	203 (14.9)	63 (12.2)	**2 (4.0) ***	**4 (5.5) ***	**121 (18.9) ****	13 (14.6)
Smoking Status *Number (%)*	Current [16]	1170 (23.2)	349 (23.6)	**165 (32.0) ****	**18 (36.0) ***	21 (28.8)	**127 (19.9) ****	18 (20.2)
	Non-smoker	2194 (43.4)	575 (42.2)	196 (38.0)	19 (38.0)	25 (34.2)	298 (46.6)	38 (42.7)
	Ex-smoker	1493 (29.5)	428 (31.4)	151 (29.2)	12 (24.0)	26 (35.6)	209 (32.7)	33 (37.1)
	Not known	197 (3.9)	11 (0.8)	4 (0.8)	1 (2.0)	1 (1.4)	5 (0.8)	0 (0)

Table 7.8- *Continued…*

Covariate			Condition [a]						
			No IRC(n=5054)	**All IRCs**(n=1363)	**RA** (n=516)	**AS** (n=50)	**PsA** (n=73)	**PMR** (n=639)	**GCA** (n=89)
Obesity *Number (%)* [17]			617 (12.2)	**197 (14.5) ***	**102 (19.8) *****	4 (8.0)	12 (16.4)	73 (11.4)	6 (6.7)
Alcohol dependence *N (%)* [18]			88 (1.7)	21 (1.5)	12 (2.3)	1 (2.0)	3 (4.1)	**3 (0.5) ***	2 (2.2)
Number of primary care contacts (12 months pre-index)	Mean (SD)		13.0 (11.5)	20.2 (12.1)	20.1 (12.1)	13.2 (8.3)	15.2 (9.4)	21.1 (11.9)	23.0 (15.0)
	(n/10,000 people, 95% CI)	0-5	3146 (3048, 3208)	477 (465, 486)	484 (474, 494)	1600 (1669, 1631)	1507 (1477, 1537)	297 (291, 303)	225 (220, 230)
		6-20	4982 (4884, 5080)	5360 (5255, 5465)	5426 (5320, 5532)	6600 (6470, 6730)	5616 (5506, 5726)	5258 (5155, 5361)	5506 (5398, 5614)
		21-50	1743 (1709, 1777)	3822 (3747, 3897)	3818 (3743, 3893)	1800 (1765, 1835)	2877 (2821, 2933)	4116 (4034, 4198)	3596 (3525, 3667)
		>50 [19]	129 (126, 132)	**301 (295, 307) *****	**271 (266, 276) ***	0 (0, 0)	0 (0, 0)	**329 (323, 345) *****	**674 (661, 687) *****

Abbreviations; HF (heart failure), IHD (ischaemic heart disease), DM (diabetes mellitus), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), RA (rheumatoid arthritis), AS (ankylosing spondylitis), PsA (psoriatic arthritis), PMR (polymyalgia rheumatica), GCA (giant cell arteritis), SD (standard deviation), n (number).

a All IRCs and individual IRCs are compared to people without IRCs. P-values for the association between different covariates and overall/ different IRCs are represented as *p<0.05, **p<0.01, ***p<0.001. Where no asterix is given, associations are not statistically significant.

b Reference categories for each covariate analysed are listed in footnotes 1-20 below.

[1] Aged 18-50 years Vs not aged 18-50 years, [2] Aged 51-65 years Vs not aged 51-65 years, [3] Aged 66-75 years Vs not aged 66-75 years, [4]Aged 76-95 years Vs not aged 76-95 years, [5] Female Vs male gender, [6] Most Deprived Vs less deprived, [7] 1 or more comorbidities in addition to IRC Vs no additional comorbidities, [8] HF Vs no HF, [9] IHD Vs no IHD, [10] DM Vs no DM, [11] PVD Vs No PVD, [12] COPD Vs no COPD, [13] Asthma Vs no asthma, [14] Stroke Vs no stroke, [15] Cancer Vs no cancer, [16] Current Smoker Vs non-smoker, [17] Obese Vs not obese, [18] Alcohol dependence Vs no alcohol dependence, [19] Primary Care Contacts >50 Vs Primary Care Contacts ≤50.

7.4.2.3 Association between IRCs and anxiety alone, in addition to anxiety and/ or depression

In this section I will discuss the number of new mood consultations, then will report the median follow-up time to a mood consutation post-index date. Subsequently, for anxiety alone, then for anxiety and/ or depression, I will discuss the incidence rate (IR) and the risk of mood problems in people with IRCs compared to those without, expressed as a HR with an associated 95% CI. These results are summarised in table 7.9 (p229).

7.4.2.3.1 Number of new mood consultations

The proportion of new anxiety diagnoses was slightly higher in overall IRCs compared to those without IRCs (9.0% Vs 8.8%). New anxiety diagnoses were lower in people with PsA (6.4%) and AS (3.7%), though considerably higher in people with GCA (14.6%), compared to people without IRCs (8.8%).

The proportion of new anxiety and/ or depression diagnoses was higher in overall IRCs compared to those without IRCs (14.7% Vs 12.4%). Although the proportion of new anxiety and/ or depression diagnoses was lower in people with AS (10.0%), the proportion in all other IRCs was higher, particularly in people with RA (15.5%) and GCA (19.1%).

7.4.2.3.2 Median follow-up time to mood consultation

The median follow-up time to an anxiety consultation date post-index was longer in individuals with IRCs (5.6 years (interquartile range (IQR) 2.4-9.1)), compared to those without IRCs (5.1 years (IQR 2.6-9.6)). This suggests that overall, people with IRCs presented to their general practice later with symptoms of anxiety than those without IRCs. Considering individual IRCs, the follow-up time to an anxiety consultation

was shorter in individuals with GCA (4.5 years (IQR 2.3-7.6), but longer for people with RA, AS, PsA and PMR, when compared to those without IRCs. Individuals with AS and PsA had the longest median follow-up time to anxiety consultation of 6.6 years, compared to 5.1 years in people without IRCs.

The median follow-up time to an anxiety and/or depression consultation post-index was slightly longer in individuals with IRCs (4.9 years (IQR 2.2-9.1)), compared to those without IRCs (4.8 years (IQR 2.2-8.7)), suggesting that people with IRCs presented to their general practice marginally later with symptoms of anxiety and/or depression than those without IRCs. Considering different IRCs, the follow-up time to an anxiety and/or depression consultation was shorter in individuals with GCA (4.2 years (IQR 1.7-7.6), but longer for people with RA, AS and PsA, when compared to those without IRCs.

7.4.2.3.3 Incidence rate and risk of anxiety alone, in addition to anxiety and/or depression

The incidence rate (IR) of new anxiety following diagnosis with an IRC per 1000 person years was marginally lower in people with IRCs (IR= 14.21 (95% CI= 11.95, 16.91)) compared to those without IRCs (IR= 14.62 (95% CI= 13.37, 15.98)). However, the IR of anxiety did vary according to the type of IRC, being higher in individuals with GCA and PMR, though lower in individuals with RA, PsA, and AS, compared to those without IRCs. The IR of anxiety was notably high in people with GCA (IR=26.76 (95% CI=15.85, 45.18)).

There was no significant difference between the risk of new anxiety in people with IRCs, compared to those without IRCs (adjusted HR= 0.95 (95% CI=0.80, 1.15)). Considering different IRCs, the risk of anxiety was reduced in RA, AS and PsA, but

increased in PMR and GCA. The increased risk of anxiety in GCA was significant (adjusted HR=1.76, 95% CI=1.05, 2.95)), though other associations were not significant.

The IR of new anxiety and/or depression was higher in people with IRCs (IR= 24.38 (95% CI=21.21, 28.04)) compared to those without IRCs (IR= 21.50 (95% CI=19.88, 23.24)). The IR of anxiety and/or depression was particularly high in individuals with GCA (IR= 38.15 (95% CI=23.72, 61.37)), compared to other IRCs. However, the IR of anxiety and/or depression did vary, being much lower in individuals with AS (IR= 16.16 (95% CI=6.73, 38.82)) and PsA (IR= 17.16 (95% CI=8.93, 32.98)), compared to those without IRCs.

The adjusted risk of new anxiety and/or depression in people with IRCs was increased compared to those without IRCs (HR= 1.10 (95% CI=0.93, 1.29)), though this difference was not statistically significant. Considering different IRCs, the risk of anxiety and/or depression was reduced in RA, AS and PSA, though increased in PMR and GCA. The increased risk of anxiety and/ or depression was statistically significant in people with PMR when unadjusted (1.29 (95% CI=1.02, 1.65)), though significance was lost on adjustment (1.24 (95% CI=0.97, 1.59)). The other associations were not significant.

For anxiety, in addition to anxiety and/or depression, when the proportional hazards (PH) assumption was tested, all p values were >0.05, meaning the ratio of the hazards for any two individuals over time was constant.

Table 7.9- *The association of anxiety alone, in addition to anxiety and/or depression, with overall and different IRCs over time.*

Condition [1]	Anxiety alone [2]					Anxiety and/ or depression [3]				
	New anxiety diagnoses *N (%)*	Median f/u time to mood consultation (IQR)	IR (95% CI) *(per 1000 person years)*	Risk of anxiety in people with, compared to without IRCs		New anxiety and/or depression diagnoses *N (%)*	Median f/u time to mood consultation (IQR)	IR (95% CI) *(per 1000 person years)*	Risk of anxiety and/or depression in people with, compared to without IRCs	
				Unadjusted HR (95% CI)	Adjusted HR (95% CI) *				Unadjusted HR (95% CI)	Adjusted HR (95% CI) *
No IRC	482 (8.8)	5.1 (2.6, 9.6)	14.62 (13.37,15.98)	0.98 (0.81, 1.19) p=0.84	0.95 (0.80, 1.15) p=0.59	629 (12.4)	4.8 (2.2, 8.7)	21.50 (19.88,23.24)	1.04 (0.85, 1.27), p=0.73	1.10 (0.93, 1.29), p=0.26
All IRCs	128 (9.0)	5.6 (2.4, 9.1)	14.21 (11.95,16.91)			200 (14.7)	4.9 (2.3, 9.1)	24.38 (21.21, 28.04)		
RA	47 (8.7)	5.7 (2.8, 10.0)	13.32 (10.01,17.73)	0.84 (0.61, 1.15) p=0.28	0.81 (0.59, 1.11) p=0.18	80 (15.5)	6.5 (2.3, 9.4)	25.12 (20.15, 31.32)	1.02 (0.79, 1.31), p=0.88	0.96 (0.95, 1.24), p=0.78
AS	2 (3.7)	6.6 (3.2, 10.1)	5.39 (1.35, 21.57)	0.45 (0.10, 1.94) p=0.28	0.42 (0.09, 1.96) p=0.27	5 (10.0)	6.5 (2.9, 9.3)	16.16 (6.73, 38.82)	0.86 (0.33, 2.28), p=0.77	0.78 (0.28, 2.17), p=0.63
PsA	5 (6.4)	6.6 (2.8, 12.0)	6.97 (2.62, 18.57)	0.45 (0.16, 1.27) p=0.13	0.43 (0.15, 1.22) p=0.11	10 (13.7)	6.5 (2.5, 12.0)	17.16 (8.93, 32.98)	0.84 (0.41, 1.72), p=0.63	0.74 (0.35, 1.57), p=0.44
PMR	61 (9.2)	5.4 (2.6, 8.9)	15.40 (11.98,19.79)	1.16 (0.87, 1.55) p=0.31	1.12 (0.84, 1.50) p=0.43	89 (13.9)	4.8 (2.3, 8.6)	23.93 (19.42, 29.50)	**1.29 (1.01, 1.65), p=0.04**	1.24 (0.97, 1.59), p=0.08
GCA	14 (14.6)	4.5 (2.3, 7.6)	26.76 (15.85,45.18)	**1.91 (1.01, 3.61) p=0.04**	**1.76 (1.05, 2.95) p=0.03**	17 (19.1)	4.2 (1.7, 7.6)	38.15 (23.72, 61.37)	1.64 (0.94, 2.90), p=0.08	1.63 (0.92, 2.89) p=0.10

HR= hazard ratio, IQR= Interquartile Range, IR= Incidence Rate, CI= confidence interval, N= number of individuals.

** Adjusted for age, gender, ethnicity, smoking status, obesity, alcohol problems and comorbidities (HF, IHD, DM, PVD, COPD, Asthma, Stroke, Cancer).*

[1] For all associations, overall IRCs and individual IRCs have been compared to people without IRCs.

[2] Number of individuals with IRCs for anxiety alone calculations; No IRC (n=5456), IRC (n=1423), RA (n=539), AS (n=54), PsA (n=78), PMR (n=660), GCA (n=96).

[3] Number of individuals with IRCs for anxiety and/ or depression calculations; No IRC (n=5054), IRC (n=1363), RA (n=516), AS (n=50), PsA (n=73), PMR (n=639), GCA (n=89).

7.4.2.3.4 Association between IRCs and anxiety alone at different follow-up time points

Table 7.10 shows the association between IRCs and time to diagnosis of new anxiety over different time periods between 0-5+ years. Due to the small numbers of individuals with AS (n=2), PsA (n=5) and GCA (n=14) who developed anxiety post-index, analysis for these conditions was not possible. Therefore, analysis across different time periods was limited to RA (n=47) and PMR (n=61), for which there were a greater number of individuals who developed anxiety post-index.

Table 7.10- *Association between RA, PMR and time to diagnosis of anxiety over different time periods.*

Association between IRCs and time to *anxiety* diagnosis		**Condition**		
		Overall IRCs (n=128)	**RA (n=47)**	**PMR (n=61)**
HR over different time periods	**0-1 years** [1]	1.07 (0.74, 1.54)	0.81 (0.44, 1.48)	1.45 (0.84, 2.51)
	1-2 years [2]	0.75 (0.45, 1.25)	0.76 (0.34, 1.61)	0.91 (0.42, 1.98)
	2-5 years [3]	1.00 (0.80, 1.42)	1.10 (0.64, 1.89)	1.02 (0.67, 2.17)
	5+ years [4]	0.94 (0.61, 1.44)	0.49 (0.21, 1.15)	1.20 (0.67, 2.17)

HR= hazard ratio, χ 2(p)= chi-squared and p-value

[1] Number with; overall IRCs (n=39), RA (n=13), PMR (n=20)
[2] Number with; overall IRCs (n=28), RA (n=10), PMR (n=11)
[3] Number with; overall IRCs (n=34), RA (n=16), PMR (n=14)
[4] Number with; overall IRCs (n=27), RA (n=8), PMR (n=15)

In individuals with RA, the risk of new anxiety was increased between 2-5 years, but reduced before 2 years and over 5 years after diagnosis of RA. However, in individuals with PMR, the risk of anxiety was increased across all time periods apart from 1-2 years. However, none of these associations were statistically significant. The risk of

anxiety was highest between 0-1 years after diagnosis of PMR, suggesting individuals with PMR were at a greater risk of developing anxiety soon after being diagnosed with an IRC, compared to individuals with RA, whom had an increased risk of anxiety between 2-5 years post-index. These results also suggest that the risk of developing new anxiety remains increased over a longer time period following a diagnosis of PMR, when compared to RA.

7.4.2.3.4 Association between IRCs and anxiety and/ or depression at different follow-up time points

Table 7.11 (p232) shows the association between IRCs and time to diagnosis of new anxiety and/or depression over different time periods between 0-5+ years. Due to the small numbers of individuals with AS (n=5), PsA (n=10) and GCA (n=17) who developed anxiety and/or depression post-index, analysis for these conditions was not possible. Therefore, analysis across different time periods was limited to RA (n=80) and PMR (n=89), for which there were a greater number of individuals who developed anxiety and/or depression post-index.

In people with RA, the risk of new anxiety and/or depression was only increased between 1-2 years, whereas in people with PMR, the risk of anxiety and/or depression was increased across all time periods, being highest between 0-1 years after diagnosis. Although no associations were statistically significant, results suggest that people with PMR are at a higher risk of developing anxiety and/or depression at an earlier time point after being diagnosed with an IRC, compared to people with RA. These results also suggest that the risk of developing new anxiety and/or depression remains increased over a longer time period following a diagnosis of PMR, when compared to RA.

Table 7.11- *Association between RA, PMR and time to diagnosis of anxiety and/or depression over different time periods.*

Association between IRCs and time to diagnosis of *anxiety and/ or depression*		**Condition**		
		Overall IRCs (n=200)	**RA (n=80)**	**PMR (n=89)**
HR over different time periods	**0-1 years** [1]	1.26 (0.95, 1.66)	0.74 (0.40, 1.38)	1.51 (0.97, 2.35)
	1-2 years [2]	1.89 (0.59, 1.33)	1.17 (0.75, 1.81)	1.24 (0.69, 2.24)
	2-5 years [3]	1.19 (0.90, 1.56)	0.79 (0.40, 1.56)	1.18 (0.77, 1.81)
	5+ years [4]	0.92 (0.60, 1.40)	0.98 (0.64, 1.51)	1.15 (0.63, 2.07)

HR= hazard ratio, χ 2(p)= chi-squared and p-value

[1] Number with; overall IRCs (n=57), RA (n=21), PMR (n=27)
[2] Number with; overall IRCs (n=67), RA (n=27), PMR (n=23)
[3] Number with; overall IRCs (n=42), RA (n=15), PMR (n=21)
[4] Number with; overall IRCs (n=34), RA (n=17), PMR (n=18)

7.4.5 Summary of Results

Overall, anxiety alone affected similar proportions with and without IRCs, whilst anxiety and/ or depression were more common in people with IRCs, compared to those without IRCs. Over time, people with IRCs were less likely to develop anxiety alone, though more likely to develop anxiety and/ or depression. People with IRCs had a longer median follow-up time to first anxiety consultation, and first anxiety and/ or depression consultation, compared to people without IRCs.

Considering different IRCs, the prevalence of anxiety alone, in addition to anxiety and/ or depression, was higher in RA, AS, PsA and GCA, though lower in PMR, compared to people without IRCs. Whilst individuals with AS and PsA were *less* likely to develop anxiety alone, or anxiety and/or depression over time, people with PMR and GCA were

more likely to develop mood problems, when compared to people without IRCs. Meanwhile, people with RA were *less* likely to develop anxiety alone, though *more* likely to develop anxiety and/ or depression over time.

When the association between RA, PMR and time to diagnosis with a mood problem was assessed over different time periods, individuals with PMR were noted to be at a greater risk of developing mood problems soon after being diagnosed with an IRC. Individuals with RA only had an increased risk of developing anxiety between 2-5 years post-index, whilst their risk of developing anxiety and/ or depression was increased between 1-2 years post-index. Only individuals with GCA had a shorter median follow-up time to first mood consultation, compared to individuals without IRCs.

7.5 Discussion

7.5.1 Cohort characteristics

The proportion of individuals with different IRCs, their ages and gender ratios, reflected patterns observed in other population epidemiological studies. Interestingly, individuals with IRCs were not significantly less deprived than those without IRCs, apart from in the incidence of anxiety and/ or depression cohort, where a significant association was found between AS and deprivation (table 7.8). This contrasts with the literature, which suggests individuals with long-term conditions (LTCs) are more likely to be socioeconomically deprived (Barnett et al., 2012, Elliot, 2016). Deprivation status was calculated using the IMD, which is linked to an individuals' postcode. It is possible that individuals' postcodes did not accurately reflect their living standards. Housing has become less affordable in the 21st century (HM Land Registry, 2019), hence younger people with AS could have been forced to rent accommodation, or buy housing in a less

affluent area, compared to someone earning an equivalent amount 20 years ago. Meanwhile, older people with PMR or GCA could have been living in the same home all their life, which may not reflect their ability to afford good living standards.

Ethnicity was not reported, as a large proportion with IRCs (19%) and without IRCs (27%) had no recorded ethnicity. For those with a Read code for their ethnicity, the majority (98%) were white British. This could have been a reflection of local population demographics, though it is possible other ethnicities could have been under-represented due to poor coding within general practice records.

More people with IRCs were current smokers and obese, though there was no significant difference between the proportions with and without IRCs who had a Read code for alcohol misuse or dependence. The literature suggests individuals with LTCs, including IRCs, are more likely to smoke, be overweight and consume excess alcohol (Velten et al., 2018), though alcohol dependence was not more frequent in people with IRCs. Although more people with PsA had a Read code for alcohol dependence, significantly less people with AS and PMR had a history of alcohol dependence, compared to people without IRCs. It is possible that many individuals who consumed excess alcohol alcohol were not identified, due to Read codes for alcohol misuse and dependence being used to define excessive consumption of alcohol (as discussed in section 7.3.3.4 and listed in appendix 20), rather than the number of units consumed by individuals. However, the amount of alcohol consumed by individuals is often not explored or coded during primary care consultations, with the literature suggesting that alcohol disorders are under-recognised within general practice in the UK (Cheeta et al., 2008). Evidence also suggests that people under-report the amount of alcohol they consume (Boniface & Shelton, 2013), potentially leading to under-recognition of alcohol

disorders. In addition, some individuals with IRCs could also have been counselled against consuming alcohol due to potential interactions with their medication. Furthermore, differences in smoking behaviour and obesity observed between people with and without IRCs, could have been due to surveillance bias, whereby individuals with IRCs had more primary care contacts, providing more opportunities for lifestyle factors to be discussed and recorded. It is also possible that some differences didn't meet statistical significance due to the small sample of individuals, particularly with AS and PsA.

In common with existing literature (Naylor et al., 2012), individuals with IRCs had significantly more comorbidities than those without IRCs. An older mean age and glucocorticoid treatment side-effects could have contributed to the increased number of comorbidities, particularly cardiovascular disease (CVD), observed in people with GCA and PMR, compared to other IRCs. Meanwhile, the increased prevalence of cancer in PMR could have been due to overlapping symptoms of PMR and different malignancies (NICE, 2013b), leading to some individuals with early cancer being misdiagnosed with PMR. Meanwhile, the lower mean age of people with AS and PsA could explain the reduced prevalence of IHD, cancer and stroke in these IRCs, compared to those without IRCs. The increased prevalence of COPD in overall IRCs could have been contributed to by increased numbers of current smokers, compared to those without IRCs.

The number of primary care contacts was higher in people with IRCs compared to those without IRCs. This could have been due to flares of the IRC requiring treatment or due to individuals with IRCs having more comorbidities requiring review in primary care. However, a limitation of this study was that primary care contacts included letters scanned onto a patients' record, or blood results (with several tests entered on one day

counting as a single contact), in addition to other entries such as telephone or face-to-face consultations. Therefore, the higher contact rate in individuals with IRCs could have been due to rheumatology clinic letters and disease modifying anti-rheumatic drug (DMARD) monitoring blood tests being entered on the primary care records, rather than due to increased face-to-face contacts. A more accurate impression could have been gained by only recording telephone and face-to-face contacts with patients, though this would have required a manual review of thousands of peoples' records, which was not feasible.

7.5.2 Prevalence of mood problems in people with IRCs

The prevalence of anxiety alone, in addition to anxiety and/or depression, was higher in overall IRCs, RA, AS, PsA and GCA, when compared to those without IRCs. This would fit with the background literature, which suggests anxiety and depression are more prevalent in RA, as discussed in section 2.9.1 (Isik et al., 2006; Matcham et al., 2013). These findings would also support the literature discussed in section 2.9.3 which reported an increased prevalence of anxiety and depression in AS (Hopkins & Moulton, 2016; Shen et al., 2016) and PsA (McDonough et al., 2014). These findings would also support limited research showing a higher prevalence of depression in individuals with GCA (Li, Neogi & Jick, 2017), whilst providing new evidence of an increased prevalence of anxiety in GCA.

However, the prevalence of anxiety alone, in addition to anxiety and/or depression, was lower in individuals with PMR, compared to individuals without IRCs. This contrasts with the limited background literature on mood problems in PMR, that

suggests 15-22% have self-reported symptoms of depression (Vivekanatham et al., 2018; Muller et al., 2016) and 13% anxiety (Muller et al., 2016).

It is unclear why anxiety or depression were less prevalent amongst individuals with PMR. As reported in table 7.2, primary care contacts were higher in individuals with PMR compared to those without IRCs, providing more potential opportunities for the recognition and coding of mood problems. However, compared to the other IRCs analysed, PMR is a condition that is more frequently managed within primary care. Therefore, primary care consultations could have been more focussed on medical management, including the prescription of glucocorticoids for treatment of the primary condition, leaving less time to discuss potential mood problems. In contrast, when consulting individuals with other IRCs largely managed by secondary care, such as RA, primary care practitioners may have had more opportunity to focus on comorbid problems during consultations. However, it could be argued that as PMR is more frequently managed in primary care, practitioners would have more opportunity to build rapport with affected patients over a series of consultations, facilitating disclosure and discussion of mood concerns.

Prevalence rates were calculated over 12 months pre-index (12 months before the date of an IRC first being coded in the EMIS record). Therefore, glucocorticoid treatment could not have affected the prevalence of mood problems, as it would not have been started, unless the patient was prescribed glucocorticoid treatment for another condition. Alternatively, after developing symptoms, individuals with PMR could have presented earlier to primary care, or could have been diagnosed and managed more promptly than other IRCs, leaving less opportunity over the 12 months prior to diagnosis for mood problems to develop.

Following adjustment, the odds of anxiety alone became marginally reduced in individuals with IRCs, though the odds of anxiety and/or depression were increased, when compared to individuals without IRCs. However, these differences were not statistically significant. The reduced odds of anxiety alone in people with IRCs, contrasts with the prevalence results, which suggested that anxiety was more frequent in individuals with IRCs.

When different IRCs were analysed, the odds of anxiety alone, in addition to anxiety and/ or depression, were increased in people with RA, AS, PsA and GCA, though reduced in people with PMR, compared to people without IRCs. However, the only statistically significant associations were found between PsA and GCA, and increased anxiety and/or depression. These associations remained significant after adjustment for covariates. As 46% of individuals with IRCs in the prevalence dataset had PMR, they heavily influenced the overall association between IRCs and anxiety. In addition, lower adjusted ORs between RA, AS, GCA and anxiety, when compared to anxiety and/or depression, could have contributed to the reduced overall odds of anxiety in IRCs.

Of interest, the prevalence of anxiety, in addition to anxiety and/or depression, was highest in individuals with PsA and GCA, whilst the adjusted odds of anxiety and/or depression were also significantly increased in individuals with PsA and GCA. This is noteworthy, given that past research has largely focused on the association between RA and mood problems, as these findings suggest that comorbid mood problems are a potentially greater problem amongst individuals with PsA and GCA.

When the association between covariates in people with IRCs and mood problems were analysed, the odds of having a Read coded mood problem were found to be reduced in people aged 66-75 years. The literature suggests that older people

frequently normalise mood problems, or can be more self-reliant, which can be barriers to them presenting to their GP or seeking help for mood problems (Wuthrich & Frei, 2015). In addition, primary care practitioners may not recognise depression in older adults due to normalising it as an understandable aspect of ageing (Burroughs et al., 2006), hence it is possible the odds of having a Read coded mood problem were reduced in older people due to under-recognition in this age group. In contrast, the odds of individuals with IRCs having anxiety alone, and anxiety and/ or depression were significantly increased in people aged 18-50 years. Recent research has shown a rise in mood disorders in younger general population cohorts, particularly females, potentially related to cultural trends, including an increase in electronic communication and digital media use, in addition to a reduction in sleep quality (Twenge et al., 2019).

Prior to adjustment, female gender also had a significant association with anxiety and/ or depression. This reflects the literature on mood problems in the general population, which suggests women have a higher lifetime prevalence of depression and anxiety disorders, compared to men (Riecher-Rossler, 2016). In addition, a high number of primary care contacts were significantly associated with mood problems, likely due to these contacts providing a more opportunities for discussion of potential anxiety or depression. It is also possible that those with more primary care contacts had other comorbidities which could have increased their risk of developing a mood problem.

No association was found between deprivation and anxiety and/ or depression, in contrast to the literature which suggests deprivation is associated with increased mood problems (Freeman et al., 2016). It is possible that the cohort of patients included in this study were less deprived than a general population cohort, though the CiPCA database does include people from a range of socioeconomic backgrounds. Alcohol

dependence was associated with mood problems in people with IRCs, mirroring associations seen within the general population (Raimo & Schuckit, 1998).

The odds of anxiety and depression were increased in people with IRCs who had one or more additional comorbidities, though this association was not statistically significant. This is surprising as the literature suggests that people with several LTCs are significantly more likely to develop mood problems (Read et al., 2017). Cancer was the only comorbidity analysed found to have a significant association with mood problems in people with IRCs after adjustment, despite other LTCs such as COPD (Naylor et al., 2012), DM (Salinero-Fort et al., 2018) and coronary heart disease (CHD) (Bankier, Januzzi and Littman, 2004), having well established links with mood problems.

An increased number of primary care contacts were significantly associated with mood problems in overall IRCs, in addition to RA and PMR, when they were analysed separately. Evidence suggests that mood problems can affect help-seeking behaviour, with anxious or depressed people potentially consulting more often (Fine et al., 2018). Whilst these individuals could have been consulting more for management of their anxiety or depression, they may also have been consulting due to increased pain or stiffness in relation to their IRC. Evidence suggests depression in people with IRCs is associated with increased disease activity (Matcham et al., 2016b), whilst my systematic review, discussed in chapter 6, also highlighted links between anxiety in people with IRCs and increased disease activity.

7.5.3 Incidence of mood problems in people with IRCs

The time to first mood consultation was longer in people with IRCs, compared to those without IRCs. However, the time to first mood consultation varied between

different IRCs, being shorter in people with GCA, though longer in people with RA, AS, PsA and PMR compared to those without IRCs. Overall, this suggests that people with IRCs presented later with symptoms of mood problems. It is possible that this trend was observed due to primary care consultations for people with IRCs focussing on the management of their inflammatory condition or other comorbidities, which are more frequent in people with IRCs. These competing priorities could have been a barrier to discussion of, or coding of mood problems. However, individuals with GCA were noted to present earlier with mood symptoms than people with other IRCs. A higher burden of multimorbidity could have led to individuals with GCA being more likely to be consulters, where they could have been asked about mood problems, contributing to earlier recognition of comorbid anxiety and depression. In particular, people with other LTCs, such as DM or COPD, could have attended a nurse-led annual review for this comorbid condition, where they could have been asked about potential mood problems.

Overall, the incidence and adjusted HR of anxiety were reduced in people with IRCs, compared to those without IRCs. However, when different IRCs were analysed, the incidence and HR of anxiety were increased in individuals with PMR and GCA, though reduced in people with RA, AS and PsA, compared to those without IRCs. Of note, the adjusted HR of anxiety was significantly increased in GCA. These findings support limited literature showing an increased incidence of anxiety symptoms in people with PMR (Muller et al., 2016), whilst also adding to the literature by highlighting a particularly increased incidence and risk of anxiety in people with GCA. However, the findings for RA, contrasted with limited literature showing an increased incidence of anxiety in RA

(Marrie et al., 2018b, Qui et al., 2019) and AS (Shen et al., 2018), whilst providing evidence to suggest a reduced incidence of anxiety in PsA.

Alternatively, it is possible that anxiety in individuals with RA, AS and PsA were not recognised or coded in the clinical records. As shown in table 7.2, primary care contact rates were lower in individuals with AS and PsA, than those without IRCs. The burden of comorbidities was also lower in people with AS and PsA compared to individuals with other IRCs, meaning people with these conditions would have had less opportunities to discuss potential mood problems. In addition, there were less individuals with AS (n=54) and PsA (n=78) in the anxiety incidence dataset compared to other IRCs, which could have limited the reliability of results.

However, these reasons could not be used to explain the reduced incidence of anxiety in people with RA, as the sample size was comparatively larger for RA (n=539), whilst individuals with RA had higher primary care contact rates and a greater burden of comorbidities than people without IRCs, which would have provided further opportunities for the potential recognition of anxiety. However, 95% CI's reported with the HR's for anxiety were particularly wide in RA, AS and PsA, suggesting a greater sample size still would have been required to accurately determine the association between these IRCs and anxiety. It is also possible that the burden of mood problems was not as high as expected due to this study using a primary care cohort. Individuals may have had less severe symptoms, compared to those managed in secondary care, where most of the prior prevalence studies were based.

The incidence and adjusted HR of anxiety and/or depression was increased in people with IRCs, compared to those without IRCs. However, results again varied between different IRCs. Whilst the incidence of anxiety and/or depression was

increased in PMR and particularly GCA, it was reduced in people with AS, and PsA, compared to those without IRCs. Results were mixed for RA, with an increased incidence though a reduced adjusted HR of anxiety and/ or depression. Findings were supported by limited background literature, showing the incidence of anxiety and depression to be increased in PMR (Muller et al., 2016), GCA (Li, Neogi and Jick, 2017) and RA (Marrie et al., 2018b). However, findings for AS and PsA, contrasted with the literature, which suggests the incidence of anxiety and depression is increased in people with AS (Meesters et al., 2014; Wu et al., 2017, Shen et al., 2016), whilst the incidence of depression has also been found to be higher in people with PsA (Zusman et al., 2018). It is possible that the aforementioned reasons, including lower primary care contact rates and small sample sizes for AS and PsA contributed to the disparity in these results.

When the risk of anxiety, in addition to anxiety and/or depression, in people with RA and PMR was examined over time, the risk of mood problems in PMR was raised over most time periods, particularly between 0-1 years after diagnosis. In contrast, the risk of mood problems in RA was only raised between 2-5 years after diagnosis for anxiety, and 1-2 years after diagnosis for anxiety and/or depression, suggesting that case-finding for comorbid anxiety and depression needs to be considered at an earlier time point after diagnosis in people with PMR, compared to those with RA. It is possible that the higher risk of mood problems after diagnosis of PMR could relate to the side-effects of glucocorticoid treatments, which are known to potentially cause mood disturbances (Brown, 2009).

7.5.4 Comparison of Prevalence and Incidence Results

The prevalence of anxiety was increased, though the adjusted odds of anxiety reduced in people with IRCs, compared to those without IRCs. The incidence and

adjusted HR of anxiety were also reduced in people with IRCs compared to those without IRCs. These contrasting non-significant results suggest further research is needed using a larger dataset to more accurately determine the association between IRCs and anxiety.

Considering different IRCs, the prevalence and odds of anxiety were increased in RA, AS and PsA, though the incidence of anxiety reduced. Meanwhile, the prevalence of anxiety in PMR was reduced, though the incidence of anxiety was increased. The only IRC in which the incidence and prevalence of anxiety were increased was GCA. As prevalence rates were calculated over a 12-month period before the diagnosis of an IRC, whilst IR's were calculated from the date of diagnosis with an IRC, differences in prevalence and incidence rates could have related to variations in treatment response. For example, although the prevalence of anxiety was less in PMR, its' incidence was increased, suggesting treatment for PMR with glucocorticoids could have adversely affected mood. In addition, the increased prevalence, though reduced incidence of anxiety, in people with RA, AS and PsA, could have reflected an improvement in mood in response to better disease control following initiation of a DMARD.

The incidence and prevalence of anxiety and/or depression were increased in people with IRCs, compared to those without IRCs. Considering different IRCs, although the incidence and prevalence of anxiety and/or depression were increased in people with RA and GCA, results varied for other IRCs. For example, the prevalence of anxiety and/or depression was reduced in PMR, though the incidence of mood problems was increased. The reverse was found in people with PsA and AS, who had an increased prevalence, though a reduced incidence of anxiety and/ or depression. Again, changes in mood in response to treatment could partially explain these contrasting results.

Whilst glucocorticoids could potentially provoke or worsen mood problems in individuals with PMR, leading to an increased incidence of anxiety and/or depression, treatments including anti-inflammatories or DMARDs could have led to reduced disease activity, hence a reduced incidence of anxiety and/or depression in individuals with AS and PsA. However, the incidence of mood problems remained high in RA, suggesting that despite treatment of the inflammatory condition, mood problems continued to effect people with this condition over time. The incidence and prevalence of anxiety and/or depression was highest in GCA, suggesting a particularly significant burden of mood problems in people with this IRC.

7.5.5 Strengths and Limitations

A strength of this study is that it utilised the CiPCA database, a well established database of anonymised medical record data from a subset of general practices in North Staffordshire, which have followed the Keele consultation data audit, training and validation programme, hence code clinical activity to a high standard (Porcheret et al., 2004). Therefore, the quality of data is comparable to larger national databases (Jordan et al., 2007). However, a national database such as the CPRD would have provided more generalisable results due to data being derived from a larger number of more diverse individuals from across the UK. Due to the greater number of individuals in the CPRD database, statistical power would have been increased, enabling stronger conclusions to be made about the association between IRCs and mood problems, with less chance of type 1 errors, where a null hypothesis is incorrectly rejected. Having a larger number of individuals within the dataset would also have enabled analysis of the association between AS, PsA and GCA, and mood problems over time to be completed.

As discussed in section 7.3.3.1, the reliance on coded consultation data meant that depression alone could not be accurately analysed, due to it often being recorded using the Read code “anxiety with depression”. A depression Read code list excluding the code “anxiety with depression” could have been used, though this could have led to a large number of people with mood problems being excluded from the analysis. Although depression alone was not examined, the depression and anxiety Read code lists were combined to enable analysis of individuals with anxiety and/ or depression.

Although anxiety alone was analysed, it is possible some cases were missed that were only recorded in the clinical record in combination with depression. However, when an individual consults their GP with predominantly anxiety symptoms, a Read code for anxiety is usually recorded, not “anxiety with depression”. In addition, analysing anxiety alone was felt to be important, due to the lack of literature reporting the prevalence of anxiety in different IRCs, in addition to the findings of the systematic review discussed in chapter 6, which suggested a significant association between anxiety in people with RA, and QoL and disease activity.

Missing data on smoking, alcohol and obesity has been shown to not be missing at random in electronic health record datasets, hence multiple imputation techniques were not used. Instead, a more simplistic approach was used, where separate categories were created for those with missing data. A further potential limitation was unmeasured confounding. It is possible that some influential confounding factors could not be accounted for due to them being poorly recorded in the electronic health records, for example, a family history of mental illness.

As this study relied on primary care consultation data, it is possible that some codes could have been misclassified. In addition, the use of consultation data could have

led to the incidence and prevalence of mood problems being under-estimated, Individuals may not have presented to primary care, or disclosed symptoms of anxiety or depression, due to lacking candidacy for care of mood problems (Coventry et al., 2011), or fearing of potential stigmatisation (Anderson et al., 2012). In addition, clinicians may not have recognised or recorded symptoms of potential mood problems. Evidence suggests that less than half of common mental disorders (CMDs), including anxiety and depression, are identified in primary care consultations (Goldberg & Huxley, 1991). In particular, when people with psychological disorders normalise their symptoms, general practitioners are less likely to diagnose a mood disorder (Kessler, Lewis & Gray, 1999).

7.6 Patient and Public Involvement and engagement

The results of this study were discussed during a patient and public involvement and engagement (PPIE) meeting, attended by six individuals with different IRCs. Participants were interested to hear that the prevalence of anxiety, in addition to anxiety and/or depression was highest amongst individuals with PsA and GCA, rather than RA, as they had previously only heard about mood problems being linked to RA, not other IRCs. They were also interested to hear that individuals with PMR and GCA were more likely to develop mood problems over time, compared to other IRCs. Participants were surprised that mood problems were not more prevalent in people with PMR, like the other IRCs analysed, and queried whether mood problems were potentially not being recognised in people with IRCs within primary care. Therefore, they felt it would be important to share the results with patients to raise awareness of

the increased risk of comorbid mood problems in people with IRCs, whilst also informing primary care practitioners about the results.

Suggestions for dissemination included a presentation to the patient user group at the local rheumatology hospital and discussion with the members of the national rheumatoid arthritis society based in Stoke-on-Trent. Further ideas included to use social media to reach out to younger people with certain types of IRCs and to inform national organisations such as Versus Arthritis about research outcomes. Participants reflected that the wider multidisciplinary team in general practice may have more time than GPs to explore potential mood problems, hence they suggested a practice bulletin could be used to help inform healthcare assistants, nurses, pharmacists and physician associates. A dissemination plan was developed, taking account of these suggestions. Appendix 27 contains details of the presentations I have given to help disseminate my results, including those made to different lay audiences.

7.7 Conclusion

This study has provided new evidence of an increased prevalence of mood problems in people with GCA, whilst providing further evidence to support an increased prevalence of mood problems in people with RA, AS and PsA. Despite past research into mood problems in people with IRCs being focused on RA, this study found the prevalence of anxiety and/or depression to be highest in individuals with PsA and GCA. This study has also provided new evidence of an increased incidence of anxiety, in addition to anxiety and/or depression in people with PMR and GCA. As a consequence, future research needs to focus on the impact of comorbid mood problems in AS, PsA, PMR and GCA, to build on past research, which has focused on the impact of mood

problems in people with RA. Intervention studies could help to determine the most feasible and acceptable approach to improving the recognition and management of comorbid anxiety and depression in people with different IRCs. Guidelines also need to reflect evidence of an increased incidence and prevalence of mood problems in certain IRCs, particularly anxiety and/ or depression in people with PsA and GCA, to encourage improved recognition and management.

This study has also shown the risk of anxiety alone, in addition to anxiety and/or depression to be highest at an earlier time point after diagnosis in individuals with PMR, compared to people with RA. This difference could potentially be related to the side-effects of glucocorticoid treatment. However, it highlights the need for clinicians to consider case-finding for potential mood problems at an early stage after diagnosis in people with PMR.

Overall, this study highlights the scale of mood problems in people with IRCs and the requirement to improve pathways to identify and manage comorbid mood problems, which could potentially reduce associated morbidity and mortality.

7.8 Connection to the subsequent study

I conducted this study concurrently with my systematic review, which highlighted the burden of anxiety in people with RA, justifying the need for anxiety and depression to be given equal priority. Informed by the suggestions of my PPIE group in chapter 5 (section 5.8), and taken in response to a lack of literature on mood problems, particularly anxiety, in people with PMR and GCA, I conducted this cohort study to determine the incidence and prevalence of mood problems in different IRCs.

Through this cohort study, I have determined that mood problems are more common in different IRCs, particularly PsA and GCA. However, the incidence and prevalence rates of mood problems may have been under-estimated, as I have relied on Read codes from primary care data. Individuals with IRCs may not have recognised mood symptoms or sought help within primary care. In addition, practitioners may not have identified or recorded mood problems in the electronic health records of people with IRCs presenting with mood symptoms. My qualitative study in chapter 5, highlighted the many potential barriers to the recognition of mood problems in people with RA.

Therefore, for my final study, I have used the case-finding questions to determine the proportion of people living with different IRCs who have anxiety or depression. This research has been conducted as part of the INCLUDE study, a pilot trial aiming to determine the feasibility and acceptability of a nurse-led review for people with IRCs. Drawing on my qualitative study outcomes, systematic review findings and cohort study results, in addition to the suggestions made by PPIE group members, this review has taken place within the context of a nurse-led review, based in primary care. I have aimed to determine the prevalence of mood problems in people with different IRCs participating in the INCLUDE study, through the analysis of responses to the case-finding questions for anxiety and depression within baseline questionnaires. This has helped me to clarify the potential number of unrecognised mood problems in people with IRCs, by comparing differences between the proportion of mood problems which are recognised and recorded within primary care electronic records, to the number of mood problems identified following the use of the case-finding questions, within the INCLUDE baseline questionnaires.

CHAPTER 8
INCLUDE Study

8.0 INCLUDE STUDY

8.1 Background

As described in section 2.9.1, people with RA are at an increased risk of common comorbidities, including anxiety and depression, which are often not recognised or treated, and can contribute to increased morbidity and mortality.

Nurse-led care focussed on comorbidity management for individuals with rheumatoid arthritis (RA), has been found to increase the number of interventions taken to manage related comorbidities, such as initiation of lipid-lowering therapy and medication to treat osteoporosis (Dougados et al, 2015). However, this care is often delivered by specialist rheumatology services, rather than in primary care, where clinicians have more experience in providing care for individuals with multimorbidity (Smith et al., 2012).

As discussed in section 2.9.1, the National Institute for Health and Care Excellence (NICE) quality standards for RA (QS33), recommend that clinicians should regularly reassess mood within the context of a holistic annual review (NICE, 2013c). Although the Quality and Outcomes Framework (QOF) provides an incentive for an RA annual review, the content of this is not specified, meaning important aspects could be missed. A national General Practitioner (GP) survey performed in 2015 found that primary care reviews frequently lack key elements, such as case-finding for depression (Hider et al., 2015), meaning potential opportunities for intervention are being missed.

Evidence suggests that people with other inflammatory rheumatological conditions (RCs), including ankylosing spondylitis (AS), psoriatic arthritis (PsA), polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) can also be at an increased

risk of developing comorbidities such as cardiovascular disease (CVD) (Jamnitski et al., 2013) (Hancock et al., 2012), osteoporosis (Gullick and Scott, 2011) and anxiety and depression (Meesters et al., 2014; McDonough et al., 2014; Vivekanatham et al., 2018; Li, Neogi & Jick, 2017). Literature reporting the prevalence of mood problems in IRCs is discussed within the background chapter (section 2.9.3), highlighting the lack of evidence available, particularly for PMR and GCA. Results from the cohort study (chapter 7), have provided some evidence of the links between IRCs and mood problems. Despite the increased risk of comorbidities in AS, PsA, PMR and GCA, there are no incentives within the QOF for individuals with these conditions to have an annual review. In addition, NICE guidelines for these conditions do not suggest a similar annual review to improve the identification and management of potential comorbidities.

To examine the feasibility and acceptability of a nurse led comorbidity review for these patients, a research study, INCLUDE (INtegrating and improving Care for patients with infLammatory rheUmatological DisordErs in the community: A pilot randomised controlled trial), (Hider et al., 2018) was conducted.

Within the INCLUDE study, patients with RA, AS, PsA, PMR and GCA from intervention practices, were invited to attend a nurse-led review at their registered practice. These patients were compared to those from control practices who continued to receive usual care. Individuals from control and intervention practices were sent questionnaires at baseline, 3 and 6 months to help assess the impact of the review. Within the questionnaires, multiple domains were assessed, including mood, through use of the EuroQol 5-Dimension Scale (EQ-5D), Patient Health Questionnaire (PHQ)-8 and Generalised Anxiety Disorder (GAD)-7 questions.

The review was delivered by a rheumatology specialist nurse. During their review, patients were assessed for comorbidities linked to their long-term condition (LTC), including CVD, fracture risk, anxiety and depression. Patients were offered appropriate lifestyle advice, signposted to self-management resources or advised to attend a follow-up appointment with their practice nurse (PN) or GP, for additional comorbidity management (Hider et al., 2018).

8.2 Aims and Objectives

Using data from the INCLUDE study, my aim was to determine the self-reported prevalence of anxiety and depression symptoms in people with different IRCs (RA, AS, PsA, PMR and GCA) and factors associated with self-reported mood problems.

8.3 Methods

The INCLUDE study methods are described in detail within the published protocol (Hider et al., 2018), but brief context to the study design and methods is provided below. A flow chart for the INCLUDE study, sourced from the published protocol, is displayed in figure 8.1 (p255) (Hider et al., 2018).

8.3.1 Design and setting

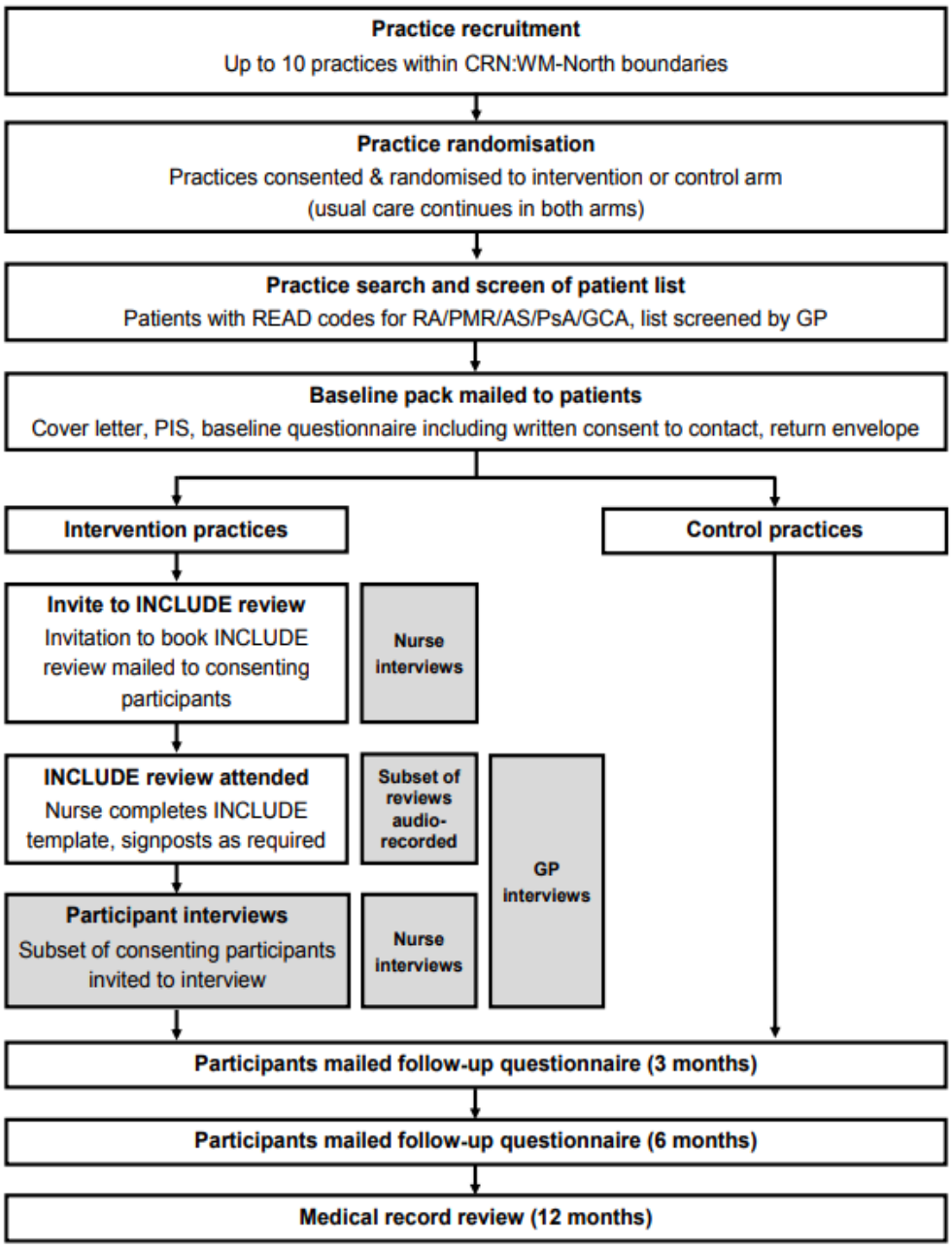
The INCLUDE study is a pilot cluster feasibility study based in primary care in the United Kingdom (UK). Within this study, the units of randomisation were participating general practices and the units of observation, adults meeting the eligibility criteria outlined in section 8.3.2.2.

8.3.2 Participants

8.3.2.1 General Practices

General practices were recruited from the West Midlands North via the National Institute for Health Research (NIHR) Clinical Research Network (CRN). Practices were eligible for inclusion if they were willing to participate and provide clinical rooms, and if they used the clinical operating system, EMIS Web (EMIS Health, 2019).

Figure 8.1- *INCLUDE study flowchart (from Hider et al., 2018).*



8.3.2.2 Eligibility criteria

People were eligible to participate if they were adults aged 18 years or older, capable of giving written consent in English and registered with a participating practice, with a Read code in their electronic record for one of the 5 IRCs of interest (RA, AS, PsA, PMR and GCA). Prior to randomisation, the lead GP for each practice excluded any nursing home residents, palliative and/or vulnerable patients (eg. severe enduring mental illness or significant cognitive impairment).

8.3.2.3 Randomisation

Randomisation to the intervention or control group was performed at the GP practice level using stratified block randomisation. Stratification was by practice size (splitting by order of highest/lowest practice sizes) and using block sizes of 2 and/or 4 within each stratum to ensure balanced clusters and individual patient numbers across study arms. All participants were sent baseline, 3 and 6 month questionaires. Patients within control practices continued to receive usual care from their GP practice, whilst eligible patients within intervention practices were invited to an INCLUDE review appointment.

8.3.2.4 Study Procedures

Eligible patients at control and intervention practices were posted a study baseline pack which included an invitation letter (appendix 22), patient information sheet (appendix 23), baseline questionnaire with consent form (appendix 24) and a prepaid return envelope. They were asked to complete and return the questionnaire and consent form. Reminder postcards were sent after 2 weeks and a reminder

invitation pack after 4 weeks. Patients who did not respond or consent at baseline were considered non-responders or decliners, and were not contacted again. In addition, patients who did not provide a date of birth to enable their age to be confirmed as 18 or over were also deemed ineligible. Participants who consented and self-reported having one of the IRCs of interest remained in the study unless they requested to be withdrawn, whilst participants who did not report having one of the conditions of interest were deemed ineligible and excluded. All consenting responders were sent further postal questionnaires at 3 and 6 months.

8.3.3 Data Collection

8.3.3.1 Questionnaire data

To retain patients' anonymity, all data was non-identifiable and stored in password-protected, encrypted files, separate from signed consent forms. Outcome measures used in the baseline questionnaire are summarised in table 8.1 (p258).

Follow-up questionnaires were sent to participants at 3 and 6 months, when further questions were included to assess healthcare utilisation and the acceptability of treatment. However, for this thesis, only the baseline data has been used.

Anxiety and depression were assessed using the GAD-7 and PHQ-8 questions (Spitzer et al., 2006; Kroenke et al., 2009). As discussed in section 2.7, the GAD-7 tool has been found to have acceptable pooled sensitivity and specificity for anxiety (Plummer et al., 2016). A meta-analysis of the PHQ-9 tool also found it to have a high negative predictive value (Mitchell et al., 2016), though its' positive predictive value was found to be 52% with a threshold score of ≥10 (Levis et al., 2019).

Table 8.1- *Assessments and outcome measures recorded in the INCLUDE baseline questionnaire.*

Assessment domain	Assessments/ outcome measures
IRC	Checklist (RA/ AS/ PsA/ PMR/ GCA)
General Health	Comorbidities checklist (Diabetes Mellitus (DM), Angina, Depression/ Anxiety, Hypertension (HTN), Myocardial Infarction (MI), Stroke, Osteoporosis)
Impact of your inflammatory condition	Numerical Rating Scales (NRS) for pain, stiffness and fatigue
	Pharmacological treatments for the IRC
General Health and Mood	EuroQol 5-Dimension Scale (EQ-5D-5L)
	Physical function (modified health assessment questionnaire (MHAQ))
	Fatigue (Functional Assessment of Chronic Illness Therapy (FACIT))
	Generalised Anxiety Disorder (GAD)-7
	Patient Health Questionnaire (PHQ)-8
Your understanding of your health condition	Patient activation measure
	Multimorbidity Treatment Burden Questionnaire
	Self-efficacy measure
Demographic/ socioeconomic factors	Demographics (date of birth, gender, ethnicity)
	Socioeconomic factors (living alone, employment, fitness to work)
Lifestyle factors	Alcohol consumption and smoking status
Measurements	Height and weight (for body mass index (BMI) calculation)

Alternatively, the Hospital Anxiety and Depression Scale (HADS) questions could have been utilised, though these have also been found to lack specificity (Poole et al., 2006), with some studies reporting a lower sensitivity for depression (Roberge et al., 2013), compared to the reported sensitivity of the PHQ-9 tool. Meanwhile, a comparison of the accuracy of PHQ-9 and HADS for diagnosing major depression in cancer patients found the PHQ-9 had the best screening performance (Hartung et al., 2017). As the PHQ tool is widely reported in the literature, use of this tool facilitated

comparison with prior research. In addition, as discussed in section 2.7, the PHQ-2 can be useful as an initial screening tool, hence this was utilised within the INCLUDE review to help identify individuals who would benefit from further exploration of mood, through use of the PHQ-9. Therefore, using the same tool within the INCLUDE questionnaires facilitated comparison of questionnaire findings with clinic outcomes.

The 9th question of the PHQ tool, "thoughts that you would be better off dead, or thoughts of hurting yourself in some way" (Kroenke, Spitzer & Williams, 2001), was not included in the INCLUDE study questionnaires, due to the potential clinical risk posed by someone disclosing suicidal ideas, which would not necessarily be acknowledged until several days later after receipt of the questionnaire through the post. However, this question was included within the INCLUDE review, when the consulting nurse had the opportunity to assess suicidal risk if required.

Other key outcome measures included health-related quality of life (EuroQol 5-Dimension Scale (EQ-5D-5L)) (Herdman et al., 2011), pain intensity (Numerical Rating Scale (NRS) 0–10), physical function (Modified Health Assessment Questionnaire (MHAQ)) (Pincus et al., 1983), fatigue (Functional Assessment of Chronic Illness Therapy (FACIT)) (Webster et al., 2003), the Patient Activation Measure (Hibbard et al., 2005), Multimorbidity Treatment Burden Questionnaire (Duncan et al., 2018) and the Self-Efficacy for Managing Chronic Disease scale (Borkovec and Nau, 1972). Patients also reported demographic, socioeconomic and lifestyle characteristics. Self-reported height and weight measurements were used to calculate body mass index (BMI). Multimorbidity, the presence of two or more comorbidities, was considered as a further outcome measure due to reported links between multimorbidity in people with IRCs and mood problems (Vancampfort et al., 2017; Read et al., 2017). However, individuals

selected for this study already had at least one morbidity (an IRC). Therefore, the presence of one or more comorbidities in addition to an IRC was included as a covariate in the analysis.

8.3.2.2 INCLUDE review data

In addition to the questionnaires mailed to all participants, consenting patients from intervention practices were invited to attend an INCLUDE review appointment at their GP practice. At the INCLUDE review, a trained study nurse conducted a holistic consultation which included case-finding for anxiety and depression (GAD-2 and PHQ-2), with full measures (GAD-7 and PHQ-9) used as appropriate. An individualised management plan was developed and a summary sheet provided to the patient at the end of the consultation. The review was recorded using an EMIS template specifically developed for the study.

8.3.4 Data analysis

For the purposes of this thesis, a descriptive analysis of the baseline questionnaire data was performed using SPSS (version 24). Patient characteristics and responses to outcome measures were summarised using means and standard deviations for continuous measures and frequencies and percentages for categorical measures. Logistic regression analysis was used to help determine factors associated with self-reporting of anxiety and depression symptoms; associations were expressed in terms of odds ratios (OR) and corresponding 95% confidence intervals (CI). Adjustments were made for covariates that had a significant unadjusted association. This was to avoid overadjustment, due to a lack of significant unadjusted associations found between covariates and mood problems.

8.3.5 Ethical Approval

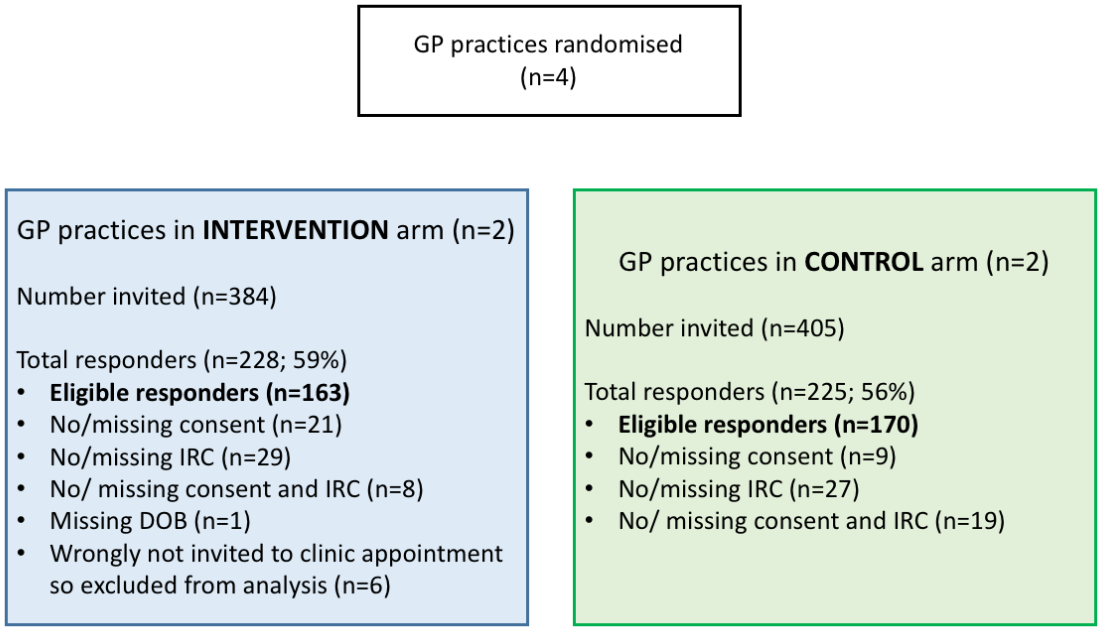
The INCLUDE study was approved by the Wales REC 5 Research Ethics Committee (REC reference 17/WA/0427). Health Research Authority approval for the study was obtained on 11 January 2018. The document confirming ethical approval for this study is in appendix 25.

8.4 Results

8.4.1 Recruitment of individuals to the INCLUDE study

Patient recruitment commenced in March 2018. As shown in figure 8.2, four GP practices were randomised to control and intervention arms. 384 individuals were invited to participate from the intervention arm, from whom there were 163 eligible responders. From 405 individuals invited to participate from the control arm there were 170 eligible responders. 333 baseline questionnaires from eligible participants were returned for analysis.

Figure 8.2- *INCLUDE participants in the intervention and control arms.*



8.4.2 Proportions with different IRCs

As shown in table 8.2, the highest proportion of individuals reported having RA (51.7%), followed by PMR (26.4%), AS (15.9%), PsA (13.8%) and GCA (5.1%). This is similar to prevalence estimates reported for different IRCs in the general population, with the prevalence of RA being approximately 0.67% (Abhishek et al., 2017), compared to lower estimates of 0.13% for AS (Dean et al., 2016), 0.22% for PsA (Egeberg et al., 2017) and 0.25% for GCA (Yates et al., 2016). Potentially more individuals with PMR would have been expected, as PMR has an estimated prevalence of 0.91-1.53% (Yates et al., 2016).

Of note, whilst 298 (89.5%) participants reported having one IRC, 35 (10.5%) participants self-reported having more than one IRC, hence the number of individuals with different IRCs when summed exceeds the overall number of participants. The most commonly observed combinations of IRCs were RA and PMR, in addition to RA and PsA.

Table 8.2- *Proportions self-reporting different IRCs within the INCLUDE baseline questionnaire*

Proportion self-reporting different IRCs in the INCLUDE baseline questionnaires	
IRC	N (%) *
Rheumatoid Arthritis	172 (51.7)
Ankylosing Spondylitis	53 (15.9)
Psoriatic Arthritis	46 (13.8)
Polymyalgia Rheumatica	88 (26.4)
Giant Cell Arteritis	17 (5.1)

N= number of individuals, IRC= inflammatory rheumatological condition

** Some participants self-reported having more than one IRC, hence the total number of individuals with different IRCs does not add up to the total number of participants (333).*

Considering the combination of RA and PsA observed, an epidemiological study has reported the prevalence of RA in people with PsA to be increased (Tsai et al., 2011). In addition, it is possible that individuals with psoriasis incorrectly self-reported having PsA, leading to the more frequent observation of PsA in combination with RA in this dataset. The literature also suggests that late-onset RA and PMR can be difficult to distinguish, as both can involve peripheral arthritis (Cutolo, Cimmino & Sulli, 2009). Furthermore, a prospective study evaluating the clinical features of people with PMR and late-onset RA with a PMR-like onset, found that 23% of individuals with PMR developed RA during the 1-year follow-up period (Caproali et al., 2001). This suggests that individuals with PMR could be more likely to develop RA over time, though it is possible that due to overlapping symptoms, individuals at an early disease stage could have been given the wrong diagnosis. To help to determine the impact of having more than one IRC, the association of one verus two or more self-reported IRCs with mood problems, has been explored by logistic regression in table 8.10 (section 8.4.7.5, p280).

8.4.3 Demographic and socio-economic factors

Table 8.3 (p265), contains a summary of population demographics and socioeconomic factors, self-reported by individuals completing the baseline questionnaire. These include the proportion living alone, the employment status of participants and their fitness to work. The age of individuals ranged from 21.8-91.9 years, with a mean of 68.2 years. Overall, 58.3% of responders were female. Reflecting gender ratios reported for different IRCs in the population, more females had RA (Abhishek et al., 2017), PMR (Crowson et al., 2011) and GCA (Dasgupta et al., 2010), whilst AS affected more males (Sieper, 2009) and PsA affected almost equal proportions

of males and females (Gladman et al., 2005). Considering ethnicity, 95.8% were white British, with similar high proportions also observed among different IRCs, reflecting the predominantly white British population living in North Staffordshire. Due to the small numbers reporting other ethnicities (Asian, Black/ African/ Caribbean, Mixed/ multiple ethnic groups) these have been grouped together under “other ethnicities”.

Only 18.6% of participants reported living alone. This compares to 28% of the national UK population who live alone, almost half of whom are aged over 65 years (Knipe, 2017). The proportion living alone was similar in different IRCs, though a higher proportion of individuals with PMR and GCA did not give a response. These were older individuals who would have been more likely to be living alone, hence this missing data, in addition to the relative minority of younger adults living with IRCs, could have contributed to the proportion of individuals living alone being lower in this dataset than in the general population.

The majority were retired (59.2%), reflecting the older mean age of the population. 4.8% reported not working due to ill health, whilst 20.4% described being employed and 2.7% reported being a housewife/ husband. From those who reported working, 74.7% were doing their usual job. However, over a quarter of those employed were doing lighter duties (3.4%), working fewer hours (16.1%) or on sick leave (5.7%).

Considering individual IRCs, the highest proportion of employed people had PsA (41.3%), whilst the highest proportion of retired people had GCA (88.2%). These groups had the youngest and oldest mean ages respectively. The highest proportion not working due to ill health had AS (5.7%). From those working, more people with RA had lighter duties at work (6.7%), or were working fewer hours (24.4%), compared to other IRCs.

Table 8.3- *Demographic factors self-reported by individuals completing the INCLUDE baseline questionnaire*

Demographic/ Socio-economic factors		**Condition**					
		All IRCs (333) *N (%)*	**RA** (172) *N (%)*	**AS** (53) *N (%)*	**PsA** (47) *N (%)*	**PMR** (88) *N (%)*	**GCA** (17) *N (%)*
Age *(years)*	Range	21.8-91.9	25.0-91.9	21.8-88.2	25.2-89.3	48.0-91.3	64.3-86.1
	Mean (SD)	68.2 (13.4)	67.6 (12.7)	67.9 (13.1)	59.2 (14.8)	75.7 (8.6)	77.9 (6.7)
Age Groups *(years)*	18-50	39 (11.7)	17 (9.9)	6 (11.3)	15 (31.9)	1 (1.1)	0 (0)
	51-65	83 (24.9)	49 (28.5)	10 (18.9)	13 (27.7)	14 (15.9)	2 (11.8)
	66-75	109 (32.7)	61 (35.5)	24 (45.3)	14 (29.8)	25 (28.4)	5 (29.4)
	76-95	102 (30.7)	45 (26.1)	13 (24.5)	5 (10.6)	48 (54.6)	10 (58.8)
Gender *N (%)*	Female	194 (58.3)	111 (64.5)	24 (45.3)	24 (52.2)	53 (60.2)	10 (58.8)
	Unknown/ ambiguous	8 (2.4)	5 (2.9)	1 (1.9)	1 (2.1)	2 (2.3)	0 (0)
Ethnicity *N (%)*	White	320 (95.8)	163 (94.8)	52 (98.1)	46 (97.9)	85 (96.6)	16 (94. 1)
	Other ethnicities	11 (3.3)	6 (3.5)	1 (1.9)	0 (0)	3 (3.4)	1 (5.9)
	Unknown/ ambiguous	3 (0.9)	3 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)
Living alone *N (%)*	Yes	62 (18.6)	30 (17.5)	8 (15.1)	8 (17.4)	16 (18.2)	3 (17.6)
	No	212 (63.7)	111 (64.5)	39 (73.6)	30 (65.2)	46 (52.3)	9 (52.9)
	Unknown/ ambiguous	59 (17.7)	31 (18.0)	6 (11.3)	8 (17.4)	26 (29.5)	5 (29.5)
Employment Status *N (%)*	Employed	68 (20.4)	36 (20.9)	9 (17.0)	19 (41.3)	9 (6.8)	0 (0)
	Retired	197 (59.2)	98 (57.0)	34 (64.2)	18 (39.1)	67 (76.2)	15 (88.2)
	Not working due to ill health	16 (4.8)	9 (5.2)	3 (5.7)	2 (4.3)	3 (3.4)	0 (0)
	Housewife/ husband	9 (2.7)	6 (3.5)	0 (0)	0 (0)	3 (3.4)	0 (0)
	Unemployed/ seeking work	14 (4.2)	6 (3.5)	3 (5.7)	2 (4.3)	3 (3.4)	0 (0)
	Unknown/ ambiguous	29 (8.7)	17 (9.9)	4 (7.5)	5 (10.9)	6 (6.8)	2 (11.8)
Fitness to work (if working) *N (%)*	Doing usual job	65 (74.7)	28 (62.3)	9 (75.0)	20 (87.0)	8 (88.9)	0 (0)
	Lighter duties	3 (3.4)	3 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)
	Sick leave	5 (5.7)	3 (6.6)	1 (8.3)	0 (0)	1 (11.1)	0 (0)
	Working fewer hours	14 (16.1)	11 (24.4)	2 (16.7)	3 (13.0)	0 (0)	0 (0)

N= Number of individuals, SD= Standard deviation

8.4.4 Lifestyle factors

Lifestyle factors, including smoking history, alcohol consumption and BMI are reported in table 8.4, (p268). Considering smoking history, the majority of individuals completing the INCLUDE baseline questionnaire had never smoked (46.5%), whilst 42.3% were ex-smokers. Only 6.9% of individuals reported being a current smoker. The proportion of current smokers was highest in people with RA (12.2%) whilst the proportion of ex-smokers was highest in people with PMR (43.2%) and GCA (47.1%). These groups had the highest mean age, potentially indicating that they quit smoking after health campaigns highlighted the negative impact of smoking.

47.7% of people with IRCs reported regularly consuming alcohol, whilst 12.3% had never consumed alcohol and 23.4% reported only consuming alcohol on special occasions. Compared to other IRCs, more people with AS (56.6%) and PsA (58.7%) reported that they regularly consumed alcohol (≥ once per week), potentially reflecting their younger mean age. Alcohol consumption could have been comparatively lower in people with RA (43.6%) due to more individuals with this condition taking medication that would potentially be affected by alcohol consumption.

BMI was calculated using self-reported weight and height (weight in kilograms/ (height in centimetres)^2) (NHS, 2018). BMI ranged between 17.4-47.6, with a mean of 28.6, indicating that the average individual completing the INCLUDE baseline questionnaire was overweight. 27.3% of individuals with IRCs were obese (BMI ≥30). Considering different IRCs, obesity was least frequent in people with AS (15.1%), though more frequent in people with RA (31.4%), compared to other IRCs.

8.4.5 Comorbidities

Self-reported comorbidities are summarised in table 8.4 (p269). More than two thirds of individuals who completed the baseline questionnaire (68.4%), reported having at least one comorbidity from a prespecified morbidity checklist, in addition to their IRC, indicating multimorbidity. Multimorbidity was most frequent in people with GCA (82.3%) and least frequent in people with PsA (56.5%), compared to other IRCs. It is likely that age contributed to these trends, as people with GCA had the highest mean age (77.9 years) and PsA the lowest (59.2 years), and multimorbidity is associated with ageing (Barnett et al., 2012).

The commonest self-reported comorbidity was hypertension (46.4%), followed by anxiety or depression (21.3%), diabetes (15.6%) and osteoporosis (11.1%). The proportion with hypertension was highest in RA (50.6%), whilst anxiety or depression was most frequent amongst individuals with PsA (37%). Interestingly, no individuals with GCA self-reported a history of anxiety or depression, whilst fewer people with PMR (14.8%) reported a history of mood problems, compared to other IRCs. More individuals with AS had diabetes (28.3%) compared to other IRCs, whilst osteoporosis was most frequent in people with PMR (23.9%) and GCA (23.5%), potentially due to individuals with these conditions being older or due to these conditions being treated with glucocorticoids which can reduce bone density. It could be argued that the frequency of osteoporosis in people with PMR and GCA should be lower, as guidelines suggest that individuals with these conditions, who are at high risk of osteoporosis, should be on bone protection. However, is possible that individuals who self-reported having osteoporosis, did so due to being on treatment for this.

Table 8.4- *Lifestyle factors and comorbidities self-reported by individuals completing the INCLUDE baseline questionnaire*

Lifestyle Factors			**Condition**					
			All IRCs (333)	**RA** (172)	**AS** (53)	**PsA** (47)	**PMR** (88)	**GCA** (17)
Smoking Status *N (%)*	Current smoker		23 (6.9)	21 (12.2)	6 (11.3)	3 (6.5)	5 (5.7)	0 (0)
	Never smoked		155 (46.5)	71 (41.3)	27 (50.9)	21 (45.7)	41 (46.6)	9 (52.9)
	Previously smoked		141 (42.3)	27 (15.7)	20 (37.8)	19 (41.3)	38 (43.2)	8 (47.1)
	Unknown/ ambiguous		14 (4.2)	41 (23.8)	0 (0)	3 (6.5)	4 (4.5)	0 (0)
Alcohol *(How often do you drink alcohol?) N (%)*	Regularly (≥ once a week)		106 (47.7)	75 (43.6)	30 (56.6)	27 (58.7)	44 (50.0)	8 (54.4)
	1 to 3 times a month		41 (12.3)	22 (12.8)	4 (7.5)	6 (13.0)	10 (11.4)	3 (17.6)
	Special occasions only		78 (23.4)	41 (23.8)	12 (22.7)	7 (15.2)	19 (21.6)	5 (29.4)
	Never		41 (12.3)	26 (15.1)	6 (11.3)	5 (10.9)	11 (12.5)	1 (5.9)
	Unknown/ ambiguous		14 (4.2)	8 (4.7)	1 (1.9)	1 (2.2)	4 (4.5)	0 (0)
BMI	Mean (SD)		28.6 (5.0)	29.2 (5.0)	28.7 (5.0)	28.5 (5.0)	28.5 (4.9)	28.9 (4.0)
	Range		17.4-47.6	19.0-42.6	19.2-41.6	19.2-41.6	17.4-47.6	21.7-37.7
	Proportion under/ over-weight or obese *N (%)*	Underweight (<18.5)	3 (0.9)	0 (0)	0 (0)	0 (0)	3 (3.4)	0 (0)
		Normal (18.5-24.9)	70 (21.0)	23 (13.4)	16 (30.2)	10 (21.4)	18 (20.5)	3 (17.6)
		Overweight (25-29.9)	108 (32.4)	58 (33.7)	18 (34.0)	12 (25.5)	22 (25.0)	6 (35.3)
		Obese ≥30	91 (27.3)	54 (31.4)	8 (15.1)	13 (27.7)	24 (27.3)	6 (17.6)
	Unknown/ ambiguous *N (%)*		68 (20.4)	35 (20.3)	11 (20.8)	11 (23.9)	19 (21.6)	2 (11.8)
Comorbidities *N (%)*	Diabetes Mellitus (DM)		52 (15.6)	28 (16.3)	15 (28.3)	9 (19.6)	12 (13.6)	2 (11.8)
	Angina		24 (7.2)	12 (7.0)	4 (7.5)	4 (8.7)	6 (6.8)	4 (23.5)
	Depression/ anxiety		70 (21.3)	40 (23.3)	13 (24.5)	17 (37.0)	13 (14.8)	0 (0)
	Hypertension (HTN)		154 (46.2)	87 (50.6)	24 (45.3)	17 (37.0)	42 (47.7)	8 (47.1)
	Myocardial infarction (MI)		25 (7.5)	17 (9.8)	4 (7.5)	3 (6.5)	7 (8.0)	2 (11.8)
	Stroke		18 (5.4)	13 (7.6)	3 (5.7)	2 (4.3)	3 (3.4)	0 (0)
	Osteoporosis		37 (11.1)	25 (14.5)	6 (11.3)	5 (10.9)	15 (17.0)	4 (23.5)
	Unknown/ ambiguous		94 (28.2)	42 (24.4)	11 (20.8)	20 (43.5)	21 (23.9)	3 (17.6)
One or more comorbidities in addition to an IRC* *N (%)*			228 (68.4)	126 (73.3)	39 (73.5)	26 (56.5)	61 (69.4)	14 (82.3)

*N= number of individuals, BMI= Body Mass Index *Number of comorbidities (self-reported history of DM, angina, depression/ anxiety, HTN, MI, stroke and osteoporosis).*

8.4.6 Pain, stiffness and fatigue

8.4.6.1 Pain, stiffness and fatigue reported using a numerical rating scale

To help understand the daily burden of symptoms related to an individuals' IRC, participants were asked to report their current pain, stiffness and fatigue in relation to their condition. On a NRS of 0-10 where 0 is none and 10 is the worst, the mean reported pain score was 4.9, whilst the mean score for stiffness was 5.0 and for fatigue, 5.2. This would suggest that on average, participants had moderate pain, stiffness and in particular, fatigue.

As shown in table 8.5 (p270), the highest mean pain (5.5) and fatigue (5.8) scores were in people with RA, whilst the highest mean scores for stiffness were amongst individuals with AS (5.7) and RA (5.6). All scores were lowest in people with GCA, suggesting treatments are potentially more effective for GCA, resulting in a lower symptom burden in prevalent cases.

8.4.6.2 Fatigue reported using the FACIT questionnaire

The FACIT score is reported on a scale of 0-52, with higher scores indicating less fatigue. The mean FACIT score for individuals completing the INCLUDE baseline questionnaire was 33.2. Scores were lowest amongst individuals with RA (31.7 (standard deviation (SD) 11.6), AS (31.7, SD (12.2)) and PsA (31.3, SD (12.0)), indicating greater fatigue than in individuals with PMR (34.5, SD (11.4)) and GCA (34.7, SD (13.9)). The range of FACIT scores included lower values in people with RA (range 1-51) compared to other IRCs (range 6-52), suggesting this group included individuals with the worst fatigue. This would be consistent with results from the NRS for fatigue, which are reported with the FACIT scores in table 8.5 (p270).

Table 8.5- *Pain, stiffness and fatigue reported by individuals with different IRCs completing the INCLUDE baseline questionnaire.*

Pain, Stiffness and Fatigue Scores			**Condition**					
			All IRCs (333)	**RA** (172)	**AS** (53)	**PsA** (47)	**PMR** (88)	**GCA** (17)
Numerical Rating Scale [1]	Pain Score	*Mean (SD)*	4.9 (2.6)	5.5 (2.5)	5.1 (2.9)	4.9 (2.7)	4.4 (2.8)	3.2 (3.2)
		Range	0-10	0-10	0-10	0-9	0-10	0-9
	Stiffness Score	*Mean (SD)*	5.0 (2.6)	5.6 (2.4)	5.7 (2.6)	5.1 (2.6)	4.3 (2.7)	3.3 (3.1)
		Range	0-10	0-10	0-10	0-9	0-10	0-8
	Fatigue	*Mean (SD)*	5.2 (2.7)	5.8 (2.6)	5.5 (2.5)	5.6 (3.0)	4.6 (2.7)	3.8 (3.0)
		Range	0-10	0-10	0-10	0-9	0-10	0-8
FACIT Score [2]	Mean (SD)		33.2 (11.6)	31.7 (11.6)	31.7 (12.2)	31.3 (12.0)	34.5 (11.4)	34.7 (13.9)
	Range		1-52	1-51	6-51	8-52	8-52	8-52

SD= standard deviation

[1] *The Numerical Rating Scale is a 0-10 scale where 0 is "no pain, stiffness or fatigue" and 10 is "pain, stiffness or fatigue as bad as could be".*

[2] *The FACIT Score is a 0-52 scale where a higher score indicates less fatigue.*

8.4.7 Anxiety and Depression

8.4.7.1 Responses to PHQ-8 score for depression

Table 8.6 (p272), shows the overall responses to the PHQ-8 questions. The most frequently reported symptoms were "trouble falling or staying asleep, or sleeping too much" and "feeling tired or having little energy". These symptoms could reflect depression, but could also represent symptoms directly related to the underlying IRC, such as fatigue and pain related to the inflammatory process disrupting sleep. As shown in table 8.7 (p273), the mean score on PHQ-8 for depression, (where 5-9 indicates mild depression, 10-14 moderate, 15-19 moderately severe and 20-24 severe depression) (Kroenke et al., 2009), was 5.8. Mean scores were highest in GCA (6.5) and AS (6.3) and

lowest in RA (5.1). Median scores were lower, at 4 for all IRCs, implying that distribution of scores were skewed to the right.

The literature suggests a cut off score of ≥10 should be used to indicate depression, (Kroenke et al., 2009; Levis et al., 2019). The proportion of individuals meeting this threshold, who had moderate, moderately severe or severe symptoms of depression, was 21.5%. The highest proportions with moderate to severe depression had GCA (33.4%) and PMR (30.2%), whilst the proportion with depression was lowest in people with RA (18.3%). A notable proportion of people with AS (26.0%) and PsA (28.2%) also reported moderate to severe symptoms of depression.

8.4.7.2 Responses to GAD-7 score for anxiety

Table 8.6 (p272), shows the overall responses to the GAD-7 questions. The most frequently reported symptoms were "worrying too much about different things", "trouble relaxing" and "becoming easily annoyed or irritable". Table 8.7 (p273), shows the total and mean scores for GAD-7. The overall mean score for individuals completing the GAD-7 score for anxiety, (where 5-9 indicates mild symptoms, 10-14 moderate and >15 severe symptoms) (Spitzer et al., 2006) was 4.67. The highest mean GAD-7 scores were in individuals with PsA (5.63) and RA (5.44). Median scores were lower, between 2-4, implying that the distribution of scores was skewed to the right.

The literature suggests a cut off score of ≥10 should be used to indicate anxiety (Spitzer et al., 2006; Plummer et al., 2016). The proportion of individuals meeting this threshold who had moderate or severe symptoms of anxiety was 17.4%. The highest proportion with moderate or severe anxiety scores had PsA (23.9%) whilst the lowest proportion had PMR (10.3%). A notable proportion of people with RA (21.0%), AS (23.5%) and GCA (17.7%), also reported moderate or severe anxiety symptoms.

Table 8.6- *Overall responses to the PHQ-8 and GAD-7 questions.*

Mood problem	Over the past 2 weeks, how often have you been bothered by the following problems?	Number (%)				
		Not at all	Several days	> half the days	Nearly every day	Missing/ ambiguous
Depression (PHQ-8 questions) [1]	Little interest or pleasure in doing things	178 (53.3)	106 (31.7)	28 (8.4)	14 (4.2)	8 (2.4)
	Feeling down, depressed or hopeless	191 (57.2)	91 (27.2)	31 (9.3)	14 (4.2)	7 (2.1)
	Trouble falling or staying asleep, or sleeping too much	113 (33.8)	98 (29.3)	56 (16.8)	61 (18.3)	6 (1.8)
	Feeling tired or having little energy	69 (20.7)	149 (44.6)	52 (15.6)	58 (17.4)	6 (1.8)
	Poor appetite or overeating	192 (57.5)	70 (21.0)	36 (10.8)	29 (8.7)	7 (2.1)
	Feeling bad about yourself or that you are a failure or have let yourself or your family down	214 (64.1)	72 (21.6)	16 (4.8)	24 (7.2)	8 (2.4)
	Trouble concentrating on things, such as reading the newspaper or watching television	223 (66.8)	63 (18.9)	26 (7.8)	15 (4.5)	7 (2.1)
	Moving or speaking so slowly that other people could have noticed, or moving around a lot more than usual	249 (74.6)	51 (15.3)	22 (6.6)	4 (1.2)	8 (2.4)
Anxiety (GAD-7 questions) [2]	Feel nervous, anxious or on edge	169 (50.8)	110 (33.0)	29 (8.7)	16 (4.8)	9 (2.7)
	Not being able to stop or control worrying	177 (53.2)	101 (30.3)	23 (6.9)	21 (6.3)	11 (3.3)
	Worrying too much about different things	143 (42.6)	127 (38.1)	36 (10.8)	22 (6.6)	6 (1.8)
	Trouble relaxing	153 (45.9)	112 (33.6)	34 (10.2)	26 (7.8)	8 (2.4)
	Being so restless that its hard to sit still	217 (65.2)	74 (22.2)	23 (6.9)	10 (3.0)	9 (2.7)
	Becoming easily annoyed or irritable	136 (40.8)	127 (38.1)	37 (11.1)	25 (7.5)	8 (2.4)
	Feeling afraid as if something awful might happen	216 (64.9)	64 (19.2)	28 (8.4)	17 (5.1)	8 (2.4)

[1] *PHQ-8 questions (Spitzer et al., 2006).* [2] *GAD-7 questions (Kroenke et al. 2009).*

Table 8.7- *Total, mean and median PHQ-8 and GAD-7 scores.*

Depression and Anxiety Severity			Condition					
			All IRCs	RA	AS	PsA	PMR	GCA
Depression [1] (From 317 completed PHQ-8 Scores)	**Depression Severity** *Number (%)*	Minimal Depression (0-4)	167 (52.7)	97 (59.1)	23 (46.0)	21 (45.7)	42 (50.6)	7 (46.6)
		Mild Depression (5-9)	82 (25.9)	37 (22.6)	14 (28.0)	12 (26.1)	25 (30.1)	3 (20.0)
		Moderate Depression (10-14)	38 (12.0)	16 (19.8)	8 (16.0)	10 (21.7)	8 (15.1)	4 (26.7)
		Moderately Severe Depression (15-19)	20 (6.3)	9 (5.5)	2 (4.0)	3 (6.5)	6 (11.3)	1 (6.7)
		Severe Depression (20-24)	10 (3.2)	5 (3.0)	3 (6.0)	0 (0)	2 (3.8)	0 (0)
	Mean PHQ-8 Score (SD)		5.8 (5.5)	5.1 (5.4)	6.3 (5.8)	6.2 (4.7)	5.8 (5.5)	6.5 (6.8)
	Median PHQ-8 Score (IQR)		4 (6)	4 (7)	4 (7)	4 (7)	4 (8)	4 (7)
Anxiety [2] (From 315 completed GAD-7 scores)	**Anxiety Severity** *Number (%)*	Minimal Anxiety (0-4)	176 (55.7)	77 (47.5)	26 (51.0)	21 (45.7)	55 (62.5)	10 (58.8)
		Mild Anxiety (5-9)	85 (26.9)	51 (31.5)	13 (25.5)	14 (30.4)	19 (21.6)	4 (23.5)
		Moderate Anxiety (10-14)	39 (12.3)	23 (14.2)	9 (17.6)	8 (17.4)	7 (8.0)	2 (11.8)
		Severe Anxiety (15-21)	16 (5.1)	11 (6.8)	3 (5.9)	3 (6.5)	2 (2.3)	1 (5.9)
	Mean GAD-7 Score (SD)		4.7 (4.8)	5.4 (5.0)	5.2 (5.2)	5.6 (5.0)	3.4 (3.9)	4.3 (4.7)
	Median GAD-7 Score (IQR)		3 (7)	2 (6)	3 (7)	3 (7)	4 (7)	3 (7)

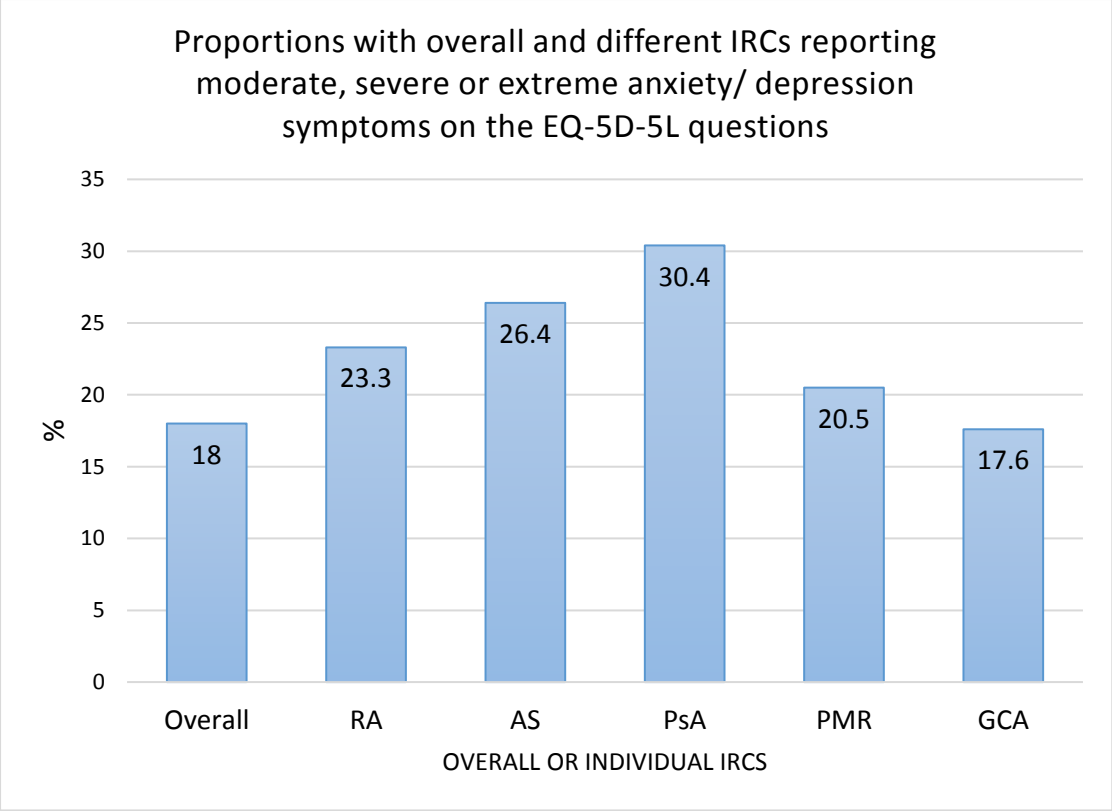
SD= standard deviation, IQR= interquartile range

[1] PHQ-8 score (Spitzer et al., 2006). [2] GAD-7 score (Kroenke et al., 2009).

8.7.3 Responses to EQ-5D-5L anxiety/ depression questions

As reported in table 8.8 (p275), 17.1% of people with IRCs responding to the EQ-5D-5L anxiety/ depression questions reported moderate symptoms, 2.1% severe and 0.3% extreme symptoms of anxiety or depression. Meanwhile, 33.6% reported slight symptoms and 44.7% no symptoms of anxiety or depression. 2.1% gave no or more than one response. Considering individual IRCs, 23.3% of people with RA reported moderate, severe or extreme anxiety or depression, compared to 26.4% with AS, 30.4% with PsA, 20.4% with PMR and 17.6% with GCA. Therefore, self-reported symptoms of anxiety and/or depression were highest amongst individuals with AS and PsA. These results are displayed graphically in figure 8.3 below.

Figure 8.3- *The proportions with IRCs who self-reported moderate, severe or extreme symptoms of anxiety or depression, according to the EQ-5D-5L questions.*



IRC= Inflammatory rheumatological condition, RA= rheumatoid arthritis, AS= ankylosing spondylitis, PsA= psoriatic arthritis, PMR= polymyalgia rheumatica, GCA= giant cell arteritis.

Table 8.8- *Responses to the EQ-5D-5L anxiety and depression questions in overall and different IRCs.*

Responses to the EQ-5D-5L questions [1]		**Condition** [2]					
		All IRCs (n=333)	**RA** (n=172)	**AS** (n=53)	**PsA** (n=46)	**PMR** (n=88)	**GCA** (n=17)
Severity of mood symptoms *Number of individuals (%)*	I am *not* anxious or depressed	149 (44.7)	67 (38.7)	22 (41.5)	15 (32.6)	48 (54.5)	11 (64.7)
	I am *slightly* anxious or depressed	112 (33.6)	65 (37.8)	17 (32.1)	17 (36.9)	20 (22.7)	3 (17.6)
	I am *moderately* anxious or depressed	57 (17.1)	29 (16.9)	13 (24.5)	12 (26.1)	18 (20.5)	3 (17.6)
	I am *severely* anxious or depressed	7 (2.1)	6 (3.5)	1 (1.9)	0 (0)	0 (0)	0 (0)
	I am *extremely* anxious or depressed	1 (0.3)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
	No/ more than one response	7 (2.1)	4 (2.3)	0 (0)	2 (4.3)	2 (2.3)	0 (0)
Proportion with moderate, severe or extreme anxiety or depression *N (%)*		60 (18.0)	40 (23.3)	14 (26.4)	14 (30.4)	20 (20.5)	3 (17.6)

n= number of individuals

[1] EQ-5D-5L (Herdman et al., 2011).

[2] Some participants reported having more than one IRC, hence the total number of individuals with different IRCs does not add up to the total number of participants (333).

8.4.7.4 Comparison of PHQ-8, GAD-7 and EQ-5D-5L anxiety and depression responses

In table 8.9 the proportions with mild, moderate and severe mood problems according to the EQ-5D-5L, GAD-7 and PHQ-8 scores are compared, then displayed as a bar chart in figure 8.4 (p277). The comparison includes 295 individuals who completed responses to all three sets of questions.

Table 8.9- *Comparison of anxiety and depression severity according to the EQ-5D, GAD-7 and PHQ-8 scores.*

Comparison of symptom severity according to different anxiety/ depression scales *(295 individuals who completed the EQ-5D-5L, GAD-7 and PHQ-8 questions)*				
Anxiety and/or depression scale	**Symptom Severity** (number/ %)			
	No/ minimal symptoms	**Mild symptoms**	**Moderate symptoms**	**Severe symptoms**
EQ-5D-5L [1]	141 (47.8)	94 (31.9)	52 (17.6)	8 (2.7)
GAD-7 [2]	168 (56.9)	77 (26.1)	34 (11.5)	16 (5.4)
PHQ-8 [3]	155 (52.5)	78 (26.4)	36 (12.2)	26 (8.9)

[1] No/minimal symptoms= "I am not anxious or depressed", mild symptoms= "I am slightly anxious or depressed", moderate symptoms= "I am moderately anxious or depressed", severe symptoms= "I am severely anxious or depressed" or "I am extremely anxious or depressed".

[2] No/minimal symptoms=0-4, mild symptoms=5-9, moderate symptoms=10-14, severe symptoms=15-21.

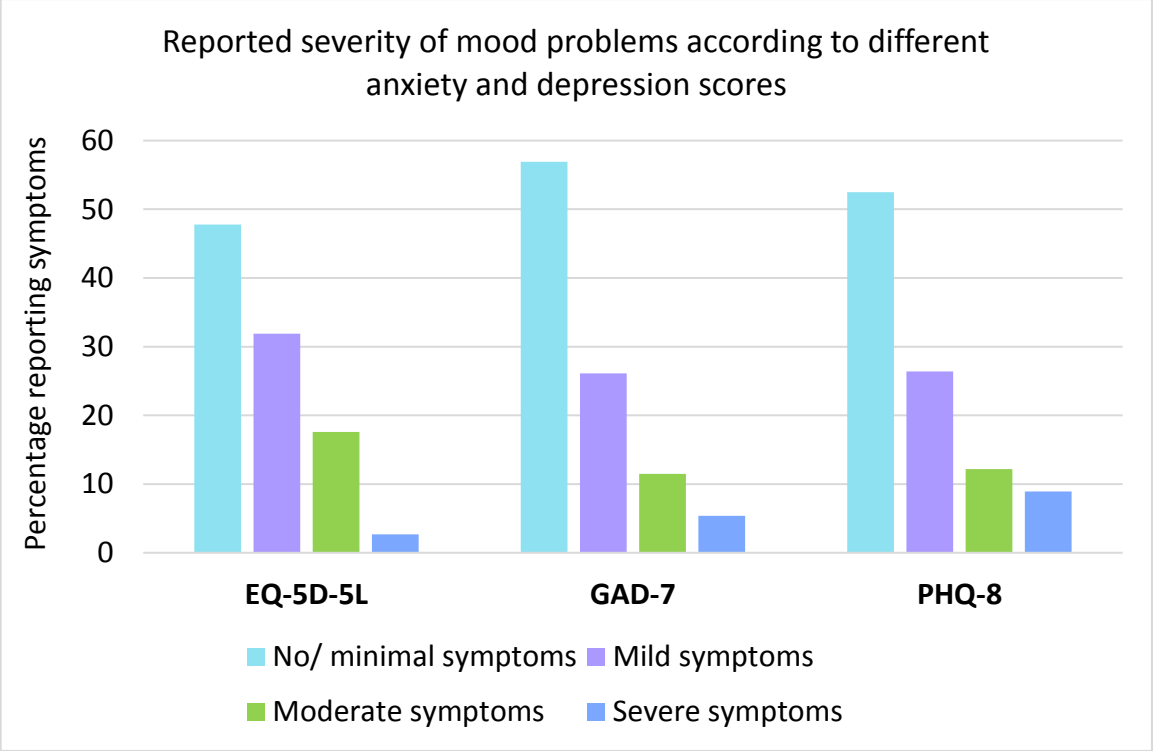
[3] No/minimal symptoms=0-4, mild symptoms=5-9, moderate symptoms=10-14, severe symptoms=15-24.

When comparing different anxiety/ depression scales, the proportion with moderate to severe mood symptoms was 20.3% for the EQ-5D-5L, 16.9% for GAD-7, and 21.1% for the PHQ-8. This suggests that depression (PHQ-8) was more frequent than anxiety (GAD-7) in people with IRCs. As the EQ-5D-5L assesses for anxiety and depression, it is interesting that the proportion with moderate to severe symptoms was lower on comparison to the PHQ-8, which assesses for depression alone. However, more

individuals reported mild mood symptoms when assessed using the EQ-5D-5L, compared to GAD-7 or PHQ-8. This would suggest that the EQ-5D-5L potentially has a higher threshold for moderate to severe mood symptoms, compared to the GAD-7 and PHQ-8 questions.

Within the INCLUDE baseline questionnaire, when participants were asked about their existing comorbidities, 21% self-reported a history of anxiety or depression (table 8.4). This is marginally higher than the proportion with moderate and severe symptoms of mood problems when assessed using EQ-5D-5L (20.3%) and GAD-7 (16.9%) scales, and similar to the proportion with moderate to severe depression when assessed using the the PHQ-8 (21.1%) questions. It is possible that individuals perceived milder symptoms to indicate a mood problem. If mild symptoms of anxiety and/ or depression are taken into account, the proportion with anxiety and depression is much higher; EQ-5D-5L (52.7%), GAD-7 (44.3%) and PHQ-8 (47.3%).

Figure 8.4- *Severity of mood problems according to different scores.*



8.4.7.5 Covariates associated with reporting of moderate or severe anxiety and depression

In table 8.10 (p280), the association between different covariates (demographic and lifestyle factors, comorbidities, IRC symptom severity, number of IRCs, number of comorbidities) and depression (PHQ-8 ≥10) and anxiety (GAD-7 ≥10) are reported.

Significant associations were found between pain (adjusted OR (95% CI) = 1.17 (10.4, 1.31)), stiffness (adjusted OR (95% CI) = 1.22 (1.08, 1.37)) and depression. One or more comorbidities in addition to an IRC, were associated with depression, though this association was not statistically significant (adjusted OR (95% CI) = 1.65 (0.96, 2.84)).

The odds of anxiety were slightly increased in people with one or more comorbidities, in addition to their IRC (adjusted OR (95% CI) = 1.14 (0.27, 1.98)). Significant unadjusted associations were also found between obesity, a self-reported history of anxiety and/ or depression, increased IRC symptom severity (higher NRS scores for pain, stiffness and fatigue, and reduced FACIT scores) and anxiety. However, after adjustment, the only remaining significant associations were between increased fatigue and anxiety (NRS fatigue and anxiety, OR (95% CI) = 1.24 (1.03, 1.44)) (FACIT score and anxiety OR (95% CI) = 0.87 (0.81, 0.94)).

No significant associations were noted between age, gender, living alone, smoking, regularly consuming alcohol, comorbidities and anxiety or depression. However, the odds of being aged 51-65 years and having depression, or being 18-65 years old and having anxiety, were increased. Smoking was also associated with increased adjusted odds of anxiety or depression, whilst regular alcohol consumption was associated with anxiety, though these associations were not significant. Of note, in people with more than one IRC, the adjusted odds of mood problems, particularly

anxiety (OR (95% CI) = 1.81 (0.26, 3.87)) were increased, though this difference was not statistically significant.

Further analysis of the association between covariates and mood problems in RA was performed, to determine if there were any significant differences compared to the associations found between covariates and mood problems in overall IRCs. There were too few individuals with AS, PsA, PMR or GCA, to accurately determine statistical associations. The results have been reported in appendix 26, as they were similar to overall IRCs. A statistically significant adjusted association was found between increased NRS scores for pain (OR (95% CI) = 1.22 (1.02, 1.46)) and stiffness (OR (95% CI) = 1.42 (1.15, 1.75)), and depression, as observed in overall IRCs. Significant unadjusted associations were found between pain, stiffness, fatigue and anxiety, though after adjustment, these associations all became non-significant. However, a significant adjusted association was found between lower FACIT scores, indicating worse fatigue, and anxiety in people with RA (OR (95% CI) = 0.89 (0.84, 0.94)), as observed in overall IRCs.

Table 8.10- *Association between covariates and moderate to severe anxiety and depression in individuals with IRCs.*

Covariate		Moderate to severe depression (PHQ-8 score≥10)		Moderate to severe anxiety (GAD-7 score ≥10)	
		Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Unadjusted OR (95% CI)	Adjusted OR (95% CI) *
Age Groups	18-50 years	0.95 (0.48, 1.86) p=0.88	0.39 (0.23, 0.69) p<0.01	1.85 (0.84, 4.07) p=0.62	1.91 (0.13, 6.32) p=0.92
	51-65 years	1.43 (0.86, 2.39) p=0.17	1.70 (0.89, 3.26) p=0.11	1.10 (0.57, 2.12) p=0.77	1.98 (0.62, 6.38) p=0.25
	66-75 years	0.96 (0.60, 1.55) p=0.87	1.03 (0.58, 1.84) p=0.91	1.08 (0.59, 2.00) p=0.81	0.84 (0.29, 2.48) p=0.76
	76-95 years	0.78 (0.48, 1.25) p=0.30	0.75 (0.42, 1.32) p=0.32	0.56 (0.28, 1.15) p=0.11	0.60 (0.17, 2.20) p=0.45
Female gender		0.95 (0.60, 1.50) p=0.82	1.09 (0.61, 1.93) p=0.78	1.92 (1.01, 3.65) p=0.05	2.46 (0.75, 8.12) p=0.14
Living alone		0.58 (0.32, 1.06) p=0.08	0.93 (0.45, 1.94) p=0.85	0.71 (0.31, 1.63) p=0.42	0.79 (0.23, 2.76) p=0.71
Current smoker		1.28 (0.53, 3.10) p=0.60	1.42 (0.48, 4.23) p=0.53	1.98 (0.73, 5.32) p=0.18	1.18 (0.01, 2.96) p=0.23
Regular alcohol consumption ≥ weekly		1.21 (0.77 1.90) p=0.41	1.01 (0.57, 1.78) p=0.98	0.65 (0.35, 1.19) p=0.16	1.44 (0.41, 5.01) p=0.57
Obesity (BMI ≥30)		0.70 (0.41, 1.18) p=0.18	1.28 (0.66, 2.51) p=0.47	**2.01 (1.03, 3.94) p=0.04**	1.91 (0.31, 2.70) p=0.08
≥1 comorbidities in addition to an IRC		1.08 (0.67, 1.73) p=0.76	1.65 (0.96, 2.84) p=0.06	1.46 (0.76, 2.83), p=0.26	1.14 (0.27, 1.98) p=0.36
Diabetes		0.78 (0.42, 1.43) p=0.41	1.14 (0.56, 2.31) p=0.73	1.64 (0.79, 3.39) p=0.18	1.34 (0.09, 1.34) p=0.12
Cardiovascular Disease [1]		0.81 (0.59, 1.10) p=0.17	0.89 (0.57, 1.42) p=0.63	1.10 (0.75, 1.62) p=0.62	1.07 (0.38, 2.98) p-0.90
Osteoporosis		0.77 (0.38, 1.56) p=0.47	0.92 (0.43, 1.95) p=0.83	1.70 (0.75, 3.84) p=0.21	1.37 (0.38, 4.87) p=0.63
Anxiety/ depression		0.71 (0.41, 1.21) p=0.21	0.82 (0.44, 1.51) p=0.52	**3.63 (1.94, 6.83) p<0.01**	1.98 (0.67, 5.89) p=0.22
≥2 IRCs		0.87 (0.42, 1.77) p=0.69	1.23 (0.55, 2.77) p=0.62	2.10 (0.94, 4.67) p=0.07	1.81 (0.26, 3.87) p=0.99
Pain Score		**1.25 (1.02, 1.54) p<0.01**	**1.17 (1.04, 1.31) p<0.01**	**1.30 (1.14, 147) p<0.01**	1.19 (0.85, 1.66) p=0.32
Stiffness Score		**1.26 (1.01, 1.56) p<0.01**	**1.22 (1.08, 1.37) p<0.01**	**1.25 (1.11, 1.42) p<0.01**	1.01 (0.73, 1.40) p=0.94
Fatigue Score		1.00 (0.92, 1.08) p=0.95	1.07 (0.96, 1.20) p=0.22	**1.30 (1.14, 1.49) p<0.01**	**1.24 (1.03, 1.44) p=0.02**
FACIT score		1.01 (0.99, 1.03) p=0.48	0.99 (0.97, 1.02) p=0.58	**0.89 (0.86, 0.92) p<0.01**	**0.87 (0.81, 0.94) p<0.01**

OR= odds ratio, CI=confidence interval, BMI= Body Mass Index. [1] Cardiovascular disease= stroke, angina, myocardial infarction and hypertension
* Adjustments made for significant unadjusted associations. Bold entries statistically significant.

8.5 Discussion

8.5.1 Summary of findings

Analysis of the INCLUDE baseline questionnaires revealed that the burden of comorbidity was high in people with IRCs. A history of anxiety and/ or depression was self-reported by 21.3% of individuals with IRCs, being most frequent in people with PsA (37.0%) and AS (24.5%), and least frequent in people with PMR (14.8%) and GCA (0.0%).

On the EQ-5D-5L questions, 19.5% of individuals with IRCs reported moderate, severe or extreme symptoms of anxiety and/ or depression, which is slightly less than those self-reporting a history of comorbid mood problems (21.3%). However, 33.6% also reported mild anxiety and/ or depression symptoms on the EQ-5D-5L questions. Considering individual IRCs, the proportions reporting moderate, severe or extreme anxiety and/ or depression, were particularly high in people with AS (26.4%) and PsA (30.4%), though lower in people with PMR (20.5%) and GCA (17.6%), mirroring the proportions self-reporting a history of comorbid anxiety and/ or depression.

Considering anxiety in particular, on assessment using the GAD-7 questions, 17.4% of individuals with IRCs had moderate or severe anxiety. The highest proportions with moderate or severe anxiety had PsA (23.9%) and AS (23.5%), and the lowest proportions, GCA (17.7%) and PMR (10.3%), mirroring the trends observed with other mood assessments.

This would fit with the background literature discussed in sections 2.8.1 and 2.8.3, which reported anxiety to be more prevalent in people with RA (Covic et al., 2012), with limited studies also reporting an increased prevalence of anxiety in people with PsA

(Zusman et al., 2018), AS (Martindale et al., 2006) and PMR (Muller et al., 2016). This study provides new evidence of an increased prevalence of anxiety in people with GCA.

An association between one or more comorbidities (in addition to an IRC), and anxiety was found, though this was not statistically significant. The literature supports an association between anxiety and multimorbidity. A cross sectional study examining the association between nine chronic physical conditions, multimorbidity and anxiety, used data from 181,845 adults participating in the World Health Survey (Vancampfort et al., 2017). After adjustment for confounders, one comorbidity was associated with an almost twofold increased odds of anxiety symptoms (OR (95% CI) = 1.94 (1.76,2.13)), whilst this figure rose in those with ≥5 conditions (OR (95% CI) = 5.49 (3.73, 8.09)).

A significant unadjusted association was also found between a self-reported history of mood problems, and anxiety. This association would be supported by the literature. For example, a study involving 429 participants with a history of at least one lifetime anxiety disorder, who were remitted at baseline, found that 23.5% developed a recurrent anxiety disorder over 2-years follow-up (Scholten et al., 2013).

In addition, a significant unadjusted association between increased IRC symptom severity (pain, stiffness and fatigue) and anxiety was found. However, only the association between fatigue and anxiety remained significant after adjustment. I would have expected a significant association between pain and stiffness to have been maintained after adjustment, due to my systematic review (chapter 6), finding anxiety to be associated with increased disease activity. The literature supports the strong association found between anxiety and fatigue (Stebbings et al., 2010).

Compared to anxiety, different trends were observed on assessment for depression using the PHQ-8 questions. Overall, 20.4 % of individuals with IRCs reported

moderate to severe depression symptoms. Unlike comorbid anxiety, the proportions with moderate to severe depression were highest in people with GCA (33.4%) and PMR (30.2%). A large proportion of people with AS (26.0%) and PsA (28.2%) also reported moderate to severe symptoms of depression, with the proportion being lowest in people with RA (18.3%). These findings would fit with the background literature, which suggests depression is more prevalent in people with RA, compared to people without IRCs, as discussed in section 2.9.1 (Matcham et al., 2013). These findings would also support the literature discussed in section 2.9.3, which reported an increased prevalence of depression in AS (Hopkins & Moulton, 2016) and PsA (Zusman et al., 2018), in addition to limited evidence of a higher prevalence of depression in people with PMR (Vivekanatham et al., 2018; Muller et al., 2016) and GCA (Li, Neogi & Jick, 2017).

These findings suggest that depression is a more common comorbidity than anxiety in people with PMR and GCA. The most frequently reported depression symptoms, such as sleep problems and fatigue, were noted to potentially overlap between physical and mental health problems. Therefore, the increased symptoms of depression reported on the PHQ-8 questions, could have related to worse overall physical health. However, pain, stiffness and fatigue scores were actually lowest in people with PMR and GCA, suggesting that the higher depression scores were not necessarily attributable to a greater physical health burden.

The odds of depression were increased in people with one or more comorbidities in addition to their IRC, compared to no comorbidities, though this difference was not statistically significant. Strong links between multimorbidity and depression have been reported in the literature (Read et al., 2017). It is possible that a statistically significant

difference was not found, due to some comorbidities not being asked about within the INCLUDE questionnaires, whilst recall bias could have contributed to the under-reporting of comorbid conditions.

Evidence suggests depression is a highly recurrent disorder (Burcusa & Iancono, 2007), hence it is surprising that a self-reported history of anxiety or depression was not associated with depression, when determined using the PHQ-8 questions within the INCLUDE baseline questionnaires (PHQ-8 ≥10). This could suggest depression was under-recognised in this population, or through recall bias, it may not have been correctly recorded by participants.

Pain and stiffness had a significant association with depression in people with IRCs. This association would be supported by previous studies which have reported depression to be associated with increased disease activity, including pain, in people with RA (Matcham et al., 2016b).

However, fatigue and depression were not associated. This is surprising, as one of the PHQ-8 questions is about "feeling tired or having little energy" and a systematic review examining psychological correlates of fatigue in RA found a frequent association between low mood and fatigue (Matcham et al., 2015). It is possible that this association was not found in the INCLUDE cohort, due to individuals completing the questionnaire having milder disease than that seen in hospital-based cohorts, leading them to report less fatigue. Lower FACIT scores, indicating worse fatigue, have been reported in hospital-based cohorts of people with RA (Smolen et al., 2017). For example, in a study comparing treatment response to a placebo or biologic drug treatment in people with RA, the placebo cohort of 176, had a mean baseline FACIT score of 22.2 (SD 10.6) (Smolen et al., 2017), compared to 33.2 (SD 11.6), in the INCLUDE cohort. Study

participants had moderate to severe RA, hence their overall disease activity could have been worse than in the INCLUDE cohort, potentially contributing to increased fatigue.

Fatigue, pain and stiffness were frequently worse in people with RA compared to people with GCA. People with GCA may have reported less pain and stiffness due to their predominant initial symptom being a headache, rather than joint pain or stiffness. Furthermore, once GCA is treated with glucocorticoids there is usually a more rapid relief of symptoms, whilst individuals with RA may have a more protracted diagnosis, take longer to respond to treatment, or could have underlying joint damage, leading to persistent symptoms. FACIT scores were consistent with NRS scores for fatigue, indicating worse fatigue in people with RA, AS and PsA, though less fatigue in people with GCA and PMR.

8.5.2 Strengths and limitations

This study is the first to determine the self-reported prevalence of anxiety and depression in five different IRCs. The use of validated questions to identify participants with mood problems helped to improve the sensitivity and specificity of the questionnaire for the identification of mood problems (Mitchell et al., 2016), and facilitated comparability with the literature. By obtaining data on demographic and socio-economic factors, in addition to comorbidities, potential associations between covariates and mood problems could be explored.

Face-to-face interviews could have had higher specificity for diagnosing mood problems (Levis et al., 2019), though people with work or care commitments, or those from isolated areas, may have been less likely to participate. Alternatively, telephone interviews could have been more acceptable, though this would still have been time

consuming and would not have enabled data to be gathered over a short time period for over 300 participants. Questionnaires required less time to complete, potentially enabling a more diverse sample of individuals to participate.

However, participants did need to ensure that the questionnaire was returned using the stamped, addressed envelope provided, hence those with poor mobility and no relatives or friends to seek assistance from, could have struggled to return the questionnaire by post. In addition, poor visual acuity or reduced literacy could have impacted on a participants' ability to complete the questionnaire. Furthermore, individuals with more severe depression, anxiety or joint pain could have struggled to complete the questionnaire, potentially meaning those with the most severe symptoms could have been missed. All of these factors could have contributed to response bias, meaning that those individuals who completed the questionnaire could have been systematically different from those who did not. However, as discussed in the study methods, considerable efforts were made to ensure a good response rate. In addition, involvement of patients in the development of patient facing documents, who advised on the content, layout, wording and length of the INCLUDE study questionnaires, helped to ensure that the questionnaire would be easy for patients to understand and complete, improving response rates and reducing potential response bias. Patient and public involvement and engagement (PPIE) is discussed further in section 8.6.

Some participants may have felt more inclined to disclose mood symptoms on a questionnaire, due to feeling anonymous. In comparison, during a face-to-face interview, participants could have felt more concerned about potential stigmatisation. However, it could be argued that through the development of rapport during an

interview, people could have felt more encouraged to provide accurate and honest responses to questions about their mood.

As data was derived from self-completed questionnaires, through recall bias, it is possible that some individuals did not self-report their IRCs or comorbidities correctly. Poor memory or concentration, a lack of knowledge about their health conditions or a lack of interest in the questionnaire could have contributed to recall bias. Medical record review would have enabled the comparison of self-reported and Read coded conditions. This is planned within the INCLUDE study, 12 months after participants consented to participate in the study.

From 333 individuals completing the baseline questionnaires, 35 (10.5%) self-reported having more than one IRC. The most frequent combinations of IRCs reported were RA and PMR, in addition to RA and PsA. Is is feasible that the combinations of IRCs reported were correct. As discussed in section 8.4.2, the prevalence of RA in people with PsA has been reported to be increased (Tsai et al., 2011), whilst the literature suggests that late-onset RA and PMR can be difficult to distinguish, (Cutolo, Cimmino & Sulli, 2009), with some people who are diagnosed with PMR, later being diagnosed with RA (Caproali et al., 2001). The presence of more than one IRC could have confounded differences seen between the proportion with mood problems in different IRCs, though when analysed, the odds of developing anxiety or depression were not significantly increased in people with more than one IRC, when compared to those with a single IRC. Individuals reporting combinations of IRCs could have been analysed separately, though due to the small numbers involved in this pilot study, this would not have been feasible.

Seven key comorbidities were asked about within the questionnaire, hence some conditions, including chronic obstructive pulmonary disease (COPD) and asthma,

were not accounted for, which potentially could have confounded the associations between IRCs and mood problems. Comorbidities on the questionnaire included osteoporosis, angina, MI, hypertension, stroke and anxiety or depression. These were chosen due to the INCLUDE review being focused on the identification of these comorbidities (Hider et al., 2018), which are known to be more frequent in people with IRCs (Gullick & Scott, 2011; Jamnitski et al., 2013; Maruotti, Corrado & Cantatore, 2014). Although I contributed to discussions about the questionnaire content, final decisions regarding its' content were made by the whole INCLUDE team. It is possible that associations between IRCs and mood problems calculated would have been more accurate if other comorbidities, such as common respiratory conditions, were accounted for.

A further limitation was the relatively small number of individuals included in this study, all from the same demographic area. This was due to it being a pilot feasibility study rather than a full trial. In particular, the small sample size for rarer conditions such as GCA limited the generalisability and power of findings. However, a future full trial of the INCLUDE intervention would provide a larger dataset with more generalisable findings, within which different combinations of IRCs could be analysed separately.

8.6 Patient and Public Involvement and engagement

The initial idea for the INCLUDE study arose from a PPIE group who met to discuss the qualitative study described in chapter 5. Patients had been recruited to this study after attending a nurse-led annual review at a community hospital, for a holistic review of their arthritis and associated comorbidities. When hearing the review was based at a community hospital, participants suggested that it should be performed in

primary care, where they already had reviews for other LTCs. They also queried why the review was limited to people with RA and did not include those with other IRCs.

Following these suggestions, members of the Haywood User Group and the Keele University Research User Group (RUG) continued to contribute to the study. Haywood User Group members helped to review grant applications and documents for ethical approval, whilst a RUG member participated in the trial steering committee. After being recruited via a leaflet, shared through outpatient clinics and the RUG, six PPIE members with different IRCs met regularly throughout the study.

At the first PPIE meeting, participants were enthusiastic about the proposed review, agreeing it would be important to prioritise comorbid mood problems, CVD, and bone health. Another key priority for patients was fatigue, which was incorporated into study questionnaires. Following this meeting, health professional stakeholders from primary care, rheumatology and nursing, also met to discuss the practicalities of implementing the review and to ensure that relevant QOF metrics (e.g. QRisk2) were captured.

During subsequent PPIE meetings, participants suggested improvements to patient-facing documents, including questionnaires, study invitation letters and patient information leaflets. The group also suggested it would be useful for patients to have three key action points communicated via a summary sheet following their review, which they helped to develop.

8.7 Conclusion

Analysis of baseline questionnaire data from the INCLUDE study has provided evidence of the burden of comorbid mood problems in RA, AS, PsA, PMR and GCA.

Despite depression in RA being the main focus of past research into comorbid mood problems in people with IRCs, this data shows depression is even more frequent and severe in people with other IRCs, whilst also highlighting the burden of comorbid anxiety in people with IRCs.

This study has shown the prevalence of anxiety to be particularly high in people with PsA, AS, and RA, though comparatively lower in people with GCA and particularly PMR. Therefore, results suggest a particular need to focus case-finding for anxiety on individuals with PsA, AS and RA. Meanwhile, the prevalence of depression was increased in all IRCs, particularly in GCA and PMR. This suggests a requirement for case-finding for depression in all IRCs, with a focus on people with GCA and PMR, in whom the burden of comorbid depression is the highest.

The evidence discussed supports the need for a review for people with IRCs, to enhance the recognition of and signposting for management of comorbid mood problems. Ultimately, through improved recognition and management of comorbidities, the quality of life (QoL) and potential life expectancy of people with IRCs could be improved.

CHAPTER 9
Discussion

9.0 DISCUSSION

Within this discussion chapter, I will provide an overview of the results from all studies, before contextualising them with the literature in section 9.2. I will summarise the strengths and limitations of my four studies, which are further detailed within each individual chapter. Subsequently, I will discuss the implications of my findings for clinical practice, education, training and research, before reflecting on how my clinical background has impacted on my research and vice versa.

9.1 Summary of findings

Through the use of mixed methods over 4 connected studies, I have explored the perspectives of people with rheumatoid arthritis (RA) of case-finding for anxiety and depression, determined the impact of comorbid anxiety in people with RA via a systematic review, and investigated the incidence and prevalence of comorbid mood disorders in people with different inflammatory rheumatological conditions (IRCs).

Using qualitative methods, I have established that people with RA variably perceive an interaction between their arthritis and mood. Whilst most interview participants reported their RA to negatively impact on their mood, several perceived anxiety or depression to precipitate RA flares. Some only recognised a link between their RA and mood, when this was highlighted by a healthcare professional.

There were multiple barriers to help-seeking for mood problems in people with RA, including fear of stigmatisation, lack of time in appointments and poor continuity of care. Some participants lacked candidacy for care, normalising their mood symptoms,

whilst others perceived their general practitioner (GP) to prioritise physical above mental health concerns, recursively affecting help-seeking. Meanwhile, participants perceived rheumatologists were only responsible for physical health care. However, establishment of rapport and continuity of care, either with a particular GP, or the annual review clinic nurse, were reported to facilitate disclosure of mood concerns.

21% of people attending the RA annual review clinic scored ≥ 3 on the Patient Health Questionnaire (PHQ)-2 questions, whilst 24% scored ≥ 3 on the Generalised Anxiety Disorder (GAD)-2 questions, suggesting a requirement for further assessment to identify potential depression or anxiety. From those interviewed, the case-finding questions were perceived to be acceptable in the context of a nurse-led annual review clinic. Participants recognised the holistic focus of the review and appreciated the opportunity to learn about the wider impact of their RA. Disclosure of mood concerns was facilitated by the clinic nurse being perceived as approachable and having time to listen.

A patient and public involvement and engagement (PPIE) group, acknowledging the need for patients with RA to be educated about comorbid mood problems, helped to collaboratively develop a patient information leaflet. The PPIE group also reflected on how often interview participants had discussed ways that their mood problems had prevented them from accessing care. In particular, those interviewed had described how anxiety had prevented them from seeing their GP or accessing psychological services, whilst several had also reported a perception that anxiety caused flares of their RA. However, a lack of literature was found reporting the impact of anxiety on quality of life (QoL) and disease activity in people with RA.

A systematic review and meta-analysis were performed to determine the association between anxiety in people with RA, and quality of life (QoL) and disease activity. Anxiety was found to be cross-sectionally associated with a reduced QoL, though a lack of studies reported the prospective association between anxiety and QoL. On review of short form (SF)-36 subscale effect sizes, the largest impact of anxiety was seen on vitality, social functioning and mental health scores. Relatively larger effect sizes for reduced social functioning and mental health scores could have reflected symptoms of anxiety in addition to components of QoL, whilst the correlation between anxiety and vitality could have been confounded by known associations between mood and fatigue (Matcham et al., 2015).

Anxiety in people with RA was also associated with increased disease activity, both cross-sectionally, and at 3, 6 and 12 months. The 2 larger studies reporting the association between anxiety and disease activity over time found the impact of baseline anxiety to reduce over time, potentially due to people with anxiety adapting to their RA diagnosis, leading to a reduction in subjective component scores within the Disease Activity Score in 28 joints (DAS28). The association found between anxiety and increased disease activity cross-sectionally in the systematic review may, in part, have been due to anxious people reporting higher patient global assessment of health (PtGA) scores and other subjective measures of disease activity, rather than their disease activity being objectively increased.

The systematic review built on findings from the preceding qualitative study by providing further evidence of the negative impact of anxiety in people with RA, highlighting the need for a focus on the identification and management of comorbid anxiety in addition to depression. Further associated studies were guided by other

suggestions from the PPIE group, who queried why guidelines recommending an RA annual review did not extend to other IRCs. This led me to identify a lack of literature reporting the burden of anxiety in people with AS and PsA, in addition to anxiety and depression in people with polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). Consequently, I performed a cohort study to determine the incidence and prevalence of anxiety and depression in different IRCs using a primary care dataset.

Although the numbers of people reporting mood problems in GCA were small, and hence the results should be interpreted with caution, novel evidence of an increased prevalence of mood problems in people with GCA was identified, with further evidence being found to support an increased prevalence of anxiety alone, in addition to anxiety and/ or depression in people with RA, ankylosing spondylitis (AS), and psoriatic arthritis (PsA). Despite past research into mood problems in IRCs focusing on RA, the prevalence of anxiety and/ or depression was highest in people with PsA and GCA, whilst there was also a statistically significant increase in the adjusted odds of new anxiety and/or depression in these conditions.

The incidence of anxiety alone was reduced in people with RA, AS and PsA, whilst the incidence of anxiety and/or depression was also reduced in people with AS and PsA, compared to those without IRCs. It is possible that mood problems were under-recognised in these conditions. There were also less individuals with AS and PsA compared to the other IRCs analysed, which could have limited the reliability of results. Individuals with AS and PsA had fewer comorbidities and a lower number of primary care contacts, compared to people with other IRCs, hence had less opportunities for the potential recognition or discussion of mood problems. In addition, 95% CIs reported with the HR's for anxiety were particularly wide in people with RA, AS and PsA,

suggesting a greater sample size would have been required to accurately determine the association between these IRCs and anxiety. In contrast, the incidence of anxiety alone and anxiety and/ or depression, was increased in people with PMR and GCA. A statistically significant increase in the risk of new anxiety was found in people with PMR and GCA, which remained significant after adjustment in people with GCA.

Through the use of primary care consultation data, it was recognised that mood problems could have been underestimated, due to patients not identifying symptoms or consulting, or due to clinicians not recognising or recording potential mood problems. For example, the literature suggests that older adults may normalise depression (Wuthrich & Frei, 2015), whilst primary care practitioners may not recognise depression in older adults due to normalising it as an understandable aspect of ageing, on a spectrum with loneliness and reduced functioning (Burroughs et al., 2006). Alternatively, through the use of questionnaires, data could have been obtained to compare the difference between self-reported mood symptoms and consultation for anxiety or depression. Otherwise, patients with IRCs could have been invited to a consultation where they could have been asked questions to identify potential mood problems. Supported by evidence from the cohort study and informed by the preceding qualitative study and systematic review findings, these alternative approaches, using both questionnaires and face-to-face consultations were utilised within the INCLUDE pilot trial (Hider et al., 2018).

The INCLUDE study aimed to determine the feasibility and acceptability of a nurse-led review for people with IRCs, based in primary care, aiming to identify and facilitate the management of comorbidities. Due to mood problems in people with IRCs potentially not being recognised or coded in primary care records, I analysed responses

to the case-finding questions for mood problems from baseline questionnaires, completed by the INCLUDE study participants. This enabled me to compare differences between the proportion of mood problems recognised and recorded within primary care electronic health records, to the number of mood problems identified following the use of the case-finding questions within the INCLUDE study questionnaire.

Analysis of the INCLUDE baseline data showed the burden of self-reported mood problems to be high, with anxiety (defined as GAD-7 ≥10) affecting 17.4% and depression (defined as PHQ-8 ≥10) affecting 20.4% of study participants. The proportion with anxiety was particularly high in people with PsA and AS, though comparatively lower in people with PMR and GCA. In contrast, my cohort study, found the adjusted odds of anxiety to be particularly high in people with GCA, compared to other IRCs. Meanwhile, on further analysis of the INCLUDE data, depression was found to be most frequent in people with GCA and PMR, though a large proportion of people with AS and PsA also reported moderate to severe symptoms of depression. Although the prevalence of depression was lowest in people with RA, this was still much higher than the proportion reported to have depression in the general population (NatCen Social Research, 2016), as described in sections 2.5 and 2.8.

The most frequently reported depression symptoms were sleep problems and fatigue, which could have related to worse physical health symptoms, rather than low mood. However, in people with GCA and PMR, for whom the prevalence of depression was highest, pain, stiffness and fatigue scores were actually lower, when compared to other IRCs, suggesting an underlying mood disorder as the cause of a high PHQ-8 score, rather than increased IRC symptoms. It is possible that steroid treatment could have

contributed to the increased prevalence of depression in people with PMR and GCA (Brown & Chandler, 2001).

In overall IRCs, statistically significant associations were found between pain, stiffness, and current depression, whilst a significant association was also found between fatigue and anxiety. The presence of one of more comorbidities (in addition to an IRC) was associated with increased odds of anxiety and depression, though these associations were not statistically significant. Similar associations between covariates and mood problems were found in people with RA, when compared to overall IRCs. There were too few participants to enable analysis of the associations between covariates and mood problems in other IRCs.

9.2 Comparison with existing literature

My qualitative study (chapter 5), was the first to explore patients' perspectives of case-finding for comorbid mood problems in people with RA, during a nurse-led annual review. Reflecting findings for other long-term conditions (LTCs), this research suggested that patients may recognise an interaction between their RA and mood (DeJean et al., 2013; Dures et al., 2016b), though individuals who don't perceive their RA and mood to be connected may not understand why they are asked about their mood during LTC reviews (Anderson, Foy & House, 2015).

Qualitative studies have been performed in other IRCs, in which participants have reflected on the interaction between their inflammatory condition and mood. In a qualitative study exploring the impact of AS, some participants perceived stress to trigger flares of pain (Primholdt et al., 2017), whilst in a study exploring patients' experiences of living with PMR (Twohig et al., 2015), participants reflected on the

negative impact of their disability on their mood. Within a qualitative study exploring patients' perspectives of GCA (Liddle et al., 2017), participants often connected anxiety symptoms to fear about their disease prognosis, including the risk of visual loss.

Within my qualitative study, patients with RA, similarly to those with other LTCs (Coventry et al., 2011), were often found to lack candidacy for care, meaning they didn't seek help for anxiety or depression due to perceiving changes in their mood to be a normal response to living with a LTC. During interviews, people with RA discussed stigma as a barrier to help-seeking for mental health problems, echoing findings in other LTCs (Anderson et al., 2012).

Considering further barriers to help-seeking, when a questionnaire was used to explore the preferences of people with inflammatory arthritis for psychological support, several participants described feeling unheard or struggling to ask for help for psychological problems (Dures et al., 2016b). This mirrored the perspectives of people with RA during my qualitative study, who perceived GPs to be dismissive of mood concerns. Further barriers to help-seeking for mood problems identified in my study included a perception of doctors prioritising physical above mental health concerns, a lack of time, anxiety-provoking appointments and poor continuity of care, all of which recursively affected help-seeking. However, several participants did describe being more receptive to discussing mood problems once they had been able to build a rapport with their GP, facilitated by continuity of care. Within the nurse-led RA annual review clinic, participants described the approachability of the nurse, who had time to listen, to facilitate disclose of mood concerns.

My systematic review (chapter 6), was the first to examine the association between anxiety in people with RA, and QoL and disease activity. Anxiety in people with

RA was found to be cross-sectionally associated with reduced QoL. This complemented previous research examining the impact of depression in people with RA, which found depression to be associated with reduced physical and mental QoL (Bazzichi et al., 2005; Senra et al., 2017).

My systematic review also demonstrated anxiety in people with RA to be associated with increased disease activity cross-sectionally, and at up to 12-months follow-up. This built on the findings of a study assessing the impact of combined anxiety and depression in people with RA. Both baseline and persistent mood problems, assessed using the EuroQol 5-Dimension Scale (EQ-5D), were associated with significantly increased DAS28 scores (Matcham et al., 2016b). Other studies have also found associations between depression in people with RA and increased disease activity. For instance, a systematic review found a temporal association between depression in people with RA and increased disease activity (Rathbun, Reed & Harrold, 2013), whilst further studies have found baseline depressive symptoms to be associated with a reduced response to RA treatment over time (Matcham et al., 2018; Hider et al., 2009; Hancock et al., 2012; Maruotti, Corrado & Cantatore, 2014) and a lower disease remission rate (Cook et al., 2016).

My systematic review suggested that the association between anxiety and increased disease activity could, in part, have been due to people with anxiety reporting higher patient global assessment (PtGA) scores and other subjective measures of disease activity, rather than their disease activity having objectively increased. People with RA, particularly those with psychological comorbidities, have been found to rate their disease activity higher than their physicians (Liu, Bathon & Giles, 2015; Duarte et al., 2015). Patient-reported measures such as the Visual Analogue Scale (VAS), which

forms part of DAS28, have been found to be more strongly influenced by psychological variables (Cordingley et al., 2014).

My cohort study (chapter 7), characterised the incidence and prevalence of anxiety, in addition to anxiety and/ or depression, in a range of different IRCs. The prevalence of anxiety alone, in addition to anxiety and/or depression was higher in overall IRCs, RA, AS, PsA and GCA, when compared to those without IRCs. This was consistent with the background literature, which suggested anxiety and depression were more prevalent in RA (Isik et al., 2006; Matcham et al., 2013), AS (Hopkins & Moulton, 2016; Shen et al., 2016) and PsA (McDonough et al., 2014), compared to the general population (NatCen Social Research, 2016). These findings also supported limited research showing a higher prevalence of depression in people with GCA (Li, Neogi & Jick, 2017), whilst providing new evidence of an increased prevalence of anxiety.

However, the prevalence of mood problems was lower in people with PMR, compared to those without IRCs. This contrasts with the limited background literature, that suggests 15-22% of people with PMR have symptoms of depression (Vivekanatham et al., 2018; Muller et al., 2016) and approximately 13% have symptoms of anxiety (Muller et al., 2016). This also contrasts with data from the INCLUDE study questionnaires, which have found the prevalence of depression to 30.2%, and anxiety 10.3%, in people with PMR.

Compared to the other IRCs analysed, PMR is a condition that is more frequently managed exclusively within primary care. Therefore, primary care consultations could have been more focussed on medical management, including the prescription of glucocorticoids for treatment of the primary condition, leaving less time for discussion

of potential mood problems. Conversely, it could be argued that within primary care, if an individual with PMR had regularly attended follow-up with a clinician, they could have had more opportunity to develop a rapport, increasing their propensity to disclose mood concerns.

In my cohort study, mood problems were most prevalent in people with PsA and GCA. This would reflect the findings of Freire et al. (2011), who estimated the prevalence of moderate anxiety and depression in people with PsA to be 17.6% and 29.7% respectively. Results would also be consistent with a study by Li, Neogi and Jick (2017), who estimated the prevalence of depression in people with GCA to be 17.6%. There was also a statistically significant increase in the adjusted odds of anxiety and/or depression in people with PsA and GCA. The adjusted odds of mood problems were increased in people with RA, though this increase was not statistically significant, despite the literature suggesting the prevalence of anxiety (Covic et al., 2012) and depression (Matcham et al., 2013) in people with RA to be high.

Overall, the incidence of anxiety was reduced in people with IRCs, though increased in people with PMR and GCA, compared to those without IRCs. In addition, the risk of anxiety in people with overall IRCs, RA, AS and PsA was lower than in those without IRCs. However, the risk of anxiety in people with PMR and GCA was increased. This increase was statistically significant in people with GCA, compared to those without IRCs. These findings support limited literature showing an increased incidence of anxiety symptoms in people with PMR (Muller et al., 2016), whilst also adding to the literature by highlighting a particularly increased incidence of anxiety in people with GCA. However, the findings for RA and AS, contrast with literature showing an increased incidence of anxiety in these conditions (Marrie et al., 2018b, Qui et al., 2019; Shen et

al., 2018), whilst providing evidence to suggest a reduced incidence of anxiety in PsA. However, for the reasons discussed in section 7.5.3, including fewer comorbidities requiring nurse-led reviews, lower primary care contact rates and small sample sizes for AS and PsA, it is possible that the incidence of anxiety in some IRCs was under-estimated. Also, as people were recruited for my cohort study from primary care, the burden of mood problems may not have been as high as in a secondary care cohort, in which people could have had more severe IRC symptoms, contributing to anxiety or depression.

The incidence of anxiety and/ or depression was reduced in people with AS and PsA, though increased in people with RA, PMR and GCA, compared to those without IRCs. In addition, the risk of anxiety and/ or depression in people with RA, AS and PsA was lower than in those without IRCs. However, the risk of anxiety and/ or depression in people with PMR and particularly GCA was increased, compared to those without IRCs. Limited background literature supports the findings for PMR and GCA, reporting an increased incidence of anxiety and depression in people with PMR (Muller et al., 2016), and an increased incidence of depression in people with GCA (Li, Neogi & Jick, 2017). However, findings for AS and PsA, contrast with the literature, which suggests the incidence of mood problems is increased in people with AS (Meesters et al., 2014; Wu et al., 2017; Shen et al., 2016) and PsA (Zusman et al., 2018). Again, it is possible these differences were seen due to under-recognition of mood problems in some IRCs, a point I will discuss further, when comparing the cohort and INCLUDE study results.

Within the INCLUDE study (Hider et al., 2018), validated tools such as the GAD-7 and PHQ-8 questions were used to determine the prevalence of anxiety and depression in a range of different IRCs. Considering the GAD-7 assessment, the highest proportion

with moderate or severe anxiety had PsA (23.9%) and AS (23.5%), reflecting previously reported prevalence rates of moderate anxiety in people with PsA (29%) (Freire et al., 2011) and AS (25%) (Martindale et al., 2006). The lowest proportions with moderate or severe anxiety had PMR (10.3%) and GCA (17.7%). This mirrored limited literature on the prevalence of anxiety in people with PMR (Muller et al., 2016), whilst providing new evidence of of moderate prevalence of anxiety in people with GCA.

Unlike comorbid anxiety, the proportions with moderate to severe depression were highest in GCA (33.4%) and PMR (30.2%). Limited prior literature on comorbid depression in people with GCA, suggests the prevalence of depression to be much lower, at 17.6% (Li, Neogi & Jick, 2017), whilst the prevalence of depression in people with PMR has previously been estimated at 22% (Muller et al., 2016). Therefore, this new evidence suggests the burden of self-reported depression in GCA and PMR is higher than previously thought.

A large proportion of people with AS (26.0%) and PsA (28.2%), also reported moderate to severe symptoms of depression, higher than previously reported in the literature, which estimates the prevalence of moderate to severe depression to be 8.2%-18.0% in AS (Hopkins & Moulton, 2016; Zhao et al., 2018) and 17.6% in PsA (Freire et al., 2011) respectively. This evidence suggests that the burden of depression in AS and PsA is also higher than previously thought. The proportion with depression was lowest in people with RA (18.3%), lower than the 38.8% previously reported to have depression in a meta-analysis of PHQ-9 scores (Matcham et al. 2013).

A statistically significant adjusted association was found between fatigue and anxiety, which would be supported by the literature (Stebbings et al., 2010), whilst significant unadjusted associations were also found between pain, stiffness and anxiety.

Links between anxiety and increased disease activity, hence pain and stiffness, would be supported by my systematic review (chapter 6), whilst the literature also supports an association between mulitmorbidity and anxiety (Vancampfort, 2017).

Although one or more comorbidities in addition to an IRC were associated with increased odds of depression, this association was not statistically significant. This is surprising, as strong links between multimorbidity and depression have been noted in the literature (Read et al., 2017). However, just seven key comorbidities were asked about within the questionnaire, hence some comorbid problems, such as asthma and chronic obstructive pulmonary disease (COPD), were not accounted for. Recall bias may also have contributed to the under-recording of comorbidities.

Depression was significantly associated with increased pain and stiffness, supported by literature reporting strong links between low mood and increased disease activity (Rathbun, Reed & Harrold, 2013). However, no significant association between fatigue and depression was found. This contrasts with a systematic review examining psychological correlates of fatigue in RA, which found a frequent association between low mood and fatigue (Matcham et al., 2015). It is possible that no significant association was found due to individuals in the INCLUDE cohort having milder disease than that seen in hospital-based cohorts, leading them to report less fatigue. Lower FACIT scores, indicating worse fatigue, have been reported in hospital-based cohorts of people with RA (Smolen et al., 2017).

Anxiety was more frequent, though moderate to severe depression less frequent, in people with two or more IRCs, compared to one IRC. There were no statistically significant associations found between having more than one IRC and

developing anxiety or depression, suggesting the presence of more than one IRC did not impact significantly on the development of mood problems.

The prevalence of mood problems, when determined using primary care consultation data, was much lower than when determined using the case-finding questions within the INCLUDE study questionnaires. The prevalence of anxiety was 4.2% (range 2.8-9.4%) according to primary care data, compared to 17.4% (range 10.3-23.9%) when determined using the case-finding questions. Meanwhile, the prevalence of anxiety and/ or depression was 8.3% (range 6.0-14.4%) according to primary care data, whilst the prevalence of depression was 20.4% (range 18.3-33.4%) when determined using the case-finding questions. Similar trends were observed when individual IRCs were analysed.

The proportion of people with IRCs found to have mood problems, when determined using the case-finding questions for anxiety and depression, was far in excess of the prevalence of mood problems found in the general population. For example, in 2014, a survey in England found approximately 5.9% of the general adult population to have self-reported symptoms of anxiety and 3.3%, symptoms of depression in the preceding week (NatCen Social Research, 2016). However, the prevalence of anxiety in people with IRCs was lower than that reported in the general population, when determined using primary care electronic health records, with anxiety and/ or depression affecting similar proportions with and without IRCs.

As discussed in section 2.9, the literature suggests that the prevalence of mood disorders in people with RA is high, with approximately 20% having anxiety (VanDyke et al., 2004) and 38.8% depression (Matcham et al., 2013). The prevalence of depression in other IRCs has been reported as 18% in AS (Zhao et al., 2018), 20% in PsA (Zusman et

al., 2018) and 15% in PMR (Vivekanatham et al., 2018). Therefore, I would have expected the analysis of Read codes within primary care electronic health records to show a higher prevalence of mood problems, on comparison with general population. However, the prevalence of anxiety and depression was much lower when determined using primary care data, compared to when the case-finding questions were used wthin the INCLUDE questionnaires. This suggests that mood problems are under-recognised in people with IRCs, within primary care.

The literature suggests that depression (Goldberg & Huxley, 1991) is under-recognised in primary care, whilst recent research has also highlighted the under-recognition of anxiety in people with LTCs (Barnes et al., 2019). A study involving adolescents, compared the prevalence of common mental disorders (CMDs) according to electronic primary care data, to the prevalence of CMDs determined by interviews. Many individuals who were found to have a CMD during interviews, had no record of a mental health problem in their electronic primary care record, suggesting that research using clinical databases could under-estimate the burden of mental health problems in a population (Cornish et al., 2016).

It is possible that primary care consultations for people with IRCs focus on their inflammatory condition, leaving less time for discussion of mood concerns. The literature also suggests that there are barriers which can prevent people with mood problems from accessing care. People with LTCs have been reported to lack candidacy for care of mood problems (Coventry et al., 2011), whilst people with RA have discussed stigma as a barrier to help-seeking for anxiety or depression (Anderson et al., 2012). In chapter 5, my qualitative study revealed further potential barriers to people with RA

and mood problems from accessing care, which could have prevented potential anxiety or depression from being identified and recorded.

Research suggests that when people with psychological disorders normalise their symptoms, general practitioners are less likely to diagnose anxiety or depression (Kessler, Lewis & Gray, 1999). In particular, older adults may normalise depression (Wuthrich & Frei, 2015), whilst primary care practitioners may not recognise depression in older adults due to normalising it as an understandable aspect of ageing (Burroughs et al., 2006).

There were some consistencies between the cohort study and INCLUDE study data. For instance, the prevalence of anxiety was highest in people with PsA within both studies. In addition, the prevalence of anxiety and/ or depression was highest in people with GCA within the cohort study, whilst data from the INCLUDE study showed the prevalence of depression to be highest in people with GCA. Both studies also found the prevalence of anxiety in people with PMR to be lower, when compared to other IRCs. However, whereas the overall prevalence of mood problems in people with IRCs was high within the INCLUDE study, the cohort study did not find the prevalence of anxiety to be increased in people with IRCs, whilst the prevalence of anxiety and/or depression was only marginally increased in people with IRCs, compared to those without IRCs. This highlights the difference between prevalence rates when determined using the case-finding questions within the INCLUDE study, compared to those determined using primary care electronic health records, within my cohort study.

9.3 Strengths and limitations

The strengths and limitations of each study have been discussed in detail in each respective chapter (section 5.10.2, section 6.5.2, section 7.5.5 and section 8.5.2). Brief summaries of the strengths and limitations of each study are given below.

9.3.1 Qualitative Study

Use of exploratory methods, followed by further analysis using a framework, enabled deeper insights into the barriers and facilitators to patients with RA accessing care for psychological problems. As only patients with a high PHQ-2 or GAD-2 score were interviewed, different views could have been articulated by individuals without mood problems. In addition, participants were predominantly white British and female, hence a greater range of perspectives are likely to have been gained from a more diverse population, though a range of different socioeconomic statuses were represented within the sample interviewed, whilst attempts were made to purposively sample participants of different ages.

9.3.2 Systematic Review

A broad search strategy for the review helped to ensure all evidence on this topic was considered. However, several studies that did not report anxiety separately from depression had to be excluded. In addition, several conference abstracts that did not report sufficient data had to be excluded, after attempts made to contact the authors of all the abstracts to obtain relevant data were unsuccessful. The quality of studies varied, with several sources of potential heterogeneity identified. Meta-analysis was also limited by the small number of studies providing suitable data for statistical pooling

of results. Nonetheless, this review provided evidence supporting an overall association between anxiety in people with RA, and reduced QoL and disease activity.

9.3.3 Cohort Study

Although the data quality in the Consultations in Primary Care Archive (CiPCA) database is comparable to larger national databases, use of a national database such as the Clinical Practice Research Datalink (CPRD) would have provided a larger sample size, hence more generalisable results, enabling stronger conclusions to be made about the association between IRCs and mood problems.

Results could have been biased by missing data and unmeasured confounding, though adjustments were made for a range of lifestyle factors and comorbidities known to be associated with mood problems. It is possible that some codes were misclassified. In addition, mood problems could have been underestimated due to patients not identifying symptoms or consulting for their mood concerns (Wuthrich & Frei, 2015), whilst clinicians may not have recognised or recorded potential mood problems (Burroughs et al., 2006). The reliance on coded consultation data meant that depression alone could not be accurately analysed, due to it often being recorded using the Read code "anxiety with depression". However, the anxiety and depression Read code lists were combined to enable analysis of individuals with anxiety and/ or depression. In addition, given the frequent focus of the thesis on anxiety, I analysed anxiety codes separately, though it is possible that these results were an underestimate, since some cases of anxiety could have been missed that were only recorded as "anxiety with depression" in the clinical record.

9.3.4 INCLUDE Study

This feasibility study was strengthened by the use of validated measures (PHQ-8 and GAD-7) to identify mood problems within a questionnaire developed with patients, to help ensure ease of completion. The use of face-to-face interviews could have facilitated a more accurate diagnosis of depression, though this would not have enabled data to be collected for over 300 people within a short period of time. As data was derived from self-completed questionnaires, it is possible there was some recall bias, though a medical record review is planned within the INCLUDE study, 12 months after participants consented to participate, to enable self-reported conditions to be compared to those recorded in patients' electronic health records using Read codes.

Respiratory conditions, which could have confounded associations between IRCs and mood problems, were not asked about within the questionnaire, due to questions being focused on the comorbidities being explored within the INCLUDE review. 10.5% reported having more than one IRC, which also could have confounded differences seen between the proportion of mood problems in different IRCs, though the odds of having a mood problem were not significantly increased in people with more than one IRC compared to those with a single IRC.

The number of participants was relatively small in the INCLUDE pilot study and they were all from the same demographic area, making it difficult to generalise findings. More than a third of invited people did not return the baseline questionnaire, hence it is possible that there was also a response bias, though efforts were made to ensure a good response rate.

9.4 Implications for clinical practice, education, training and research

9.4.1 Implications for clinical practice

Guidelines produced by the National Institute for Health and Care Excellence (NICE) outline how depression should be identified and treated in adults with chronic physical health problems (NICE, 2009b), though no similar guideline has been published to assist the recognition and management of anxiety in LTCs. This is surprising, given that both anxiety and depression in LTCs are under-recognised, under-treated (Cepoiu et al., 2007), and linked to increased morbidity and mortality (Ang et al., 2005). Therefore, guidelines are needed to inform clinicians about how to optimise the identification and treatment of anxiety in people with LTCs.

Through use of case-finding questions, my research has highlighted an increased prevalence of comorbid mood problems in people with IRCs. However, the prevalence of mood problems in people with IRCs was higher when responses to the case-finding questions were analysed, compared to Read codes within electronic health records, suggesting a potential burden of undiagnosed mood problems in people with IRCs. This implies that annual reviews should be recommended for people with a range of different IRCs, including AS, PsA, PMR and GCA, in addition to people with RA.

The requirement for an annual review to identify potential mood problems in people with IRCs would be supported by my qualitative study, during which I found several patients did not perceive a connection between their RA and mood until this link was highlighted by a healthcare professional. Quality and Outcomes Framework (QOF) incentives specifying an assessment of mood could also help to encourage GPs to

establish regular annual reviews for their patients with IRCs, to improve the recognition of comorbid anxiety and depression within general practice.

Condition specific guidelines need to be updated to reflect the high proportions of people with IRCs who have comorbid mood problems. This would be supported by my research examining the self-reported prevalence of mood symptoms, in addition to my systematic review, which highlighted the potential impact of anxiety in people with RA.

The impact of anxiety on disease activity suggests that rheumatologists and allied health care professionals should consider case-finding for mood problems in people who fail to respond to RA treatments, especially if subjective disease activity measures (PtGA, tender joint count (TJC)) are high relative to more objective scores (swollen joint count (SJC), erythrocyte sedimentation rate (ESR)). Managing mood alongside RA could lead to improved outcomes.

9.4.2 Implications for education and training

My research supports the requirement for all healthcare professionals to be aware of the burden of anxiety and depression in people with IRCs, and to be confident and competent to identify and respond to cues for mood problems, especially in those with multimorbidity. My qualitative study reveals that patients can find doctors to be dismissive of mood concerns, or perceive them to prioritise physical above mental health problems. However, development of rapport was reported to facilitate disclosure, hence improved continuity of care could help patients to disclose mood concerns. Furthermore, encouraging health care professionals to complete Improving Access to Psychological Therapies (IAPT) referrals on behalf of patients, particularly for

people who are anxious about self-referral, or older adults who are under-represented in IAPT services (Pettit et al., 2017), could help to facilitate access to psychological therapies, as highlighted within my qualitative study.

A qualitative study exploring nurses' experiences of recognising depression in older people with multimorbidity, revealed that nurses can lack confidence discussing mood with their patients, often perceiving it to not be their responsibility (Waterworth et al., 2015). Practictioners have also reported struggling to incorporate the case-finding questions into reviews, finding them too mechanistic (Maxwell et al., 2013). However, my qualitative study found the case-finding questions to be acceptable, when delivered in the context of a nurse-led review. Therefore, there is a training requirement for practitioners, who need to be encouraged to case-find for potential mood problems and give equal priority to physical and mental health concerns.

For a nurse-led review to improve the QoL and overall outcomes for people with IRCs, patients' health priorities will need to be taken account of, to facilitate shared treatment decisions. For example, when discussing the management of mood problems in IRCs, patients have often expressed a preference for psychological therapies to avoid the burden of further medication (Machin et al., 2017; Withers et al., 2015). Consequently, healthcare practitioners will need to be trained to optimise care for adults, whilst limiting treatment burden (Boyd et al., 2014) as much as possible, principles highlighted within NICE guidelines (NG 56) for the assessment and management of patients with multimorbidity (NICE, 2016).

Some practitioners have been reported to favour an individualised approach to identifying potential mood problems, although it can take additional time to develop rapport (Maxwell et al., 2013). Due to increasing demands on GPs in primary care,

expanding the role of allied healthcare professionals is a key part of the GP five year forward view (NHS England, 2017a). Supporting other practitioners to be confident in the use of case-finding questions and managing mood problems, could improve the recognition of anxiety and depression. For instance, when practice nurses (PNs) were trained to deliver a psychosocial intervention within a collaborative care (CC) framework for people with depression and LTCs, patients valued a PN being able to listen to their mood concerns, though the need for more formal supervision to support PNs in undertaking the role of a case manager for people with depression and LTCs was emphasised (Webster et al., 2016). Provision of time and the approachability of the clinic nurse were integral factors in facilitating disclosure of mood concerns by patients with RA who participated in my qualitative study. Furthermore, a nurse-led review focused on comorbidity management for individuals with RA, has been found to increase the number of interventions taken to treat related comorbidities (Dougados et al, 2015). Therefore, educating and supporting nurses to deliver reviews for people with IRCs, that include case-finding for potential mood problems, could improve overall outcomes.

Within my cohort study (chapter 7), the prevalence of mood problems recorded using Read codes in primary care electronic health records, was highest in people with GCA, whilst within the INCLUDE study baseline questionnaires, self-reported symptoms of depression were particularly high in people with PMR and GCA (chapter 8). Consequently, when primary care practitioners consult patients with these conditions, alongside assessments for steroid side-effects, they could consider opportunistic case-finding for mood problems.

My research has also highlighted an educational need for patients around comorbid mood problems in IRCs, which I have promoted via dissemination activities, including the co-production of a patient information leaflet about mood problems in people with RA, which is available locally.

9.4.3 Implications for research

Evidence suggests there is an association between baseline anxiety and depression in people with RA, and increased disease activity, both from my systematic review and other reported literature (Matcham et al., 2016b; Rathbun, Reed and Harrold, 2013), in addition to a reduced treatment response (Matcham et al., 2018). Further research is required to determine whether treating mood problems leads to improved rheumatological outcomes. This could be addressed by the following research question.

Does the identification and treatment of comorbid anxiety and/ or depression in people with IRCs lead to an improved QoL or reduced disease activity?

A randomised controlled trial (RCT), similar to the INCLUDE study (Hider et al., 2018), could be used to respond to this question. However, the INCLUDE intervention involved the assessment and management of cardiovascular risk and bone health alongside potential anxiety and/ or depression in people with IRCs. Therefore, to determine outcomes solely related to the identification and treatment of mood problems, adjustments for other comorbidities identified and treated would need to be made.

Alternatively, people with different IRCs identified from electronic primary care

records, could be invited to participate in a new trial. All participants could be assessed for potential mood problems by questionnaire. People with symptoms of anxiety and/ or depression (GAD-7/ PHQ-9 ≥10) could then be randomised to an intervention group or control group. The intervention could involve cognitive behavioural therapy (CBT), or alternatively, behavioural activation, a therapy that encourages people with depression to approach activities they may have been avoiding, and to define goals (Jacobson, Martell & Dimidjian, 2001). These therapies could be delivered by a psychological wellbeing practitioner over six to eight weekly sessions, as used in the COINCIDE trial (discussed in section 2.7), an RCT testing the effectiveness of an integrated collaborative care model for people with depression and long-term physical conditions (Coventry et al., 2015). To integrate care, as in the COINCIDE trial, a short collaborative meeting between the patient, psychological wellbeing practitioner and PN from the patients' general practice, could take place during the middle and towards the end of the intervention, to review any progress made and to ensure that goals established during meetings with the psychological practitioner do not have any negative impact on physical comorbidities. The control group would continue to receive routine care. At baseline, 6 and 12 months, patients would be asked to complete questionnaires, including questions to assess mood (GAD-7/ PHQ-9), QoL (SF-36) and disease activity (VAS Pain). Outcomes between the intervention and control groups could then be compared, with adjustments made for potential confounding factors.

This proposed trial would help to determine the effectiveness of a primary care intervention to identify and treat mood problems in people with IRCs. Alternatively, to help assess the impact of treating comorbid mood problems on treatment response, morbidity and mortality, people commencing biological drug treatments or disease

modifying anti-rheumatic drugs (DMARDs) could be recruited from secondary care. All participants at baseline could be assessed using questionnaires for mood problems, and if identified, could be randomised to a similar intervention, involving behavioural activation or CBT delivered by a psychological wellbeing practitioner. Follow-up questionnaires at six and twelve months could include questions to assess treatment response, in addition to QoL and mood. Alternatively, follow-up assessments could involve face-to-face clinic appointments, supported by blood tests, to enable DAS28 scores to be calculated. Determining the impact of treating mood problems on rheumatological outcomes could support guideline changes to inform rheumatologists to routinely monitor mood, consider the impact of anxiety and depression on DAS28 scores when making treatment decisions, and signpost patients for the treatment of mood problems.

Despite literature reporting the negative impact of depression in people with RA, further research is required to determine the impact of comorbid mood problems in AS, PsA, PMR and GCA, on disease activity and treatment response. This could be addressed by the following research question.

What is the impact of comorbid anxiety and/ or depression on disease activity and treatment response in people with AS, PsA, PMR and GCA?

As all of these IRCs are managed differently, some more predominantly within primary care, separate studies could be performed for each condition. For example, a secondary care cohort of people with PsA starting on a DMARD or biological drug treatment could be identified. All of the cohort could be assessed for mood problems by questionnaire and have their baseline disease activity recorded. During follow-up

assessments at three, six and twelve months, mood problems and disease activity could be reassessed. The association between symptoms of anxiety and/ or depression and disease activity over time could then be determined.

A cross-sectional study would enable the impact of mood problems on disease activity in several IRCs to be analysed within a single study. However, this would not enable causal associations over time to be determined. Participants could be identified using electronic primary care records. Questionnaires could be sent to people with AS, PsA, PMR and GCA, including questions to identify potential mood problems (PHQ-8 and GAD-7) and to assess disease activity, for example using VAS Pain, or a numerical rating scale (NRS) for pain and stiffness. The cross-sectional association between anxiety and/ or depression and VAS Pain or the NRS scores for pain and stiffness could then be analysed. These potential studies would help to inform clinicians about the impact of mood problems on treatment response, whilst also supporting guideline changes to reflect the need for regular case-finding for mood problems in a range of different IRCs.

My systematic review meta-analysis was limited by lack of data for statistical pooling. As anxiety frequently exists in isolation from depression and can be associated with different help-seeking behaviour (Fine et al., 2008), future studies analysing comorbid mood problems should consider reporting anxiety and depression separately, to enable their individual effects to be analysed. The future availability of suitable data could then allow stronger conclusions to be drawn from a meta-analysis of the impact of anxiety on QoL and disease activity in people with RA.

Future analysis of the incidence and prevalence of mood problems in people with IRCs could take advantage of a larger national database such as CPRD, which would help to increase statistical power, enabling stronger conclusions to be made, whilst also

providing more generalisable results.

A full trial of the INCLUDE review would also provide more questionnaire data, to enable further analysis of the prevalence of mood problems in different IRCs. As some people have more than one IRC, this should be considered as a potential confounding factor, when examining associations between particular IRCs and outcome measures in future studies. A larger amount of data, derived from a national population would make results more generalisable and increase the strength of evidence, to ensure an effective, evidence-based annual review is developed for implementation nationally, to improve overall outcomes for people with IRCs.

9.5 Reflections

My research experiences have had wide-ranging impacts on my clinical practice, whilst my work as a GP has reciprocally influenced my academic work. Background reading in relation to my studies has led me to improve my knowledge of QOF targets, particularly in relation to RA. As a consequence, I have recommended a more robust system of annual reviews delivered by a nurse at my practice, to ensure that reviews include case-finding for potential mood problems, FRAX risk calculation and case-finding for potential anxiety and depression.

Meanwhile, my knowledge of the features of IRCs has significantly improved. On seeing an individual with evidence of synovitis consistent with a potential IRC, I refer to rheumatology without waiting for the results of blood tests, to help avoid any unnecessary delays in diagnosis and treatment.

The most significant impact my background reading and subsequent studies have had on my clinical practice, relates to the identification and management of mental

health problems in people with LTCs, which I will later reflect on further, as I discuss the impact my four studies have had on my work as a GP. Alongside each of these studies I will also reflect on my academic learning and progress.

Considering my first qualitative study, I felt confident approaching patients who had attended local rheumatology clinics to interview them about their experiences, due to regularly meeting new people through my clinical work. However, through my early GP training, I had been required to develop communication skills that enabled me to complete consultations within 10 minutes. Therefore, I had to adapt my usual style of communication. Whereas in a GP consultation, I would begin with an open question, then used more closed questions to obtain details required to make a clinical decision, I had to keep my questioning open, to facilitate deeper insights and obtain richer data.

The length of my interviews was varied, with the first being particularly short. At first I was concerned that this was due to me not effectively building rapport, though through subsequent interviews I came to recognise that the length was largely influenced by different peoples' personalities. In particular, more extroverted or lonely interview participants were inclined to diverge from the questions asked, hence longer interviews were not necessarily more insightful.

During interviews, I had to closely interact with participants, during which time my role as an interviewer and a GP, potentially influenced patients' perspectives. Denscombe described the "interviewer effect", whereby an individuals' perception of their interviewer influences their response to questions (Sim & Wright, 2000, p109), with social differences such as nationality, race, class, age, gender and socioeconomic status all potentially affecting the establishment of rapport. When GPs participating in qualitative studies were interviewed by a peer, rather than a researcher from another

discipline, more personal accounts were obtained from interview participants. However, for several participants, the GP interviewer was identified as an expert and judge of clinical decision making, potentially making them afraid of saying something clinically inaccurate or reluctant to disclose negative views (Chew-Graham, May & Perry, 2002).

For my qualitative study, I intended to interview patients, to explore their perspectives of mood problems, including their interactions with GPs. If I had informed participants that I was a GP prior to interviewing them, they could have been more reluctant to disclose negative views of clinicians, or afraid of saying something clinically inaccurate. Therefore, to try and obtain more insights, I introduced myself as a researcher and not a GP when conducting interviews.

As discussed in my methodology chapter, for my qualitative study, I undertook a "value-bound" approach (Sim & Wright, 2000), acknowledging that by interacting with patients during interviews, I would become an integral part of the research. However, I understood that I needed to be open about how my own preconceptions and experiences as a GP could have influenced the study. I also recognised that I needed to reflect on any changes to myself, precipitated by my involvement in the research. As described by Lincoln and Guba (1985), through a process of reflexivity, I tried to maintain my awareness of these processes by making diary entries after interviews to reflect on. I also regularly discussed interview extracts and my interpretation of these with colleagues. Had I just discussed extracts with one, more senior researcher, I may have struggled to challenge their views. In addition, if we had both held similar world viewpoints, we may have overlooked hidden meanings within interview extracts. Therefore, two supervisors with different clinical and research expertise contributed to

the interpretation of interview extracts. Having multiple investigators on a study has been shown to promote dialogue and potentially reveal hidden beliefs or perspectives from qualitative data (Barry et al., 1999).

Interviewing patients in my qualitative study, conversely impacted on my clinical consulting style. Patients' perspectives of GPs as frequently dismissive or lacking time to discuss mood concerns, made me more aware of ensuring I responded to patient cues, particularly in relation to comorbid mental health problems. However, I recognised that it would not be practical to always give the time patients wanted within a 10 minute GP consultation. Therefore, I drew on other patients' perspectives disclosed during interviews. For example, some participants had reported that rapport with their GP, encouragement to attend follow-up and continuity of care all facilitated disclosure of mood concerns. I tried to ensure that any further concerns were acknowledged and arranged a follow-up appointment with myself, to enable time to discuss these concerns further.

Throughout these studies, I developed and applied a wide range of research skills. I helped to complete an application for ethical approval, developed and amended topic guides, performed semi-structured interviews, coded data and completed a thematic analysis. In addition, I lled my first PPIE group to discuss the interpretation of interview extracts and to seek advice regarding dissemination to patients. I also collaborated with patients to develop a patient information leaflet and presented my first research, orally and as a poster at several conferences (see appendix 27 for a list of conference presentations). Through these conferences, I learnt about the importance of networking and started to gain confidence with succinctly communicating my

research aims and outcomes. I also gained experience of preparing my first research article for publication.

During my second study, a systematic review, I learnt about how to perform a meta-analysis to pool data on the correlations between anxiety and different outcome measures, whilst building on my knowledge of quality assessment and the appraisal of research studies by attending a systematic review course, in addition to a course on the critical appraisal of research articles. This knowledge was applicable to my work as a GP, helping me to evaluate new research evidence and make informed decisions about whether to implement recommendations in my clinical practice. In particular, when patients approached me with newspaper articles regarding a "medical breakthrough", I felt more confident evaluating the research behind these statements and communicating findings in lay language. I further developed my skills in the appraisal of research evidence, by reviewing research articles using a variety of study methods, submitted to several journals.

I anticipated that PPIE involvement in a systematic review would be difficult, but by avoiding the use of jargon when explaining the principles of a systematic review, I was able to ensure that participants understood the reasoning behind my study. Their understanding was demonstrated by their subsequent questions about the size of different studies included in the review, the comparability of different research articles and the quality of evidence found.

One main challenge of my systematic review was recruiting different researchers to help select relevant articles and extract data. I negotiated to help on a colleagues' systematic review in return for their assistance, whilst in exchange for another colleague's help, I agreed to co-author an article reporting on the extra-articular impacts

of RA (in list of publications, appendix 2). Competing demands on their time meant that the review took longer than anticipated. In addition, feedback on a draft article to submit for publication was delayed, and as further relevant literature was published, I had to update my search. However, I later found that by setting a target submission date, I was able to facilitate more timely responses from colleagues.

For my cohort study, my clinical knowledge was valuable when determining which covariates to include, that could have potentially confounded the association between anxiety and QoL or disease activity. I also used my clinical expertise to review Read code lists for different covariates, to help determine which were applicable. Through this process, I drew on training I had received completing a masters' module in statistics and epidemiology, interpreting the meaning of data obtained, whilst I also built my confidence in using different statistical software, including SPSS and Stata. One of the main challenges with this study were time delays in obtaining data for analysis, which meant I had to be flexible with my schedule and spend time on other projects. I reflected that on planning any future research project I would need to anticipate potential time delays, though this was not achievable within my fixed-term PhD.

As a co-applicant in the INCLUDE study, I learned about the procedures involved in a pilot trial. I helped to review grant applications and a research protocol, whilst by attending regular multidisciplinary team meetings, I was able to learn from the variety of professionals involved, from statisticians to health informatics, qualitative and mixed methods researchers. In particular, I learnt about the role of trial steering committees and the support offered by the Clinical Trials Unit.

Drawing on my primary care expertise, I co-facilitated a stakeholder group, attended by GPs, nurses and healthcare assistants, to obtain advice about the feasibility

and practical application of the INCLUDE review. I used my clinical knowledge to co-develop and deliver the INCLUDE nurse training, which included slides, role play, use of simulated patients and in practice training using EMIS software. Through this process, I gained teaching experience and solidified my own confidence in the assessment and communication of risk to patients. In particular, I gained confidence in discussing QRisk2 results in lay language, calculating FRAX risk scores and assessing suicide risk. These experiences of teaching and mentoring will be applicable in the future when I become involved in training and supporting a wider primary care team.

For the INCLUDE study, I also helped to design an EMIS template for the nurses to use to record the review. The skills I acquired through this process will enable me to develop clinical templates in practice, to ensure appropriate information is recorded within patients' records during consultations. In addition, I helped to develop the INCLUDE study questionnaire. Through this process, I learnt about the importance of clear, lay instructions. I also reflected on the challenges of determining what essential questions to include in a questionnaire, without allowing it to become too long, which could adversely affect completion rates.

As a member of the qualitative team on INCLUDE, I also contributed to the development of a qualitative protocol and helped to formulate topic guides for the patient, GP and nurse interviews. I helped to complete fidelity checks of the INCLUDE consultations, gaining experience of developing a fidelity checklist and helping to evaluate the success of training and determine points for future improvement. Attending regular qualitative meetings, I was also able to contribute to the analysis of interview extracts, which frequently drew parallels with my original qualitative study, when patients' experiences of case-finding for mood problems were discussed.

By leading PPIE involvement throughout the INCLUDE study, I was able to take account of patients' perspectives when determining priorities for the INCLUDE review, developing patient-facing study documents and writing topic guides for interviews. PPIE members also gave suggestions for how to disseminate the INCLUDE study findings and potential improvements that could be made prior to a full trial of the intervention. I was also able to use my own knowledge of the strengths and potential limitations of general practice when testing a new intervention, to evaluate suggestions made by participants. I have been able to share and present my experiences of PPIE involvement within the INCLUDE study at conferences and have wrote a blog for the SPCR highlighting the potential contributions of patients to a pilot trial (https://www.spcr.nihr.ac.uk/news/blog/involvement-within-the-include-study).

Analysing the INCLUDE baseline questionnaire data after completing my cohort study, has prompted me to draw comparisons between data from different sources and question the appropriateness of different research techniques. Statistical knowledge gained from my cohort study and through the analysis of data from the INCLUDE study, has further enhanced my abilities to evaluate and explain research to patients, as tested in the associated PPIE groups. When discussing these studies with a PPIE group, they were surprised by the disparity in prevalence rates between mood problems recorded using Read codes in primary care electronic health records, compared to anxiety and depression identified through the use of the case-finding questions within the INCLUDE study questionnaires.

PPIE involvement across my studies has enhanced my understanding of the potential breadth and depth of contributions that patients and the public can make to research. Alongside the PPIE meetings I have led, I have attended local meetings of

patients and research users, where I have been able to present and further disseminate my research findings. I have worked with patients who are members of national arthritis societies, helping to lead meetings to inform local people about IRCs. In addition, I have met with members of trial steering committees, people who help to review grant applications, individuals who are co-investigators on research studies and members of the public who volunteer as journal reviewers or have co-written articles for publication. Rather than being consulted about research, patients and the public can be active collaborators in designing, implementing and evaluating research, roles highlighted by national standards for public involvement (Involve, 2019), which crucially help to ensure that research remains relevant to patients.

In the future, I hope to apply my experiences of working with patients in primary care by facilitating meetings of our practices' patient participation group. As well as influencing my consulting style and communication with patients, working as a researcher has developed my skills in communicating key points when making written referrals or seeking advice from specialists on the telephone. In particular, presenting my thesis in 3 minutes has developed my ability to communicate ideas and concepts succinctly.

Furthermore, my exposure to academic general practice has enabled me to promote careers in academic primary care to medical students I have mentored, as a personal development tutor. I have also been able to educate and inform clinical colleagues about the amount of valuable work academic GPs do in advancing clinical practice, which I feel often requires greater appreciation. It has been rewarding to offer clinical insights to academic colleagues, struggling to comprehend medical concepts.

Within my academic position, I have also learned about further opportunities for involvement in research within primary care, for instance, as a research ready practice.

At times, I have sacrificed my work/ life balance in order to grasp new opportunities or meet deadlines. Reflection on these experiences has taught me to be more confident in evaluating my ability to take on work, be aware of my personal limits and learn to decline extra work when appropriate. However, I have particularly enjoyed the opportunities to travel around the country, meet new and inspiring people and compete with other researchers when presenting my work, and I feel I have been resilient in responding to the demands of a portfolio career.

CHAPTER 10
Conclusions

Through 4 connected studies reported in this thesis, I have explored the perspectives of people with rheumatoid arthritis (RA) on comorbid mood problems, determined the impact of anxiety in people with RA on quality of life (QoL) and disease activity and investigated the incidence and prevalence of mood problems in different inflammatory rheumatological conditions (IRCs), using Read codes from primary care electronic health records, in addition to patients' responses to the case-finding questions.

I have determined that mood problems in people with IRCs are common, potentially under-recognised within primary care, and associated with increased disease activity and a reduced QoL. Through my qualitative study, I have established that the case-finding questions for anxiety and depression are acceptable for people with RA, when delivered in the context of a nurse-led annual review.

Through my extensive dissemination activities, I have shared my results with a broad range of primary and secondary care physicians, researchers and most importantly the public. I have raised awareness of the frequency and impact of comorbid mood problems, whilst also emphasising the positive impact that improved recognition of anxiety and depression could have on the lives of people living with IRCs. In addition, I have highlighted the need for clinicians to give mental and physical health problems equal priority and to build rapport with patients over time to facilitate disclosure of concerns. I have also worked to inform and empower patients with IRCs, to help them to identify and seek appropriate support to manage comorbid anxiety and depression.

The findings from my 4 studies, alongside the valuable contributions of patients involved in my research, have contributed to the development of a pilot nurse-led

review for people with different IRCs, based in primary care. If successful, the intervention will go to trial, potentially helping to improve the recognition of comorbid mood problems in people with IRCs nationally. In addition to this planned study, future research could aim to determine whether active assessment for and management of mood problems, could improve overall outcomes for people with IRCs.

CHAPTER 11
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CHAPTER 12
Appendices

Appendix 1- Research prizes

Prizes from research completed as part of the thesis

- PhD student of the year nomination, Find a PhD, 2019.
- 3 minute thesis prize, ILAS Postgraduate Conference, Keele University, 2018.
- Systematic review prize, Postgraduate Symposium, Keele University, 2018.
- Highly commended poster prize, SPCR Research Showcase, 2018.
- Highly commended prize, "Best example of innovation in PPIE", SPCR, 2018.
- Oral presentation first prize, GPACF Conference, Sheffield, 2017.
- Oral presentation prize, West Midlands Annual Clinical Academic Training Event, Birmingham, 2017.
- Poster prize, RCGP Midland Faculty Annual Education, Research and Innovation Symposium, 2016.
- Research poster prize, RCGP Annual Conference, Harrogate, 2016.
- Best poster prize, Celebration of 10 years of PPIE at the Keele Research Institute, 2016.

Prizes from research completed alongside the thesis

- Best poster prize, A person-centred approach to physical-mental multimorbidity conference, Keele University, 2019.
- Audit poster prize- shortlisted, RCGP Annual Conference, Harrogate, 2016.
- Clinical case best poster prize, RCGP Midland Faculty Annual Education, Research and Innovation Symposium, Warwick University, 2016.

Appendix 2- Publications

Publications from thesis research

Machin, A.R., Hider, S., Dale, N. & Chew-Graham, C.A. (2017). Improving recognition of anxiety and depression in Rheumatoid Arthritis: a qualitative study in a community clinic. *British Journal of General Practice.* 67(661), e531-e537. doi: 10.3399/bjgp17X691877.

Hider, S.L., Blagojevic-Bucknall, M., Cooke, K., Cooke, K., Finney, A., Goddin, D., Healey, E.L., Hennings, S., Herron, D., Jinks, C., Lewis M., Machin, A., Mallen, C., Wathall, S., Chew-Graham, C.A. (2018). The INCLUDE study: INtegrating and improving Care for peopLe with inflammatory rheUmatological DisordErs in the community; indentifying multimorbidity: Protocol for a pilot randomized controlled trial. *Journal of Comorbidity*. 8(1). doi: 2235042X18792373.

Other research published whilst completing the thesis

Scott, I.C., Machin, A., Mallen C., Hider, S.L. (2018). The extra-articular impacts of rheumatoid arthritis: moving towards holistic care. *BMC Rheumatology*. 2, 32. doi.org/10.1186/s41927-018-0039-2.

Muller, S., Hider, S., Machin, A., Stack, R., Hayward R.A., Raza, K., Mallen, C. (2019). Searching for a prodrome for rheumatoid arthritis in the primary care record: A case-control study in the Clinical Practice Research Datalink. *Seminars in Arthritis & Rheum*atism. 48(5), 815-820. doi: 10.1016/j.semarthrit.2018.06.008.

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Blog

Machin A. Patient involvement within the INCLUDE study. Available from: https://www.spcr.nihr.ac.uk/news/blog/involvement-within-the-include-study [Accessed 1st August 2019].

Appendix 3: BJGP Paper reporting qualitative study

Research

Annabelle Machin, Samantha Hider, Nicky Dale and Carolyn Chew-Graham

Improving recognition of anxiety and depression in rheumatoid arthritis:

a qualitative study in a community clinic

Abstract

Background
Comorbid anxiety and depression are common in patients with rheumatoid arthritis (RA) but are often under-recognised and treated, contributing to worse outcomes. National Institute for Health and Care Excellence (NICE) recommends that patients with RA should be offered a holistic annual review, including an assessment of mood.

Aim
To explore patients' perspectives of anxiety and depression in RA and preferences for disclosure and management of mood problems.

Design and setting
Qualitative interview study with patients recruited from a nurse-led RA annual review clinic in the Midlands, England.

Method
Patients attending the clinic who scored ≥3 on the case-finding questions (PHQ-2 and GAD-2) were invited for interview. Data were analysed thematically using principles of constant comparison.

Results
Participants recognised a connection between their RA and mood, though this was perceived variably. Some lacked candidacy for care, normalising their mood problems. Fear of stigmatisation, a lack of time, and the perception that clinicians prioritise physical over mental health problems recursively affected help-seeking. Good communication and continuity of care were perceived to be integral to disclosure of mood problems. Participants expressed a preference for psychological therapies, though they reported problems accessing care. Some perceived medication to be offered as a 'quick fix' and feared potential drug interactions.

Conclusion
Prior experiences can lead patients with RA and comorbid anxiety and depression to feel they lack candidacy for care. Provision of equal priority to mental and physical health problems by GPs and improved continuity of care could help disclosure of mood concerns. Facilitation of access to psychological therapies could improve outcomes for both mental and physical health problems.

Keywords
anxiety; arthritis, rheumatoid; case-finding; depression; GAD-2; PHQ-2.

INTRODUCTION

Rheumatoid arthritis (RA) is a common inflammatory long-term condition (LTC) leading to joint pain, swelling, and deformity.[1] In common with other LTCs,[2] RA is associated with an increased prevalence of both depression and anxiety (estimated to affect 39% and 20% respectively).[3,4] Coexistent mood disorders in RA are associated with reduced remission rates,[5] increased morbidity and mortality,[6] and raised healthcare costs.[2] Despite this, studies suggest that anxiety and depression are under-recognised and under-treated.[7] Therefore, the recognition and treatment of mood disorders in RA should be a healthcare priority to improve outcomes.

Although the Quality and Outcomes Framework (QOF) incentivises an annual review of RA, this does not specify mood assessment.[8] However, the National Institute for Health and Care Excellence (NICE) does recommend that clinicians assess mood within the context of an annual review.[9] Whether this should occur in primary or secondary care or how mood should be assessed is not specified.[9]

Despite QOF incentives and NICE guidelines promoting an RA annual review, evidence suggests that the care of patients with RA is fragmented.[10] A recent national GP survey showed that primary care RA annual reviews focus on cardiovascular disease (CVD) and osteoporosis screening, leading to duplication of some tests, while other key elements, such as case-finding for anxiety and depression, are lacking.[11]

The NICE guidelines for identification of depression in adults with chronic physical health problems[12] suggests that the most sensitive tools for case-finding are the General Health Questionnaire (GHQ-28) and the two-stem questions of the Patient Health Questionnaire (PHQ-9), with the two-stem questions (Generalised Anxiety Disorder Scale (GAD)-2 and PHQ-2) being popular due to their ease of use.[13]

There is evidence that psychological interventions in RA are effective in the management of anxiety, depression, and pain.[14,15] Self-management interventions to support patients to manage aspects of their RA independently have also been found to have positive effects on pain and psychological wellbeing.[16,17]

There is limited literature exploring patient and practitioner perspectives on the identification and management of mood disorders in RA.

Because RA is associated with an increased prevalence of anxiety and depression, and because the case-finding questions are useful screening tools in other LTCs, further research is required

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How this fits in

Anxiety and depression are common in RA and negatively impact on outcomes. Patients reported normalising their mood problems, perceived clinicians to prioritise physical over mental health concerns, and reported GP appointments to be anxiety-provoking, recursively affecting help-seeking. Use of the PHQ-2 and GAD-2 questions in the context of an annual review for patients with RA may promote discussion about mood, thus enabling mood problems to be addressed through signposting to appropriate interventions, improving care and outcomes.

to identify barriers and facilitators to disclosure.

A nurse-led RA annual review clinic was established at two community hospitals in the Midlands, England. This study aimed to recruit patients with RA and comorbid mood disorders from the annual review clinic to interview, in order to explore their perspectives of anxiety and depression in RA and preferences for disclosure and management of mood problems.

This article reports analysis of interviews with patients who had attended the review clinic.

METHOD

Recruitment

Patients with established RA normally attending consultant rheumatology clinics for review were invited to attend a pilot nurse-led annual review clinic that aimed to offer a more holistic assessment than their routine secondary care review. Patients were asked to complete a short questionnaire, including key domains highlighted by NICE.[18] This had been jointly designed with a local patient group who suggested changes to make it more easily readable. This included work status, self-reported comorbidities, disease activity, and physical function, together with the PHQ-2 and GAD-2, to case-find for comorbid anxiety and depression.[19,20]

Between October 2015 and August 2016, patients scoring ≥3 on the PHQ-2 and/or GAD-2 (Box 1) were invited to take part in a single face-to-face interview. Ethical approval was obtained.

Interviews

Interviews were conducted by an academic GP registrar supervised by an experienced qualitative researcher. The interviewer introduced themselves as a researcher and did not disclose their identity as a GP registrar, to ensure that participants spoke more freely about their experiences of consulting healthcare professionals. Written consent was obtained prior to each interview.

Interviews were face to face and semi-structured, supported by a topic guide. The interviewer explored patients' perspectives of anxiety and depression in RA, views of the nurse-led annual review clinic, experiences of discussing mood problems with healthcare professionals, and preferences for management. The topic guide was refined during the course of the study, taking account of emerging analysis. This included the addition of questions to further explore past experiences of help-seeking for anxiety and depression.

All interviews were audiorecorded and lasted between 12–73 minutes, with an average length of 34 minutes. Fourteen interviews were required to reach data saturation.

Analysis

The first seven interviews were transcribed verbatim by the interviewer to increase familiarity with the data. An independent transcription company was subsequently used, but each transcript was checked against the digital recording and anonymised by the interviewer. Analysis began as soon as the first transcript was available. Therefore, data collection and analysis were conducted concurrently, enabling modification of the topic guide to reflect emerging themes.

Data were analysed using principles of constant comparison.[21] In order to generate conceptual themes, inductive coding of text segments, followed by re-coding and memo writing, was used. Regular meetings took place between the study team members to agree analysis and salient themes.

Following analysis of the first seven transcripts, 'access to care' was noted to be a key emerging theme. Therefore, a secondary analysis was performed using a framework approach.[22] This included three important concepts surrounding Dixon-Woods's model of access to care.[23,24]

Candidacy. This referred to the process by which a person's eligibility to use a service is formulated through their local interactions with health services.

Concordance. This indicated the importance of a match between a user's and practitioner's narrative, and successful access to an intervention.

Box 1. The case-finding questions for anxiety and depression[19,20]

Case-finding questions	PHQ-2	GAD-2
During the past month have you been bothered by ...	Feeling down, depressed, or hopeless	Feeling nervous, anxious, or on edge
	Having little interest or pleasure in doing things	Not being able to stop or control worrying

GAD-2 = Generalised Anxiety Disorder Scale-2 . PHQ-2 = Patient Health Questionnaire-2.

Recursivity. This referred to the influence of a user's experiences of health services on their future help-seeking.

RESULTS

There were 171 patients attending the nurse-led annual review clinic who completed the questionnaire, with 48 (28%) scoring ≥3 on the case-finding questions, suggesting that they were anxious and/or depressed. Of 29 invited to be interviewed, 14 agreed to participate. From the 15 who did not participate, five did not respond to telephone calls, two declined due to poor physical health, one reported they were too busy, and the rest who declined disclosed no reason. Table 1 summarises the characteristics of the 14 participants, who were all white British, reflecting the demographics of the local area. More females participated, reflecting the higher prevalence of RA in women and the proportion of females attending the clinic (68%). The majority were retired, with an average age of 63 years.

Key themes that will be presented include 'making the link', 'stigma and shame', 'who to talk to?', and 'what's on offer?'. Data are given to support analysis, with a participant (P) identifier: sex: male (M), female (F); age, years; and employment status.

Table 1. Characteristics of participants (*n* = 14)

Sex	
Male	2
Female	12
Ethnicity	
White British	14
Age, years	
40–49	1
50–59	4
60–69	7
≥70	2
Employment status	
Employed	3
Retired	4
Retired through ill health	6
Unemployed	1
Index of Multiple Deprivation (IMD)[a]	
Mean	5.4
SD	2.8
Range	1–9
PHQ-2 score	
Mean	4.6
SD	1.1
GAD-2 score	
Mean	4.9
SD	1.1

[a]*Measure of relative deprivation for neighbourhoods in England, expressed in deciles from 1 (most deprived) to 10 (least deprived). GAD-2 = Generalised Anxiety Disorder Scale-2 . PHQ-2 = Patient Health Questionnaire-2. SD = standard deviation.*

Making the link

Participants perceived their RA to negatively impact on their mood, suggesting this was due to joint pain or loss of function. Some normalised this as an expected response to any LTC:

'I think with any illness low mood could be a problem. Especially when you've been used to being able to do so much, then you come down to doing so little really. It's a huge change.' (P10, M, 70, retired)

Some participants perceived their mood to negatively impact on their RA, precipitating flares:

'She said, "Do you get depressed?" and I said, "Not a lot, no, not really", but it's only until afterwards when you think about it and you think, "Yes, you do really", and it is connected to the arthritis. It does give me flare-up, no question about it.' (P8, F, 62, retired through ill health)

However, other participants, perceived their mood and RA to be separate:

'I think a lot of my anxiety and depression is to do with my personality, and I'm the person I am, with or without my arthritis.' (P7, F, 61, retired through ill health)

Some participants described having only recognised the link between their RA and mood when this was pointed out by a healthcare professional:

'... when she was saying it I was thinking, God, I feel like that, you know, it's so, it's so, like when somebody else said it, I thought, well I'm not on my own, somebody else must feel like that.' (P14, F, 71, retired)

Thus, most participants recognised an interaction between their RA and mood, though this was perceived variably. Some only recognised a link when this was suggested by a healthcare professional, facilitating discussion of mood problems

during future RA reviews. Others normalised mental health problems, potentially resulting in them not seeking help.

Stigma and shame

Several participants reported having felt too embarrassed to disclose their mental health concerns to their GP, with some perceiving their low mood as a sign of weakness:

'It was particularly at first because I had been active and I suppose periodically, you might anyway, feel a bit low you know, when things get on top of you a bit ... but certainly I did at first, I felt a bit inadequate and don't like to admit weakness and stuff like that ...' (P12, F, 70, retired)

Thus, fear of stigmatisation was a significant barrier to help-seeking for mood problems.

Who to talk to?

Several participants described appointments with their GP as anxiety-provoking, which recursively affected future help-seeking for mental health problems. Some admitted telling their doctor they were fine in order to finish their consultation quickly, meaning any underlying problems were not addressed:

'I get ever so anxious. I'm not good with, when I have doctor's appointments or medical appointments. I tend to go in and say yeah I'm fine, just so I can get out again.' (P7, F, 61, retired through ill health)

Some participants suggested that GPs prioritise physical above mental health problems:

'... doctors are busy enough with physical complaints.' (P10, M, 70, retired)

Several participants described past negative experiences of help-seeking as barriers to disclosure of mental health concerns. In addition to a lack of time, some participants perceived that their GP did not listen to their concerns:

'There are a lot of people in that surgery and you go in, you sit down, and you've got 5 or 10 minutes and then you're coming back out again and you forget half the stuff you want to really talk about because I've only gone, usually, for my medication. It's just when he does actually say, "How do you feel?" I just say, "I feel really down" and he briefly asks me why and I don't feel like I have time to tell him before he's giving me the leaflet.' (P13, F, 45, employed)

Some participants perceived their GP to be intimidating, which recursively affected future help-seeking for psychological problems:

'And you go in and he just looks at you, you know, and I think to myself, well I'm not telling you how I feel, you know ... God, well he just sits there and he's very stern looking, and you go in, and he'll say "What can I do for you?", and you think nothing, I'm out the door!' (P14, F, 71, retired)

Several participants also described a lack of continuity of care and difficulty accessing appointments when required with their GP as barriers to the disclosure of mood problems:

'I've been there years and years. I just find them a waste of time. You never get to see a doctor. You get palmed off with anybody. You're lucky if you see a doctor there, anybody. I don't feel they are bothered.' (P9, F, 68, retired)

Other participants described establishing positive relationships with their GP influenced by body language and rapport, which helped to facilitate disclosure of mental health concerns:

'I just think he'd got a really big heart and I think he was very, very understanding of how you might be feeling and very, very supportive indeed.' (P11, F, 53, employed)

Participants recognised the pressure of restricted appointment times on GPs, but felt that provision of time during individual appointments and encouragement to attend follow-up would be integral to disclosure of psychological concerns:

'I suppose it's because they are so busy and as I've said, I do understand where they're coming from, they have so many people to deal with ... and they've only got a certain length of time, you know, they're not, whilst there's some brilliant doctors about and there undoubtedly is, GPs I mean, they do have a really tough job ...' (P12, F, 70, retired)

'He's just very approachable. You just can talk to him about anything. I did go a few times and he said I must come back.' (P8, F, 62, retired through ill health)

In summary, some participants perceived their GP prioritised physical above mental health concerns and reported their appointments to be anxiety-provoking, recursively affecting help-seeking. Lack of time and poor continuity of care were perceived to be further barriers to disclosure of mood problems. However, participants suggested that good communication and encouragement to attend follow-up would facilitate discussion of psychological concerns.

What's on offer?

Participants had different views on the use of medication for anxiety and depression. Some cited a preference for non-pharmacological treatments over antidepressants:

'I think at the end of the day I think I'd go down the line of, because I take a lot of medication, go down the line of perhaps talking to somebody first, definitely try that before I had any medication.' (P14, F, 71, retired)

Another participant was prompted by the RA annual review nurse to consider that a medication change could be helpful:

'... she said to me, have you tried a different antidepressant, because I've been on the fluoxetine for several years, and she said there are antidepressants that are for social anxiety ...' (P7, F, 61, retired through ill health)

Others perceived medication to be offered as a 'quick-fix' option, due to reduced funding for psychological therapies. As a result, they had considered private therapy:

'I've got a friend who's, well she's retired now but she is a psychotherapist and I've often thought, perhaps I should talk to X, because she knows my mum as well so well, she worked privately but she did do work for the NHS because she did work across there for the surgery at that time, but of course cutbacks, they cut all that sort of stuff out and they dish out the pills these days, more of them I think sadly.' (P12, F, 70, retired)

Some participants reported problems accessing talking treatments when signposted by their GP:

'I think once you start offloading to one person and then you have to come home and make a phone call to go and see other counsellors, it puts people off because there are waiting times. They're ridiculously long.' (P13, F, 45, employed)

For those who had been able to access psychological support, it was perceived as beneficial:

'... this cognitive behaviour. And I found it really useful, because it's challenging your own thoughts, and I thought, yes, I am my own worst enemy.' (P7, F, 61, retired through ill health)

Overall, participants expressed a preference for non-pharmacological treatments, particularly psychological therapies. Some reported problems accessing treatment, recursively affecting future help-seeking, though those receiving psychological support perceived it to be helpful.

DISCUSSION

Summary

Most participants recognised the negative impact of RA on their mood, with some also perceiving low mood or anxiety to precipitate RA flares, though several only acknowledged a link between RA and their mood when this was highlighted by a healthcare professional.

Some participants lacked candidacy for care, normalising their mood problems as an expected response to suffering from RA. Others were prevented from seeking help due to fear of stigmatisation. Perceived prioritisation of physical above mental health concerns by GPs recursively affected help-seeking. A lack of time and poor continuity of care were reported as further barriers to disclosure.

However, several participants reported establishing positive relationships with their GP and felt continuity of care with encouragement to attend follow-up would be integral to the disclosure of mental health concerns.

Participants cited a preference for psychological therapies, though several reported problems accessing care. Whereas some participants were open to pharmacological treatments, others perceived medication to be offered as a 'quick fix' by their GP and feared potential drug interactions.

Strengths and limitations

Use of qualitative methods with an exploratory approach ensured new phenomena were identified. A second

stage of more detailed framework analysis enabled deeper insights into the barriers and facilitators to patients accessing care for psychological problems.

The topic guide was piloted with patients and practitioners to ensure face validity. This was also refined over the course of the study to ensure exploration of emerging themes.

A potential limitation was that only patients with a high PHQ-2 or GAD-2 score were interviewed. It is likely that different views would have been articulated by patients who did not have anxiety or depression.

Participants were predominantly retired white British females (reflecting the local demographics), hence a greater range of perspectives may have been obtained from a more diverse sample. Participants were identified and recruited through a secondary care clinic, meaning they were all from the same area of England. However, a range of different socioeconomic statuses were included (Table 1).

Comparison with existing literature

In common with other LTCs,[25] this research suggests that patients with RA may recognise an interaction between their chronic physical illness and anxiety or depression. However, those who do not perceive a relationship between their mood problems and LTC may not understand the intention behind asking about mood during LTC reviews.[26]

Patients with RA, in addition to other LTCs,[27] can lack candidacy for care, failing to seek help for their anxiety and depression due to perceiving this to be a normal response to suffering from a chronic physical illness.

Patients with LTCs may not seek help for mental health problems due to associated stigma.[28] This finding was echoed in a study of Hispanic patients with RA,[29] who perceived psychological problems as a sign of weakness. Further barriers to help-seeking for anxiety and depression in patients with RA were identified within this study. These included a perception of GPs being dismissive of mental health concerns and appointments being anxiety-provoking, recursively affecting help-seeking. Further barriers to help-seeking included a lack of time and poor continuity of care.

However, patients reported being more receptive to the discussion of mood concerns when they had established rapport with their GP.

In common with existing literature,[29,30] patients with RA expressed a preference for talking treatments, wishing to avoid medication due to potential side effects or interactions with existing RA treatments. Patients with RA reported struggling to access psychological therapies due to long waiting times and perceived cuts in funding, suggesting a need for improvement in access to psychological support, as recognised in a survey of rheumatology nurses in 2012.[24]

Implications for research and practice

Though some patients with RA and comorbid anxiety and/or depression recognise the interaction between their arthritis and mood problems, others only make this link when it is highlighted by a clinician. Therefore, it is important that mood is explored as part of an annual review for RA patients, whether this is conducted in primary or specialist care, as improved recognition and management of anxiety and depression could lead to reduced overall morbidity and mortality.

GPs need to give equal priority to mental and physical health problems to facilitate disclosure of distress. Provision of time during individual appointments and encouragement to attend follow-up with the same GP to support continuity of care could be integral to the disclosure of mood concerns.

It is a policy imperative for improving access to psychological therapies (IAPT) to deliver care for people with depression and LTCs, hence, for patients who are anxious about self-referral, GPs should make referrals to IAPT. Given the negative impact of mood on outcomes in RA, such an intervention should be a priority.

Given the primary care expertise in managing multimorbidity, developing practice nurse-led models of care may improve outcomes for patients with RA, providing patient and cost benefits by preventing duplication of care while enabling earlier intervention and management of multimorbidities.

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Ethical approval

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Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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Appendix 4- *The 2010 ACR-EULAR Classification Criteria for Rheumatoid Arthritis* (Aletaha et al., 2010).

Target population includes people who:

1. have at least 1 joint with definite clinical synovitis (swelling)
2. with the synovitis not better explained by another disease

Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of 6 or more out of 10 is needed for a patient to be classified as having definite RA)

Classification Criteria	Score
A. Joint Involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	4
B. Serology (at least one result is needed for classification)	
Negative rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA)	0
Low-positive RF or low-positive ACPA	1
High-positive RF or high-positive ACPA	2
C. Acute Phase Reactants (at least 1 test result is needed for classification)	
Normal c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
Less than 6 weeks	0
6 weeks or more	1

Appendix 5- Patient invitation to RA annual review clinic

Haywood Hospital
High Lane
Burslem
Stoke on Trent ST6 7AG
[Date]

Dear [Patient Name]

Invitation to attend the Rheumatoid Arthritis Annual Review Clinic

We are writing to tell you about a new nurse led Rheumatoid Arthritis Annual Review clinic which we are starting at the Haywood hospital. When you come for your next appointment you will be offered the opportunity to attend this new clinic. To see how well this clinic works and whether patients find it useful we are also asking patients who come to the clinic to take part in a research study.

We are writing to because you have been seen at our clinic and may be eligible to come to this new clinic if you would like to. We have included an information sheet about the research study and if you would like to take part this will be discussed with you when you come to the clinic.

Your decision regarding whether to take part in the study will not affect any future care you have at this Trust.

Thank you very much for reading this letter,

Yours sincerely,

Dr SL Hider & Dr SN Kamath
Consultant Rheumatologists
Haywood Hospital

Appendix 6- RA annual review clinic patient questionnaire

Rheumatoid Arthritis Annual Review

|

Patient Questionnaire.

Thank you for agreeing to take part in the Rheumatoid Arthritis Annual Review Study.

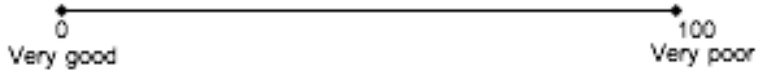
Before seeing the nurse today we would be grateful if you could complete the following questionnaire about your arthritis and health problems.

Once you have completed it please hand it to the nurse.

Clinic Use Only:

Date		Weight
Study ID		Height
Unit No		BP

1. Please place a mark on the line below. Considering all the ways your arthritis has affected you, how do you feel your arthritis is **today**?



2. We are interested in learning how your illness affects your ability to function in daily life. Please tick the **one** response which best describes your usual abilities over the **past week**:

Are you able to	Without **any** difficulty	With **some** difficulty	With **much** difficulty	Unable to do
1. Dress yourself, including tying shoelaces and doing buttons?				
2. Get in and out of bed?				
3. Lift a full cup or glass to your mouth.				
4. Walk outdoors on flat ground?				
5. Wash and dry your entire body?				
6. Bend down to pick up clothing from the floor?				
7. Turn taps on and off?				
8. Get in and out of the car?				

3. What is your current employment status? (Please put a cross in **one** box only)

Employed		Unemployed or seeking work		Homemaker	
Retired		Working part-time or not working due to ill health		Other	

4. If you are working, what is your job title, or if you are not working, or are retired, what was your last job title?

_____

5. Over the **last year** have you had any of the following? (please tick)

	Yes	No		Yes	No
Falls?			An infection requiring antibiotics?		
Fractured or broken a bone?			Been admitted to hospital?		
Shingles?					

Do you smoke?	Yes		No		Ex-smoker	
Have you had a flu-jab in the last year?	Yes		No		Not offered one	
Had you had a pneumonia jab in the last 5 years?	Yes		No		Not Offered one	
Have you **ever** had a bone density scan (DEXA) scan	Yes		No			

6. The following is a list of medical problems. Please tick yes if you have **ever had** these problems. If you do have a medical problem, please tick whether you have treatment for it and tick whether it limits your activities.

Problem	**Do you have the problem?**			**Do you receive Treatment for it?**			**Does it limit your activities?**		
	No	Yes	Don't know	No	Yes	Don't know	No	Yes	Don't know
Heart disease									
Angina/ Heart attack									
Stroke									
High Blood Pressure									
Lung Disease									
Diabetes									
Ulcer or Stomach disease									
Kidney disease									
Liver Disease									
Anaemia/ Blood disease									
Cancer									
Depression									
Osteoarthritis									
Back Pain									
Other Disease? (please list)									

7. Over the past **two weeks**, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than one-half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Not being able to stop or control worrying	0	1	2	3
Feeling nervous, anxious or on edge	0	1	2	3

8. How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy? (please tick one)

Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

9. By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today**.

Mobility:		**Self-Care:**	
I have no problems in walking about		I have no problems washing or dressing	
I have slight problems in walking about		I have some problems washing or dressing	
I have moderate problems in walking about		I have moderate problems washing or dressing	
I have severe problems in walking about		I have severe problems washing or dressing	
I am unable to walk about		I am unable to wash or dress myself	
Anxiety/Depression:		**Pain/Discomfort:**	
I am not anxious or depressed		I have no pain or discomfort	
I am slightly anxious or depressed		I have slight pain or discomfort	
I am moderately anxious or depressed		I have moderate pain or discomfort	
I am severely anxious or depressed		I have severe pain or discomfort	
I am extremely anxious or depressed		I have extreme pain or discomfort	
Usual Activities (e.g. work, study, housework, family or leisure activities)			
I have no problems doing my usual activities			
I have slight problems doing my usual activities			
I have moderate problems doing my usual activities			
I have severe problems doing my usual activities			
I am unable to do my usual activities			

10. Are you taking drug treatment for your RA? If so please tick **one** of the following

	Yes	No
Do you feel you understand enough about your RA drugs? (e.g. when to stop medication)		
Do you feel updating your knowledge about your RA drugs would be of benefit to you?		

If **yes** would you prefer to have (please tick one)

A drug information leaflet		Other (Please state)
A drug counselling appointment		

11. Is there anything about your arthritis that you'd like to discuss with the nurse today?

Thankyou for completing this questionnaire. Please hand it to the nurse.

Appendix 7- Ethical approval for qualitative study

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 3
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
www.nhsggc.org.uk

Dr Samantha L Hider
Senior Lecturer & Honorary Consultant Rheumatologist
University of Keele
Arthritis Research UK Primary Care Centre
Primary Care Sciences
ST5 5BG

Date 2nd April 2015
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail WOSREC3@ggc.scot.nhs.uk

Dear Dr Hider

Study title: **Understanding the role of an annual review clinic for patients with rheumatoid arthritis (RA).**
REC reference: **15/WS/0063**
IRAS project ID: **170210**

Thank you for your responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Liz Jamieson, wosrec3@ggc.scot.nhs.uk. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]	1.0	08 March 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Keele Insurance letter]		28 July 2015
GP/consultant information sheets or letters [Revised GP letter]	2.0	02 April 2015
Interview schedules or topic guides for participants	1.0	20 March 2015
Letter from sponsor [Sponsorship letter]		12 March 2015
Letters of invitation to participant	1.0	20 March 2015
Non-validated questionnaire [Pt questionnaire]	1.0	05 January 2015
Other [Response to REC]		31 March 2015
Other [2nd response REC]		02 April 2015
Participant consent form [Main study consent]		05 January 2015
Participant consent form [Re-revised Interview Consent]	4.0	02 April 2015
Participant information sheet (PIS) [Main study PIS]		08 March 2015
Participant information sheet (PIS) [Re-Revised Interview PIS]	4.0	02 April 2015
REC Application Form [REC_Form_18032015]		18 March 2015
Research protocol or project proposal	1.0	05 January 2015
Summary CV for Chief Investigator (CI) [Hider CV]		05 January 2015
Summary CV for student [Machin CV]		06 January 2015
Summary CV for supervisor (student research) [CCG CV]		

Summary, synopsis or diagram (flowchart) of protocol in non technical language	1.0	01 December 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/WS/0063	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Liz Jamieson

Liz Jamieson
REC Manager
On behalf of Eoin MacGillivray, Vice Chair

Enclosures: *"After ethical review – guidance for researchers"*

Copy to: *Ms Jacqueline Gray*
Ms Christine Woolvern, NIHR CRN West Midlands

Appendix 8- Patient information leaflet on face-to-face interview

Rheumatoid Arthritis (RA) Annual Review Interview Study

You are invited to take part in a research study. Before you decide to take part or not, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear, or if you would like more information. Please take time to decide whether or not you wish to take part.

What is the purpose of the study?

The aim of this study is to understand the views of patients about a new clinic for Rheumatoid Arthritis (RA). This is a nurse-led clinic and aims to offer patients an opportunity to discuss with the nurse specialist any problems they have with their RA, but also problems in other areas of their life, in particular problems with mood.

Why have I been chosen?

You have been chosen because you attended the RA clinic and had a consultation with the specialist nurse. You also ticked one of the boxes in the initial patient questionnaire which suggested you might have problems with low mood or anxiety.

Do I have to take part?

No – it is your decision entirely. If you decide to take part, you are still free to withdraw from the study at any time and without giving a reason. All information we have collected from you will be destroyed if you wish.

What will happen if I take part?

- If you choose to take part, you will be given a copy of this Information Sheet and a signed Consent Form to keep.

- The researcher, Annabelle Machin, will contact you to invite you to participate in a one to one interview. The interview will take place at the Haywood hospital or your home – whichever is you prefer. The interview will be audio-recorded with your consent and is likely to last between 30 and 45 minutes.

- The audio-recordings of the interview will be typed up and anonymised so that any personal information (such as patients' and doctors' names, addresses, or places of work) will not be included in the research. The information will be stored on secure computers at Keele University and accessible by password to the researchers.

What about confidentiality?

Although we will inform your GP that you have taken part in the study, we will not tell them details of what you have said. We will not tell anyone else what you have said, and we will not tell you anything that anyone else in the study has told us. However, should something be disclosed during the interview which gives cause

for concern, then there is a duty of care to report such disclosure to appropriate agencies.

All information collected during this study will be kept confidential. Although names will be used during the interviews, they will not be included when the recordings are transcribed. The audio recordings will be marked with an identification number only and then stored securely. Once transcribed, all audio recording will be destroyed.

Only authorised persons will have access to any information about you. You will not be named or identified in any reports of the study. We may include brief quotations from some focus groups in our reports, but we will always remove details such as names and places so nobody can be identified.

What are the possible risks and benefits of taking part?

We do not anticipate any risks. We hope this study will benefit the care of future patients with RA and the clinicians involved in their care. Some people find that taking part in studies of this sort is useful because they have a chance to air their views.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions.

If they are unable to resolve your concern or you wish to or you would like to receive free independent advice please contact PALS (Patient Advice and Liaison Service) on 0800 0851 067.

How will the data collected about me be stored and used?

All data collected for this study will be kept safely and securely on computer and on transcribed paper records. **Professor Carolyn Chew-Graham** will be the custodian of all study data. With your permission, transcripts of audio recordings of the interview will be archived and stored at Keele University for 5 years after the end of this study for possible use in future studies. Access to these by researchers not involved in the current study will be subject to further ethical review. If you do not wish this to happen, your transcript will not be made available in this way.

After all identifying details have been removed from the transcribed records the interview will be analysed by the study team. The results will be published in reports and scientific journals, but it will not be possible to identify any individuals from these reports. We will send you a summary of the results at the end of the study if you would like one.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by West of Scotland REC 3.

What do I need to do next?

If you are happy to take part, please complete the reply slip and return it to us in the stamped and addressed envelope.

Appendix 9- Interview Consent Form

Rheumatoid Arthritis (RA) Annual Review Study

Interview Study Consent Form

Identification Number: | | | | |

Name of researcher: Dr Annabelle Machin

initial box	**Please**	
1. I confirm that I have read and understand the information sheet dated 2/4/15 (version 4.0) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.		
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.		
3. I understand that audio recordings will be made as part of this study, and that brief quotations from the interview may be included in study reports without giving my name or disclosing my identity.		
4. I agree to transcriptions *(a* written or electronic record) of the interview being stored at Keele University for up to 5 years after the end of this study. I understand that these will be held securely and that access to these by researchers not involved in the current study will be subject to further ethical review.	Yes	No
5. I agree to my GP being informed that I will be taking part in the study.		
6. I understand that relevant sections of the data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access these notes.		
7. I would like to receive a summary of the findings at the end of the study.	Yes	No
8. I agree to take part in the study.		

Name of participant	Date	Signature
Name of researcher	Date	Signature

When completed, one copy for participant, one for researcher file.

Appendix 10- Topic Guides

Topic Guide 20th August 2015

Introductions, Express thanks for participating.
Explanation of purpose of interview (answer any queries); reassure re confidentiality; and gain signed Consent (x2 copies- one for patient, one for us)
Turn recorder on.

Can you tell me a bit about your health condition(s)?
(Allow patient to initially describe all health conditions before moving on. Check if they have any other annual reviews eg. for diabetes)

- Could you tell me
    - How long you have had RA?
    - How your Rheumatoid Arthritis affects you?
- Who do you see for support in managing your RA?
    - explore role of GP, PN, hospital, other
    - how often seen?
    - What do each do?
    - Any other support (family/friends/complementary therapies)

Can you tell me what you expected before you came to the clinic?

- Did you know who you were going to see and what they would do?
- Can you tell me what was covered in the clinic?
- How did you feel about completing the questionnaires?
- Were you asked about your mood at the clinic?
    - Did you expect this?
    - Did you feel able to talk about your mood?
    - If yes, how did this feel?
    - If no, did you want to? (or did you not have any mood problems to discuss)
- Do you think this clinic is the place to discuss problems with mood?
    - If so, why?
    - If not, why not?

Was there anything else you would have wanted to discuss with the nurse?...explore

At the clinic, did you feel involved in making decisions regarding your care? …explore

Topic Guide 11th September 2015 (New questions underlined and in italic)

Can you tell me a bit about your health condition(s)?
(Allow patient to initially describe all health conditions before moving on. Check if they have any other annual reviews eg. for diabetes)

- Could you tell me
  - How long you have had RA?
  - How your Rheumatoid Arthritis affects you?
- Who do you see for support in managing your RA?
  - explore role of GP, PN, hospital, other
  - how often seen?
  - What do each do?
  - Any other support (family/friends/complementary therapies)

Can you tell me what you expected before you came to the clinic?

- Did you know who you were going to see and what they would do?
- Can you tell me what was covered in the clinic?
- How did you feel about completing the questionnaires?
- Were you asked about your mood at the clinic?
  - Did you expect this?
  - Did you feel able to talk about your mood?
  - If yes, how did this feel?
  - If no, did you want to? (or did you not have any problems to discuss)

Would you have felt better discussing your mood with someone other than this clinic nurse? (like with your GP, practice nurse or hospital doctor, other)?

- *If yes, why was this?*
- *If no, why did you prefer to discuss your mood at the clinic?*
- *Do you think this clinic is the best place to discuss problems with mood?*
  - *If so, why?*
  - *If not, why not?*

Did the clinic nurse talk with you about treatments available for low mood/anxiety?

- *Did the nurse refer you onto another service for help with anxiety or depression? If so, which?*
- *Would you have liked the nurse to do anything else?*

Was there anything else you would have wanted to discuss with the nurse?...explore

At the clinic, did you feel involved in making decisions regarding your care? …explore

Topic Guide 30th September 2015 (New questions underlined and in italic)

Introductions, Express thanks for participating.
Explanation of purpose of interview (answer any queries); reassure re confidentiality; and gain signed Consent (x2 copies- one for patient, one for us)
Turn recorder on.

Can you tell me a bit about your health condition(s)?

(Allow patient to initially describe all health conditions before moving on. Check if they have any other annual reviews eg. for diabetes)

- Could you tell me
    - How long you have had RA? How long have you been attending the Haywood?
    - How your Rheumatoid Arthritis affects you? (Social, family and work impact/ losses)
    - Who do you see for support in managing your RA? explore role of GP, PN, hospital, other
    - how often seen?
    - What do each do? *Who co-ordinates your care?*
    - *What is your role?*
    - Any other support (family/friends/complementary therapies)
- Some people with RA get anxious or low in mood. Has this ever been a problem for you?
  How has it affected you?
  Do you feel your anxiety/ low mood is linked to your RA or separate?

Can you tell me what you expected before you came to the clinic?

- Did you know who you were going to see and what they would do?
- Can you tell me what was covered in the clinic? *How did this clinic appointment differ from your usual ones?*
- Do you recall completing a questionnaire by yourself or with the nurse? *How did you find that? (would the patient have preferred to complete the questionnaire themselves/ for the nurse to complete it)*
- Were you asked about your mood at the clinic?
    - Did you expect this?
    - Did you feel able to talk about your mood?
    - If yes, what was it about the nurse that enabled you to open up? How did it feel to talk about your mood?
    - If no, did you want to? (or did you not have any mood problems to discuss)
- Do you think this clinic is the place to discuss problems with mood?

- If so, why?
- If not, why not?

Would you have felt better discussing your mood with someone other than this clinic nurse? (like with your GP, practice nurse or hospital doctor, other)?

- If yes, why was this?
- If no, why did you prefer to discuss your mood at the clinic?

Did the clinic nurse talk with you about treatments available for low mood/anxiety?

- Did the nurse refer you onto another service for help with anxiety or depression? If so, which?
- Would you have liked the nurse to do anything else?

Was there anything else you would have wanted to discuss with the nurse?...explore
At the clinic, did you feel involved in making decisions regarding your care? …explore

Topic Guide 22nd October 2015 (New questions underlined and in italic)

Introductions, Express thanks for participating.
Explanation of purpose of interview (answer any queries); reassure re confidentiality; and gain signed Consent (x2 copies- one for patient, one for us)
Turn recorder on.

Can you tell me a bit about your health condition(s)?
(Allow patient to initially describe all health conditions before moving on. Check if they have any other annual reviews eg. for diabetes)

- Could you tell me
    - How long you have had RA? How long have you been attending the Haywood?
    - How your Rheumatoid Arthritis affects you? (Social, family and work impact/ losses)
    - Who do you see for support in managing your RA? explore role of GP, PN, hospital, other
    - how often seen?
    - What do each do? Who co-ordinates your care?
    - What is your role?
    - Any other support (family/friends/complementary therapies)
- Some people with RA get anxious or low in mood. Has this ever been a problem for you?
  How has it affected you?
  Do you feel your anxiety/ low mood is linked to your RA or separate?

Can you tell me what you expected before you came to the clinic?

- Did you know who you were going to see and what they would do?
- Can you tell me what was covered in the clinic? How did this clinic appointment differ from your usual ones?
- Do you recall completing a questionnaire by yourself or with the nurse?
  How did you find that? (would the patient have preferred to complete the questionnaire themselves/ for the nurse to complete it)
- Were you asked about your mood at the clinic?
    - Did you expect this?
    - Did you feel able to talk about your mood?
    - If yes, what was it about the nurse that enabled you to open up? How did it feel to talk about your mood?
    - If no, did you want to? (or did you not have any mood problems to discuss)
- Do you think this clinic is the place to discuss problems with mood?

    - If so, why?
    - If not, why not?
- *What have been your previous experiences seeking help for mood-related problems?*

Would you have felt better discussing your mood with someone other than this clinic nurse? (like with your GP, practice nurse or hospital doctor, other)?

- If yes, why was this?
- If no, why did you prefer to discuss your mood at the clinic?

Did the clinic nurse talk with you about treatments available for low mood/anxiety?

- Did the nurse refer you onto another service for help with anxiety or depression? If so, which?
- Would you have liked the nurse to do anything else?

Was there anything else you would have wanted to discuss with the nurse?...explore

At the clinic, did you feel involved in making decisions regarding your care? …explore

Topic Guide 28th December 2015 (New questions underlined and in italic)

Introductions, Express thanks for participating.
Explanation of purpose of interview (answer any queries); reassure re confidentiality; and gain signed Consent (x2 copies- one for patient, one for us)
Turn recorder on.

Can you tell me a bit about your health condition(s)?
(Allow patient to initially describe all health conditions before moving on. Check if they have any other annual reviews eg. for diabetes)

- Could you tell me
    - How long you have had RA? How long have you been attending the Haywood?
    - How your Rheumatoid Arthritis affects you? (Social, family and work impact/ losses)
    - Who do you see for support in managing your RA? explore role of GP, PN, hospital, other
    - how often seen?
    - What do each do? Who co-ordinates your care?
    - What is your role?
    - Any other support (family/friends/complementary therapies)
- Some people with RA get anxious or low in mood. Has this ever been a problem for you?
  How has it affected you?
  Do you feel your anxiety/ low mood is linked to your RA or separate?
  Do you ever feel like your anxiety or low mood affect the care you receive for your arthritis?

Can you tell me what you expected before you came to the clinic?

- Did you know who you were going to see and what they would do?
- Can you tell me what was covered in the clinic? How did this clinic appointment differ from your usual ones?
- Do you recall completing a questionnaire by yourself or with the nurse?
  How did you find that? (would the patient have preferred to complete the questionnaire themselves/ for the nurse to complete it)
- Were you asked about your mood at the clinic?
    - Did you expect this?
    - Did you feel able to talk about your mood?
    - If yes, what was it about the nurse that enabled you to open up? How did it feel to talk about your mood?
    - If no, did you want to? (or did you not have any mood problems to discuss)

- Do you think this clinic is the place to discuss problems with mood?
    - If so, why?
    - If not, why not?
- What have been your previous experiences seeking help for mood-related problems?

Would you have felt better discussing your mood with someone other than this clinic nurse? (like with your GP, practice nurse or hospital doctor, other)?

- If yes, why was this?
- If no, why did you prefer to discuss your mood at the clinic?

Did the clinic nurse talk with you about treatments available for low mood/anxiety?

- Did the nurse refer you onto another service for help with anxiety or depression? If so, which?
- Would you have liked the nurse to do anything else?

Was there anything else you would have wanted to discuss with the nurse?...explore

At the clinic, did you feel involved in making decisions regarding your care? …explore

Topic Guide 18th March 2016 (New questions underlined and in italic)

Introductions, Express thanks for participating.
Explanation of purpose of interview (answer any queries); reassure re confidentiality; and gain signed Consent (x2 copies- one for patient, one for us)
Turn recorder on.

Can you tell me a bit about your health condition(s)?
(Allow patient to initially describe all health conditions before moving on. Check if they have any other annual reviews eg. for diabetes)

- Could you tell me
    - How long you have had RA? How long have you been attending the Haywood?
    - How your Rheumatoid Arthritis affects you? (Social, family and work impact/ losses)
    - Who do you see for support in managing your RA? explore role of GP, PN, hospital, other
    - how often seen?
    - What do each do? Who co-ordinates your care?
    - What is your role?
    - Any other support (family/friends/complementary therapies)
- Some people with RA get anxious or low in mood. Has this ever been a problem for you?

  How has it affected you?
  Do you feel your anxiety/ low mood is linked to your RA or separate?
  Do you ever feel like your anxiety or low mood affect the care you receive for your arthritis?

Can you tell me what you expected before you came to the clinic?

- Did you know who you were going to see and what they would do?
- Can you tell me what was covered in the clinic? How did this clinic appointment differ from your usual ones?
- Do you recall completing a questionnaire by yourself or with the nurse?
  How did you find that? (would the patient have preferred to complete the questionnaire themselves/ for the nurse to complete it)
- Were you asked about your mood at the clinic?
    - Did you expect this?
    - Did you feel able to talk about your mood?
    - If yes, what was it about the nurse that enabled you to open up? How did it feel to talk about your mood?
    - If no, did you want to? (or did you not have any mood problems to discuss)

- Do you think this clinic is the place to discuss problems with mood?
    - If so, why?
    - If not, why not?
- What have been your previous experiences seeking help for mood-related problems?

Would you have felt better discussing your mood with someone other than this clinic nurse? (like with your GP, practice nurse or hospital doctor, other)?

- If yes, why was this?
- If no, why did you prefer to discuss your mood at the clinic?

Did the clinic nurse talk with you about treatments available for low mood/anxiety?

- Did the nurse refer you onto another service for help with anxiety or depression? If so, which?
- *Would you have any preferences for treatment of anxiety or depression (including complementary therapies)?*
- Would you have liked the nurse to do anything else?

Was there anything else you would have wanted to discuss with the nurse?...explore

At the clinic, did you feel involved in making decisions regarding your care? …explore

Appendix 11: Excel document used to store patient contact details for interview participants/ record why some interviews didn't take place

Name	Patient ID	Interview date	Address	Phone number	GP Surgery	Reason if interview not performed
	1	21/9/15				n/a
	2	26/9/15				n/a
	Not Interviewed	n/a				No time
	Not Interviewed	n/a				Busy having an operation
	3	5/10/15				n/a
	4	5/10/15				n/a
	5	29/10/15				n/a
	Not Interviewed	n/a				Didn't want to participate
	Not Interviewed	n/a				Didn't want to participate
	Not Interviewed	n/a				Didn't want to participate
	6	30/11/15				n/a
	7	30/11/15				n/a
	Not Interviewed	n/a				Didn't answer phone (x3)
	Not Interviewed	n/a				Didn't answer phone (x3)
	8	30/11/15				n/a
	Not Interviewed	n/a				Meeting arranged but didn't open door when I attended
	9	28/12/15				n/a
	10	2/2/16				n/a
	Not Interviewed	n/a				Cancelled- too busy
	Not Interviewed	n/a				Didn't want to participate
	Not Interviewed	n/a				Too poorly to participate
	Not Interviewed	n/a				Didn't want to participate
	Not Interviewed	n/a				Didn't answer phone (x3)
	Not Interviewed	n/a				Didn't want to participate
	11	25/4/16				n/a
	12	31/5/16				n/a
	13	7/6/16				n/a
	Not Interviewed	n/a				Number didn't exist
	14	11/8/16				n/a

Appendix 12: Excel document used to store patient demographics and GAD-2/ PHQ-2 scores for interview participants

Patient ID	Gender	Age	Ethnicity	Employment					GAD-2	PHQ-2	1st Part of Postcode
				Employed	Off Sick	Retired	Retired through ill health	Unemployed			
1	F	54	white British	NA	ESA Benefits	NA	NA	NA	5	6	
2	F	56	white British	Part-time radiographer	NA	NA	NA	NA	3	4	
3	F	64	white British	NA	NA	NA	Y	NA	5	5	
4	F	58	white British	NA	NA	NA	Y	NA	5	4	
5	F	78	white British	NA	NA	Y	NA	NA	6	6	
6	M	70	white British	NA	NA	Y	NA	NA	3	3	
7	F	61	white British	NA	Seeking PIP	NA	Y	NA	6	4	
8	F	62	white British	NA	ESA Benefits	NA	Y	NA	5	5	
9	F	68	white British	NA	NA	NA	NA	Y	5	4	
10	M	61	white British	NA	NA	NA	Y	NA	3	3	
11	F	53	white British	Part-time teacher	NA	NA	NA	NA	6	6	
12	F	70	white British	NA	NA	Y	NA	NA	5	4	
13	F	45	white British	Part-time cleaner	NA	NA	NA	NA	5	5	
14	F	71	white British	NA	NA	Y	NA	NA	6	6	

Appendix 13: Rheumatoid Arthritis and Mood Leaflet

MOOD PROBLEMS IN RHEUMATOID ARTHRITIS

At least **one in every five people** with Rheumatoid Arthritis is affected by mood problems (anxiety and/or depression)

5. SUMMARY

Don't be afraid to open up to someone if you think you may have a mood problem. Seeking help could potentially improve both your mood and your Rheumatoid Arthritis.

Produced by Dr A Machin, NIHR Academic GPST4, Keele University

This project was funded by the Scientific Foundation Board of the Royal College of Practitioners (grant number: SFB 2015-02)

Keele University

2. WHO TO TALK TO...

If you have Rheumatoid Arthritis and think you may be suffering from mood problems, consider talking to your GP, consultant or rheumatology nurse for advice.

1. RESEARCH EVIDENCE

Local research in North Staffordshire has found that people with Rheumatoid Arthritis often struggle to open up about mood problems.

People with low mood or anxiety may not respond as well to treatments for their Rheumatoid Arthritis.

Therefore, it is important that mood problems are recognised and treated.

3. TREATMENT

TALKING THERAPIES

MIND and the Wellbeing Service offer talking therapies for people with mood problems. You can make an appointment to discuss whether this may help you by calling the numbers below. Information is also available online.

mind
for better mental health

01782 262100
mind.org.uk

North Staffordshire Wellbeing
01782 711651
northstaffswellbeing.co.uk

4. TREATMENT

MEDICATION

If your GP suspects you have anxiety or low mood, they may offer treatment with medication.

This is often more effective when combined with talking therapy.

If your mood does not improve despite talking therapy and/ or medication, referral to a psychiatrist may be offered.

Appendix 14- Systematic Review Protocol (registered on PROSPERO)

Title	A systematic review to determine the impact of anxiety on quality of life and disease activity in patients with rheumatoid arthritis
First reviewer	Dr Annabelle Machin (AM)
Other reviewers	Dr Randula Haththotuwa (RH)- 2nd Reviewer Dr Ian Scott (IS)- 2nd Reviewer Opeyemi Babatunde (OB)- 3rd Reviewer to resolve disagreements
Funding source	18 months part-time funding from the school of primary care research (SPCR) and 6 months part-time funding from the Haywood Foundation.
PROSPERO ID	CRD= 42017062580

1. Background to review

Rheumatoid Arthritis (RA) is a long-term condition characterised by synovial joint inflammation, affecting 1% of the adult population. Patients typically present with persistent joint pain, swelling and stiffness.

It is well established that patients with RA have higher rates of depression. This is often under-recognised (Cepoiu et al., 2007), which can result in increased pain, fatigue, morbidity and mortality (Ang et al., 2005). The prevalence of anxiety in patients with RA is also significantly higher than within the general population, affecting up to 20% (VanDyke et al., 2004), (Isik et al., 2006) (Covic et al., 2012). This is also under-recognised and under-treated, though the impact of anxiety in RA on quality of life and treatment outcomes is not as well researched.

This systematic review aims to determine the impact of anxiety in patients with RA on quality of life and disease activity. Improved understanding of the impact of anxiety will provide evidence to facilitate better identification and management of anxiety in patients with RA, contributing to improved overall outcomes.

2. Specific objectives/questions the review will address
A systematic review to determine how anxiety impacts on quality of life and disease activity in adults with Rheumatoid Arthritis. (Quality of life will be assessed using the 36-Item Short-Form Health Survey (SF-36) and disease activity, using the Disease Activity Score in 28 joints (DAS28). Secondary outcome measures will be considered.)

3. a) Eligibility Criteria for including studies in the review	
i. Population, or participants and conditions of interest	People aged ≥ 18 years with Rheumatoid Arthritis
ii. Interventions/Exposure/item of interest	Anxiety
iii. Comparisons or control groups, if any	People aged ≥ 18 years with Rheumatoid Arthritis without anxiety
iv. Outcomes of interest	Quality of Life (SF-36) and Disease Activity (DAS28)
v. Setting	Any setting
vi. Study designs	Any study design will be included, though it is anticipated that the majority of relevant papers will be cross-sectional or cohort studies.

3. b) Criteria for excluding studies not covered in inclusion criteria
• Patients <18 years • Data not specific to anxiety and rheumatoid arthritis • When efforts to retrieve a full text have not been successful or when a conference abstract lacks sufficient data and the authors do not respond to requests to provide additional data • When an interpreter can not be found for a paper not written in the English language

4. Search methods	
Electronic databases & websites Please list all databases that are to be searched and include the interface (eg NHS HDAS, EBSCO, OVID etc) and date ranges searched for each.	• Web of Science • PsycINFO • CINAHL • Embase • Medline
Other methods used for identifying relevant research ie contacting experts and reference checking, citation tracking	• Reference checking • Citation tracking of index papers • Search using “www.opengrey.eu”

5. Methods of review	
How will search results be managed & documented?	Refworks will be used to import search results and remove duplicates. Title, abstract and full text screening will then be performed using covidence.
Selection process	Two reviewers (AM and RH/IS) will independently screen the titles and abstracts, followed by the remaining full-text articles. A third reviewer (OB) will resolve disagreements.
Quality assessment	Newcastle Ottawa Scale
How is data to be extracted?	Data extraction form in Microsoft excel. This will first be piloted by two reviewers (AM/ OB).
Outcomes to be extracted & hierarchy/priority of measures	Data on outcomes of interest (SF-36/DAS-28) will be recorded. Secondary outcome measures will be considered if there are a lack of studies reporting the above outcome scores.

Narrative synthesis	Narrative synthesis will be carried out using a framework which consists of four elements; 1. Developing a theory of how anxiety impacts on quality of life/ treatment response in RA (narrative/ diagrams) 2. Developing a preliminary synthesis of findings of included studies (tabulation/ vote counting) 3. Exploring relationships within and between studies (Idea webbing/mapping, subgroup analysis of quality of life and treatment response, graphical tools to bring together scores for SF-26/DAS-28/HAQ) 4. Assessing the robustness of the synthesis (Critical reflection on synthesis process)
Meta-analysis	When we are able to carry out a meta-analysis of primary outcome measures (SF-36 and DAS28), we will seek to report pooled data and comment on any potential sources of heterogeneity.

6. Presentation of results	
Outputs from review	Plan to submit paper for publication and present at a national rheumatology conference.

Appendix 15- Search Strategies

Ovid MEDLINE Search Strategy

The following table is an explanation of the symbols used in this search strategy.

Symbols used in this search strategy	
/	indicates an index term (MeSH heading)
exp	before an index term indicates that all subheadings were selected
.ti,ab.kw	indicates a search for a term in title/ abstract/ keyword
$	at the end of a term indicates that this term has been truncated
adj*n*	indicates a search for two terms where they appear within *n* words of each another

1. exp arthritis, rheumatoid/
2. (rheumat$ adj3 (arthrit$ or diseas$ or condition$ or nodule$)).ti,ab,kw
3. (felty$ adj2 syndrome).ti,ab,kw
4. (caplan$ adj2 syndrome).ti,ab,kw
5. (sjogren$ adj2 syndrome).ti,ab,kw
6. (sicca adj2 syndrome).ti,ab,kw
7. (still$ adj2 disease).ti,ab,kw
8. or/1-7

9. exp anxiety disorders/
10. exp anti-anxiety agents/
11. (anxiet$ or anxious).ti,ab,kw
12. exp panic/
13. (agoraphobi$ or phobi$ or panic) adj3 (disorder$ or attack$)).ti,ab,kw
14. (obsess$ adj3 compuls$).ti,ab,kw
15. exp stress disorders, post-traumatic/
16. ((posttraumatic OR post traumatic OR post-traumatic) adj1 stress$).ti,ab,kw
17. (PTSD).ti,ab,kw
18. (feel$ adj5 (apprehens$ or dread$ or disaster$ or fear$ or worr$ or terr$)).ti,ab,kw
19. or/9-18

20. 8 AND 19

Ovid EMBASE

Symbols used in this search strategy	
/	indicates an index term (MeSH heading)
exp	before an index term indicates that all subheadings were selected
.ti,ab.kw	indicates a search for a term in title/ abstract/ keyword
*	at the end of a term indicates that this term has been truncated
adj*n*	indicates a search for two terms where they appear within *n* words of each another

1. exp arthritis, rheumatoid/
2. (rheumat* adj3 (arthrit* or diseas* or condition* or nodule*)).ti,ab,kw
3. (felty* adj2 syndrome).ti,ab,kw
4. (caplan* adj2 syndrome).ti,ab,kw
5. (sjogren* adj2 syndrome).ti,ab,kw
6. (sicca adj2 syndrome).ti,ab,kw
7. (still* adj2 disease).ti,ab,kw
8. or/1-7

9. exp anxiety/
10. exp anxiolytic agent/
11. (anxiet* or anxious).ti,ab,kw
12. exp panic/
13. (agoraphobi* or phobi* or panic adj3 (disorder* or attack*)).ti,ab,kw
14. (obsess* adj3 compuls*).ti,ab,kw
15. exp post-traumatic stress disorder/
16. ((posttraumatic OR post traumatic OR post-traumatic) adj1 stress*).ti,ab,kw
17. (ptsd).ti,ab,kw
18. (feel* adj5 (apprehens* or dread* or disaster* or fear* or worr* or terr*)).ti,ab,kw
19. or/9-18

20. 8 AND 19

EBSCO-CINAHL

Symbols used in this search strategy	
+	indicates a subject heading
TI, AB, KW	indicates a search for a term in title/ abstract/ keyword
*	at the end of a term indicates that this term has been truncated
N*n*	indicates a search for two terms where they appear within *n* words of each another

1. arthritis, rheumatoid+
2. (TI or AB or KW) “rheumat* N3 (arthrit* or diseas* or condition* or nodule*)”
3. (TI or AB or KW) “felty* N2 syndrome”
4. (TI or AB or KW) “caplan* N2 syndrome”
5. (TI or AB or KW) “sjogren* N2 syndrome”
6. (TI or AB or KW) “sicca N2 syndrome”
7. (TI or AB or KW) “still* N2 disease”
8. or/1-7

9. anxiety+
11. antianxiety agents+
12. (TI or AB or KW) (anxiet* or anxious)
13. panic disorder+
14. (TI or AB or KW) (agoraphobi* or phobi* or panic N3 (disorder* or attack*))
15. (TI or AB or KW) (obsess* N3 compuls*)
16. stress disorders, post-traumatic+
17. (TI or AB or KW) (posttraumatic or post traumatic or post-traumatic N1 (stress*))
18. (TI or AB or KW) (ptsd)
19. (TI or AB or KW) (feel* N5 (apprehens* or dread* or disaster* or fear* or worr* or terr*))
20. or/9-19

21. 8 AND 20

EBSCO- PsycINFO

Symbols used in this search strategy	
+	indicates a subject heading
TI, AB, KW	indicates a search for a term in title/ abstract/ keyword
*	at the end of a term indicates that this term has been truncated
N*n*	indicates a search for two terms where they appear within *n* words of each another

1. rheumatoid arthritis/
2. (TI or AB or KW) (rheumat* N3 (arthrit* or diseas* or condition* or nodule*))
3. (TI or AB or KW) (felty* N2 syndrome)
4. (TI or AB or KW) (caplan* N2 syndrome)
5. (TI or AB or KW) (sjogren* N2 syndrome)
6. (TI or AB or KW) (sicca N2 syndrome)
7. (TI or AB or KW) (still* N2 disease)
8. or/1-7

9. anxiety/
10. tranquilizing drugs/
11. (TI or AB or KW) (anxiet* or anxious)
12. panic/
13. (TI or AB or KW) (agoraphobi* or phobi* or panic N3 (disorder* or attack*)
14. (TI or AB or KW) (obsess* N3 compuls*)
15. posttraumatic stress disorder/
16. (TI or AB or KW) ((posttraumatic OR post traumatic OR post-traumatic) N1 stress$)
17. (TI or AB or KW) (complex ptsd)
18. (TI or AB or KW) (feel* N5 (apprehens* or dread* or disaster* or fear* or worr* or terr*)
19. or/9-18

20. 8 AND 19

Web of Science

Symbols used in this search strategy	
ts	Indicates a search for topic terms within the title, abstract or keywords
$	at the end of a term indicates that this term has been truncated, and the symbol can be substituted for zero or one character
*	at the end of a term indicates that this term has been truncated, and the symbol can be substituted for zero or more characters
NEAR/*n*	indicates a search for two terms where they appear within *n* words of each another

1. ts=(rheumat* NEAR/3 (arthrit* or diseas* or condition* or nodule*))
2. ts=(felty* NEAR/3 syndrome)
3. ts=(caplan* NEAR/3 syndrome)
4. ts=(sjogren* NEAR/3 syndrome)
5. ts=(sicca NEAR/3 syndrome)
6. ts=(still* NEAR/3 disease)
7. or/1-6

8. ts=(anxiet* or anxious)
9. ts=((agoraphobi* or phobi* or panic) NEAR/3 (disorder*$ or attack*)).
10. ts=(obsess$* NEAR/3 compuls*)
11. ts=((posttraumatic or post traumatic or post-traumatic) NEAR/3 (stress*)).
12. ts=(ptsd).
13. ts=(feel* NEAR/5 (apprehens* or dread* or disaster* or fear* or worr* or terr*)).
14. or/8-13

15. 7 AND 14

Appendix 16- Quality Assessment of Studies

Quality Assessment of Cross-Sectional Studies

Author/ Year	Selection				Comparability	Outcome		Total Score 0-9
	Representativeness of the sample *	Sample size *	Non-respondents *	Ascertainment of the exposure **	Control for confounding factors **	Assessment of outcome *	Statistical test *	
Al-Fadl et al., 2014	Recruited from outpatient clinic of the Rheumatology and Rehabilitation Department, Sohag University. Sampling method not described.	26 patients. Small sample size not justified.	No description.	Self-report using HAM-A.	22 Age and Sex Matched Controls.	Questionnaire completed. No description of whether this was with trained staff or self-completed.	Students' T test and Pearson's correlation test.	Moderate quality
	0	**0**	**0**	**	**	**0**	*	**5**
Alpi et al., 2016	Non-random sample of patients attending the foundation city of Botoga.	62 patients.	No description.	Self-report using HADS.	Unadjusted.	Self-report via questionnaire.	Pearson's correlation test and Linear regression.	Moderate quality
	*	*	**0**	**	**0**	**0**	*	**5**
Celiker and Borman, 2001	Recruited from Hacettepe University outpatient clinics. Sampling method not described.	20 patients. Small sample size not justified.	No description.	Self-report using the Spielberger State and Trait Anxiety Inventory.	20 healthy female controls.	Self-report via questionnaire.	Student's T test, X^2 test and Pearson's correlation test.	Low quality
	0	**0**	**0**	*	*	**0**	*	**3**
Grosso et al., 2015 (abstract)	No description.	200 patients. 46 with anxiety.	No description.	Self-report using HADS.	107 healthy controls.	Self-report via questionnaire.	Kruskall-Wallis test.	Moderate quality
	0	*	**0**	**	*	**0**	*	**5**
Ichikawa et al., 1995	Patients regularly attending researchers' outpatient clinics. Sampling method not described.	92 patients.	No description.	Self-report using Zung's self-rating anxiety scale.	24 healthy controls.	Self-report via questionnaire.	X^2 test, Wilcoxon's rank sum test, Wilcoxon's signed rank test and Linear regression.	Moderate quality
	0	*	**0**	**	*	**0**	*	**5**
Karahan et al., 2016	Recruited from Rheumatology outpatient clinics at Necmettin	148 patients.	No description.	Self-report using BAI.	100 healthy controls without	Self-report via questionnaire.	X^2 or Fisher's exact test. Pearson's correlation test, Linear regression.	Moderate quality

	University. Sampling method not described.				rheumatological conditions.			
	0	*	**0**	**	*	**0**	*	**5**
Kojima et al., 2009	Recruited from outpatient rheumatology clinics at Nogoya University Hospital. Sampling method not described.	120 patients.	303/321 consented to participate. 57 excluded for not attending blood tests. 120/246 completed all examinations and questionnaires. Comparability between those included and excluded not discussed.	Self-report using HADS-A.	Adjustments made for age, sex, marital status and educational level.	Self-report via questionnaire.	Pearson's correlation test, multivariate logistic regression and principal factor analysis.	Moderate quality
	0	*	**0**	**	**	**0**	*	**6**
Miwa et al., 2002	Recruited from outpatient clinics at the Department of Internal Medicine, Showa University. Sampling method not described.	82 patients.	No description.	Self-report using HADS.	Unadjusted.	Self-report via questionnaires and medical record review.	Pearson's correlation test and regression analysis.	Moderate quality
	0	*	**0**	**	**0**	**0**	*	**4**
Mok et al., 2012	Recruited consecutively from outpatient rheumatology clinics at Pok Oi Hospital.	200 patients.	No description.	Psychiatrist interview using the Chinese Bilingual Studied interview from DSM-IV Axis 1 disorders.	Adjustments made for age, sex, income, years of education, employment status, marital status, RA duration, medical comorbidities, fatigue.	Self-report via questionnaires, facilitated by a research assistant.	Pearson's correlation test and Linear regression.	Moderate quality
	*	*	**0**	*	**	**0**	*	**6**
Nas et al., 2011	Recruited consecutively (October 2006 to March 2009) from joint database of rheumatology clinics of	26 patients.	No description.	Turkish version of HADS.	Adjustments made for age, disease duration and education.	Self-report via questionnaires and medical record review.	Pearson's correlation test and multivariate logistic regression.	Moderate quality

	five University hospitals located in Eastern Turkey.							
	*	**0**	**0**	**	**	**0**	*	**6**
Ozcetin et al., 2007	All patients attending the outpatient department of Physical medicine and Rehabilitation Unit of Duzce Medical Faculty for the first time between October 2001 and March 2002 recruited.	34 patients.	No description.	Self-report using BAI	Logistic regression analysis performed to determine the influence of age, gender, occupation, marital status, education and duration of disease on outcomes.	Self-report via questionnaires.	Independent sample t-test, one-way ANOVA, pearson's correlation test and logistic regression.	Moderate quality
	*	**0**	**0**	**	**	**0**	*	**6**
Ruhaila & Cheng, 2018	Convenience sample from rheumatology outpatient unit in Melaka hospital.	192 patients.	189/192 patients approached completed questionnaires.	Self-report using DASS(21).	No adjustments reported.	Self-report via questionnaires.	Pearson's correlation test.	Moderate quality.
	*	*	*	*	**0**	**0**	*	**5**
Wan et al., 2015	Convenience sampling from rheumatology clinic at a tertiary centre in Singapore.	108 patients.	108/124 patients approached completed questionnaires (87.1% response rate).	Self-report using HADS.	Subgroup analysis according by marital status, educational level, income, employment status and ethnicity. No statistical difference in outcome values between subgroups.	Self-report via questionnaires, facilitated by a research assistant.	Pearson's correlation test and linear regression.	High quality
	*	*	*	**	**	**0**	*	**8**
Zulgerel and Nandin Erdene, 2014 (abstract)	Patients recruited from rheumatology outpatient's clinic.	51 patients.	No description.	Speilberg Chennai Test. No description of this measurement tool.	Unadjusted.	Self-report via questionnaire.	Statistical tests not described.	Low quality
	0	*	**0**	**0**	**0**	**0**	**0**	**1**

BAI= Beck's Anxiety Inventory, **DASS**= Depression, anxiety and stress scale, **HADS**= Hospital Anxiety and Depression Scale, **HAM-A**= Hamilton Anxiety Rating Scale, **RA**= Rheumatoid arthritis

Quality Assessment of Cohort Studies

Author/ Year	Selection				Comparability	Outcome			Total Score (0-9)
	Representative of the exposed cohort *	Selection of non-exposed cohort *	Ascertainment of exposure *	Demonstration that outcome of interest was not present at start of study *	Comparability of cohorts **	Assessment of outcome *	Was follow-up long enough for outcomes to occur *	Adequacy of follow-up cohorts *	
Dyball et al., 2018 (abstract)	Data from BRAGGSS cohort, a multicenter, observational study of RA patients with severe active disease undergoing biological therapy.	Compared to patients without anxiety drawn from same BRAGGSS cohort.	HADS, though not clarified if patients self-completed the questionnaire or if it was completed by clinician interview.	Baseline disease activity recorded using DAS28.	Adjustments for pre-treatment DAS28, gender, body mass index and synthetic DMARD use.	DAS28 using clinical, biochemical and patient self-reported data.	6 months.	Not reported.	Moderate quality
	*	*	0	*	**	0	*	0	6
Fragoulis et al., 2018 (abstract)	Data from SERA inception cohort of newly diagnosed RA patients followed up at 6 month intervals.	Compared to patients without anxiety from same cohort.	HADS, though not clarified if patients self-completed the questionnaire or if it was completed by clinician interview.	Baseline disease activity recorded using DAS28.	No reported adjustments.	DAS28 using clinical, biochemical and patient self-reported data.	12 months.	Not reported.	Moderate quality.
	*	*	0	*	0	0	*	0	4
Kuijper et al., 2018	Data from the tREACH cohort in which patients were ramdomised to triple DMARD therapy or methotrexate monotherapy. Participants had early RA with a high risk of developing persistent arthritis.	Compared to patients without anxiety drawn from the same cohort.	HADS, though not clarified if patients self-completed the questionnaire or if it was completed by clinician interview.	Baseline disease activity recorded using DAS28.	Adjustments made for baseline DAS28, age, gender, rheumatoid factor positivity and anti-citrullinated protein status.	DAS28 using clinical, biochemical and patient self-reported data.	15 months.	120/281 had missing data, though missing values completed using multiple imputation. Patients with complete and incomplete follow-up were similar with respect to most baseline characteristics.	High quality
	*	*	0	*	**	0	*	*	7

Matcham et al, 2016	Patients consecutively approached in the waiting room when attending rheumatology outpatient appointments at King's College, London.	Compared to patients without baseline anxiety from the same cohort.	Self-report using HADS.	Baseline and 1yr outcomes compared. Adjustments made for baseline score of outcome variables.	Adjusted for disease duration, age, baseline score of outcome variables.	DAS28 results obtained from patient medical records at 1 year appointments (+/- 3 months).	1 year.	13/56 had missing data. No systematic difference between patients with and without missing data.	High quality
	*	*	**0**	*	**	*	*	**0**	**7**
Overman et al., 2011	Patients recruited from 6 outpatient clinics of the Utrecht Foundation for Research in the Netherlands.	Compared to patients without baseline anxiety from the same cohort.	Impact of rheumatic diseases on general health and lifestyle questionnaire, derived from the Spielberger state-trait anxiety inventory, though not clarified if patients self-completed the questionnaire or if it was completed by clinician interview.	Baseline disease activity recorded using ESR and Thompson articular index.	Adjusted for rheumatoid factor positivity, age and female sex.	Biochemical results (ESR) and Thompson articular index. Not stated if this was self-reported or completed by clinician interview.	5 years.	545 patients, with 436 completing >60% of clinical and psychological assessments. The 119 who completed <60% of assessments did not differ significantly from the other group.	Moderate quality
	*	*	**0**	*	**	**0**	*	**0**	**6**
Sergeant et al., 2018	Patients recruited to the Rheumatoid Arthritis Medication Study (RAMS), a UK multi-centre study of patients with RA or undifferentiated polyarthritis, commencing methotrexate for the first time.	Compared to patients without baseline anxiety from the same cohort.	Self-report using HADS questionnaire.	Baseline disease activity recorded using DAS28.	All clinical, biochemical and psychosocial variables assessed for association with non-response (change in DAS28) using logistic regression.	DAS28 by patient interview, supplemented by biochemical tests and information from medical records.	6 months.	From 1656 consenting to participate, due to death, withdrawal or missing data, 304 lost at 3M and further 302 at 6M. Characteristics of those lost to follow-up not described.	High quality
	*	*	**0**	*	**	*	*	**0**	**7**

RA= Rheumatoid arthritis, **DAS28**= Disease activity score in 28 joints, **DMARD**= Disease modifying anti-rheumatic drug, **ESR**= Erythrocyte sedimentation rate**, HADS**= Hospital Anxiety and Depression Scale.

Appendix 17- Meta-analysis data

Disease Activity Data- DAS28		
Author/ Year	**Number of participants**	**Results**
Al-Fadl et al., 2014	26	Anxiety (HAM-A) and DAS-28, r= 0.47 (p<0.05)
Karahan et al., 2016	148	Anxiety (BAI) and DAS-28, r=0.159 (not significant)
Matcham et al., 2016	56	Anxiety (HADS) and DAS-28, Baseline, r= 0.29 (p<0.05)
Ruhaila & Cheng, 2018	189	Anxiety (DASS21) and DAS-28, r=0.233 (p=0.001)
Zulgerel et al., 2014	51	Anxiety (Spielberg Chennai test) and DAS-28, r=0.126 (p=0.380)

DAS28 Meta-analysis						
Author/ Year	**r**	**n**	**r [Z']**	**SE (r[Z'])**	**95% CI (r[Z'])**	**95%CI (r)**
Al fadl et al., 2014	0.47	26	0.5101	0.209	0.101, 0.919	0.101, 0.725
Karahan et al., 2016	0.159	148	0.1604	0.083	-0.002, 0.323	-0.002, 0.312
Matcham et al., 2016	0.29	56	0.2986	0.137	0.029, 0.568	0.029, 0.514
Ruhaila & Cheng, 2018	0.233	189	0.2374	0.074	0.094, 0.381	0.093, 0.364
Zulgerel et al., 2014	0.126	51	0.1267	0.144	-0.156, 0.410	-0.155, 0.388

Quality of Life Data- SF-36			
Author/ Year	**Number of participants**	**Ascertainment of outcome**	**Results**
Al-Fadl et al., 2014	26	PCS and MCS of SF-36	Anxiety and PCS of SF-36: r=-0.38 (p<0.05) Anxiety and MCS of SF-36: r=-0.34 (p<0.05)
Kojima et al., 2009	120	PCS and MCS of SF-36	HADS-A and PCS of SF-36: r=-0.25 (p=0.01) HADS-A and MCS of SF-36: r=-0.51 (p<0.001)
Nas et al., 2011	421	SF-36 subscales	Anxiety and SF-36 subscale score for physical functioning: r=-0.28 (p<0.001) Anxiety and SF-36 subscale score for mental health: r=-0.48 (p<0.001)
Ozcetin et al., 2007	34	SF-36 subscales	Anxiety and SF-36 subscale score for physical functioning: r=-0.672 (p<0.001) Anxiety and SF-36 subscale score for mental health: r=-0.655 (p<0.001)

SF-36 Meta-analysis- Physical QOL						
Author/ Year	**r**	**n**	**r [Z']**	**SE (r[Z'])**	**95% CI (r[Z'])**	**95%CI (r)**
Al-Fadl et al., 2014	-0.38	26	-0.400	0.209	-0.809, 0.0086	-0.669, 0.009
Kojima et al., 2009	-0.25	120	-0.255	0.092	-0.437, -0.074	-0.411, -0.074
Nas et al., 2011	-0.28	421	-0.288	0.049	-0.384, -0.192	-0.366, -0.190
Ozcetin et al., 2007	-0.672	34	-0.814	0.180	-1.166, -0.462	-0.823, -0.432

SF-36 Meta-analysis- Mental QoL						
Author/ Year	**r**	**n**	**r[Z']**	**SE (r[Z'])**	**95%CI (r[Z'])**	**95%CI (r)**
Al-Fadl et al., 2004	-0.34	26	-0.3541	0.209	-0.763, 0.055	-0.643, 0.055
Kojima et al., 2009	-0.51	120	-0.5627	0.092	-0.744, -0.382	-0.631, -0.364
Nas et al., 2011	-0.48	421	-0.523	0.049	-0.619, -0.427	-0.550, -0.403
Ozcetin et al., 2007	-0.655	34	-0.784	0.180	-1.136, -0.432	-0.813, -0.407

CI= confidence interval, n= number of individuals, r = pearsons correlation coefficient, r(z') = Fisher's z scores, SE= standard error.

BAI= Beck's Anxiety Inventory, **DAS28**= Disease activity score 28, **DASS (21)**= Depression, anxiety and stress scale, **HADS**= Hospital Anxiety and Depression Score, **HAM-A**= Hamilton's Anxiety Rating Scale, **MCS**= Mental Component Summary, **NHP**= Nottingham Health Profile, **PCS**= Physical Component Summary, **QoL**= Quality of life, **RA**= Rheumatoid arthritis, **SF-36**= Short-form 36

Appendix 18- GRADE Assessment

Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Large Effect (Strength of Association)	Dose-Response Gradient
Disease Activity	**From 14 studies reporting disease activity outcome measures, there were several potential sources of bias;** -5 lacked detail on their sampling method -9 did not describe non-respondents **However;** -13 had a good sample size improving generalizability -All used validated tools to determine the exposure and outcome -10 controlled for confounding factors	**Meta-analysis** -Relatively narrow CI with low heterogeneity **Narrative synthesis** -Some differences in source populations, sampling methods and adjustments made for confounding factors could explain some heterogeneity in results	**Differences in population (applicability)** -Populations from different global areas. All had validated diagnoses of rheumatoid arthritis, with most recruited from rheumatology outpatient clinics, though some studies lacked detail on their sampling methods. **Differences in outcome measures** -Studies reporting DAS28, a validated outcome measure analysed together for consistency. Secondary validated outcome measures discussed in narrative synthesis.	Majority of 95% CI's were relatively narrow, not including 'no effect'. Just one study (31) had a small sample size, with the majority having moderate to large sample sizes.	Most results reported as correlations. Effect sizes small/ moderate.	Overall, increased anxiety correlated/ associated with higher disease activity
	Not downgraded	Upgrade 1 level	Not downgraded	Upgrade 1 level	Not downgraded	Upgrade 1 level

Quality of life	**From 9 studies reporting disease activity outcome measures, there were several potential sources of bias;** -5 lacked detail on sampling method -8 did not describe non-respondents -4 had small sample sizes limiting generalisability **However;** -All used validated tools to determine the exposure and outcome -8 controlled for confounding factors	**Meta-analysis** -Relatively narrow CI with low heterogeneity for mental QoL (10.3%) but high heterogeneity for physical QoL (78.5%). Differences in the source populations, sampling methods and adjustments made for confounding factors could account for heterogeneity. **Narrative synthesis** -Findings largely consistent across studies. Most effect sizes mild/ moderate. Some heterogeneity could be explained by above reasons given.	**Differences in population (applicability)** -Populations from different global areas. All had validated diagnoses of rheumatoid arthritis, though some studies lacked detail on their sampling methods or did not describe non-respondents. **Differences in outcome measures** -Studies reporting SF-36, a validated outcome measure analysed together for consistency. Secondary validated outcome measures discussed in narrative synthesis.	Majority of 95% CI's were relatively narrow, not including 'no effect'. However, 4/9 studies had a small sample size.	All results reported as correlations. Effect sizes small/ moderate.	Overall, increased anxiety correlated/ associated with higher disease activity
	Not downgraded	Not downgraded	Not downgraded	Not downgraded	Not downgraded	Upgrade 1 level

Appendix 19- CiPCA Data Application

DESCRIPTION OF PROPOSED RESEARCH (Max 2000 words)

TITLE

The incidence and prevalence of anxiety and depression in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, polymyalgia rheumatica and giant cell arteritis: a matched retrospective cohort study.

PLAIN ENGLISH SUMMARY (Max 300 words)

I aim to find out how many people with inflammatory arthritis suffer from anxiety and depression. I also want to understand how many people develop mood problems after they are diagnosed with inflammatory arthritis. People with mood problems may not respond as well to treatments for their arthritis. Showing how many people with inflammatory arthritis have or develop anxiety and depression could help to improve how mood problems are recognised and treated. This could lead to an improved quality of life for those affected.

Types of inflammatory arthritis include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and polymyalgia rheumatica. These long-term conditions can cause pain, swelling and stiffness of the joints. Another type of inflammatory arthritis, giant cell arteritis, can cause headaches.

One in five people with rheumatoid arthritis suffer from mood problems, though there has been a lack of research into mood problems in other types of inflammatory arthritis. In particular, we do not understand how many people develop mood problems after they are diagnosed with inflammatory arthritis.

I plan to find out how common anxiety and depression are in patients with different types of inflammatory arthritis by reviewing GP records. I will also look at how many people with inflammatory arthritis develop anxiety or depression over time and compare this to people without inflammatory arthritis. To do this I will use data from nine GP practices in North Staffordshire from the year 2000-2015.

I will lead a patient and public involvement group to discuss what the results mean, how they could be shared with patients and further research needed.

I will share my results with researchers and doctors nationally through presentations and publications. I will present my results to arthritis patient groups, and produce posters for display in GP surgeries taking part.

BACKGROUND AND RATIONALE (include brief summary of previous relevant research and explain potential clinical or policy impact)

An estimated 15 million people in the United Kingdom (UK) suffer from long-term conditions (LTCs) (Naylor et al., 2012). These encompass a range of illnesses that can be managed, but not cured. Examples include diabetes, asthma and rheumatoid arthritis.

Depression and anxiety are more prevalent in LTCs. The 2014 Adult Psychiatric Morbidity Survey reported 3.3% of the general population to have depression and 5.9% anxiety (NatCen Social Research, 2016). In contrast, up to 20% of patients with LTCs are estimated to suffer from depression. Patients with LTCs are also two to three times more likely to suffer from anxiety (Naylor et al., 2012). Unfortunately, mood problems can often be under-recognised and treated in people with LTCs (Cepoiu et al., 2007).

Inflammatory rheumatic conditions are LTCs which can involve inflammation of the joints, bones, cartilage, ligaments, muscles and internal organs. Rheumatoid Arthritis is an inflammatory rheumatic condition characterised by synovial inflammation, that affects 1%

of the adult population (Silman and Pearson, 2002). In common with other LTCs, RA is linked to an increased incidence and prevalence of anxiety and depression. Studies have suggested the prevalence of anxiety in RA to be between 13-14% (Isik et al., 2006) (Covic et al., 2012), whilst a meta-analysis found the prevalence of depression in RA to be 38.8% (Matcham et al., 2013).

Bidirectional interactions between RA and depression have been identified (Rathbun et al., 2012). These include biological, psychological and behavioural processes (Rathbun et al., 2012). In terms of biological processes, depression has been linked to a rise in pro-inflammatory cytokines (Maes et al., 1995). A small study has also suggested that anti-tumour necrosis factor could interact with serotonin transmission, potentially affecting mood, though the need for further research has been highlighted (Cavanagh et al., 2010). Cytokine dysregulation is pivotal in the pathogenesis of RA, hence, pro-inflammatory cytokines produced in RA could potentially precipitate or exacerbate depression and vice-versa.

In terms of psychological processes, negative thoughts in patients with depression could influence how symptoms of RA are perceived (Rathbun et al., 2012). Depression could also affect behaviour, potentially causing a decrease in exercise, deconditioning, reduced endorphin release and increased pain (Covic et al., 2003). Greater disability in relation to RA could lead to reduced participation in valued social activities, contributing to depression (Neugebauer, Katz and Pasch, 2003).

The presence of comorbid mental illness in LTCs such as RA has been estimated to raise total healthcare costs by 45% (Naylor et al., 2012). Specific links have also been identified between depression in RA and disease progression (Rathbun et al., 2012).

A recent secondary analysis of a RCT aimed to examine the impact of anxiety and depression on treatment response, disease activity and physical disability. Mood problems were linked to a reduction in treatment response, higher disease activity scores and poorer overall health outcomes (Matcham et al., 2015).

The literature suggests that depression in RA is also a risk factor for increased mortality (Ang et al., 2005). A cohort of patients with RA were followed-up at clinic appointments over 18 years. The primary independent variable was the mean Arthritis Impact Measurement Scale (AIMS) depression scores during the first 4 years of entry into the clinic cohort. After adjusting for covariates, the hazard ratio (HR) for each unit increase in the average 4-year depression score on mortality was 1.14 ($p < 0.0001$), suggesting that depression in RA was linked to increased mortality.

Despite it being well established that patients with RA have higher rates of depression, the literature suggests it is often under-recognised (Cepoiu et al., 2007), which can result in increased pain, fatigue, morbidity and mortality (Ang et al., 2005). In recognition of the links between anxiety and/ or depression in RA and increased morbidity and mortality, NICE have created Quality Standards for the management of RA (QS33), to facilitate early recognition of comorbid mood problems (NICE, 2013). Within this Quality Standard, NICE recommends that clinicians should regularly reassess mood within the context of an annual review clinic (NICE, 2013). However, there is no specific guidance advocating an annual review for patients with other inflammatory rheumatological conditions.

Past research exploring mood problems in patients with inflammatory rheumatic conditions has mainly focused on the prevalence of depression in RA. As a consequence, the scale and burden of mood problems, particularly anxiety, has been under-researched in other inflammatory conditions, such as psoriatic arthritis (PsA), ankylosing spondylitis (AS), giant cell arteritis (GCA) and polymyalgia rheumatica (PMR). In particular, there has been a lack of research to explore the incidence of mood problems in people with inflammatory rheumatic conditions.

In AS, estimates of the prevalence of depression vary. A population-based cohort study found that 10% with AS had doctor-diagnosed depression (Meesters et al., 2014). However, other estimates vary between 15-30% (Martindale et al., 2006; Barlow et al, 1993). There is a lack of literature on anxiety in AS. One study estimated a prevalence of

anxiety in AS of 25%, though the study involved less than 100 patients hence would have limited generalisability (Martindale et al., 2006).

In PsA, a small study found the prevalence of anxiety and depression to be higher than in the general population (36.6% and 22.2%, respectively) (McDonough et al., 2014). In PMR, a recent study using a cross-sectional questionnaire found the prevalence of depressive symptoms to be 15% (Vivekanantham et al., 2017). There has been a lack of research exploring anxiety in PMR and mood problems in GCA.

Given the known links between RA, comorbid anxiety and/ or depression and increased morbidity and mortality, further research is needed to determine the incidence and prevalence of mood problems in patients with other types of inflammatory rheumatic conditions.

Therefore, I aim to perform a matched retrospective cohort study to investigate the incidence and prevalence of anxiety and depression in patients with RA, PsA, AS, PMR and GCA. In particular, this study will improve our understanding of the proportion of patients with inflammatory rheumatic conditions that will become affected by anxiety and depression. Highlighting the scale of mood problems will help to promote pathways to improve the recognition and management of comorbid anxiety and depression. Ultimately, this could help to reduce associated morbidity and mortality.

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OBJECTIVES

The objectives are:

(1) Assess whether there is a possible causal association between the diagnosis of inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polymyalgia rheumatica and giant cell arteritis) and the subsequent consultation for anxiety and depression.

(2) Investigate the prevalence of, and factors associated with, anxiety and depression among patients with inflammatory arthritis.

METHODS (include study population(s), exposure(s), outcome(s), confounder analysis)

Design and study population

This study will be a matched retrospective cohort study using CiPCA, a well-established local database of primary care electronic health records. The cohort will include men and women aged ≥18 years with recorded Read code diagnosis of inflammatory arthritis (RA, AS, PsA, AS, GCA) between 1/1/2001 and 31/12/2015 (the date of the diagnosis defined as the index date). The cohort will be followed up until 31/08/2016 (latest available data in CiPCA). Individuals below the age of 18 are excluded as the incidence of inflammatory arthritis is expected to be low in this group. A comparison group without inflammatory arthritis will be drawn by assigning each individual with inflammatory arthritis at their index date to up to four age (within 3 years), gender and general practice concurrent matched individuals without a record of inflammatory arthritis up to the point of their matched case's index date and who were alive and contributing data at the time. Comparison individuals will be assigned the same index date as their matched inflammatory arthritis individuals. All individuals will be followed up from index date until occurrence of the events (anxiety, depression) of interest, or end of study defined as the earliest of date of death, end of registration at the practice, or 31/08/2016. Individuals with a record of inflammatory arthritis before the index date will be excluded. All individuals are required to have at least 12 months registration history before the index date.

Details for objective 1 (incidence study)

Study population

As outlined above but with exclusion of any individuals that had a record of anxiety or depression 12 months before the index date.

Exposure

The exposure of interest will be inflammatory arthritis, as used to define the cohort for analysis. Inflammatory arthritis will be defined using Read codes for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polymyalgia rheumatic and giant cell arteritis. All the relevant lists of Read codes are available at www.keele.ac.uk/mrr.

Outcome

Outcomes of interest will be the time from the index date to first diagnosis of anxiety OR depression. Anxiety and anxiety and/or depresion will be analysed as separate outcomes. Anxiety and depression will be defined using relevant Read codes (available at www.keele.ac.uk/mrr).

Covariates

Covariates believed to potentially confound the relationship between inflammatory arthritis and anxiety/depression will include age and gender (mostly accounted for through the matched study design), Index of Multiple Deprivation (IMD), select comorbidities (COPD, asthma, diabetes mellitus, congestive heart failure, ischaemic heart disease, peripheral vascular disease, stroke, malignancy), obesity, alcohol use and smoking status. These potential confounders will be identified via Read codes and will be required to be identified in the record at any time prior to the diagnosis of inflammatory arthritis to avoid them potentially occurring onto the causal pathway. Charlson comorbidity index[1] will also be calculated on the day prior to index date via a technique by Khan et al[2]. For confounders that can change over time (e.g. obesity, alcohol use), the information recorded closest to the index date will be used. Categories for missing data will be defined for obesity, alcohol and smoking in order to preserve sample size.

Analysis

Characteristics of individuals at index date will be compared between those with and without inflammatory arthritis using frequencies and percentages; success of matching will be described. Cox proportional hazard regression models will be used to obtain associations between inflammatory arthritis and time to occurrence of anxiety and depression, in terms of hazard ratios (HRs). Corresponding 95% confidence intervals (CIs)

will be based on robust standard errors to account for clustering due to matching. Both crude and covariate-adjusted HRs will be estimated. Proportionality of hazards assumption will be tested graphically and via Schoenfeld residuals. if the assumption fails for any covariate, interaction of that covariate with appropriate function(s) of time will be included in the model. Right censoring will be assumed non-informative and will be taken as the earliest of date of death, end of registration at the practice, or 31/08/2016. We may also explore the association of inflammatory conditions and anxiety/depression at different times, with follow-up being truncated at one year, two years, five years and ten years.
Data will be managed and analysed in SPSS and STATA.

Subgroup/sensitivity analyses

Subgroup analyses by gender (male/ female) and different age groups will be performed. Sensitivity analyses will concern assessment of results arising from complete case analyses which ignore missing data on obesity, alcohol and smoking. Multiple imputation will not be considered for these variables as previous studies using primary care electronic health records (such as CPRD) have indicated that missing data on these variables are not missing at random[3].

Details for objective 2 (prevalence study)

Prevalence estimates for anxiety and depression (separately and combined) in the 12 months prior to index date will be calculated among those with inflammatory arthritis (and among those without for comparison purposes). Among those with inflammatory conditions, logistic regression models will be used to obtain estimates of association, in terms of odds ratios and associated 95% CIs, between covariates (age, gender, IMD, COPD, asthma, diabetes mellitus, congestive heart failure, ischaemic heart disease, peripheral vascular disease, stroke, dementia, obesity, alcohol use, smoking status) and anxiety/depression. Estimates of unadjusted associations will be obtained first, followed by adjustment for other covariates.

[1] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[2] Khan NF, Perera R, Harper S, et al. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Fam Pract 2010;11:1
[3] Clarson, L.E., et al., Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK clinical practice research datalink. Ann Rheum Dis, 2015. 74(4): p. 642-7.

Is this a pilot study? **No**

Time period for download:	Age and gender criteria:
1/1/2000-31/08/2016 (or whenever the end of available data is)	**≥18 years**

Please detail the clinical advice/support available for the project:
Dr Samantha Hider- Reader in rheumatology
Dr Annabelle Machin- GP

Please detail statistical advice / support available for the project:
Dr Milisa Blagojevic-Bucknall

Outline how you have identified Read codes, and prescription lists for the study to define the study population, exposures, outcomes, and covariates. Please note established Institute code lists are available at www.keele.ac.uk/mrr and through the CiPCA Data Manager.

For rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polymyalgia rheumatica, depression, I will use established read code lists available at www.keele.ac.uk/mrr. For anxiety, I will use an established read code list from the SAIL-2 study based at Keele, which Kelvin Jordan has provided me with. For giant cell arteritis I will use an established read code list from a previous study lead by James Prior at the Keele Research Institute.

Outline funding for the study

School of Primary Care Research (18M funding) and Haywood Foundation (6M funding).

In which of the Research Programmes / Groups is this study contained? Has it been discussed and agreed by the Research Programme / Group?

This work is nested within the inflammatory research group and the ideas have followed on from the pilot study INCLUDE. The proposed study has been discussed with the inflammatory research group.

Have you discussed the proposed project with the CiPCA Data Manager and/or another member of the CiPCA Academic Custodianship Committee? *Please give brief details*

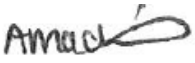
The proposal has been discussed with M. Blagojevic-Bucknall (who is one of the co-supervisors for the proposed work).

Please indicate the format you would like the data to be provided (i.e. STATA, SPSS, Excel)
STATA/ SPSS

I agree to:

- comply with the Institute's data security and confidentiality procedures
- to retain the data on the Institute's password-protected server at all times
- undertake all analysis within the Institute
- use the data only for the purposes of the project detailed here
- not to attempt to identify any people included in the data received
- not to link, or attempt to link, to any other sources of patient data
- not release any data to any third party
- allow the CiPCA Academic Custodianship Committee to audit use of released data if requested
- include appropriate funding and other acknowledgements in all publications
- inform the CiPCA Data Manager of all publications and presentations resulting from this project

NAME: Dr Annabelle Machin

SIGNATURE: 

DATE: 02/08/2017

Appendix 20- Read Code lists

Alcohol misuse/ dependence
Acute alcoholic intoxication
Admitted to alcohol detoxification centre
Alcohol dependence syndrome
Alcohol disorder monitoring
Alcohol problem drinking
Alcohol withdrawal syndrome
Alcoholic psychoses
Alcoholism
Chronic alcoholism
Chronic alcoholism in remission
Delirium tremens
Referral to community alcohol team
Referral to specialist alcohol treatment centre
Under care of community alcohol team
Wernicke-Korsakov syndrome

Obesity
Attends obesity monitoring
Body mass index 30+ - obesity
Body mass index 40+ - severely obese
Body mass index 25-29- overweight
Central obesity
Follow-up obesity assessment
Has seen dietician- obesity
Initial obesity assessment
Intervention for risk to health associated with obesity
Morbid obesity
O/E- weight >10% over ideal
Obesity
Obesity due to excess calories
Obesity monitoring
Obesity monitoring 1st letter
Obesity monitoring verbal inv.
Overweight
Refuses obesity monitoring
Simple obesity NOS
Treatment of obesity started
Weight management plan started
Weight management programme offered
[V] Dietary surveillance and counselling

Current smoker
Trivial smoker - < 1 cig/day
Occasional smoker
Light smoker - 1-9 cigs/day
Moderate smoker - 10-19 cigs/d
Heavy smoker - 20-39 cigs/day
Pipe tobacco consumption
Ready to stop smoking
Thinking about stopping smoking
Not interested in stopping smoking
Thinking about stopping smoking
Not interested in stopping smoking
Cigarette smoker
Smoker
Smoking started
Smoking restarted
Current smoker
Smoking reduced
Chews tobacco
Cigarette consumption
Cigar consumption
Tobacco dependence
Tobacco dependence; unspecified
Tobacco dependence; continuous
Smoking cessation advice
Tobacco dependence NOS
Smoking cessation advice declined
Current smoker annual review - enhanced services
Current smoker annual review
Tobacco dependence
Tobacco dependence; unspecified
Tobacco dependence; continuous
Tobacco dependence NOS
[V]Tobacco use
[V]Tobacco abuse counselling
Failed attempt to stop smoking

Non smoker
Never smoked
Never smoked tobacco
Non-smoker

Ex-smoker
Ex smoker
Date ceased smoking
Ex-smoker annual review - enhanced services
Ex-smoker annual review
Tobacco dependence in remission
Nicotine replacement therapy provided
Nicotine replacement therapy using nicotine patches
Nicotine replacement therapy using nicotine gum
Nicotine replacement therapy using nicotine inhalator
Nicotine replacement therapy using nicotine lozenges
Smoking cessation drug therapy
Other specified smoking cessation therapy
Smoking cessation therapy NOS
Nicotine replacement therapy
Nicotine replacement therapy provided free
Over the counter nicotine replacement therapy
Smoking free weeks
Stopped smoking
Recently stopped smoking
Ex roll-up cigarette smoker
Ex pipe smoker
Ex pipe smoker
Ex cigar smoker
Ex-trivial smoker (<1/day)
Ex-light smoker (1-9/day)
Ex-moderate smoker (10-19/day)
Ex-cigarette smoker
Ex-smoker - amount unknown

Appendix 21- Association between covariates and mood problems in people with RA and PMR

*Association between covariates and anxiety, in addition to anxiety and/or depression, in people with **RA***

Covariates		Anxiety		Anxiety and/ or depression	
		Unadjusted OR (95% CI) p value	Adjusted OR * (95% CI) p value	Unadjusted OR (95% CI) p value	Adjusted OR * (95% CI) p value
Age Group (years)	18-50	**2.90 (0.85, 4.24) p=0.01**	**2.70 (1.15, 6.32) p=0.02**	**2.01 (1.12, 3.66) p=0.02**	**2.07 (1.06, 4.04) p=0.03**
	51-65	0.83 (0.35, 1.94) p=0.67	0.94 (0.39, 2.26) p=0.89	1.10 (0.60, 2.03) p=0.75	2.27 (0.78, 6.65) p=0.14
	66-75	0.28 (0.06, 1.18) p=0.08	0.26 (0.06, 1.13) p=0.07	**0.28 (0.10, 0.81) p=0.02**	0.35 (0.12, 1.06) p=0.06
	76-95	1.45 (0.53, 3.96) p=0.47	0.81 (0.26, 2.53) p=0.72	0.82 (0.34, 1.99) p=0.66	0.44 (0.15, 1.29) p=0.14
Gender	Female	1.64 (0.65, 4.17) p=0.30	1.26 (0.48, 3.29) p=0.64	1.74 (0.87, 3.49) p=0.12	1.13 (0.54, 2.36) p=0.74
Deprivation Status	Low	0.66 (0.19, 2.24) p=0.51	0.85 (0.24, 2.97) p=0.78	0.56 (0.22, 1.45) p=0.23	0.70 (0.26, 1.88) p=0.48
	Mid	1.17 (0.51, 2.67) p=0.71	1.25 (0.52, 3.01) p=0.62	1.17 (0.63, 2.17) p=0.61	1.31 (0.68, 2.54) p=0.42
	High	1.08 (0.43, 2.75) p=0.87	0.83 (0.30, 2.28) p=0.72	1.18 (0.80, 2.35) p=0.63	0.88 (0.42, 1.86) p=0.74
Multimorbidity		0.97 (0.41, 2.26) p=0.93	0.60 (0.24, 1.53) p=0.29	1.56 (0.86, 2.85) p=0.15	1.22 (0.62, 2.38) p=0.57
Current Smoker		1.31 (0.58, 2.95) p=0.51	1.46 (0.63, 3.39) p=0.38	1.35 (0.74, 2.46) p=0.33	1.17 (0.61, 2.26) p=0.63
Obesity		0.96 (0.35, 2.61) p=0.94	0.94 (0.34, 2.64) p=0.91	1.04 (0.50, 2.160 p=0.91	0.84 (0.38, 1.86) p=0.66
Number of primary care contacts	21-50	**2.27 (1.00, 5.14) p=0.04**	**3.17 (1.27, 7.90) p=0.01**	**2.54 (1.38, 4.70) p<0.01**	**3.72 (1.88, 7.36) p<0.01**
	50+	**10.19 (2.47, 42.07) p<0.01**	**19.10 (4.07, 89.64) p<0.01**	**7.78 (2.12, 28.64) p<0.01**	**19.82 (4.65, 84.42) p<0.01**

OR= Odds ratio, CI= confidence interval
*Adjusted for significant unadjusted associations.

*Association between covariates and anxiety, in addition to anxiety and/or depression, in people with **PMR***

Covariates		Anxiety		Anxiety and/ or depression	
		Unadjusted OR (95% CI) p value	Adjusted OR * (95% CI) p value	Unadjusted OR (95% CI) p value	Adjusted OR * (95% CI) p value
Age Groups [1]	51-65	2.17 (0.81, 5.82) p=0.13	2.52 (0.90, 7.01) p=0.08	1.12 (0.50, 2.48) p=0.79	2.52 (0.90, 7.01) p=0.08
	66-75	0.68 (0.24, 1.91) p=0.46	0.58 (0.19, 1.81) p=0.35	0.99 (0.51, 1.94) p=0.99	0.58 (0.19, 1.81) p=0.35
	76-95	0.83 (0.33, 2.90) p=0.70	0.82 (0.31, 2.14) p=0.68	0.99 (0.53, 1.87) p=0.99	0.82 (0.31, 2.14) p=0.68
Gender	Female	2.54 (0.74, 8.80) p=0.14	3.58 (0.80, 15.90) p=0.09	1.70 (0.80, 3.64) p=0.17	3.58 (0.80, 15.90) p=0.09
Deprivation Status	Low	0.89 (0.29, 2.71) p=0.83	0.89 (0.28, 2.84) p=0.85	0.80 (0.36, 1.76) p=0.58	0.89 (0.28, 2.84) p=0.85
	Mid	1.25 (0.49, 3.22) p=0.64	1.21 (0.45, 3.23) p=0.71	1.03 (0.54, 1.95) p=0.94	1.21 (0.45, 3.23) p=0.71
	High	0.80 (0.23, 2.77) p=0.72	0.85 (0.24, 3.01) p=0.80	1.22 (0.57, 2.12) p=0.62	0.85 (0.24, 3.01) p=0.80
Multimorbidity		1.07 (0.42, 2.76) p=0.89	0.48 (0.16, 1.45) p=0.20	1.47 (0.78, 2.78) p=0.24	0.48 (0.16, 1.45) p=0.20
Current Smoker		1.08 (0.35, 3.31) p=0.89	0.92 (0.26, 3.30) p=0.90	0.98 (0.44, 2.17) p=0.96	0.92 (0.26, 3.25) p=0.90
Obesity		2.79 (0.98, 7.97) p=0.06	2.46 (0.83, 7.31) p=0.11	1.60 (0.68, 3.73) p=0.28	2.46 (0.83, 7.31) p=0.11
Number of primary care contacts	21-50	**3.52 (1.24, 9.99) p=0.02**	**5.74 (1.62, 20.34) p<0.01**	**2.36 (1.20, 4.65) p=0.01**	**5.74 (1.62, 20.34) p<0.01**
	50+	**9.95 (1.96, 30.65) p<0.01**	**30.25 (4.43, 206.63) p<0.01**	**7.57 (1.88, 30.53) p<0.01**	**30.25 (4.43, 206,63) p<0.01**

OR= Odds ratio, CI= confidence interval

*Adjusted for significant unadjusted associations.

[1] No individuals with PMR and mood problems aged <50 years, so this age category has been excluded from the analysis.

Appendix 22- INCLUDE study invitation letter

«title» «Given Name» «surname»
«Address Line 1»
«Address Line 2»
«Address Line 3»
«Postcode»

Our ref: «Study ID»
Date: «Day» «Month» «Year»

Dear «title» «surname»,

Invitation to take part in the INCLUDE study

***INCLUDE**: **IN**tegrating and improving **C**are for patients with inf**L**ammatory rhe**U**matological Disord**E**rs in the community: A pilot randomised controlled trial.*

Our GP practice, together with researchers at Keele University, is carrying out a study called INCLUDE which aims to find out more about the impact of inflammatory rheumatological conditions on quality of life.

You are being invited to take part in the INCLUDE study because you have been identified as a patient registered at our practice with one of the inflammatory conditions being studied (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polymyalgia rheumatica or giant cell arteritis). Enclosed with this letter is an information sheet explaining the study in more detail and how you can take part. Please take time to read this carefully.

We hope that you will be able to spare some time to complete and return the enclosed questionnaire. We think it should take you about 20 minutes to complete. This questionnaire asks about how your condition affects you and about any associated health problems that you have. Your responses will help us to understand how the care of people with inflammatory conditions might be improved in the local area.

All the information you provide to Keele University will be treated in strict confidence and in accordance with the 1998 Data Protection Act. This means that any personal information you provide during the study (e.g. name and address) will be shared with your GP practice but not passed on to any other organisation and will only be used in connection with this study.

Your participation is voluntary and it is up to you whether you take part or not. We can assure you that, whether or not you take part in the study, your healthcare will **not** be affected in any way, now or in the future.

If you do not reply to this questionnaire, you will be sent two reminders about this study in approximately two and four weeks' time. We would be very grateful if you would complete and return the questionnaire in the pre-paid envelope provided as soon as you can. **You do not need a stamp.**

If you would like to know more about this study, or have any questions, please contact the INCLUDE Study Coordinator at Keele Clinical Trials Unit on **01782 732950**.

Thank you very much for your help with this research study.

Yours sincerely,
«GP Name»

Appendix 23- INCLUDE study patient information sheet

INCLUDE study: INtegrating and improving Care for patients with InfLammatory rheUmatological DisordErs in the community: A pilot randomised controlled trial.

Patient Information Sheet

You are invited to take part in the INCLUDE research study. Before you decide to take part or not, it is important for you to understand why the research is being done and what it will involve. Thank you for taking the time to read the following information.

What is the purpose of the study?

It is important that we ask people about their health to make sure that we are providing the right types of care services in the NHS.This study focuses on five main types of inflammatory conditions (**rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polymyalgia rheumatica and giant cell arteritis**) and aims to investigate the impact these conditions may have on quality of life.

Your participation will help us to understand more about the health problems linked to these conditions and whether they are being identified and treated.

Why have I been invited to take part?

You have been identified because your GP record suggests you may have one of these inflammatory conditions (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polymyalgia rheumatica and giant cell arteritis). Patients registered at this practice who have any of these conditions are being invited to complete the enclosed questionnaire to take part in the study.

What does taking part in the INCLUDE study involve?

You are asked to complete the enclosed questionnaire and return it in the pre-paid envelope provided. We think it should take about 20 minutes to complete.

On the last page of the questionnaire we ask for your consent to contact you regarding the next stage of the study. If you consent to further contact and provide your contact details, you will be sent another similar questionnaire in the post after 3 months and 6 months. Some participants will be offered an INCLUDE review appointment with a nurse at their GP practice, at which the nurse will assess your risk of other health problems which can be associated with inflammatory conditions and provide advice and signposting where relevant. This review is in addition to your routine care which will continue as normal. At the appointment, you could be asked if you agree for the review to be audio-recorded. You may also be invited to an informal interview to discuss your experiences. More information, and your consent, for audio-recording and interview would be provided separately and it would be up you to decide whether to take part or not.

In order to find out what types of treatments and tests people with inflammatory conditions have, we also ask for your permission to look at your healthcare record held by your GP. We ask for your permission to do this on the last page of the questionnaire.

Do I have to take part?

No. Taking part in this study is entirely voluntary. If you decide not to take part, **this will not affect the care you receive at this practice or elsewhere.**

If you decide to take part, you are still free to withdraw from the study at any time and without giving a reason. Again, withdrawing from the study **will not affect the care you receive at this practice or elsewhere.**

Will my taking part in this study be kept confidential?

Yes. All the information you give us will be treated in the **strictest confidence**. When you return your completed questionnaire to Keele University, this will be securely stored under a unique study number. Your questionnaire answers (data) will only be associated with this number, not your personal details. Anonymous data held on this basis may be used in other research studies. Your consent form, containing your personal identifiable details, will also be stored securely at Keele University but separately to your data. Your personal details will only be retained for the duration of the study, after which they will be destroyed.

To ensure continuing care, we will inform your GP of your participation of the study and, if you attend an INCLUDE review appointment, the information collected will be saved in your GP healthcare record. When reviewing GP records, your name will not be used so you cannot be identified personally. Certain anonymised questionnaire data (such as your age, health status, and all Patient Activation Measure® data) will be securely shared with the licence holder Insignia Health® (USA) for the purposes of product improvement only.

What will happen to the results of the study?

After the study has finished and we have reviewed the results, the main findings from the study will be displayed on a poster in your GP practice and will be available on the Keele University website www.keele.ac.uk/pchs

The results of this study will also be shared at high profile international conferences and through publication in academic journals which are read by a large number of health professionals. You will not be identified individually in any poster, report or publication.

What are the possible risks and benefits of taking part?

We do not foresee any risk in taking part in the INCLUDE study. The only potential burden is on your time completing the questionnaires and you may be invited to a review appointment with a nurse at your GP practice.

Although there may not be any direct benefit to you, your participation will help us learn more about improving care for people with inflammatory rheumatological conditions.

Who is funding and organising the research?

This study is jointly funded by the Haywood Rheumatism Research & Development Foundation and the West Midlands National Institute of Health Research Collaborations for Leadership in Applied Health Research and Care West Midlands (NIHR WM CLAHRC). The Research Institute for Primary Care and Health Sciences and Keele Clinical Trials Unit at Keele University are working with General Practitioners within the West Midlands to organise this research.

Who has reviewed the study?

The scientific quality of the INCLUDE study has undergone independent peer review as part of the funding application process. The study has also been reviewed and approved for conduct in the NHS by the Wales Research Ethics Committee 5 (REC reference: 17/WA/0427).

Contact for further information

If you have any questions or would like further information about the INCLUDE study, please contact the INCLUDE Study Coordinator on **01782 732950**. If you have any questions or concerns about taking part in research you can also contact NHS England: Tel: 0300 311 2233, email: england.contactus@nhs.net or your GP practice.

Thank you for taking the time to read this information sheet.

Appendix 24- INCLUDE baseline questionnaire

2297

TeleForm ID

Keele UNIVERSITY

IN CLUDE

INtegrating and improving Care for patients with infLammatory rheUmatological DisordErs in the community

Baseline Questionnaire

Version 2.1 - 06 February 2018

IRAS ID: 229592

HAYWOOD foundation for arthritis research

Funded by NHS National Institute for Health Research

This study is part funded by the NIHR Collaborations for Leadership in Applied Health Research and Care West Midlands (NIHR WM CLAHRC)

INSTRUCTIONS FOR THIS QUESTIONNAIRE

Thank you for considering taking part in the INCLUDE study.

We want to find out more about different types of inflammatory conditions including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, polymyalgia rheumatica and giant cell arteritis and how they affect people. These questions are about your inflammatory condition, how it affects you and what other health problems you may have.

Your answers will help us to better understand what health checks for people with inflammatory conditions should involve.

Please answer **all** the questions.

We think it will take about 20 minutes to complete the questionnaire.

Most questions can be answered by putting a cross in a box like this: ☒

When you have finished, please check that you have answered all the questions and return the questionnaire in the pre-paid envelope enclosed. **You do not need a stamp.** We would be grateful if you could return the questionnaire in the next two weeks.

The answers you give in the questionnaire will be treated in the **strictest confidence**. Whether you take part in this research or not, the care you receive at your GP practice or elsewhere will **not** be affected.

If you have any questions please contact the INCLUDE Study Coordinator on

01782 732950

Thank you again for your help with this research study.

SECTION A: Your inflammatory condition

1. Which of the following inflammatory conditions do you have?
(Please put a cross in **ANY** box that applies to you)

Rheumatoid Arthritis (RA)	☐	Polymyalgia Rheumatica (PMR)	☐
Ankylosing Spondylitis (AS)	☐	Giant Cell Arteritis (GCA)	☐
Psoriatic Arthritis (PsA)	☐	None of the above	☐

If you marked "None of the above", please skip to section K on page 13

SECTION B: Your health conditions

1. Have you ever been told that you have, or had any of the following?
(Please put a cross in **ANY** box that applies to you)

Diabetes	☐	High blood pressure	☐	Stroke	☐
Angina	☐	Heart attack	☐	Osteoporosis	☐
Depression/Anxiety	☐	None of the above	☐		

2. Have you ever fractured or broken any of the following bones?
(Please cross **only those that apply**)

Hip	☐	Wrist	☐	Spine/vertebrae	☐	Other bones	☐

3a. Have you ever had a bone density scan (DEXA scan)?

Yes ☐ No ☐

b. If so, approximately how long ago?

☐☐ months ☐☐ years

SECTION C: Impact of your inflammatory condition

Your pain, stiffness and fatigue

These questions are about how you are currently affected by your inflammatory condition.
(Please put a cross in **ONE** box only)

1. How would you rate the overall level of **pain** from your inflammatory arthritis on a 0-10 scale, where 0 is "no pain" and 10 is "pain as bad as could be"?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	**Pain as bad as could be**

2. How would you rate the overall level of **stiffness** from your inflammatory arthritis on a 0-10 scale, where 0 is "no stiffness" and 10 is "stiffness as bad as could be"?

	0	1	2	3	4	5	6	7	8	9	10	
No stiffness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	**Stiffness as bad as could be**

3. How would you rate the overall level of **fatigue** from your inflammatory arthritis on a 0-10 scale, where 0 is "no fatigue" and 10 is "totally exhausted"?

	0	1	2	3	4	5	6	7	8	9	10	
No fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	**Totally exhausted**

Treatments for your inflammatory condition

4. Please indicate if you are currently taking any of the following medications.
(Please put a cross in **ANY** box that applies to you)

a. Paracetamol ☐

b. Paracetamol with codeine ☐

c. Non-steroidal anti-inflammatories ☐
e.g. ibruprofen, naproxen

d. Strong painkillers on prescription ☐
e.g. tramadol, butrans patch, morphine

e. Specialist arthritis medications ☐
e.g. methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine, gold injections

f. Injections prescribed by the hospital for your arthritis ☐
e.g. anti-TNF medication, etanercept, rituximab

g. Medicine to protect your stomach and digestive system ☐
e.g. omeprazole, lansoprazole

h. Calcium and Vitamin D ☐
e.g. adcal, calcichew

i. Medicines for osteoporosis ☐
e.g. alendronate, risedronate, zolendronate

j. Medicines for depression or anxiety ☐
e.g. fluoxetine, citalopram, sertraline, mirtazapine

k. Steroid tablets ☐
e.g. prednisolone

l. Other (please specify below) ☐

_____

SECTION D: Your understanding of your health condition

For each of the statements below, please put a cross in the **ONE** box which applies to you.		Disagree strongly	Disagree	Agree	Agree strongly	Not applicable
1.	When all is said and done, I am the person responsible for taking care of my health.	☐	☐	☐	☐	☐
2.	Taking an active role in my own health care is the most important thing that affects my health.	☐	☐	☐	☐	☐
3.	I am confident that I can help prevent or reduce problems associated with my health.	☐	☐	☐	☐	☐
4.	I know what each of my prescribed medications do.	☐	☐	☐	☐	☐
5.	I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself.	☐	☐	☐	☐	☐
6.	I am confident I can tell a doctor concerns I have even when he or she does not ask.	☐	☐	☐	☐	☐
7.	I am confident that I can follow through on medical treatments I may need to do at home.	☐	☐	☐	☐	☐
8.	I understand my health problems and what causes them.	☐	☐	☐	☐	☐
9.	I know what treatments are available for my health problems.	☐	☐	☐	☐	☐
10.	I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising.	☐	☐	☐	☐	☐
11.	I know how to prevent problems with my health.	☐	☐	☐	☐	☐
12.	I am confident I can figure out solutions when new problems arise with my health.	☐	☐	☐	☐	☐
13.	I am confident that I can maintain lifestyle changes, like eating right and exercising, even during times of stress.	☐	☐	☐	☐	☐

Patient Activation Measure - 13 item (Hibbard et al, 2005)

SECTION E: The effort of looking after your health

We are interested in finding out about the effort you have to make to look after your health and how this impacts on your day-to-day life. Please tell us how much difficulty you have with the following: (Please cross the box that most applies to you)

		Not difficult	A little difficult	Quite difficult	Very difficult	Extremely difficult	Does not apply
1.	Taking lots of medications	☐	☐	☐	☐	☐	☐
2.	Remembering how and when to take medication	☐	☐	☐	☐	☐	☐
3.	Collecting prescription medication	☐	☐	☐	☐	☐	☐
4.	Monitoring your medical conditions (e.g. checking your blood pressure or blood sugar, monitoring your symptoms etc)	☐	☐	☐	☐	☐	☐
5.	Arranging appointments with health professionals	☐	☐	☐	☐	☐	☐
6.	Seeing lots of different health professionals	☐	☐	☐	☐	☐	☐
7.	Attending appointments with health professionals (e.g. getting time off work, arranging transport etc)	☐	☐	☐	☐	☐	☐
8.	Obtaining clear and up-to-date information about your condition	☐	☐	☐	☐	☐	☐
9.	Making recommended lifestyle choices (e.g. diet and exercise)	☐	☐	☐	☐	☐	☐
10.	Having to rely on help from family and friends	☐	☐	☐	☐	☐	☐

SECTION F: Living with your condition

We would like to know how confident you are in doing certain activities. For each of the following questions, please choose the number that corresponds to your confidence that you can do the tasks regularly at the present time,
(Please cross **ONE** box per line.)

1. How confident do you feel that you can keep the fatigue caused by your disease from interfering with the things you want to do?

Not at all confident										**Totally confident**
0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

2. How confident do you feel that you can keep the physical discomfort or pain of your disease from interfering with the things you want to do?

Not at all confident										**Totally confident**
0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

3. How confident do you feel that you can keep the emotional distress caused by your disease from interfering with the things you want to do?

Not at all confident										**Totally confident**
0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

4. How confident do you feel that you can keep any other symptoms or health problems you have from interfering with the things you want to do?

Not at all confident										**Totally confident**
0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

5. How confident do you feel that you can do the different tasks and activities needed to manage your health condition so as to reduce your need to see a doctor?

Not at all confident										**Totally confident**
0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

6. How confident do you feel that you can do things other than just taking medication to reduce how much your illness affects your everyday life?

Not at all confident										**Totally confident**
0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Self-Efficacy for Managing Chronic Disease 6-item Scale (Lorig et al.,2001)

SECTION G: Your general health

The following questions are aimed at assessing your views about your health status, as well as some activities that you might do in everyday life.

1. In general would you say your health is? (Please put a cross in **ONE** box)

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. For each of the five sets of statements below, please put a cross in the **ONE** box that best describes your own health state **TODAY**.

Mobility:		**Self-Care:**	
I have no problems in walking about	☐	I have no problems washing or dressing myself	☐
I have slight problems in walking about	☐	I have slight problems washing or dressing myself	☐
I have moderate problems in walking about	☐	I have moderate problems washing or dressing myself	☐
I have severe problems in walking about	☐	I have severe problems washing or dressing myself	☐
I am unable to walk about	☐	I am unable to wash or dress myself	☐
Usual Activities: (e.g. *work, study, housework, family or leisure activities)*		**Pain/Discomfort:**	
I have no problems doing my usual activities	☐	I have no pain or discomfort	☐
I have slight problems doing my usual activities	☐	I have slight pain or discomfort	☐
I have moderate problems doing my usual activities	☐	I have moderate pain or discomfort	☐
I have severe problems doing my usual activities	☐	I have severe pain or discomfort	☐
I am unable to do my usual activities	☐	I have extreme pain or discomfort	☐
Anxiety/Depression:			
I am not anxious or depressed	☐		
I am slightly anxious or depressed	☐		
I am moderately anxious or depressed	☐		
I am severely anxious or depressed	☐		
I am extremely anxious or depressed	☐		

3. We are interested in learning how your illness affects your ability to function in daily life. Please put a cross in the **ONE** box on each line which best describes your usual abilities over the past **WEEK:**

Are you able to:	Without any difficulty	With some difficulty	With much difficulty	Unable to do
a. Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
b. Get in and out of bed?	☐	☐	☐	☐
c. Lift a full cup or glass to your mouth?	☐	☐	☐	☐
d. Walk outdoors on flat ground?	☐	☐	☐	☐
e. Wash and dry your entire body?	☐	☐	☐	☐
f. Bend down to pick up clothing from the floor?	☐	☐	☐	☐
g. Turn taps on and off?	☐	☐	☐	☐
h. Get in and out of the car?	☐	☐	☐	☐

Modified Health Assessment Questionnaire (MHAQ) (Maska et al., 2011)

SECTION H: Fatigue

1. Below is a list of statements that other people with your illness have said are important. Please put a cross in **ONE** box on each line to indicate your response as it applies to the **past 7 days.**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
a. I feel fatigued	☐	☐	☐	☐	☐
b. I feel weak all over	☐	☐	☐	☐	☐
c. I feel listless ("washed out")	☐	☐	☐	☐	☐
d. I feel tired	☐	☐	☐	☐	☐
e. I have trouble **starting** things because I am tired	☐	☐	☐	☐	☐
f. I have trouble **finishing** things because I am tired	☐	☐	☐	☐	☐
g. I have energy	☐	☐	☐	☐	☐
h. I am able to do my usual activities	☐	☐	☐	☐	☐
i. I need to sleep during the day	☐	☐	☐	☐	☐
j. I am too tired to eat	☐	☐	☐	☐	☐

	Not at all	A little bit	Somewhat	Quite a bit	Very much
k. I need help doing my usual activities	☐	☐	☐	☐	☐
l. I am frustrated by being too tired to do the things I want to do	☐	☐	☐	☐	☐
m. I have to limit my social activity because I am tired	☐	☐	☐	☐	☐

FACIT-Fatigue (Cella et al., 2002)

SECTION I: How you feel and your mood

This section of the questionnaire will help us to know how you are feeling. Read each item and put a cross in the box which comes closest to how you have been feeling.

1. Over the **last 2 weeks**, how often have you been bothered by any of the following problems? (Please put a cross in **ONE** box on each line)

	Not at all	Several days	More than half the days	Nearly every day
a. Feel nervous, anxious or on edge	☐	☐	☐	☐
b. Not being able to stop or control worrying	☐	☐	☐	☐
c. Worrying too much about different things	☐	☐	☐	☐
d. Trouble relaxing	☐	☐	☐	☐
e. Being so restless that it is hard to sit still	☐	☐	☐	☐
f. Becoming easily annoyed or irritable	☐	☐	☐	☐
g. Feeling afraid as if something awful might happen	☐	☐	☐	☐

GAD-7 (Spitzer et al., 2006)

2. Still thinking about the **last 2 weeks**, how often have you been bothered by any of the following problems? (Please put a cross in **ONE** box on each line)

	Not at all	Several days	More than half the days	Nearly every day
a. Little interest or pleasure in doing things	☐	☐	☐	☐
b. Feeling down, depressed or hopeless	☐	☐	☐	☐
c. Trouble falling or staying asleep, or sleeping too much	☐	☐	☐	☐
d. Feeling tired or having little energy	☐	☐	☐	☐
e. Poor appetite or overeating	☐	☐	☐	☐

	Not at all	Several days	More than half the days	Nearly every day
f. Feeling bad about yourself or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
g. Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	☐	☐	☐	☐

Modified PHQ-9 (PHQ-8) (Kroenke, 2001)

SECTION J: About you

This section contains some questions about you.

1. What is your date of birth? D D M M M Y Y Y Y

For example, if you were born on 6th April 1970, this would be entered as 06 APR 1970

2. Are you: Male ☐ Female ☐ Prefer not to say ☐

3. Which ethnic group do you consider yourself to belong to?
(Please put a cross in **ONE** box only)

White	☐	Black/African/Caribbean/Black British	☐
Asian/Asian British	☐	Mixed/multiple ethnic groups	☐
Other	☐	Prefer not to say	☐

4. What is your current employment status? (Please put a cross in **ONE** box only)

Employed	☐	Not working due to ill health	☐
Retired	☐	Housewife/husband	☐
Unemployed or seeking work	☐	Other (please state below)	☐

_____

5. **If you are working**, what is your job title, or **if you are not working, or are retired**, what was your last job title?

_____

6. **If you are working**, are you currently...
(Please put a cross in **ONE** box only)

Doing your usual job ☐ Doing lighter duties ☐ On unpaid sick leave ☐

Working fewer hours ☐ On paid sick leave ☐

7. Do you live alone?

Yes ☐ No ☐

8. What is your current smoking status? (Please put a cross in **ONE** box only)

Never smoked ☐ Previously smoked ☐ Current smoker ☐

9. On average, how often do you drink alcohol? (Please put a cross in **ONE** box only)

Daily or almost daily ☐ 3 or 4 times a week ☐ Once or twice a week ☐

1 to 3 times a month ☐ Special occasions only ☐ Never ☐

10. What is your weight?

☐☐ stones ☐☐ lbs **or** ☐☐☐ kgs

11. What is your height?

☐ feet ☐☐ inches **or** ☐☐☐ cms

Thank you for completing this questionnaire.
Please complete the section overleaf.

For Office Use Only:	
Logged 1	DB Logged
Data Entry	Quality Checked

Study ID:

SECTION K: Continuing to help with this study

Please ensure that you have read the enclosed INCLUDE Patient Information Sheet (v2.0, 04 Jan 2018) which explains the study in detail. **Please read and complete the following consent form.**

CONSENT FORM

Please answer each statement by putting a cross in **ONE** box on each line.

I confirm that I have read and understood the Patient Information Sheet and am willing to take part in the INCLUDE study.	Yes ☐
I understand that taking part in this research involves completing this questionnaire and follow-up questionnaires in 3 and 6 months' time.	Yes ☐
I understand that I can withdraw from the study at any time without giving a reason, and that this will not affect the care I receive in any way.	Yes ☐
I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from regulatory authorities or the Sponsor, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	Yes ☐

OPTIONAL ELEMENTS

I give permission for my medical records to be reviewed by an authorised person from the research team at Keele University.	Yes ☐	No ☐
I give my consent to be contacted again about related and future studies.	Yes ☐	No ☐

Please PRINT your name and contact details and sign below:

Title: _____ First name: _____ Last name: _____

Address: _____

_____

_____ Postcode: _____

Telephone 1 (please include area code if providing landline): _____

Telephone 2 (please include area code if providing landline): _____

Signature: _____ Date: _____

Please check that you have answered all the questions and return the questionnaire in the pre-paid envelope provided. **You do not need a stamp**. Even if you would prefer us not to review your medical records, the answers you have given in this questionnaire are still very important to us.

If you have any questions about the study or this questionnaire please contact the INCLUDE Study Coordinator on **01782 732950**.
Thank you for your help with this research study.

Office note: Detach and store separately from questionnaire after logging

Appendix 25- Letter of ethical approval for the INCLUDE study

NHS
Health Research Authority

Professor Carolyn Chew-Graham
Professor of General Practice Research
Arthritis Research UK Primary Care Centre
Research Institute for Primary Care & Health Sciences
Keele University
Staffordshire
ST5 5BG

Email: hra.approval@nhs.net

11 January 2018

Dear Professor Chew-Graham

Letter of HRA Approval

Study title:	**INCLUDE: INtegrating and improving Care for patients with infLammatory rheUmatological DisordErs in the community: A pilot randomised controlled trial.**
IRAS project ID:	**229592**
Protocol number:	**RG-0013-16-IPCHS**
REC reference:	**17/WA/0427**
Sponsor	**Keele University**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from the HRA website.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found through IRAS.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

IRAS project ID	229592

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details on the HRA website.

Your IRAS project ID is 229592. Please quote this on all correspondence.

Yours sincerely

Kelly Rowe
Assessor

Email: hra.approval@nhs.net

Copy to:

Dr Clark Crawford, Keele University, Sponsor Contact
Ms Gail White, NIHR Clinical Research Network: West Midlands, Lead NHS R&D contact

Appendix 26- *The association between covariates and moderate to severe anxiety (n=34) and depression (n=30) in people with **RA**.*

Exposure	Moderate to severe depression (PHQ-8 score≥10)		Moderate to severe anxiety (GAD-7 score ≥10)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Unadjusted OR (95% CI)	Adjusted OR (95% CI) *
Age	0.99 (0.97, 1.02) p=0.51	0.98 (0.94, 1.02) p=0.42	0.98 (0.95, 1.00) p=0.09	0.97 (0.92, 1.01) p=0.14
Female gender	1.22 (0.62, 2.39) p=0.57	1.09 (0.47, 2.51) p=0.84	1.60 (0.67, 3.85) p=0.29	1.24 (0.41, 3.73) p=0.67
Living alone	0.66 (0.27, 1.59) p=0.35	0.76 (0.25, 2.27) p=0.62	0.88 (0.30, 2.59) p=0.82	0.78 (0.21, 2.87) p=0.71
Current smoker	2.57 (0.80, 8.22) p=0.11	3.24 (0.75, 14.05) p=0.12	1.83 (0.52, 6.36) p=0.35	2.03 (0.43, 9.56) p=0.37
Regular alcohol ≥ weekly	1.12 (0.59, 2.12) p=0.73	1.03 (0.45, 2.37) p=0.95	0.49 (0.21, 1.11) p=0.09	0.62 (0.22, 1.71) p=0.36
Obesity (BMI ≥30)	0.47 (0.22, 0.99) p=0.05	0.63 (0.24, 1.65) p=0.35	1.61 (0.69, 3.79) p=0.27	1.39 (0.46, 3.96) p=0.56
≥1 comorbidity in addition to RA	1.09 (0.23, 1.89) p=0.84	1.15 (0.54, 1.76) p=0.32	1.34 (0.56, 3.21), p=0.52	1.19 (0.49, 3.96) p=0.20
≥2 IRCs	1.27 (0.53, 3.03) p=0.59	1.73 (0.62, 4.80) p=0.29	2.01 (0.78, 5.16) p=0.15	2.96 (0.96, 9.11) p=0.06
Pain Score	**1.19 (1.04, 1.36) p=0.01**	**1.22 (1.02, 1.46) p=0.03**	**1.26 (1.06, 1.51) p=0.01**	1.13 (0.92, 1.40) p=0.25
Stiffness Score	**1.26 (1.09, 1.45) p<0.01**	**1.42 (1.15, 1.75) p<0.01**	**1.21 (1.02, 1.44) p=0.03**	1.10 (0.89, 1.36) p=0.39
Fatigue Score	1.10 (0.97, 1.25) p=0.15	1.09 (0.92, 1.30) p=0.33	**1.22 (1.03, 1.45) p=0.02**	0.99 (0.82, 1.22) p=0.99
FACIT score	1.00 (0.97, 1.03) p=0.82	1.00 (0.96, 1.04) p=0.94	**0.88 (0.84, 0.92) p<0.01**	**0.89 (0.84, 0.94) p<0.01**

OR= odds ratio, CI=confidence interval, BMI= Body Mass Index.
* Adjustments made for significant unadjusted associations. Significant associations are in bold.

Appendix 27- Conference and lay audience presentations

Conference Presentations

- Machin AR, Blagojevic-Bucknall M, Chew-Graham CA, Hider SL. The incidence of anxiety and depression in patients with inflammatory rheumatological conditions. *Poster presentation, British Society of Rheumatology (BSR) conference, 2019.*
- Machin AR, Haththotuwa R, Opeyemi B, Scott I, Blagojevic-Bucknall M, Corp N, Chew-Graham CA, Hider SL. The impact of anxiety on quality of life and disease activity in rheumatoid arthritis: A systematic review. *Oral presentation as part of the poster showcase and poster presentation, BSR conference, 2019.*
- Machin AR, Hider SL, Jinks C, Herron D, Paskins Z, Cooke K, Chew-Graham CA. Development of an integrated nurse-led review based in primary care to identify and manage comorbidities in inflammatory rheumatological conditions: The INCLUDE study. *E-Poster presentation, BSR conference, 2019.*
- Machin AR, Herron D, DeSilva E, Jinks C, Hider SL, Paskins Z, Cooke K, Chew-Graham CA. Evaluation of nurse training to deliver an integrated care review for patients with inflammatory rheumatological conditions in primary care: a mixed methods study. *A person-centred approach to physical-mental multimorbidity conference. Poster presentation, Keele University, 2019.* ***(Best Poster Prize).***
- Herron D, Machin AR, DeSilva E, Jinks C, Hider SL, Paskins Z, Cooke K, Chew-Graham CA. Acceptability of a nurse-led integrated care review for patients with inflammatory rheumatological conditions. Preliminary findings from a

qualitative study in the INCLUDE trial. *A person-centred approach to physical-mental multimorbidity conference. Poster presentation, Keele University, 2019.*

- Machin AR, Haththotuwa R, Opeyemi B, Scott I, Blagojevic-Bucknall M, Corp N, Chew-Graham CA, Hider SL. The impact of anxiety on quality of life and disease activity in rheumatoid arthritis: A systematic review. *Poster presentation, School for Primary Care Research (SPCR) Research Showcase, 2018.* ***(Highly commended poster prize).***
- Machin AR, Herron D, Jinks C, Hider S, Cooke K, Chew-Graham CA. Evaluation of nurse training to deliver an integrated care review for patients with inflammatory rheumatological conditions in primary care: a mixed methods study. *Oral presentation, Society for Academic Primary Care (SAPC) North, 2018.*
- Machin AR, Herron D, Jinks C, Hider S, Cooke K, Chew-Graham CA. Evaluation of nurse training to deliver an integrated care review for patients with inflammatory rheumatological conditions in primary care: a mixed methods study. *Oral presentation, SAPC North, 2018.*
- Machin AR, Hider SL, Chew-Graham CA, Blagojevic-Bucknall M. The prevalence of anxiety and depression in patients with and without inflammatory rheumatic conditions. *Poster presentation, SAPC North, 2018.*
- Herron D, Machin AR, DeSilva E, Jinks C, Hider SL, Paskins Z, Cooke K, Chew-Graham CA. Acceptability of a nurse-led integrated care review for patients with inflammatory rheumatological conditions: a qualitative study. *Poster presentation, SAPC North, 2018.*

- Machin AR. Anxiety and depression in people with inflammatory arthritis*. Bob Beattie Student of the Year Awards Ceremony. 3 Minute Thesis Final, Keele University, 2018.*
- Machin AR. Anxiety and depression in people with inflammatory arthritis. Institute for Liberal Arts and Science (ILAS) Postgraduate Conference 2018. *3 Minute Thesis, Keele University, 2018* ***(3 minute thesis prize).***
- Machin AR, Haththotuwa R, Babatunde O, Scott I, Corp N, Bucknall M, Chew-Graham CA, Hider SL. A systematic review to determine the impact of anxiety on quality of life and treatment response in patients with rheumatoid arthritis. *Keele Postgraduate Symposium, Poster Presentation, 2018* ***(Systematic Review Prize).***
- Grose-Hodge E, Scott I, Hider SL, Machin AR, Dale N, Ryan S. Prevalence of impaired health literacy in patients with Rheumatoid Arthritis and its association with medication understanding and patient outcomes. *Poster Presentation, BSR conference, 2018.*
- Muller S, Hider SL, Machin A, Stack R, Hayward RA, Raza K, Mallen C. Searching for a prodrome for rheumatoid arthritis in the primary care record: A case-control study in the Clinical Practice Research Datalink. *Poster Presentation, BSR conference, 2018.*
- Machin AR, Haththotuwa R, Babatunde O, Scott I, Corp N, Bucknall M, Chew-Graham C, Hider S. A systematic review to determine the impact of anxiety on quality of life and treatment response in patients with rheumatoid arthritis. *West Midlands RCGP Symposium, Oral Presentation, Keele University, 2018.*
- Machin AR, Chew-Graham C, Hider S. The role of PPIE in developing a research protocol. *Oral Presentation, GP Academic Clinical Fellows (ACF) Conference, 2018.*

- Machin AR, Haththotuwa R, Babatunde O, Scott I, Corp N, Bucknall M, Chew-Graham C, Hider S. A systematic review to determine the impact of anxiety on quality of life and treatment response in patients with rheumatoid arthritis. *Poster presentation, GPACF Conference, Oxford, 2018.*
- Machin AR, Haththotuwa R, Babatunde O, Scott I, Corp N, Bucknall M, Chew-Graham C, Hider S. A systematic review to determine the impact of anxiety on quality of life and treatment response in patients with rheumatoid arthritis. *British Journal of General Practice Conference, Poster Presentation, 2018.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Perceived barriers and facilitators to the uptake of treatments for anxiety and depression in rheumatoid arthritis. *GPACF Conference Oral Presentation, Sheffield, 2017.* ***(Best oral presentation prize).***
- Machin AR, Hider S, Dale N, Chew-Graham CA. Perspectives of patients with rheumatoid arthritis on case-finding for anxiety and depression within a nurse-led annual review clinic. *BSR Conference 2017. Poster Presentation.*
- Higginbottom A, Blackburn S, Campbell L, Rhodes C, Taylor R, Machin A, Hider S, Roddy E, Chew-Graham CA. Celebrating ten years of patient involvement in research of inflammatory conditions. *Poster presentation, Annual European Congress of Rheumatology, 2017.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient preferences for management of comorbid anxiety and depression in rheumatoid arthritis: a qualitative study. *Elevator Pitch, SAPC, Warwick, 2017.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Poster presentation on improving the recognition of anxiety and depression in patients with rheumatoid arthritis.

Poster presentation at Annual Clinical Academic Training Event, Keele, 2017. ***(Best poster presentation prize).***

- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient perspectives on case-finding for anxiety and depression in patients with rheumatoid arthritis: The impact of PPIE. *Oral presentation at Primary Care Mental Health Conference, Keele, 2017.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient perspectives on case-finding for anxiety and depression in patients with rheumatoid arthritis- the impact of patient and public involvement and engagement. *Oral presentation, Keele Postgraduate Student Symposium, 2017.*
- Hider SL, Ryan S, Dale N, Stanyer N, Machin A, Chew-Graham CA. Assessing depression in patients with established rheumatoid arthritis- how do different approaches compare? *Poster presentation, Annual European Congress of Rheumatology Conference, 2017.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient perspectives on case-finding for anxiety and depression in patients with rheumatoid arthritis. *Poster presentation at RCGP Conference, Harrogate, 2016.* ***(Best poster presentation prize).***
- Machin AR, Hider S, Dale N, Chew-Graham CA. Disclosure of anxiety and depression in rheumatoid arthritis- the importance of candidacy and recursivity: a qualitative study. *Oral presentation at West Midlands Annual Clinical Academic Training Event (Birmingham), 2016.* ***(Best oral presentation prize).***

- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient perspectives on case-finding for anxiety and depression in patients with rheumatoid arthritis**.** *Oral Presentation at SAPC North, Kendal, 2016.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient perspectives on case-finding for anxiety and depression in patients with rheumatoid arthritis: a qualitative study. *Oral presentation, GPACF annual conference, Brighton, 2016.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient perspectives on case-finding for anxiety and depression in patients with rheumatoid arthritis. *Poster presentation at Postgraduate Student Symposium, Keele University, 2016.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient perspectives on case-finding for anxiety and depression in patients with rheumatoid arthritis- the impact of patient and public involvement. *Poster presentation at Mental Health Research Group Symposium, Keele University, 2016.*
- L Varadhan, A Machin, T Humphreys, Nayak UA, Jose B, Walker AB, Varughese GI. The dynamic changes of Diabetic Maculopathy with intensification of glycaemic control with GLP-1 agonist therapy. *Poster Presentation at European Association for the Study of Diabetes conference, 2013.*

Lay Audience Presentations

- Investigating mood disorders in people with inflammatory rheumatological conditions: A mixed methods study. *Oral Presentation, Haywood Foundation, 2019.*
- Machin AR. Improving how mood problems are identified and treated in people with inflammatory arthritis. *Oral presentation, Haywood User Group, 2018.*

- Machin AR. Improving how mood problems are identified and treated in people with inflammatory arthritis. *Oral presentation, Stoke NRAS Meeting, 2018.*
- Machin AR. Developing a patient information leaflet on mood problems in rheumatoid arthritis. *Poster presentation, Annual Research User Group meeting, Keele University, 2018.*
- Machin AR, Hider S, Dale N, Chew-Graham CA. Patient perspectives on case-finding for anxiety and depression in patients with rheumatoid arthritis: The impact of PPIE. *Poster Presentation at event celebrating 10 years of PPIE at the Keele Research Institute, 2016.* ***(Best poster presentation prize).***
- Machin A. Mood problems in rheumatoid arthritis. *Oral presentation, Haywood User Group, 2016.*

Other Conference Presentations

- Machin A. "Is there a different medication I could have doctor? These anxiety pills are useless!" *Poster presentation, RCGP Midland Faculty Annual Education, Research and Innovation Symposium, 2016.* ***(Best poster presentation prize winner).***
- Machin, A. Audit of antibiotic prescribing for acute otitis media in a semi-rural GP practice. *Poster presentation, RCGP annual conference 2016.* ***(Shortlisted for a prize).***
- Machin, A. Audit of rheumatoid arthritis annual reviews including mood exploration within an urban GP practice. *Poster presentation at RCGP annual conference 2016.*

- Machin, A. Audit of Primary Care Physical Health Monitoring in Patients with Severe Mental Illness. *Poster Presentation, Improving physical health for patients with severe mental illness, South Staffordshire and Shropshire NHS Foundation trust, 2016.*
- Machin, A. Audit of Physical Health Monitoring in Psychosis and Schizophrenia. *Poster presentation, RCGP annual conference, 2014.*