Acute flares in knee osteoarthritis

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Doctor of Philosophy

June, 2020

Keele University

ACKNOWLEDGEMENTS

There are a number of people who I owe my gratitude to and who have been instrumental throughout my PhD. In the first instance I would like to thank the participants who gave up their time to complete the daily diaries for up to 3 months and those who allowed me to come into their home and interview them. None of this work would have been possible without them.

A huge thanks to my lead PhD supervisor Professor George Peat for his guidance, expertise and patience throughout. I would also like to thank Associate Professor Reuben Ogollah, Professor Carolyn Chew-Graham and Dr Lisa Dikomitis for all of their support and encouragement.

A special thanks goes to the members of the PPIE group who gave up their time and for their invaluable insights that helped shape three of my studies. I would also like to thank the systematic review team for their help in shaping my review protocol.

I would like to express my gratitude to the West Midlands Clinical Research Network for their input in recruiting for my studies, with a special thanks to Sam Hunt. Also, to Alicia Bratt who was the study administrator for the cross-sectional survey and diary study.

I would like to thank my funders: the National Institute for Health Research, the School for Primary Care and the Royal College of General Practitioners Scientific Foundation Board. Without their funding none of this work would have been possible.

A special thanks goes to my colleagues, in particular Martin Thomas who was a co-reviewer on the systematic review.

To my husband Chris and children, Joseph and Alice I want to give my profound thanks for their unwavering love and support. And lastly to my parents who have always believed in me and provided me with endless love and encouragement. This PhD is dedicated to my dad, who sadly passed away toward the end of my doctoral research studies. I know he would have been proud.

ABSTRACT

Osteoarthritis affects 8.75 million people in the United Kingdom. Acute episodes of pain (“acute flares”) may be an important, although poorly understood, part of its natural history. This thesis is a mixed methods study of acute flares in knee osteoarthritis, exploring how to define them for the purposes of research, their frequency, nature, impact, and possible causes.

My systematic review of 69 studies found a variety of ad hoc definitions and concluded that key domains used to define acute events in other chronic conditions - worsening signs/symptoms, minimum duration, speed of onset, impact - could provide the basis for future consensus. Based on worsening symptoms alone, a secondary analysis of existing cohort data estimated that 23-32% of symptomatic adults over 50 years report significant variability in their knee symptoms. A prospectively designed cross-sectional survey and nested pen-and-paper daily diary study, designed with lay member input, found that flares were often disruptive and associated with changes in pain quality, nature of knee symptoms and increased health care utilisation, and self-care activity. Findings from the analysis of 15 patient semi-structured interviews supported these associations with flares, but also highlighted the variable nature of the pain experience and the impact ‘major’ flares had on their daily functioning. The participants described the differences between daily variability in pain and flares, and this highlighted the importance of using a minimum duration in flare definitions to differentiate between them.

Findings from the secondary analysis of the Knee Clinical Assessment Study (CAS(K)) data and diary study suggest that nearly a half of adults aged over 50 years

with knee OA may experience an acute flare. Flares impact on daily activities and social participation, and may take a median of 8 days to settle although this appears highly variable. While not consistently demonstrated, susceptibility (for example previous knee surgery and higher body mass index) and extrinsic mechanical exposures (such as squatting and heavy lifting) are implicated as causes of acute flares in knee OA although larger-scale studies to confirm and extend these findings are needed.

ABBREVIATIONS

ACR	American College of Rheumatology
ARA	American Rheumatism Association
AS	Ankylosing Spondylitis
CAS(K)	Knee Clinical Assessment Study
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COSMIN	Consensus-based standards for the selection of health measurement instruments
COX-2	Cycloogenase-2
CRN	Clinical Research Network
EULAR	European League Against Rheumatism
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
GDP	Gross Domestic Product
GOLD	Global initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GORD	Gastro-oesophageal reflux disease
HADS	Hospital Anxiety and Depression Scale
HCP	Health Care Practitioner
IBD	Inflammatory Bowel Disease
KL	Kellgren and Lawrence
KOFUS	Knee Osteoarthritis Flare-Up Score
LK	Likert Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS	Numerical Rating Scale
NSAID	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International

OMERACT	Outcome Measures in Rheumatology Clinical Trials
PPIE	Patient and Public Involvement and Engagement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	The International prospective register of Systematic Reviews
QUADAS	Quality assessment tool for diagnostic accuracy studies
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
SPCSC	School of Primary, Community and Social Care
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedures
USA	United States of America
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
YLD	Years Lived with Disability

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PUBLICATIONS AND PRESENTATIONS ARISING FROM THE WORK DESCRIBED IN THIS THESIS

Peer reviewed Publications:

Parry E, Ogollah R, Peat G. The natural history of flare-ups: a daily diary study of patients with, or at high risk of, knee osteoarthritis. *Osteoarthritis and cartilage,* 2019; 26, S1: S36. DOI: https://doi.org/10.1016/j.joca.2018.02.088

Parry E, Thomas M, Peat G. The definition and classification of acute flares in knee osteoarthritis: a systematic review. *BMJ Open,* 2018; *8*(7), e019804. doi: 10.1136/bmjopen-2017-019804

Parry E, Ogollah R, Peat G. Significant pain variability in persons with, or at high risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of cohort data. *BMC Musculoskeletal Disorders,* 2017; 18: 80. DOI: 10.1186/s12891-017-1434-3.

Oral presentations:

Parry E, Ogollah R, Peat G The natural history of flare-ups in knee osteoarthritis: descriptive findings from a prospective daily diary study. NIHR *School for Primary Care Research Trainees Event, Oxford, Sep 2018*

Parry E, Ogollah R, Peat G. The natural history of flare-ups:
A daily diary study of patients with, or at high risk of, knee osteoarthritis.
Osteoarthritis Research Society International Congress, Liverpool, April 2018

Parry E, Ogollah R, Peat G. The natural history of flare-ups in knee osteoarthritis: findings from a prospective daily diary study. *Keele Postgraduate Symposium, Keele, May 2017.* [Won PPIE Choice Award]

Parry E, Ogollah R, Peat G The natural history of flare-ups in knee osteoarthritis: descriptive findings from a prospective daily diary study. *Society for Academic Primary Care Annual Scientific Meeting, Warwick, July 2017*

Clarke E, Ogollah R, Peat G. OA exacerbations on knee OA: A cross sectional survey. *National ACF Conference*, Oxford, March 2014.

Clarke E, Ogollah R, Peat G. OA exacerbations on knee OA: A cross sectional survey. *Keele Postgraduate Research Symposium*, Keele, May 2014.

Clarke E, Thomas M, Peat G. Defining Acute Exacerbations in Knee Osteoarthritis: A Systematic Review. *Society for Academic Primary Care North Conference*, November 2014.

Clarke E, Peat G. Research proposal-Exacerbations in osteoarthritis: an observational study. *Australian Academic Registrar Online Symposium*, 2012.

Poster presentations:

Clarke E, Ogollah R, Peat G. Exacerbations in knee osteoarthritis: estimates from a population cohort with repeated measures based on retrospective recall. *Society for Academic Primary Care Annual Scientific Meeting*, Nottingham, July 2013.

1. Background

This thesis is concerned with the occurrence of acute episodes or flare-ups in knee osteoarthritis. The central contention is that acute flares are a feature of the natural history of osteoarthritis, at least for some individuals, and that the observation of these might ultimately give useful insights into the pathogenesis of osteoarthritis, earlier identification and have practical application for improved episode management, and intervention studies.

1.1 Diagnosis of osteoarthritis

Osteoarthritis is primarily diagnosed and managed in primary care (1). There are no single accepted set of diagnostic criteria for osteoarthritis. The National Institute for Health and Care Excellence (NICE), which provides evidence based guidelines for healthcare in England, offers the most user friendly recommendation where OA is diagnosed based on clinical symptoms alone:

> *"Adults aged 45 or over are diagnosed with osteoarthritis clinically without investigations if they have activity-related joint pain and any morning joint stiffness lasts no longer than 30 minutes." (2)*

European League Against Rheumatism (EULAR) recommendations include the addition of reduced function and clinical examination findings such as crepitus, reduced range of movement, and bony enlargement (3). The American College of Rheumatology (ACR) goes one step further offering alongside clinical diagnosis radiographic and laboratory diagnostic criteria (4). These added items lead to improved diagnostic accuracy but may not be practical in primary care.

Radiographic findings, although not required to make a diagnosis of OA, when present include joint space narrowing, osteophytes, subchondral bone sclerosis, and subchondral 'cysts' (3). Radiographic findings often conflict with clinical status and are usually reserved for research studies or where there is diagnostic uncertainty (5).

1.2 Management

The mainstay of management in OA takes place in the community (1). There are a number of international guidelines on the management of osteoarthritis that reflect the need to take a community based approach, these include the European League Against Rheumatism (EULAR) (6, 7), Osteoarthritis Research Society International (OARSI) (8), and ACR (9). In English primary care, management of OA is generally guided by NICE (2). The guidelines, however, predominantly focus on the management of chronic OA, with little reference to acute events.

In knee osteoarthritis (and osteoarthritis in general) international and national guidelines place a firm emphasis on the importance of education, exercise, weight loss, and self-management (2, 6-9). Non-pharmacological treatments for knee OA that are mentioned but recommended inconsistently across guidelines include: appliances, walking aids, footwear including insoles, femoral taping, acupuncture, and electrotherapy (2, 6-9).

The most commonly recommended analgesics include paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs). Paracetamol has come under recent scrutiny due to lack of efficacy shown in a recent meta-analysis (10) and safety concerns. In future guidelines, it may therefore only be recommended as an adjunct to other therapies. Topical NSAIDs are known to be effective and have a low side effect profile (11), and

are advised first line on their own or in combination with paracetamol (2, 6, 8, 9). Oral NSAIDs are generally effective against pain but concerns about side effects (gastrointestinal and cardiovascular) means they are only recommended second line if paracetamol and topical NSAIDs are ineffective. Opioids are generally advised to be used with caution due to adverse events; notably dependence (2, 6, 8, 9). Intraarticular corticosteroids are recommended for flares of knee pain due to their short-lived duration of action and when oral medication is contraindicated or has failed. There is conflicting advice on the recommendation of glucosamine and chondroitin, and intraarticular injection of hyaluronic acid. ACR draws attention to the use of duloxetine for severe symptoms but has little mention in other guidelines (9).

The role of arthroscopy in the management of knee osteoarthritis is now reserved for cases of knee locking and referral for knee arthroplasty is advised where there is severe pain and functional limitation (2, 6, 8, 9).

NICE is the only guideline to offer recommendation on review and follow up of patients with OA which includes reviewing symptoms, progression, continued education and supporting self-management, and reviewing therapy.

Despite a number of guidelines, primary care clinicians find optimising management of osteoarthritis challenging (12). In the context of multimorbidity, (the presence of two or more chronic conditions (13)) other conditions are usually prioritised over OA, for example angina. This may be due to patient safety concerns (e.g. focussing on the condition which has the greater threat to the patient's health), financial incentives attached to other conditions, the limited availability of resources to manage OA, for example physical therapy and lack of treatment options (14). When consulting about OA, patients feel that OA is normalised, that the information given is vague and that

education on disease course is lacking (14, 15). General Practitioners (GPs) find managing OA challenging due to the limited management options and resources available, and a perception that patients are unwilling to change their lifestyle leading to avoidance of conversations on weight management which can lead to suboptimal care (15). Successful pilots of physiotherapists as the first point of contact for musculoskeletal problems has been trialled which reduced demand on GPs, optimised management and reduced referrals to secondary care (16). A greater range of healthcare practitioners are now providing care to primary care patients,, notably: physician associates, paramedics, pharmacists and advanced nurse practitioners (17). It is important that all of those delivering care have an understanding of different presentations of osteoarthritis and its management in order to improve patient experience outcomes.

1.3 Aetiopathogenesis of osteoarthritis

Osteoarthritis is defined as both a clinical syndrome of use-related joint pain, stiffness and reduced function, and a pathological process affecting synovial joints or an ‘illness’ and a ‘disease’ (18). It has been argued that the aetiopathogenesis of OA is best understood as a process of repeated failure of the repair mechanisms of the joint in response to abnormal biomechanical and biochemical forces acting on the joint (19). While the relative contributions of mechanical factors and inflammation to osteoarthritis pathogenesis remain the subject of considerable debate (20), there is general acceptance, particularly with the advent of MRI-based studies, that osteoarthritis involves all joint tissues in the synovial joint including articular cartilage, subchondral bone, synovium, ligaments, and muscles (3, 21). Bone remodelling,

leading to the development of outgrowths, osteophytes, and sclerotic lesions (22) are well known features of OA.

Articular cartilage has been the focus for much previous research on osteoarthritis and it has been argued that since it is not innervated clinical features may only become apparent later on in the degradation process (19).

Pathological changes in all of these tissues may contribute to osteoarthritis pain. The role of inflammation in osteoarthritis has been the subject of considerable recent interest, having traditionally been viewed as relatively minor. Studies have demonstrated synovial inflammation in patients with OA using MRI, Ultrasound and histological specimens (23). It is hypothesised that resultant inflammation in the synovial fluid, possibly from 'cartilage debris and catabolic mediators' leads to an imbalance in degradation and repair mechanisms (19). Increased amounts of inflammatory mediators have been demonstrated in patients with early knee OA compared to late OA (24). Furthermore, some studies suggest that even before OA develops, inflammation is present within the joint, for example, either from increased adipose tissue in obese patients which activates mechanoreceptors on chondrocytes, from products produced through the ageing process (advanced glycation end products) or increased proinflammatory cytokines as a result of decreased ovarian function in post-menopausal females (25).

In reality, it is likely that both inflammation and mechanical factors work together resulting in joint failure, however it is difficult to disentangle this complex process particularly due to the complex inter-play of contributing factors.

1.4 Risk factors for onset and progression of OA

Risk factors have been identified for the development of OA, the progression of OA, and for OA-related disability and this topic has been discussed in several reviews (22, 26-28). Age is probably the most notable risk factor and this is likely due to factors relating to the ageing process and a cumulative effect of certain exposures (27, 29). Other factors that were associated with risk of knee OA in a recent systematic review and meta-analysis included: being overweight or obese, having previous knee injury, and being a female gender (30). The increased incidence of OA and the presence of more severe radiographic changes in menopausal women has led to a hypothesis on the protective impact of oestrogen although this is poorly understood (26). Obesity increases the risk of development of OA and risk of radiographic progression (26). This is likely due to a number of factors, both mechanical resulting from increased loading on knee joints and metabolic from mechanisms related to increased adipose tissue (31).

Activity that puts repeated strains or stressors on the knee, for example, high levels of physical activity and repeated occupational exposures such as heavy lifting and knee bending have also been associated with increased risk of OA (30, 32). Of note not all types of physical activity lead to knee OA and evidence is conflicting as to whether it is the activity itself, injury or both that leads to OA (22).

Knee injury, particularly trauma to the anterior cruciate ligament, meniscal tears, and articular cartilage damage can lead to damage to surrounding structures and subsequent development of osteoarthritis (26)**.** Where injury occurs at an early age, this may contribute to a considerable number of years lived with pain and potential disability.

1.5 Epidemiology of OA

1.5.1 Prevalence

Prevalence estimates for osteoarthritis are highly sensitive to case definition, data source and target population (33). Prevalence estimates from four (34) primary care databases ranged from 164 to 426 per 10,000 people aged 15 years and over for osteoarthritis. In the United Kingdom, data from general practices in North Staffordshire, has been analysed to estimate that 8.75 million people in the UK have osteoarthritis (35) and that over 2 million consult their general practitioner (GP) each year in Britain with OA related symptoms (36).

At the knee, the most commonly affected joint, estimates of the prevalence of knee pain in community-dwelling adults middle-aged and older adults (minimum 40 years) range from 6.5% to 28% and at least half of these report some restriction of daily activity (1). An estimated 11-13% of adults will have symptomatic radiographic knee OA (1). The Global Burden of Disease project estimated the prevalence of symptomatic radiographic knee OA in the total population (i.e. all ages) to be 3.8% (37).

Prevalence has been shown to be higher in women and increases with age (38, 39). The most common joints affected are the hip, knee, hand, foot, and spine (38). Knee osteoarthritis is one of the most prevalent conditions in later life (39, 40).

1.5.2 Incidence

The incidence of osteoarthritis, that is the number of new cases during a specified time period, is much harder to define given the insidious onset to the condition. Using data from Spanish primary care, Prieto-Alhambra et al, found that consultation incidence rate for knee OA was 6.5 per 1000 person-years (95% CI: 6.4, 6.6). The incidence rate was higher for females than for males (8.3 cf 4.6 per 1000 person-years) (41). This is likely to be an under-estimate as it relies on GPs being confident in their diagnosis and Read-coding this rather than reported symptoms, for example, knee pain.

1.5.3 Lifetime risk

Estimates of lifetime risk of knee OA in US populations range from 14% (diagnosed symptomatic knee OA from age 25 years) to 45% for symptomatic radiographic knee OA, from age 45 years in a predominantly rural, obese population with high proportions of African-American residents (42). Losina et al produced more recent lower estimates of lifetime risk of symptomatic knee OA of 13.8% (43). These results were based on nationwide household interview results so may be more generalisable to the wider population. No comparable estimates are published for the UK. However, an analysis of the UK General Practice Research Database suggests lifetime risks of total knee replacement at age 50 years in 2005 of 11.6% for women and 7.1% for men (44). This gives an indication of the number with severe symptoms and is likely to be a reliable estimate given the source of the data.

1.6 Economic burden

A report in 2010 from Oxford Economics extrapolated evidence on direct costs, indirect costs and quality of life costs of osteoarthritis in the UK (45)**.** Direct costs, which include GP and nurse consultations, hospital attendance, specialist services (physiotherapy, chiropractors etc), and prescription medication, were estimated at £5.2 billion per year. Indirect costs, from permanent retirement, absenteeism, reduced productivity and informal carers were estimated at £14.8 billion. However, these estimates were based in part on sources of data that included people with rheumatoid arthritis (RA), on US figures and generally relied on primary care data or information from patients who had sought healthcare. In higher income countries socio-economic costs of OA are estimated to between 0.25-0.50% of Gross Domestic Product (GDP) (46).

The Global Burden of Disease Study in 2010 estimated years lived with disability (YLD) in those with knee osteoarthritis to be 206 per 100, 000 (95% Confidence Interval (CI) 142-290) which was a 26.8% increase compared to the 1990 survey (47). Comparing this to the UK, the disability adjusted life years (DALY) for osteoarthritis in 2010 was estimated to be 351 (95% CI 221-520) per 100,000 (48).

These estimates are important to consider in relation to funding challenges within the National Health Service (NHS) and how this impacts on primary care. In 2017/18 8.1% of the NHS budget was spent on general practice compared to 9.6% in 2005/6, however, it has been estimated that 11% is needed to help sustain general practice and meet capacity (49)**.** Added to this, patient demand is rising with 312 million appointments estimated to have taken place between November 2018 to October 2019 compared to 307 million appointments between November 2017 and October

2018(50, 51). With an ageing population, growing demand and a decrease in real terms funding, this will have consequences on the optimal management of OA. Improving patient education on the existence of flares, how they are different to chronic OA, how long they last, potential triggers and potential management strategies may help improve episode management.

1.7 Pain experience

One of the earliest markers of OA appears to be knee pain associated with increased knee loading, for example, climbing stairs which can be present up to 3 years prior to incident radiographic OA (52). Pain in OA can be classified by duration, quality, and intensity, for example intermittent, severe pain which is usually sharp, stabbing, and intense to longer acting, milder pain which is more likely to be described as dull, aching, and throbbing (53). Pain quality can also be classified by neuropathic descriptors such as burning and numbness (54).

Symptoms other than pain that are usually reported in OA include morning stiffness, reduced range of movement, crepitus, effusion, joint instability, muscle weakness, fatigue, and psychological distress (28). Some of these factors were utilised in a diagnostic tool for identification of knee OA flare. The Knee Osteoarthritis Flare-up Score (KOFUS) tool is a weighted measure, developed using a primary care database and validated using a rheumatological database, which includes; morning stiffness for longer than 20 minutes, nocturnal awakenings, knee effusion, limping, joint effusion, and increased warmth (55). However, this has not been widely used in research or in clinical practice possibly due to time needed to complete the scoring or because the outcome may not alter management.

Once knee OA is diagnosed the disease trajectory is not necessarily one of consistent decline as was previously thought. A number of longitudinal studies have shown variability in the disease course (56-60). However, the design of these studies are unable to account for fluctuations of pain that take place during the day or over a few weeks. Qualitative studies have noted that osteoarthritis is interspersed with intermittent episodes of pain that may become more frequent and bothersome with time (61). Hawker et al, identified stages of OA which were characterised in the early stages with intermittent predictable pain that came on with activity that progressed to intermittent pain that became more severe, unpredictable, and had greater impact on function in the latter stages (53). Cedraschi et al noted patient descriptions of short and intense “stabbing pain” which came on suddenly and caused alarm (62). The existence of intermittent pain has also been noted in daily diary studies which have shown the daily variability of OA pain (63), and in focus groups on assessing chronic knee and hip pain (64). The duration of episodes of increased pain have been described in qualitative studies as lasting between a few seconds to 15 minutes (61). However, the distinction between variability of pain as part of the nature of the condition and a distinct disease flare have not been made.

1.8 Flares in osteoarthritis

Flares in osteoarthritis are starting to receive more attention in the medical literature, however, until recently they were only briefly mentioned in clinical guidelines (2) and reviews (65, 66). Most reference to flares is in Randomised Controlled Trials (RCTs), where flare design studies have been used for a number of years (67-69). In this type of study design, participants are usually required to stop their usual pain medication

and inform the study team when they experience a flare, at which point they are entered into the treatment part of the study.

There is a small body of evidence that supports the role of inflammation in acute flares of knee OA. Despite small sample sizes, synovial fluid composition and volume of knee effusion have been shown to change during a flare-up (70, 71). Historically, OA was not thought of as an inflammatory disease as it did not have an underlying autoimmune process like rheumatoid arthritis. However, evidence in the past 20 years have supported the role of inflammation by identifying inflammatory mediators and also results from pharmacological studies showing preference of NSAIDs over paracetamol for pain relief (72).

The impact of intermittent pain in OA has been explored in terms of ability to carry out valued activities (53, 61, 62). The impact of OA flares were looked at specifically in a random telephone study of US workers aged 40-65 which found that over a 2 week period, in which 38% of workers with arthritis self-reported an exacerbation. Those more likely to experience exacerbations were in low-demand/high control jobs (for example, labourers) and female (73). Understanding more about the impact of flares, who they are more likely to be problematic for, why some flares cause more disruption that others and how this can be minimised is important for improving patient understanding and promoting self-management.

Disease flare seems to be more likely in the context of worse mental health, previous knee injury and a history of knee buckling (74, 75). However, there appear to be no studies identifying additional patient characteristics that might contribute to increased risk of flares or if there are certain short-term physical exposures (for example, heavy lifting) that might trigger them. Identifying those individuals who are more likely to

have disease flare is important to support early identification and self-management of episodes.

Investigations of acute flares in other chronic conditions are more advanced. Bodies of evidence exist for what constitutes a disease flare, how to recognise them and how to best manage them. For example, in the field of Chronic Obstructive Pulmonary Disease (COPD), exacerbations are generally defined as “an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD” (76). A similar approach to defining osteoarthritis exacerbations may be possible.

As has been done in the COPD literature, a larger body of work is needed to determine characteristics of those who frequently experience flares (77) to find out in who they are a problem, assess burden (78), and guide flare prevention (79)**.** Only recently have a preliminary set of domains been agreed amongst expert, healthcare professionals and patients as to what constitutes a rheumatoid arthritis flare (80).

1.9 Summary

Osteoarthritis is a common condition with important consequences for individuals and societies. Individuals can experience acute episodes of pain and these may contribute to time spent in states of severe pain and disability. However, the nature, frequency, duration, and risk factors for these episodes or flares of pain are poorly understood.

The thesis has been designed to investigate and describe flares in osteoarthritis using a number of linked studies that include a secondary analysis of cohort data, a systematic review of knee OA flare definitions, prospectively gathered daily diary measurements and a qualitative study using semi-structured interviews. These preliminary studies are intended to inform future large-scale studies, and to support the future prevention, early recognition, and effective management of exacerbations as part of overall OA management.

Evidence for flares at the time this PhD started (2012) was largely centred around qualitative work that described intermittent acute pain in OA with the exception of a diagnostic tool (the Knee Osteoarthritis Flare-up Score) that had been proposed by Marty et al (55) but not widely adopted. During this thesis (2012-2019) there has been growing interest in these acute episodes of pain or flares. This has included further qualitative studies focusing on intermittent pain and flares in knee osteoarthritis (61, 62), the formation of an OMERACT (Outcome Measures in Rheumatology) OA flare group in 2017 who are attempting to define disease flare in OA (81) and studies seeking to identify potential risk factors which are led by Hunter et al (75, 82) and the ACT-FLARE study which is led by Peat et al (83). These will be discussed further in light of study findings presented in this thesis.

2. Thesis aims and objectives

This chapter introduces the overall aims of this thesis and how these will be met with the specific objectives. It also gives an overview of my position as a GP researcher in relation to this thesis.

2.1 Thesis aims

This thesis is a mixed methods study of acute flares in knee osteoarthritis, whose overall aim was to explore how to define them for the purposes of research, and understand their frequency, nature, impact, and possible causes.

2.2 Thesis objectives

The overall aim of this doctoral thesis will be achieved through the following objectives:

2.2.1. Undertake a systematic review to compare and contrast definitions of knee osteoarthritis flares used in published medical journal articles in clinical trials, observational studies, reviews and qualitative studies (Chapter 4)

2.2.2. Conduct a secondary analysis of cohort data to estimate what proportion of adults with knee pain report ‘significant symptom variability’ (a potential proxy for experiencing acute flare) and identify potential risk factors (Chapter 5)

2.2.3. Conduct a cross-sectional survey to further explore the self-reported frequency of flares and associated risk factors in patients with, or at high risk of, knee osteoarthritis (Chapter 6)

2.2.4. To undertake a daily diary study to provide a detailed description of the natural history, associated features, self-management and potential short-term triggers of prospectively defined acute flares in patients with, or at high risk of, symptomatic knee osteoarthritis (Chapter 7)

2.2.5. To conduct a qualitative study using semi-structured interviews to explore patients' understanding on flare-ups or exacerbations in knee osteoarthritis and explore self-management and help-seeking strategies used (Chapter 8).

These objectives will be addressed through a mixed methods approach, incorporating a systematic review of the medical literature (Chapter 4), secondary analysis of population cohort data (Chapter 5), cross-sectional survey and nested daily diary study (Chapters 6 and 7), and a qualitative study using semi-structured interviews with patients (Chapter 8). The qualitative study will provide a deeper understanding and explanation of findings found in the quantitative studies in addition to giving unique insights into patient experiences of flares.

2.3 Author's position in relation to thesis

What attracted me to this research was the potential for the study findings to have a direct impact on patients, through improving education of patients and clinicians and identification of flares. It will provide further understanding to allow for comparison of

management options in flare design trials and also identify areas for further observational research.

As a GP I regularly see people with musculoskeletal problems and am aware of the impact of these symptoms. This prior knowledge has shaped the approach I have taken to this research, the way in which the studies have been conducted, the analysis and findings. I have tried to remain reflexive throughout and to be transparent about my position and the impact this had on the study designs, data collection, analysis and interpretation of findings.

2.4 Contributions and interests of the wider research team

My lead supervisor Professor George Peat has a background in physiotherapy and epidemiology. His main research area is osteoarthritis and he provided the initial idea for the thesis. Associate Professor Reuben Ogollah provided statistical support for the studies in Chapters 5, 6 and 7. Professor Carolyn Chew-Graham is an academic GP who specialises in qualitative research with particular interest in mental health. Professor Lisa Dikomitis is a social anthropologist by background.

Dr Martin Thomas (MJT) who is a physiotherapist with interests in epidemiology and osteoarthritis was second reviewer for the systematic review in Chapter 4. I received further support for the cross-sectional study and diary study presented in Chapter 6 and 7 from a study administrator in Keele Clinical Trials Unit. They helped at the mailing stage with mailing out study packs and logging initial responses.

3. Methodology

3.1 Introduction

This chapter considers the ontological and epistemological assumptions of quantitative, qualitative, and mixed methods research with specific reference to the lines of inquiry used in this thesis. The importance of quality and reflexivity with regard to qualitative research will be discussed. Finally, the importance of Patient and Public Involvement and Engagement (PPIE) in this thesis will be described.

3.2 Quantitative methodology

Quantitative research generally produces numbers as data. It is concerned with estimation and deductive hypothesis testing (using evidence to support a conclusion), looking at associations between variables, and utilises methods to quantify variables (84). The findings in quantitative research are usually assumed to be potentially generalisable to a notional target population and replicable (84). One of the common underlying epistemological stances in quantitative research is positivism. Here the researchers remain detached from what they are studying, knowledge is gathered through observation and accumulating facts, only concepts that are observed are treated as knowledge, and there is thought to be one single objective reality (85, 86). However, positivism has been challenged as not everything we know about the world is directly observable and a theory cannot necessarily be proved by multiple observation (87). Post-positivists challenge the assumptions of positivism and state that truth can only be estimated from observation and cannot be explained perfectly (87). However, positivist and post-positivists both share the

underlying principle that an objective reality lies outside the individual who is experiencing it (85).

There are a number of different quantitative methods and questionnaires or surveys are one of the most common tools used (87). Surveys have a number of advantages: they are cheap, time efficient, you can gather data from a large number of responders, responders can complete the survey in their own time, data analysis is generally straightforward, and it removes interviewer bias (87). Surveys or questionnaires can gather data on attributes, attitudes, beliefs, reported behaviour, health states, knowledge, or psychological traits (85). Designing questionnaires, however, can be challenging. Items within the survey need to be valid and reliable, they require a certain level of literacy, the wording and structure may bias response, items should not be leading, it can also be difficult to interpret missing data, or ambiguous responses (85, 87).

In the quantitative setting, diaries can collect similar data to surveys but over extended periods of time. Diaries are an important tool in research and its application ranges from collecting unstructured thoughts and reflections where the participant has more control over the data, to a more structured approach where the same information is collected each time and the participant has less control over the data collected (85). Inherent problems with diaries include: none or partial completion, retrospective completion, burden of data inputting, complexity of analysis, they require a certain of level of literacy and conditioning (85, 88). Daily diaries are thought to be sensitive to day-to-day changes in symptoms, they can provide rich information on health behaviour and help-seeking, help to reduce recall bias, and are thought to provide more valid and reliable descriptions of minor events and frequent events compared to interviews (88).

The above examples are methods of primary data collection and analysis, however secondary data analysis can be a valuable way of gaining new insights to existing information. Secondary data analysis can be defined as data collected by someone else for another purpose (89) or *'any data that are examined to answer a research question other than the question for which the data was originally intended' (90)*.

Advantages of this method include its cost effectiveness and time efficiency as the data is already collected, inputted and cleaned for analysis, and it is convenient (87, 89-91). However, problems inherent in secondary data analysis include: inability to select all desired variables, difficulty gaining knowledge on how data variables have been collected, data quality, validity of items used, incomplete data, and potential for data mining (87, 89, 90). In mixed methods research, secondary data analysis can have a number of advantages. It can identify initial themes and hypothesis, which may be tested through surveys and other research methods, in this way it also provides validity (87).

3.2.1 Quantitative methods used in this thesis

Secondary analysis of cohort data

A secondary data analysis of the Clinical Assessment of the Knee (CAS(K)) study (a prospective, population-based cohort study that aimed to investigate classification and prognosis of knee pain in older adults), was undertaken as one of the initial enquiries into the natural history of flares in knee osteoarthritis as part of this thesis (92). This dataset was used to gather preliminary estimates and early insights to help inform the original studies presented in this thesis. The data set used for this study was large and comprehensive including the majority of variables to be explored. One

inherent challenge with secondary data collection is not being involved in the study design. The secondary data researcher, therefore, may not have a comprehensive knowledge of data collection procedures, instruments selected and understanding of the variables chosen (89-91). To overcome these challenges, detailed information was sought about the data collection methods, cleaning process, how missing data was dealt with and the intended aim of the primary research was sought.

Cross-sectional Survey

Postal surveys are able to gather large quantities of data, over a large geographical area or problem space in a relatively quick time frame and at low cost (93). In designing my doctoral research, a survey was thought to be an efficient method to collect data on baseline characteristics and 'normal' knee symptoms, in a population of participants with knee OA or high risk of knee OA, who experienced flares.

One of the disadvantages of surveys is the potential impact of non-response on bias and imprecision of estimates. A number of strategies to improve response to surveys have been studied (94). Strategies known to increase response that were utilised in this study include limiting the number of items, including the participants name on cover letters, stamped return address envelopes, follow-up contact with repeated mailings (a reminder postcard 2 weeks after the initial mailing followed by re-sending of the cross-sectional survey 4 weeks after the first mail-out), assuring confidentiality and university sponsorship. Incentives are known to improve response rates however; due to lack of funds this was not possible in this study (95). The cross-sectional survey contained no open questions to ensure that it was quick to fill in and reduced responder burden (96).

Daily diary study

The daily diary study used intensive repeated measurements to collect and analyse variables with reference to the baseline symptoms reported in the cross-sectional survey using a ‘what is normal for me’ approach adapted from a similar design used in the COPD literature (97). This allowed for comparison of baseline and prospectively collected measurements.

A key strength of the diary data collection method was their ability to obtain frequent re-measurement. Daily measurements were chosen over, for example weekly measurements as they have been found to be more sensitive to individual changes over time, they reduce systematic and random sources of error and recall bias (98). Daily measurements are able to capture changes in pain and symptoms. Additional advantages of diaries include allowing causes and consequences to occur naturally and controls for third variables using participants as their own controls (98). This was important in this study, where triggers were also being assessed. Asking patients to recall symptoms over longer time periods has been shown to lead to overestimation of pain and symptoms (99).

While recall bias may be reduced by obtaining frequent measurements with short recall periods, some bias related to pain recall can still remain. It has been demonstrated that in daily pain diaries that average pain is rated as higher on days where the participant has experienced more intense pain (100). One method of overcoming this would be to ask participants to record pain levels at a number of set times during the day or randomly after being instructed to by an alarm using Experience Sampling Methods. However, in this study in order to reduce burden it was decided to ask participants to complete the diary once a day in the evening.

Paper diaries have been shown to have better compliance rates compared to electronic and telephone diaries in a study looking at gastro-oesophageal reflux disease (GORD) symptoms over 4 weeks (101). However, it is difficult to determine the extent to which the diaries were filled in retrospectively. Participants in the GORD study found paper diaries more acceptable to use than telephone diaries. In contrast, a study lasting 12 months showed better compliance and satisfaction with electronic diaries over paper diaries (102). As the diary study in this thesis invited participants to complete diaries for a minimum of one month and a maximum of three months it was thought that paper diaries would have sufficient compliance rates and this was supported by the PPIE members (Table 6.1).

Paper diaries are familiar to participants and easy to use. However, there is a risk of honest forgetfulness and retrospection error which leads to uncertain compliance which is difficult to estimate (98). To minimise this, diaries were sent and returned at monthly intervals. This also had the added benefit of maintaining contact throughout the study. Participants were also instructed to leave the day blank if they forgot to fill it in on the day.

Electronic diaries have the benefit of allowing signalling, time stamps for responses, prevent out of range responses, minimise risk of skipped questions and for data entry, management and accuracy (98). Due to cost constraints electronic diaries were not available in this study. One of the major drawbacks to paper based diaries is the need to input large quantities of data which can lead to inaccuracies (98). To overcome this data was inputted by myself and each questionnaire and diary underwent 1 in 10 checks by an administrator.

A systematic review looking at pain measurement in electronic diaries found that completion was improved if the diaries were shorter, participants were older adults, they were manual and used alarms (103). The majority of diaries were 1-2 weeks in duration and had fewer than 20 items. The types of questions asked included pain intensity, location, quality, interference with normal daily activities, coping and mood. The number of items in the diaries in this thesis was decided on given compliance rates from previous studies and after discussion with members of the PPIE group.

In a study which assessed asthma symptoms by daily diary for 4 weeks versus monthly retrospective recall of data, diaries were found to be a more sensitive tool and that the burden was worth the effort. Burden can be reduced and compliance increased with shorter instruments that take several minutes to complete (98) therefore the number of diary items in this study (Chapter 7) were minimised to 9 with an average completion time of one minute.

Further problems with diary studies include reactivity which can occur where a participant changes their behaviour as a result of being in the study. This has less of an effect in longer studies due to habituation (98). However, this can lead to patients skimming over certain questions. In the diary study I tried to minimise the number of questions to reduce this and the PPIE group inputted into the sequence of questions. Missing data and frequently missing questions were analysed in the results to see if this was a phenomena that occurred. The PPIE group also suggested having a different colour for the front of the diary for each month and to include tips to ensure good compliance on the inside cover of the diaries for example ‘leave the diaries on your nightstand’.

3.3 Qualitative methodology

Qualitative research emphasises the importance of the individual participants' perspectives. It provides depth and richness of data allowing for an understanding of complex subjects (86, 104). It is concerned with understanding and exploring the way people interact with their environments and the meanings they attach to their own perception of reality (86, 105). The researchers are important in the data collection process, they are close to the data, they often interact with the participants and the outputs are influenced by the researcher's own interpretations (86). Qualitative research, as described by Ritchie, 2003 (p.5) is therefore, good for "questions that require further explanation or understanding of social phenomena or their contexts" (86).

One important epistemological standpoint in qualitative research is interpretivism. Interpretivist thinking is central to qualitative research, whereby emphasis is put on the participant's and the researcher's perspective on the observation, interpretation and reflection of peoples interaction with the social world; and what shapes their understanding of this world, for example social, cultural, and historical aspects (86). This contrasts with positivism where phenomena have to be directly observed to be counted as knowledge. In interpretivist thinking it is recognised that there are other methods of knowing about the world other than through observation (86).

An important tradition in qualitative research, linked to interpretivism, is phenomenology which is concerned with experiences and understanding meaning within a world that is socially constructed. It highlights the importance of the interpretations of the researcher along with the research participants in the study process (87). Multiple realities are thought to exist due to the wide experiences and understandings of the individuals involved in the research (85). However, these

realities exist in different contexts and understanding these contexts is important (85).

Constructivism is another important ontological position whereby there are multiple realities that are a product of the different way in which individuals interact with the world and this is in a constant state of change (106). In the research setting, constructivists believe reality is based on interaction of the researcher with the research participant, that this is “constructed” rather than “discovered” from the data and shaped by existing knowledge (107).

The underlying epistemological stance in this thesis is pragmatism which will be discussed later. However, the qualitative study utilises phenomenological and constructivist approaches. The interviews were conducted to understand further participants’ experiences of flares and their understanding of them in the context of their own social reality.

Qualitative research studies people in their own environment paying attention to how they interact with this. The role and background of the researcher and their interaction with participants is also important (87, 108). The main differences between quantitative and qualitative research are summarised below in Table 3.1.

Table 3.1. Differences between quantitative and qualitative research (Adapted from Bryman, 2012, p.408) (106)

	Quantitative	**Qualitative**
Data collected	Numbers	Words
Point of view most important	Researcher	Participant
Position of the researcher to the data	Distant	Close
Underlying theory	Testing	Emergent
Data collection and analysis	Static	Process, ongoing
Design	Structured	Unstructured
Findings	Generalisable	Contextual understanding
Generated data	Hard, reliable	Rich, deep
Sample size	Large	Small
Focus of analysis	Behaviour	Meaning
Study setting	Artificial	Natural

The main methods used are interviews and focus groups (86). Focus groups involve bringing together a group of people to discuss a particular topic. They provide an insight into group discussions on a topic, how ideas are formed and they allow space for individual reflection which can provide deeper responses (86). Interviews provide rich detailed descriptions, gathering data on meanings and interpretations, within the social contexts of the research participants (109). They also offer flexibility allowing the interviewer to clarify points and encourage the interviewee to expand on their experiences (110). Face to face interviews provide in depth discussion and allow the interviewer to pick up on non-verbal cues (111). Compared to focus groups, interviews probe the individual experience, gaining a greater depth of personal perspectives along with clarification of points and understanding (86). Semi-structured interviews allow the interviewer to explore specific areas and a topic guide helps provide the structure and prompts (86). Topic guides allow the researcher to introduce topics in a common way across interviews with non-leading questions and

prompts to facilitate participant elaboration of the key areas (112). Face-to-face interviews were chosen in this study to gain a greater depth of understanding of the topic area and to explore individuals' experiences.

Diagrams can be useful tools in interviews as they can provide clarification, prompt discussion, convey thoughts to others and they help in visualising complex information (113). In studies using diagrams, the diagrams may be created by the research subjects alone, in conjunction with the researcher or they may be performed by the research team. Diagrams can be helpful in interviews as a visual representation to illustrate important points (114). Diagrams can prompt participants to recall things they may have forgotten, they act as a source of further questioning and combined with verbal information can create a greater depth of understanding (115).

Pain graphs have been used successfully in previous research looking at changes in back pain over time, for example in studies using the painDETECT questionnaire (116) and to assess pain patterns in ankylosing spondylitis. Pain graphs provide a tool by which patients can describe the temporal changes in their pain intensity and are generally easy to use, however they can be limited by patient recall (117). In the interviews in the qualitative study (Chapter 8) pain graphs were used to provide clarification and facilitate discussion.

3.4 Mixed methodology

Mixed methods research, as described by Creswell (118) is:

> An approach to research in the social, behavioural, and health sciences in which the investigator gathers both quantitative (closed-ended) and qualitative

(open-ended) data, integrates the two, and then draws interpretations based on the combined strengths of both sets of data to understand research problems.

Mixed methods can strengthen the approach taken to a research question in a number of ways. Using different research methods allows for a more comprehensive approach to a research question (119) and can overcome the limitations of one method alone. The results can provide different perspectives or points of view and, can be used as a method to challenge previous findings (120) . A richer description of the underlying phenomenon can be gained from multiple observations and methods (121). Bringing together opposing philosophical stances has faced criticism and there are concerns that one method can dominate over the other (86, 122). Mixed methods research is therefore largely underpinned by pragmatism which is less concerned with philosophical assumptions and utilises both quantitative and qualitative research designs (123)**.**

In this thesis, a partly pragmatic stance was taken, whereby the research method was selected based on which would be better to answer the research question. Pragmatism, however, has been criticised for undermining the methodological underpinnings of research (124). Realism has been proposed as a stance that successfully incorporates both qualitative and quantitative approaches and involves the belief that there is more than one way of knowing about reality (124). It can be useful for research methods where you want to explore patient understanding, where hypothesis are not being tested and theories are emerging and where research is conducted in a more natural setting (124). This view, which incorporates both a ‘critical’ and ‘subtle’ ontological realist stance ensured the aims of this doctoral thesis would be met.

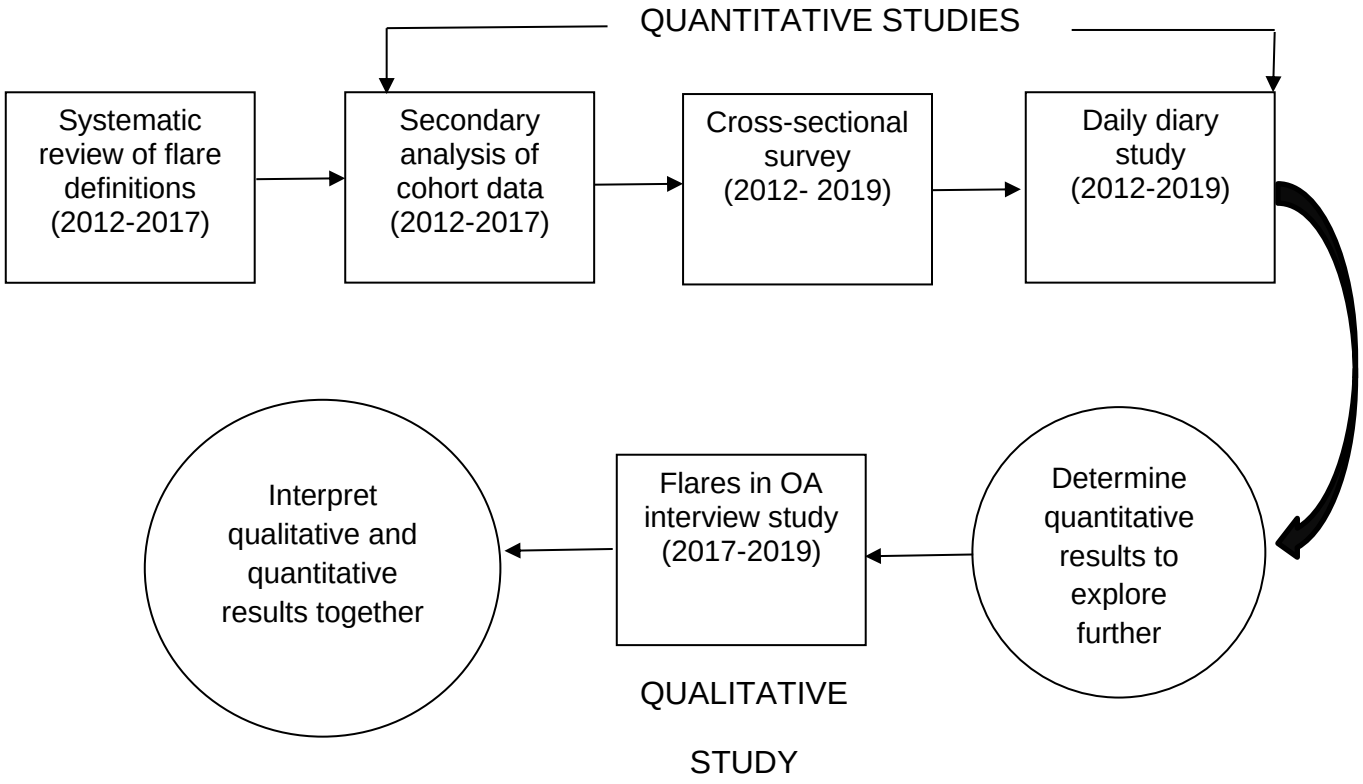
There are a number of important considerations when undertaking mixed methods research as described by Creswell (118). These include timing of the quantitative and qualitative data collection in relation to each other, whether the two methods have equal or unequal emphasis overall, and how best to integrate them. The three main types of mixed methods designs are: exploratory sequential (where qualitative data collection and analysis is undertaken in the first phase, these results are then used to develop an instrument or intervention in the second phase which is then assessed by a quantitative data collection and analysis methods), an explanatory sequential design (where quantitative data collection and analysis is initially undertaken followed by a qualitative phase which is used to explain the quantitative results), and a convergent design (where quantitative and qualitative data are collected separately and results are merged for data analysis) (118).

This thesis used a predominantly explanatory sequential design, whereby the findings from an initial study were utilised in the design of the proceeding study. It was not practical to fully complete one study to the point of publication prior to the start of the next study, a pragmatic approach was therefore taken and a number of the studies were undertaken at different stages in parallel. In the explanatory sequential design, each data collection phase builds on and informs the next stage. Its key strength is the ability of the qualitative stage to build on the quantitative stages with inferences drawn at the end (125). This method was chosen as the initial plan at the start of this thesis was to undertake each study in stages, with each subsequent enquiry applying findings from previous ones. The qualitative interviews were designed to be the final study in this thesis as interviews can provide a deeper understanding, exploration and different perspectives on a subject matter (86, 120). Utilising this approach, it was planned that the qualitative study would enrich findings

from the quantitative stage and also allow exploration of further queries or gaps in knowledge that were identified from analysing the statistical data.

An informal literature review was conducted in 2011-2012 to gain an initial understanding of the flare definitions that were being used in the literature to help inform the definition used in the planned secondary analysis of cohort data (Chapter 5) and the cross-sectional and diary studies (Chapters 6 and 7). The range of ad hoc definitions being used led to a formal systematic review of the medical literature to gauge the extent to which there might be a shared definition of OA flares. The first review was conducted in 2012 however due to the complexity of the data, a similar review being published after mine had been sent for peer review (126) and two periods of maternity leave the search was repeated two further times and finally published in 2018. The secondary analysis of cohort data (Chapter 5) was conducted in 2013 and published in 2017. Data collection for the cross-sectional survey and diary study (Chapters 6 and 7) was conducted in 2013 and the final results were published in 2019. The data for the qualitative study (Chapter 8) was collected, analysed and written up in 2019 (Figure 3.1).

Figure 3.1: Overview of the explanatory sequential design used in this thesis (Adapted from Creswell (125))



Despite the studies not being finished in the order in which they started, undertaking a sequential design meant that the findings from the initial studies could inform the latter studies. For example, understanding the risk factors that might be associated with flares in the secondary analysis of cohort data (Chapter 5) helped inform the independent variables to be included in the cross-sectional study (Chapter 6). The qualitative study (Chapter 8) aimed to understand flares from the patient's perspective and to allow discussion of the findings from the diary study (for example, impact of variability in flare frequency and intensity and reasons for help seeking). Qualitative research is often used after statistical analysis where a greater understanding of the underlying problem is required, to provide further clarification or explanation, where more detail or depth is needed to further explore the research question (86, 120). In this thesis, once each studies results had been presented,

each study was revisited to enable reflection, assimilation and integration of all study findings. This enabled overall conclusions for the thesis to be drawn and also allowed for findings from the latter studies to explain findings from earlier studies that had previously been unclear. For example, the findings from Chapter 8 gave a potential explanation for the distribution of reported flare frequency seen in Chapter 6. This integration of findings and revisiting previous results helped strengthen the findings presented in this thesis and highlighted the importance of using a mixed methods approach for this PhD.

3.5 Quality

Triangulation helps to improve the reliability and validity of the data by using a number of different methods, for example from using different data collection methods, data types, and different investigators (85, 87, 123). Triangulation has been described as a method of overcoming the weaknesses of one study design used alone (123). Critics, however have pointed out that ontologically there is no single reality and using multiple methods cannot overcome this fact, secondly from an epistemological view a completely concordant standpoint can never be achieved (86). In this thesis, a number of different data collection methods, data types and observers (supervisors with different backgrounds of expertise) were used to gain a greater depth of understanding of the natural history of flare-ups and to improve the integrity of the findings.

Approaches to improve quality include transparency during the data collection and analysis process, having a number of members of the study team involved in data analysis and interpretation (87, 127). Another important facet is credibility or member

checking whereby the interpretations of the data are discussed with the participants (87). This has a number of advantages, for example clarifications can be made where there are uncertainties, to get feedback on interpretations, and open up other areas for exploration (127). Disadvantages include the participant reflecting on their own experience and potentially discrediting the researcher's interpretations as they view the data compared to themselves rather than as a whole (127). In this thesis, the PPIE group were consulted to sense check and corroborate the findings from the qualitative analysis and highlight areas in the data that might need exploring further. As people with personal experience of OA they provided a unique insight into the interpretation of the findings, however being expert patients and not participants in the research themselves they were able to look at the data as a whole rather than on just an individual level.

3.6 Reflexivity

It is important to understand the role of the researcher, their previous knowledge and background and the impact that has on the research question, the data collection methods chosen, data analysis, interpretation, and communication (128). When analysing and interpreting the data it is paramount to consider the relationship between the interviewer and the interviewee and how this may affect the responses (128). Being aware of how these prior assumptions and experiences can affect the research process helps to maintain quality (119) .

The researcher and her/his background impacts on all stages of the qualitative study process, from the area of study they wish to pursue, to the methods they use, the results that are considered to be important, and communication of the findings.

Preconceptions about the research need not be seen as bias as long they are acknowledged (121). Acknowledging, reflecting and reporting on these issues and giving a detailed account of how the research is conducted helps to ensure quality and transparency (128, 129). I am a GP and had prior in-depth knowledge of OA flares. It was important to be aware of preconceived ideas throughout the study process and the influence this will have had on data collection and interpretation of that data.

The setting of the interview and characteristics of the interviewer can impact on data collection. The interaction may be different depending on certain characteristics of the participant. For example, in a qualitative study that was conducted by a GP, differences were found between how people from different social classes and gender interacted with the researcher compared to a researcher from a non-medical background. Middle-class males were more likely to assume commonality with the GP researcher compared to those from working classes (128). When the same interviews were conducted by a sociologist, unfavourable comments related to health care professionals were more likely to be mentioned. When the interviewer initially communicates with the participant and during the interview, she/he should consider whether they introduce themselves as a researcher or whether to disclose their full professional background. Full disclosure may help with interview flow (130) however there are implications of the disclosure, for example being asked medical questions if the researcher is a health professional and may also limit discourse related to bad experiences in health care settings. This may be partly overcome by the researcher distancing themselves from their profession, for example when discussing advice given by health professionals use terms such as ‘they say..’ in order to encourage in depth discussion (130).

Previous experience as a GP may be beneficial to the interview process as there are some similarities with consultation skills, for example with asking open ending questions and responding to non-verbal cues (130). However, GPs are trained to ask their questions under a time pressure, and focus discussion down, rather than open the discussion up, in order to achieve a diagnosis or agreement with a patient on the problem so may be naturally inclined to cut answers short if they do not feel they are adding to the data. GP consultations are therefore very different to a research interview.

3.7 PPIE involvement

Patient and Public Involvement and Engagement (PPIE) is defined as “research that is carried out ‘with’ or ‘by’ members of the public rather than ‘to’, ‘about’ or ‘for’ them” (131). PPIE is important at all stages of the research process starting with prioritising research questions, ensuring that the research performed is relevant to consumers, they identify important questions, they highlight important outcomes and ensure resources are not wasted (132, 133). They give advice on recruitment strategies, input into participant information, undertake research, help interpret results, and help or give advice on dissemination (132, 133). There are some limitations of PPIE involvement that have been reported: those that are involved with PPIE may not be representative of the groups they are intended to represent, the more one takes part in PPIE the more ‘expert’ they become, individual opinions may be variable, and particularly for new members there may be unrealistic expectations of what the research can accomplish (132). However, despite this PPIE is generally viewed as valuable, and the greater the level of engagement on the part of the research team the richer the experience with PPIE (134). Within the context of a doctoral thesis,

PPIE engagement can be challenging due to funding, however it can add to the methodological rigour of the research, adding new perspectives and experiences, in addition to improving the skill set of the early career researcher (135).

The PPIE group were involved at a number of stages during this thesis. The School of Primary, Community and Social Care (SPCSC) at Keele University hosts members of the PPIE group (136). It has 130 members, who have personal experience of a range of conditions who are actively supporting around 115 live projects. There is a PPIE Steering Group with 11 members who meet 6 times a year who provide an overall viewpoint of the wider PPIE group. The PPIE members are involved in projects in numerous ways: as an advisory group member, as a lay co-applicant on grant applications, and as Trial Steering Committee members. The PPIE members are recruited from social media, word of mouth, through PPIE recruitment leaflets in nearby hospitals and general practices, newspaper articles, and by invitation from academic clinicians.

PPIE members involved in this thesis were recruited based on their personal experience with osteoarthritis. Due to the length of time of my doctoral research (seven years) members that inputted into planning the cross-sectional survey and diary study were not the same as those who inputted into planning the qualitative study and reviewing the analysis.

4. Defining acute flares in knee osteoarthritis: a systematic review

This chapter reports on the design, conduct, and findings of a systematic review of the medical literature that sought to identify, describe and critically evaluate definitions of acute flares in knee osteoarthritis. The overall purpose of the review was to gauge the extent to which the phenomenon of acute exacerbations (or flare-ups) of knee osteoarthritis is recognised and reported in the medical literature and the potential for a shared, common definition for use in research and clinical practice.

4.1 Introduction

In many chronic diseases, acute exacerbations appear to be a well-recognised feature of their natural history although the accepted language used to label these varies between diseases (e.g. an acute exacerbation of chronic obstructive pulmonary disease or asthma, an attack of gout, a rheumatoid arthritis flare). A determined effort to define these events has followed the recognition of their significance. Definitions for exacerbations in chronic obstructive pulmonary disease (COPD) (137, 138)**,** asthma (139), systemic lupus erythematosus (SLE) (140), ankylosing spondylitis (AS) (117) presently exist or there are working groups trying to define them (e.g. rheumatoid arthritis (80), gout (141), atopic dermatitis/eczema (142) (Table 4.1)). These definitions, despite different terms being used, share some key components:

- the onset or worsening of symptoms and signs above normal day-to-day variation;

- speed of onset;
- duration of sustained worsening;
- change in medication/healthcare usage.

Table 4.1: Published definitions of acute exacerbation or flare in several chronic diseases

Respiratory conditions	
COPD	"an acute worsening of respiratory symptoms that result in additional therapy"(138)
	"a sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset" (137)
Asthma	"episodes of a progressive increase in symptoms of shortness of breath, cough, wheezing and a progressive decrease in lung function." (139)
Rheumatological conditions	
SLE	"a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment" (140)
AS	"exacerbation of the disease that may have required additional treatment or necessitated a visit to a health care professional" (117)
Gout	Fulfil 3 of the following criteria: "patient defined flare, pain at rest score of >3 on a 0-10 NRS, presence of at least 1 swollen joint, and presence of at least 1 warm joint"(141)
Cancer	
Cancer breakthrough pain	"transitory increase in pain to greater than moderate intensity (that is, to an intensity of "severe" or "excruciating"), which occurs on a baseline pain of moderate intensity or less (that is, no pain or pain of "mild" or "moderate" intensity)(143)

AS Ankylosing Spondylitis; COPD Chronic Obstructive Pulmonary Disease; SLE Systemic Lupus Erythematosus

The process of finding a shared common definition is long and difficult. In the field of rheumatoid arthritis the OMERACT working group was initially established in 2006 and first reported in 2009 (144). During this time a systematic literature review and two separate Delphi exercises with key stakeholders including experts, patients and health care professionals have been undertaken, followed by preliminary validation studies. In COPD, despite there being a widely accepted definition this is still subject to contention (145, 146). Despite some commonalities, the fundamental nature of these acute events is likely to represent pathophysiological processes specific to the underlying disease process and so it is unlikely that straightforward parallels between diseases can be drawn on how to define exacerbations.

Yet the fact that such prolonged and difficult work has been undertaken testifies to the perceived and actual benefits of having a common shared definition. Firstly, a common shared definition facilitates communication between researchers, practitioners, patients and other relevant parties. Secondly, it may allow more direct comparisons between studies on the frequency, determinants, and course of these events. Thirdly, this effort may facilitate new insights into novel pathophysiological mechanisms and treatments by providing a valid, homogeneous case definition of these events. Fourthly, in clinical practice, a common, shared definition that is also practicable at the point of care may enable prompt diagnosis and management (including self-diagnosis and self-management where the definition is able to be applied by patients and their carers).

While acute ‘exacerbations’, ‘flares’, or ‘attacks’ are common parlance in these chronic diseases and definitions for these have been derived (even if not universally agreed), this does not appear to be true of osteoarthritis. For gout, COPD, and asthma, an estimate from an EMBASE search suggests that 9%, 8% and 6%

respectively of journal articles published in the last 10 years contain the words “exacerbation”, “flare” or “attack” in their title or abstract. The corresponding figure for osteoarthritis is <0.7. These words do not appear in the NICE guideline on osteoarthritis (2). Yet the term “flare up” appears in patient literature on osteoarthritis (for example “Some people take an anti-inflammatory painkiller for short spells, perhaps for a week or two when symptoms flare up.”(147)) and there is growing recognition of exacerbations in OA both in quantitative and qualitative studies. In qualitative interviews, Hawker et al (53) found that as disease progressed, patients reported sharper bouts of intermittent pain, initially predictable, but later on in the disease course becoming more unpredictable and associated with increasingly more distress. Furthermore, in 2009 Marty et al (55) proposed a knee OA flare-up score which included the following components: nocturnal awakenings, knee effusion, morning stiffness and limping. Marty et al, used general practitioners to determine whether patients with knee OA were experiencing a flare-up. Using a logistic regression model they found factors independently associated with flare-ups (55). Each factor was assigned a weighted score dependent on the odds ratio. This Score was then validated using a rheumatology database. It is not known how the general practitioners identified flare-ups in the initial study and one key disadvantage of the flare-up scoring tool is that it does not include pain, potentially due to collinearity of pain with other factors in the model.

These different sources provide some indications that a concept of flares exists as part of the natural history of OA although it appears to be neither as prominent or well-recognised a feature in OA as in some other chronic diseases. OA may not receive the attention of other chronic diseases as it generally does not lead to hospital admission (there are 185 people admitted per day with asthma) and is not

listed as a cause of death (asthma contributes to >1200 deaths per year) (148). There is a perception amongst some that little can be done for OA and that doctors seem disinterested which may preclude consultation with a GP (15). Furthermore, by the time patients do present to a clinician their symptoms may have improved which is contrary to patterns in other diseases.

The systematic review intends to examine the degree to which the medical literature provides a description of OA exacerbations or flares and the possibilities for a shared definition for research and clinical application.

4.2 Aims and objectives

Aim

To compare and contrast definitions of knee osteoarthritis flare-ups used in published medical journal articles in clinical trials, observational studies, reviews and qualitative studies.

Objectives:

- To gauge the extent to which a concept of acute exacerbations or flare-ups in OA has been reported in the medical literature
- To identify published medical journal articles that define and describe knee osteoarthritis “exacerbations” and the terminology used to label these
- To evaluate whether and how each of the published definitions and descriptions cover the core domains featuring in other chronic diseases, namely (1) the onset or worsening of symptoms and signs above normal day-to-day variation; (2)

speed of onset; (3) duration of sustained worsening; (4) change in medication/healthcare usage

- To identify any domains additional to those listed above
- To critically examine the rationale and evidence of validity of published definitions and descriptions

4.3 Method

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in 2013 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

4.3.1 Eligibility criteria

The following predetermined eligibility criteria was used (Table 4.2).

Table 4.2: Eligibility criteria for systematic review

Inclusion	Exclusion
• Adults aged 18 and over with knee osteoarthritis (diagnosed by physician, radiography or reported knee symptoms) • Journal articles, conference abstracts and proceedings, review articles • General population, community, primary care or hospital • Contained a description or definition, with or without classification criteria based on measurement(s), of an acute exacerbation of knee osteoarthritis (or flare or other synonym) • Clinical trials, observational studies, reviews, qualitative studies • All languages were included	• Inflammatory cause for knee pain, total knee replacement • Animal studies • Book chapters, guidelines, theses, dissertations

4.3.2 Information sources

The following databases were searched from inception to July 2017: ASSIA, EMBASE, Web of Science, HMIC (Health Management Information Consortium), SPORTDiscus, Medline, CINAHL, Psychinfo, AMED, Ageline and Cochrane Database of Systematic Reviews and Cochrane Controlled Clinical Trials (CENTRAL).

4.3.3 Search Strategy

The search strategy was developed with help from supervisors and the SPCSC (School for Primary, Community and Social Care) systematic review team. The search strategies for each database used are included in a separate Appendix A.

Articles in all languages were included (translation was available for full text articles included). Articles that were unable to be sourced through library request or contact with the author were excluded. Papers were also excluded if there was an inflammatory cause for knee pain or previous total knee replacement.

To confirm findings the first 15 pages of Google Scholar were searched to ensure no eligible articles had been missed. Conference abstracts were included and used to find corresponding full text articles where possible. References of all included full text articles were hand searched.

Where the definition of exacerbation was not included in the full text authors were contacted to clarify this.

4.3.4 Selection of studies

The search strategy was initially piloted to ensure relevant articles were included in the search. The search and article retrieval was conducted by the first reviewer (myself). Articles were downloaded into RefWorks. Duplicates were deleted. All titles were screened by the first reviewer to meet inclusion criteria. The first 20 titles were checked by two reviewers to check consistency (myself and a co-author). For qualitative studies it was decided that full papers may need to be searched as the title and abstract may not give the full information about the article content.

All abstracts were reviewed by two reviewers (myself and a co-author). Full texts were then screened by two reviewers to find full texts to be included in data extraction. Where there was disagreement a third reviewer (my lead supervisor) was asked to screen and their decision was final.

The final articles were checked to ensure results from the same studies were not counted as separate studies as this is known to introduce bias as the dataset would more strongly affect the results of the review (149). For pooled studies the original studies were sought and included in the main analysis instead of the article showing the pooled studies if available. If the original articles were not referenced or not available the pooled studies were kept and a note made of this in the analysis.

4.3.5 Data extraction process and items

Information was extracted by the first reviewer, using a standard extraction table that was developed for this review. The results were recorded in an Excel spreadsheet. Every tenth article was independently checked by a blinded second reviewer.

The following data were extracted from full text-articles: Study characteristics (setting, participant characteristics, joint defined, baseline OA severity, and study design) and exacerbation definitions (terminology used to refer to ‘exacerbations’, coverage of core domains indicated from other chronic diseases: namely onset/worsening of symptoms and signs, temporal characteristics, change in medication or healthcare usage and additional domains such as minimum symptom threshold). In addition, the measurement tools and operational criteria used were noted and any evidence or rationale on validity of the definition.

4.3.6 Analysis and synthesis

A narrative synthesis using words and text to summarise and explain findings from multiple studies was performed and this enabled the development of a conceptual framework (150). In undertaking the narrative synthesis of findings for this review, the four-stage process proposed by Popay et al (2006) (151) was used as a guide. This comprises of: developing a theoretical model, undertaking the initial synthesis of included studies, explore relationships of the results, and then assessing the strength of the synthesis (151). This is an iterative process and the stages are not necessarily conducted in order.

In the first stage a preliminary synthesis of findings from included studies was undertaken. This involved initial descriptions of studies and description of patterns. Extracted data including study design, patient characteristics and exacerbation definition was tabulated. From this, groupings were made for example drug withdrawal design and non-drug-withdrawal design studies. ‘Vote-counting’ was used to tabulate the frequencies of components thought to be important in definitions, for

example: onset/worsening of symptoms; signs/symptoms above day-to-day variability (including minimum threshold); speed of onset of symptoms; duration of worsening and increased medication/healthcare usage.

The following stages involved exploring relationships within the data. After tabulating and initial grouping of results the definitions and components used within these definitions were analysed for patterns. This was done thematically and inductively to identify the important themes and concepts across the multiple studies. Concept mapping was used to highlight key concepts and represent relationships. Differences between drug withdrawal (predominantly flare design studies where usual medication is withdrawn with the aim of inducing a 'flare') and non-drug withdrawal studies (predominantly non flare design) were examined.

The robustness of the synthesis is usually examined using a quality assessment tool. Quality assessment tools consider the relevance of study design to the research objectives, risk of bias, choice of outcome measure, statistical issues, reporting quality, quality of intervention, and generalisability where applicable (CRD Systematic review guideline). The information of concern in this study was the description or definition of an osteoarthritis exacerbation that was used. Risk of bias in the treatment effect estimates within trials or exposure-outcome association in observational studies was of no direct interest and so conventional quality assessment/risk of bias directed at these was not at issue.

However, the relative merits of those definitions which claimed some degree of 'validity' and which provided some supporting evidence deserved critical scrutiny. Unfortunately, as there was an absence of available quality assessment tools for this, potentially relevant domains in diagnostic studies (e.g. QUADAS-2 (Quality

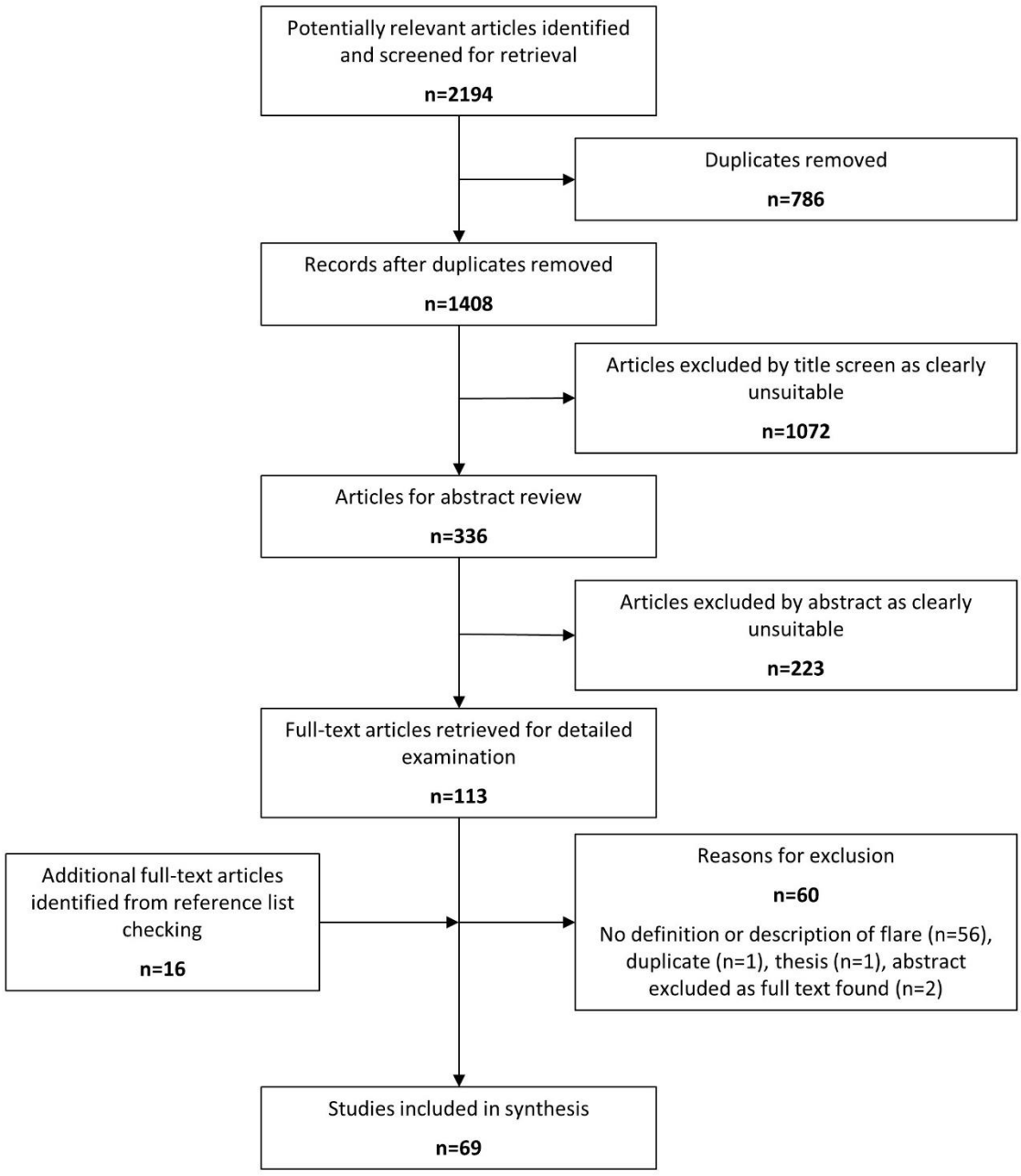
Assessment too of diagnostic accuracy studies) (152) and outcome measurement (e.g. COSMIN (Consensus-based standards for the selection of health measurement instruments) (153), and classification criteria (e.g. ACR 2006) were not applicable to this review. However, statements were sought that gave evidence of rationale behind the definitions chosen.

4.4 Results

4.4.1 Description of studies

The literature search produced 2194 results however 786 were duplicates (Figure 4.1). After screening titles 336 abstracts were studied. Of these 223 were not relevant, and for 4 studies the complete article could not be obtained despite considerable effort to identify and contact principle investigators. 113 articles were fully analysed which resulted in a further 60 being excluded. In this phase a further 16 were included from the reference lists of the papers chosen for the study.

Figure 4.1**:** Flow chart of stages of systematic review (Reproduced from Parry et al, 2018 (154))



Types of studies and setting

In total, 69 studies were included in the systematic review. The studies included a range in participant numbers from 15 to 6085 (55, 155) with an age range of 18-91. In total 46 studies used a drug withdrawal randomised controlled trial (RCT) design (67-69, 155-197), 4 of these were from pooled studies (68, 159, 162, 186) and one used a cohort drug withdrawal design (198) (Table 4.3a). There were 17 observational studies (55, 71, 73-75, 82, 199-209), 3 non-drug withdrawal RCTs (210-212), one survey (213) and one qualitative study (61) (Table 4.3b).

Table 4.3a: Characteristics of all included studies: drug withdrawal design studies

First author, year of publication	Setting, geographic location	N	Age	Joint	Severity	Study design
Altman, 2015 (67)	Multi-centre, recruitment not specified, US	403	≥40y	Knee and hip	KL grade 2-3	RCT, flare design
Baer, 2005 (157)	17 medical centres recruiting from community and physician private practice; Canada	216	40-85y	Knee	Radiographic evidence of OA (severity not defined)	RCT, flare design
Baraf, 2011 (158)	Primary care, internal medicine, orthopaedic, rheumatology; US	602	≥25y	Knee	Radiographically mild to moderate (KL grade 1-3)	RCT, flare design
Battisti, 2004 (159)	Clinical centres, out patients; US	3980	≥40y	Knee	ACR functional class rating of I,II or III	RCT, pooled 4 trials, flare design
Bingham, 2007 (156) Bingham 2011 (191)	2x74 outpatient clinics; US	1207	≥40y	Knee and hip	ARA Functional capacity classification I-III	RCT, flare design
Birbara, 2006 (160)	Investigative sites; US	808	≥40y	Knee	ARA functional class, I, II, or III	RCT, flare design
Bocanegra, 1998 (161)	Clinic; US	572	28-88y	Knee and hip	ARA Functional capacity classification I-III	RCT, flare design
Boswell, 2008 (162)	50 centres (Europe & Australia) + 187 centres (Europe & US)	1908	≥40y	Knee	KL scale 2 or 3 and ARA class rating of I,II or III	Pooled RCTs (2; one flare design, one non-flare), flare design
Brandt, 2006 (198) (pilot studies)	Community; US	30	mean 62y	Knee	KL ≥2	Cohort design, flare design
Case, 2003 (163)	Hospital-rheumatology centre; Chicago, US	82	40-75y	Knee	KL ≥1, and clinical criteria (pre-enrolment ambulatory pain; moderate pain by a 5-point Likert scale or increased pain.	RCT, flare design

First author, year of publication	Setting, geographic location	N	Age	Joint	Severity	Study design
Day, 2000 (189)	49 investigative sites in 26 countries	809	mean 62-65y	Knee and hip	ARA functional class I-III, symptomatic for at least 6 months	RCT, flare design
Ehrich, 1999 (164)	Clinical centres; US	219	>40y	Knee	ARA functional class, I, II, or III	RCT, flare design
Essex, 2012 (165)	Clinical centre; African-American, US	322	≥45y	Knee	ARA Functional capacity classification I-III	RCT, flare design
Essex 2013 (192)	Hispanic population, 31 US centres	318	≥45y	Knee	ACR criteria, Functional capacity classification I-III	RCT, flare design
Gibofsky, 2014 (166)	Not specified, US	305	41-90y	Knee and hip	KL 2-3	RCT, flare design
Gineyts, 2004 (167)	Subset of larger study; France	201	mean 61-62y	Knee and hip	ARA I-III	RCT, flare design
Goldberg, 1988 (168)	Investigative sites; US	214	40-85y	Knee and hip	Radiographic evidence of knee OA-not further defined	RCT, flare design
Gottesdiener, 2002 (169)	Investigative sites; US	617	≥40y	Knee	ARA functional class I,II,III	RCT, flare design
Hochberg, 2011 (68)	Centres; US	1234	≥50y	Knee	ACR functional class I-III	Pooled RCTs (2), flare design
Katz, 2010 (170)	Clinical sites; US	113	28-83y	Knee and hip	OA of hip and knee as diagnosed using ACR criteria-no definition of severity	RCT, flare design
Kivitz, 2001 (171)	Investigative sites; US	491	28-91y	Knee	Confirmation of OA on weight bearing radiograph- no definition of severity	RCT, flare design
Kivitz, 2004 (190)	Outpatient sites; US	1042	≥40y	Knee	ACR rating of I, II, III.	RCT, flare design
Leung, 2002 (172)	Clinic; US	677	≥40y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design
Luyten, 2007 (172)	Centres; Belgium	181	≥40y	Knee and hip	ACR Functional capacity classification I-III	RCT, flare design

First author, year of publication	Setting, geographic location	N	Age	Joint	Severity	Study design
Manicourt, 2005 (174)	Outpatient clinic; Belgium	90	50-81y	Knee and hip	Clinical and radiographic evidence of OA-severity not defined.	RCT, flare design
Mazzuca, 2002 (155)	Not specified, US	15	≥45y	Knee	KL 2-3	Observational, flare design
McIlwain, 1989 (175)	Investigative sites; US	139	mean 65y	Knee	Radiological evidence of moderate or severe osteoarthritis- not further defined	RCT, flare design
Mendelsohn, 1991 (176)	Investigative sites; US	139	21-88y	Knee	Radiological evidence of moderate or severe osteoarthritis- not further defined	RCT, flare design
Moskowitz, 2006 (177)	Investigative sites; US	530	≥45y	Knee	ACR Functional capacity classification I-III	RCT, flare design
Pareek, 2009 (69)	Multi-centre study, India	199	40-70y	Knee	Lequesne criteria-score of 5 and above	RCT, flare design
Pareek, 2010 (178)	Hospital; India	220	40-70y	Knee	Clinical and radiological evidence of OA- severity not defined.	RCT, flare design
Roth, 2004 (194)	Physicians private practice or community; US	326	40-85y	Knee	Radiological evidence of OA- severity not defined.	RCT, flare design
Rother, 2007 (197)	Outpatient units; Germany	397	≥40y	Knee	KL 2-3	RCT, flare design
Schnitzer, 2005 (179)	Investigative sites; International (7 countries)	583	18-75y	Knee and hip	Diagnosis based on ACR criteria-severity not defined.	RCT, flare design
Scott-Lennox, 2001 (180)	Investigative sites; US	182	mean 61y	Knee	Not defined	RCT, flare design
Silverfield, 2002 (181)	Centres; US	308	35-75y	Knee and hip	Clinical evidence of OA- severity not defined	RCT, flare design
Simon, 2009 (195)	Outpatient centres; Canada, US	775	40-85y	Knee	Clinical and radiological evidence of OA- severity not defined	RCT, flare design

First author, year of publication	Setting, geographic location	N	Age	Joint	Severity	Study design
Strand, 2011 (182)	Investigative sites; Multinational-not specified including US	875	18-80y	Knee and hip	OA according to ACR criteria and requiring NSAID treatment to control symptoms in the month preceding screening	RCT, flare design
Weaver, 1995 (196)	Investigative sites; US	328	>50y	Knee	ACR clinical criteria-diagnostic	RCT, flare design
Wiesenhutter, 2005 (183)	Medical Centres; US	528	40-89y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design
Williams, 2001 (184)	Clinical sites; US	718	mean 61-62y	Knee	ACR clinical and radiographic criteria I-III	RCT, flare design
Wittenberg, 2006 (185)	Centres (not specified); Germany	364	50y	Knee	Moderate to severe symptomatic OA of the knee according to ACR criteria.	RCT, flare design
Yeasted, 2014 (186) (Pooled, abstract)	US	219 137	>40y	Not specified	ACR criteria-diagnostic	2 longitudinal observational studies, placebo arms of 2 RCTs
Yocum, 2000 (193)	62 study centres; US	774	≥40y	Knee or hip	Diagnosis confirmed by XR and clinical symptoms (not further specified)	RCT, flare design
Young, 2014 (187) (abstract)	Multicentre	305	>40y	Knee or hip	KL 2-3	RCT, flare design
Zhao, 1999 (188)	Centre (not specified); US, Canada	1004	≥18y	Knee	ACR Functional capacity classification I-III	RCT, flare design

ACR American College of Rheumatology; ARA American Rheumatism Association; GP General Practitioner; KL Kellgren and Lawrence; RCT Randomised Controlled Trial; US United States of America

Table 4.3b: Characteristics of all included studies: non-drug withdrawal design studies

First author, year of publication	Setting, geographic location	N	Age	Joint	Severity	Study design
Atukorala, 2016 (204) (abstract)	Not specified, Australia	213	mean 62y	Knee	Not specified	3-month, web based longitudinal study
Atukorala, 2016 (199) (abstract)	Not specified, Australia	345	mean 62y	Knee	Not specified	3-month, web based longitudinal study
Bartholdy, 2016 (210)	OA out-patient clinic, Denmark	131	≥40y	Knee	Radiographic evidence of OA (severity no defined) and BMI 20-35 kg/m^2	RCT
Bassiouni, 2015 (205) (abstract)	Not specified, Egypt	60	Not specified	Knee	Not specified	Observational
Cibere, 2004 (211); Cibere, 2005 (212)	Community, Canada	137	40-83y	Knee	KL ≥2 on anteroposterior radiograph	RCT
Conrozier, 2012 (71)	Hospital-rheumatology unit, France	44	mean 68y	Knee	Radiographic evidence of knee OA- not further defined	Observational
D'Agostino, 2005 (201)	Hospital-European multicentre	600	≥18y	Knee	KL grade 1-4	Observational
Erfani, 2014 (200), Erfani, 2014 (206), Ferreira, 2016 (82), Hunter, 2014 (207), Makovey, 2015 (208)	Australia (from same study)	268 345 345 267 Not specified	≥40y	Knee	ACR criteria- meet at least one, KL ≥2	Web based cross over
Jawad, 2005 (213)	GPs in France	3000		Knee	Not defined	n/a, review of surveys. Definition relates to survey of 3000 French GPs
Marty, 2009 (55)	Community and hospital, France	6085	mean 66y	Knee	OA diagnosis based on ACR criteria- severity not defined	Observational

First author, year of publication	Setting, geographic location	N	Age	Joint	Severity	Study design
Murphy, 2015 (61)	Community based, pain clinics; USA	45	37-83y	Knee	ACR criteria- severity not defined	Qualitative
Parry, 2017 (209)	Community, UK	719	≥50y	Knee	Self-reported knee pain in previous 12 months	Observational
Ricci, 2005 (73)	Community, USA	329	40-65y	Knee and hip	Clinical evidence of OA- severity not defined	Nested case control
Wise, 2010 (74)	Primary care, hospital, USA	303	≥50y	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment- not further defined	Observational
Zhang, 2009 (202)	Primary care, hospital, USA	303	≥50y	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment-not further defined	Observational
Zhang, 2011 (203) (abstract)	Not specified	52	50-72y	Knee	KL>2	Case-crossover
Zobel, 2016 (75)	Hospital databases, Australia	297	>40y	Knee	ACR criteria, KL ≥2, or patellofemoral OA on radiograph	Web based case-cross over

ACR American College of Rheumatology; ARA American Rheumatism Association; GP General Practitioner; KL Kellgren and Lawrence; RCT Randomised Controlled Trial; US United States of America

4.4.2 Rationale given for flare definitions used

Six studies attempted to validate or give rationale for the definition used in their study (55, 61, 73, 180, 209, 211). Marty et al sought to validate a diagnostic tool for OA flare-ups. A flare-up score was initially determined using a general practitioner database and this was then validated using a study with rheumatologists. The tool consisted of a number of weighted items including; knee effusion, limping, stiffness, and nocturnal awakenings (55).

Scott-Lennox et al (180) explored whether certain measures for flare intensity could be combined to form a reliable and valid tool using data from an RCT using confirmatory factor analysis. These included: patient's self-assessment of pain scores, physician's assessment of pain scores, patient's global OA assessment and physician's global OA assessment. The group identified three flare intensity groups (low, moderate and severe).

Cibere et al (211) highlighted their face validity checks with study rheumatologists. The flare definition used had been established by study rheumatologists to be a change in the WOMAC score that was thought to be clinically important. The definition used by Murphy et al (61) was determined using the researchers own experience and from two flare design studies. Ricci et al (73) used both previous experience and that determined by the data. Parry et al (209) specified that their definition was based on those used in flare design studies and exacerbation definitions used in other chronic disease, for example, COPD and back pain.

4.4.3 Exacerbation definitions in drug withdrawal studies

4.4.3.1 Terminology used

The majority of drug withdrawal design studies (n=42) used the term ‘flare’ in their definition or description (Table 4.4a) (67, 68, 155-160, 162, 165-175, 177-188, 190-199). One used the term ‘flare-up’ (69), two referred to ‘worsening of symptoms’ in their description (161, 176) and for three no specific label was used (163, 164, 189).

Table 4.4a: Definition, terminology and measurement instruments used in all included studies: drug withdrawal design studies

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Altman, 2015 (67)	"Flare"	**Pain**: WOMAC Pain (0-100); increase ≥15mm	**Pain:** WOMAC Pain; ≥40mm	-	- ; - ; -
Baer, 2005 (157)	"Flare"	**Pain:** WOMAC LK3.1 Pain (0-20); increase ≥2 points and ≥25%	**Pain:** WOMAC Pain (0-20); ≥6 and ≥1 item rated 'moderate, severe, or extreme'	Unclear	- ; - ; -
Baraf, 2011 (158)	"Flare"	**Pain on movement:** VAS (0-100mm); increase ≥5mm	-	1w washout	- ; - ; -
Battisti, 2004 (159)	"Flare"	**Global assessment (investigator):** single item, 5-point LK; Worsening ≥1 point	**Pain:** VAS (0-100mm); ≥40mm	-	- ; - ; -
Bingham, 2007 (156) Bingham 2011 (191)	"Flare"	(1) **Pain walking on flat surface:** WOMAC VAS3.0 Q1 (0-100mm); increase ≥15mm (2) **Global assessment of disease status (investigator):** single item, 5-point LK; Worsening ≥1 point	(1) **Pain walking on flat surface:** ≥40mm on WOMAC VAS3.0 Q1 (0-100) (2) **Global assessment (investigator)**: single item, 5-point LK; fair, poor, very poor (*acetaminophen users only*) (3) **Global assessment of disease status (patient):** VAS 0-100mm; ≥40mm (*acetaminophen users only*)	-	- ; - ; -
Birbara, 2006 (160)	"Flare"	(1) **Pain walking on flat surface:** WOMAC VAS Q1 (0-100mm); increase ≥15mm (2) **Global assessment (investigator):** single item, 5-point LK; Worsening ≥1 point	(1) **Pain walking on flat surface:** WOMAC VAS3.0 Q1 (0-100); ≥40mm (2) **Global assessment (investigator):** single item, 5-point LK; Fair, poor or very poor (*paracetamol arm only*)	4-15d washout	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Bocanegra, 1998 (161)	"Worsening of symptoms"	Two out of the following three: (1) **Global assessment (physician):** single item, 5-point LK; Increase ≥1 grade (2) **Global assessment (patient):** Patients global assessment (current symptoms and limitation of activity) 5-point LK; Increase ≥1 grade (3) **Composite index:** Lequesne OA Severity Index (0-24); Increase ≥2 points	(1) **Global assessment (physician):** single item, 5-point LK; 'poor/very poor' (2) **Global assessment (patient):** Patients global assessment (current symptoms and limitation of activity) 5-point LK; 'poor/very poor' (3) **Composite index:** Lequesne OA Severity Index (0-24); ≥7	3-14d washout	- ; - ; -
Boswell, 2008 (162)	"Flare"	(1) **Pain walking on flat surface:** WOMAC VAS Q1 (0-100mm); increase ≥15mm (2) **Global assessment (patient):** Patient Global Assessment of Arthritis Condition (PGAC) (unspecified); Worsening ≥1 point	-	-	- ; - ; -
Brandt, 2006 (198)	"Flare"	Not specified	**Pain:** WOMAC LK Pain subscale (5-25); ≥15 points	5 half-lives of NSAID washout	- ; - ; -
Case, 2003 (163)	Not used	(1) **Pain walking on flat surface:** VAS (0-100mm); Increase ≥10mm (2) **Ambulatory pain**; 5-point LK; worsening ≥1 point	Not specified	14d washout	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Day, 2000 (189)	Not used	(1) **Pain walking on a flat surface:** WOMAC VAS Q1 (0-100mm); increase ≥15mm (2) **Global Assessment (investigator):** single item, 5-point LK; worsening ≥1 point (3) **Global assessment (patient):** VAS (0-100mm); increase ≥15mm (*acetaminophen users only*)	(1) **Pain walking on a flat surface**: WOMAC VAS Q1 (0-100mm); ≥40mm; (2) **Global Assessment (investigator):** single item, 5-point LK; 'Fair, poor, or very poor'; (3) **Global assessment (patient):** VAS (0-100mm); ≥40mm	>5 plasma half-lives washout	- ; - ; -
Ehrich, 1999 (164)	Not used	**Pain:** VAS (0-100mm); increase ≥15mm	**Pain:** VAS (0-100mm); ≥40mm	Longer than 5 plasma half-lives washout of NSAID	- ; - ; -
Essex, 2012 (165)	"Flare"	(1) **Global Assessment (Physician):** 5-point LK; increase ≥1 grade (2) **Global Assessment (patient):** 5-point LK; increase ≥1 grade	(1) **Global Assessment (Physician):** 5-point LK; 'Fair, poor or very poor' (2) **Global Assessment (patient):** 5-point LK; 'Fair, poor or very poor' (3) **Pain**: VAS (0-100mm); 40-90mm	48h withdrawal	- ; - ; -
Essex 2013 (192)	“Flare”	Not specified	(1) **Global Assessment of arthritis (Physician):** Minimum rating of 3 (2) **Global Assessment of arthritis (patient):** Minimum rating of 3 (3) **Pain**: VAS (0-100mm); 40-90mm	48h withdrawal	- ; - ; -
Gibofksy, 2014 (166)	“Flare”	**Pain:** WOMAC Pain VAS; increase ≥15mm	**Pain:** WOMAC Pain VAS; ≥40mm	-	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Gineyts, 2004 (167)	"Flare"	(1) **Pain walking on a flat surface:** WOMAC VAS Q1 (0-100mm); increase ≥15mm (2)**Global Assessment (investigator):** 5-point scale: worsening ≥1 point	(1) **Pain walking on a flat surface:** WOMAC VAS Q1 (0-100mm); ≥40mm	5 half-lives of NSAID washout	- ; - ; -
Goldberg, 1988 (168)	"Flare"	(1) **Pain:** Investigator assessed pain grade (None/mild/mod/severe): (i) at rest, (ii) on passive motion, (iii) on palpation, (iv) weight bearing; increase ≥1 grade in two items OR increase ≥2 grade in one item	Not specified	2-14d washout until flare	- ; - ; -
Gottesdiener, 2002 (169)	"Flare"	(1) **Pain on walking**: VAS (0-100mm); increase ≥15mm (2)**Global Assessment (Investigator):** 5-point LK; Increase ≥1 point	(1) **Pain on walking**: VAS (0-100mm); ≥40mm	3-15d washout	- ; - ; -
Hochberg, 2011 (68)	"Flare"	(1) **Pain walking on a flat surface:** WOMAC VAS Q1 (0-100mm)**;** Increase ≥15mm (2) **Global Assessment (patient):** 5-point LK; worsening ≥1 point	(1) **Pain walking on a flat surface:** WOMAC VAS Q1 (0-100mm)**;** ≥40mm	-	- ; - ; -
Katz, 2010 (170)	"Flare"	Not specified	**Pain**: Pain score (0-10); ≥5	-	- ; - ; -
Kivitz, 2001 (171)	"Flare"	**Pain:** Patients Assessment of Pain Score (0-10) (unspecified); increase ≥2 points	**Pain:** Patients Assessment of Pain Score (0-10) (unspecified); ≥5	5 drug half-lives or 48h	- ; - ; -
Kivitz, 2004 (190)	"Flare"	(1) **Pain on walking:** VAS (0-100mm); worsening ≥15mm (2) **Global Assessment (investigator):** 5-point LK; worsening ≥1 point	Not specified	NSAID dependent half-life washout	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Goldberg, 1988 (168)	"Flare"	(1) **Pain:** Investigator assessed pain grade (None/mild/mod/severe): (i) at rest, (ii) on passive motion, (iii) on palpation, (iv) weight bearing; increase ≥1 grade in two items OR increase ≥2 grade in one item	Not specified	2-14d washout until flare	- ; - ; -
Gottesdiener, 2002 (169)	"Flare"	(1) **Pain on walking**: VAS (0-100mm); increase ≥15mm (2)**Global Assessment (Investigator):** 5-point LK; Increase ≥1 point	(1) **Pain on walking**: VAS (0-100mm); ≥40mm	3-15d washout	- ; - ; -
Hochberg, 2011 (68)	"Flare"	(1) **Pain walking on a flat surface:** WOMAC VAS Q1 (0-100mm)**;** Increase ≥15mm (2) **Global Assessment (patient):** 5-point LK; worsening ≥1 point	(1) **Pain walking on a flat surface:** WOMAC VAS Q1 (0-100mm)**;** ≥40mm	-	- ; - ; -
Katz, 2010 (170)	"Flare"	Not specified	**Pain**: Pain score (0-10); ≥5	-	- ; - ; -
Kivitz, 2001 (171)	"Flare"	**Pain:** Patients Assessment of Pain Score (0-10) (unspecified); increase ≥2 points	**Pain:** Patients Assessment of Pain Score (0-10) (unspecified); ≥5	5 drug half-lives or 48h	- ; - ; -
Kivitz, 2004 (190)	"Flare"	(1) **Pain on walking:** VAS (0-100mm); worsening ≥15mm (2) **Global Assessment (investigator):** 5-point LK; worsening ≥1 point	Not specified	NSAID dependent half-life washout	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Leung, 2002 (172)	"Flare"	(1) **Pain on walking on a flat surface:** WOMAC VAS Q1 (0-100mm); Increase ≥15mm (2) **Global Assessment (investigator):** 5-point LK; worsening ≥1 point	(1)**Pain on walking on a flat surface:** WOMAC VAS Q1 (0-100mm); ≥40mm (2) **Global Assessment (patient): (**0-100mm); ≥40mm (*acetaminophen users only*) (3) **Global Assessment (investigator):** 5-point LK; 'Fair, poor, or very poor' (*acetaminophen users only*)	Determined by drug half-life washout	- ; - ; -
Luyten, 2007 (173)	"Flare"	(1) **Global Assessment (Patient):** 5-point LK; Increase ≥1 grade (2) **Global Assessment (physician):** 5-point LK; increase ≥1 grade (3) **Composite definition:** Lequesne Osteoarthritis Severity Index (0-24); increase ≥2 points	(1) **Global Assessment (Patient):** 5-point LK; 'Fair, poor or very poor' (*Not on treatment – 'Poor or very poor'*) (2) **Global Assessment (physician):** 5-point LK; 'Fair, poor or very poor' (*Not on treatment – 'Poor or very poor'*) (3) **Composite definition:** Lequesne Osteoarthritis Severity Index (0-24); ≥7 (4) **Pain**: VAS (0-100mm); ≥40mm	2-14d washout	- ; - ; -
Manicourt, 2005 (174)	"Flare"	**Pain when walking on a flat surface:** VAS (0-100mm) ; ≥10mm	-	7-10d washout	- ; - ; -
Mazzuca, 2002 (155)	"Flare"	**Pain on standing**: WOMAC LK Pain Q5 'severe or extreme' after the washout AND decreased after resumption of usual analgesic drugs and/or NSAIDs	-	Drug washout 5 half lives	- ; - ; -
McIlwain, 1989 (175)	"Flare"	No measurement instrument: Increase in pain on motion, swelling, tenderness, redness and/or heat (unspecified if patient/physician/investigator reported)	-	2-14d washout	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Mendelsohn, 1991 (176)	"Worsening of arthritis condition"	(1) **Pain:** Pain scale (0-3) (0=none, 3=severe); worsening score (2) **Global (physician):** (0-100); worsening score	-	Up to 14d washout	- ; - ; -
Moskowitz, 2006 (177)	"Flare"	(1) **Global assessment (patient)**: 5-point LK; increase ≥1 grade (2) **Global Assessment (physician)**: 5-point LK; ≥ 1 grade increase (3) **Composite index:** Lequesne OA Severity Index (0-24); increase ≥2 points	(1) **Global assessment (patient):** 5-point LK; '(Fair), poor, or very poor' (2) **Global Assessment (physician):** 5-point LK; '(Fair), poor or very poor' (3) **Composite index**: Lequesne OA Severity Index (0-24); Minimum ≥7 (4) **Pain walking on a flat surface:** VAS (0-100mm); ≥40mm	NSAID washout of 5 half-lives or at least 2d	- ; - ; -
Pareek, 2009 (69)	"Flare-up"	(1) **Pain:** 11-point NRS; increase ≥ 2 points during previous 2-5 days (2) Signs and symptoms suggestive of inflammation, morning stiffness and nocturnal pain interfering with sleep	**Pain**: Pain intensity of at least 4 on a 11-point NRS during physical activity for past 24 hours	Placebo washout for 24-48h	2-5d; - ; -
Pareek, 2010 (178)	"Flare"	Flare symptoms noted but not part of definition: morning stiffness, erythema, nocturnal pain, and swelling/inflammation	(1) **Pain with physical activity**: VAS 0-10; ≥6 (2) **Composite index:** WOMAC Total LK; ≥25. (3) **Composite index**: Lequesne OA Severity Index (0-24); ≥5	-	2-5d; - ; -
Roth, 2004 (194)	"Flare"	**Pain:** WOMAC LK3.1 Pain subscale (0-20); increase ≥2 points and ≥25%	**Pain:** WOMAC LK3.1 Pain subscale (0-20); Score ≥'moderate' on at least 1 of the 5 items, (ii) Pain score ≥6	Washout period ≥3d per week past month	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Rother, 2007 (197)	"Flare"	(1) **Pain on walking:** VAS (0-100mm); Increase ≥15mm (2) **Global Assessment (patient):** 5-point LK; increase ≥1 grade	(1) **Pain on walking:** VAS (0-100mm); ≥40mm (2) **Global Assessment (patient):** 5-point LK; 3-5	-	- ; - ; -
Schnitzer, 2005 (179)	"Flare"	No tool: increase in pain	**Pain:** VAS (0-100mm); ≥40mm	-	24h; - ; -
Scott-Lennox, 2001 (180)	"Flare"	(1) **Pain:** VAS (0-100mm)**;** ≥20mm (2) **Pain (physician):** 4-point LK; worsening ≥1 point (3) **Global Assessment (patient):** 4-point LK; worsening ≥1 point (4) **Global Assessment (physician)**:4 point LK; worsening ≥1 point	(1) **Pain:** VAS (0-100mm)**;** ≥40mm at baseline) (2) **Pain (physician):** 4-point LK; ≥2 (3) **Global Assessment (patient):** 4-point LK; ≥2 (4) **Global Assessment (physician)**: 4 point LK; worsening ≥2	14d washout	- ; - ; Confirmatory Factor Analysis
Simon, 2009 (195)	"Flare"	**Pain:** WOMAC LK3.1 Pain subscale; increase ≥2 and ≥25%	**Pain:** WOMAC LK3.1 Pain subscale; ≥'moderate' on ≥1 item	14d washout	- ; - ; -
Silverfield, 2002 (181)	"Flare"	**Pain:** No measurement tool; significant increase	-	-	- ; Pain requiring supplemental analgesic medication and/or an increase in NSAID dose ; -
Strand, 2011 (182)	"Flare"	**Global Assessment (patient):** 5-point LK; Increase ≥1	(1) **Global Assessment (patient):** 5-point LK; 'Fair, poor or very poor' (2) **Pain**: (0-10 NRS); ≥4 but <9 (3) **Global Assessment (physician)**: 5-point LK; 'Fair, poor or very poor'	14d washout	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Weaver, 1995 (196)	"Flare"	(1) **Global Assessment (Physician)**: 5-point Likert; increase ≥1 grade (2) **Global Assessment (patient)**: 5-point LK; increase ≥1 grade (3) **Pain:** Worsening pain on motion and weight bearing	(1) **Global Assessment (Physician)**: 5-point Likert; ≥2 (2) **Global Assessment (patient)**: 5-point LK; ≥2	2-14d washout	- ; - ; -
Wiesenhutter, 2005 (183)	"Flare"	(1) **Pain on walking on flat surface:** WOMAC VAS3.0 Q1 (0-100mm); increase ≥15mm (2) **Global Assessment (Investigator):** 5-point LK; worsening ≥1 unit	(1) **Pain on walking on flat surface:** WOMAC VAS3.0 Q1 (0-100mm); ≥40mm	-	- ; - ; -
Williams, 2001 (184)	"Flare"	(1)**Global Assessment (patient):** 5-point LK; Increase ≥1 point (2) **Global Assessment (physician)**: 5-point LK; increase ≥1 point(3) **Composite Index**: Lequesne OA Severity Index (0-24); Increase ≥2 points	(1) **Global Assessment (patient):** 5-point LK; '(Fair), poor or very poor' (2) **Global Assessment (physician)**: 5-point LK; '(Fair), poor or very poor' (3) **Composite Index**: Lequesne OA Severity Index (0-24); ≥7 (4) **Pain:** VAS (0-100mm); ≥40mm	2-14d	- ; - ; -
Wittenberg, 2006 (185)	"Flare"	**Pain:** VAS (0-100mm); Increase ≥10mm	**Pain:** VAS (0-100mm); ≥40mm	2-7d washout	- ; - ; -
Yeasted, 2014 (186) (Pooled, abstract)	"Flare"	**Pain:** 0-10 NRS; Increase ≥2 points over the mean pain score from the previous 3 days	**Pain:** Average daily 0-10 NRS; 4-9	-	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Yocum 2000 (193)	“Flare”	**Disease activity** (1) **Global (Investigator)**: Reduction of ≥ 1 grade (2) **Global Assessment (Patient)**: 100-mm VAS; Increase of ≥10mm (3) **Pain: Overall assessment (patient):** 100-mm VAS; ≥35mm	-	≥3d washout	- ; - ; -
Young, 2014 (187)	"Flare"	(3) **Pain:** WOMAC pain subscale; increase >15mm	**Pain:** WOMAC Pain subscale >40mm	-	- ; - ; -
Zhao, 1999 (188)	"Flare"	No measurement tool: Worsening of signs and symptoms after discontinuation of NSAIDs of analgesics	-	2-7d washout	- ; - ; -

COPD Chronic Obstructive Pulmonary Disease; d day; h hour; KOFUS Knee Osteoarthritis Flare-up Score; LK Likert Scale; NRS Numerical Rating scale; VAS Visual Analogue Score; w week; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

4.4.3.2 Coverage of key components

Onset/worsening of symptoms and signs above normal day-to-day variation

All studies included increased pain intensity in their definition and 44 included onset or worsening of signs and symptoms (67, 68, 155-169, 171-197). A further two specified other signs and symptoms including: swelling, tenderness, erythema and/or heat (175) and morning stiffness, erythema, nocturnal pain and swelling/inflammation (178).

Temporal characteristics

Speed of onset was not specified in the drug withdrawal design studies however they did describe withdrawal or 'washout' periods. These were specified periods of time the potential participants had to experience 'flare' symptoms, after stopping usual medication, in order to be eligible for the study. Thirty studies stipulated a withdrawal period (69, 155, 158, 160, 161, 163-165, 167-169, 171-177, 180, 182, 184, 185, 188-190, 192-196, 198).

A minimum duration of symptoms was required in four studies and this ranged from 24 hours to 5 days (69, 178, 179, 181).

Change in medication or healthcare usage

Only one study included increase medication; 'pain requiring supplemental analgesic medication and/or an increase in NSAID dose' (181).

Additional domains

Thirty-six studies specified a minimum threshold, whereby the participant had to reach a certain pain intensity level to be classified as having a flare (67-69, 156, 157, 159-161, 164-167, 169-174, 177-180, 182-187, 189, 191, 192, 194-198).

4.4.4 Exacerbation definitions in non-drug withdrawal design studies

4.4.4.1 Terminology used

The majority of non-drug withdrawal design studies (n=11) used the term ‘flare’ in their definition or description (Table 4.4b) (55, 61, 71, 74, 199, 201, 204, 205, 209, 210, 212). Eight used the term ‘exacerbation’ however 5 of these publications were from the same research team. Two studies used both ‘exacerbation’ and ‘flare’ (73, 202). None of the studies referred to ‘worsening of symptoms’ or did not use a specific label.

Table 4.4b: Definition, terminology and measurement instruments used in all included studies: non-drug withdrawal design studies

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Atukorala, 2016 (204); Atukorala, 2016 (199)	"Flare"	**Pain:** (10-point NRS); increase >2 points from the mildest knee OA pain intensity reported at day 0	-	-	- ; - ; -
Bartholdy, 2016 (210)	“Flare”	-	**Pain:** (10-point NRS): Pain >5	-	- ; - ; -
Bassiouni 2015 (205)	“Flare”	-	**Global Assessment (physician):** KOFUS ≥7	-	- ; - ; -
Cibere, 2004 (211); Cibere, 2005 (212)	"Flare"	(1) Patients perception of worsening of symptoms (2) **Pain walking on flat surface**: WOMAC VAS3.0 Q1 (0-100mm); increase ≥20mm (3) **Global Assessment (physician):** 5-point LK; worsening ≥1 grade	-	-	- ; - ; Definition determined by study rheumatologists to be a clinically important change in WOMAC-Ehrich2000/Bellamy 1998
Conrozier 2012 (71)	"Flare"	Fulfilled 4 following criteria: (1) **Pain:** No measurement tool; ‘sudden aggravation of knee pain’ (2) causing nocturnal awakenings, (3) clinical evidence of effusion.	-	Sudden aggravation of knee pain, whose beginning was identifiable	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
D'Agostino, 2005(201)	"Flare"	-	**Pain intensity during physical activity:** VAS-(0-100mm); ≥40mm	-	48h ; - ; -
Erfani, 2014 (200); Erfani, 2014 (206); Ferreira, 2016 (82); Hunter, 2014 (207); Makovey, 2015 (208)	Exacerbation	**Pain:** VAS (0-100mm); Increase ≥20mm from mildest pain score reported at baseline	-	-	- ; - ; -
Jawad, 2005 (213)	Exacerbation	**Pain symptoms:** Increased morning stiffness, night pain and synovial fluid effusion	-	-	- ; - ; -
Marty, 2009 (55)	"Flare"	No measurement tool: Morning stiffness >20mins, nocturnal awakening, limping, knee effusion, increased warmth	-	-	48h ; - ; Regression analysis of cross-sectional data to validate proposed flare criteria

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Murphy, 2015 (61)	"Flare"	(1) Investigator definition: Inadequate pain relief for an episode of intense pain that is usually brought on by too much activity. (2) Participant definitions: Described in terms of pain quality, timing (onset and duration), antecedents and consequences. (3) **Pain magnitude:** increase in pain or 'intense' or 'severe' level of pain	**Pain:** ≥40 of 100mm or ≥4 of 10 on NRS	Patients described: 'Quick' or 'sudden'	Patients: 10 seconds to 15 minutes Patients: Rest or take additional medication For investigator definition: Battisti 2004, Pareek 2010. Plus researchers own experience.
Parry, 2017 (209)	“Flare”	**Pain:** Recalled worst pain intensity in previous 6 months 0-10 NRS; ≥5	**Pain:** Recalled worse pain to be ≥2 points higher than recalled average pain (0-10 NRS) in previous 6 months	-	- ; - ; Based on previous studies defining knee flares in OA and flares in diseases such as back pain and COPD.
Wise, 2010 (74)	"Flare"	-	**Pain:** WOMAC Pain subscale (0-10); score in highest 30% of all WOMAC scores	-	- ; - ; -
Zhang, 2009 (202)	"Exacerbation or flare"	-	(1) Pain: WOMAC pain subscale 0-10 (total score of 50 normalised to a 0-10 scale); score of ≥5, a score corresponding to highest 33% of all WOMAC scores	-	- ; - ; -

First author	Terms used	Change in symptoms/signs	Minimum absolute level of symptoms/signs	Speed of onset	Duration; Change in medication/healthcare use; Rationale
Zhang, 2011 (203)	"Exacerbation"	**Pain:** WOMAC Pain score VAS (0-500); increase ≥100 units	-	-	- ; - ; -
Zobel, 2016 (75)	Exacerbation	**Pain:** 0-10 NRS; Increase ≥2	(1) Disabling pain	-	8h ; - ; -

COPD Chronic Obstructive Pulmonary Disease; d day; h hour; KOFUS Knee Osteoarthritis Flare-up Score; LK Likert Scale; NRS Numerical Rating scale; VAS Visual Analogue Score; w week; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

4.4.4.2 Coverage of key components

Onset/worsening symptoms and signs above normal day-to-day variation

Onset or worsening of symptoms was used in 16 of 22 studies (61, 71, 73, 75, 82, 199, 200, 203, 204, 206-209, 211-213) in their definition. Pain intensity was not used as part of the definition in two studies (55, 205). In three studies, other symptoms were included as part of the definition (55, 71, 213): nocturnal awakenings, effusion, morning stiffness, night pain, limping and warmth.

A mixed methods study by Murphy et al (61), included an investigator definition of flare-ups and explored participant experience and individual definitions of flare-ups through face-to-face interviews. Both the investigator and participant definitions included onset or worsening of symptoms and signs; however there was no differentiation of pain above day-to-day variation.

Temporal characteristics

Only one study attempted to define the speed of onset and this was simply described as ‘sudden’ (71). Participants in the Murphy et al study used terms such as ‘quick’ and ‘sudden’ in their description of flare onset and participants described the duration lasting between 10 seconds to 15 minutes (61). In three studies, a minimum duration of symptoms was described ranging from 8 to 48 hours (55, 201, 214).

Change in medication or healthcare usage

The study by Murphy et al, described that participants either rested or used additional medication in response to flares (61). No other studies described change in medication or healthcare usage.

Additional domains

Two studies from the Longitudinal Examination of Arthritis Pain Cohort used "distribution-based" minimum threshold for flare (189, 203). Amongst the participants this was the highest 30% (203) or 33% (189) of WOMAC Pain subscale scores (total score 50 was normalised on a 0-10 scale).

4.4.5 Measurement Instruments and Operational Criteria

Forty-four drug-withdrawal design studies used measurement tools (67-69, 155-174, 176-180, 182-187, 189-198) and 20 non-drug withdrawal design studies used the tools (61, 71, 73-75, 82, 199-212). There were 19 different single-item scales and 6 multi-item scales used. The most commonly used tools were the Pain VAS (0-100mm), WOMAC Q1 3.0 VAS 'pain walking on a flat surface' (0-100mm), Investigators Assessment of Disease Status and the Patient Global Assessment of Arthritis (Table 4.5)

Table 4.5: Summary of number and type of single and multi-item measurement tools used.

Single item scales:	
Pain on activity:	WOMAC Q1 3.0 VAS 'pain on walking on a flat surface' (0-100mm) [n=11]
	Pain on walking VAS (0-100mm) [n=5]
	Pain on movement VAS (0-100mm) [n=1]; Ambulatory pain (5-point Likert) [n=1]; Pain with physical activity VAS 11-point scale [n=2]
Pain (not further specified):	Pain VAS (0-100mm) [n=15]
	Patients Assessment of Pain Score (0-10) [n=1]; Pain Scale (0-3)[n=1]; Pain NRS (0-10) [n=11]
Standing knee pain	Item 5 WOMAC pain scale [n=1]
Global rating (physician/ investigator)	Investigator Assessment of Disease Status [n=11]
	Physicians Global Assessment of Arthritis [n=6]
	Physician Global Assessment of OA [n=2]
	Physician Global Assessment of Disease Status [n=2]; Investigator Assessed Pain Grade [n=1]; (Physician) Overall Disease Activity (0-100) [n=1]; Physicians Pain Assessment (4-point LK) [n=3]
Global rating (patient)	Patients Global Assessment of Arthritis [n=7]
	Patient Global Assessment of OA [n=3]
	Patient Global Assessment of Disease Status [n=4]
Multiple-item scales:	
	Lequesne OA Severity Index [n=5]
	WOMAC LK3.1 (0-20) [n=3]
	WOMAC LK Pain subscale (0-25); WOMAC OA Index Questionnaire [n=1]; WOMAC knee pain score (0-500) [n=7]; KOFUS (0-14) [n=1]

KOFUS Knee Osteoarthritis Flare-up Score; n number of included studies; OA osteoarthritis; VAS visual analogue scale; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

Onset/worsening of symptoms and signs beyond normal-day-to-day variability

There were 52 studies that used measurement tools to define onset-worsening of symptoms and signs (67-69, 73, 75, 82, 155-169, 171-174, 176, 177, 180, 182-187, 189-191, 193-197, 199, 200, 203, 204, 206-209, 211, 212). The most commonly used tools used for determining onset/worsening of signs and symptoms were: the Western Ontario and McMaster Universities Arthritis index (WOMAC) Q1 (pain on walking on a flat surface) 100mm Visual Analogue Scale (VAS) (n=10),the Investigator Assessment of Disease Status (n=10), Global Assessment of Disease Status (physician) (5-point Likert scale) (n=9) and Pain NRS (0-10) (n=7).

There were some inconsistencies in the use of global scales and their format, as was use and reporting of the WOMAC (215). Despite this, the items used covered four general areas: pain on activity (for example, walking), pain (not further specified), physician or investigator global ratings and patient global ratings.

Additional domains- minimum threshold

In general the minimum thresholds used for the different measurement tools were the same. For example, threshold of 40mm on a 0-100mm scale was used in studies using the WOMAC VAS 3.0 Q1 ‘pain on walking on a flat surface’ (68, 156, 160, 167, 172, 183, 189, 191). However, there were inconsistencies with scales and minimum thresholds used in reporting the Patient Global Assessment of Disease Status. Four studies using a 100mm VAS used a minimum threshold of 40mm (156, 164, 172, 191) and those using a 5-point Likert used ‘fair, poor or very poor’ (165, 173, 182, 184) or ‘poor, very poor’ (161). In studies using the Physician or Investigator Global Assessments the majority (n=10) used a minimum threshold of ‘fair, poor or very poor’ (156, 160, 165, 172, 173, 177, 182, 184, 189, 191). In studies using the

Lequesne index (0-10) the majority of studies (n=4) used a minimum threshold of 7 (161, 173, 177, 184) and one used 5 (178).

4.5 Discussion

This review has found common core domains amongst the descriptions and definitions used for knee OA flare-ups in the medical literature. These domains will be helpful in reaching a consensus definition which can be used clinically to promptly identify these acute events and help focus management strategies. A consensus definition will also ensure reproducibility and comparability of results in research studies.

The key core domains identified in this review were: onset/worsening of symptoms and signs above normal day-day variation, duration of symptoms, speed of onset/worsening of symptoms and minimum symptom threshold. Other domains which received less attention included change in medication and healthcare usage.

The majority of studies required an increase in pain intensity above ‘usual’ or ‘baseline’. A wide range of measurement instruments were used, but several selected an increase of at least 2 points on a 0-10 scale. This could indicate a starting point for reaching consensus. Distinguishing these increases in pain intensity from day-to-day variability, which is a known feature in OA (63, 216), is important and a definition with an increase in pain intensity alone is unlikely to achieve this. Duration of flare-ups, which ranged from 10 seconds to 5 days in this review, may be a critical component. Day-to-day variability in pain intensity is likely to encompass these short lived episodes of pain however it is probably unrealistic to include durations as short as 10 seconds in a definition of flares. Interestingly, duration does

not appear to be an important feature in other chronic diseases. In the COPD literature a ‘sustained worsening’ of symptoms (137) is described however this is not mentioned in other chronic diseases. Clinically, it might be more straightforward to rely on individual patient judgement as to whether symptoms have increased above normal variation. However, it remains unclear how accurately patients can report this.

Speed of onset was not well defined in this review. When mentioned it was described descriptively, for example ‘sudden’. In drug withdrawal studies, washout periods between 2-15 days were specified, but this is unlikely to be synonymous with speed of onset. It may be unrealistic to operationalise time, and experience from the respiratory field, where the term ‘acute’ is often used (137), seems to suggest that this has not been a barrier in making progress.

There was general agreement with the minimum symptom threshold used, for example, 40mm on a 0-100mm scale. This may represent the level for minimally important clinical difference in symptoms. COPD exacerbation definitions describe a symptom increase ‘which is beyond normal day-today variations’ (137) and the SLE definition includes; ‘must be considered clinically significant by the assessor’ (140), both of which rely on judgement.

Increase in medication or healthcare usage was not identified as a key component of definitions of OA flares despite it featuring in others: AS (117), SLE (140), IBD (217) , COPD (137). Interference with function was not a key feature in our review, nor did it feature in the definitions used in other chronic diseases, such as back pain (218), COPD (138), asthma (139), AS (117) and SLE (140).

Reaching an agreed definition through consensus exercises can be a lengthy process and usually involves key stakeholders, experts and patients in addition to

appraisal of the relevant literature using numerous methods. Each component of the definition presents its own challenges in achieving a consensus. Following an OMERACT initiative from 2006 to find a consensus definition for RA flares the working group have undertaken a number of stages (Table 4.6).

Table 4.6: Progress of the OMERACT group in reaching a consensus definition for rheumatoid arthritis flare ups

2009: Bingham CO et al. (144)	
Aim:	Literature review to identify publications and abstracts with flare definitions applied to RA, JIA and lupus RCT as well as concerning patient perspectives on disease worsening. SIG for patients (n=120) and investigators (n=11) held. Discuss various aspects of disease worsening.
Outcome:	Following consensus obtained: working definition of flare should indicate worsening of disease activity (88%), persistence, and duration as critical elements (77%), and a consideration of change or increase in therapy (74%). “Worsening of signs and symptoms if sufficient intensity and duration to lead to change in therapy.
2011: Bingham CO et al. (219)	
Aim:	Patient research partners-iterative driven Delhi process, preliminary list of key domains identified
Outcome:	Consensus achieved in addition to existing core set for RA including fatigue, stiffness, symptom persistence, systemic features and participation.
2012: Bartlett SJ et al. (220)	
Aim:	125 RA pts from 10 countries and 108 HCPs from 23 countries rated 14 domains, Delphi consensus
Outcome:	Core domains: Pain (93%), function (89%), swollen joints (84%), tender joints (81%), participation (81%), stiffness (79%), patient global assessment (76%), and self-management (75%), fatigue
2013: Lie E et al. (221)	
Aim:	Assess construct and content validity of the potential RA flare domains. Assessed convergent and construct validity variables representing same domains.
Outcome:	Domains appeared to be discriminatory for flare
2016: Bykerk et al. (80)	
Aim:	Evaluate reliability of flare identification and construct validity of key components representing the OMERACT RA Flare Core Domain Set.
Outcome:	The 5 flare domains (pain, fatigue, stiffness, function and participation) showed good construct validity but reliability was not proven.

HCP Healthcare professional; JIA Juvenile idiopathic arthritis; OMERACT RA Rheumatoid arthritis; RCT Randomised controlled trial; SIG Special interest group

A consensus definition is important in order to ensure reproducible and comparable research than can accurately provide estimates of disease burden which will be helpful for resource planning. Furthermore, it allows consistent recognition and

identification in clinical practice. The characterisation of acute episodes in a number of chronic diseases, such as COPD (137, 138), asthma (139), and AS (117) rely on descriptive definitions. These definitions tend to be the ones adopted in clinical guidelines, for example, NICE and the Global Initiative for Chronic Obstructive Lung Disease (GOLD). However, they are generally not adopted for research purposes, where measurement-based criteria are preferred (222).

Marty et al (55) and Scott-Lennox (180) et al were the only groups that attempted to propose and/or validate prediction models for OA flares, although these have not been widely implemented. This may be due to the difficulty in reaching a widely accepted model. Using different definitions can be problematic, hindering comparisons between studies, for example, comparing estimates of incidence (223) and effect sizes in RCTs (222). In this review, the majority of non-drug withdrawal design studies relied on patient reported outcomes which contrasts with the drug withdrawal studies which relied heavily on investigator or physician reported outcomes. The use of symptom versus healthcare-defined definitions (based on, for example, change in therapy or contact with healthcare professional) has also been shown to affect reported mean yearly rates with healthcare defined rates being higher (2.3 per year vs 2.8) when estimating COPD exacerbation rates (224).

The main strengths of this systematic review are that it included a broad search strategy using a wide range of databases, bibliography checks, attempted contact with authors, included conference abstracts, did not have any language restrictions and there was a low threshold for inclusion (for example any description or definition of a flare was used). A similar review was conducted by Cross et al which aimed to identify the key domains in the medical literature that were used by patients and clinicians to described knee and hip OA flares. The review presented in this chapter

however was more comprehensive including 69 versus 23 studies (126). Five studies that were included in the Cross et al review were not included in ours as four did not contain a clear definition of flare and the Sands et al (225) paper was not included as the original study was included instead. The key components identified by Cross et al share some similarities with my study. These include pain onset (which encompassed timing, an increase in pain and duration), other symptoms (for example swelling, warmth, limping, taking medication) and change in scores on single and multi-item measurement tools, for example the WOMAC.

Limitations of this study include not searching the grey literature. There were terms that may be synonymous with a flare that were not included in the search strategy: ‘attack’, ‘fluctuation’ and ‘episode’. These terms were thought to be related to comorbidities and other phenomena and would have made the search strategy less efficient. Data extraction was only performed by a single reviewer. Only two of the included studies attempted to derive and validate a prediction model for OA flares (55, 180). Despite this, their models have not been widely adopted. The majority of definitions in this systematic review were from flare design trials. The participants generally underwent a period of drug washout in order to bring on a flare. These were ‘investigator-induced’ flares and so may be different to ‘naturally occurring’ ones both in the symptomatology, severity and speed of onset. Despite this, flare design trials might give some useful information with regards to naturally occurring flares for those people whose flares are triggered by them stopping their medication. A further limitation of the study is lack of validation of definitions used within the literature. The majority of pain measurement tools used have been previously validated, for example, WOMAC. However, they have not been specifically validated for their ability to detect flares.

My review was conducted three times over the course of this thesis; initially in 2013, secondly in 2016 to update the search after returning from maternity leave and finally in 2017 after a similar review had been published. Since 2017 there have been a few studies published that would have been relevant to my review; the Flare in OA OMERACT group published their study identifying preliminary domains for a consensus definition (81), the protocol for the ACT-Flare web cased crossover study assessing risk factors for knee OA flares (83), a cross-sectional study exploring flare onset following sit to stand activities (226), and a study exploring daily pain trajectories in knee and hip OA and their association with certain patient characteristics (227).

This review has highlighted the range of ad hoc definitions used for knee OA flare-ups in the literature. Despite this they share common core domains: onset worsening of symptoms and signs, attainment of minimum symptom threshold, speed on onset or worsening of symptoms, and duration of increased symptoms. Reaching a consensus definition can be a lengthy process. However, achieving a widely accepted definition that is reliable, sensitive to repeated measures, feasible, acceptable and validated would help ensure research findings were comparable. Furthermore, a definition that provides prompt diagnosis and is acceptable clinically would ensure prompt management through healthcare providers or though self-management strategies.

4.6 Conclusion

This review has shown that the cardinal features of a flare-up of knee osteoarthritis include; increased pain intensity with a minimum symptom threshold. The findings show the range of definitions that currently exist and demonstrate the need for a consensus definition that is reliable, validated, feasible and acceptable to use in clinical practice and research.

The core domains described in this chapter informed the definitions used for acute events in the secondary analysis of cohort data (Chapter 5), the cross-sectional survey (chapter 6) and the diary study (Chapter 7), and that used in the patient literature of the qualitative study (Chapter 8).

5. Significant pain variability in persons with, or at high risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of cohort data

This chapter describes the design and findings of a secondary analysis of cohort data intended to provide estimates of significant pain variability or potential flare-up intervals and the factors associated with these as a preliminary investigation of the frequency and risk factors for acute flare.

5.1 Introduction

Longitudinal studies with repeated measures over 5-6 years have shown that trajectories in osteoarthritis symptoms and disabilities, for the majority of participants, are relatively stable over periods lasting up to 10 years (56-59, 228). However, these studies mask the variability of pain intensity that occurs within persons (62, 229, 230). This variability in pain may represent day-to-day variation but more importantly may represent acute events or flares of pain which are suggested to occur in early and advanced OA and be associated with distress and impact on function, particularly when unpredictable (53)

More frequent pain measurements are more sensitive to changes in pain intensity. Schneider et al (230) gathered pain intensity data daily for 7 and 28 days and demonstrated high within and between-person variability in pain. However, this sample was recruited from rheumatology clinics and only half of the population had a diagnosis of OA as it also included those with RA, lupus and fibromyalgia so it is not

clear who these findings are generalisable to. Baseline factors that might determine variability in symptoms and help understand who might be more at risk of an unstable disease course were not presented, for example gender, age, baseline severity, employment and duration of symptoms. Despite this increased variability was seen in those with depression and persistent pain. Variability in OA pain is likely to exist on a spectrum with part of this variability being attributed to episodes of uncharacteristically severe pain or acute flares. It was suggested by Hawker et al that these events take place in both the early stages of OA where they are usually predictable and in the late stages where they become unpredictable (53). Hawker et al, undertook focus groups on patients that were recruited from advertisements and flyers and had a radiographic diagnosis of OA. Response bias may have led to those with more severe symptoms replying, however the authors did try to sample across the spectrum of OA severity. Despite this it is not reported how many fell into the mild, moderate or severe pain groups. Furthermore, there were few people in the 'early' OA group. It is therefore difficult to draw conclusions on whether flares are more likely to occur at a certain disease stage, something which may be helpful for resource planning and identifying those patients at greatest risk of flares.

Findings from the systematic review (Chapter 4) undertaken to identify, describe and evaluate definitions of knee OA flare used in the medical literature found a number of common domains including: onset/worsening of symptoms above normal day-to-day variability, speed of onset, duration of sustained worsening, and a minimum threshold of pain. The majority of these studies were from flare design trials, in which usual medication is withdrawn in order to bring about an acute increase in symptoms during a specified time period. Findings from the systematic review and definitions

from the flare design studies have been used to define symptom variability or ‘flares’ in this study.

Induction of flares in the context of drug withdrawal trials is well established. Usual medication is withdrawn with the aim of inducing a ‘flare’ within a specified time period to evaluate a new regime or pharmacological therapy (158, 161, 162, 178, 231). A recent systematic review assessing NSAID response found 22 flare design and 11 possible flare design trials in the literature. These ‘induced’ flares however are likely to be different to ‘naturally’ occurring flares which in comparison have received less attention. Increasingly, studies on these phenomena, termed ‘acute events’, ‘flares’, or ‘exacerbations’ are starting to emerge. Studies include those that have attempted to identify diagnostic criteria for a flare-up (55), identify triggers (74), explore impact on productivity (73) and the role of inflammation (70, 71).

Few studies have attempted to estimate flare frequency. Those that have attempted this have only used short observation periods of 1-2 weeks (73, 232). Amongst participants in these studies nearly 80% experienced a flare. In one study this was based on predetermined flare criteria which required a minimum increase of 2 points (on a 0-10 scale) from baseline (73) and in the second it was based on participant self-identification (232). The short but intensive data collection period suggests that a high proportion of people with OA seem to experience something we might call ‘flares’.

While previous short-term studies support the idea that many patients with osteoarthritis may experience significant variability in pain over time, population-based studies could usefully estimate the proportion and characteristics of patients

experiencing such variability. To attempt this, I undertook a secondary analysis of available data from the Clinical Assessment Study of the Knee (CAS-K) cohort.

5.2 Aims and Objectives

Aim

The aim of this study was to estimate what proportion of adults with knee pain in the general population report ‘significant symptom variability’ (a potential proxy for experiencing flare) and how those individuals differ from those who do not report significant symptom variability.

Objectives

- To estimate potential frequency of symptom variability
- To determine risk factors for symptom variability

5.3 Methods

5.3.1 Description of dataset: Clinical Assessment Study of the Knee (CAS(K))

Descriptive summary of cohort and dataset

The secondary dataset used in this study was the Clinical Assessment Study of the Knee (CAS(K)) which comprised a large prospective community based cohort study of 819 participants with knee pain and knee OA based in North Staffordshire, UK. The CAS(K) study was granted approval by the North Staffordshire Local Research Ethics Committee (project number 1430 baseline, 03/94 18 months, 05/Q2604/72 3 years, 06/Q2707/327 54 months, 08/H1206/171 6 years).

All patients aged 50 years and over registered at three general practices in North Staffordshire were eligible for inclusion. Patients were recruited between 2002 and 2003 and followed up at 18 month intervals until 2009. The general aim of the longitudinal aspect of this study was to describe the clinical course of healthcare utilisation of older adults with knee pain in the general population, developing prognostic indicators of clinical course and consultation (92).

The dataset is held by the SPCSC and data was requested to answer specific questions relevant to this thesis. No further ethical application was required for this study.

5.3.2 Sampling and data collection

Eligible patients were mailed a Health Survey questionnaire that included socio-demographic characteristics, general health status, and questions on recent knee pain. Those who reported knee pain in the past 12 months and consented to further contact were sent a Regional Pain Survey questionnaire which included the Western Ontario and McMaster Universities OA index (WOMAC LK 3.0) (233). Participants who completed both questionnaires were invited to a research clinic where they underwent digital photography of the lower limbs and hands, plain radiography of both knees and both hands, a standardised clinical interview and physical examination of the knees and hands by a trained physiotherapist, simple anthropometric measurements and a brief self-complete questionnaire.

The content of the standardised clinical interview and physical examination had been developed using literature review and consensus methods, and underwent initial testing and evaluation of inter- and intra-rater reliability (234-236). A brief,

standardised examination of both hands was conducted which allowed for clinical classification of hand OA (237) and nodal OA. Reliability was good for much of the clinical history (236) but several items in the physical examination were found to have relatively high inter- and intra-observer variability (234) leading to some of these items being dropped or amended before the main study.

At the baseline clinic visit three radiographic views of the knees were undertaken according to standardised protocols: weight bearing posteroanterior (PA) semi-flexed/metatarsophalangeal (MTP) (238), a supine skyline view and supine lateral view; the latter two with the knee flexed to 45^{o}. Films were scored by a single reader blinded to all questionnaire and clinical data using Kellgren and Lawrence (K&L) score, and standard atlases (239-241). Severity of radiographic OA in the knee as a whole (across tibiofemoral and patellofemoral joints) was classed as none, mild, moderate, or severe, according to a pre-defined scheme (242). Intra-reader reliability scores were very good (unweighted κ=0.81–0.98); inter-reader scores were also good (κ=0.49–0.76).

For the purposes of the current analysis, interview, examination and radiographic variables were used only for the index knee (the most painful as rated by the participant). If both knees were rated equally painful, the index knee was randomly assigned by a statistician.

Body mass index (BMI) was calculated from weight and height measured in baseline clinic.

At baseline and at each of the follow up surveys (mailed at 18, 36, 54 and 72 months), the Von Korff Chronic Pain Grade (243) was collected and related to the previous 6 months. This is a measure of global severity of knee pain, consisting of 7

items relating to pain intensity, disability, and interference with activities. Using simple scoring rules pain severity was graded into four hierarchical classes. Only selected items were used in this secondary analysis, and these will be discussed in further detail in the next section.

5.3.3 Study participants

The study population at baseline, i.e. those that had responded to the Health Survey, reported knee pain in the previous 12 months, consented to further contact, responded to the Regional Pain Survey and attended the research clinic was 54% female. The age categories were as follows: 50-59 (29%), 60-69 (38%), 70-79 (27%) and 80 and over (6%).

5.3.4 Response at baseline and follow-up

Information about participation rates from baseline to 3 years was extracted from publications from the CAS(K) and from the custodian of the data set.

Baseline

There were 2226 responders reporting knee pain and consenting to further contact of which 819 attended the research clinic for assessment and radiographs.

Follow up

A postal survey was sent to participants at 18, 36, 54 and 72 months (*n*=776, 707, 602 and 512 responders respectively) (59).

An analysis of the baseline and 18 month follow up found that the following were associated with selective non-participation: age over 80, not being married/cohabiting, lower educational attainment, manual occupations and possible or probable anxiety or depression symptoms (244). The majority of responders were Caucasian (99.5%) (244). These factors limit the generalisability of findings.

Physical SF-12 mean scores from the Health Survey at the initial mail out was 41.0 (12.5) compared to 37.6 (11.90) at the research clinic. This may suggest that those with worse physical symptoms were less likely to attend the research clinic. However, WOMAC scores were stable between initial mailing and the research clinic.

5.3.5 CAS(K): Critical evaluation of CAS(K) as a secondary data source for this thesis

The CAS(K) dataset was chosen for this study as it was easily accessible, free, known to contain potentially relevant items, and based within a UK population. An estimate of frequency of symptom variability could be determined from answers given to the chronic pain grade and the baseline variables were those that have been previously been shown to be associated with knee OA progression (245, 246)**.** As this was a preliminary study of symptom variability and risk factors it was decided to look initially at factors that had already been identified to be associated with knee OA.

Bias

A longer duration of recall period and increased pain close to the measurement time point has been shown to affect accuracy of pain recall leading to recall bias (100,

247). The Chronic Pain Grade has been shown to be more sensitive to change when used over a 4-week recall period (248). Furthermore, a long period of recall can be subject to forward telescoping where an event is reported more recently than it actually happened (249), thus leading to an overestimate in pain rating which may have influenced ‘worst pain’ scores. Selection bias, whereby the inclusion of participants in the study depends on the exposure of interest, may in this study have led to selective non-response and loss to follow up.

Summary

The CAS(K) dataset had a number of advantages and key limitations. The definition of symptom variability was possible with the available data and it contained the range of variables that I wanted to explore further. However, limitations included the long recall period for worst and average pain intensity: the sampling frame was restricted to one geographical area, limited to those over 50 years of age and Caucasians; and the additional selection bias from selective non-response and loss to follow-up.

5.3.6 Availability of key data

The CAS(K) study provided a wide range of baseline data including demographics, physical function status, knee pain, psychological status, social factors, knee history, knee examination findings, knee symptoms and results from knee radiographs.

From the initial mailing stage 2226 responders reported knee pain and consented to further follow up and 819 attended the research clinic (59).

Follow up surveys, which included assessment with the Von Korff Chronic Pain Grade(243) over the past 6 months and current pain on an 11-point numerical rating

scale, which was also assessed at baseline, were mailed to participants at 18 months, 36 months, 54 months and 72 months (*n*= 776, 707, 602 and 512 responders) (59).

Patients were excluded at baseline if they had incomplete radiographs, inflammatory arthritis, total knee replacement and a diagnosis of gout from medical record review at baseline or at 18 month follow up. Participants who reported total knee replacement (TKR) in either knee after baseline and up to 3 years were also excluded. Patients reporting TKR in either knee at 3-6y were excluded at the 3-year time point.

The outcome variable chosen was worst and average pain in the past 6 months on a 0-10 scale. On this scale '0' was no pain and '10' was as bad as it could be (250).

Variables that were selected from the CAS(K) data were those that have been shown to be risk factors for knee OA (251, 252), incidence of knee OA progression (253-255), association with pain outcomes (256) or triggers of acute exacerbations (74). Those included are described below.

Age and gender

Age ("date of birth") and gender ("male/female") was determined using standard single questions.

Anthropometric measures

Body Mass Index (BMI) was calculated from height and weight recorded at the baseline clinic visit.

Measures of severity and function

Measures of disease severity and function included SF-36 (257), WOMAC knee pain score (258), WOMAC knee function score (258) and severity of knee effusion. Measures of radiographic severity included were overall severity of index knee and radiographic component compartment combinations of index knee.

The WOMAC is designed to assess pain, stiffness and physical function in those with hip or knee OA. It consists of 24 items divided into 3 subscales: pain (5 items), stiffness (2 items) and physical function (17 items) (258). The pain and physical function items were included in this analysis. The pain items ranged from a scale of 01-20 and the physical function items from 0-68.

For small and large effusions the ‘bulge’ test was performed (259). For moderate effusions, where the bulge sign could not be elicited due to too much fluid but where the patellar tap sign was not present the ‘balloon sign’ was used. These tests were assigned a dichotomous rating and in addition to this an ordinal-scale was used regarding overall judgement of the severity of the effusion (259) where 1 is no effusion, 2 is mild, 3 is moderate and 4 is gross effusion. This was based on direct observation and palpation to closely reflect clinical practice.

Knee related factors

Knee related factors requiring dichotomous responses included previous knee injury, new knee problem in the last 12 months, experience difficulty to get moving in morning, knee given way in last 12 months and seen a hospital doctor about knee.

Duration of knee symptom was subdivided into the following categories: less than 12 months, 1-less than 5 years, 5-less than 10 years and over 10 years. If the

participant indicated difficulty in getting moving (also known as inactivity gelling (236)) they were asked to categorise this as ≤30minutes or over 30 minutes.

Psychological factors

Severity of anxiety and depressive symptoms were assessed by the respective subscales of the Hospital Anxiety and Depression scale (HADS) (0-21 each) (260). This brief self-complete scale includes seven items for anxiety and seven for depression each scored on a scale of 0-3, where 3 indicates more frequent symptoms and higher total scores on the HADS indicating more distress.

Nodal OA

The presence of nodal hand osteoarthritis was determined if KL score was ≥2 in two or more inter-phalangeal joints (IPJs) and if there were at least 2 Heberden or Bouchard nodes present across either hand (261).

Physical activity

Of the twenty-one physical activity items in the Health Questionnaire, six items were chosen (based on those items that were felt to be more objective, for example ’walks of 2 miles or more’), grouped into broad levels of physical activity intensity, and item responses dichotomised to yield three binary predictor variables (Table 5.1)

Table 5.1: Derived variables for physical activity

Derived variable	Items* used to construct derived variable	Positive response defined as
Frequent sedentary activity	Spend most or all of day in bed or chair	Responded “all, most or some days”
Frequent moderate physical activity	(a) Walks of a least a quarter of a mile (b) Walks of two miles	Responded “all, most or some days” to at least one item
Frequent vigorous physical activity	(a) Play a sport (b) Heavy gardening (c) Heavy DIY work at home	Responded “all, most or some days” to at least one item

* Items relate to reported frequency of doing each activity in the past 4 weeks

5.3.7 Defining symptom variability

The components that constituted the flare-up definition used for the current study were items that were adapted from the Von Korff Chronic Pain Grade in the CAS(K) study. The Chronic Pain Grade was originally validated in primary care patients with lower back pain, headache and temporomandibular joint disorder. It was adapted for the CAS(K) for knee pain. The two pain intensity items used for the flare definition asked participants to rate their worst and average pain in the past 6 months on a 0-10 scale. On this scale ‘0’ was no pain and ‘10’ was as bad as it could be. It has been shown to have good reliability and convergent through correlations with similar items on the SF-36 general health questionnaire and construct validity by assessing whether patients scored higher if they had recently sought help for their pain or frequently took analgesia (250).

Using these items the following *a priori* definition of a flare up was composed; an interval within which one or more periods of symptom variability had occurred was

defined by ‘recalled worst pain intensity in the past 6 months that was (a) ≥5, and (b) ≥2 points higher than recalled average pain intensity in the same 6 month period’.

This definition was chosen after referring to previous studies of osteoarthritis exacerbations where flares were described as worsening usual pain (55, 70), within defined limits using pain scales from flare design trials (157, 178, 180-182). Definitions used in other musculoskeletal conditions such as lower back pain (218) and non-musculoskeletal conditions such as COPD were used (76, 262) where worsening of symptoms is used in addition to requiring different or extra medication. The definitions are all reliant on change and difference in pain. The core domains identified from OA flare definitions identified in the systematic review (Chapter 4) were included within the limitations of the data available. The definition composed included onset/worsening of symptoms and minimum threshold.

To be included in the denominator, individuals had to be ‘at risk’ during that follow-up interval (i.e. average pain intensity <9 out of 10). Participants were classed as not having a flare if they returned the self-complete survey but there was missing data at all time points on average and worst pain, if they had an average pain score of ≥9 at all-time points or they did not meet the flare criteria. For example, if a participant scored an average pain of ≥9 at three time points and had missing data at the other two time points they would be classified as not having a flare.

5.3.8 Statistical analysis

Selective loss to follow up

A chi-squared test was used to test for differences in the proportions lost to follow-up at each time point in those reporting significant pain variability at baseline compared to those reporting no significant pain variability at baseline

Frequency of symptom variability at each time point

The frequency and proportion of participants experiencing at least one exacerbation was reported for each time point. A baseline table was presented to compare the demographic and clinical characteristics of patients experiencing at least one flare-up over the 5 time-points against those with no flare-up. All continuous variables were summarised using mean and standard deviation, or medial and interquartile range as appropriate while frequency and percentages of observed levels were reported for all categorical measures.

Association between putative predictors and symptom variability

To estimate the association between the putative predictor variables and time to potential flare-up, discrete-time survival analysis was used. This was because the flare-up, though continuous in the sense that it may occur literally at any time, was recorded in discrete time as only the time interval in which the event occurred was known (263). Furthermore, there was a wide interval (18 months) between each measurement time point which also supports the use of this type of analysis. Discrete-time hazard survival models become models for dichotomous response when the data have been expanded to person-period data with one observation for each year the

person is at risk (264). At each follow up time point, an indicator variable was created to determine whether a potential flare-up or episode of pain variability had been experienced in the previous 6 month period and estimated the hazard of flare-up using logistic discrete-time hazards model (263). This ensured that sample hazard probabilities would be computed for each time period that a flare-up occurred and no data was ignored (264). Right censoring was performed on the outcome at 72 months (the last follow-up period). Censoring was also implemented for those that were lost to follow-up or withdrew from the study before their follow-up data was recorded. To account for variation in flare-up rates over time, at each follow-up period dummy variables were included in all models. The following 2 sets of analysis were performed: a) modelling the time to first flare-up or period of symptom variability, disregarding additional flare-ups i.e. after a flare-up occurs no additional records are included for that case; b) taking into account the recurrent flare-ups or periods of significant symptom variability. To take into account the recurrent flare-ups, multilevel discrete-time survival (frailty) models were used. In the frailty model, the association between flare-up times was explicitly modelled as a random-effect term (265). The frailty model was estimated using logistic discrete-time hazards model with random effects. All analyses were performed using Stata 13 (StataCorp, 2013).

Based on the literature, a large number of baseline variables were selected to be tested for an association with symptom variability (266). The method used to select the significant variables to use in the final multivariable model involved two steps. The first step involved the test of each variable to symptom variability association. In this case the alpha-level for rejecting the null hypothesis of no association was raised to 0.20 (267). Since some of these variables were strongly correlated among themselves, and including all of them in the model would inflate the variance of the parameter estimates,

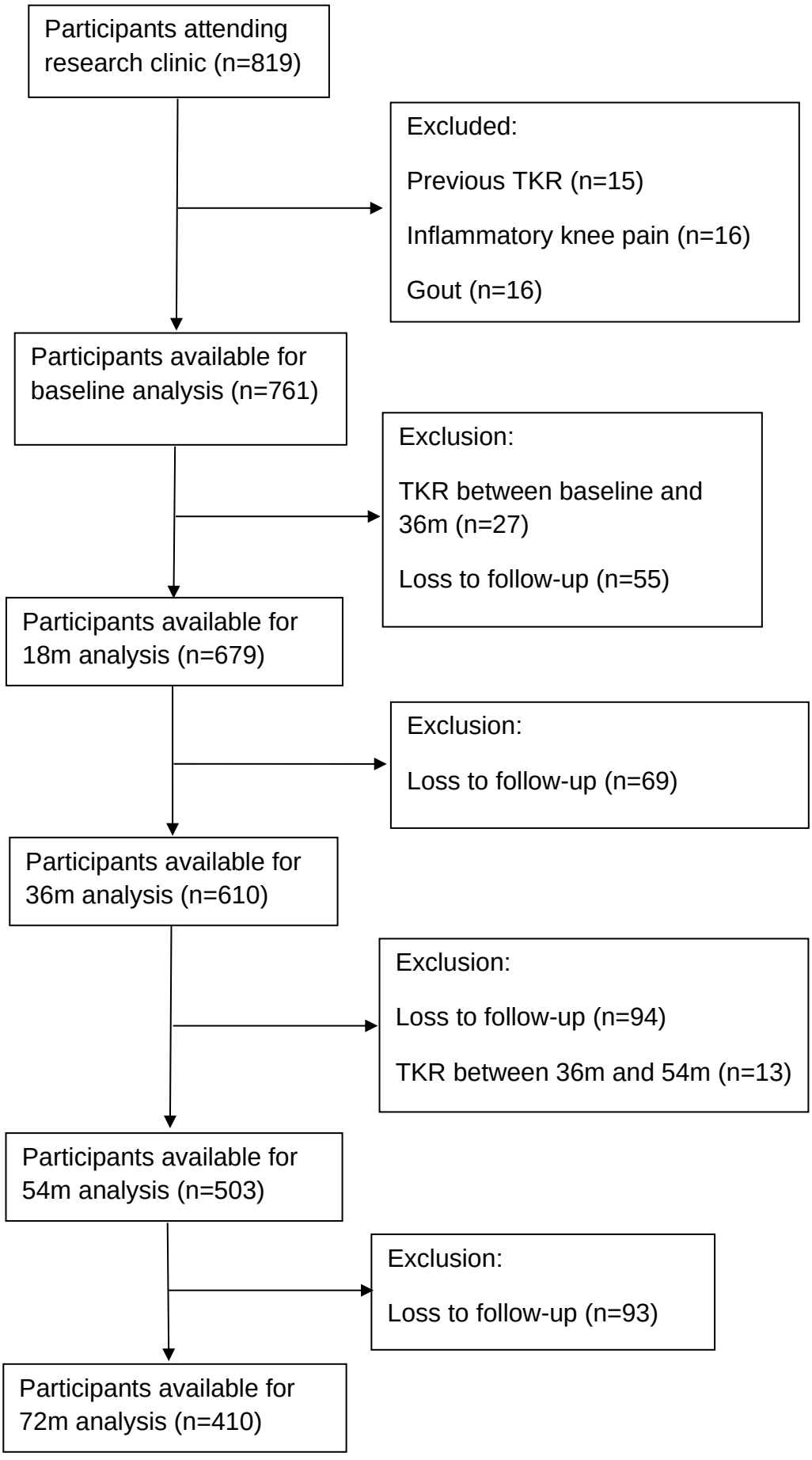
a test of multicollinearity was performed (268). This was done by first examining the correlations (continuous) and associations (categorical) between the independent variables, followed by multicollinearity diagnostic statistics for linear regression analyses (variance inflation factor), to check for the existence of multicollinearity when several potential predictors are adjusted for simultaneously (269). If multicollinearity existed, one of the correlated variables was dropped from the model; the choice of the variable to be included in the model was based on how strong it was related to the outcome (267). The second step involved simultaneous adjustment of all significant variables in the univariable model, followed by deletion in sequence of the least significant variables (270). The significance of each variable in the model was examined and if a variable appeared non-significant it was removed from the model and the model was refitted. The reduced model was compared with the complex model using the likelihood-ratio test. This was repeated until only factors with a $p<0.05$ were retained in the final model (267).

5.4 Results

Of 819 participants that attended the research clinic, 761 were eligible for data analysis at baseline (54% female; mean age 64.5 (SD 8.7) years; mean BMI 29.4 (SD 5.1) kg/m^2; average knee pain score (0-10 NRS) 4.4 (SD 2.4)).

The flowchart in Figure 5.1 gives a description of data available for analysis at each time point and exclusions.

Figure 5.1: Flow chart of data available for analysis at each time in CAS(K)



Selective loss to follow-up

There was no evidence of selective loss to follow up amongst those who experienced significant pain variability versus those that did not experience significant pain variability (Table 5.2).

Table 5.2: Comparison of responder status and presence of symptom variability at each follow-up time point

	Responders (%)	Non-responders (%)	Chi^2 (p-value)
18 months	207 (32)	20 (29)	0.31 (0.58)
36 months	188 (32)	39 (29)	0.45 (0.50)
54 months	156 (32)	71 (30)	0.40 (0.53)
72 months	134 (34)	93 (29)	2.48 (0.12)

Frequency of significant symptom variability

At baseline 32% of participants experienced symptom variability, this reduced to 23% at 36 months and increased to 30% at 72 months (Table 5.3). There did not appear to be any trend over time.

Table 5.3: Proportion of patients reporting significant pain variability or flare-up at each time point

	Measurement point				
	Baseline ***(n=761)***	**18 months** ***(n=679)***	**36 months** ***(n=610)***	**54 months** ***(n=503)***	**72 months** ***(n=410)***
Eligible responders reporting significant pain variability[†]: n (%)	227 (32)	163 (26)	126 (23)	129 (27)	114 (30)
Average pain intensity in past 6 months (0-10NRS)	4.7 (1.7)	4.6 (1.8)	4.5 (1.6)	4.4 (1.5)	4.9 (1.9)
Worst pain intensity in past 6 months (0-10NRS)	7.6 (1.6)	7.5 (1.5)	7.3 (1.5)	7.1 (1.5)	7.6 (1.6)
Eligible responders reporting no significant pain variability: n (%)	493 (68)	462 (74)	433 (77)	336 (72)	260 (70)
Average pain intensity in past 6 months (0-10NRS)	3.9 (2.3)	3.5 (2.5)	3.9 (2.6)	3.5 (2.7)	3.8 (2.5)
Worst pain intensity in past 6 months (0-10NRS)	4.1 (2.3)	3.7 (2.4)	4.1 (2.6)	3.8 (2.7)	4.1 (2.5)
Ineligible responders[‡]: n (%)	41 (5)	42 (6)	40 (7)	31 (6)	30 (7)
Missing: n (%)	0 (0)	12 (2)	11 (2)	10 (2)	6 (1)

Figures are mean (standard deviation) unless otherwise stated. NRS Numerical Rating Scale

[†]worst pain intensity in past 6 months ≥5 and ≥2 points higher than average pain intensity in past 6 months

[‡]average pain intensity in past 6 months ≥ 9/10

Participants classed as having at least one period of 'significant pain variability'

Across the entire cohort follow up period 363 (47%) participants reported no periods, 202 (27%) reported one period, 90 (12%) reported two periods, 63 (8%) reported three periods, 30 (4%) reported four periods and 13 (2%) reported five periods of significant pain variability. Table 5.4 presents the descriptive statistics for participants reporting at least one period of significant pain variability.

Table 5.4: Comparison of patient baseline characteristics of participants reporting at least one period of significant pain variability or potential flare**.**

	Periods of significant pain variability	
	≥1	**None**
	n=398	*n=363*
Female gender	211 (53)	191 (56)
Age (years): mean (SD)	63.6 (8.2)	67.4 (8.7)
Employed	106 (27)	59 (17)
Attended full time education after school	68 (17)	45 (13)
Married/cohabiting	317 (76)	236 (68)
Current smoker	43 (11)	36 (10)
Body Mass Index (kg/m^2): mean (SD)	30.01 (5.28)	28.75 (4.76)
Routine/manual occupational class†	191 (48)	191 (56)
PF-10 physical function subscale (0-100): mean (SD)	56.06 (27.91)	58.73 (30.09)
WOMAC knee pain (0-20): mean (SD)	6.51 (4.18)	5.56 (4.27)
WOMAC knee function (0-68): mean (SD)	21.06 (14.48)	18.53 (14.70)
HADS Anxiety (0-21): mean (SD)	6.84 (4.06)	6.28 (4.02)
HADS Depression (0-21): mean (SD)	4.77 (3.36)	4.20 (3.10)
Compartmental distribution of radiographic OA – index knee		
Normal	133 (33)	105 (31)
Isolated tibiofemoral	18 (5)	12 (3)
Isolated patellofemoral	90 (23)	87 (25)
Combined tibiofemoral and patellofemoral	158 (40)	139 (41)
Overall severity of radiographic OA - index knee		
Normal	133 (33)	105 (31)
Mild	111 (28)	104 (30)
Moderate/severe	155 (39)	134 (39)
Severity of knee effusion – index knee		
None	261 (67)	219 (66)
Mild	94 (23)	82 (23)
Moderate/gross	44 (10)	42 (11)
Nodal symptomatic hand OA	59 (15)	61 (18)
Previous knee injury		
None	244 (65)	216 (71)
Unilateral	101 (26)	67 (23)
Bilateral	35 (9)	15 (5)

	Periods of significant pain variability	
	≥1	**None**
	n=398	*n=363*
Time since onset of knee problem		
< 12 months	32 (8)	60 (16)
1 year to < 5 years	143 (36)	116 (35)
5 years to < 10 years	83 (21)	64 (19)
≥ 10 years	141 (35)	103 (30)
Duration of morning stiffness		
None	135 (35)	155 (46)
≤ 30 minutes	238 (60)	174 (50)
> 30 minutes	25 (6)	14 (4)
Knee given way during past month	129 (32)	91 (27)
Seen hospital doctor about knee	106 (27)	69 (20)
Frequent sedentary activity	43 (11)	27 (8)
Frequent moderate activity	211 (54)	186 (55)
Frequent vigorous activity	110 (28)	95 (28)

Figures are column percentages unless otherwise stated.

HADS Hospital Anxiety and Depression scale [54]; OA Osteoarthritis; PF-10 Medical Outcomes Study SF-36 Physical Functioning subscale [55]; SD Standard deviation; WOMAC Western Ontario & McMaster Universities Osteoarthritis Index [56]

† Derived from National Socio-economic Classification [57]

Factors associated with time to first period of significant pain variability

Based on the outcome of time to first period of significant symptom variability, baseline measures associated with a higher risk of symptom variability in the adjusted analysis were: younger age (OR (per year): 0.96; 95% CI 0.94, 0.97), higher BMI (per kg/m^2: 1.03; 1.01, 1.06), higher WOMAC knee pain scores (per unit: 1.05; 1.03, 1.10), longer time since onset (e.g. 1-5 yrs vs < 1 yr: 1.79; 1.16, 2.75) and morning stiffness (≤ 30 minutes vs none: 1.43; 1.10, 1.85) (Table 5.5).

Table 5.5: Patient baseline characteristics associated with significant pain variability or potential flare based on discrete-time logit model (first outcome)

		Unadjusted		Adjusted*	
	Reference	OR	(95% CI)	aOR	(95% CI)
Male gender	Female	1.15	(0.92, 1.45)	1.22	(0.96, 1.55)
Age (years)	per year	0.96	(0.95, 0.98)	0.96	(0.94, 0.97)
Body mass index (kg/m^2)	per kg/m^2	1.05	(1.03, 1.08)	1.03	(1.01, 1.06)
Occupational class	Managerial/ professional				
Intermediate		0.90	(0.56, 1.45)		
Routine and manual		0.76	(0.51, 1.12)		
PF-10 physical function (0-100)	per unit	0.99	(0.99, 0.99)	ns	ns
WOMAC knee pain (0-20)	per unit	1.08	(1.05, 1.11)	1.06	(1.03, 1.10)
WOMAC knee function (0-68)	per unit	1.02	(1.01, 1.03)	mc	mc
Compartmental distribution of radiographic OA†	Normal				
Isolated tibiofemoral		1.03	(0.58, 1.81)		
Isolated patellofemoral		0.94	(0.70, 1.28)		
Combined tibiofemoral and patellofemoral		1.06	(0.81, 1.38)		
Overall severity of radiographic OA†	Normal				
Mild		0.94	(0.70, 1.25)		
Mod/severe		1.08	(0.82, 1.41)		
HADS anxiety (0-21)	per unit	1.04	(1.01, 1.07)	mc	mc
HADS depression (0-21)	per unit	1.07	(1.03, 1.10)	ns	ns
Previous knee injury	None			ns	ns
Unilateral		1.25	(0.95, 1.64)		
Bilateral		1.82	(1.17, 2.85)		
Time since onset of knee problem†	<1 year				
1 year to < 5 years		1.97	(1.29, 3.01)	1.79	(1.16, 2.75)
5 years to < 10 years		1.94	(1.23, 3.05)	1.82	(1.15, 2.89)
≥ 10 years		2.02	(1.32, 3.08)	1.82	(1.18, 2.82)
Duration of morning stiffness†	None				
≤ 30 minutes		1.63	(1.28, 2.07)	1.43	(1.10, 1.85)
> 30 minutes		2.26	(1.34, 3.81)	1.44	(0.83, 2.50)

		Unadjusted		Adjusted*	
Knee given way during past month†	No	1.38	(1.08, 1.77)	ns	ns
Seen hospital doctor about knee†	No	1.61	(1.23, 2.10)	ns	ns
Severity of effusion†	None				
Mild		0.99	(0.77, 1.30)		
Moderate/gross		1.15	(0.79, 1.67)		
Nodal symptomatic hand OA	No	0.90	(0.66, 1.24)		
Frequent sedentary activity	No	1.59	(1.07, 2.35)		
Frequent moderate activity	No	0.85	(0.68, 1.07)		
Frequent vigorous activity	No	0.88	(0.68, 1.13)		

* Adjusted for all other variables; - indicates variables entered but not retained in multivariable model

† For index (most problematic) knee

HADS Hospital Anxiety and Depression scale [54]; OA Osteoarthritis; OR Odds ratio; PF-10 Medical Outcomes Study SF-36 Physical Functioning subscale [55]; WOMAC Western Ontario & McMaster Universities Osteoarthritis Index [56]; 95%CI 95 percent confidence interval

ns Non-significant in multivariable model

mc Variables omitted in the multivariable model due to multi-collinearity

Factors associated with recurrent periods of significant pain variability

Based on the outcome of recurrent periods of significant symptom variability, i.e. allowing for those experiencing more than one episode, baseline measures associated with a higher risk of potential symptom variability in the adjusted analysis were: younger age (0.94; 0.91, 0.98), higher BMI (1.04; 1.00,1.08), higher WOMAC knee pain scores (1.10; 1.03,1.17), longer time since onset (e.g. 1-5 yrs vs < 1 yr: (2.23; 1.11, 4.46), and morning stiffness (≤ 30 minutes vs none: 1.67; 1.07, 2.61) (Table 5.6). Longer time since onset and morning stiffness had a slightly stronger association in comparison to the time to first episode of symptom variability analysis.

Table 5.6: Patient baseline characteristics associated with significant pain variability or potential flare based on discrete-time frailty model (recurrent outcome)

		Unadjusted		Adjusted*	
	Reference	OR	(95% CI)	aOR	(95% CI)
Male gender	Female	1.30	(0.86, 1.97)	1.40	(0.93, 2.09)
Age (years)	per year	0.95	(0.92, 0.98)	0.94	(0.91, 0.98)
Body mass index (kg/m^2)	per kg/m^2	1.07	(1.02, 1.12)	1.04	(1.00, 1.08)
Occupational class	Managerial/ professional				
Intermediate		0.95	(0.53, 1.70)		
Routine and manual		0.77	(0.49, 1.22)		
PF-10 physical function (0-100)	per unit	0.99	(0.99, 0.99)	ns	ns
WOMAC knee pain (0-20)	per unit	1.12	(1.04, 1.21)	1.10	(1.03, 1.17)
WOMAC knee function (0-68)	per unit	1.03	(1.01, 1.05)	mc	mc
Compartmental distribution of radiographic OA†	Normal				
Isolated tibiofemoral		1.05	(0.49, 2.24)		
Isolated patellofemoral		0.93	(0.62, 1.40)		
Combined tibiofemoral and patellofemoral		1.07	(0.75, 1.53)		
Overall severity of radiographic OA†	Normal				
Mild		0.93	(0.63, 1.36)		
Mod/severe		1.10	(0.77, 1.57)		
HADS anxiety (0-21)	per unit	1.05	(1.00, 1.10)	mc	mc
HADS depression (0-21)	per unit	1.11	(1.02, 1.21)	ns	ns
Previous knee injury	No			ns	ns
Unilateral		1.27	(0.92, 1.76)		
Bilateral		1.96	(1.02, 3.79)		
Time since onset of knee problem†	<1 year				
1 year to < 5 years		2.38	(1.14, 4.97)	2.23	(1.11, 4.46)
5 years to < 10 years		2.32	(1.10, 4.89)	2.20	(1.08, 4.48)
≥ 10 years		2.40	(1.18, 4.92)	2.11	(1.12, 4.05)
Duration of morning stiffness†	None				
≤ 30 minutes		2.23	(1.17, 4.23)	1.67	(1.07, 2.61)
> 30 minutes		3.75	(1.16, 12.16)	1.71	(0.73, 3.98)

		Unadjusted		Adjusted*	
	Reference	OR	(95% CI)	aOR	(95% CI)
Knee given way during past month	No	1.42	(1.06, 1.90)	ns	ns
Seen hospital doctor about knee	No	1.89	(1.41, 3.13)	ns	ns
Severity of effusion	None				
Mild		0.99	(0.69, 1.42)		
Moderate/gross		1.18	(0.72, 1.92)		
Nodal symptomatic hand OA	No	0.80	(0.48, 1.35)		
Frequent sedentary activity	No	2.00	(0.96, 4.19)		
Frequent moderate activity	No	0.79	(0.56, 1.13)		
Frequent vigorous activity	No	0.79	(0.51, 1.23)		

* Adjusted for all other variables; - indicates variables entered but not retained in multivariable model

†relates to index (most problematic) knee

Hospital Anxiety and Depression scale [54]; OA Osteoarthritis; OR Odds ratio; PF-10 Medical Outcomes Study SF-36 Physical Functioning subscale [55]; WOMAC Western Ontario & McMaster Universities Osteoarthritis Index [56]; 95%CI 95 percent confidence interval

ns Non-significant in final model

mc Variables omitted in the multivariable model due to multi-collinearity

5.5 Discussion

This study estimated that up to a third of adults aged over 50 years with knee pain experienced significant symptom variability or disease flare. These were associated with younger age, longer duration of knee problem, higher BMI and more severe knee symptoms at baseline. Potential flare-ups were also more common in males, those who reported prior bilateral knee injury, regular sedentary behaviour, increased functional limitation, and higher baseline scores for anxiety and depression scores although these correlations were not statistically significant after covariate adjustment.

Estimates of flare frequency vary depending on definition used, period of time and frequency of data collection. In this study the definition of 'significant pain variability' used was based on recall to provide an initial approximate estimate of what proportion of people with knee symptoms/OA might experience symptom variability over a 6-month period. In previous studies, estimates amongst those with osteoarthritis ranged from 37-78% (55, 61, 73) . Results from this study may be an underestimate of actual frequency within this population due to one off measurements recording pain at 18 month intervals. The definition of symptom variability or 'flare' used in this study is limited to worsening of symptoms and a minimum threshold. However, as noted by Marty (55) and in consensus work on flare-ups in other musculoskeletal conditions (271, 272), flare-ups are most likely to consist of a number of components. Information that was shown to be important in the systematic review (Chapter 4): speed of onset, duration, associated features (e.g. stiffness, swelling) and change in medication usage was not available in this data. These features may be important in distinguishing flare-ups from day to day variability in symptoms.

Associations found in this study are comparable for some studies but not others. Increased BMI has been shown to be associated with increased risk of flares in other studies (273). In previous case-crossover studies physical activity (203), buckling and knee injury (75), and worsening mental health (74) have been associated with flares. This study did not find a significant association with these factors which may be due to the need to consider these factors as time-varying, proximal triggers. No correlation was found between severity of radiographic OA and flares in this study which suggests flares may occur throughout the disease course. Removing those who had a TKR during study follow up is likely to have removed those with more severe disease from the analysis. This may partly explain the lack of correlation between severity of radiographic OA and flares, as those who went onto have a TKR may have been more likely to experience flares.

Frequency of flare-ups in this study is less than has been reported in other studies. Ricci et al's (73) estimate from telephone consultations of US workers found that 38% of those aged 45-65 years reported exacerbations. A similar magnitude of pain increase was used to define exacerbation (2 or more on a 0-10NRS), however a 2-week recall period was used.

An important limitation of this study is the potential misclassification bias as a result of recall error. It is hypothesised that patients with increased pain closer to the measurement time points may have overestimated their average and worst pain scores whereas those with fewer pain fluctuations or no increase in pain close to the measurement time points are likely to have underestimated their pain scores over the previous 6 months. The overall impact of this on the results is uncertain. In addition, the long period of recall may be particularly prone to 'forward telescoping' where an event is reported more recently than it actually happened (274). In this analysis

‘average’ and ‘worst’ pain scores were taken from the Von Korff pain grade. These were chosen as they were similar but unfortunately not comparable to outcomes used in flare design trials. Flare-ups are identified in drug withdrawal trials by comparing baseline pain scores to worst pain scores. These limitations are only likely to be resolved by prospective studies with frequent repeated measures over clinically relevant time periods incorporating the concept of pain variability.

Limitations of using secondary datasets include the potential for the study population and measures available to not match what the secondary data researcher would have collected, and it may be difficult to fully understand the data collection processes or why certain tools were selected to gather data (90, 91). If I was involved in the design of the secondary dataset I would have tried to overcome some of its limitations. This would have included measuring time-varying variables such as mental health markers, BMI and physical activity at all data collection time points as my secondary analysis was not able to detect short term changes in these variables and assess their impact. Furthermore, I would have asked about patient recall of flares over the previous 6 months and compared this to the imposed definition of flares that I used in this study. This would have given an estimate of self-reported flare frequency and how this item compared with an imposed definition.

This study has given a preliminary estimate of frequency of symptom variability and factors associated with them. These findings will help in the design of the diary study both in terms of estimating sample size but also to help decide on which factors to assess in the daily diary study. Interviews with patients will help gain an insight into triggers patients believe are attributable to flares and how and if they explain the differences between flare-ups and symptom variability.

5.6 Conclusion

The results from this study have shown that up to a third of community dwelling symptomatic adults recall significant variability in their knee pain in a given 6 month period. Younger males may be a higher risk group for experiencing symptom variability which may be occupation related and may be an area of focus for further research. Daily intensive longitudinal measurement may help give a more precise measure of frequency estimates of flares, allow them to be more accurately described and discover if associated factors in this secondary analysis are consistent. The following chapters will report on a cross-sectional survey and a daily diary study which will explore the natural history of flares in further detail.

6. ‘Acute flare-ups’ in patients with, or at high risk of knee osteoarthritis: a cross-sectional survey

Building on flare definitions used in previous studies, this chapter reports a study that uses patient recall of flares to estimate flare frequency, determinants of flares, and variables associated with them. Importantly, it also establishes participants’ baseline or ‘normal’ level of knee symptoms which was critical for the linked study presented in Chapter 7. A consideration of developmental work and lay member input will be presented prior to the methods and results.

6.1 Developmental work

The developmental work for both the cross-sectional survey and diary study (Chapter 7) are inextricably linked. They will therefore be presented together in this chapter.

The systematic review (Chapter 4) revealed disparity in the way flare-ups of knee osteoarthritis were being defined in the medical literature and highlighted the paucity of evidence for which these definitions were based on. The secondary analysis of cohort data undertaken in Chapter 5 was an exploratory study which gave an estimate of flare frequency but also identified important potential associated factors with flare-ups. These two key pieces of work informed the definition for flare-ups used in the cross-sectional and diary study and identified key factors of interest to be explored further; for example, duration of knee problem, previous knee injury, BMI, physical activity measures, and questions on symptoms such as knee stiffness. At the time this study was designed, to my knowledge, there were no other studies that had set out to identify factors associated with flares. Ricci et al, who aimed to explore

the relationship between OA pain exacerbation and lost productive time at work in the US found that exacerbations were more likely in those who were younger and female, although non-significant (73). However, this study is limited in that it was a telephone study conducted during the day time which may not be generalisable to the entire working population.

The items included in the cross-sectional survey were informed by a number of sources including standardised questions previously used in studies; for example, those capturing demographical data and from other larger scale studies, such as the Osteoarthritis Initiative which was used to establish the presence of knee symptoms and previous knee injury. These studies were also a source of estimates for anticipated response rates and consent rates.

The format and duration of data collection of the diary, length of the data collection instrument and methods to improve response rates and completeness of data entry were informed by: i) a non-systematic search conducted 2011-12 to identify daily diary studies in the literature (63, 98, 101, 102, 275), ii) the SPCSC Patient and Public Involvement and Engagement (PPIE) group, and iii) discussion with SPCSC experts with experience in diary studies.

The domains of interest that were included in the diaries for example, the pain descriptors and knee symptoms were adapted from previous studies (53, 55, 276, 277). The methods for recruitment were informed by the PPIE group, SPCSC experts, and the West Midlands North Clinical Research Network team who also advised on the number of practices to approach to reach the necessary response rate.

The SPCSC's Clinical Trials Unit's Standard Operating Procedures (SOP) were consulted for information on standardised and validated data collection instruments and study procedures. This was complemented by completion of in-person Good Clinical Practice training which covered the wider role of research within the NHS, standards, study set up, informed consent, data entry and safety reporting.

The knee was chosen because it is the most common joint affected by knee osteoarthritis (278), diagnostic criteria include those 45 years and over (2), and clinical signs are easily recognisable, for example, swelling (55).

6.1.1 Patient and Public Involvement and Engagement

The aims of PPIE group in relation to the cross-sectional survey and daily diary study were:

- To ascertain overall acceptability of the studies
- Discuss format and design of the data collection instruments
- Discuss content of the data collection instruments
- Discuss strategies to improve response rates of the data collection instruments
- Advise on individuals to approach for the study and how best to approach them
- Advise on acceptable terminology

Two meetings were held with the PPIE group 11 months apart. Both meetings were attended by members of the research team, a lay facilitator, and a senior researcher with responsibility for oversight of the group. At the first meeting six PPIE members attended and nine were present at the second.

The length of the diary stage of the study was discussed and it was advised that twelve months would be too long, and that six months might be more acceptable. The group felt that the length of the diary stage depended on how often these flare-ups occur. It was suggested that they might not be more frequent than every 2-3 months and estimated that each individual would contribute a maximum of 2 flare-ups in a 6-month period.

Discussion on the format of the diary centred on participants themselves graphing their symptoms versus entering data through the use of tick boxes and numbers. It was suggested that there should be one page per day to minimise potential for people to modify their entries in response to previous days or weeks.

Several members of the PPIE members had previously been involved in diary studies. Although incentives were not specifically discussed the group strongly supported the idea of reading the diary entries when they came in (possibly entering the data at the same time) and keeping in touch with people during the study (such as by telephone). Participants could be offered the option of whether they wanted to be contacted.

With respect to diary content, it was advised to discuss this with other researchers within the SPCSC who had undertaken diary studies particularly those that were about OA although it was noted that most of these differed from the current proposal in collecting qualitative data and adopting a flexible, participant-centred approach to diary entries. Copies of published articles from these studies were forwarded to the research team for consideration (275, 279).

The group agreed that pain intensity should be included. There were no objections to swelling, stiffness, nocturnal pain and limp. It was also mentioned that weather and fatigue, which may be an early warning sign, should also be included. This naturally led on to discussions on potential triggers for flare-ups. A striking point made by members of the PPIE group was that people may consciously undertake activities that they know will result in a flare-up but judging that it was worth the consequences ('pay for it later'). This may reflect concepts of activity-rest cycling (280) and activity pacing (281) that have been described in chronic pain management. It was also noted that participants may already have established patterns of activity avoidance to reduce or prevent the occurrence of flare-ups. Although the exact implications for this on study design were not fully explored there was encouragement for the study to explore this and for the research team to consider collecting self-reported information on potential triggers. Linked to this was the role of medication in masking pain. Without knowing what analgesia individuals were taking, it would be difficult to interpret pain intensity ratings. A range of other possible factors, namely seasonal variation due to patterns of activity (e.g. gardening) were also mentioned.

On the issue of selecting potential participants, two main points were made in the discussion. Firstly, that the nature of osteoarthritis flare-ups may vary markedly between joints and this implied the need either to focus the study on a particular joint (e.g. knee) or to record the joint site being reported and be cautious of combining data from different joints in the analysis. Secondly, there was support for a pre-diary questionnaire to: (a) identify potential participants who have a recent history of flare-ups; (b) collect descriptive information (e.g. duration of problem, treatments). This stepped approach would identify those with recent history of flare ups and those willing to take part and comply with the diary stage.

The discussions were, in general, highly constructive and the response was supportive. The PPIE members also helped refine the outcomes of the study and suggested a number of future avenues for research arising from this work. They advised that this study might help identify early warning signs for a flare-up and that this might lead to the development of interventions. It was thought that diaries could be used as an educational tool for patients with long term conditions in order to help them understand the pattern of their symptoms and identify any potential triggers for increases in their pain. In addition, findings could help educate patients with newly diagnosed knee OA. Furthermore, the study could help identify if flare-ups do exist and if there are shared features across patients.

The PPIE recommended several features that could encourage diary completion and minimise respondent burden. These included having a bright colour for the cover of the diary to ensure that it stood out and acted as a reminder to the patient, using a minimum of 12-point font, and having one day per page with the day clearly labelled at the top of the page. To ensure conformity in answering questions, it was recommended to use tick boxes for all questions. The use of a filter question, to direct participants to fill out all of the items for the day or just a reduced number based on whether their pain score had changed from the previous day, was discussed but the PPIE group felt that this was too confusing and that it would not be much extra burden to ask participants to fill out all questions every day.

The wording was discussed and it was agreed to avoid using the terms that patients may not understand such as; ‘exacerbation’ or ‘flare-up’ in the patient literature but instead to use ‘we understand that symptoms can go up and down, we are interested in....’. This lack of clarity in terminology was seen also among published studies that

used a variety of terms and phrases to denote an exacerbation or flare-up (See Chapter 4). The terminology for the patients' usual or normal pain for them was discussed and it was decided that 'normal for me' should be used. It was also recommended that all questions be in the same format to avoid confusion and ensure it was clear what the patient should do, such as 'tick box' or 'write comment'.

There were miscellaneous comments regarding the format and content of specific sections of the diary. For example, for knee pain descriptors the PPIE members felt that some patients' pain might not fit into the suggested descriptors included, and they proposed the addition of an 'other' response option box with space for comment.

Finally, on the inside of each diary, and in the patient information sheet, tips for remembering to fill out the diary were included as suggested by the PPIE members. Tips included leaving the diary on the nightstand, next to the television, or near evening medication.

Summary and critical reflection

Table 6.1 provides a summary of the main observations and proposals made by PPIE members over the two meetings, the decision made for the main study design and any relevant comments or justification for those decisions.

The PPIE group were invaluable in determining the main study design, they helped modify the aims and objectives, and their feedback on format of the diary and wording of questions was informative. The main advice adopted included font, layout and colour, and wording of questions and responses. The PPIE group were keen to explore psychological impacts of pain and fatigue however that was beyond the

scope of this research; nevertheless this was identified as an area for future research.

Table 6.1: Summary of observations and proposals at PPIE meetings and final decisions on main study design

Aspect	PPIE group observation/proposal	Decision for main study design	Comments/justification
Length of diary stage	12 months too long; consider 6 months	3 months	Following discussions with researchers who had previously completed diary studies 3 months was agreed as a suitable time length as longer periods had worse compliance rates
Diary format	Monthly/weekly format might encourage people to modify entries in response to previous days; try day per page	One day per page	
Engagement with participants	Read diaries as they are returned; offer option of telephone contact during study period	No telephone contact planned; monthly thank-you letters with reminder of the number to contact if they should have any queries	The ethical review committee thought that regular telephone follow-up would be burdensome for patients. Furthermore, there were resource implications with making regular telephone contact (no independent study co-ordinator or research nurse; insufficient administrative resource)
Diary content	Discuss and learn from lessons from previous diary studies with SPCSC researchers	Completed	
	Include items on weather and fatigue	Not included	Not main objective; concern regarding respondent burden
	Offer ‘other’ option for pain descriptors	Adopted	
	Gather information on triggers	Information on selected physical triggers included	Emotional triggers and life events not included. These had been studied previously (e.g. Wise et al., 2010) and concerns again re respondent burden
	Information on analgesia may be needed to interpret pain ratings	Adopted	Challenge to find suitable short format of questions (type, dose, frequency, accuracy of report, respondent burden)
Selection/recruitment of participants	Nature of flare-ups likely to vary between joints	Restrict to knee	

Aspect	PPIE group observation/proposal	Decision for main study design	Comments/justification
	Use stepped approach to recruitment	Adopted; cross-sectional survey then daily diary to consenting responders	
Encouraging diary completion / minimising respondent burden	Use bright coloured cover	Adopted	
	12 point minimum font	Adopted	
	Clearly label each day	Adopted	
	Use standard tick box response options where applicable	Adopted	
	Remove daily filter question	Adopted	Potentially increases respondent burden by requiring completion of all questions everyday but this was felt on balance to be better than potentially confusing filter question and loss of data
	Include list of tips on remembering to complete the diary	Included on the inside of each diary, and in the patient information sheet	
Terminology / language / jargon	Avoid using the terms ‘exacerbation’ or ‘flare-up’; instead ‘we understand that symptoms can go up and down, we are interested in....’	Adopted	
	Use “‘normal’ for me”	Adopted	

6.2 Aims and objectives

Aim

The overall aim was to identify self-reported flares and associated risk factors among participants with, or at high risk, of knee osteoarthritis.

Objectives

In a sample of community dwelling adults with, or at high risk of symptomatic knee osteoarthritis:

- Estimate flare frequency based on patient recall in the previous 12 months
- Explore association of self-reported flares and selected risk factors
- Establish participants 'normal' knee symptoms (linked to subsequent diary study (Chapter 7)

6.3 Methods

6.3.1 Study Design Type

Observational study, comprising a cross-sectional survey component and a longitudinal daily diary component (detailed methods in Chapter 7).

6.3.2 Setting

Two General Practices based in market towns in Shropshire.

6.3.3 Sampling and Recruitment

Target Population

The target population were community-dwelling adults with, or at high risk, of knee osteoarthritis. Inclusion and exclusion criteria for the cross-sectional survey are listed in Table 6.2.

Table 6.2. Inclusion and exclusion criteria for cross-sectional survey

Inclusion criteria
Aged 45 years and over
Registered with a participating practice at the time of the survey
Read-coded consultation for knee osteoarthritis or knee pain/arthralgia in the previous 2 years
Male or female
Exclusion criteria
No knee pain in the last 12 months
Patient reported diagnosis of inflammatory or crystal disease (rheumatoid arthritis, ankylosing spondylitis, polymyalgia rheumatica, gout)
Previous total knee replacement in index knee
Those judged to be vulnerable/inappropriate to survey by their general practitioner (e.g. dementia, terminal illness)

Sampling frame

Population registers from local general practices was chosen as the sampling frame in order to obtain a sample of primary care patients. Adverts in local papers were thought to be too costly, had ethical implications and would create extra administration in terms of having to notify participants GP**.** Orthopaedic clinics were initially considered but ultimately not used due to the fact that patients in this setting would selectively represent those with more severe disease; intermittent pain has been shown to occur in those with milder, less advanced osteoarthritis and so may have been missed (53). It is difficult to assess the adequacy of this sampling frame due to the challenge of estimating the proportion of the population registered with a general practice. This is due to inaccuracy of population registers and over-counting

amongst general practices (282)**.** Attempts have been made using hospital attendances in England by unregistered patients, to estimate inpatient and outpatient attendances in 2009/10 (which were 99, 000 and 370, 000 respectively) (283). The majority of these patients were male and either asylum seekers, prisoners, homeless or military personal. It is likely that our sampling frame did not have coverage of these groups.

Sampling method

Census sampling of adults aged 45 years and over registered with participating practices at the time of the study and with evidence of a consultation for knee osteoarthritis or knee pain/arthralgia in the previous 2 years.

Sampling procedures

Participants involved in this study were recruited from general practice members of the Primary Care Research Network (PCRN) of Central England North Spoke. Participating practices were given a study pack containing the study protocol and data collection instruments (cross-sectional survey: Appendix C; Sample Diary: Appendix D) and the patient information sheet (Appendix E)

Using electronic registers, all registered patients aged 45 years and older at the time of the study, with a Read-coded general practice consultation for knee osteoarthritis or knee pain/arthralgia in the past 2 years were identified (Appendix F). This list was given to the patients' general practitioners, who were asked to exclude patients who were in vulnerable groups; for example, those patients with new onset dementia or severe/terminal illness.

Members of the West Midlands Clinical Research Network downloaded details of potential participants from the electronic registers. All participants were given a unique study identification number, to allow anonymisation of data. A secure database was designed for this study to ensure the protection of confidential information.

6.3.4 Data Collection Procedures

The SPCSC's standard three-stage mailing procedure of initial mailing-reminder-repeat mailing was used.

Stage 1: Potential participants were sent study packs including a cross-sectional survey (Appendix C), patient information sheet (Appendix E), and sample diary template (Appendix G), together with a cross-sectional survey cover letter (Appendix H) from their general practice inviting them to take part in the study; this was mailed in June/July 2013. Participants were asked to complete their cross-sectional survey and provide written informed consent to take part in the diary study on the final page. All patients were given the contact number of a researcher working on the project who would give any other information about the project as needed.

Stage 2: Non-responders at 2 weeks were sent a reminder postcard (Appendix I).

Stage 3: Non-responders at 4 weeks were sent another study pack with reminder Cover Letter from their general practice (Appendix J).

Non-responders after 6 weeks were assumed to have declined participation and were not contacted again for the study.

Replies to the cross-sectional survey mailing were collected and logged on the survey mailing database. Responses to pre-selected questions were also inputted, at this stage, into the mailing database in order to identify eligible participants for the diary stage of the study.

Patients who indicated they did not wish to take part in the cross-sectional survey had this recorded in the database and all their identifiable data was stripped from the mailing database at this point. If patients returned the cross-sectional survey but declined to participate in the diary study, this was recorded and data from the survey inputted. They received no further mailing.

6.3.5 Data Collection Instrument

Cross-sectional survey

The initial step in data collection was a 5-page, self-complete survey. The cross-sectional survey contained 29 questions, split into 4 sections: (1) participant's knee pain in their worst affected knee and exclusion of selected non-OA causes of knee pain; (2) participants knee symptoms on a 'normal' day for them; (3) demographic data and general health; (4) consent to take part in the diary study (Table 6.3) (Appendix C).

The purpose of the cross-sectional survey was to:

- Gather simple descriptive information on participants and non-consenting responders, including their recall of flare-ups in the past 12 months.

- Permit the exclusion of non-eligible responders.
- Obtain written informed consent to take part in the diary study
- Establish a baseline level of 'normal' pain severity and analgesic intake for participants against which researchers and participants can judge day-to-day variations in the diary study.
- Establish frequency of self-reported flare-ups
- Explore risk factors associated with flare-ups

Section One-Knee Symptoms

Items in section one collected data on current and past knee symptoms, healthcare utilisation and established whether a flare-up of knee pain had occurred in the previous 12 months (Table 6.3). Of particular note, self-reported recalled frequency of acute flare-ups of knee pain in the past 12 months was defined using the following single item: "In the **last 12 months** how many times have you had an increase of your knee pain (that is times when your knee pain is worse than normal which may have stopped you from doing your normal activities or meant you have had to take or increase your pain medication)?". This item was created de novo as a validated patient self-report measure for identifying OA flare-ups does not exist. The phrasing of the item was adapted from results of the systematic review in Chapter 4, from wording of flares in other chronic diseases (117, 137, 140) and with help from the SPCSC's PPIE group.

Section Two-What is 'normal' for me?

Items in section 2 reflected the questions that were included in the diaries. These were based on a daily diary card produced by Trappenburg et al for patients with

COPD (97). They established the participants' baseline symptoms by asking them to describe 'what is normal for me'.

Section Three- demographic data

Section three collected demographic and lifestyle data and were largely reproduced from standardised questionnaires used within the SPCSC.

Table 6.3: Items included in the cross-sectional survey

Domain	Empirical measure
Demographic/ socioeconomic	
Age	Free text
Sex	Female/ male
Lives alone	Yes/no
Marital status	Married, separated, divorced, widowed, cohabiting, single
Ethnicity	White UK or European, African, Afro-Caribbean, Asian, Chinese, other
Employment status	Employed, not working due to ill health, retired, unemployed/seeking work, housewife/husband, other
Job title	Free text
Job title for most of working life	Free text
Educational attainment	O-level/ CSE/GCSE or equivalent, A-level/BTEC/HNC or equivalent, degree or postgraduate education, other work related or vocational qualification, other qualification, no qualification
Lifestyle	
Smoking status	Never smoked, previously smoked, currently smoking
Alcohol consumption	Daily or most days, once or twice a week, once or twice a month, once or twice a year, never
Height and weight	Free text
Current/previous knee symptoms	
Presence of knee symptoms	Pain, aching or stiffness in left or right knee in past 12 months (yes/no for each knee) (284)
Worst affected knee	Right/left
Pain intensity	Normal level of pain intensity (0-10 NRS), adapted from IMMPACT (285)
Description of knee symptoms	Normal day: knee swelling, limping, knee stiffness for more than 20 minutes, being woken at night by knee pain (yes/no for each), adapted from (55)
Pain descriptors	Normal day: dull, throbbing, numbness, sharp, aching, burning, stabbing, pins & needles, other (yes/no for each), adapted from (53, 276, 277)
Knee history	
Total length of history from problem onset	1 year or less, 2-5 years, 6-10 years, more than 10 years, adapted from (92)
Frequency of flare-ups in past 12 months	0, 1-2, 3-4, 5-6, 7-8, 9-10, more than 10
Previous knee injury	Yes/no (284)
Knee-related healthcare utilisation	
GP consultation	Whether the GP has been consulted for knee pain in past 12 months (yes/no)

Domain	Empirical measure
Previous knee replacement surgery	Yes/no (left/right/both)
Medication	Normal day usage of prescribed or over the counter medication (yes/no; State name, dose, regular/as needed)
Past medical history	
Inflammatory knee pain	Previous diagnosis: polymyalgia rheumatic, rheumatoid arthritis, gout, ankylosing spondylitis (yes/no for each)
Physical activity exposures	
Potential triggers	Normal day, undertake following activities: kneeling for 30 minutes or more, climbing more than 5 flights of stairs, lifting/moving heavy objects, squatting for 30 minutes or more, climbing ladders (yes/no for each), adapted from (32)
Vigorous physical activity	Times a week 20 minutes or more vigorous intensity physical activity (none, 1-2 times, 3 or more), adapted from (286)
Moderate physical activity	30 minutes or more of walking; 30 minutes or more of moderate intensity activity (none, 1-2, 3-4, 5 or more for each), adapted from (286)

BTEC Business and Technology Education Council; CSE Certificate of Secondary Education; GCSE General Certificate of Secondary Education; GP General practitioner; HNC Higher National Certificate; NRS Numerical rating scale

6.3.6 Database and Data Handling

In line with the SPCSC's Research and Governance Framework all personal identifiable information were kept separately from the cross-sectional survey and diary database during the mailing period. Participants were identified by the study codes. Only the research team had access to the research data and this information was kept on the SPCSC's central network secure drive. No information on patients' details or research data were stored on personal computer hard drives, laptops, disks, or other means where data could be transferred. Future linkage of the study codes to personal identifiable data may only be achieved through re-contacting the patients' GP.

There are secure, physical storage arrangements for the hard copy data at the SPCSC within lockable filing cabinets. Personal information in the questionnaire, such as on the consent form, was removed on arrival to SPCSC and locked in cabinets. In addition, any hard copy research data that has been printed for checking, will be destroyed by shredding. The SPCSC also operates a key code entry system to ensure only appropriate persons are within the building.

All staff at the SPCSC have an explicit requirement with the duty of confidentiality, equivalent to standards maintained within the NHS and written into their contracts of employment. Staff induction includes training and awareness relating to data security and confidentiality and the Data Protection Act. Identifiable data is only held as long as it is needed and removed as soon as is feasible.

Data collected from the cross-sectional survey and diaries (Chapter 6 and 7) were manually inputted by myself into a customised Microsoft Access database. One in ten checks were performed at all stages by the study administrator.

Data cleaning

Data cleaning was undertaken by myself and the study statistician to ensure accuracy of inputted data. Prior to data analysis the data was checked for missing data, anomalies and any ambiguous data.

During the data cleaning process frequency tables were produced for variables to check for missing data, check the coding of the missing data and to check that coding was within the acceptable range. Where anomalies were identified the original

questionnaire or diary was referred back to for clarification. Any errors that were found were described.

One in ten checks for accuracy of inputted data was performed for the cross-sectional survey and monthly diaries by the study administrator. Out of the 11 sampled cross-sectional surveys, one error was reported where 11.0 stone was recorded instead of 11.9.

Derived and recoded variables

The variables were labelled and recoded accordingly. Body mass index (BMI) was calculated from height and weight and categorised for analysis into normal, underweight, and overweight using established cut-offs. For several variables categories were collapsed due to insufficient numbers within one or more of the original categories

6.3.7 Ethical Considerations

The study was submitted for proportionate ethical review to the North of Scotland NRES committee on 29th April 2013. REC reference: 13/NS/0049. Favourable ethical approval was received on 7th May 2013 following minor amendments (Appendix N).

6.3.8 Statistical Analysis

Power Calculation

The selection of the survey sample size was based not on formal power calculations but on practical considerations of feasibility and cost with attention ultimately on potential numbers of responders likely to participate in the linked diary study. Based on an annual person-consulting rate for diagnosed knee osteoarthritis of 69 per 10,000 registered population, and 170 per 10,000 if knee pain/arthralgia cases were also included, it was anticipated that three practices with an average registered population of 6,000 each, would provide approximately 306 potentially eligible participants. Searching the previous 2 years was expected to increase this by a factor of 1.67 on the assumption that a third of consulters in a given year also consult in the previous year, which gave an estimated 511 potentially eligible responders. Response rates for observational daily diary studies range from 37-54%, however most diary studies are only for a period of one month. Response rates to previous SPCSC (School for Primary, Community and Social Care) studies using a single postal questionnaire in this age group tended to range from 50-70%. Using a range of conservative estimates: 50-70% response to cross-sectional survey, 80-90% responders' eligible, gives an estimated response rate of 204-322 survey responders.

Analysis

The primary planned analysis is briefly summarised below. The data were analysed using Stata Version 13 (Stata Corporation, College Station, Texas, USA).

Flow of response

A flowchart was completed to summarise the flow of participants from the initial mailing through to analysis.

Evaluation of selective response

The response rate to the cross-sectional survey was calculated.

Key baseline patient characteristics (age, sex) were compared between responders and non-responders using descriptive statistics; mean (SD), median (inter-quartile range) or frequencies (percentages) as appropriate.

Descriptive characteristics and missing data

After excluding ineligible responders, such as history of inflammatory disease, previous TKR, no knee problem last 12 months, the descriptive characteristics of eligible responders were summarised using descriptive statistics as previously mentioned. Within eligible responders, the amount of missing data for each questionnaire item was also described.

Frequency and determinants of recalled flare-ups

A flare-up, in the cross-sectional survey was determined using patient recall of increases in knee pain in the previous 12 months that stopped the participant from doing their normal activities or led to an increase in pain medication. This was presented using simple percentages.

Variables potentially associated with recalled flare-ups

A number of baseline factors were examined for an association with recalled flare-ups. These were chosen based on results from the secondary analysis performed in Chapter 5.

- Demographic variables: age, gender, living alone, marital status, employment status, socioeconomic class (individual occupational class), ethnicity, educational attainment
- Lifestyle variables: alcohol, smoking status, physical activity, BMI
- Knee related: previous knee injury, duration knee problem, normal knee pain intensity, normal knee symptoms

The frequency of flare-ups was categorised into three groups; 0-2 flares, 3-10 and over 10. These were chosen as there were a subset of participants reporting 10 flares or more so the decision was made to divide the sample into those who reported flares frequently, moderately or infrequently. Ordinal logistic regression was initially performed to analyse for any association between these groups and the predictor variables (287)**.** This method keeps categories ordered unlike multinomial models for example. The model has to meet a number of assumptions, the most important being the proportional odds assumption, assuming the same effects for different cumulative logits i.e. each independent variable has the same effect at each cumulative split of the ordinal dependent variable (287, 288) .

Univariable models were fitted initially. Variables for the univariable model were chosen based on previous known associations from previous studies (289). Each variable was then tested for the proportional odds assumption using firstly a

likelihood ratio test with the null hypothesis that there is no difference in the coefficients between the cumulative response categories and then a Brant test (290). A significant test statistic ($p<0.05$) indicated that the assumption had been violated. The assumption was violated for 4 variables (climbing stairs, NRS, aching, and walking) and for 4 variables the Brant test could not be calculated due to insufficient numbers (squatting, numbness, stabbing, pins and needles). As the proportional odds assumption was not met for all variables, a generalised ordered logit model also known as the partial proportional odds model (291) was used. This model takes into consideration the potential different weightings of the categories and produces a regression coefficient for each of the compared groups (290). The model was fitted using gologit2 routine in Stata (292)

For variables where the proportional odds assumption was not met, two sets of odds ratios were estimated, one comparing the category 0-2 versus (3-10, and >10) and the second comparing category (0-2, and 3-10) to >10. The effects of the variables that met the proportional odds assumption was presented as one parameter and interpreted similar to ordinal logistic regression model.

The method used for the multivariable model involved two stages. The first step involved selecting variables from the univariable model which had a p value of ≤0.20, this is the alpha level for rejecting the null hypothesis (267). A test of multicollinearity was then performed. This was done by first examining the correlations (continuous) and associations (categorical) between the independent variables, followed by multicollinearity diagnostic statistics for linear regression analyses (variance inflation factor) to check for the existence of multicollinearity when several potential predictors are adjusted for simultaneously (269). A variance inflation factor of greater than 5

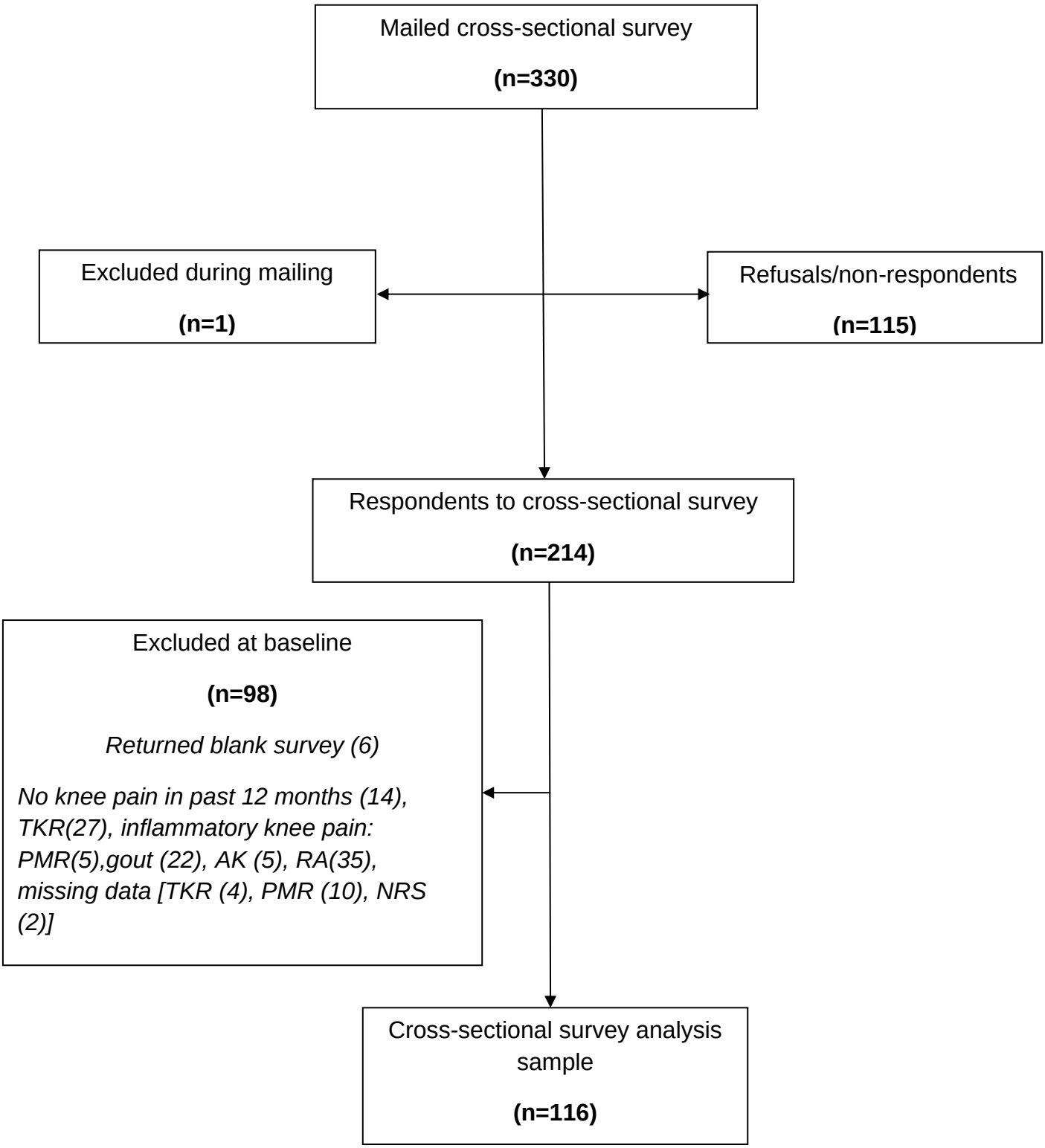
was considered as evidence of collinearity. All variables that were not correlated were included in a multivariable model and a manual backward elimination performed to remove variables from the multivariable model until only variables with a *p*-value <0.05 were retained in the final model .

6.4 Results

6.4.1 Response rate

The survey was mailed out to 330 adults aged 45 years and over at two general practices. There were 214 responders (67%) (Figure 6.1).

Figure 6.1: Flowchart of baseline response for cross-sectional survey



Compared with non-responders, responders to the cross-sectional survey were more likely to be female, older, and to live in less deprived neighbourhoods (Table 6.4).

Table 6.4: Comparison of survey responders and non-responders

	All mailed participants *(n=330)*	Non responders *(n=116)*	Responders *(n=214)*
Female gender, n (%)	182 (55)	61 (53)	121 (57)
Age (years), mean (SD)	63.8 (11.7)	62.4 (12.5)	64.6 (11.2)
Area-level deprivation†, n (%)			
Most deprived	110 (33)	45 (39)	65 (30)
Middle	137 (42)	46 (40)	91 (43)
Least deprived	83 (25)	25 (22)	58 (27)

† Tertiles of Index of Multiple Deprivation based on patient postcode

Completeness of data items

Of 38 variables, 5 had no missing, the median percentage missing for the remaining 33 items was <3%, with 8 items having >5% missing (pain in left knee, pain in right knee, worst knee, kneeling, climbing stairs, heavy lifting, squatting and climbing ladder.

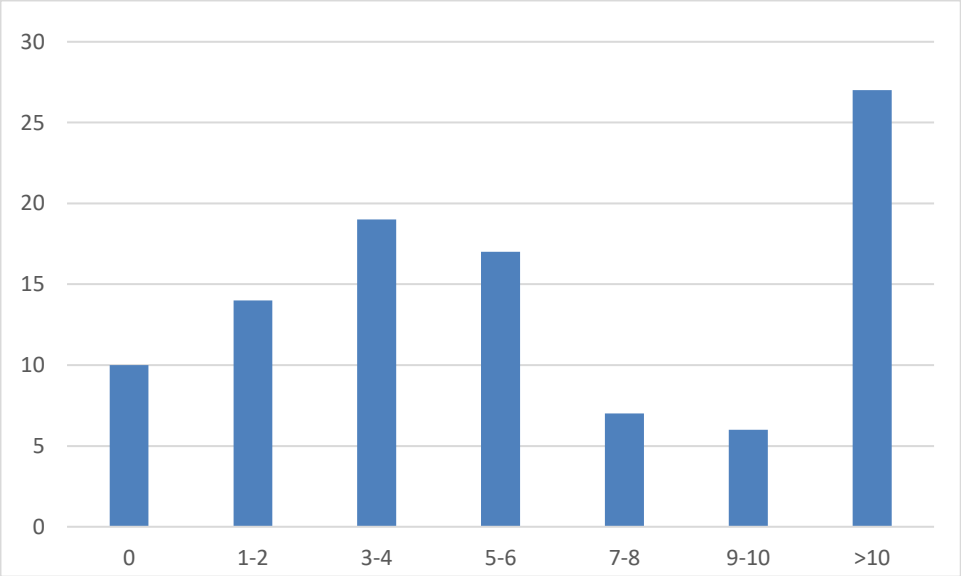
6.4.2 Responders eligible for inclusion in cross-sectional survey analysis

After excluding ineligible responders (TKR, no knee pain reported in past 12 months, self-reported inflammatory disease) and those with blank questionnaires and missing data for pain intensity on a 'normal' day), the total number included in the cross-sectional survey analysis was 116 (35%). Of the 116 eligible responders 59% were female; mean age 62.1 (SD 10.7); mean BMI 23.9 (SD 4.9). There were 115 participants who were from white UK or European background.

6.4.3 Frequency of reported flares

The majority of eligible responders recalled experiencing at least one flare-up in the previous 12 months with only 10% stating that they had experienced no flares. Over a quarter of participants reported experiencing more than 10 flare-ups in the previous 12 months (Figure 6.2).

Figure 6.2: Histogram of frequency of recalled flare-ups over the previous 12 months presented as proportions



6.4.4 Comparison of baseline characteristics and recall of flare frequency over the previous 12 months

The categories used in the questionnaire to collect data on recalled frequency of flare-ups in the previous 12 months were collapsed for analysis into those reporting a low frequency of flare-ups (0-2), those reporting a medium frequency of flare-ups (3-10) and those reporting a high frequency of flare-ups (>10).

The mean (SD) age was lower in those reporting a high frequency of flare-ups (61.3 (10.1) vs 65 (10.3)). Those in current employment reported a higher frequency of flare-ups (20 (63%) vs 9 (32%) (Table 6.5).

The final multivariable model consisted of only two variables: being employed and normal knee pain intensity. An alternative model of 4 variables: having seen GP, currently employed, previous surgery and taking medication was possible but this excluded normal knee pain intensity. When normal knee pain intensity was in this model the other variables became insignificant. The initial model was selected as these variables better explained the probability of having a flare-up.

Table 6.5: Demographic and socioeconomic characteristics of eligible responders, by recalled frequency of flares in the previous 12 months

	Recalled frequency of flares in previous 12 months		
	Low 0-2 *(n=28)*	Medium 3-10 *(n=55)*	High >10 *(n=33)*
Age (years): mean (SD)	65 (10.3)	61.2 (11.2)	61.3 (10.1)
Age (years) categories:			
45-64	14 (50)	35 (64)	21 (64)
65-74	9 (32)	10 (18)	9 (27)
75+	5 (18)	10 (18)	3 (9)
Female gender	15 (54)	36 (66)	18 (55)
Highest qualification:			
O-level, CSE, GCSE or equivalent	5 (18)	10 (19)	9 (28)
A-level, BTEC, HNC or equivalent	2 (7)	7 (13)	2 (6)
Degree or postgraduate qualification	4 (14)	4 (8)	6 (19)
Other work related or vocational qualification	2 (7)	12 (23)	4 (13)
Other qualification	3 (11)	5 (9)	0
No qualification	8 (29)	14 (26)	7 (22)
Ambiguous answer	4 (14)	1 (2)	4 (13)
Living alone	2 (11)	8 (15)	4 (12)
Married	23 (82)	35 (64)	23 (70)
Currently employed	9 (32)	21 (38)	20 (63)

Figures are column percentages unless otherwise stated

BTEC Business and Technology Education Council; CSE Certificate of Secondary Education; GCSE General Certificate of Secondary Education; HNC Higher National Certificate

Younger age and being employed were associated with a higher frequency of flare-ups. However, only the association with current employment was statistically significant (Table 6.6).

Table 6.6: Association of selected demographic and socioeconomic characteristics with recalled frequency of flares based on an ordered logistic regression model

		Unadjusted outcome comparison (frequency of flare)	
		Medium/High vs Low	High vs Med/Low
	Reference	OR (95% CI)	OR (95% CI)
Older age	per year	0.98 (0.95, 1.01)†	
Female gender	Male	1.01 (0.50, 2.06) †	
Highest qualification	No qualification		
O-level, CSE, GCSE or equivalent		2.11 (0.70, 6.33) †	
A-level, BTEC, HNC or equivalent		1.24 (0.33, 4.73) †	
Degree or postgraduate qualification		0.87 (0.22, 3.51) †	
Other work related or vocational qualification		1.45 (0.46, 4.58) †	
Other qualification		0.46 (0.10, 1.98) †	
Living alone	Not living alone	1.12 (0.41, 3.06) †	
Married	No	0.66 (0.31, 1.37) †	
Employed	Not Employed	2.45 (1.19, 5.07) †*	

OR unadjusted odds ratio from partial proportion odds model; 95%CI 95 percent confidence interval

† Where only one odds ratio is presented, this indicates the partial proportional odds model fit the data and proportional odds assumption was not violated

* aOR (95% CI): 0.27 (0.12, 0.59)

More frequent flares were reported by those who were underweight or overweight/obese and higher levels of physical activity (Table 6.7; Table 6.8).

Table 6.7: Lifestyle characteristics, including knee-specific physical exposures, of eligible responders, by recalled frequency of flares in the previous 12 months

	Recalled frequency of flares in previous 12 months		
	Low 0-2 *(n=28)*	Medium 3-10 *(n=55)*	High >10 *(n=33)*
BMI (kg/m^2): mean (SD)	23.5 (4.1)	23.7 (5.4)	24.5 (4.6)
BMI (kg/m^2):			
Underweight (<18.5)	2 (7)	6 (11)	4 (12)
Normal weight (18.5 -24.9)	17 (61)	30 (55)	15 (46)
Overweight/obese (≥25.0)	9 (32)	19 (35)	14 (42)
Smoking status:			
Never smoked	12 (43)	19 (35)	17 (52)
Previously smoked	15 (54)	28 (52)	10 (30)
Currently smoking	1 (4)	7 (13)	6 (18)
Alcohol intake:			
Never	3 (11)	6 (11)	4 (12)
Once or twice a year	3 (11)	10 (18)	4 (12)
Once or twice a month	5 (18)	9 (16)	10 (30)
Once or twice a week	10 (36)	19 (35)	6 (18)
Daily or most days	7 (25)	11 (20)	9 (27)
Physical activity:			
Vigorous activity	10 (36)	23 (42)	15 (46)
Moderate intensity	13 (46)	30 (55)	20 (61)
Walking	21 (75)	48 (87)	23 (70)
Knee-specific physical exposures:			
Prolonged kneeling	4 (14)	9 (17)	4 (12)
Repetitive stair climbing	5 (18)	21 (39)	6 (18)
Lifting/moving heavy objects	4 (14)	17 (32)	10 (30)
Prolonged squatting	0	2 (4)	3 (9)
Climbing ladders	2 (7)	9 (17)	3 (9)

Figures are column percentage unless stated otherwise

Table 6.8: Association of lifestyle characteristics with recalled frequency of flares based on an ordered logistic regression model

		Unadjusted outcome comparison (frequency of flare)	
		Medium/High vs Low	High vs Med/Low
	Reference	OR (95% CI)	OR (95% CI)
BMI (kg/m^2)			
Underweight	Normal	1.75 (0.55, 5.57)†	
Overweight/obese	Normal	1.48 (0.70, 3.12) †	
Smoking status:	Never smoked		
Previously smoked		0.59 (0.28, 1.25) †	
Currently smoking		1.96 (0.64, 6.04) †	
Alcohol intake	No alcohol		
Once or twice a year		0.94 (0.25, 3.61) †	
Once or twice a month		1.32 (0.36, 4.85) †	
Once or twice a week		0.61 (0.18, 2.02) †	
Daily or most days		0.90 (0.25, 3.22) †	
Vigorous activity‡	No	1.42 (0.71, 2.87) †	
Moderate activity¶	No	1.50 (0.75, 3.01) †	
Walking§	No	1.46 (0.53, 4.02) †	
Prolonged kneeling††	No	0.77 (0.29, 2.03) †	
Repetitive stair climbing‡‡	No	0.49 (0.17, 1.44)	2.41 (0.83, 7.00)
Lifting/moving heavy objects	No	0.62 (0.29, 1.35) †	
Prolonged squatting¶¶	No	cne	-
Climbing ladders	No	1.12 (0.41, 3.05) †	

BMI Body mass index; cne could not estimate due to small n; OR unadjusted odds ratio from partial proportion odds model; 95%CI 95 percent confidence interval

† Where only one odds ratio is presented, this indicates the partial proportional odds model fit the data and proportional odds assumption was not violated

‡ Vigorous activity for 20 minutes or more (e.g. heavy lifting, jogging, aerobics)

¶ Moderate intensity physical activity for 30 minutes or more (e.g. carrying light loads, bicycling at a regular pace)

§ Walking for 30 minutes or more

†† Kneeling for 30 minutes or more

‡‡ Climbing more than 5 flights of stairs (only variable where proportional odds assumption was violated)

¶¶ Squatting for 30 minutes or more

Those with a previous knee injury, previous knee surgery, who visited their GP in the last 12 months and take regular medication appeared to have a higher frequency of flare-ups (Tables 6.9, 6.10).

Table 6.9: Knee past history and healthcare use among eligible responders, by recalled frequency of flares in the previous 12 months

	Recalled frequency of flares in previous 12 months		
	Low 0-2 *(n=28)*	Medium 3-10 *(n=55)*	High >10 *(n=33)*
Duration knee problem:			
<1 year	8 (29)	11 (20)	8 (29)
1-5 years	12 (43)	23 (42)	21 (38)
>5 years	8 (29)	21 (38)	13 (39)
Previous knee surgery	4 (15)	9 (16)	14 (42)
Previous knee injury	10 (36)	20 (36)	16 (49)
Seen GP in last 12 months	12 (43)	38 (70)	24 (73)
Takes medication regularly	5 (19)	27 (49)	19 (58)

Figures are column percentages unless otherwise stated

Table 6.10: Association of knee history and healthcare use with recalled frequency of flares based on an ordered logistic regression model

		Unadjusted outcome comparison (frequency of flare)	
		Medium/High vs Low	High vs Med/Low
	Reference	OR (95% CI)	OR (95% CI)
Duration of knee problem			
1-5 years	<1 year	1.11 (0.45, 2.76)†	
> 5 years	< 1 year	1.43 (0.56, 3.62) †	
Previous knee surgery	No	3.66 (1.53, 8.73) †	
Previous knee injury	No	1.59 (0.78, 3.25) †	
Seen GP in last 12m	No	2.59 (1.22, 5.52) †	
Takes regular medication	No	3.28 (1.57, 6.86) †	

OR unadjusted odds ratio from partial proportion odds model; 95%CI 95 percent confidence interval

† Where only one odds ratio is presented, this indicates the partial proportional odds model fit the data and proportional odds assumption was not violated

Amongst those reporting a high frequency of flare-ups normal knee pain intensity was higher, knee symptoms such as swelling, limping, stiffness and night pain were reported more frequently and knee pain descriptors such as throbbing, sharp, burning, and stabbing were reported more frequently. Amongst those experiencing a low frequency of flare-ups knee descriptors such as dull and numbness were reported more frequently (Tables 6.11, 6.12).

Table 6.11: ‘Normal’ knee symptoms among eligible responders, by recalled frequency of flares in the previous 12 months

	Recalled frequency of flares in previous 12 months		
	Low 0-2 *(n=28)*	Medium 3-10 *(n=55)*	High >10 *(n=33)*
Normal knee pain intensity (0-10 NRS): mean (SD)	1.7 (1.8)	4.3 (2.3)	5.0 (2.1)
Other knee symptoms:			
Knee swelling	10 (36)	32 (58)	20 (61)
Limping	9 (32)	37 (67)	25 (76)
Stiffness	7 (25)	24 (44)	19 (58)
Night pain	5 (18)	22 (40)	20 (61)
Knee pain descriptors:			
Dull	9 (32)	16 (29)	8 (24)
Throbbing	3 (11)	13 (24)	9 (27)
Numbness	2 (7)	3 (6)	0
Sharp	5 (18)	21 (38)	15 (46)
Aching	10 (36)	44 (80)	20 (61)
Burning	3 (11)	11 (20)	9 (27)
Stabbing	0	13 (24)	13 (39)
Pins and needles	1 (3)	1 (2)	0

Figures are column percentages unless otherwise stated
NRS Numerical rating scale; SD standard deviation

Table 6.12: Association of ‘normal’ knee symptoms with recalled frequency of flares based on an ordered logistic regression model

		Unadjusted outcome comparison (frequency of flare)	
		Medium/High vs Low	High vs Med/Low
	Reference	OR (95% CI)	OR (95% CI)
Normal knee pain intensity (0-10NRS)	per unit	1.92 (1.47, 2.53)*	1.39 (1.15, 1.69)*
Other knee symptoms			
Knee swelling	No	2.20 (1.08, 4.48) †	
Limping	No	4.46 (2.05, 9.74) †	
Stiffness	No	2.54 (1.23, 5.21) †	
Night pain	No	3.99 (1.88, 8.50) †	
Knee pain descriptors			
Dull	No	0.72 (0.34, 1.56) †	
Throbbing	No	2.02 (0.88, 4.64) †	
Numbness	No	-	
Sharp	No	2.45 (1.17, 5.11) †	
Aching	No	5.24 (2.10, 13.04)	0.98 (0.41, 2.31)
Burning	No	2.16 (0.91, 5.14) †	
Stabbing	No	cne	3.89 (1.54, 9.82)
Pins and needles	No	-	

cne could not estimate due to small n; NRS Numerical Rating Scale; OR unadjusted odds ratio from partial proportion odds model; 95%CI 95 percent confidence interval

† Where only one odds ratio is presented, this indicates the partial proportional odds model fit the data and proportional odds assumption was not violated

*aOR (95% CI): 1.66 (1.38, 2.00)

6.5 Discussion

The modest sized cross-sectional survey found that the majority of patients accessing healthcare for knee pain likely to be attributable to osteoarthritis, recalled experiencing what might be called ‘acute flare-ups’ in the previous 12 months; 25% reported more than 10 such episodes in the previous 12 months. Patient factors that appear to be associated with higher frequency of flare-ups included being currently employed, being under/overweight, higher levels of physical activity, longer duration

of knee problems, previous knee surgery, and (to a lesser degree and statistically non-significant) injury. Patients reporting frequent flares also reported higher knee pain intensity, knee swelling, limping, morning stiffness, night pain, a sharp, throbbing, stabbing or burning pain, and higher levels of healthcare use for their knee problem.

A large proportion of people (n=104) reported flare-ups highlighting that it is a common problem. The distribution of those reporting frequency of flare-ups has a very large tail and a suggestion of a bimodal distribution. It is possible that people are reporting two different phenomena when thinking about ‘flare-ups’. These may be short-lived flares that occur frequently as observed by Murphy et al (61) and those that last longer leading to higher pain intensities and have a greater impact on activity limitation. This leads to questions on whether these are separate phenomena and whether they should be more clearly defined for research purposes and in the clinical setting. Minimum duration was important as a criterion for flare definition in the earlier systematic review (Chapter 4). The existence of this, particularly in the research setting, may be to exclude minor episodes or ‘twinges’ of pain that are part of the daily variability in the condition. The definition of flare based on patient recall in this cross-sectional survey, did not use a minimum duration and may therefore be capturing these ‘minor’ episodes of pain. In a 2-week study of flare-up rates among US workers, 38% reported flare-ups during the study period (73). Although the study periods are not comparable and mine was based on recall, the Ricci et al study highlights that flare-ups can have a significant impact on workers in terms of lost productive time. Studies using pre-defined flare criteria tend to have lower estimates (209).

There is some agreement with factors in this study and those found to be associated with flare-ups in the CAS(K) secondary analysis (Chapter 5); younger age (albeit non-significant), longer history of knee problem, increased BMI and increased severity of knee symptoms. Patients who are a younger age are likely to still be working and may be undertaking more activities that cause stress on the knee joint. BMI is a known factor for OA onset and progression and puts undue stress on the knee. The higher the pain rating scale at baseline or the worse the severity of symptoms at baseline appears to be associated with flare-ups.

Strengths of the study include items contained within the data collection instruments being from standardised questions where possible; such as, previous SPCSC studies or from the Osteoarthritis Initiative. The pain intensity measure, for example, was chosen after careful consideration of existing literature. Studies looking at the validity of pain scales, found the NRS to be the most responsive (293) and have confirmed its validity (294). The NRS was therefore chosen for the thesis study. Validity is important as it relates to the soundness of the data. A high degree of validity also assumes a high degree of reliability (85).

Key limitations include the small sample size and the use of some non-validated measures; for instance, flare frequency, descriptors of knee symptoms, pain descriptors, medication usage, self-report of inflammatory knee pain and potential triggers. Use of non-validated measures and uncertainty surrounding reliability may lead to systematic and random error (85). These items were therefore based on findings from previous research where possible, for example, the description of knee symptoms were based on the KOFUS (55), the pain descriptors were based on those that were described in interviews (53); however it is difficult to assess the extent to

which the information provided in response is reliable and valid as they were not pre-tested. A COSMIN (Consensus based standards for the selection of health measurement instruments) checklist could not be followed for these items, however, consensus within the study team and PPIE was reached with regard to their suitability as no other validated measures existed for measuring these domains.

Generalisability of results is limited due to the sampling frame where responders were predominantly white ethnicity and more likely to be female, older and from less deprived neighbourhoods. The sampling frame was not as large as intended. The original plan was to mail out to 511 potential participants from 3 general practices. However, due to capacity within the CRN this was not possible. Despite this, the response rate of 214 still fell within the anticipated range of 204-232 and was thought sufficient to base preliminary estimates on. Formal power calculations were not undertaken however an estimate of sample size was performed in order to establish the number of potential participants who may have participated in the linked diary study. Ideally, a formal sample size calculation would have been performed to minimise bias when interpreting the results, to ensure the results were more generalisable and to detect differences between groups (85). Due to practical and resource implications this was not performed.

There is potential for selection bias related to response where those experiencing flare-ups were more likely to respond (295), which may have led to an overestimation of flares. Inaccuracy of flare frequency may also have stemmed from misclassification of flare-ups due to recall bias, which may have affected validity and reliability (296). It is possible that those with greater pain intensity closer to the data collection period were more likely to report an increased frequency of flare-ups. Certain factors that could have been important but were not included, for example,

were assessments of mental health status including depression. The cross-sectional nature of associations gives potential for the possibility of reverse causality which could be likely for some physical exposures, for example, some individuals experiencing flare-ups may adapt and stop or cut down on self-identified provocative activities like kneeling or squatting (297).

6.6 Summary

This modest-sized cross-sectional survey found that around 90% of responders with knee pain/OA recalled frequent flares within the previous year. A higher frequency of such recalled flares appeared to be associated with patient factors such as being currently employed, abnormal BMI, higher levels of physical activity, longer duration of knee problems, and previous knee surgery. Frequent flares were also reported in those with higher knee pain intensity, associated symptoms such as swelling, morning stiffness, night pain and limping, and pain was described as stabbing, sharp, throbbing or burning. Overall these findings corroborate with findings in Chapter 5 apart from sex and physical activity measures, however these did not reach statistical significance in either study. In addition to the small size of this study, flares were defined based on recall and an operational definition that used a single item and which imposed no minimum duration or other quantitative criteria to define a flare.

7. ‘Acute flare-ups’ in patients with, or at high risk of, knee osteoarthritis: a daily diary study with case crossover analysis

Previous studies in this thesis have relied on patient recall to define flares. In the study reported in this chapter it was possible to define acute flare-ups using prospectively collected daily ratings of pain from a sample of survey responders. After considering the characteristics of this sample, the findings on the rate, nature and severity of flare-ups are presented, followed by a case-crossover analysis of potential triggers and prodromal symptoms for flare-ups.

7.1 Aims and objectives

Aim

To provide a detailed description of the natural history, associated features, self-management and potential short-term triggers of prospectively defined acute flares in patients with, or at high risk of symptomatic knee osteoarthritis.

Objectives

In a sample of community dwelling adults with, or at high risk of, symptomatic knee osteoarthritis:

- To describe the time course of flares
- To describe the rate of flares
- To describe the nature of a flare
- To describe severity of a flare.
- To explore the role of selected physical exposures in triggering flares and the presence of prodromal symptoms.

- To describe how people manage flares, with specific reference to analgesic intake and seeking help from health professionals.

7.2 Method

A detailed description of the recruitment process can be seen in Chapter 6.

7.2.1 Eligibility criteria for diary study

Those that consented (using the consent form attached to the cross-sectional survey) and were willing to complete at least one diary and had filled out question 2.1 and 2.2 on the cross-sectional survey (questions on normal knee pain and knee symptoms) (Appendix C) were invited to take part in the diary study.

7.2.2 Data Collection procedures

Daily diary

Eligible, consenting responders to the cross-sectional survey (presented in Chapter 6) were included in the diary phase of this study. Participants were invited to complete at least one diary and up to a maximum of three diaries over 3 consecutive months between August and October 2013.

Participants were mailed the Daily Diary Booklets (Appendix D) one week prior to the start of the month to be completed. They were asked to return the diaries at the end of each month in pre-paid envelopes which were provided.

For each month, if the completed diary had not been returned within 1 week of that month's diary completion, a Diary Return Reminder Letter (Appendix L), with a

further prepaid envelope, was sent out. If the diary was not received following this, the response variable was left blank. The participant was still sent future diaries unless they contacted us to withdraw from the study. Refusals and withdrawals were recorded along with the reason, where applicable, at each stage.

At any stage if the participant contacted the SPCSC to state they had lost or not received the diary the relevant documents were resent with a repeat covering letter for that month.

All of the diaries contained a sticker on the inside cover of the first page which showed the participants responses to certain questions in the cross-sectional survey. These included the responses participants had indicated for their 'normal' level of knee pain on the NRS scale, knee descriptors, usual medication, and potential knee triggers on a normal day for them.

At the end of the study, patients who had been involved in the diary stage were mailed a thank you letter (Appendix M).

7.2.3 Data collection instruments

The diaries were A4 sized, 12-point font, with bright colours on the outside pages which changed for each month. Each day took up one side. There were nine items to be filled each day. Participants were asked to fill out each item at the end of each day and to consider their answers in relation to the previous 24 hours. The questions required the answer to be either a cross in a box or free text (Table 7.1).

Table 7.1: Items included in the daily diaries (note all measurements relate to past 24 hours)

Domain	Description	Empirical measure
Pain intensity	Average knee pain over the preceding 24 hours	0-10 NRS (adapted from (195))
Description of knee symptoms	Presence of any knee swelling, limping, knee stiffness for more than 20 minutes, being woken at night by knee pain in preceding 24 hours	Yes/no (adapted from (17))
Pain descriptors	Description of pain experiences in preceding 24 hours	Single items: dull, throbbing, numbness, sharp, aching, burning, stabbing, pins & needles, other (adapted from (16,176,177))
Changes in medication	Changes to normal medication in preceding 24 hours	Same/more/less; free text comments
Potential triggers	Activities undertaken in preceding 24 hours kneeling for 30 minutes or more, climbing more than 5 flights of stairs, lifting/moving heavy objects, squatting for 30 minutes or more, climbing ladders	Yes/no (adapted from (197))
Pain interference with activities	Pain interference with activities in preceding 24 hours	Yes/no
GP consultation	Been to see GP because of knee pain in preceding 24 hours	Yes/no (adapted from (196))
Triggers	Perception of triggers for any changes in knee pain in preceding 24 hours	Free text
Comments	Space for additional comments thought important by participant	Free text

GP General practitioner; NRS Numerical rating scale

Numerical Rating Scale (NRS)

To determine pain severity a number of scoring methods were considered. From previous studies numerical rating scales were found to be easier to use and have better compliance rates (298). The NRS as a tool for pain assessment has been validated in a number of studies (294, 299-302).

Characteristics associated with knee flare up

Characteristics associated with a flare up: knee swelling, limping, knee stiffness for more than 20 minutes, and woken at night from knee pain, were adapted from Marty's validation of the Knee Osteoarthritis Flare-Up Score (55).

Pain descriptors

Description of pain experiences have been adapted from a qualitative study with focus groups and one-to-one interviews, part of which was describing pain experienced (53). The answers included an 'other' box so that if the participants description of their pain did not fit into any of the descriptors included they had the option to free text this. They are also adapted from the McGill Pain Questionnaire (276, 277).

Physical triggers

A study looking at previous occupational exposure and risk of knee osteoarthritis asked participants about the following activities: bending for 2 or more hours, walking for 2 hours or more on level ground, kneeling for 30 minutes or more, squatting for 30 minutes or more, climbing a total of 5 or more flights of stairs, lifting or moving heavy objects weighing 25lbs, and driving for 4 hours or more (32, 303). Occupational

exposure to frequent squatting kneeling and heavy lifting were associated with risk of cartilage degeneration.

A systematic review looking at long- term cumulative occupational exposure and knee OA found strong associations between squatting and kneeling (304). There was also an association with climbing ladders (in males), climbing stairs, and lifting heavy objects. In the diary study these exposures were included to assess short-term transient exposure (on the assumption that there is sufficient within-person day-to-day variability in whether or not people are 'exposed' to these activities) and that these might constitute short-term triggers for flare-ups.

Participants were also invited to free text any triggers they thought may have caused a change in their pain, in order to try and capture triggers not included in the diaries or identify new ones.

Change in pain medication

This item ascertained if there were any changes in medication usage compared to baseline and was created de novo.

Interference with normal activities

In studies that have used definitions for knee OA flares, interference with normal activities was sometimes included (55, 180). It has also been used in the definition of worsening back pain (305)**.**

Consultation with GP

This has been included to see if there is an association between consultation rates and increases in knee pain.

Other comments

A free text space was included at the end of each day for comments.

7.2.4 Data cleaning

One in ten checks for accuracy of inputted data was performed for the completed diaries by the study administrator. All diaries were subsequently re-checked by myself to ensure the agreed coding framework had been followed.

A number of important coding decisions were made during the cleaning process. For example, where an entire page was left blank then all the items for that day were coded as missing. If two numbers were crossed on the NRS the higher number was used. On days where at least one item had been filled in correctly then responses to Q2, Q3, and Q5, if not crossed were presumed to be ‘no’ and coded as such.

During the cleaning process it became clear that three of the study participants, who had reported exclusions (one indicated a diagnosis of rheumatoid arthritis and two others had left the ‘previous inflammatory disease’ question blank in the cross-sectional survey) had received diaries, some of which had been completed. The decision was made to delete these diary observations from the diary analysis.

7.2.5 Statistical analysis

Evaluation of selective participation

Descriptive characteristics of responders and non-responders to the diaries were compared, using information in the cross-sectional survey (age, gender and deprivation). In all instances simple descriptive statistics (mean, SD; median, inter-quartile range; frequencies and percentages) were used. A flowchart of response was also completed.

Frequency of missing data

The proportion of completed entries in returned diaries was described, in total (e.g. 3000 out of a total of 5000 person-days), by month (for example 2000 of 3000 for Month 1; 750 of 1500 for M2, 250 of 500 for M3), and by person (for example 40% of responders to M1 diary had complete entries for all days; 50% had 1-7 entries missing; 10% had >7 entries missing).

Objective 1: Nature of flare-ups

Definition of a flare-up:

The following *a priori* definition of a flare-up was used:

1. Increase of at least 2 points from baseline in the average pain in the past 24 hours reported on an 11-point NRS
2. The increase to have occurred for at least 2 consecutive days

This definition was chosen after referring to previous studies of osteoarthritis flare-ups (55, 70, 157, 178, 182), OA flare design trials (180, 181), and flare-ups in other musculoskeletal (218) and non-musculoskeletal conditions (76, 306).

The following *a priori* definition of the resolution of a flare-up was used:

1. Reduction of average pain in the past 24 hours reported on an 11-point NRS to at or below baseline level
2. The return to at or below baseline levels to have occurred for at least 5 consecutive days

Flare-up rate

The proportion of persons experiencing at least one flare-up was calculated and, among those experiencing at least one flare-up, the number of flare-ups per person.

The overall rate of flare-ups for the study period was calculated as an incidence density using Poisson regression in order to take into account recurrent events (307). The incidence density was expressed per 100 person-days at risk along with the 95%CI.

Flare-up nature

Scatterplots of individual daily NRS scores

Scatterplots were used to display daily reported NRS score per individual.

Scatterplot of time course of NRS scores across flare-ups

For each participant's initial flare-up, the mean NRS score for the 7 days prior and 30 days after the flare up, was calculated and plotted on a scatterplot. The same method was used for plotting the time course of symptoms such as swelling, limping, stiffness, night pain and for medication changes.

Baseline characteristics of those experiencing flare-ups

The baseline characteristics of those experiencing flare-ups was reported using descriptive statistics (mean (SD) or frequency (proportions) where appropriate).

A logistic regression model was used to assess associations between those experiencing flare-ups in the diary study and baseline characteristics. Odds ratios were calculated for each variable (267). A multivariable model was not possible due to the small number of events.

Changes in diary variables during a flare-up, resolution and at-risk period

Descriptive statistics (means, SD or proportions) were used to describe how often a flare-up, resolution or at-risk period was accompanied by change in certain diary variables. A mixed-effect model appropriate for each outcome (logistic for binary and linear for continuous outcomes) was used to compare the occurrence (expressed as odds ratios) and severity (expressed as regression coefficients) of symptoms on flare-up versus non-flare-up days accounting for the clustered nature of the observations (308).

Variability

The Variability Index (VI) was obtained by splitting the diary data into half monthly blocks (14-16 days). The standard deviation of the daily pain intensity scores within each block was calculated for each participant and used as the primary measure of variability. The standard deviation was chosen as it is the most common measure of variability which averages the absolute deviation of each day's pain intensity from the mean pain over the 14-16 days period, thus capturing any pain fluctuations. This method has also been used in a previous study investigating pain variability of patients with fibromyalgia (309). Single days were not used due to varying length of the month over the three months study period hence the block size slightly varied from 14-16. The 14-16 block was chosen based on the number of available data points and to allow for reliable estimation of SD due to the distribution assumptions.

The Variability Index was calculated for the population as a whole, for only participants who had not experienced a flare, for only those who had experienced a flare, and for all the population but only using 'at-risk' days.

The association of baseline factors with differing levels of variability was then calculated. A histogram to assess the distribution of the SD was created which showed that the data was not normally distributed. The SD was therefore log transformed. A linear mixed model was used to examine the association between variability in the daily pain scores and a number of baseline factors. The model accounted for the correlation of the variability index within each time period (each time period having the same VI). The coefficient and 95% confidence intervals are presented in a univariable model.

Objective 2: Duration and severity of flare-ups

The duration of flare-ups was calculated as the number of days between the first day of flare-up to the first day of the resolution period and was summarised across all flare-ups as median (IQR) and range.

Severity of flare-ups

The severity of flare-ups was calculated as the change from baseline to peak pain intensity during a flare-up.

Comparison of normal NRS score reported at baseline and frequency of flare-up for each pain rating

A comparison of the 'normal' NRS score reported in the cross-sectional survey and frequency of flare-ups for each pain rating was reported using a table, i.e., the number of flare-ups reported in the diary study was compared to each pain intensity rating in the cross-sectional survey.

Objective 3: Triggers and prodromal symptoms

To determine whether certain triggers were associated with a flare-up, a case-crossover type approach (310, 311) was used with individuals used as their own control. A case-crossover analysis is useful where the outcome of interest is acute in onset and the triggers occur over a brief time period (312)**.** Case windows for exposure were defined as the 48 hours prior to the first day of a flare-up. Each case, where possible had four matched controls. Controls were the 48-hour periods prior to a period of time that did not precede a flare-up but were from corresponding days to the case to account for any differences in activity that might occur on particular days. Where possible, two controls were selected prior to the case period and two after the

case period. Controls were not selected from days when the participant was having a flare-up or when they were in a resolution period. If there were insufficient days to select two controls before and two controls after the case period, then controls were selected from available days. The assumption in a case-crossover analysis is that risk is similar throughout the study period and is called the exchangeability assumption (312).

The frequency of different exposures (for instance heavy lifting), prodromal symptoms (such as increased limping), and changes to medication in the case and control windows was described.

Unadjusted exposure odds ratios (OR) were calculated based on the conditional maximum likelihood estimate with 95% mid-P exact confidence intervals using OpenEpi (www.OpenEpi.com)**.**

Objective 4: Actions in response to flare-ups

Proportion changes for days in a flare, resolution and 'at risk' period were reported for seeing a GP and changes in medication using percentages. Changes in medication usage compared to baseline were presented as a proportion change for combined data for the 7 days prior to and 30 days proceeding a flare-up.

7.3 Results

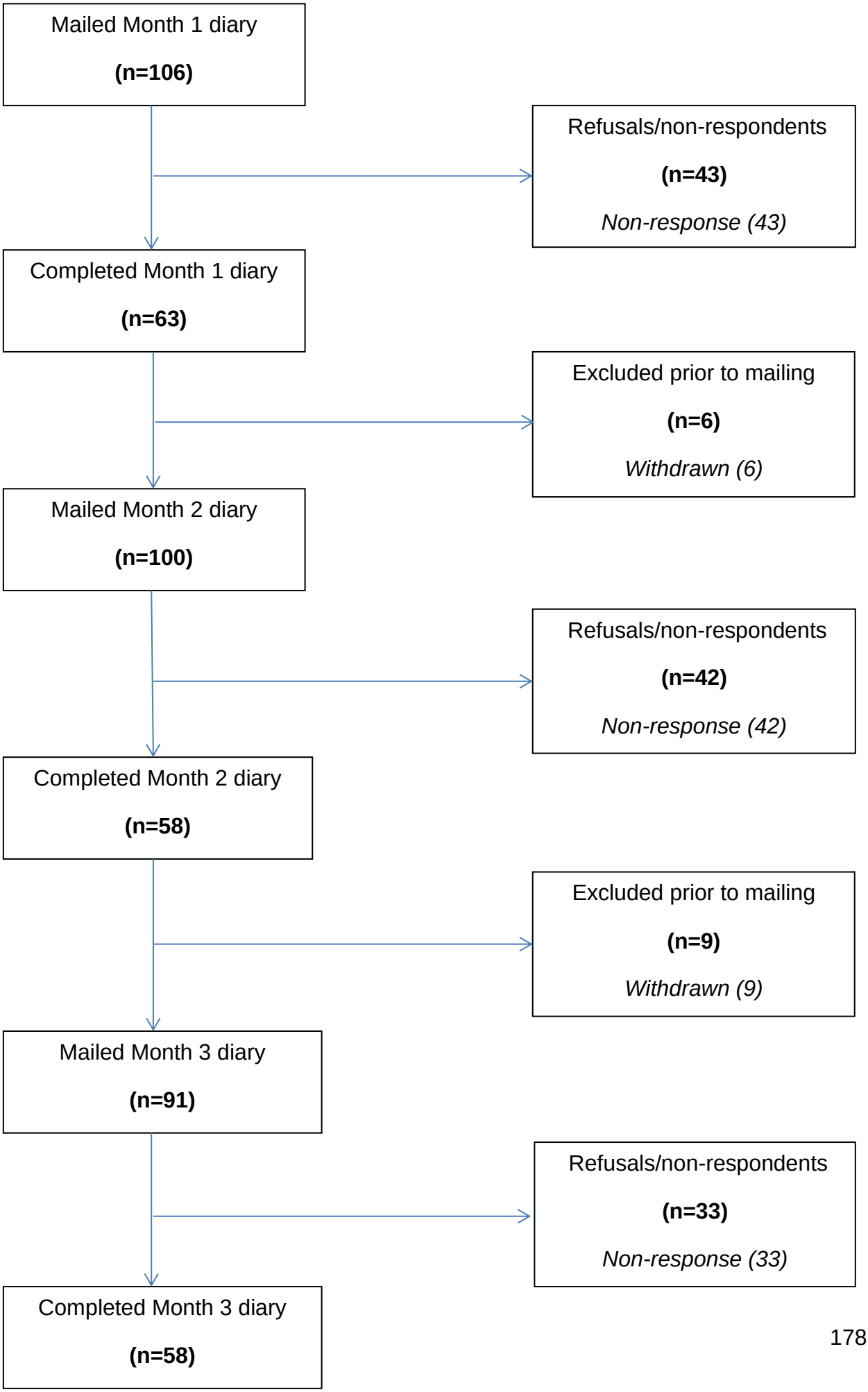
7.3.1 Evaluation of selective participation

Figure 7.1 displays the response rate to each of the monthly diaries. The Month 1 Diary was mailed out to 106 participants who were eligible and consented from responders of the cross-sectional survey. There were 63 responders (61%) to the

Month 1 Diary. Four participants withdrew after month 1, and 58/100 (58%) responded to the Month 2 Diary. Nine participants withdrew after month 2 and 58/91 (64%) responded to the Month 3 Diary.

Overall 52 participants completed three monthly diaries, 8 participants completed two diaries and 7 participants completed only one diary during the data collection period. Of the 67 responders who completed at least one diary over the 3 months, 37 (55%) were female, mean (SD) age was 62.2 (10.6) with a mean (SD) BMI of 24.6 (5.3), and ethnicity of White UK or European 66 (99%).

Figure 7.1: Flowchart for response to Month 1, Month 2 and Month 3 Diaries.


Mailed Month 1 diary
(n=106)
Refusals/non-respondents
(n=43)
Non-response (43)
Completed Month 1 diary
(n=63)
Excluded prior to mailing
(n=6)
Withdrawn (6)
Mailed Month 2 diary
(n=100)
Refusals/non-respondents
(n=42)
Non-response (42)
Completed Month 2 diary
(n=58)
Excluded prior to mailing
(n=9)
Withdrawn (9)
Mailed Month 3 diary
(n=91)
Refusals/non-respondents
(n=33)
Non-response (33)
Completed Month 3 diary
(n=58)

There were no major differences between responders and non-responders to the monthly diaries in terms of age and gender (Table 7.2), and for the subsequent diaries. However, those that lived in the most deprived areas were less likely to complete the diaries.

Table 7.2: Comparison of those that completed at least one diary versus non-completers

	Responders (n=67)	Non-responders (n=39)
Female, n (%)	37 (55)	25 (64)
Age, years (mean (SD)	62.2 (10.6)	61.7 (11.0)
Area-level deprivation*, n (%):		
Most deprived	17 (25)	13 (33)
Mid	33 (49)	17 (44)
Least deprived	17 (25)	9 (23)

* Tertiles of Index of Multiple Deprivation based on patient postcode

7.3.2 Frequency of missing data of daily diary items

There were 111 of a total of 5491 (2%) person days where all items were missing and 4328 (79%) person days where all items were completed. The most common items which were missed were change in medication, whether a GP had been seen that day, and if pain stopped usual activities. Items with the least amount of missing data included the pain descriptors and triggers.

The number of complete missing days increased throughout the study: 17 (0.9%) person days in month 1, 36 (2%) person-days in month 2, and 58 (3%) person-days in month 2.

7.3.3 Objective 1: Nature of flare-ups

Flare-up rate

There were 54 flare-ups in the sample amongst 30 participants over the three month period. The majority experienced only one flare-up (16 participants). However, six experienced 2 flare-ups, six experienced 3 flare-ups and two participants experienced 4 flare-ups.

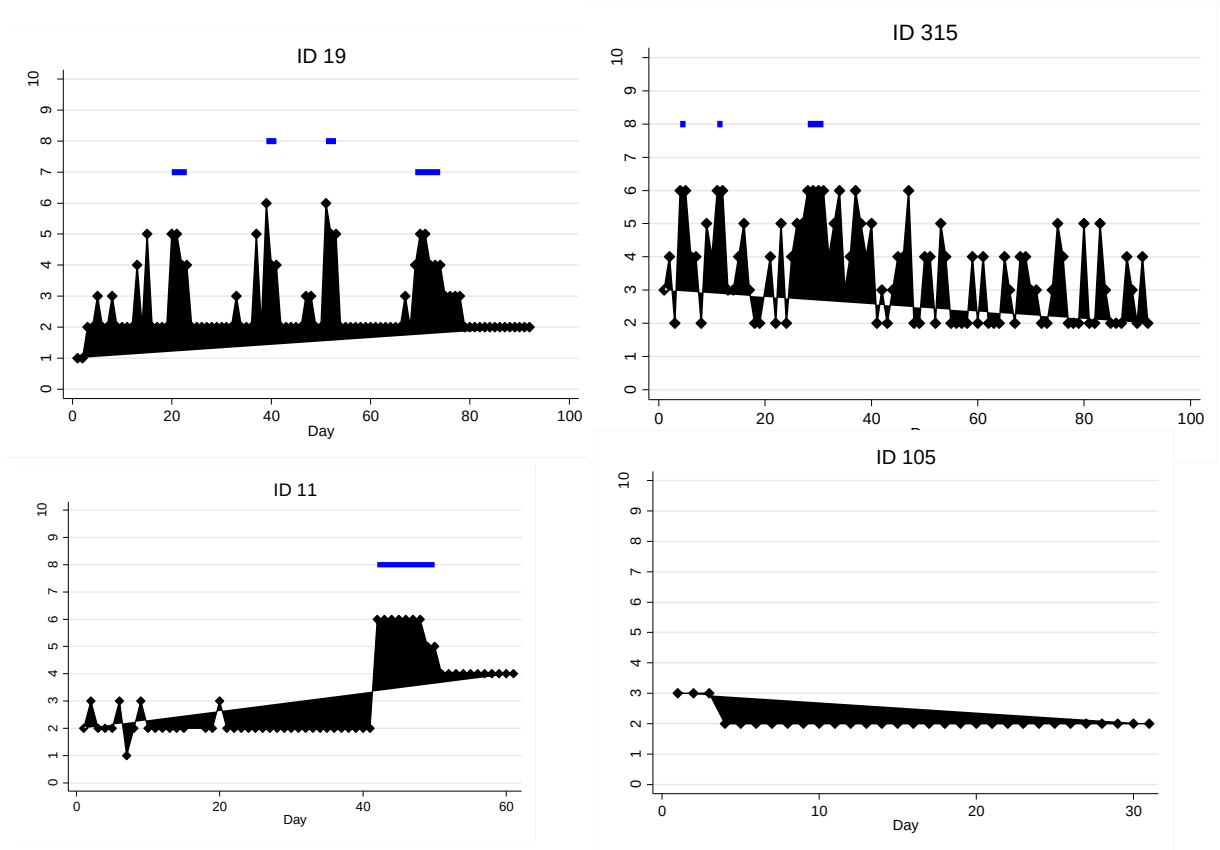
The incidence density of flare-ups for the entire study period was 1.12 (95% CI 0.80, 1.57) per 100 person days.

There was no difference in overall response rate between responders and non-responders and those that did and did not experience flare-ups.

Flare-up nature

The daily reported average NRS per individual was plotted for all person-days available and annotated to show where a flare-up had occurred where applicable. Some participants reported large fluctuations in daily pain and had frequent flare-ups (patient ID 19 and 315 in Figure 7.2). Other participants reported minimum variability in pain scores (ID 11 in Figure 7.2) and some showed stable pain scores throughout (ID 105 in Figure 7.2). See Appendix O for all Daily NRS graphs.

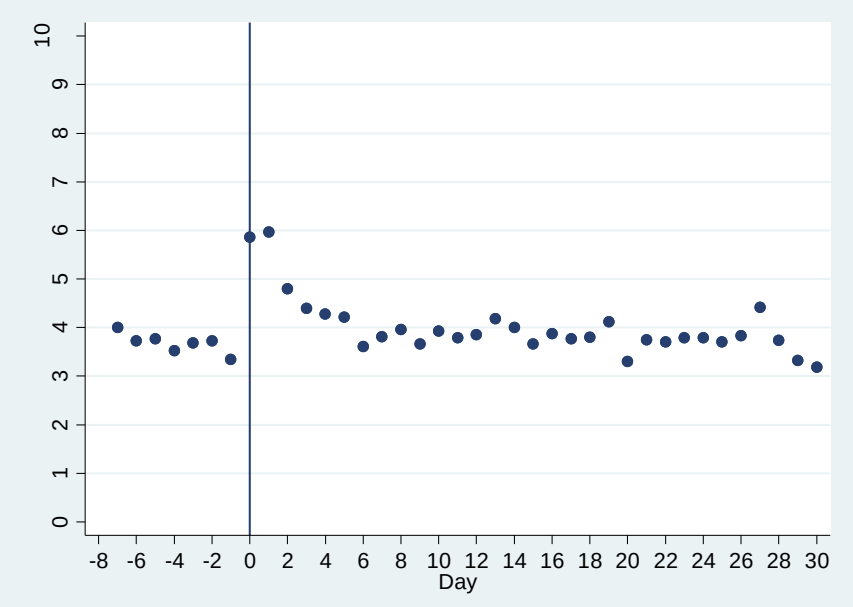
Figure 7.2: Daily NRS for ID 11, 19, 105 and 315.



Flare-ups are indicated in blue.

Analysing combined mean NRS scores of all first flare-ups, for all individuals who experienced a flare-up for the 7 days preceding and 30 days proceeding the start of a flare-up it can be seen that the mean NRS does not appear to gradually increase prior to a flare. After the first 2 days the pain appears to gradually reduce back to pre-flare levels and which takes up to 30 days (Figure 7.3).

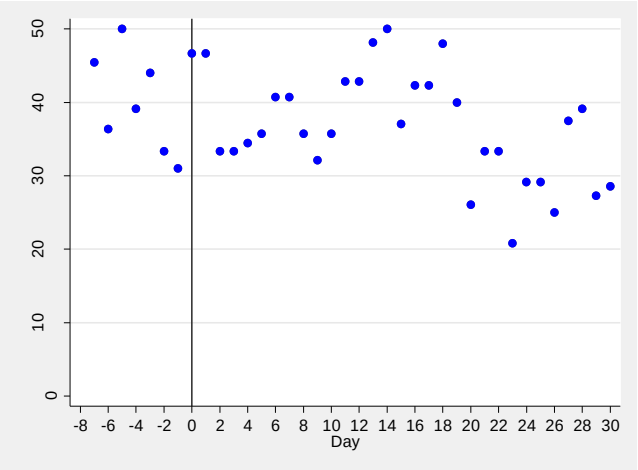
Figure 7.3: Time course of pain intensity for all first flare-ups during the study period. (Reproduced from Parry et al, 2019 (313))

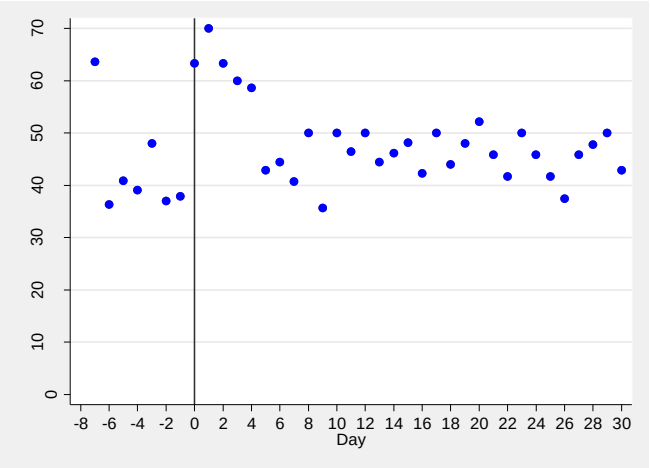


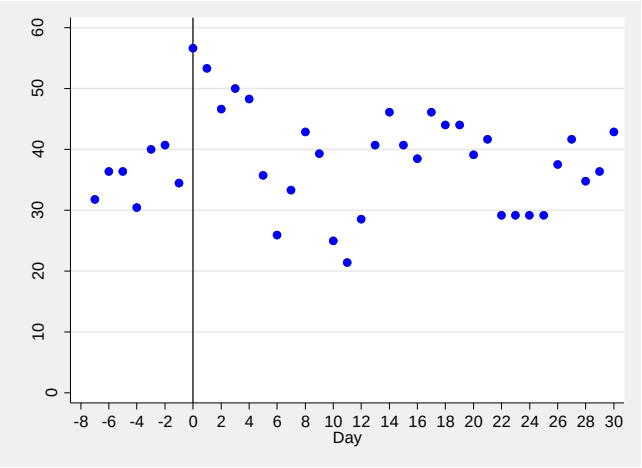
Footnote: Expressed as mean NRS-score for each of the 7 days prior and 30 days proceeding onset of a flare-up where day 0 is the first day of the flare.

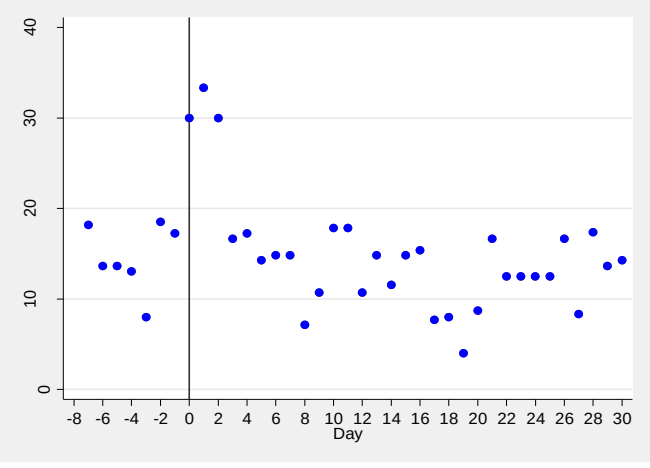
The proportions of certain knee symptoms reported, for example, swelling, stiffness, limping and night pain were plotted to see if there was a change in these symptoms leading up to a flare and proceeding it (Figure 7.4). All of the symptoms appear to increase suddenly in terms of proportion of participants reporting them on the first 2 days of a flare-up. For stiffness there appears to be an upward trend prior to the onset of a flare-up then a greater increase on day 1 of the flare-up, followed by a generalised decline. Night pain follows a similar pattern with a potential increase in participants reporting night pain prior to a flare-up, with a peak during the flare-up and a decline afterwards. Swelling and limping do not have a similar pattern.

Figure 7.4: Time course of symptoms of swelling, limping, stiffness and night pain for each first flare-up in the 30 participants who experienced flare-ups. (Expressed as proportion for each of the 7 days prior and 30 days proceeding onset of a flare-up where day 0 is the first day of the flare.)



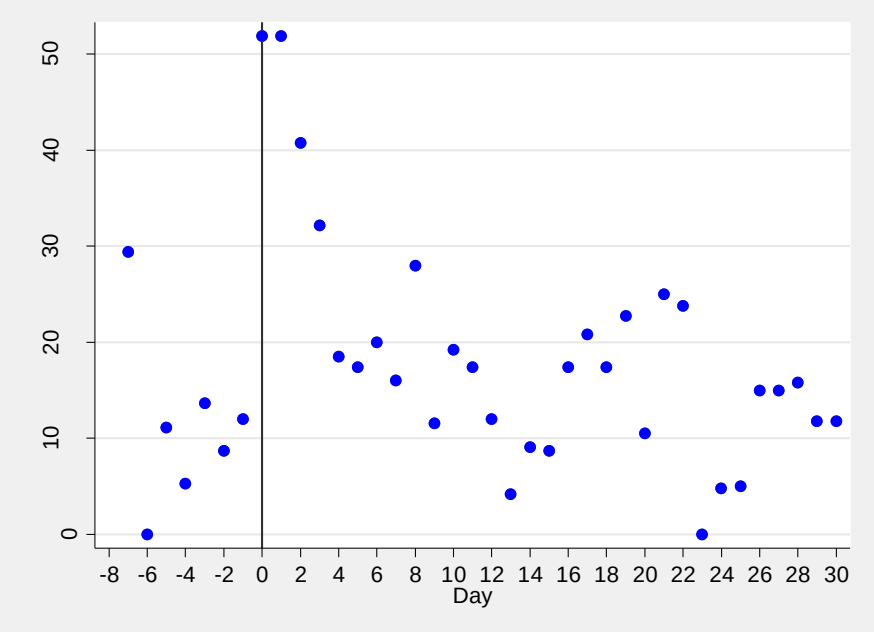






Looking at how participants might manage flare-ups it appears that more medication is taken at the onset of a flare-up and the following day but after this the proportion of participants reporting taking an increase in their medication gradually declined. There does not appear to be any increase in medication prior to a flare-up (Figure 7.5).

Figure 7.5: Time course changes in medication where more or less medication was taken than normal for each first flare-up in the 30 participants who experienced flare-ups. (Expressed as proportion for each of the 7 days prior and 30 days proceeding onset of a flare-up where day 0 is the first day of the flare.)



Baseline characteristics of those experiencing flare-ups

Mean age of those experiencing flare-ups was 62.4 (SD 8.2) years which was similar to those who did not experience flare-ups (62.8 years (SD 11.9)). The proportion of females experiencing flare-ups was less than those who did not experience flare-ups (15 (50%) versus 22 (60%)). Mean BMI was higher in the flare-up group (25.5 kg/m^2 (SD 5) versus 23.9 kg/m^2 (SD 6)). There were no significant associations at the $p>0.05$ level between any baseline factors assessed and experiencing a flare-up in the diary studies. However, there were positive associations with being male, younger age, having a higher BMI, longer duration of knee problem, previous knee injury, previous surgery, certain triggers (kneeling, climbing stairs, climbing ladders), certain knee symptoms (swelling, limping), certain knee descriptors (sharp, aching, throbbing, burning), and taking medication (Table 7.3).

Table 7.3: Comparison of baseline characteristics of those experiencing flare-ups and those not experiencing flare-ups in the diary

	Reference	Flare-up *(n=30)*	No flare-up *(n=37)*	OR	(95% CI)
Demographic and socioeconomic					
Age (years): mean (SD)		62.4 (8.2)	62.8 (11.9)	1.00	0.96, 1.18
Gender	Male	15 (50)	22 (60)	0.68	0.27, 1.80
Lives alone	No	3 (10)	5 (14)	-	-
Married	Not married	23 (77)	27 (73)	1.22	0.40, 3.71
Employed	Not employed	14 (47)	18 (49)	0.92	0.35, 2.42
Educational qualification	No qualification	24 (80)	27 (75)	1.33	0.41, 4.30
Lifestyle					
Current smoker	Current non-smoker	11 (37)	18 (49)	0.61	0.23, 1.63
Alcohol consumption*					
Low	Low	7 (23)	10 (27)	1	1
Medium		17 (23)	19 (51)	1.19	0.34, 4.14
High		6 (20)	8 (22)	0.93	0.22, 3.91
BMI (kg/m^2): mean (SD)		25.5 (5)	23.9 (6)	1.06	0.96, 1.18
Current/previous knee symptoms					
Pain intensity (NRS 0-10): mean (SD)		3.2 (2.0)	2.6 (2.4)	0.90	0.71, 1.13
Description of knee symptoms					
Swelling	No	17 (57)	17 (46)	1.54	0.58, 4.06
Limping	No	19 (63)	23 (62)	1.05	0.39, 2.85
Stiffness	No	13 (43)	17 (46)	0.90	0.34, 2.37
Night pain	No	11 (37)	17 (46)	0.68	0.25, 1.82

	Reference	Flare-up *(n=30)*	No flare-up *(n=37)*	OR	(95% CI)
Pain descriptors					
Dull	No	8 (27)	12 (32)	0.76	0.26, 2.19
Throbbing	No	8 (27)	7 (19)	1.56	0.49, 4.94
Numbness	No	1 (3)	1 (3)	-	-
Sharp	No	11 (30)	11 (37)	1.37	0.49, 3.81
Aching	No	23 (77)	25 (68)	1.58	0.53, 4.69
Burning	No	5 (17)	6 (16)	1.03	0.28, 3.79
Stabbing	No	6 (20)	10 (27)	0.68	0.21, 2.14
Pins and needles	No	1 (3)	0	-	-
Knee history					
Duration of knee problem					
1 year or less		4 (13)	8 (22)	1	1
2-5 years		13 (43)	16 (43)	1.63	0.40, 6.63
6-10 years		6 (20)	2 (5)	-	-
More than 10 years		7 (23)	11 (30)	1.27	0.28, 5.87
Previous knee injury	None	13 (43)	13 (35)	1.41	0.53, 3.79
Previous surgery to index knee	No	7 (23)	8 (21)	1.10	0.35, 3.49

	Reference	Flare-up *(n=30)*	No flare-up *(n=37)*	OR	(95% CI)
Physical activity exposures					
Potential triggers					
Kneeling for 30 minutes or more	No	4 (14)	4 (11)	-	-
Climbing more than 5 flights of stairs	No	8 (28)	8 (22)	1.38	0.45, 4.27
Lifting/ moving heavy objects	No	6 (21)	11 (30)	0.62	0.20, 1.93
Squatting for 30 minutes or more	No	0	3 (8)	-	-
Climbing ladders	No	5 (17)	4 (11)	-	-
Exercise					
20 mins vigorous activity ≥1 x week	None	12 (40)	19 (51)	0.63	0.24, 1.67
Walk for 30 minutes or more ≥1 x week	None	27 (90)	29 (78)	2.48	0.60, 10.3
Moderate exercise ≥1 x week	None	15 (50)	21 (57)	0.76	0.29, 2.00
Knee related healthcare utilisation					
Seen GP in past 12m re knee problem	No	18 (60)	25 (70)	0.66	0.24, 1.83
Takes medication	No	15 (50)	18 (50)	1.00	0.38, 2.64

Figures are column percentages unless otherwise stated

BMI Body Mass Index; NRS Numerical Rating Scale; OR crude odds ratio; SD Standard Deviation

* Alcohol: High frequency= daily or most days, medium frequency= once a month to twice a week, low frequency= maximum twice a year

Change in diary variables during a flare-up, resolution and being in an at-risk period

A comparison was made between changes in mean or proportions of diary variables dependent on person days in a flare-up, in a resolution, or an at-risk period. During flare-up days the mean NRS was higher, there was a higher proportion of knee symptoms reported (stiffness, limping, effusion, night pain), there was a higher proportion of certain knee descriptors (throbbing, numb, sharp, aching, burning, stabbing), there was a higher proportion of increased medication taken compared to baseline and a higher proportion of those experiencing pain that had stopped usual activities. The mean NRS on flare-up days was 5.4 (SD 1.9), on resolution days 3.8 (SD 1.7), on at-risk days for only those participants who experienced a flare-up 3.1 (SD 2.0), and on all at risk days regardless of whether a participant experienced a flare-up or not 2.8 (SD 2.2) (Table 7.4).

Table 7.4: Severity and occurrence of symptoms and impact experienced during flare-up, resolution or at-risk days among participants

	Total days *(n=5491)*	During flare-up period *(n=299)*	During resolution period *(n=258)*	During at-risk period (flarers only) *(n=1958)*	During at-risk period (all patients) *(n=4934)*	Relative frequency/severity on flare-up days vs non-flare-up days *
Pain intensity (0-10NRS) (mean, SD)	3.0 (2.3)	5.4 (1.9)	3.8 (1.7)	3.1 (2.0)	2.8 (2.2)	2.49 (2.34, 2.64)
Presence of associated symptoms						
Knee swelling	1375 (32)	149 (50)	73 (29)	668 (35)	1513 (31)	14.53 (8.31, 25.41)
Limping	1783 (33)	191 (64)	133 (53)	804 (42)	1459 (30)	12.37 (7.36, 20.78)
Knee stiffness	1493 (28)	178 (60)	90 (36)	505 (26)	1225 (25)	10.92 (6.96, 17.14)
Woken at night	861 (16)	103 (35)	33 (13)	189 (10)	725 (15)	6.99 (4.35, 11.23)
Pain descriptors						
Dull	1705 (32)	52 (17)	86 (34)	673(35)	1567 (33)	0.40 (0.25, 0.66)
Throbbing	723 (13)	95 (32)	52 (21)	301 (16)	576 (12)	18.10 (9.83, 33.32)
Numb	106 (2)	72 (24)	15 (6)	15 (<1)	19 (<1)	6.68 (1.93, 23.15)
Sharp	989 (18)	146 (49)	51 (20)	206 (11)	792 (16)	11.22 (6.77, 18.58)
Aching	2931 (55)	218 (73)	162 (64)	1122 (59)	2551 (53)	6.87 (4.08, 11.56)
Burning	338 (6)	73 (24)	32 (13)	171 (9)	233 (5)	6.70 (4.04, 11.11)
Stabbing	837 (16)	108 (36)	56 (22)	269 (14)	673 (14)	11.82 (7.15, 19.54)
Pins and needles	10 (<1)	1 (<1)	2 (<1)	1 (<1)	7 (<1)	3.44 (0.33, 35.89)
Other	452 (8)	9 (3)	4 (2)	45 (2)	439 (9)	1.33 (0.58, 3.08)

	Total days *(n=5491)*	During flare-up period *(n=299)*	During resolution period *(n=258)*	During at-risk period (flarers only) *(n=1958)*	During at-risk period (all patients) *(n=4934)*	Relative frequency/severity on flare-up days vs non-flare-up days *
Change in medication						
Same as normal	3048 (68)	165 (59)	165 (70)	1100 (73)	2718 (68)	-
More than normal	551 (12)	94 (34)	22 (9)	181 (12)	435 (11)	23.90 (13.81, 41.38)
Less than normal	886 (20)	19 (7)	48 (20)	225 (15)	819 (21)	0.81 (0.41, 1.60)
Pain stopped usual activities	407 (8)	44 (15)	15 (6)	76 (4)	348 (8)	
Seen GP	58 (1)	8 (3)	1 (0.4)	7 (0.4)	49 (1)	0.84 (0.44, 1.59)

Figures are frequencies in person-days and column percentages unless stated otherwise

Flare-up =period Flare-up days

Resolution period= Defined as the 5 days following a flare-up

At-risk period= Days not classified as flare-up or resolution days

* From mixed- effect model based on participants who had experiences a flare-up (n=30) (logistic for binary and linear for continuous outcome). Results are expressed as odds ratios (95% CI) except average knee pain intensity which is expressed as a regression coefficient (i.e., mean difference) and 95% CI.

Variability analysis

To examine the degree of variability across all subjects the Variability Index was calculated. The mean Variability Index was 0.76 (SD 0.54), median 0.68 (IQR 0.41-1.05). The minimum Variability Index was 0 and maximum 3.26. The between subject histogram is seen in Figure 7.10. This is skewed to the left towards lower values.

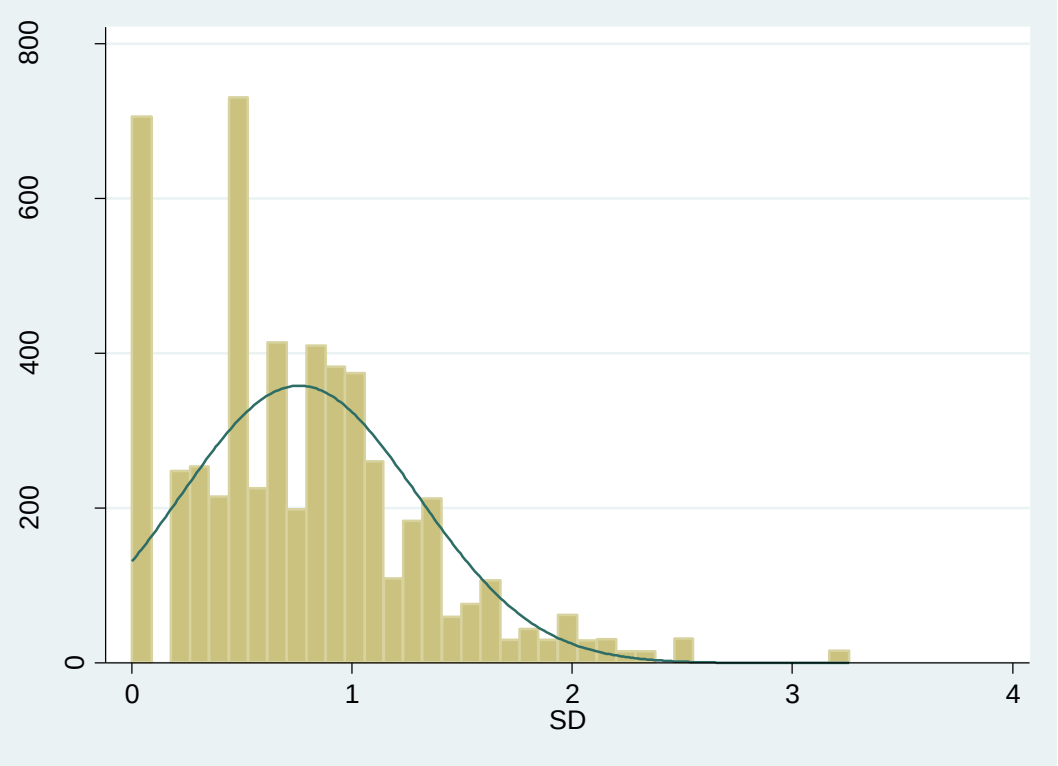
The Variability Index for only at-risk days was 0.68 (SD 0.49) with a range of 0 to 3.15.

The Variability Index was calculated for only those participants who had not experienced a flare. The mean Variability Index was 0.62 (SD 0.47), range 0 to 2.07.

The Variability Index was calculated for only those participants who had experienced a flare. The mean Variability Index was 0.92 (SD 0.57), range 0 to 3.26.

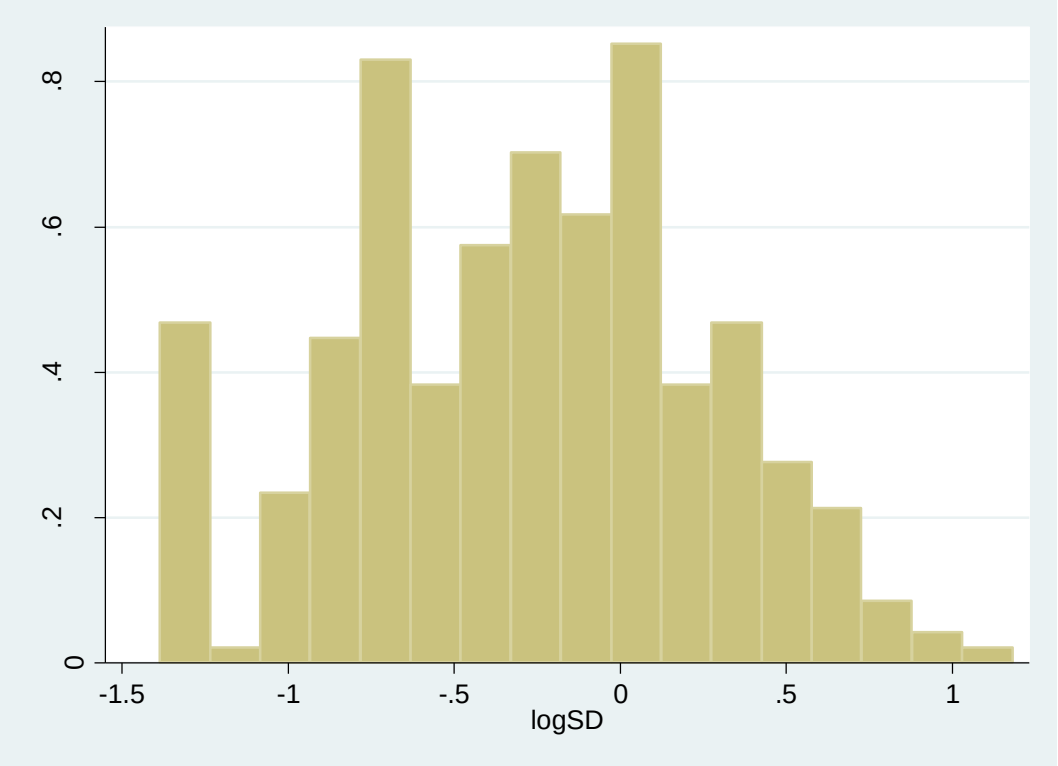
The variability Index was found to violate the normality assumptions (Figure 7.6); a log transformation was therefore performed into order to fit a linear mixed model to assess the association between variability and baseline factors (Figure 7.7).

Figure 7.6: Between subject histogram showing the Variability Index



A logarithmic transformation reduced the variability in the data and produced a variable that conformed closely to a normal distribution (Figure 7.7).

Figure 7.7: Logarithmic transformation of the Variability Index



Significant baseline factors associated with increased variability in pain scores include younger age, higher NRS score, and reporting a stabbing pain quality. Other factors with a positive association include being female, employed, undertaking at least 20 minutes of vigorous or 30 minutes of moderate intensity exercise a week, knee symptoms such as stiffness and limping, previous knee injury, previous knee surgery, longer duration knee problems, activities such as kneeling, climbing stairs, squatting, climbing ladders and reporting pain quality as throbbing sharp, aching, burning, or pins and needles (Table 7.5).

Table 7.5: Relationship of variability and baseline factors using linear mixed model.

	Reference	Log transformed β	95% CI
Demographic and socioeconomic			
Age (years)		-0.14	-0.02, -0.00
Gender	Male	-0.89	-0.31, 0.14
Employed	Not employed	0.18	-0.04, 0.40
Lifestyle			
BMI (kg/m^2)		0.11	-0.01, 0.33
Current/previous knee symptoms			
Pain intensity (0-10 NRS): mean (SD)		0.06	0.01, 0.12
Description of knee symptoms			
Swelling	No	-0.13	-0.28, 0.01
Limping	No	0.14	-0.00, 0.28
Stiffness	No	0.09	-0.05, 0.23
Night pain	No	-0.13	-0.29, 0.04
Pain descriptors			
Dull	No	-0.04	-0.16, 0.09
Throbbing	No	0.14	-0.02, 0.29
Numbness	No	-0.01	-0.88, 0.86
Sharp	No	0.03	-0.13, 0.18
Aching	No	0.01	-0.10, 0.13
Burning	No	0.07	-0.14, 0.27
Stabbing	No	0.34	0.17, 0.51
Pins and needles	No	0.12	-0.72, 0.96
Knee history			
Duration knee problem:	<1 year		
1-5 years		0.09	-0.22, 0.41
>5 years		0.18	-0.06, 0.42
Previous knee injury	No	0.09	-0.14, 0.32
Previous knee surgery	No	0.04	-0.22, 0.30

	Reference	Log transformed β	95% CI
Physical activity exposures			
Potential triggers			
Kneeling for 30 minutes or more	No	0.05	-0.15, 0.25
Climbing more than 5 flights of stairs	No	0.13	-0.05, 0.32
Lifting/ moving heavy objects	No	-0.11	-0.29, 0.07
Squatting for 30 minutes or more	No	0.12	-0.14, 0.37
Climbing ladders	No	0.05	-0.23, 0.31
Exercise			
20 minutes vigorous activity ≥ 1 x week	None	0.14	-0.09, 0.36
30 minutes + moderate intensity ≥ 1 x week	None	0.12	-0.10, 0.34
Knee related healthcare utilisation			
Seen GP in last 12 months	No	-0.00	-0.24, 0.23
Takes medication regularly	No	-0.02	-0.24, 0.21

BMI Body Mass Index; NRS Numerical Rating Scale; SD Standard Deviation

7.3.4 Objective 2: Duration and severity

The median duration for a flare-up was 8 days (IQR 3, 23). The durations ranged from 2-30 days.

The majority of participants experiencing flare-ups reported an increase of 3 and over in their NRS score between baseline and peak pain intensity (Table 7.6). For example, 44% of participants experienced a peak pain intensity which was 2 points greater than their 'normal' reported pain at baseline, for 2% (1) of participants their peak pain was 6 points greater than their 'normal' pain.

Table 7.6: Difference between baseline reported NRS and peak intensity during a flare-up

NRS point difference	Frequency (%)
2	24 (44)
3	21 (39)
4	7 (13)
5	1 (2)
6	1 (2)
Data are from 54 flares from 30 participants	

Comparison of recalled flare-ups reported at baseline in the preceding 12 months and flare-ups experienced within the diary period

Comparing recalled flare-ups reported at baseline versus flare-ups experienced during the three months of data collection suggests that there may be an element of recall bias and suggests that participants may not be able to recall accurately the flare-ups they experience. Alternatively, their interpretation of a flare-up may differ

from that imposed in this study. Those reporting a high frequency of flare-ups at baseline do not necessarily appear to be experiencing a higher frequency in the dairy studies (Table 7.7).

Table 7.7 Comparison of recalled flare-ups reported at baseline in the preceding 12 months and flare-ups experienced within the diary period

Recalled frequency of flares in previous 12 months at baseline	Flares during diary period n (%)
0	1 (3)
1-2	6 (20)
3-4	5 (17)
5-6	6 (20)
7-8	1 (3)
9-10	3 (10)
10+	8 (27)

7.3.5 Objective 3: Triggers and prodromal symptoms

A case-crossover analysis using conditional logistic regression was used to examine if there was an association between certain triggers, prodromal symptoms and descriptors and a flare-up. The analysis used discordant pairs to calculate odds ratios (310) (Table 7.8). A worked example can be seen in Appendix P.

Table 7.8: Illustration of how discordant pairs were used in the case-crossover analysis

	Ca+Co+	Ca+Co-	Ca-Co+	Ca-Co-	OR (95%CI)
Exposure X	n	n	n	n	Ca+Co- / Ca-Co+

Ca+ = exposed in the case window (i.e. prior to flare)
Ca- = not exposed in the case window
Co+ = exposed in the control window (i.e. prior to no flare)
Co- = not exposed in the control window
n = number of paired observations

In the 48 hours prior to a flare-up there is an association between any physical exposure and flare onset (Table 7.9). Climbing ladders was the only single variable significantly associated with flare-ups.

Table 7.9: Case crossover analysis of physical activity exposures using discordant pairs

	Ca+Co+	Ca+Co-	Ca-Co+	Ca-Co-	OR (95%CI)
Any exposure	36	35	16	77	2.19 (1.22, 4.05)
Kneeling for 30 minutes or more	0	12	9	143	1.33 (0.56, 3.29)
Climbing more than 5 flights of stairs	21	19	13	111	1.46 (0.72, 3.04)
Lifting/moving heavy objects	2	22	11	129	2.00 (0.98, 4.28)
Squatting for 30 minutes or more	0	4	3	157	1.33 (0.28, 7.15)
Climbing ladders	5	18	1	140	18 (3.29, 378.9)

Ca+Co+ Pairs of observations where there was exposure to the risk factor in the 48-hour case window and also in the matched 48-hour control window
OR Odds ratio, calculated from discordant pairs (Ca+Co- / Ca-Co+)

In the 48 hours prior to a flare-up there is a positive association with symptoms such as stiffness and night pain (Table 7.10).

Table 7.10: Case crossover analysis of potential prodromal symptom exposures using discordant pairs

	Ca+Co+	Ca+Co-	Ca-Co+	Ca-Co-	OR (95%CI)
Knee swelling	45	8	10	101	0.80 (0.30, 2.06)
Limping	70	7	11	76	0.64 (0.23, 1.65)
Stiffness	44	30	15	75	2.00 (1.09, 3.81)
Night pain	18	16	6	124	2.67 (1.07, 7.43)

Ca+Co+ Pairs of observations where there was exposure to the risk factor in the 48-hour case window and also in the matched 48-hour control window

OR Odds ratio, calculated from discordant pairs (Ca+Co- / Ca-Co+)

In Table 7.11 the results suggest that in the 48 hours prior to a flare-up participants may increase their usual medication. They are less likely to continue their normal medication.

Table 7.11: Case cross over analysis of potential medication changes prior to flare-ups using discordant pairs

	Ca+Co+	Ca+Co-	Ca-Co+	Ca-Co-	OR (95%CI)
Increased medication	9	19	14	122	1.36 (0.68, 2.77)
Reduced medication	27	12	13	112	0.92 (0.41, 2.05)
Normal medication	86	19	16	43	1.19 (0.61, 2.35)

Ca+Co+ Pairs of observations where there was exposure to the risk factor in the 48-hour case window and also in the matched 48-hour control window

OR Odds ratio, calculated from discordant pairs (Ca+Co- / Ca-Co+)

The pain descriptors that participants reported appeared to change prior to a flare-up (Table 7.12). Sharp and burning pain descriptors were significant factors. Other

factors, although non-significant include; throbbing, burning and stabbing.

Participants were less likely to report a dull pain in the 48 hours prior to a flare-up.

Table 7.12: Case cross over analysis of potential pain descriptors present prior to flare-ups using discordant pairs

	Ca+Co+	Ca+Co-	Ca-Co+	Ca-Co-	OR (95%CI)
Continuous pain descriptors (Dull, aching, throbbing)	118	12	9	25	1.33 (0.56, 3.29)
Dull	46	10	18	90	0.56 (0.25, 1.20)
Throbbing	27	20	17	100	1.18 (0.61, 2.28)
Aching	86	21	13	44	1.62 (0.81, 3.32)
Intermittent pain descriptors (stabbing, sharp)	48	29	9	78	3.22 (1.56, 7.19)
Stabbing	34	14	7	109	2.00 (0.81, 5.29)
Sharp	26	24	10	104	2.40 (1.17, 5.25)
Neuropathic pain descriptors (numbness, burning, pins and needles)	21	23	9	111	2.56 (1.20, 5.81)
Numbness	-	-	-	-	-
Burning	20	20	9	115	2.22 (1.03, 5.13)
Pins and needles	-	-	-	-	-

Ca+Co+ Pairs of observations where there was exposure to the risk factor in the 48-hour case window and also in the matched 48-hour control window

OR Odds ratio, calculated from discordant pairs (Ca+Co- / Ca-Co+)

7.3.6 Objective 4: Actions in response to flare-ups

The frequency of participants reporting seeing their GP was low, however the results suggest that more participants saw their GP on flare-up days compared to resolution or non-flare days (Table 7.4). How often a flare-up is accompanied by seeing a medical professional was described using proportions. On flare-up days the proportion of participants taking more medication than normal increased and those

taking less than normal reduced (Table 7.4). Figure 7.9 demonstrate the changes in medication taken prior to and after flare-up onset. It is only at flare onset that participants appear to be increasing medication and the proportion doing this steadily declines after day 2 of the flare-up.

7.4 Discussion

This study supports evidence that for some people knee OA is characterised by intermittent, acute, sudden episodes of pain with associated changes in pain quality, knee symptoms, medication and interference with activity.

In this study population, where participants were eligible for inclusion based on a recent history of knee symptoms, pain intensity was highly variable for some and relatively stable for others. It is interesting that within this highly selected group pain profiles showed considerable variation. Those with higher variability tended to experience more flare-ups. These findings are similar to those in other diary studies of OA pain (227, 314) and in other chronic diseases such as fibromyalgia (309). In a study by Murphy et al (61), 78% of the participants reported pain flare-ups, however these were short-lived so may in fact represent ‘minor’ episodes of pain rather than flares. Those with higher variability in pain scores experienced multiple flare-ups, were of a younger age, had higher pain intensity levels at baseline and were more likely to report a stabbing pain. Those with higher variability in pain scores may be undertaking activities that lead to an increase in their pain or their pain may not be controlled with their pain medication. Trouvin et al, showed similar variability in pain

scores after undertaking a 28 day daily diary study recording daily pain intensity and presence of other symptoms such as stiffness in patients with hip and knee OA, finding that over half of the participants fell into a ‘stable’ pain trajectory (n=59.5%) (227).

Nearly half of participants within this sample experienced flare-ups and approximately half of these experienced multiple flare-ups. This compares to the CAS(K) analysis where nearly a third were estimated to have had a flare and the cross-sectional survey where 90% experienced flares. These estimates will be sensitive to the definition and the population used. However, they suggest that flare-ups are a common occurrence for certain patients with knee osteoarthritis.

Identifying potential triggers are important in the management of flare-ups in terms of activity avoidance and prevention. Results from this study suggest that kneeling for 30 minutes or more, climbing more than 5 flights of stairs, lifting/moving heavy objects, squatting and climbing ladders all have some association with triggering a flare-up; climbing ladders being the only significant variable. These variables were also shown to be risk factors for OA onset (32). Recognising early changes before flare onset, such as knee stiffness, swelling, limping and night pain, which are items included in tools for diagnosing flares (55), could also be important for early episode management and prevention.

In response to a flare, over a third of participants increased their medication and a small number stopped usual activities. Some were found to take less medication prior

to a flare and it could be speculated that this contributed to flare onset. This notion is relied upon in the context of flare-design drug withdrawal studies, where participants are asked to stop their usual pain medication in order to bring on an acute event (69, 160).

Interestingly those who reported a higher frequency of flare-ups at baseline over the previous 12 months were not necessarily those who were found to have a higher frequency of flare-ups in the diary study. This may suggest inaccurate recall or misclassification. Patients may have different interpretations on what constitutes as flare. The term flare, may encompass the less and more severe episodes of pain for some people**.**

The strengths of this study include repeated, intensive measurement of variables to try and minimise recall bias. The diary was developed with input from the PPIE group. The diaries were well completed with only 2% of person days where all of the items were missing.

Limitations of the study include the small sample size, inclusion of non-validated items, and potential for retrospective completion of diary entries. To minimise this participants were advised to leave the day blank if it was missed and to return diaries at monthly intervals.

The study population was based on two general practices in two market towns in Shropshire. This population is a highly selective sample with a mostly white ethnicity, higher education levels and lower deprivation which limits the overall generalisability

of the findings. Furthermore, those who responded to the questionnaires may have been those more likely to experience flares .

The most common missing items were change in medication, whether pain had stopped usual activities and whether a GP had been seen that day. This may reflect the ordering of questions or habituation which is a known problem in daily response studies . The amount of missing items increased as the study progressed which may be due to fatigue.

There was a trend for reducing frequency of flare-ups over the study period. This may impact on validity assumptions in the case-crossover analysis as this analysis assumes risk of event stays stable over the study period. It is uncertain why flares reduced over the study period however qualitative studies have highlighted how patients avoid activities that may trigger their pain (53, 64). The reduction in flare-ups may be due to participants avoiding activities that may bring them on. This has implications for future studies, which have longer flare-ups due to the diminishing returns.

The study findings will contribute to patient education about the probable duration of flare-ups, symptoms that might be expected, and to be aware of individual potential triggers. Further larger scale research is needed to explore physical triggers and the types of activities that cause these acute events. Exploring patient understanding of flares is important in moving forward to a consensus definition of a flare that is able to

differentiate between flares and within person variability. This would be best achieved through a qualitative study.

7.5 Summary

This study with intensive longitudinal data collection confirms the earlier observations that acute flare-ups may be experienced by a substantial number of patients. It adds new evidence that these episodes often last a week or longer, are disruptive, prompt changes in self-management, and may be triggered by high-loading physical activities such as heavy lifting. It has also highlighted areas to be explored further from the patient perspective.

8. Patients' perspectives of flares in knee osteoarthritis: a qualitative study

The previous studies in this thesis have used quantitative methods to understand knee OA flares. This chapter uses qualitative methods to explore patients' understanding of flares particularly with reference to help-seeking and self-management strategies employed.

8.1 Introduction

Previous chapters have contributed to our understanding of how flares might be defined, temporal changes, variability of symptoms, potential triggers and responses to flares. However, there is a need to increase our understanding of the patients' perspective: patients' understanding and experience of flares, experience of symptom variability, self-management strategies and help-seeking behaviours, their understanding of triggers, and the overall impact of flares. Previous qualitative studies have described experiences of intermittent acute pain and the variability of OA symptoms in the context of chronic OA (53, 62, 64). Gooberman-Hill et al (2007) conducted focus groups on 14 men and 14 women aged between 57-89 years from the Somerset and Avon Health Survey who reported hip or knee pain in the previous 12 months (64). The participants described pain that was intermittent and variable changing monthly, daily and throughout the day, pain that was triggered by certain

functions and the avoidance of activities that might bring on pain which highlights the broad spectrum of onset and duration of pain in those with potential OA. Hawker et al (2008) undertook focus groups involving 143 people aged 40 years and over with hip and knee OA from the community and previous OA cohorts (53). Participants described pain that was intermittent and predictable early on in the disease course which became unpredictable and distressing, more burdensome and interfered more with activities as it progressed. The patients included, however, were more likely to have had OA for a longer duration and few had mild disease which means conclusions on pain experience related to severity of OA should be interpreted cautiously. Cedraschi et al (2013) also undertook focus groups on 14 people aged 40-75 years with severe hip and knee OA recruited from primary and secondary care clinics (62). Participants also described the variability of OA pain and highlighted that this could vary daily, and how they managed the pain by avoiding certain activities. Participants in this study had severe OA and so may not represent the pain experience of patients with less severe symptoms. Participants in these initial focus groups all described the variability of pain in OA, the potential impact of intermittent pain, avoidance and adaptation strategies, and its predictability. However, focus groups do not allow for the individual experience to be explored in detail and there can often be a 'group' effect (86).The majority of participants in these studies were white so this limits generalisability of findings. To understand these intermittent increases in pain further face-to-face individual interviews would allow flares to be explored in more depth, gaining an understanding of patient perceptions of flares,

whether patients can differentiate between different severities of flares, understanding different management strategies employed, the impact of flares, their predictability, and whether this changes over time. These are key areas that have not previously been explored in depth that I hope to address further. Murphy et al focussed specifically on flares in their study of 45 participants aged 50 years and over with confirmed knee OA recruited from pain clinics (61). They undertook a brief interview to understand patient perceptions of flares at baseline and then asked participants to record their pain 8 times a day in a logbook along with descriptions of their pain experiences that were recorded in logbooks. Participants described mostly short lived episodes of pain lasting up to 15 minutes which may not encompass the full spectrum of flares that has been reported in the previous studies presented in this thesis (61). A high frequency of this population (78%) experienced flares during the 7 day period, however the participants are likely to have had more severe symptoms than those managed in primary care as they were recruited from pain clinics. Furthermore, experiences with regards to predictability, pain descriptions reported and frequency of flares may not be generalizable. Although all of the qualitative studies mentioned intermittent pain or flares being brought on by activity, none seem to mention the concept of undertaking an activity despite knowing it would trigger a painful episode, e.g. attending an importance event, or the ability of an activity to cause delayed onset pain, for example, one to two days later. Exploring this further would be interesting in the context of the findings from the case-crossover analysis in

Chapter 7 and highlight the patient perspective of this and whether they are aware of any proximate triggers for their intermittent pain.

Gaining a deeper understanding of flares from the patients' perspectives, how they impact on their lives, increasing understanding on severe and less severe flares, patients' awareness and response to knowledge around triggers is important. Furthermore, reasons for help-seeking have not been explored before and understanding this could have an impact on how flares are managed in the community setting. Differentiating between different severities of flares may helpful for patients and clinicians in terms of how they are identified and managed. The findings from my interviews will highlight which aspects of flares are important to patients and this may guide the key components that should be considered in a consensus definition of a flare. The findings will also guide patient education material and discussions with clinicians about what is important to patients when understanding flares. Using a mixed methods approach, by comparing and contrasting findings from different methodologies, will provide a deeper and broader understanding of flares from the patient perspective and will help improve the value and quality of the findings from this thesis.

8.2 Aims and objectives

Aim

The aim of this qualitative study was to explore patients' understanding on flare-ups or exacerbations in knee osteoarthritis and explore self-management and help-seeking strategies used.

Objectives

Using qualitative methods to:

- Explore patients' views on the nature of exacerbations or flare-ups
- Explore patients' views on how best to define exacerbations or flare-ups
- Explore patients' views on precipitants and time course of flare-ups
- Describe how patients report managing flare-ups of pain including self-management strategies and help-seeking behaviours

8.3 Patient and Public Involvement and Engagement

The aims for the PPIE in this study were to strengthen the study design and comment on the initial interpretation of the data and illustrative model. These were achieved through the following objectives:

- Evaluate the study design with specific reference to the aims and objectives
- Evaluate the topic guide
- Explore the use of pain graphs during the interviews

- Explore lay members' views on interpretation of results

Two PPIE meetings were held at Keele University. PPIE group members recruited for this study had personal experience of osteoarthritis. The first meeting was held during the design stages of the study and was attended by a study researcher (EP), a PPIE project coordinator (Adele Higginbottom) and five PPIE group members with osteoarthritis. During this meeting an overview of the study was given and each member was given a topic guide and a copy of example pain graphs to help stimulate discussion. As a result of this meeting the order of the questions in the topic guide was amended. The PPIE discussed the use of pain graphs over time to give an idea of patient perceptions of their experiences of pain over the previous six months. The lay members drew their own pain graphs and felt this was a useful exercise for reflecting on how their pain had changed over time. Six months was felt to be an appropriate time frame and the PPIE felt that participants could produce informative diagrams. The PPIE suggested that these graphs could be used as discussion points for certain interview questions, for example triggers and management during flare ups. In addition, the PPIE group advised to use example graphs to give participants an idea of what a graph might look like and then ask them to draw their own. These suggestions were incorporated into the study design.

The second meeting was held during the analysis phase of the study when data generation was complete. This was facilitated by study researchers (EP and CC-G), a PPIE project support worker (Laura Campbell), and 3 PPIE group members. Members of the group were presented with data extracts from transcripts which were

used to illustrate the emerging themes and sub themes. The PPIE group members were asked if they agreed with the researchers' interpretation of the data extracts and the grouping into the overarching themes: patient understanding, experiencing pain, managing pain, help-seeking, and anticipating future. They were also asked for their additional insights and perspectives. Overall, there was agreement with the researchers' overarching themes and they provided additional insights which could be explored further, which included: guilt felt by participants after undertaking an activity they thought brought on a flare, the importance of impact of flares on quality of life and social life, use of the term 'flare' by patients, understanding the participants living status; for example if they lived alone or not and co-morbidities were thought important to understand how flares were managed, flare prevention, and help seeking from family and friends. The majority of these were explored further by the study team by revisiting the transcripts and codes, and incorporating them into the analysis. The PPIE members also commented on the proposed model to illustrate findings; this is presented at the end of the findings section (Figure 8.6)

Following the PPIE meeting, the comments on the models and the additional insights provided on the quotations were used to revisit the data. This led to the development of the final overarching themes and a new model (Figure 8.7) that highlighted the importance of the impact of flares on the individual.

The PPIE group also provided advice on dissemination, which included putting up posters in GP waiting rooms, writing patient material for Versus Arthritis, presenting

at conferences, and publication in medical journals with a primary care and/or OA focus.

The PPIE group contributed to refine the data collection methods and gave their own perspectives on the research findings. Their key contributions included ordering of the questions in the topic guide and asking participants to draw their own pain graphs and to use these as discussion points. In the analysis phase, they supported the study team's interpretations of the overall themes and suggested furthers areas to explore in the analysis. The number who attended the second PPIE meeting was small (n=3), however all members made contributions and the group gave different perspectives that had not previously been considered.

8.4 Methods

8.4.1 Study design

A qualitative study using semi-structured interviews was conducted using a topic guide to generate data.

8.4.2 Recruitment and sampling

8.4.2.1 Study population

Potentially eligible participants were identified from the patients registered at two general practices in the West Midlands. Inclusion criteria: patients who were at least

45 years or older, with a Read-coded problem in the last two years for knee osteoarthritis or knee pain/arthralgia and who were not in a vulnerable group (for example, those with cognitive impairment or a terminal illness) as judged by their general practitioner (Table 8.1). Those identified were sent the initial mailing pack after GP list screening. This included the invite letter with the consent to contact form, eligibility questions and the patient information sheet (Appendix Q).

Patients were purposively sampled and invited to take part in the interviews if they returned the reply slip indicating a willingness to take part in the study and reported a recent knee flare-up in the past 12 months by answering 'yes' to the following question: *In the last 12 months have you had an increase of your knee pain, that is times when your knee pain is worse than normal which may have stopped you from doing your normal activities or meant you had to increase your pain medication?*

8.4.2.2 Eligibility criteria

Inclusion and exclusion criteria are listed in Table 8.1.

Table 8.1: Inclusion and exclusion criteria for qualitative study

Inclusion criteria
Aged 45 years and over
Read-coded consultation for knee osteoarthritis or knee pain/arthralgia in the previous 2 years
Male or female
Returned the reply slip indicating a willingness to take part in the interviews and reported a recent knee flare-up in the past 12 months

Exclusion criteria
No knee pain in the last 12 months
Diagnosis of inflammatory disease (rheumatoid arthritis, polymyalgia rheumatic), crystal disease (gout), spondyloarthropathy (e.g. ankylosing spondylitis), and fibromyalgia at GP list screening
Previous total knee replacement in index knee
Those judged to be vulnerable/inappropriate to survey by their general practitioner (e.g. dementia, terminal illness)

8.4.2.3 Mailing

Practice staff supported by members of the National Institute for Health Research (NIHR) Clinical Research Network (CRN) of West Midlands and informatics teams, who are contracted to work in the participating GP practices and are considered part of the GP practice team, liaised with the GP practices and the study team. GP practice staff screened records to identify adults aged 45 years and over who consulted with knee pain/OA in the previous two years.

GPs were invited to screen the sample list for patients whom they considered should be excluded from the invitation mailing (e.g. vulnerable individuals).

The purpose of the initial mailing was to:

- Identify eligible responders.
- Obtain consent to contact to take part in the study.

A one stage mailing procedure was used and eligible participants were mailed study packs via Docmail. The study packs (Appendix Q) included a letter of invitation with attached reply slip and eligibility questions, patient information sheet and stamped return envelope from the patient's GP inviting them to take part in the study. The patient invitation letter contained my work telephone number and email address to give patients the option of registering interest in the study via this method, rather than by returning details by post. Patients were also able to use the contact number and email address to request any further information about the project if needed.

8.4.2.4 Consent

Participants were asked to complete a reply slip attached to the initial invite letter (Appendix Q). This enabled potential participants to register their interest in the study and allowed the study team to contact them about arranging a face-to-face interview.

At the start of the interview, each participant was asked to provide written informed consent by signing a consent form (Appendix S).

8.4.2.5 Purposive sampling

Those that returned reply slips and were eligible to take part in the interviews were purposively sampled based on age (in order to include a wide range of ages) and gender (to provide even numbers of males and females). This was to ensure the participants that were included in the study contributed data reporting a range of views and experiences (110).

8.4.2.6 Participants

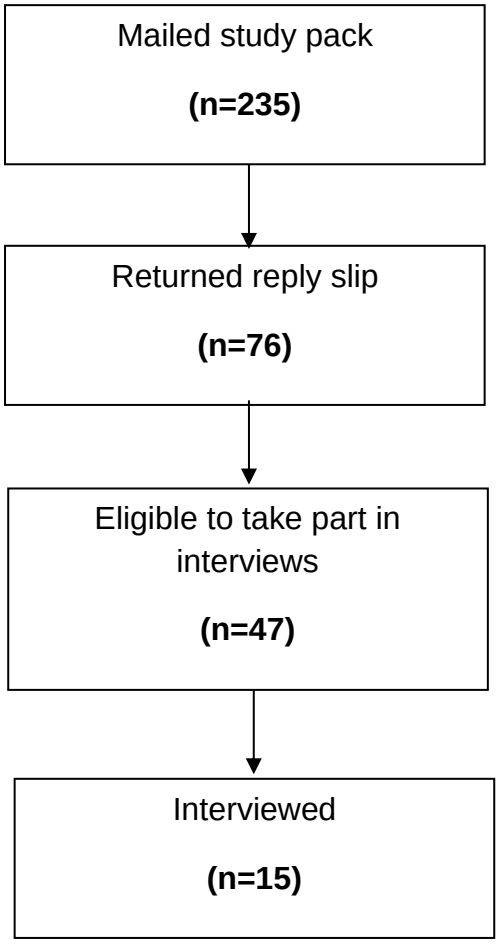
Recruitment and interviews were continued until data saturation was achieved (85, 105). Prior to this however, an estimation of the number of potential participants to approach was required. This estimation helped guide the CRN in their selection of general practices to ensure they had an adequate population size. For this study, it was estimated that between 12-15 participants would likely be required to achieve data saturation based on one previous qualitative study using in-depth interviews by Guest et al 2006, who found that by 12 participants very few new codes were being generated and little new information was being produced (315). Based on the sample size calculation required to estimate the number of eligible participants with knee pain or knee osteoarthritis in Chapter 6, it was decided to approach two general practices to produce approximately 511 eligible responders. This estimate was partly based on known response rates to previous qualitative studies; an interview study exploring knee pain from within the SPCSC received a response rate of 15% after writing to those already participating in a cohort study (316). Given that in this study not all responders would be eligible and to allow for purposeful sampling (whereby a broad range of ages and even distribution of gender would be achieved) it was deemed acceptable to mail out from two general practices to recruit sufficient participants. In total 235 people were mailed the initial mailing pack from the two practices. Of the 76 that returned the reply slip, 47 were eligible (see Table 8.1 for eligibility criteria) and were purposively sampled (Figure 8.2). To ensure an even distribution of gender and age the potential participants were split by gender and

arranged by age category (for example, 45-54 years, 55-64 years, 65-74 years, 75-84 years and 85 years and older). Contact was made to ensure each age category was represented and that this included an even distribution of gender.

8.4.3 Data saturation

Interviews were conducted until data saturation was achieved. Data saturation is when a point is reached where gathering more data does not add any new information or insights in terms of the development of categories or of the relationships between them and additional data would be counterproductive (85, 105). It is difficult to predict when data saturation might be achieved as it depends on a number of factors including method, design, topic and scope of the study (127). Data saturation is important to achieve to ensure the data reflects the views and perspectives of the participants (317).

Figure 8.1: Flowchart of response for the qualitative study



8.4.4 Ethical considerations

Favourable ethical opinion was granted by the Office for Research Ethics Committees Northern Ireland on 8th May 2017. REC reference: 17/NI/0091 (Appendix V).

8.4.5 Data collection

Interviews were conducted by me. All participants chose to be interviewed at home. The lone worker policy for Keele University was followed (https://www.keele.ac.uk/policyzone/data/loneworkingpolicy/). During the interviews I did not disclose to participants that I was a GP unless I was asked. I felt this would allow the participants to discuss their experiences, particular those of healthcare more freely.

8.4.5.1 Topic guide

A topic guide was developed to maintain structure during the interviews and to ensure all relevant topics were discussed. The topic guide was informed by the literature, previous studies presented in this thesis and was reviewed and refined by the PPIE group.

The topic guide explored the participants' experiences of knee OA flares which included how participants' described flares, how they managed them, and help-seeking strategies used (Appendix U). During the interview the participants were also invited to draw a diagram to represent disease course over time and to indicate flare-ups diagrammatically. Participants were shown example pain graphs overtime, which were adapted from Stone et al (117), to give participants an idea of different types of pain graphs (Appendix T). For participants who were not able to or were uncomfortable drawing their pain graph, they were asked to identify which of the example graphs best described their pain experience. The graphs also served as a

talking point to generate further discussion during the interview on triggers for flares and management strategies.

As interviews were undertaken and transcripts reviewed with the study team, the topic guide was modified as themes emerged (Appendix U).

8.4.6 Transcription

Interviews were digitally recorded and stored on an encrypted audio recording device. They were uploaded onto the SPCSC secure network drive in a password protected folder. The first three interviews were transcribed verbatim by me. The remaining interviews were transcribed verbatim by a transcription company approved by the SPCSC. Transcripts were upload using a secure web link. The transcripts were delivered via email. Following this they were saved onto the SPCSC's secure network drive in a password protected folder and the email was deleted. All transcripts were assigned ID numbers, checked through for accuracy and any identifiable information was removed prior to analysis. The transcriptions were managed in QSR NVivo 12, a qualitative data analysis software package (318).

8.4.7 Reflection on data collection

After each interview, I made reflective notes on thoughts that arose, potential emergent themes, what went well and what could have been improved (107). Notes

and reflections were also made during the transcription process, reading of transcripts, when undertaking coding and after supervision meetings.

8.4.8 Data analysis

8.4.8.1 Thematic analysis

Analysis began as the interviews were conducted, and the process was iterative. The data was analysed using constant comparison methods (319), where the researcher interacts and is actively involved in the data and the emerging analysis, making comparisons at each stage. The method involves comparisons of text segments through coding, recoding, and memo writing in order to generate themes and concepts.

The analysis was undertaken separately by myself and two supervisors (CC-G and LD) followed by team discussions at each of the coding stages in order to arrive at an agreed coding framework. CC-G is an academic GP and experienced qualitative researcher. LD is a social scientist and ethnographer with extensive knowledge of qualitative research methods.

8.4.9 Practical process of data analysis

The first step, also known as ‘open coding’, that was undertaken was code generation. Reading through transcripts and using the topic guide as a reference the initial categories were generated using NVivo software (Table 8.2). The next step,

also known as ‘axial’ coding, allowed connections to be made between the categories by comparing and asking questions of the data (317). During the final stage of coding, called ‘selective coding’, the codes were read through again, making further comparisons and connections. This was done by constructing a table to easily view similarities and differences of the codes in order to form the core categories (105) (Appendix W). Coding took place after each interview was transcribed. This enabled early identification of emergent themes, modification of the topic guide, and allowed the researchers to identify when data saturation had been achieved. At each of the coding stages, memos were recorded in NVivo.

Table 8.2: Stages of data analysis (adapted from Braun and Clarke, 2013) (320)

Step 1	Familiarization with transcripts
Step 2:	Initial code generation
Step 3:	Comparison of codes across transcripts
Step 4:	Identification of emergent themes
Step 5:	Agreement of final themes with PPIE

8.4.9.1 Maintaining quality

Ensuring methodological rigour in qualitative research is important. An audit trail was kept and notes were written at each point of the research process to help maintain quality. It also ensured transparency of the data collection process and analysis (119). The analysis was undertaken as part of a team, who had different professional backgrounds which allowed group comparisons of data interpretation and review of

coding frames and emergent themes (86, 321). A sample of transcripts were coded independently which helped improve the quality of the data (322). Multiple coding of parts of the data helped guide discussions particularly around disagreements in order to refine coding frames and provide alternative interpretations (321) .

8.5 Findings

The demographics of the 15 participants are given in Table 8.3.

Table 8.3: Characteristics of interviewees

ID	Gender	Age	Duration of knee pain (years)	Living status
001	Male	51	3	Lives with partner
002	Male	78	50	Lives with spouse
003	Female	66	1	Lives alone
004	Female	81	11	Lives with spouse
005	Male	59	20	Lives with spouse
006	Female	68	7	Lives with spouse
007	Male	83	3	Lives with spouse
008	Male	66	30	Lives with spouse
009	Male	64	2+	Lives alone
010	Female	69	6	Lives with spouse
011	Female	70	5	Lives with spouse
012	Male	81	60	Lives alone
013	Female	78	4-5	Lives with spouse
014	Male	85	6	Lives with spouse
015	Female	85	1	Lives with daughter

Verbatim quotes are presented using the following format:

ID (age, gender)

To gain a greater depth of understanding of the results Leventhal's self-regulatory model (SRM) was used during the analysis stage to help illustrate and understand findings. During the initial and final stages of coding and when organising codes into themes, memos were made which highlighted links to the five components in the SRM.

The SRM provides a framework to understand the perceptions, thoughts and behaviours individuals have on their own health conditions and is one of the most tested models for understanding behaviours in healthcare research (323). It has also been used to understand the patient's approach to management of their condition (324). The SRM comprises five components linked to how patients identify they have a condition, beliefs on how long it may last, the impact the condition may have, its potential causes and the extent to which symptoms can be cured or controlled (Table 8.4). These beliefs are important to understand as they can over-reaching effects, for example, they can influence beliefs on how effective a treatment is likely to be which in turn may impact on compliance. Each component of the model aligned better with the aims and objectives of this study compared to other models such as the health beliefs model where six constructs such as risk benefit are thought to determine health behaviour (325), the Burden of Treatment Theory which explores the added burden of patient self-management (326) and the Candidacy model whereby patients judge their own eligibility for healthcare based on individual experiences and the healthcare services (327).

Table 8.4: Five components of Leventhal's Self-Regulatory Model (adapted from Leventhal et al 2016 and Hale et al 2007 (324, 328))

Core component	Description
Identity	The label or name given to a condition and perceptions of its associated symptoms or conditions.
Timeline	Beliefs on temporal characteristics (e.g. onset and duration). For medication, the expected benefits incongruous to that experienced may lead to non-adherence to treatment.
Consequences	Beliefs on consequences of their illness and the impact it will have on them physically, cognitively and socially. With regard to management, the consequence of unwanted side effects of a treatment may lead to non-adherence.
Causes	Beliefs on causes of their condition or symptoms. These will be based on and modified by a number of different sources, for example, peers, healthcare professionals and previous experiences. These beliefs will also have a role in the perceived effectiveness of certain management options.
Control	The extent to which symptoms or the disease can be cured or controlled. Beliefs can impact on choice of management options.

8.5.1 Experiencing pain: Identifying flares

Participants identified and described flares in a number of ways: change in pain descriptors, change in intensity and magnitude of pain, the speed of onset, their duration, and how frequently they occurred. This resonates with the 'identity' and 'timeline' components of the SRM.

Several participants used graphic and descriptive terms to communicate the intensity of pain during flares, for example "pumping", "red-hot poker" and "tonnes of knives"

(Table 8.5). ‘Sharp’ was also a term that was commonly used to describe pain quality alongside the graphic descriptors.

Table 8.5: Terms used to describe flare pain experience

Graphic pain descriptors	*“it’s like pumping in my knee”* **P001 (M, 51)** *“it’s stronger, it’s not an ache, it’s a definite pain”* **P004 (F, 81)** *“it’s sharp and well you know it makes you wince”* **P008 (M, 66)** *“sharp intense pain”* **P012 (M, 81)** *“Just like a red-hot poker”* **P015 (F, 85)** *“tonnes of knives”* **P003 (F, 66)** *“…it’s just as though someone’s twisting me , twisting me leg”* **P014 (M, 85)** *“Sharp stabbing pain”* **P009 (M, 64)** *“Well just a sudden impact of pain… when it becomes unbearable erm”* **P007 (M, 83)**

The first flare or knee event seemed to be important to participants; they tended to recall this event with clarity, which may indicate they had ‘rehearsed’ their story. These events were described in detail despite, for some, it happening a number of years beforehand. Several participants were able to recall a specific injury that preceded their knee pain but for others it came “out of the blue”. P004 recalled the surprise of her first knee symptoms 11 years previously.

"But, er, no I have no reason why it should happen at all, as I say I was just walking quite normally in [deleted name of town] down towards [deleted name of department store] and it just suddenly gave way….I had no premonition of it, no pain before, or aches or anything, it just happened totally out of the blue." **P004 (F, 81)**

The descriptions of flares mapped onto the 'identity', 'timeline' and 'consequence' components of the self-regulatory model. Participants identified they were having flares when there was an increase in pain intensity and magnitude of pain, and a change in pain quality. The timeline of flares was described in relation to speed of onset and duration. The impact or consequence of the flares, usually in terms of limiting ability to undertake activity was also discussed. Intensity and speed of onset featured in most participant accounts. Participants described understanding what a 'flare' was despite it not being a term they usually used.

"To me it suggests something that erm it sort of comes out of the blue and just sort of suddenly attacks the knee sort of thing you know, yeah, yeah but I've never said I've had a flare-up of my knee, it's not a term I would use truly you know." **P008 (M, 66)**

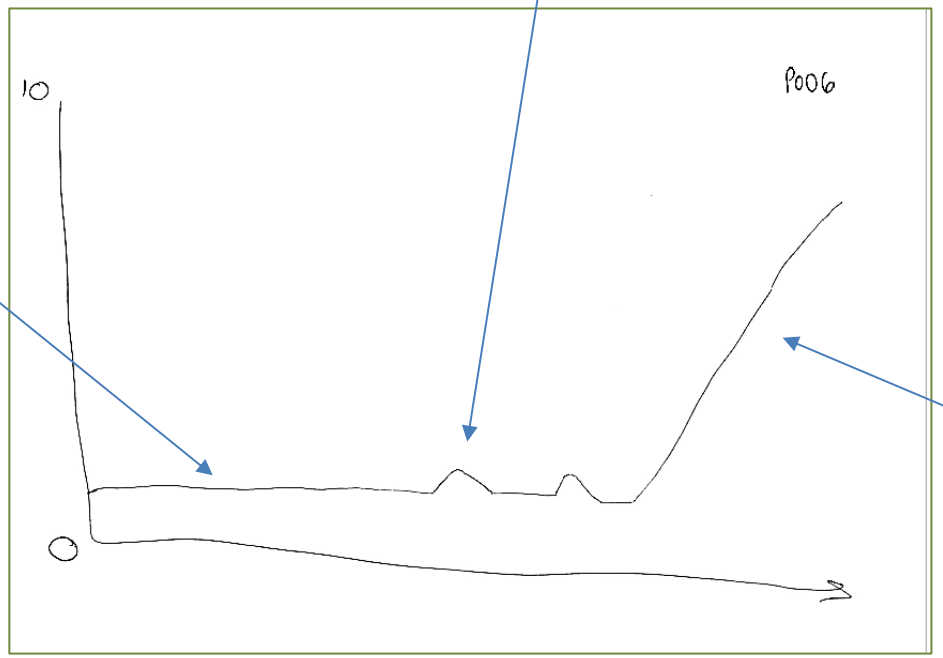
Several participants described the variability of pain intensity and differentiated between different severities of flare-ups in their narratives. They described "slight" or "minor" flares that occurred more frequently and did not have too much impact on daily life and "major" or "big" flares that were less frequent but had more of an impact.

These were also apparent in participants diagrams representing their pain experience (see Figure 8.2 as an example). Participants expressed their apprehension and fear of experiencing these in the future. P006 in Figure 8.2 described a low-level background pain the majority of the time, which was interrupted by minor increases in pain that usually lasted for short periods of time. However, she described experiencing an unexpected sudden increase in pain intensity that was severe and markedly above usual increases in pain intensity.

Figure 8.2: Diagram with quotations by P006 (F, 68) illustrating pain variability over the previous 6 months on a 0-10 numerical scale

"So this is no pain, but I am in pain all the time. But as I say, it isn't anything that I would – I suppose I probably wouldn't class it as pain, although I know it is. I mean it may really irritate some other people, but it's – it doesn't for me – say if that's no pain, my pain probably starts about here and then as I say, it's pretty constant all the way along until I might just get what you class as a slight flare."

"But to me it's probably just where the pain has increased a bit. So that probably would go up, only slightly and then it'd be down within a couple of days. Erm, so that would be probably the pattern and then I'd go again and it'd be fine and then probably again about



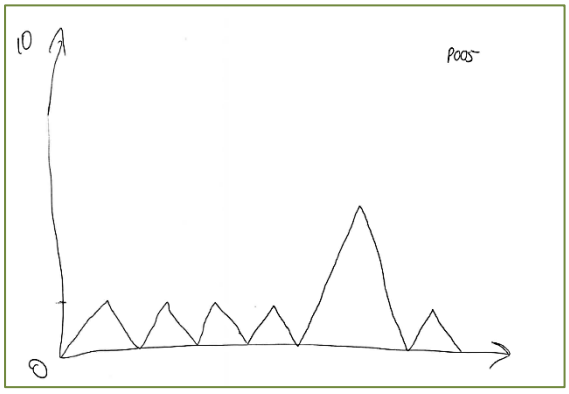
" But then as I say, the other one I've just got along with a bit of pain, but then it just hit and it went right up, really right up."

Participants gave descriptions of more severe flares and recalled, with clarity the symptoms they experienced, the impact it had, and the dates. These were contrasted to ‘minor’ flares that occurred more frequently, had minimal impact and were more likely to be referred to as “just one of those days”.

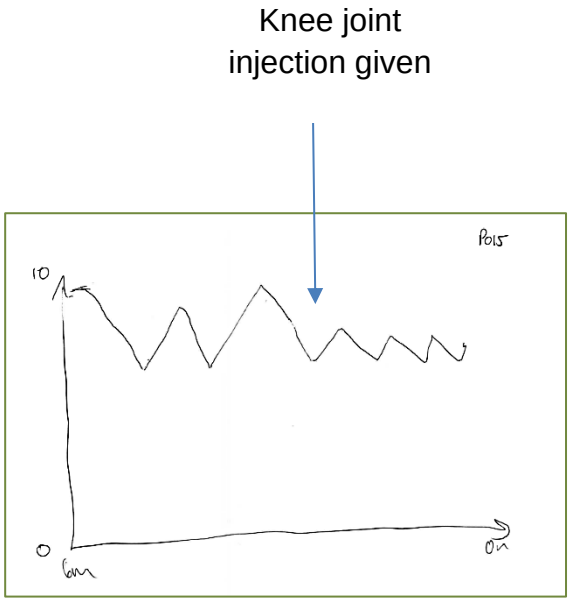
> *“Oh no there was a definite difference in that one last year because it stiffened it all. Really did I shouldn’t have walked on it really…No just the big one was a flare-up yeah. I think that’s fair to say…No, no. These minor ones I have had them for many years and I can live with it.”* **P002 (M, 78)**

The majority of participants distinguished flares or episodes of increased pain from their usual background pain. They did this by referring to the change in magnitude and intensity of the pain during a flare. The diagrams drawn by the participants in Figures 8.2 and 8.3 highlights the variability in the magnitude of the pain intensity, the frequency of increased episodes of pain and the usual level of background pain on which these episodes or flares occurred. For some the flares occurred on a background of no pain and for others it occurred on a background level of pain intensity. Figure 8.3 demonstrates this difference in background pain in two individuals, in both cases after a flare or increase in pain, the intensity returned back to baseline level. For seven participants who identified their pain experience using the example pain diagrams (Appendix T), they reported a similar pattern.

Figure 8.3: Diagrams illustrating pain variability over the previous 6 months on a 0-10 numerical scale for P005 and P015



P005 distinguished between the “big flare-up” and the minor episodes of increased pain in terms of level of pain intensity and impact on usual activities. The flares seen here were reported to be triggered by activity, such as, golf.



P015 described how she experiences the increases in pain every 1-2 months, however in the previous 6 months an injection helped to reduce their severity. The increases in pain were attributed to walking.

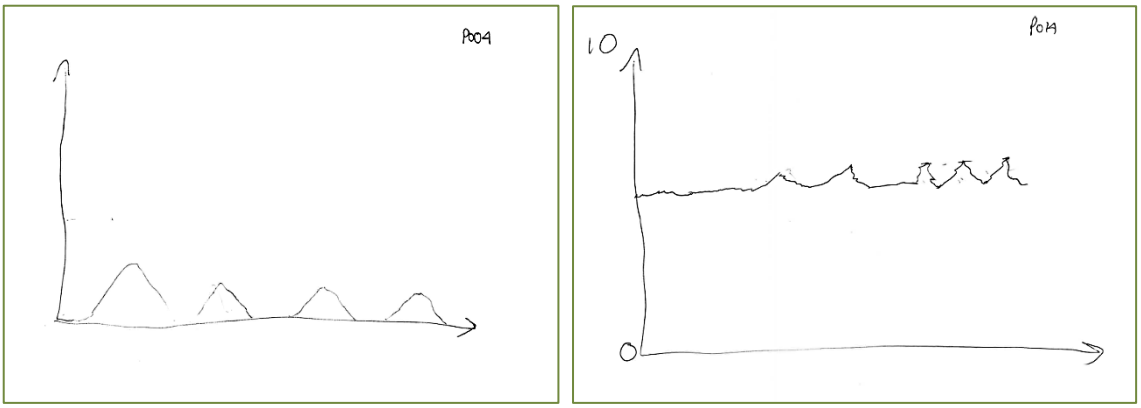
The pain graphs in Figure 8.3 highlight the changes in pain intensity compared to ‘normal’ and the variability in intensity of flares and duration. The graphs encouraged

the participants to reflect on causes for their pain (e.g. playing golf, walking) and reasons for change in severity of flares (e.g. knee joint injection).

For other individuals the magnitude of pain intensity related to flares was stable over time (Figure 8.4). There did not appear any related factors in terms of gender, age, duration of knee symptoms or living status to explain the variability of pain intensity.

P004 and P014, although they had slightly different pain experiences to P005 and P015, identified flares on their diagrams and related increases in pain to activity. P014 reflected on their diagram and was able to highlight that the frequency of his flares was increasing, depicted by the “spikes” getting closer together.

Figure 8.4: Diagrams illustrating pain variability over the previous 6 months on a 0-10 numerical scale for P004 and P014



The perception of timeline of flares featured in all participant accounts of flares. This included speed of onset, duration and frequency. Onset was described as sudden or gradual, however, this could be variable and often changed over time.

"…well I think it is starting to do it sort of straight away now whereas when I used to go up the ceilings, it was the next day, it would show up the next day." **P012 (M, 81)**

Short lived symptoms, for instance, those lasting 10-15 minutes were usually described as occurring with everyday activities. The majority of participants felt the shorter lived episodes were not 'flares'; however there was some discussion that labelling an episode as a 'flare' should be based on pain intensity rather than duration.

"*The ones that last longer I would say are the flare ups. Erm, cos I mean like I say, when it does – like I say – when it does flare up, erm it does start jumping that I have a job to sometimes keep it still."* **P003 (F, 66)**

Participants tended to classify episodes as severe if they lasted longer. Pain intensity was not reported as consistent during flares, it tended to gradually ease off the longer it persisted.

"It can last for weeks before it completely settles down. It eases off, but it doesn't go. It can take a couple of months really for it to really settle down." **P006 (F, 68)**

Duration of flares was reported as being variable. Pain that was severe and 'unbearable' could last for varying time periods. Some could be short-lived and some could last longer. Several participants described the length of episodes as changing

over time. For some participants, during the early stages the flare-ups were reported as only lasting a few days but as time progressed they lasted much longer, for example up to 10 days. This highlights how illness perceptions are changed and updated and how a change in one component of the self-regulatory framework, for example timeline can impact on another; such as change in how people identify with their condition.

> *"Erm, something damaged it in there and it just flares-up, it aggravates it when I do what I said I do, you know, if I twist it, if I've got it straight, I'm okay but if I twist it erm, that's when the pain comes and then takes me a lot longer to get over it now. It used to be a couple of days and I'd be okay but now, it drags on for like perhaps ten days, a week, ten days to get over it…"* **P012 (M, 81)**

Frequency of flares was reported to range from daily, to fortnightly, to every 2 months, and this was often variable between participants. Over time, participants had noted how their symptoms had changed. The descriptions of these changes mapped onto three trajectories: reduced frequency over time, increased frequency over time, or relatively stable over time. Participants had their own health beliefs on causes for their trajectories and put this down to lifestyle changes (positive and negative), for instance reduced activity and the weather.

> *"I think I'm getting them more often but it's probably because I don't do so much erm, they say if you don't use it, you lose it, don't they? So I mean I'm not anywhere near as active as I used to be, I mean, ride bikes and football*

and all sorts of things, swimming, but I don't do that now, so I'm not getting any exercise that I used to have so that might be affecting it cause I'm not doing the exercises which is back down to the physio, which is what the world is trying to tell me but doing the exercises they want me to do, aggravated me pain so I knocked that on the head, rightly or wrongly I don't know but I did…" **P012 (M, 81)**

Associated symptoms that participants mentioned included swelling (which was variable and sometimes present before the pain), stiffness (particularly after being sedentary), and interference with sleep due to night-time pain. Despite these symptoms, a number of participants did not align themselves with the diagnosis. When explored further this was often because they did not feel they had the full range of symptoms that they linked to OA, or because their symptoms were different to someone who they knew did have OA. These participants challenged how they identified with OA or flares based on their experiences and that of peers. Views on diagnosis were also influenced by health professionals, some still using the term "wear and tear".

"I think the doctor said, 'It's probably wear and tear but you have got some arthritis there…" **P013 (F, 78)**

8.5.2 Impact of OA flares

The impact or 'consequence' (beliefs on consequences and impact on physical, cognitive and social abilities) of illness is a key component of the self-regulatory framework (328, 329). Impact of flares was central to the participants' understanding of flares. The impact of flares, for several participants, was more influential of their flare experience than pain intensity and duration.

The ability to carry on with usual activities, despite having to adapt to them was a key part of managing their condition and minimising the impact of flares. Participants frequently talked about their frustration when flares impacted on their ability to participate in certain activities and this seemed more important than the actual severity of the symptoms.

> *"…it's not so much the pain that I can't cope with, it's the inability to, that I can't do things that I find is more debilitating than the actual pain."* **P004 (F, 81)**

Flares impacted on the participants' abilities to undertake normal everyday activities such as those that were related to work and those that were household-related, such as shopping and gardening. For several participants this led to adaptations so that they could still pursue these valued activities.

> *"It does stop me from doing what I need to do work-wise you know, it's not the most physical of work that I do. You know, it's a lot of just going in and saying*

hello to people. So you know, I'm not constantly sort of taking stuff from the car into the retailers that I visit. Erm and occasionally I suppose I have to be careful because I've got a sample storage which is probably like the size of this place [house] erm and that's stacked to the gunnels with stuff and I just have to be a little bit careful when I'm – if I'm having to step up there or step back down really." **P005 (M, 59)**

However, flares sometimes led to the patients having to completely stop the activities that they used to do. These were often recreational activities that the participants got enjoyment from. This could result in a sense of loss.

"Erm, but erm it started playing up and then so I was glad when I retired. But then it started to slowly get worse, I was restricting myself in things, I was getting no pleasure out of some stuff, you know. I couldn't go out much and erm couldn't go dancing or nothing like that you know, them days are gone." **P010 (F, 69)**

Flares also impacted on social life. For example, participants described how flares stopped them from fulfilling regular commitments like weekly meet ups with friends and family. There was also a sense that when meeting up with friends and family that they did not want to be burdensome. One participant explained that she has to pause regularly when out and mentioned that whoever she is with has to keep stopping to wait for her.

"It is stopping me from doing stuff. You know, because I've got two sisters and we used to go shopping every week and there's only sometimes I can go, like I can phone up and say 'I can come to this week' you know. But they keep slowing down for me, I have my stick and we only go to town. I sit down and I have to say 'Right, I've gotta find a seat' and have to sit down for ten minutes, then I'm alright for a little bit longer and that's how it is. And they're ever so good, they wait and hang on for me you know, so. And I go on the bus, it's nice, it's as easy to get on the bus than drive and if it's hurting, cos of this leg, it hurts, yeah. And so I've got a bus pass, I go free on the bus, but yeah, if my knee's hurting I don't drive, it really hurts then. And I'm trying to change gear and oh, it hurts." **P010 (F, 69)**

From such an account, it is apparent that flares impacted on the participant's feeling of independence. However, flares were also described as having a significant impact on the independence of their spouses. This ranged from the unaffected spouse being burdened with extra household chores to activity limitation in terms of going shopping together or undertaking shared recreational activities together.

Several participants reflected that the impact of flares was kept to a minimum if they did not interfere with their ability to carry out activities. In these examples, the flares were not described as bothersome and activities could still be completed albeit at a slower pace.

[On change in frequency over time]. "No, no they are more regular. But as I say, I can honestly say they don't really – I wouldn't say bother me, but I know that they're there and yes I have the pain, but they don't stop me doing anything other than if I have to take it a bit steadier up the stairs or an incline." **P006 (F, 68)**

For some participants there was an acceptance of flares and they had come to terms with the notion that these were part of their OA experience. They wanted to carry on doing their normal activities despite the pain.

"Erm, to me it's just normal I think now, just to have a flare-up. I get a pain and erm, yeah there maybe the odd day when it's only minimal pain, not much, but there's never not pain. Cos whenever I do anything, it hurts, but you have to do things. You know, I can't not do it." **P010 (F, 69)**

Flares could make patients feel vulnerable. They were anxious about the potential for their knee to give way and the consequences of that. Some participants described how they only felt comfortable going out if they had someone else with them or a walking aid.

"When I'm walking I feel very insecure, I don't feel safe, very vulnerable, I keep thinking my knee's going to give way and I'm going to fall. Er, I'm alright if my husband's with me and I can hold his arm, or in the supermarket and I can hold a trolley or if I've got a walking stick that gives me confidence. But

without that just walking from the back door to my washing line, I feel very vulnerable, very insecure yes." **P004 (F, 81)**

Stoicism ran throughout the participants' accounts. There was a strong sense, amongst the majority of participants, of "getting on with things" despite the pain. They did not want the pain to interfere with their ability to participate in activities. However, continuing despite the pain meant activities had to be adjusted, they often took longer, and required the patient to direct more thought towards what actions might bring on or prevent a flare of pain. Impact of flares also varied, sometimes participants were able to continue activities despite the pain, and other times the pain would cause them to stop activity.

"It's when I'm doing stuff, as soon as I'm doing stuff I do get a pain and I just have to grit my teeth and go through it and sometimes it's that bad I have to stop and go and sit down and erm just make my cup of tea and I'll wait till it eases off, then I can do a little bit more." **P010 (F, 69)**

To minimise the impact of flares, several participants described how they adapted in order to undertake activities, this could be at home, for example climbing the stairs using their "good leg" first, or being more observant about foot placement when out walking. These adaptations however, were described as being intrusive and participants seemed to be resentful about having to make them.

"I just have to be very, very careful, watch where I'm walking. I hate having to keep looking down to see where I'm going and it's tiring, like last week.

Happened to look up and didn't notice this paving stone sticking up and just caught it with my toe." **P014 (M, 85)**

8.5.3 Predicting and avoiding flares

Predicting and avoiding flares was understood in relation to the 'cause' (beliefs on causes of symptoms) and 'consequence' components of the SRM (324, 328).

For some participants flares were described as coming on without warning and they could not think of any attributable cause. The onset, duration and intensity were all noted to be unpredictable for some. The unpredictable pain was associated with distress and seemed to have more of an impact on mental wellbeing and quality of life in terms of having to cancel planned activities.

"Yeah, it's quite depressing cos if I'm planning to do something and then I sort of can't because it's started to hurt and I know it's not gonna go away quick. You know, erm it could take a while for it to calm down and I don't know why it flares up." **P010 (F, 69)**

For others pain could be predicted and it was often low bearing, everyday activities that brought on more frequent increases in their symptoms, for example standing, walking, or climbing stairs.

"I, as I say it's if I go in the kitchen or stand up in the kitchen for any length of time, well three quarters of an hour, half an hour, three quarters of an hour." **P014 (M, 85)**

Amongst the participants that could predict their flares and were aware of certain triggers (for example, walking) they were able to plan ahead in order to participate in planned activities. This helped to minimise the impact of them.

"I've been in pain since June of last year with it. And there are days when I don't have as much pain as normal, erm but I rested up on Monday because I was going out yesterday and it was a lot of walking. So this morning it is playing me up a bit." **P003 (F, 66)**

For some participants who experienced variability in their ability to predict flares, the unpredictable flares seemed to be more distressing. This was partly linked to not being able to identify an underlying cause.

"Yes definitely because you're aware. You think 'I won't do that again'. You know and if it's caused you a sharp pain, you're definitely aware that you won't be stepping on that foot again that way or whatever. But as you say, it's the unknown. It's when it comes and I have no idea why it's just suddenly started again. So I don't know, I really don't know." **P006 (F, 68)**

Being able to predict pain onset, however, did have some negative connotations. For some there was associated regret with doing the activity that brought on the pain and a sense of guilt for having overdone things.

> *"Erm, I suppose I'm like that really, I haven't got no pain, if I press on there, I can feel something, there's an ache in there but I don't class that as a pain, so I've got no pain and then if I do something, it shoots up, I get me pain and then it takes X amount of days for it to go back down again and then I haven't got any pain again until I do something similar again which you think, you stupid person, why do you keep doing things but you've got to be active haven't you, you've got to do something."* **P012 (M, 81)**

The ability to predict flares seemed important to participants as they were able to utilise strategies, such as activity avoidance, adjusting physical movements, and being observant of potential hazards in their environment to better manage their flares.

> *"I'm aware that – like yesterday, I'd had it a bit, so erm we had to go to [deleted name of town] and there were steps. So I really have to take my time, I have to think about it. I can't just go for the steps, I have to stop and think 'Oh, no' you know, which is you know, I know which is my good leg and which is my bad leg and I have to remember which leg I'm going up on. Erm, but other than that, I mean that's not a life changing thing, you know, it's just*

something I have to be aware of. So it doesn't stop me from doing anything, so from that point of view you know, it's okay, it's manageable." **P006 (F, 68)**

8.5.4 Response to OA flares

Response to OA flares resonates with the 'consequence' and 'control' (extent to which symptoms can be controlled) components of the self-regulatory model (328, 329). Immediate responses to a flare included stopping any current activity, employing self-management strategies, taking medication, or just ignoring them. In the short to medium term, people undertook adaptations, avoidance of certain activities, and sought help in the form of peers and health professionals. In the long-term people anticipated the future of the management of their knee symptoms.

8.5.4.1 Self-management of flares

Immediate response to a flare depended on what was readily available at home. Medication used ranged from over-the-counter analgesia such as paracetamol, ibuprofen and topical NSAIDs (non-steroidal anti-inflammatories) to prescribed medication such as higher strength co-codamol. There were a number of health beliefs with regards to medication. For example, some only took medication sparingly as they were either worried about the consequences, for instance masking underlying disease activity, reduced efficacy with continued use, or wanting to avoid dependence. Several participants felt that not taking medication was a positive sign as this meant their symptoms were not severe.

"Erm, Naproxen. But as I say, I do try not to take them unless it's absolutely necessary. And then when I do, I do take them until the pain has gone and then once the pain has gone, then I think 'Right, now I'll stop'. Erm cos I just think well if I keep taking them I'm never going to know whether the pain has really gone and then I think – the other thing I thought, well if I do keep taking them, then I'm not gonna feel the benefit if anything, if it does occur it's probably not gonna have the effect that it should have. So I do only take them when I really need them, yeah." **P006 (F, 68)**

A number of participants signalled the control they had of their own condition and the active role they took in self-managing their pain flares. These included strategies such as: rest, ice packs, rubbing the joint, and hot baths. These strategies varied depending on the severity of their symptoms.

"Err well see here again I am one of these people who will try and get rid of it so I was having really having hot baths, really soaking it. Really rubbing it er sitting with maybe a small hot water bottle on it so really the real pain did not last long." **P002 (M, 78)**

Participants described taking control of the management of their illness in different ways, for some, not taking medication was a method they used to stay in control. Participants' beliefs affected management choices; for example, one participant described how paracetamol had not helped them for a previous complaint and so

opted not to take any analgesia. Other participants seemed resolved to their condition but did not want to give up.

> *"How do I manage; I struggle to be honest. Erm, but I mean I keep getting on and that's it, that's what's it about isn't it?"* **P007 (M, 83)**

Use of mobility aids, walking sticks, and adaptations around the house were methods used to help prevent and minimise the impact of flares and to help avoid accidents, such as falls. They also ensured that participants could maintain a sense of themselves and continue doing usual activities like shopping.

> *"I've got a mobile scooter that gets me about if I have to go to the shop or go up to town. I have to have a walking stick as well cos if I walk without the walking stick I could fall over... I have a special chair in there [shower] and I got all like the framework where I can sit down on the toilet and get myself up."* **P001 (M, 51)**

8.5.4.2 Help-seeking behaviour

Participants sought help from healthcare professionals when their flare experience did not match with their usual illness perception. Reasons for seeking help included effect of symptoms on sleep, reached emotional limitations, exhausted self-management options, and pain experience worse than normal; for example increased severity, sustained, and a longer duration than normal. Participants consulted the health professional that they thought would be more able to help them or meet their expectations based on previous experience.

"But it was – I mean I can stand a fair bit of pain, but I think I got to the point with it because I was having no sleep, I was just worn out with it in the end. And that's why I rang the hospital, because I didn't know what else to do. Erm, I thought 'Well I could ring my doctor' but really, they're brilliant GPs, but they're GPs. I needed somebody with the arthritis [specialist knowledge]."

P006 (F, 68)

For some participants, where they were under a specialist service that they could access this would be their first point of contact because they had a 'way in'. Having greater choice allowed the participant more control over their management. For those who had only been treated in primary care, their first point of contact would be their GP or allied primary care based health professional. In general, those that had previously been treated in secondary care did not see a role for their GP in the management of their OA.

"…when I had the flare up, as you call it, last year, I mean I tried everything on my knee. I tried the heat pad, I sat one day, nearly all day with a heat pad on, but it just did nothing at all. I had a hot water bottle on it, you just try anything in the end just to get some relief. Erm, but the night I just used to dread…I was just – I was at my wits' end with it in the end. And I've never got to that point that last year was the first time where I'd really got to that point. But I was just desperate that day I rang the hospital… when I did get to the hospital, I thought it was just a nurse I was going to see, but it was a doctor and he examined it and he said 'I think we need' he said 'We don't normally give these injections

to you' he said 'But I think in this case you probably do need one'." **P006 (F, 68)**

For several participants a sense of futility about seeking help was described due to previous experiences; for example, being told not much could be done or dissatisfaction with previous management meant they did not consult. The consequences of recursivity (330) strongly shaped who the patients consulted, whether they consulted or not and expectations if they did consult.

"So when they told me they couldn't do anything with it I ain't bothered the doctor." **P009 (M, 64)**

Participants also sought help from friends and family. The power of peer advice was important and shaped theories on the relative importance of and opinions on, certain management strategies such as those that could be undertaken at home

"But a friend of mine who had had problems with, I think it was arthritic hip, a friend of mine who played golf and he [deleted name]… said "I tell you one thing I was told to take" he says, he ate plenty of pineapple." **P002 (M, 78)**

The effect of others' views on health beliefs was highlighted by the participants' negative views on knee replacement after hearing disparaging comments by their peers.

"I mean a lot of people have knee surgery don't they? I've got my golfing colleagues they've all had some say yes some have had 2 done over the

years. And wish they hadn't have done and it's not what they expected it to be." **P002 (M, 78)**

In contrast where favourable comments had been heard the participants were more encouraging.

"So I think by then, if it hasn't eased off I'll just tell him, just do it, get it over with. Because my friend had it, my mate, she had the injection and it didn't work and she had erm the replacement and it's been brilliant. I know one or two people have had problems with it, but I think on the whole it's been mostly successful. And she had it done nine years ago and she says 'I've never had a day of pain since' you know, so she said it was worth every little bit you know. Cos you do worry, you don't want surgery unless you have to, but erm I can't carry on like this forever more, it's quite depressing and it's stopping me doing stuff." **P010 (F, 69)**

8.5.4.3 Anticipating the future

Total knee replacement featured in a number of participants' accounts and this was particularly evident in those whose symptoms were worsening and where they were impacting on quality of life.

"But then it started to slowly get worse, I was restricting myself in things, I was getting no pleasure out of some stuff, you know. I couldn't go out much and erm couldn't go dancing or nothing like that you know, them days are gone. So

I have a funny feeling I'll end up having to have a replacement… you don't want surgery unless you have to…" **P010 (F, 69)**

Several participants described previous conversations with orthopaedic surgeons on knee replacement. A number of participants were either given the option of replacement but were put off it due to the risks or were told they were ineligible due to comorbidities. This led to resentment and frustration; firstly about their own lack of confidence to speak up and secondly toward the consultant specialist. Limiting potential management options may have impacted on patients by taking away their sense of control.

"I do have quite a lot of pain. Er, the surgeon that I had, first of all let's start at the beginning. About four years ago I, I had it, er, cleaned, scraped, which improved things for a while and then it started getting worse so I went back to see the surgeon and he advised me not to have anything done. I was going to have a replace, well I'd asked for a replacement and he, he said…Yeah, I'd, I'd be approaching 80 I would think when I went to see him and he said, 'You think you're in trouble now', he said, 'You think you're in pain now. If you have a replacement done you will be in even more pain afterwards', he said, 'because I cannot guarantee it. Cannot guarantee anything'. He said, 'My advice, put up with it'." **P014 (M, 85)**

In addition to ruminating over knee replacement surgery, some patients had concerns about the future management options of their knee. Some participants were

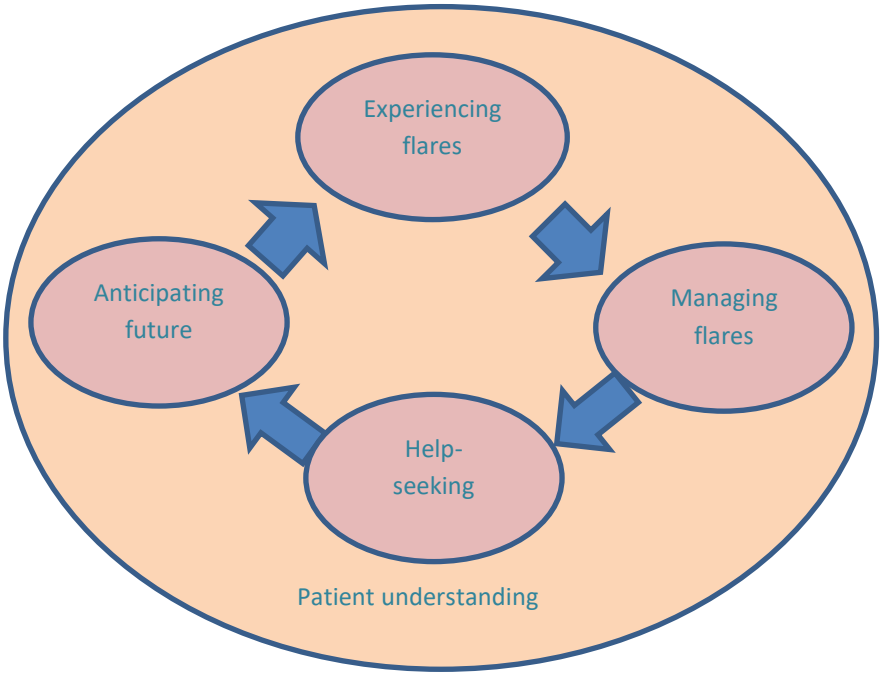
unsure about the potential management options aside from injections and knee replacement, and this may have impacted on the sense of control that participants felt they had with regards to management of their illness.

> *"You know, I'd - it's normally - I can go about every, say, six months for an injection and I've had, I think, three. So, at the moment, I'm alright to go back. Mmm, I'm not sure what I'm going to do after that."* **P011 (F, 70)**

8.5.5 Model illustrating findings

A model was created to illustrate the findings from the participant interviews. The initial model was presented to the PPIE members during workshop 2 (Figure 8.5). They felt that the arrows were not helpful as one theme did not necessarily lead onto the next one as suggested. They felt impact was important and should be more prominent in the model.

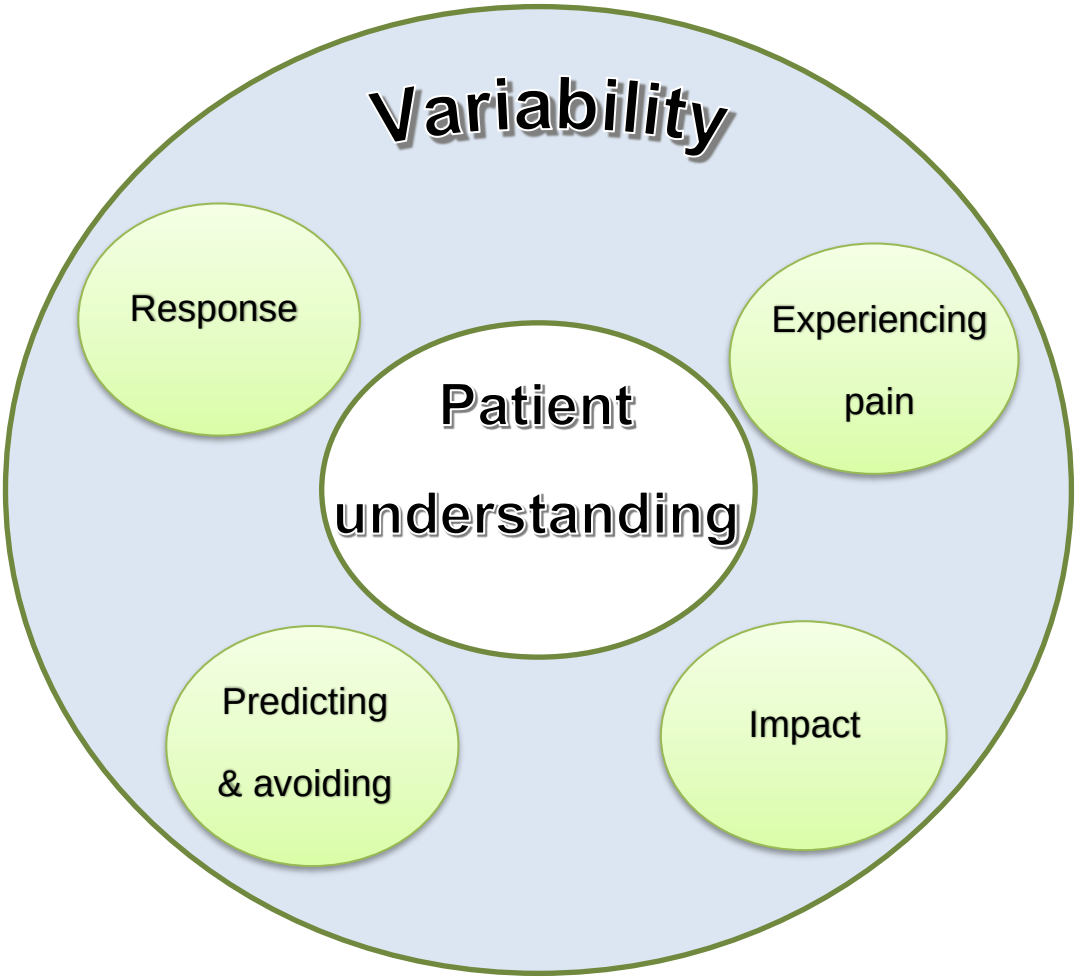
Figure 8.5: Model presented to PPIE group in Workshop 2



The model was revisited and the final model incorporates the four overarching themes that have been presented and highlights how the notion of variability runs throughout all of these themes (Figure 8.6). I felt that patient understanding was central to the participant's narratives on flares and therefore has a central place in the final model. The four overarching themes are placed around this: experiencing pain, impact of flares, predicting and avoiding flares and response to them. Experiencing pain incorporates how participants identified they were having a flare and how they described them which included temporal changes. Experiencing pain relates to 'identity' and 'timeline' of the Self-Regulatory Model The impact of flares, which links to 'consequences' of the SRM, was another key theme which included the effect flares had on ability to perform valued activities and was an important part

of patient's understanding. Predictability of flares and avoidance strategies employed was also critical to patients. The predictability part of the model resonates with 'cause' and 'consequences' of the SRM. Response to flares encompassed both immediate and longer term strategies to manage their pain as well as discussions on the future of their knee and possible joint replacement surgery. Response linked to 'consequence' and 'control' in the SRM. Variability was seen in all of these themes from variability in duration, frequency and severity of pain intensity to the impact of flares, their predictability and management of them. The final model encompasses all of these components. As one theme did not necessarily lead onto another theme the arrows from the initial model were removed.

Figure 8.6: Final model illustrating findings



8.6 Discussion

This qualitative study aimed to explore patients' understanding of flares with reference to self-management and help-seeking strategies used. The findings highlight that when discussing acute episodes of pain, participants referred to minor episodes that tended to represent daily variability in pain and more severe episodes

more likely to be referred to as ‘flares’. The descriptions of these events, the impact and responses to them was different.

Strengths of the study include the number of potential participants that responded to the mailing invite which enabled purposive sampling to give a range of different ages and gender. Data was collected until data saturation was achieved (85, 105). The analysis was conducted by a team of clinicians and researchers from different backgrounds (85, 105), which included a senior academic GP with extensive skills in qualitative research, a senior social anthropologist and myself an academic GP with knowledge of OA flares. Furthermore, the PPIE group made important contributions to the study by helping develop the study design, modify the topic guide, giving their insights into data analysis, and advising on dissemination.

Limitations of the study include all participants being white British and from the West Midlands and so limits any inferences made to the general population of people with OA. During review of my first interview both my supervisor (CC-G) and I noted where I potentially asked leading questions and areas that I could have explored further but did not, for example, when the participant mentioned about impact on mental health. During the initial interviews I found it difficult to switch from ‘GP’ consultation mode where patients are seen and managed within 10 minutes to using more explorative and probing techniques as are commonplace in qualitative interviews (86). Furthermore, my professional status as a GP may have impacted on the participants’ account of flares, particularly with regard to opinions on health professionals. The

professional status of the interviewer has been shown to impact on participant responses. Interviewees are less likely to make unfavourable comments about healthcare professionals if a healthcare professional is the researcher (128). In addition, I did not seek information on co-morbidities which, in retrospect, are important as they can affect impact of pain, management of pain and help-seeking, however, this identifies an area to be explored in future research, including exploring how flares are prioritised and managed by patients and clinicians in the context of other conditions. Ideally, the participants would have been drawn from the same sample as the daily diary study. This would have allowed comparisons from the interview data directly with the individual findings in the diary study. Due to time constraints and ethical considerations this was not possible as permission for further contact was not obtained in the original ethics application. Lastly, the PPIE group members were presented with quotes rather than the whole transcripts during the analysis meeting which have impacted on interpretation of the meaning behind the quotes.

The concept of flares or acute episodes of intermittent pain has been observed in previous qualitative studies (53, 61, 62, 64). Notable similarities with these studies include the pain descriptors used, impact of the pain, variability of symptoms, and activity related pain (which has also been highlighted in quantitative studies (226)). However, findings from my qualitative study have highlighted the consequences of activity related pain: loss of confidence, feelings of vulnerability, and dependence on others in order to participate (for example only going shopping with someone else).

Predictability was found to be an important theme in previous qualitative studies (53, 61, 62). Whilst the patient accounts in these studies focused mostly on the unpredictability of flares, findings from my study found that this could be variable and was not based on stage of OA as previously described by Hawker et al (53). In my study, predictable flares allowed patients to plan ahead in order to participate in planned activities. However, participants also described feelings of guilt and regret at knowingly participating in an activity they thought would trigger a flare, for example participating in an activity regardless of the known consequences. Unpredictable flares were described as being more bothersome due to the distress and disappointment caused at having to cancel plans.

Murphy et al (2015) noted that patient reported flares could be of variable intensity and duration (61). Participants in the current study also gave descriptions of acute episodes of pain of varying intensity. Firstly, the ‘major’ flares which were greater in intensity, infrequent, often sustained (up to 2 months in some cases), impacted on social and daily activities, and caused anxiety. Secondly, the ‘minor’ flares which were more frequent, of less intensity, shorter and often associated with everyday activities, such as climbing stairs or walking, often ceasing when the activity stopped. These ‘minor’ episodes, which some participants did not recognise as flares most likely represent normal variability of the pain experience in OA rather than distinct events.

Help-seeking for flares, which has not previously received much attention in the literature was often due to a change in usual symptoms. This included where flares

impacted on sleep, emotional limitations were reached, self-management options exhausted, and when the pain experience worse than normal. This compares with previous studies and reviews that have demonstrated that a change in symptoms, symptoms lasting longer than usual, and where symptoms are disruptive are reasons for help seeking (331, 332)**.**

Participants' sought help from who they thought would be most likely to help them and meet their expectations given their past experiences. Recursivity has been shown in previous qualitative studies on help-seeking (330). Peer advice and peer observation seemed to have a powerful impact on patients' perceptions on management strategies and modified views on total knee replacement, which has been observed in previous qualitative studies (333).

A few participants, despite describing symptoms synonymous with OA, did not identify with having the condition. This may be due to patient factors such as: only identifying with having the disease during an acute attack (334), and the symptoms being atypical so not aligning with lay beliefs which can lead to a delay in or failure to present to a healthcare professional (324, 335). Once help has been sought, clinician factors such as prioritisation of OA and time spent on education and management (331) can also affect how patients' identify with OA. The OA consultation therefore provides an important opportunity to counsel and educate on OA and flares to improve their management and identification.

One aspect of this study was the use of pain graphs to enable patients to visually describe their pain experience over the previous 6 months. The graphs demonstrated clearly episodes of increased pain intensity and variability of these. The majority of patients identified that their pain pattern consisted of flares but returning to a background level of pain or no pain in between.

Mapping the overarching themes onto the SRM (329) helped gain a greater understanding of the participants' health beliefs and perceptions. Participants identified they were experiencing flares by a change in pain quality and intensity (identity beliefs), which was usually sudden and was sustained (timeline beliefs). Flares affected participants ability to participate in valued activities (consequence beliefs). Flares were managed through a number of self-management strategies and consultation with healthcare professionals (control beliefs). Triggers for flares could sometimes be identified and these beliefs were modified based on previous experience (cause beliefs).

This study has a number of implications for clinical practice. Not all participants in this study were familiar with term 'flare' however they understood what it meant. It is important for health professionals to use language that is acceptable and understandable to patients when discussing these episodes, therefore the term 'flare' may not be useful in the patient setting. The pain graphs could be a helpful tool within the primary care consultation to enable the clinician to gain a deeper understanding of the pain experience of flares particularly where patients have difficulty describing them verbally. Clinicians could either ask the patient to point out an example pain

graph or guide them in drawing their own. This study highlighted the importance of educating patients about acute episodes of pain in those with OA so that they understand it can be part of its natural history. Some people felt there was a disconnect between flares and OA and did not always link the two.

8.7 Summary

Findings from this study highlighted the differences between flares and daily variability in symptoms. Flares in this study were described as a worsening of symptoms that are sudden in onset, sustained and impacted on daily activities (which was further exacerbated by unpredictable pain). Pain graphs were a helpful in understanding more about flares from the patient perspective and encouraged discussion on potential triggers, impact and self-management strategies.

9. Discussion

The overall aim of this thesis was to explore the natural history of flares in knee OA. The findings have provided further understanding of how flares are defined, their clinical course, how they can be triggered, who may be at risk, how they can be managed, and their impact using mixed methods. This chapter will summarise and synthesise the key findings before evaluating the main strengths and limitations. The implications of the findings for clinical practice and future research will also be discussed.

9.1 Summary of key findings

9.1.1 Describing and defining acute flares in osteoarthritis

A range of ad hoc definitions exist in the literature but several components used to define acute events in other long-term conditions appear relevant. These include: onset/worsening of symptoms and signs above normal day-day variation, duration of symptoms, speed of onset/worsening of symptoms, and a minimum symptom threshold. Definitions developed and applied in this thesis demonstrate the sensitivity of estimates of flare frequency to the definition chosen. Estimates from the secondary analysis of CAS(K) and the diary study ranged from 23% to nearly 50%. Such variation in estimates can be understood in the context of qualitative findings from my semi-structured interviews in which participants highlighted a spectrum of variability

that might be counted in quantitative studies as ‘flares’ depending on how wide the definition was. At one end participants described ‘minor’ symptom increases, that were short lived, more frequent, brought on by everyday activity and resolved with activity avoidance akin to day-to-day variability, and were often not perceived as ‘flares’ by participants. This contrasted to the severe symptom increases which lasted longer, were sometimes unpredictable, occurred infrequently, and had greater impact on valued activities. Furthermore, this daily variability may provide an understanding for the bimodal distribution of recalled flares in the cross-sectional survey (Chapter 6). The qualitative study highlights the shortcomings in the definition used for flares in the cross-sectional survey (“an increase of your knee pain (that is times when your knee pain is worse than normal) which may have stopped you from doing your normal activities or meant you have had to take or increase your pain medication”). This definition does not appear sufficient to separate the flares from the day-to-day variability of pain and suggests that specifying a minimum duration is important. Participants described pain quality as being similar for minor and major episodes of pain in the qualitative study (Chapter 8). Pain was generally reported as being ‘sharp’ and associated symptoms included swelling (in the qualitative, cross-sectional and diary study) and morning stiffness, lasting less than 30 minutes (in the cross-sectional survey and diary study).

There is some evidence to suggest from the diary study (Chapter 7) that a prodromal phase, lasting at least 48 hours may exist where participants may experience stiffness, nocturnal pain, an increase in intermittent pain descriptors such as a

sharper pain, and neuropathic pain descriptors such as burning prior to flare onset. These are important to identify as they may form a basis for early detection and prompt self-management to reduce risk of developing a full blown ‘severe’ flare which participants in the qualitative study reported being fearful of.

9.1.2 Management of acute flares

In response to a flare, patients reported help-seeking and taking more medication than usual. The interviews explored this further by discovering other self-management strategies people employed, such as rest, adaptations, activity avoidance, and rubbing the knee. Findings from the diary study showed that participants were more likely to see their GP during a flare (Chapter 7). The qualitative study explored reasons for this: instances where the pain was worse than normal, was persistent, where self-management strategies failed and the symptoms led to exhaustion (Chapter 8). Who patients sought help from was modified by past experiences and could be primary or secondary care. Peer advice was important in modifying views on certain management strategies, for example, those that could be done at home (for instance eating pineapple) to total knee replacement.

9.1.3 Risk factors and triggers for acute flares

It is harder to understand the type of people that might be affected by flares as few risk factors came out consistently in the secondary analysis of the CAS(K) data

(Chapter 5), the cross-sectional survey (Chapter 6) and diary study (Chapter 7). Notably these were increased BMI, previous knee injury, increased duration of knee pain and previous knee surgery suggesting that these were less sensitive to case definition. In the diary study participants were more likely to report their pain as sharp, throbbing and burning. This compared with descriptors used for the increased episodes of pain experienced in the qualitative study (Chapter 8). Climbing stairs was consistently associated with flares across the cross-sectional survey and diary study, and participants identified this as a cause in the qualitative study. Stair climbing along with any physical activity exposure (kneeling, heavy lifting, squatting and climbing ladders), was found to be triggers for flare onset in the case-crossover analysis. The qualitative study corroborated with findings from the quantitative studies in the pain descriptors used and potential physical triggers for flares identified. The interviews explored further the impact of these everyday physical triggers (some unavoidable such as stair climbing) and highlighted the effect of predictability. Unpredictable flares were described as distressing and had greater impact, such as having to cancel planned activities. Flares that could be predicted allowed the participant to plan ahead; for example, they rested the day before a planned outing. However, several participants described the guilt they felt after perceiving they had ‘overdone’ things. Participants reported avoiding or adapting activities, such as climbing stairs to prevent flares, sometimes resentfully.

9.2 Summary and critical reflection on the use of mixed methods

An explanatory sequential approach was adopted to conduct and integrate the studies presented in this thesis (125). Using this approach, findings from the quantitative studies were able to shape the study design of future studies. The systematic review of OA flare definitions (Chapter 4) identified a number of common core domains including: onset/worsening of symptoms above normal day-to-day variability, speed of onset, duration of sustained worsening, and a minimum threshold of pain. These domains along with definitions used in flare design studies were used to define symptom variability, a proxy for 'flares', in the secondary analysis of CAS(K) data presented in Chapter 5. The secondary analysis gave an initial estimate of potential flare frequency in those with a history of knee pain and identified potential variables associated with flares, for example: being a younger age, having a longer duration of knee problem, higher BMI and more severe symptoms at baseline. These findings were used to help determine the variables included in the cross-sectional survey (Chapter 6). The flare definition used in the secondary analysis of CAS(K) data partly informed the definition chosen in the diary study (Chapter 7) alongside definitions used in flare design studies and flare definitions in other chronic diseases. Once the quantitative data had been collected, findings were compared and contrasted to identify areas to be explored further in the qualitative study. This intermediate stage, in a mixed methods study is a common place to pause, integrate findings from the quantitative studies and determine the final study design for the next phase (336). After review of the quantitative study findings areas to be explored

further in the qualitative study included the impact of flares, their predictability, determinants of management strategies employed, help seeking behaviours and if people were aware of triggers and what they did with this knowledge.

Once each study had been completed the findings were connected and integrated in the overall discussion. The findings from each component study were compared and contrasted to see if there were any similarities or if findings from one study helped understand findings from another study. Findings from the qualitative study, for example, helped me to understand the reasons for the bimodal distribution of recalled flares reported in Chapter 6 (Figure 6.2). Findings from the patient interviews highlighted that people were reporting what seemed to be two different experiences when describing flares; a minor short lived flare that was short and had little impact on daily activity and a more severe flare, that lasted longer and had a greater impact on valued activities. When asked to recall the frequency of flares in the cross-sectional survey people may have been reporting both of these phenomena which highlights the importance of including a minimum duration to differentiate between the two. In addition, integrating findings from the different quantitative studies helped strengthen subsequent studies, for example, the ability to explore the impact of including different domains in the flare definitions was important.

In an explanatory sequential design, the patients that take part in the quantitative studies are often sampled for the qualitative study. It was my original intention to sample participants from the diary study for the qualitative study, however, due to

ethical constraints this was not possible. Utilising this sample, I would have been able to ask participants about specific questions pertaining to their diary answers, for example, I could have asked them if they could idetnify triggers for increases in their pain and if my interpretation of a flare from their diary entries matched theirs. These specific questions relating to their diary entries, however, would probably have been impacted by recall bias. In addition, the potential population to purposively sample from would have been smaller due to withdrawals and those lost to follow up. In summary, I do not think using a different sample of participants had a huge impact on the results.

Although the studies in this thesis did not follow an idealised explanatory sequential design, whereby one study was completed prior to the next study starting a pragmatic approach was taken. A number of studies in the quantitative phase were run in parallel, however, this did not prevent initial findings from earlier studies from feeding into subsequent studies. In this way the findings from earlier studies were utilised in the later studies as is seen in an explanatory sequential design.

The use of mixed methods enabled each successive component study to draw on findings from the previous study. Comparing and contrasting results across studies helped to strengthen and validate study findings through triangulation and helped in the clarification, and understanding of certain results. The qualitative study also helped to ensure that the overall thesis findings were considered in light of participant's own experiences.

9.3 Strengths and limitations

This work has a number of key strengths. The use of a mixed methods approach, whereby qualitative interviews were used to compare and contrast the results from the quantitative studies in more depth, helped to strengthen the overall findings. For example, the interviews enhanced understanding on variability of acute episodes of pain, this provided some understanding for the bimodal distribution of recalled flares in the cross-sectional survey. Inclusion of several methods, including qualitative interviews, permitted a more comprehensive investigation of acute flares. The timing and sequence of these reflected practical concerns (for example, obtaining additional funding for the qualitative study) and it might be argued that a different sequence (such as undertaking the qualitative study before the cross-sectional survey and diary study) would have offered other advantages; for instance, modifying the definition of flares used in the cross-sectional survey to ensure just flares were recorded rather than also capturing day-to-day variability of pain.

PPIE members were involved at a number of different stages during the development and analysis of findings from the survey, diary and qualitative study. Their contributions helped ensure that the studies were relevant to patients, the terms would be easily understood (for example they advised not to use the terms ‘exacerbation’ or ‘flare’ in patient information sheets or data collection instruments), offered advice on areas to explore further (such as the extent to which patients might predict flares, and take extra medication to prevent them during the diary study), and gave unique insights during the analysis stage of the qualitative study (for instance,

guilt felt after doing something that may have triggered a flare). The PPIE members involved in the survey/diary study, and first, and second meeting for the qualitative study, were not the same. This was due to the long duration between meetings. It would have been more favourable to have the same members throughout so that they would have had more insight into the previous studies and commitment. This was overcome by briefly summarising previous studies and their findings at each workshop. All of the lay members actively participated during the meetings and seemed engaged in the study, therefore it is unlikely that having different lay members affected the overall outcomes of the meetings.

As a GP researcher interested in flares in OA, I had extensive prior knowledge of the topic area. It is important to consider how my skills and knowledge as a GP may have affected the study designs, data collection and analysis. During the qualitative study, for example I had to quickly switch from GP consultation mode (i.e. identifying and managing problems within 10 minutes) to a technique that involved probing, encouraging dialogue, and allowing the participants to reflect and speak freely. I had to be mindful in the interviews to not ask leading questions. After my first interview, my supervisor (CC-G) and I identified where I may have done this and so I tried to avoid this in subsequent interviews. After each interview and during the analysis process I reflected on how my prior knowledge and experience may have affected the outcomes of these. I think my position as a GP strengthened this thesis as I was able to bring clinically relevant insights and draw experiences from other chronic diseases, for example, in relation to definitions for flares or exacerbations used.

Recall bias is a key limitation across a number of the studies included in this thesis. The qualitative study highlighted how patients tend to ruminate over causes for their pain; this can be linked to recall bias in the quantitative studies, where participants have a tendency to recall and report prior exposures when experiencing a flare compared to when experiencing their usual symptoms. This may have led to a potential overestimation of reported exposures when experiencing a flare or increase in pain in the secondary analysis of CAS(K) data and cross-sectional survey. This is potentially highlighted in the mismatch between recalled flares in the cross-sectional survey and those that were actually seen in the diary study. However, part of this may have been due to misclassification, whereby people were reporting day-to-day variability as flares.

The participant numbers in the cross-sectional survey and diary study were small which restricts the precision of the estimates derived. This factor, in addition to some variables being sensitive to case definition used, may have led to the inconsistency of some of the reported risk factors across the studies. In the survey and diary study, the populations were largely white British and from less deprived backgrounds, limiting the generalisability of the findings.

9.4 Comparisons with previous literature

Drawing on findings from the systematic review and from understanding of what was important to patients with respect to flares, key components of a flare definition were

identified. These included symptoms that were worse than normal (pain intensity above daily variability in symptoms), sustained (lasting longer than 24 hours), impacted on activity (this may be ability to carry out recreational and social activities) and potentially required additional medication. A similar systematic review of OA flare definitions, although not as comprehensive as the review in this thesis, also established that pain was a common feature (126). Recent definitions in the literature, however, are moving away from the completely symptom based identification tool developed by Marty et al (55). Although not always included in definitions used in other chronic disease (117, 137, 139-141), my qualitative study and other qualitative interviews have established the importance of the impact of acute pain for patients (53, 61, 62). This is further supported by findings from the OMERACT RA Flare Group aimed at developing a consensus definition for RA flares, who established that pain and function were the most important components to patients (220).

The definition proposed through consensus led by the OMERACT OA Flare Group (81) (who cite my systematic review in their paper) and that included in the ACT-Flare study (83) share similar domains: worsening of symptoms above usual pain or usual pain variation, a minimum duration (24 hours to a few days), impact (for example, ability to perform activities), and increased analgesia. The OMERACT group also specifies that flares should be transient and have an impact on sleep, functioning and psychological aspects. These domains share similarities with those that were important to participants in the qualitative study (Chapter 8): impact on

valued activities, pain intensity level worse than normal and persistent pain. This corroborates with domains that were important to patients in the development of a definition for RA: pain and function (220). The findings from this thesis also link directly to the stated concept of flares being more than an exacerbation of pain. Caution must be taken when developing definitions to ensure they do not overburden patients and the clinicians using them. Definitions with too many domains can lead to under-ascertainment (337). A more acceptable and useful definition is likely to be one that limits the number of domains it contains but is still sensitive to identifying flares. Ensuring that the domains included are important to patients is paramount if a definition is to be applicable for clinical use.

Differentiating between day-to-day variability and flares, by including minimum duration and impact in the definition, may be important both clinically and in the research setting. Although the existence of intermittent pain (53, 62, 64) and heterogeneity of within person variability in OA over shorter periods (for example, daily) and longer periods (for example, monthly) has previously been established (63, 314) my studies add to this by considering flares. The bimodal distribution of frequency of flares reported in the cross-sectional survey, the within and between person variability demonstrated in the diary study and patient discussions in the qualitative study on frequent, ‘minor’ episodes of pain and less frequent, ‘major’ episodes highlight where flares might be placed on this ‘spectrum’. The importance of differentiating between them lies in what aspect of osteoarthritis is trying to be

understood; for example, this might be the impact of daily variability in pain or the impact of flares.

The predictability of these acute episodes was important to patients. Unpredictable flares seemed to have the greatest impact on ability to take part in valued activities; this distress has previously been described (53, 62). My study highlighted how participants tried to navigate predictable flares by planning ahead, such as resting the day before a planned activity to go shopping. An understanding of triggers may lead to a reduction in the frequency of flares in the short to medium term due to adaptive and avoidance strategies, which may partly be related to fear avoidance (338)**.** Despite the advantages of understanding the cause of flares, some participants reported feeling guilty at knowingly 'overdone' things. It seems that there are some activities that patients will do anyway despite knowing the consequences.

9.5 Implications for clinical practice

The findings from this thesis provide a key set of domains (onset/worsening of signs and symptoms above normal day-to-day variation, that is sustained and may impact on valued activities, require additional medication, and may lead to emotional exhaustion) that could be helpful in defining OA flares. This will help in prompt identification and management of flares by patients and clinicians. Patient education on the existence of flares, although long term benefits are conflicting (339-341), is an important part of any chronic disease management. Clinician and patient awareness

of variability in OA, recognition of flares, potential triggers, likely duration, change in pain quality, and potential associated symptoms is crucial. Participants found that drawing pain graphs was helpful during the interviews and this may be one tool that could be useful during the consultation for understanding variability and experience of flares. If patients feel that the clinician has not addressed their concerns or provided them with the knowledge to manage their OA, they may not return for help for their OA or other conditions in the future (331).

There is still work to be done to acknowledge that flares are part of the natural history of OA for some people. It would be encouraging to see clearer guidance on flares being provided by key bodies such a NICE to highlight the significance of flares to clinicians and I have ensured continued discussions on flares through my position as a NICE OA guideline committee member which commenced September 2019. It would also be encouraging to see patient education resources, such as those provided by Versus Arthritis to give clear patient information on flares.

9.6 Implications for further research

Although reaching consensus definitions for flares or exacerbations of chronic disease can be a lengthy processes (342), further work is required to develop and validate a usable flare definition. A unified definition will aid comparisons across studies and help gather more accurate data on frequency estimates, healthcare usage, and consequences (e.g. absenteeism at work) which will help inform policy. A

similar body evidence, as provided in this study, may be helpful in OA affecting other joints, such as the hip, hand and foot.

Understanding the types of people who are affected by flares and who are likely to experience greater variability in pain is important to identify those at risk and try to minimise the impact of them. This could be achieved through larger studies with repeated measures, such as online based case-crossover studies. Prevention and reduction of flares or exacerbations are key areas of interest in other chronic diseases (343-345). Reducing the impact of flares may partly be achieved by promoting self-management through action plans to enable prompt treatment and reduce burden on healthcare resources (346-348). This may be achieved through a trial comparing a flare action plan to usual care. Use of symptom diary cards as flare detection tools, have found to be useful in the field of COPD (349) and a similar tool may be helpful for flare identification in OA.

9.7 Reflexivity

As a GP I had my own assumptions about what constituted a knee OA flare prior to the start of my PhD. I assumed that a flare was something that was clinically significant, i.e. a state that led to a patient consulting their healthcare practitioner for example a pain experience that was worse than normal, that lasted a number of days, interfered with activity and might not be controlled with usual medication. My presumption was based on my own clinical experience. It was important whilst

understanding more about flares from the literature that I kept an open mind as to what a flare actually was. The PPIE groups were really helpful in highlighting the different types of flares that people might experience, how they might be managed and what might prompt them to seek further help. Taking on board the discussions with the PPIE group and my supervisory team I was able to gain a better understanding of flares and appreciate them from different perspectives.

My prior knowledge of flares and osteoarthritis influenced some of the choices I made in the study design and analysis phases of a number of the studies. For example, the selection of variables for the studies in Chapter 5 and 6 were partly influenced by previous research and my own clinical experience. For example, including having seen a GP, impact on activity and duration of knee problem. During the interviews in Chapter 8 I chose not to disclose my background as a GP unless specifically asked. I was concerned that this might affect the openness of answers from the participants particularly with reference to opinions of management and interactions with healthcare professionals. I found my background as a GP enabled me to put the patients at ease at the start of the interviews by asking direct questions and prior to the interviews talking about the weather for example. I utilised skills such as mirroring, eye contact and leaning forward to show that I was interested in what the participants were saying. However, during the first interview myself and my supervisor noted that I used a leading question and that I did not explore certain areas for example, when the patient offered that the knee pain

sometimes affected their mental health. After the first interview I was conscious of this and ensured questions were phrased so they were not leading and I picked up on areas to explore further, for example using phrases such as “can you describe that in a bit more detail?”

In being aware of my background as a GP and a researcher I have tried, at each stage to mitigate any influence my past knowledge and experiences have had on my research. This has included involving PPIE in my research and have regular discussions with my supervisory team who all have different backgrounds.

9.8 Reflection on my doctoral training

Before embarking on my doctoral studies I had undertaken introductory courses on research methods in health which gave an introduction to quantitative and qualitative research method and statistics and epidemiology. I had little in the way of practical experience of undertaking a research study. My PhD gave me exposure to a number of methodologies by undertaking new studies which included a systematic review with narrative synthesis, a cross-sectional study, a self-complete prospective daily diary study and a qualitative study using semi-structured interviews, in addition to a secondary analysis of cohort data.

Using mixed methods I was able to triangulate the results of individual studies to strengthen the overall findings. Comparing and contrasting results also enabled a deeper understanding of the findings, for example analysis of the qualitative data helped to understand the distribution of recalled flares seen in the cross-sectional

study (Figure 6.2, pg 147). However, using mixed methods had a few disadvantages, for example when undertaking the qualitative study I found it difficult at first to switch from a predominately quantitative synthesis and to avoid frequency counting. Furthermore, I found it difficult describe overall themes using more patient focussed language and avoiding medical terminology, for example using the term ‘temporal characteristics’ to describe changes in frequency and duration of flares.

During my PhD I gained extensive experience in the practical aspects of conducting research from engaging with PPIE groups, writing protocols, submitting ethics applications, database design, developing data collection instruments, liaising with the Clinical Research Network, writing patient letters and information sheets, inputting data, data cleaning, using STATA and disseminating results. Undertaking these processes I have learnt the importance of good team communication, planning and having a good grasp of key people involved in getting a research project started. My background as a GP helped in the design of the individual studies from selection of putative risk factors, terminology included in the systematic review and development of the topic guide for the qualitative study. It also allowed me to understand the findings in light of my own clinical experience.

9.9 Conclusions

Unlike in other chronic disease areas, acute flares in OA are not a widely recognised characteristic of the natural history of the condition. Even in those fields (for example,

COPD, asthma, RA) agreeing a definition has been challenging requiring numerous rounds of consensus exercises. This is even more so given the spectrum of variability and varying uses and terminology in OA.

This studies in this thesis have identified core components of an OA flare definition that are important to patients, it has increased our understanding of flares in terms of what people experience, how long they last, potential triggers and early warning features. These are important for patient education and to improve self-management and early identification. Further work to understand the types of people likely to experience flares, developing a personalised care approach and to reach a consensus definition are needed, in order to assess who is more at risk of flares and to help guide prompt identification and management of them.

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11. Appendices

Appendix A: Search strategies for systematic review of OA flare definitions

Ageline/ASSIA/SportDiscus

("KNEE OSTEOARTHRITIS" OR (knee N3 pain) OR (knee N3 arthrosis) OR (knee N3 joint) OR (knee N3 osteoarthritis)) AND (exacerbation OR flare OR (pain AND (diary OR diaries)) OR (pain N3 variab*) OR (pain N3 pattern$) OR (daily N3 pain))

Medline/PsychInfo/HMIC/EMBASE/CINAHL/AMED

OSTEOARTHRITIS, KNEE/

OR (knee adj3 (pain OR painful)).ti,ab

OR (knee adj3 (arthrosis)).ti,ab

OR (knee adj3 (joint OR joints OR degenerative)).ti,ab

OR (knee adj3 (osteoarthritis)).ti,ab

AND

OR exacerbation.ti,ab

OR flare.ti,ab

OR daily adj3 (pain)).ti,ab

(pain adj3 (variab$)).ti,ab

OR (pain AND (diary OR diaries)).ti,ab

Cochrane Library

"knee osteoarthritis":ti,ab,kw or knee adj3 (pain or painful):ti,ab,kw or knee adj3 (arthrosis):ti,ab,kw or knee adj3 (joint or joints or degenerative):ti,ab,kw or knee adj 3 (osteoarthritis):ti,ab,kw

AND

exacerbation:ti,ab,kw or flare:ti,ab,kw or pain adj3 (variab or pattern$):ti,ab,kw or daily adj3 (pain):ti,ab,kw or pain and (diary or diaries):ti,ab,kw

Appendix B: Sample diary template presented to PPIE members

Day 1:

After evening dinner

Which of these activities have you done in the last 24 hours?	
Kneeling for 30 minutes or more	
Squatting for 30 minutes or more	
Climbing a total of 5 or more flights of stairs	
Lifting/moving objects weighing 25kg or more	

Have you used more pain medication than usual in the last 24 hours?

Yes ☐ No ☐

If yes, please give details

Name:_____ Dose:_____

Is your knee pain worse than a usual day for you?

A little worse☐ A lot worse ☐ No ☐

If a little or a lot worse please answer questions below

Circle the number that best describes your knee pain during the past 24 hours

0 1 2 3 4 5 6 7 8 9 10

No pain Worst

Knee swelling	Yes ☐	No ☐
Limping	Yes ☐	No ☐
Knee stiffness for more than 20 minutes	Yes ☐	No ☐
Woken at night by knee pain	Yes ☐	No ☐

None of the above ☐

Has your knee pain stopped you from doing your normal activities? Yes ☐ No ☐

Can you identify any particular trigger for this increase in pain?

_____

_____

Other comments:

_____

_____

If you are experiencing pain <u>circle all below</u> that describe your pain:

Dull Throbbing Numbness Sharp Aching

Burning Stabbing Pins & needles

Appendix C: Cross-sectional survey

Osteoarthritis Daily Diary Study

Baseline Questionnaire

REC project ref 13/NS/0049
V1.2 03/05/13

Instructions

Aim of this questionnaire

The aim of this questionnaire is to find out about knee symptoms you may be experiencing and to find out more information about yourself.

We are interested in your answers even if you have not had knee pain. If you do not have knee pain you will be instructed on which questions to fill out.

Please answer the questions stated.
Unless stated, most questions are answered by putting a cross in a box, like this: 

When you have finished please check all of the appropriate questions have been answered and then return the completed questionnaire back to us as soon as you can with your consent form. An envelope has been provided, with the address and you **do not** need a stamp.

Details about this project are available on the information sheet enclosed. If you would like further information please contact the **Study Co-ordinator**, **Dr Emma Clarke** on **01782 734683**.

Thank you for your help with this research study

SECTION 1: YOUR KNEE SYMPTOMS

The following questions are about any recent knee symptoms you may have had in your knees. Please answer all questions for both your left and right knee.

1 During the **past 12 months** have you had any pain, aching or stiffness in or around...,

a. Your **LEFT KNEE**
(please put a X in one box below)

Yes	☐
No	☐

b. Your **RIGHT KNEE**
(please put a X in one box below)

Yes	☐
No	☐

IF YOU HAVE ANSWERED 'NO' FOR BOTH KNEES, PLEASE SKIP TO SECTION 3 ON PAGE 9

2 Which knee causes you the most pain, aching or stiffness?
i.e. which is your worst knee?
(Please put a X in one box only)

Left	Right
☐	☐

For the rest of this questionnaire, the questions relate to your knee that causes the most pain. (Your answer to section 1 question 2)

3 How long ago did you first start having this problem with your knee?
(Please put a X in one box only)

1 year or less	☐
2 to 5 years	☐
6 to 10 years	☐
More than 10 years	☐

4 In the **last 12 months** how many times have you had an increase of your knee pain (that is times when your knee pain is worse than normal which may have stopped you from doing your normal activities or meant you have had to take or increase your pain medication)?
(Please put a X in one box only)

0	1-2	3-4	5-6	7-8	9-10	More than 10
☐	☐	☐	☐	☐	☐	☐

5 In the past 12 months, have you consulted your GP (family doctor) because of your knee pain?
(Please put a X in one box only)

Yes	No
☐	☐

6 Have you ever injured you knee so badly that it was difficult for you to walk on it for <u>at least one week?</u>
(Please put a X in one box only)

Yes	No
☐	☐

7 Have you ever had any kind of knee surgery on your worst knee? Please include arthroscopy (where a small camera is put in your knee), ligament repair surgery, or a menisectomy (where they repaired or cut away a torn meniscus or cartilage)
(*Please put a X in one box only)*

Yes	No
☐	☐

8 Have you ever had knee replacement surgery, where all or part of the joint was replaced?
(***Please put a X in one box only)***

a. Yes No

☐	☐

b. If yes was it your right knee, left knee or both?
(Please put a X in one box only)

Left	Right	Both
☐	☐	☐

SECTION 2: WHAT IS 'NORMAL' FOR ME?

We are interested in what your knee symptoms are like on a normal day for you.

1 On a normal day for you, how intense is your knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as it could be'?
(that is your average pain)
(Please put a X in one box only)

No Pain **Pain as bad as it could be**

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

2 On a normal day for you, do you have any of these other knee related symptoms?
(Please put a X in one box on each line)

	Yes	No
a. Knee swelling	☐	☐
b. Limping	☐	☐
c. Knee stiffness for more than 20 minutes	☐	☐
d. Being woken at night by knee pain	☐	☐

3 On a normal day for you, if you experience knee pain, what does your knee pain feel like?
(Place a X in each box that applies)

a. Dull ☐	b. Throbbing ☐	c. Numbness ☐
d. Sharp ☐	e. Aching ☐	f. Burning ☐
g. Stabbing ☐	h. Pins & needles ☐	
i. Other ☐ Please specify……		

4 On a normal day for you, do you take any medication for your knee pain that is either prescribed or from over the counter?

a. Yes	No
☐	☐

b. If yes, please state the name, dose (or strength) and whether you take them regularly or as needed.

Name	Dose (strength)	Regularly or as needed
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

5 On a normal day for you, do you do any of these activities?
(Please put a X in one box on each line)

	Yes	No
a. Kneeling for 30 minutes or more	☐	☐
b. Climbing more than 5 flights of stairs	☐	☐
c. Lifting/moving heavy objects	☐	☐
d. Squatting for 30 minutes or more	☐	☐
e. Climbing ladders	☐	☐

SECTION 3: ABOUT YOU

The questions in this section are about you and your general health.

1 Have you ever been told by your doctor that you have or have had any of the following:
(Please put a X in one box on each line)

	Yes	No
a. Polymyalgia Rheumatica	☐	☐
b. Gout	☐	☐
c. Ankylosing spondilitis	☐	☐
d. Rheumatoid arthritis	☐	☐

2 What is your age (in years)?

☐☐

3 Are you?

Male	Female
☐	☐

4 Please fill in your weight and height in the boxes below. It does not matter whether you use imperial OR metric systems.

a. Weight

☐☐.☐ OR ☐☐☐

Stone & pounds *Kilograms*

b. Height

☐☐.☐ OR ☐☐☐

Feet & inches *Centimetres*

5 Do you live alone?

Yes	No
☐	☐

6 What is your current marital status?
(Please put a X in one box only)

Married	Separated	Divorced	Widowed	Cohabiting	Single
☐	☐	☐	☐	☐	☐

7 What is your current employment status?
(Please put a X in one box only)

Employed	Not working due to ill health	Retired	Unemployed/ seeking work	Housewife/ husband	Other
☐	☐	☐	☐	☐	☐

8 If working what is your job title (examples- factory worker, lawyer, welder, office worker)?
(Please write answer in box)

9 If you are **not working** or are retired, what job have you done for **most** of your working life?
(Please write answer in box)

10 What is your ethnic origin? ***(Please put a X in one box only)***

White UK Or European	African	Afro-Caribbean	Asian	Chinese	Other
☐	☐	☐	☐	☐	☐

If other please specify……

11 What is your smoking status?
(Put a X in one box only)

- Never smoked ☐
- Previously smoked ☐
- Currently smoking ☐

12 On average, how often do you drink alcohol?
(Please put a X in one box only)

Daily or most days	Once or twice a week	Once or twice a month	Once or twice a year	Never
☐	☐	☐	☐	☐

13 What is your highest qualification?
(Please put a X in one box only)

- a. O-level, CSE, GCSE or equivalent ☐
- b. A-level, BTEC, HNC or equivalent ☐
- c. Degree or postgraduate qualification ☐
- d. Other work related or vocational qualification *(e.g. City&Guild, NVQ, technical apprenticeship)* ☐
- e. Other qualification ☐
- f. No qualification ☐

We are interested in the activities that you do at home, at work, for leisure or exercise, or for any other reason

14 How many times a week do you usually do 20 minutes or more of vigorous-intensity physical activity that makes you sweat or puff and pant? (for example heavy lifting, jogging, aerobics or fast bicycling)?
Please put a X in one box only

None	1-2 times a week	3 or more times a week
☐	☐	☐

15 How many times a week do you usually do 30 minutes or more walking? (for example walking from place to place for exercise, leisure or recreation)
Please put a X in one box only

None	1-2 times a week	3-4 times a week	5 or more times a week
☐	☐	☐	☐

16 How many times a week do you usually do 30 minutes or more of moderate-intensity physical activity that increases your heart rate or makes you breathe harder than normal? (for example carrying light loads, bicycling at a regular pace or doubles tennis)
Please put a X in one box only

None	1-2times a week	3-4 times a week	5 or more times a week
☐	☐	☐	☐

This is the end of section 3

- This is the end of the questions.
- Please continue to fill out **section 4**, the consent form, on page 13 before returning the questionnaire to us in the envelope provided. You do not need a stamp.
- If you have any further questions about this questionnaire, or the study in general, you can telephone the **Study Coordinator**, **Emma Clarke** on **01782 734683**.

Thank you

Study ID

SECTION 4: CONSENT FORM

Please read the following consent form and then sign below.

Thank you for filling out the questionnaire. The second part of this study involves filling out short diaries on your knee symptoms each day for up to 3 months. Further information regarding the study and the diaries can be found in the **patient information sheet** (version 1.1, dated 09/04/13). Please ensure you read this.

Certain questions in this questionnaire have been designed to ensure participants are eligible for the diary study, this means that not all participants who give us permission to contact them will be sent diaries.

I am happy to take part in the diary part of the study if selected and I understand that this means filling out a diary each day for up to 3 months. I understand that I can withdraw from the study at any time and that this will not affect my medical care I receive in anyway.

Please print your name:

Title: _____ First name: _____ Surname: _____

Signed:_____ Date:_____/_____/_____
(Day / Month / Year)

Please print your address:

_____

_____ Postcode: _____

Please state your date of birth:

_____/_____/_____ *(Day/Month/Year)*

If you have any questions about this study or questionnaire, please contact the Study Coordinator, Dr Emma Clarke on 01782 734683.

Appendix D: Example diary

Osteoarthritis Daily Diary Study

Month 1 Diary

V1.2, 17/04/13

APPENDIX M
Instructions on how to fill out the diary

Please try to complete this diary every day for the next month

- Start filling out the diary on the first day of the month.
- Aim to fill out the diary at the end of each day.
- The questions in the diary relate to the whole of the past 24 hours.
- The diary is designed so that it should not take you more than a **minute** to fill in each day.
- If you miss a day; just fill in the date for each day you miss and put a line through that page and continue with the diary as usual for the **present day**.
- Only complete the diary for the present day, not for days you may have forgotten to complete

The questions in the diary are similar to the 'what is normal for you' section that you may remember from the questionnaire. Do not worry if you cannot remember the answers you gave us as we have transferred them into the diary and you will find them on the next page.

Please answer all of the questions.
Unless stated the questions should be answered by putting a cross in each box like this: ☒

At the end of the month, please send this diary back to us as soon as possible in the pre-paid envelope provided **even if it is not fully complete.**

If you have any further questions about this study please do not hesitate to contact the Study Co-ordinator Emma Clarke on **01782 734683**.

Thank you once again for your help with this research study

Tips to help you remember to fill in the diary each day

- You could try putting the diary in a place you will remember to use it:
  - On your night stand
  - Next to your evening medication
  - Next to your armchair in the living room

WHAT IS NORMAL FOR ME? (your answers from the questionnaire)

1. On a normal day for you, how intense is your knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as it could be'? (that is your average pain)

2. On a normal day for you, what other knee related problems do you have?

3. On a normal day for you, if you experience knee pain, what does it feel like?

4. On a normal day for you, which of the following pain killers do you take?

5. On a normal day for you, which of these activities might you do?

DAY 1. In the last 24 hours….

1. On average, how intense was your knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as it could be'? *(Please put a X in one box only)*

No pain ***Pain as bad as it could be***

0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

2. Did you have any of these other knee related symptoms…? *(Put a X in all that apply)*

Knee swelling	☐	Knee stiffness for more than 20 minutes	☐
Limping	☐	Being woken at night by knee pain	☐

3. What has your knee pain felt like? *(Put a X in all that apply)*

Dull ☐ Aching ☐ Throbbing ☐ Stabbing ☐ Sharp ☐ Burning ☐

Numbness ☐ Pins & needles ☐ Other ☐ Please specify: ……

4. Compared to what's normal for you, did you use more, less or the same amount of pain medication? *(Please put a X one box only)*

The same as normal ☐ More than normal ☐ Less than normal ☐

If you said 'more than normal' or 'less than normal', please give more details:

……

5. Did you do any of these activities…? *(Put a X in all that apply)*

Kneeling for 30 minutes or more	☐	Lifting/moving heavy objects	☐
Climbing more than 5 flights of stairs	☐	Climbing ladders	☐
Squatting for 30 minutes or more	☐		

6. Did your knee pain stop you from doing your normal activities? **YES** ☐ **NO** ☐

7. Did you contact your GP because of your knee pain? **YES** ☐ **NO** ☐

8. Can you identify any triggers for any change in pain you may have had?

……

9. Any other notes/comments:

……

Appendix E: Patient information sheet for cross-sectional and daily diary study

Arthritis Research UK primary care centre

Arthritis Research UK Primary Care Centre
Keele University
Staffordshire
ST5 5BG
01782 734683

working with PRACTICE NAME
ADDRESS 1
ADDRESS 2
ADDRESS 3
GP Name 1
GP Name 2

Information sheet

REC approval date 07/05/2013
Version 1.1, 09/03/2013

Osteoarthritis Daily Diary Study

You are being invited to take part in a research study. Before you decide to take part, 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.

What is the purpose of the study?

Knee pain, which is most often due to osteoarthritis is a very common problem in this country. It is important that we know more about this pain so that we can help patients manage it. The main things we want to find out are:

- How often people have episodes when their knee pain is noticeably worse than the normal day-to-day ups and downs?
- How long does it take for these episodes to settle down?
- Is there anything that brings on these episodes?
- What do people do to manage these episodes?

We aim to collect this information from the baseline questionnaire involved then from short diaries which are completed daily for up to 3 months.
Only by collecting this information from people like you will we be able to understand more about these episodes. If we can identify when knee problems might get worse we might be able to stop this happening.

Why have I been invited?

We are interested in people have knee problems. In the past 2 years you have been to see your GP because of problems with one or both of your knees. If you could spare time to fill in the enclosed questionnaire you would provide information that will be of great benefit for this project.

Do I have to take part?

Whether or not you take part in this research is voluntary. If you do decide to take part, you are free to withdraw at any time without giving a reason. A decision to withdraw, or a decision not to take part, will not affect your right to access health services at your practice or elsewhere.

How long will it take?

Taking part in this study means that you are asked to complete the enclosed questionnaire. We think this will take 10-15 minutes to complete. Returning the questionnaire means you consent for the research team to use the data you provide, this will be kept confidential.

If you are willing to take part in the diary part of this study please fill out the consent form at the back of the baseline questionnaire. For this part of the study you will be asked to fill out a short diary page each day for up to 3 months. We think this will take a minute to fill out. An example diary page is enclosed in this pack. The diaries will be sent out to you monthly and we ask that you return the diaries once completed at the end of each month in the pre-paid envelopes that will be provided. The aim of the daily diary is to see how your knee symptoms change from day to day, how you manage change in pain and any possible triggers.

Not all people who give permission to be sent diaries will receive them. This depends on the answers you give us in the questionnaire.

What are the benefits to me of taking part?

Although any direct benefit to you is unlikely, what we learn from the study will help people with knee pain in the future.

Will my taking part in this study be kept confidential?

The answers you give in the questionnaire will be dealt with in **strictest confidence**. Each person who responds to the questionnaire will be given an ID code number, so the data from the study will not have any identifiable names and addresses, and cannot be traced back to you. On this basis, the data may be used in other relevant research studies. The questionnaires will be stored without identifiable names and addresses for twenty years in accordance with the Medical Research Council guidelines. Beyond this date records will be maintained if the study is still on going. The questionnaires will be stored in a secure place.

What will happen if I don't want to carry on with this study?

You can withdraw from this study by telephoning us on 01782 734683. Withdrawing means that we would no longer contact you directly, but we would still keep and use the information you have provided up to the point of your withdrawal.

What will happen to the results of the research study?

The results of this study will be available after about one year and will then be published in medical journals and reports. The main findings from the study will be displayed on a poster in your practice. If you would like any other information after seeing these we will be happy to help.

Who is funding and organising the research?

Arthritis Research UK is funding the research. It is being organised by the Arthritis Research UK Primary Care Centre at Keele University.

Who has reviewed the study?

The North of Scotland Research Ethics Committee has reviewed this study (Research Ethics Committee Reference Number: 13/NS/OO48.

Contact for further information

If you have any questions, or would like further information, about this study please contact our Study Co-ordinator, **Dr Emma Clarke** on **01782 734683**.

If you have any questions or concerns about taking part in this research you can also contact the Patient Advice and Liaison Service (PALS). Your local PALS office free phone number for Shropshire is 0800 032 1107. For further information visit their website http://www.pals.nhs.uk/.

Thank you for taking time to read this information leaflet.

Appendix F: Read codes for general practice electronic patient record search

1M10	Knee pain
N05z6	Knee osteoarthritis NOS
N05zL	Osteoarthritis NOS of knee
N051B	Primary gonarthrosis, bilateral
N052A	Post-traumatic gonarthrosis, bilateral
N052C	Post-traumatic gonarthrosis, unilateral
N06z6	Knee arthritis NOS
N094M	Arthralgia of knee

Appendix G: Sample diary template

APPENDIX G: Sample diary template **Day 1. In the last 24 hours...**

v1.1, 09/04/13

1. On average, how intense was your knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as it could be'? *(Please put a X in one box only)*

No pain										*Pain as bad as it could be*
0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
☐	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐

2. Did you have any of these other knee related symptoms...? *(Put a X in all that apply)*

Knee swelling	☒	Knee stiffness for more than 20 minutes	☐
Limping	☐	Being woken at night by knee pain	☒

3. What has your knee pain felt like? *(Put a X in all that apply)*

Dull	☐	Aching	☒	Throbbing	☐	Stabbing	☐	Sharp	☐	Burning	☒
Numbness	☐	Pins & needles	☐	Other	☐	Please specify:					

4. Compared to what's normal for you, did you use more, less or the same amount of pain medication? *(Please put a X one box only)*

The same as normal	☐	More than normal	☐	Less than normal	☒

If you said 'more than normal' or 'less than normal', please give more details:

NO PARACETAMOL TAKEN TODAY

5. Did you do any of these activities...? *(Put a X in all that apply)*

Kneeling for 30 minutes or more	☐	Lifting/moving heavy objects	☐
Climbing more than 5 flights of stairs	☒	Climbing ladders	☐
Squatting for 30 minutes or more	☐		

6. Did your knee pain stop you from doing your normal activities? **YES** ☐ **NO** ☒

7. Did you contact your GP because of your knee pain? **YES** ☐ **NO** ☒

8. Can you identify any triggers for any change in pain you may have had?

NONE

9. Any other notes/comments:

NONE

Appendix H: Cross-sectional survey cover letter

Practice Letterhead

(Participants Name) Ref: (Study ID)
(Address)
(Line 3)
(Postcode)
(Date)

Dear (**Insert name here**)

Osteoarthritis Daily Diary Study

The doctors at this practice are working with researchers from the Research Institute for Primary Care and Health Sciences at Keele University. We are writing to see if you would be willing to help with a research study about knee pain.

Researchers at Keele are interested in finding out about knee pain. We are inviting patients aged 45 years and over, registered with this practice and have been to see their GP in the past 3 years with knee pain to take part. Further details of the study are on the enclosed information sheet.

We hope that you will be able to spare some of your time to complete the enclosed questionnaire. It should take about 10-15 minutes to fill in.

All answers will be dealt with in **strictest confidence**. We can also assure you that whether you answer the questionnaire or not, this will not in any way affect the care you receive from this practice or elsewhere.

We would be grateful if you could return the questionnaire in the next two weeks in the envelope provided (no stamp needed). We will send a reminder to people whose questionnaire we have not received after two weeks. If you would like to know more about this study, please contact the Study Co-ordinator, **Dr Emma Clarke** at Keele University on **01782 734683**.

We will be asking some people if they would be willing to take part in the next stage of the research which will be to complete a short daily diary so, if you give permission, you may be contacted again. An example of the diary is enclosed.

Thank you very much for your help with this research study.

Yours sincerely,

Dr X and partners

Enclosed: Questionnaire with consent form
Patient Information Sheet
Pre-paid envelope
Sample diary template

Appendix I: Reminder postcard

We are writing to remind you of an invite letter that we recently sent you to take part in an interview on times when you get increases of pain of your knee osteoarthritis. We know that you may be busy, but if you are able to take part would you take the time to complete the consent to contact form and return it to us in the envelope that we previously provided, **you do not need a stamp.** We would be grateful if you could return this in the next two weeks.

If you have returned the form in the last few days please ignore this postcard and we apologise for troubling you again. If you have any questions please contact Dr Emma Clarke on **01782 734683**.

Thank you very much for your help with this research it is greatly appreciated.

Dr Emma Clarke

Appendix J: Reminder cover letter

Covering letter (from practice)

XXXXX Medical Practice
Address line 1
Address line 2
Town/City
Postcode

Ref: (Study ID)

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Dear (**Insert name here**)

Osteoarthritis Diary Study

We are writing to remind you of our new research study that we are carrying out with the Research Institute for Primary Care and Health Sciences at Keele University. In this research we are trying to understand more about knee pain, how it changes over time and what things may affect knee pain. We have not yet received a response from you but are still very interested to hear about your knee pain.

We have therefore enclosed another copy of the questionnaire we recently sent you and would be grateful if you could complete this, which should take about 10-15 minutes. Once complete please return the questionnaire in the envelope provided in the next two weeks or as soon as you can. **You do not need a stamp.**

If you have returned a questionnaire in the last few days we apologise for troubling you again. If you have not returned the questionnaire, we hope that you will be able to help with our research and spare a short amount of time to complete the one we have sent today.

Further details of the project are on the accompanying participant information sheet. If you would like to know more about this study please contact Dr Emma Clarke, Study Co-ordinator at Keele University on **01782 734683.**

Thank you very much for your help in supporting our research project.

Yours sincerely,

Practice GP

Enclosed: Questionnaire with consent form
Patient Information Sheet
Pre-paid envelope
Sample diary template

Appendix K: Diary cover letters

V1.1, 09/04/13

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Keele University

Ref: (Study ID)

Dear (**Insert name** here),

Osteoarthritis Daily Diary Study-Month 1

Thank you for recently returning our baseline questionnaire and agreeing to help us further. The information you have given us so far is very useful. We would now appreciate your help with filling out our short diary each day, for up to 3 months.

The diary helps us to see if there are any activities that bring on an increase in your knee pain and if your pain varies day to day.

Enclosed you will find the first months diary. We would be grateful if you could start filling it in on **Thursday 1st August 2013**. The diary should take **less than a minute** each day to fill in. At the end of the month, when you have completed the diary please send it back to us in the enclosed envelope, **no stamp needed.** Your responses will be dealt with in the **strictest confidence.**

It can sometimes be difficult to remember to fill in the diary every day. Having spoken to people who have done similar studies they advise you to leave the diary somewhere you will remember to fill it in. This could be on your nightstand, next to your evening tablets or on the coffee table in your living room.

Before the end of month 1 you should have received the diary for month 2. If you do not then please contact Dr Emma Clarke, Study Co-ordinator on **01782 734683** and we will get one posted out to you as soon as possible.

Thank you once again for supporting our research project.

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Co-ordinator

Enclosed: Month 1 diary
Pre-paid envelope

Arthritis Research UK primary care centre

Research Institute for Primary Care and Health Sciences
+44 (0)1782 733905
Fax: +44 (0)1782 733911
www.keele.ac.uk/pchs

V1.1, 09/04/13

(Participants Name)
(Address)
(Line 3)
(Postcode)
(DATE)

Ref: (Study ID)

Dear (**Insert name** here),

Osteoarthritis Daily Diary Study-Month 2

Thank you for recently returning the diary for Month 1. The information you have given us so far is very useful.

The diaries are helping us to see if there are any activities that bring on an increase in your knee pain and if your pain varies day to day.

Enclosed you will find your Month 2 diary. We would be grateful if you could start filling it in on **Sunday 1st September 2013**. The diary should take **less than a minute** each day to fill in. At the end of the month when you have completed the diary please send it back to us in the enclosed envelope, **no stamp needed**. Your responses will be dealt with in the **strictest confidence**.

Before the end of Month 2 you should have received the diary for **Month 3**. If you do not then please contact Dr Emma Clarke, Study Co-ordinator on **01782 734683** and we will post one out to you as soon as possible.

Thank you once again for supporting our research project

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Coordinator

Enclosed: Month 2 diary
Prepaid envelope

Research Institute for Primary Care and Health Sciences
+44 (0)1782 733905
Fax: +44 (0)1782 733911

V1.1, 09/04/13

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Keele University

Ref: (Study ID)

Dear (**Insert name here**),

Osteoarthritis Daily Diary Study-Month 3

Thank you for recently returning the diary for Month 2 and your continued participation in this study.

The diaries are helping us to see if there are any activities that bring on an increase in your knee pain and if your pain varies day to day.

Enclosed you will find the diary for Month 3. We would be grateful if you could start filling it in on **Tuesday 1st October 2013**. The diary should take **less than a minute** each day to fill in. At the end of the month when you have completed the diary please send it back to us in the enclosed envelope, **no stamp needed**. Your responses will be dealt with in the **strictest confidence**.

This diary is the last diary you will receive for this study.

If you have any questions, or require any further information please feel free to phone Emma Clarke, the Study Co-ordinator on **01782 734683**.

Thank you once again for supporting our research project.

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Co-ordinator

Enclosed: Month 3 diary
Prepaid envelope

Research Institute for Primary Care and Health Sciences
+44 (0)1782 733905
Fax: +44 (0)1782 733911
www.keele.ac.uk/pchs

Appendix L: Diary return reminder letters

V1.1, 09/04/13

Keele University

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Ref: (Study ID)

Dear (**Insert patient name here**),

Osteoarthritis Daily Diary Study-Month 1

Thank you for recently returning our questionnaire and agreeing to help us further. So far we do not seem to have received your diary for Month 1.

The diary is an important part of our research as it helps us to see whether there are any activities that bring on an increase in your knee pain and if your pain varies day to day.

We would be grateful if you could return the outstanding diary for Month 1 as soon as you can. Another return envelope is enclosed, **no stamp needed.**

If you have any further questions or no longer wish to take part in the study please contact Emma Clarke, Study Coordinator, at Keele University on **01782 734683**.

Thank you once again for your continued support with our research project.

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Co-ordinator

Enclosed:
Pre-paid envelope

Arthritis Research UK primary care centre

Research Institute for Primary Care and Health Sciences
+44 (0)1782 733905
Fax: +44 (0)1782 733911
www.keele.ac.uk/pchs

V1.1, 09/04/13

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Ref: (Study ID)

Dear (**Insert patient name here**),

Osteoarthritis Daily Diary Study-Month 2

Thank you for you for your continued support with our study. So far we do not seem to have received your diary for Month 2.

The diary is an important part of our research as it helps us to see whether there are any activities that bring on an increase in your knee pain and if your pain varies day to day.

We would be grateful if you could return the outstanding diary for Month 2 as soon as you can. Another return envelope is enclosed, **no stamp needed.**

If you have any further questions or no longer wish to take part in the study please contact Emma Clarke, Study Coordinator, at Keele University on **01782 734683**.

Thank you once again for your continued support with our research project.

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Co-ordinator

Enclosed:
Prepaid envelope

primary care centre

Research Institute for Primary Care and Health Sciences
+44 (0)1782 733905
Fax: +44 (0)1782 733911
www.keele.ac.uk/pchs

V1.1, 09/04/13

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Ref: (Study ID)

Dear (**Insert patient name here**),

Osteoarthritis Daily Diary Study-Month 3

Thank you for you for your continued support with our study. So far we do not seem to have received your diary for Month 3.

The diary is an important part of our research as it helps us to see whether there are any activities that bring on an increase in your knee pain and if your pain varies day to day.

We would be grateful if you could return the outstanding diary for Month 3 as soon as you can. Another return envelope is enclosed, **no stamp needed.**

If you have any further questions or no longer wish to take part in the study please contact Emma Clarke, Study Co-ordinator, at Keele University on **01782 734683**.

Thank you once again for your continued support with our research project.

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Co-ordinator

Enclosed:
Prepaid envelope

Arthritis Research UK primary care centre

Research Institute for Primary Care and Health Sciences
+44 (0)1782 733905
Fax: +44 (0)1782 733911
www.keele.ac.uk/pchs

Appendix M: Thank you letters

Thank you letter 1, V1.2, 16/04/13

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Ref: (Study ID)

Dear (**Insert patient name here**),

Osteoarthritis Daily Diary Study

We would like to take this opportunity to thank you for taking the time to complete the questionnaire.

Even though you are unable to take part in the next stage of the study your answers to the questionnaire you sent back will be very useful.

Thank you once again for your support.

If you have any further queries please do not hesitate to contact the Study Co-ordinator, Dr Emma Clarke on **01782 734683**.

Kind regards,

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Co-ordinator
01782 734683

primary care centre

Research Institute for Primary Care and Health Sciences
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www.keele.ac.uk/pchs

Keele University, Staffordshire ST5 5BG, UK
www.keele.ac.uk +44 (0)1782 732000

Keele University

Ref: (Study ID)

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Dear (**Insert patient name here**),

Osteoarthritis Daily Diary Study

We would like to take this opportunity to thank you for taking the time to complete the questionnaire.

It was mentioned in the Patient Information Sheet that not everyone who agrees to the diary part of the study will be eligible. Some of the answers you gave in the questionnaire mean that you are no longer required to fill out the diaries.

Even though you are not able to take part in the next stage of the study your answers to the questionnaire you sent back will be very useful.

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Co-ordinator

Keele University

Ref: (Study ID)

(Participants Name)
(Address)
(Line 3)
(Postcode)
(Date)

Dear (**Insert patient name here**),

Osteoarthritis Daily Diary Study

An update and our thanks for taking part

I am writing on behalf of the research team involved in this study to thank you for taking part in completing the questionnaires and diaries. This phase of the research has been successfully completed.

We have been very encouraged by the goodwill shown by people like yourself who have helped with this research. Over the past 4 months, we have received an encouraging response to the questionnaire and diaries and such a positive response enhances the quality of this research. It is also very encouraging for the research team.

Our next task is to begin analysing all the information that people kindly provided. This is a big job but it is already underway. We hope to share the main findings of this work with your GP practice when the analysis is complete.

Once again, thank you for your help in this research. If you would like any further information about this research study please do not hesitate to contact Dr Emma Clarke, Study Co-ordinator on **01782 734683**.

Yours sincerely,

Professor George Peat
Principal Investigator

Dr Emma Clarke
Study Co-ordinator

Arthritis Research UK primary care centre

Research Institute for Primary Care and Health Sciences
+44 (0)1782 733905
Fax: +44 (0)1782 733911
www.keele.ac.uk/pchs

Appendix N: Favourable ethical opinion letter for observational diary study

NRES Committees - North of Scotland
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

NHS Grampian

7 May 2013

Professor George Peat
Professor of Clinical Epidemiology
Arthritis Research UK Primary Care Centre
Primary Care Sciences
Keele University
KEELE
Staffordshire
ST5 5BG

Dear Professor Peat

Study title:	**Exacerbations in Osteoarthritis: An Observational Daily Diary Study**
REC reference:	**13/NS/0049**
Protocol number:	**N/A**
IRAS project ID:	**122962**

Thank you for your letter of 3 May 2013, 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 Ms Sue Harrison.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Carol Irvine, carolirvine@nhs.net.

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.

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" below).

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.

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).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Covering Letter		3 May 2013
Evidence of insurance or indemnity		26 July 2012
Investigator CV: George Peat		1 February 2013
Appendix D - Patient Flowchart	1.1	16 April 2013
Appendix C - Contact List	1.1	9 April 2013
Dr Emma Clarke - CV		22 April 2013
Covering Letter - Appendix K - Baseline Practice Reminder	1.1	9 April 2013
Appendix J - Reminder Postcard	1.1	9 April 2013
Appendix Q - Covering Letter - Follow up 2 Reminder	1.1	9 April 2013
Appendix R - Covering Letter - Follow up 3 Reminder	1.1	9 April 2013
Appendix S - Covering Letter - Follow up 4 Reminder	1.1	9 April 2013
Appendix N - Covering Letter Follow up 2	1.1	9 April 2013
Appendix O - Covering Letter Follow up 3	1.1	9 April 2013
Appendix P - Covering Letter Follow up 4	1.1	9 April 2013
Appendix L - Thank you Letter 1	1.2	16 April 2013
Appendix T - Thank you Letter 2	1.2	16 April 2013
Appendix U - Thank you Letter 3	1.0	16 April 2013
Appendix B - GP Cover Letter	1.1	9 April 2013

Document	*Version*	*Date*
Appendix M - Diary Instructions	1.2	17 April 2013
Appendix G - Sample Diary Template	1.1	9 April 2013
Appendix H - Covering Letter Baseline Practice	1.2	3 May 2013
Participant Consent Form: Section 4	1.1	9 April 2013
Participant Information Sheet: Appendix F	1.1	9 April 2013
Protocol	1.1	9 April 2013
Questionnaire: Month Daily Diary	1.2	17 April 2013
Questionnaire: Baseline	1.2	3 May 2013
REC application	122962/443 280/1/849	26 April 2013
Referees or other scientific critique report: Research User Group Recommendations	1.1	9 April 2013
Response to Request for Further Information		3 May 2013

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 NRES 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 website.

Further information is available at National Research Ethics Service website > After Review.

13/NS/0049	**Please quote this number on all correspondence**

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/

With the Committee's best wishes for the success of this project.

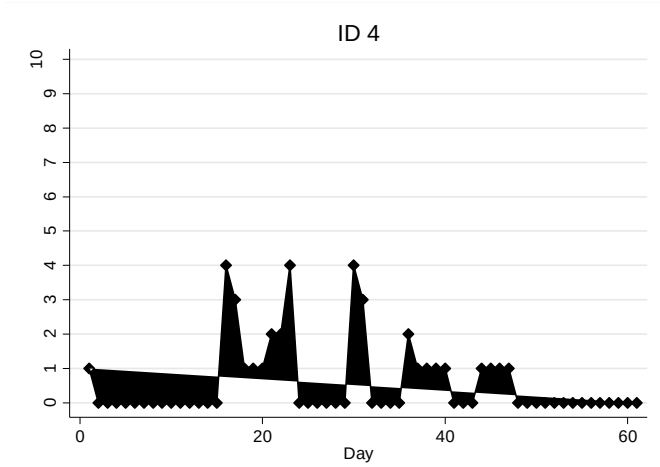
Yours sincerely

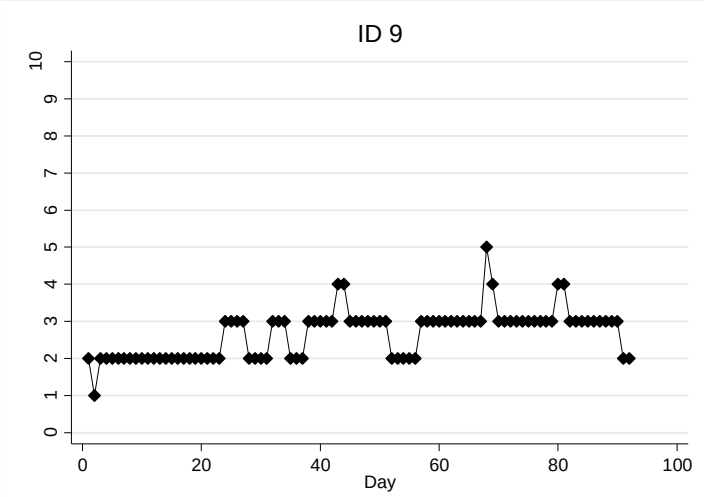
Professor Helen Galley
Chair

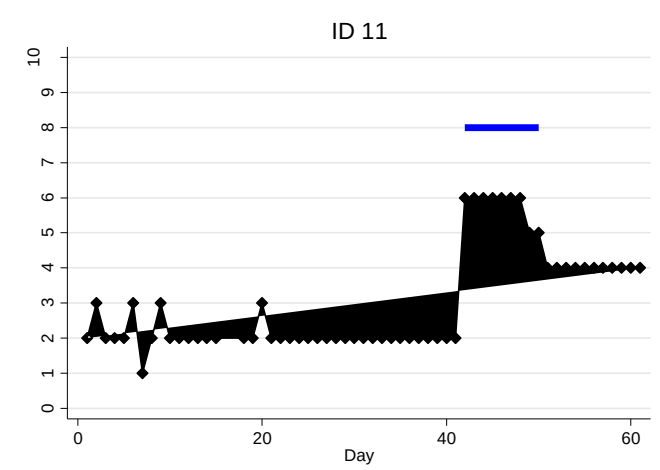
Enclosures: "After ethical review – guidance for researchers" SL-AR2

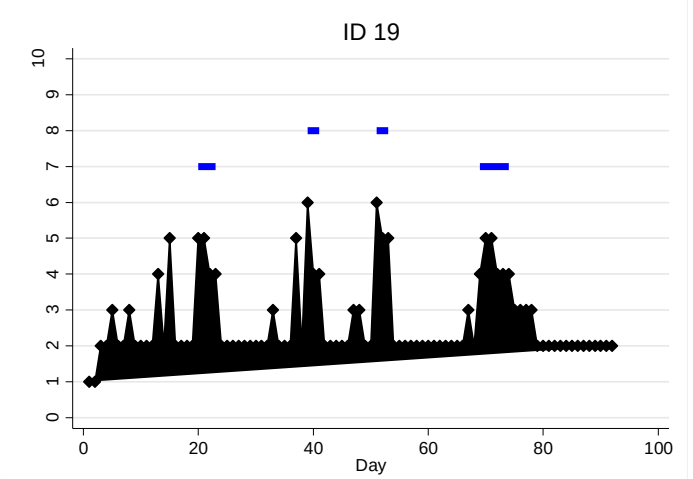
Copy to: Ms Jacqueline Gray
Dr Anthony Rathbone, Primary Care Medical Organiser and R&D lead

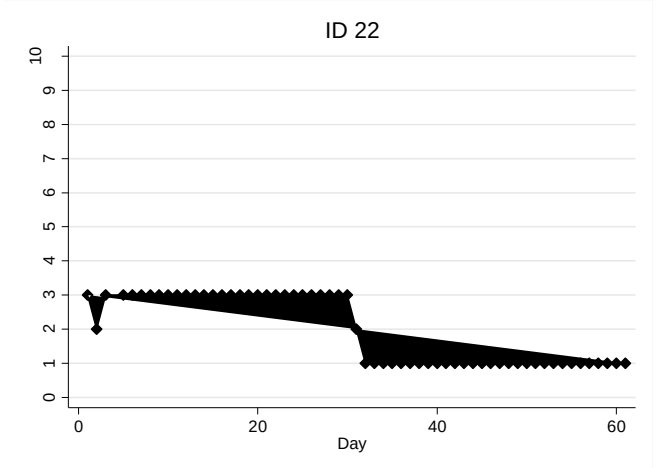
APPENDIX O: Daily NRS graphs for each individual (Flare-ups indicated by blue line)

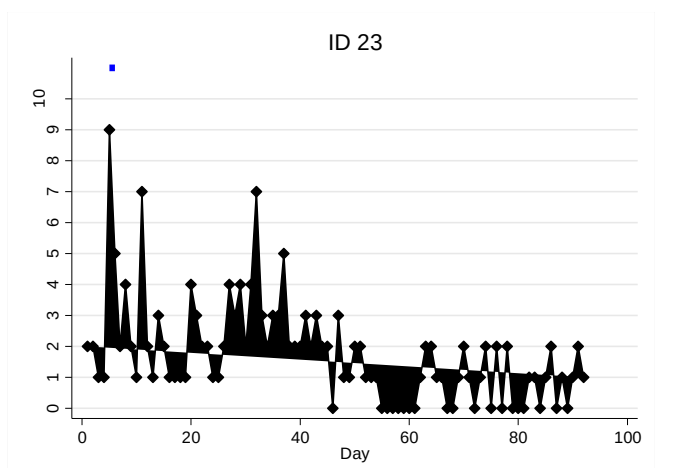


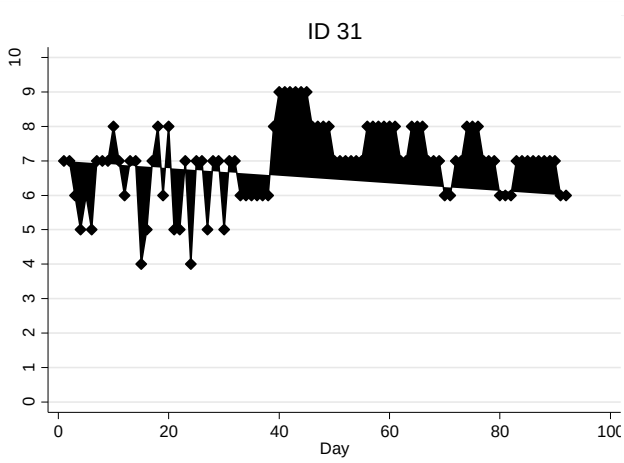








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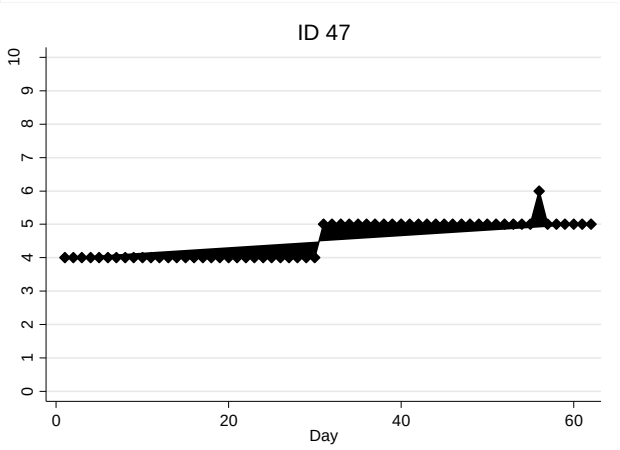
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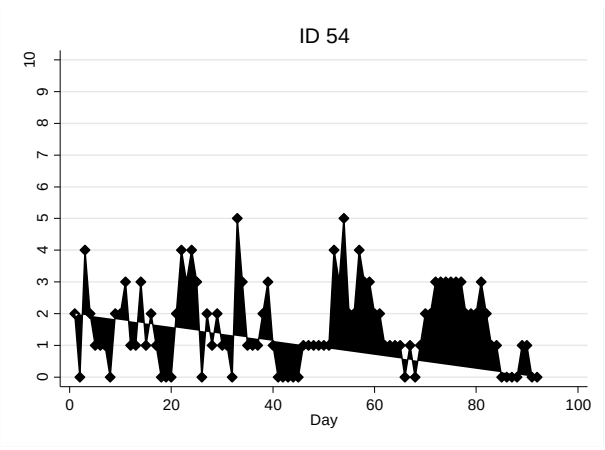
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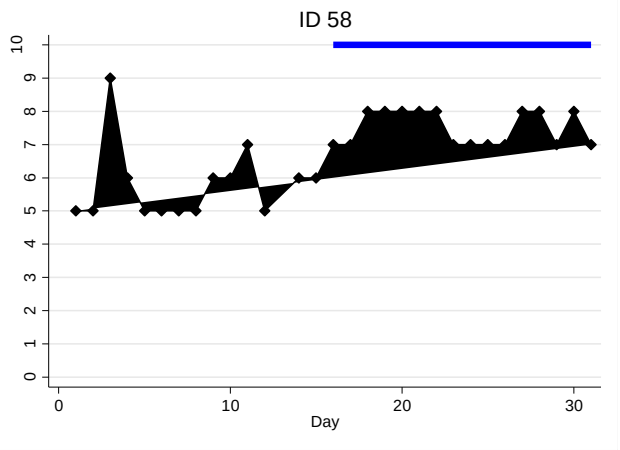
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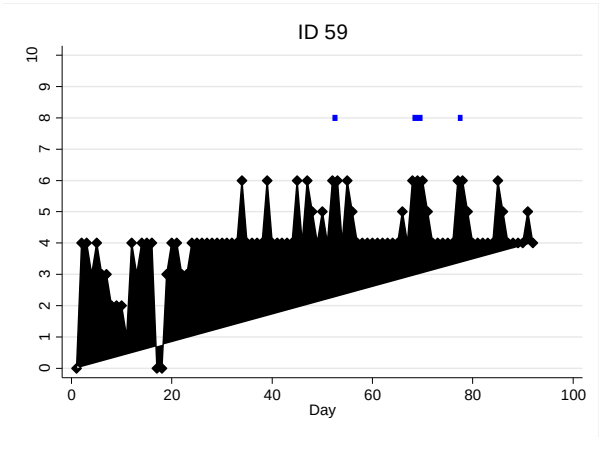
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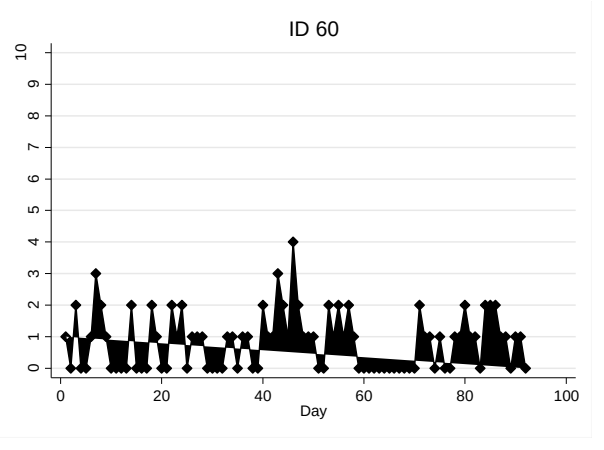
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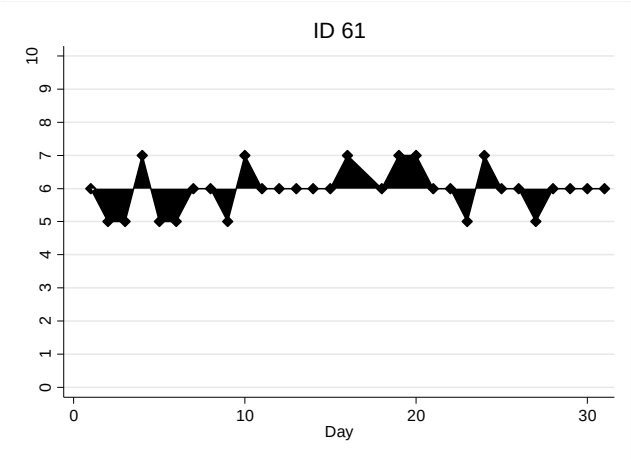
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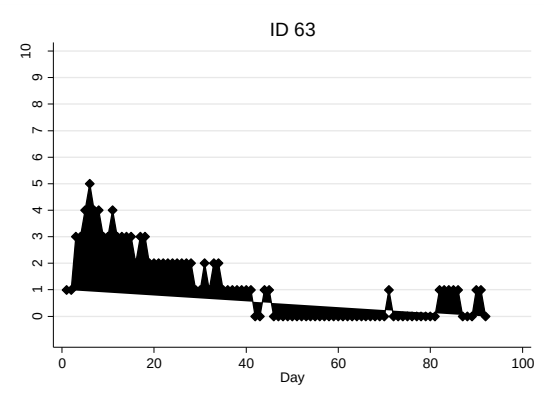
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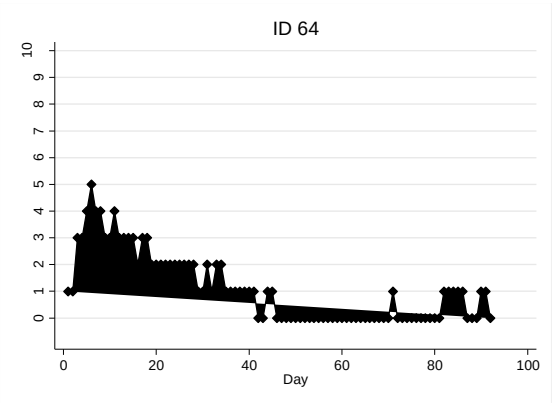
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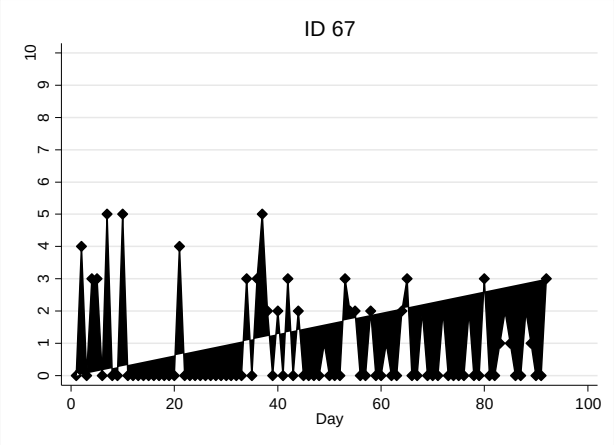
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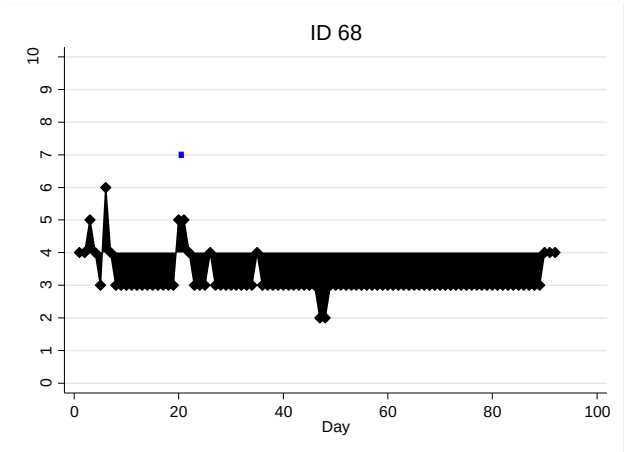
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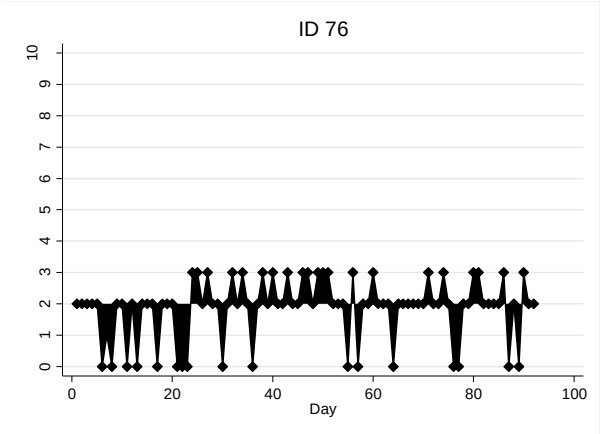
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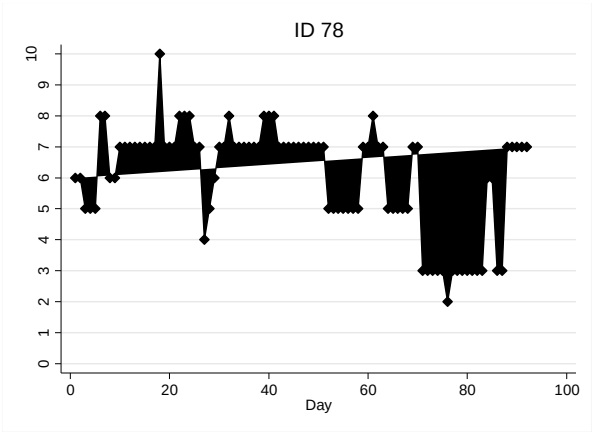
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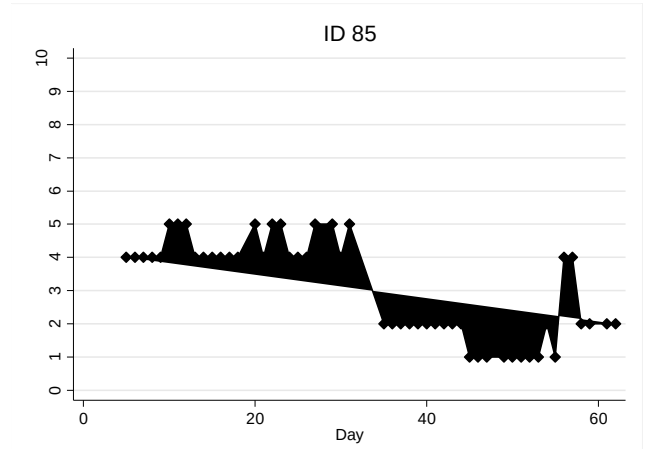
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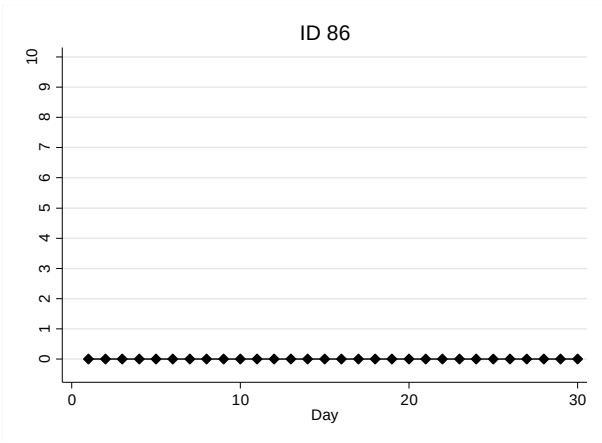
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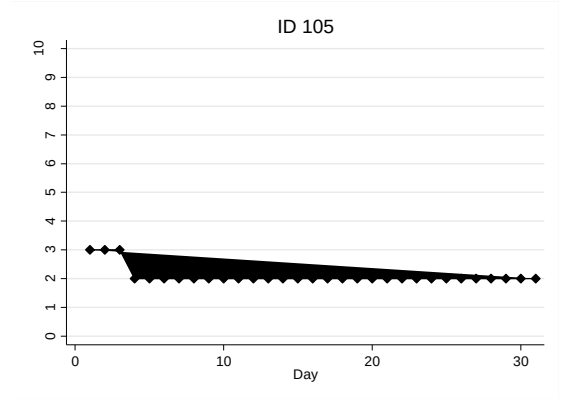
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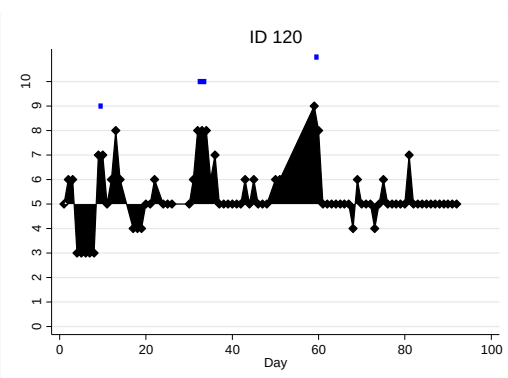
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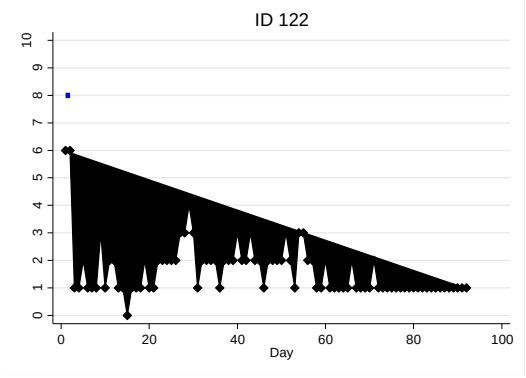
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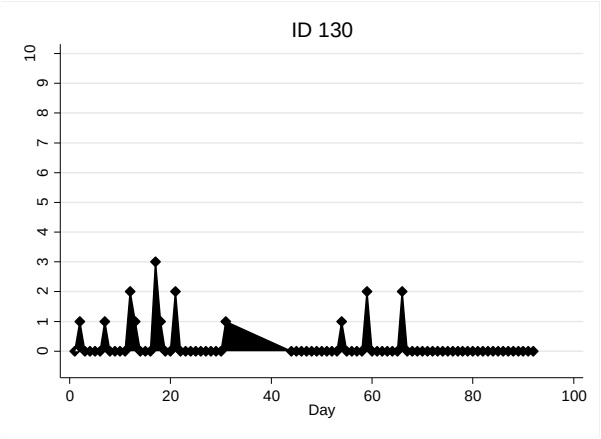
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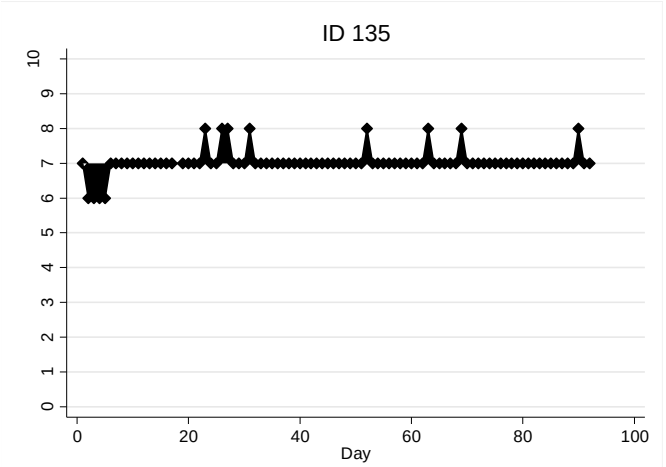
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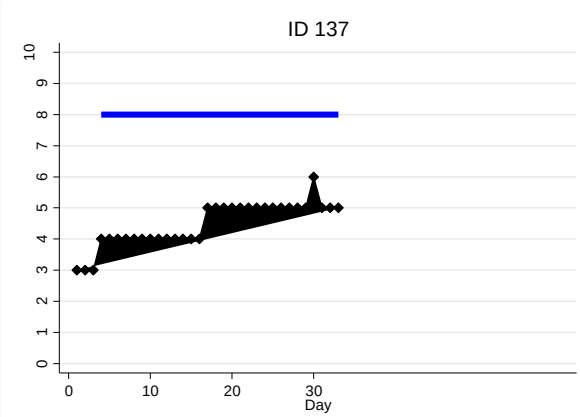
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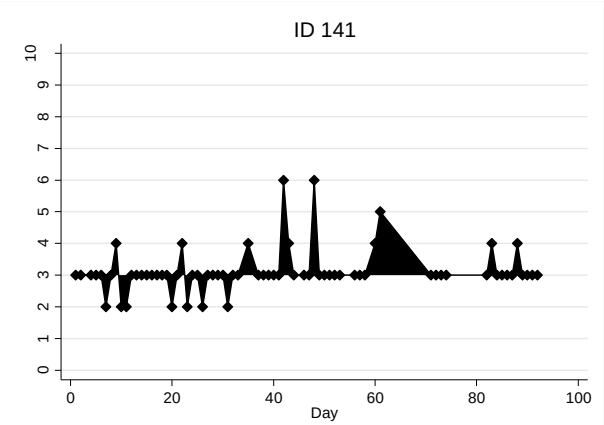
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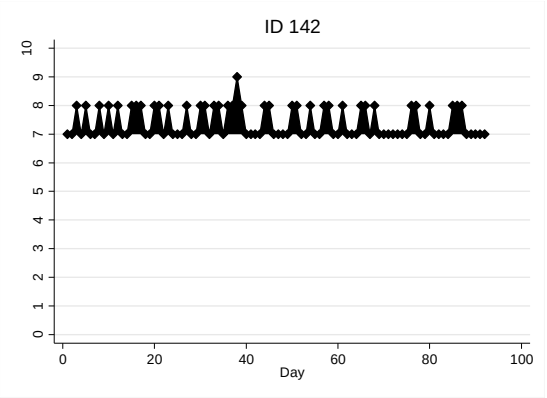
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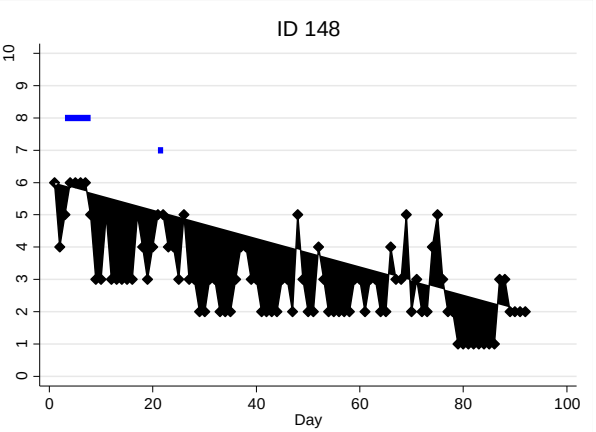
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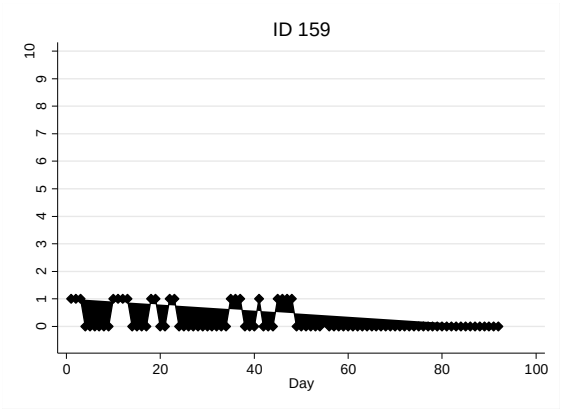
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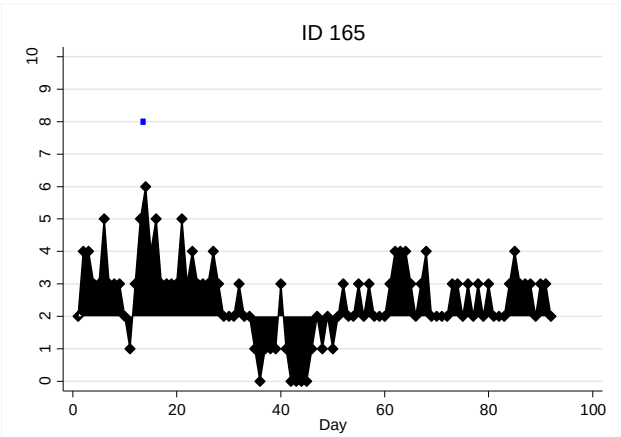
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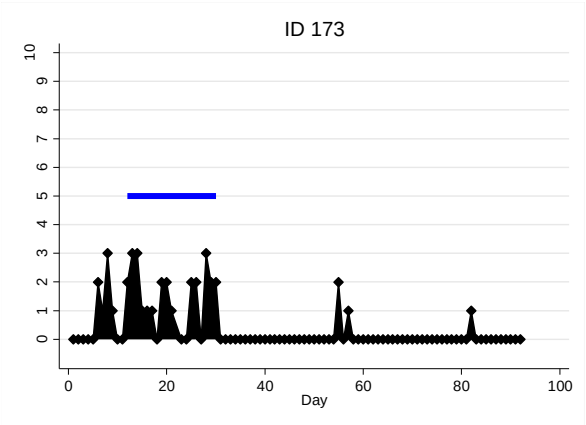
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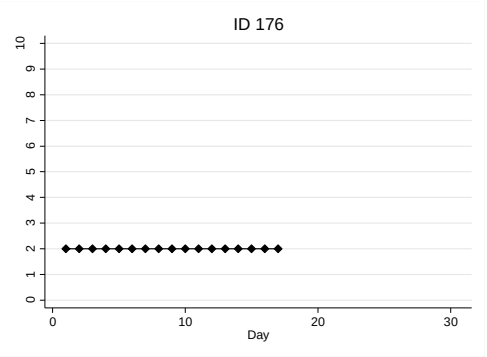
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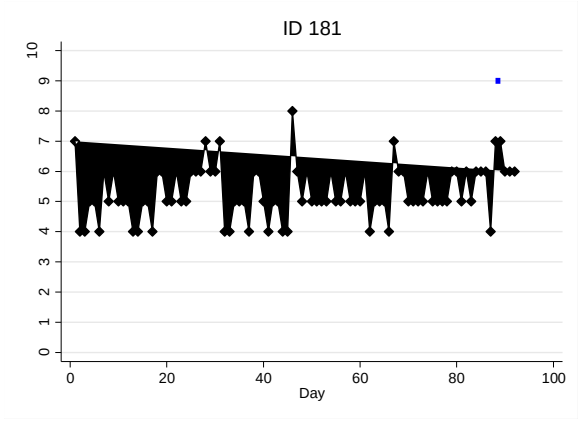
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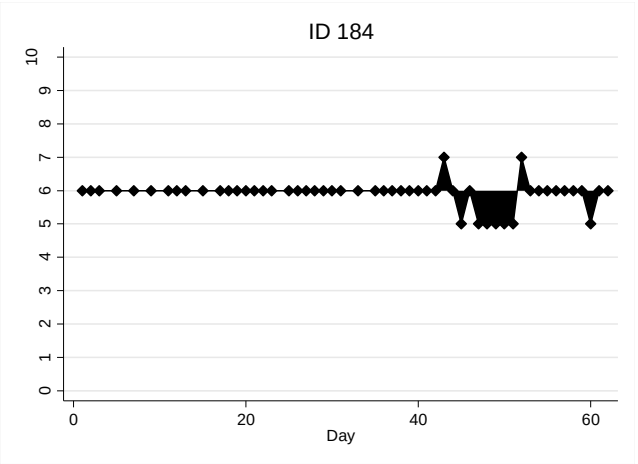
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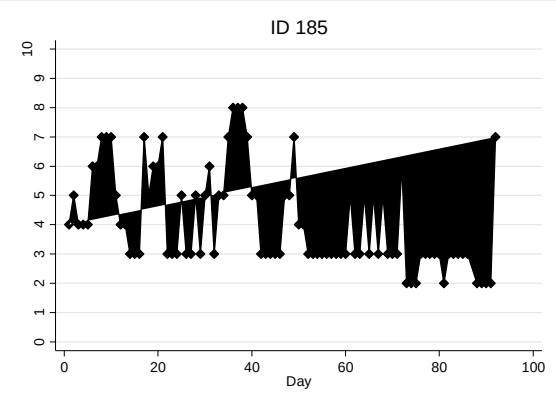
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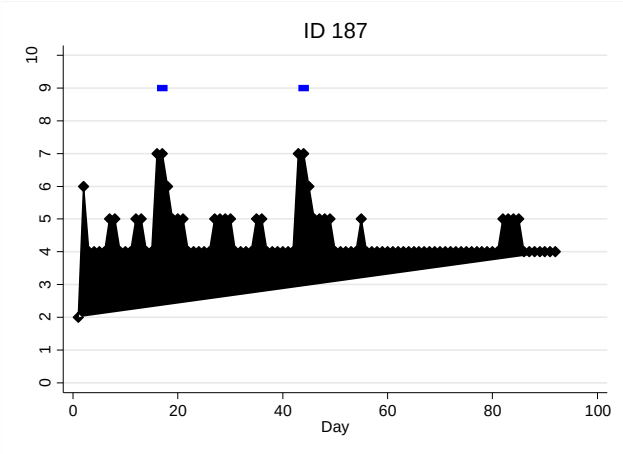
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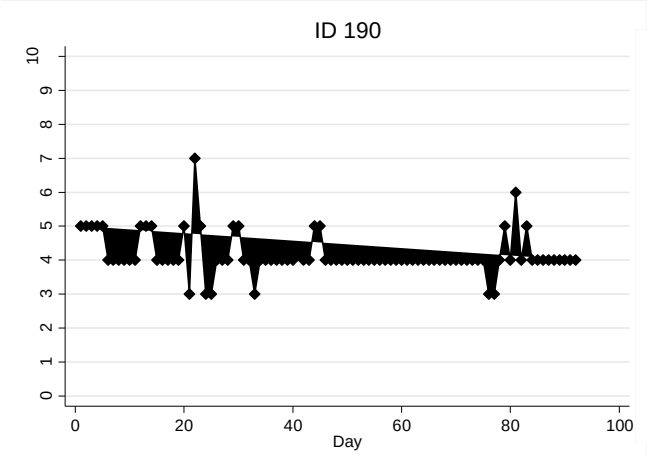
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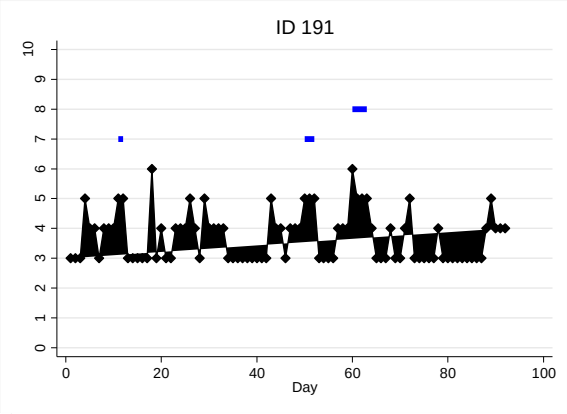
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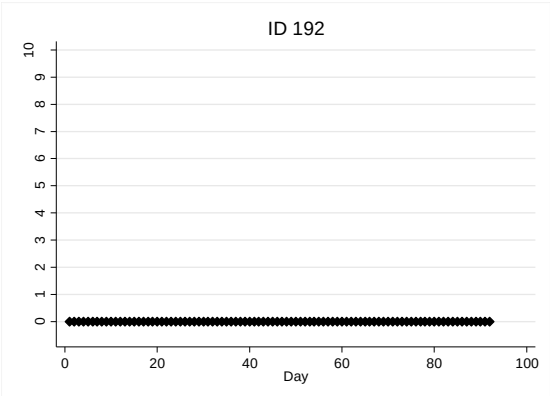
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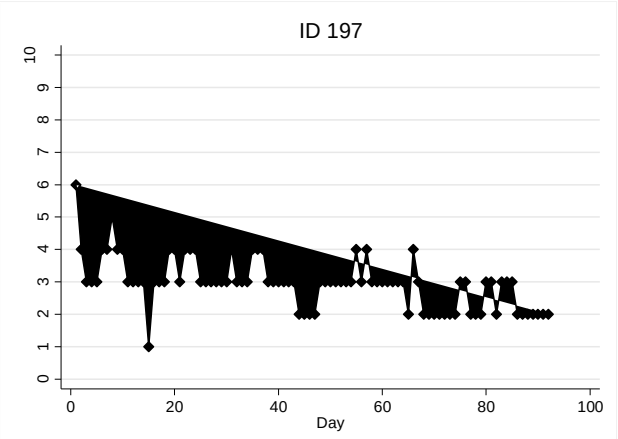
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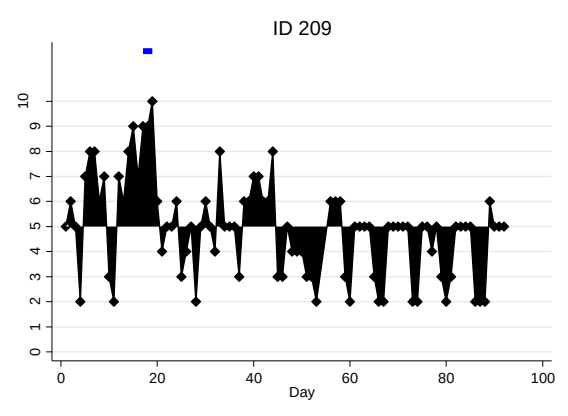
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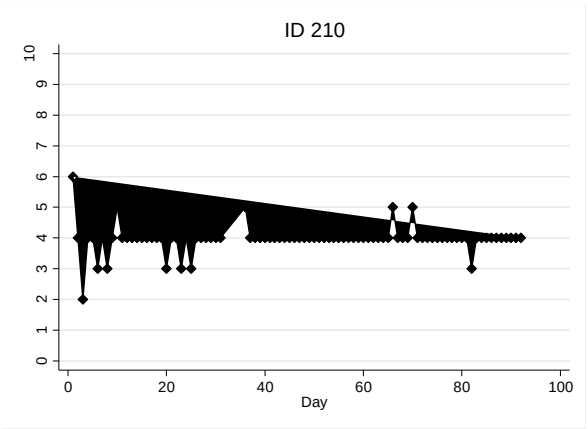
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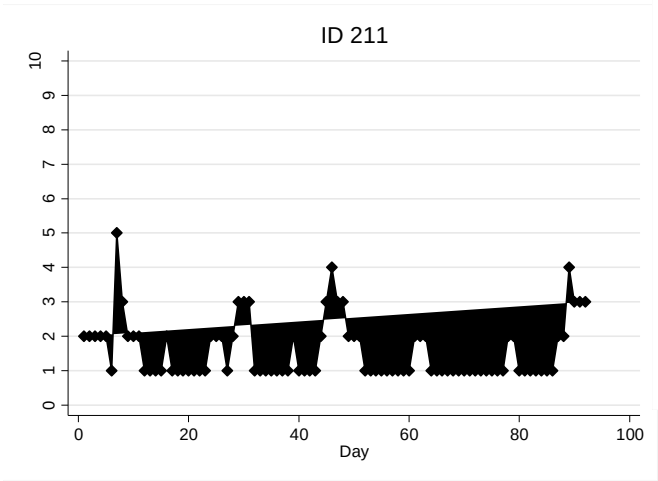
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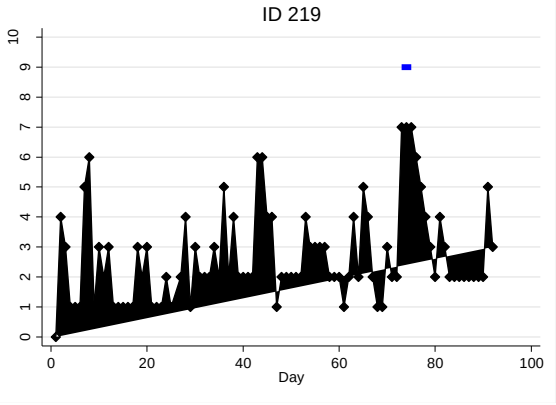
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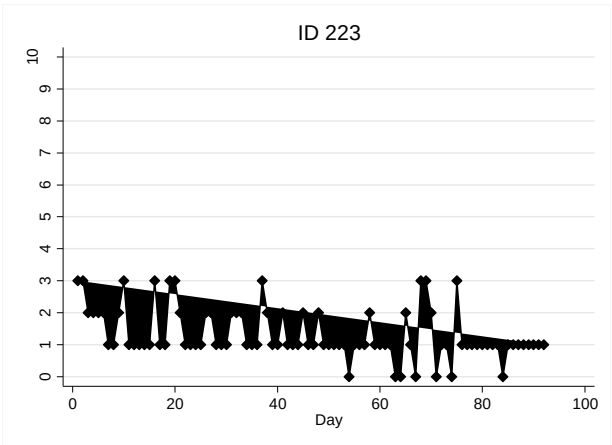
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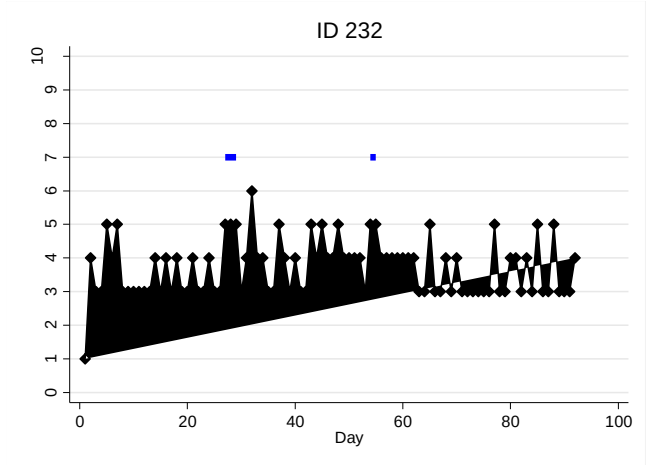
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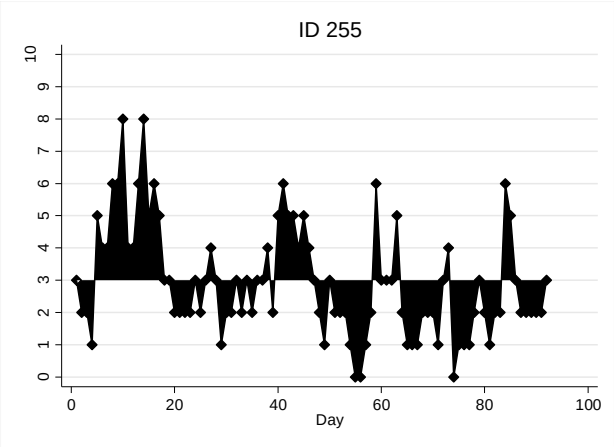
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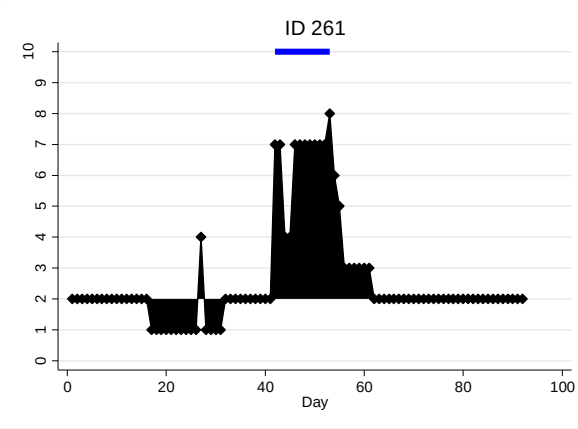
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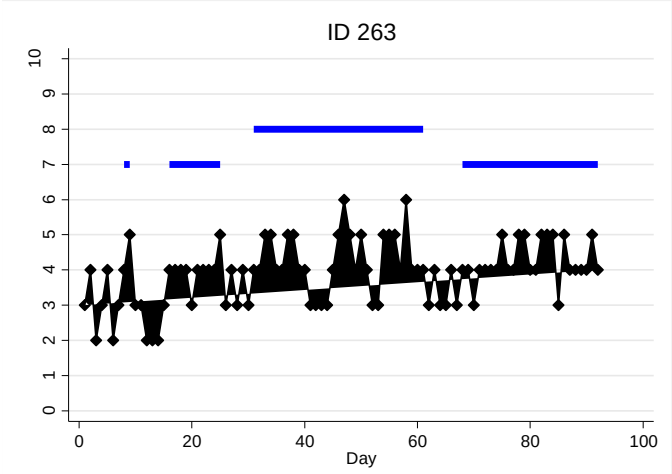
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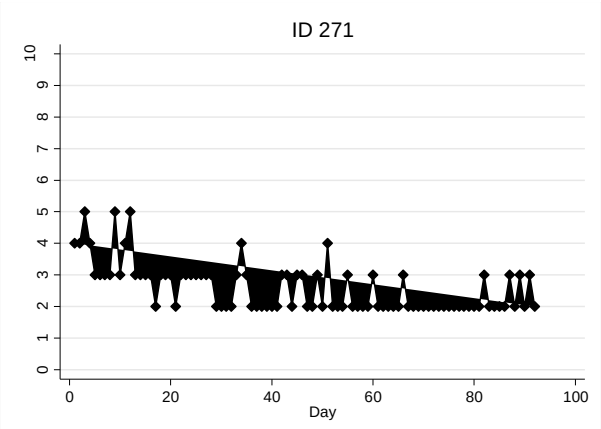
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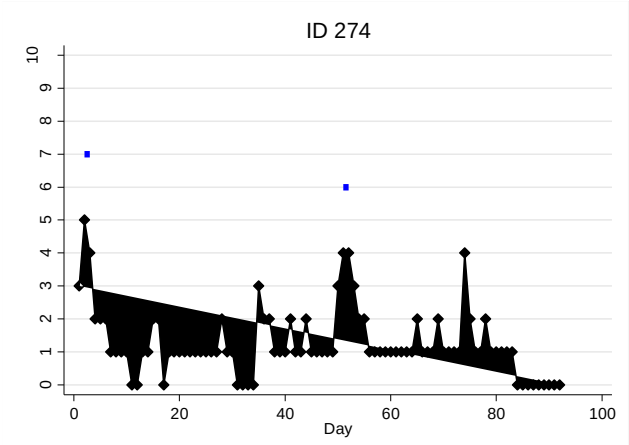
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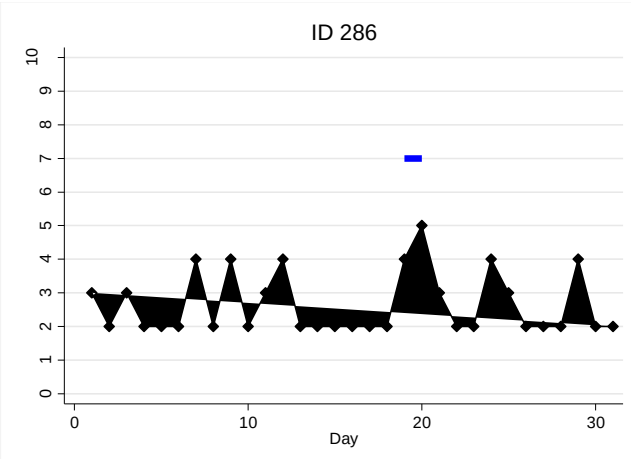
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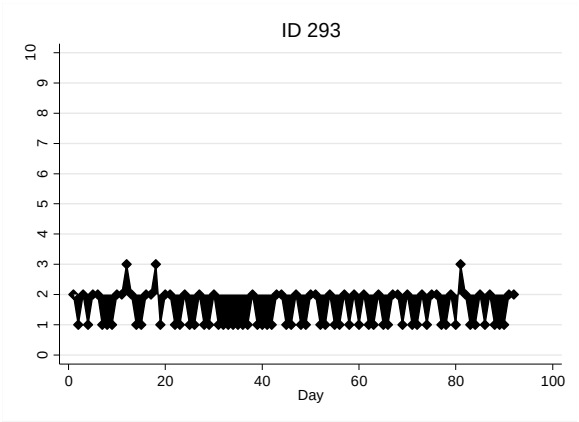
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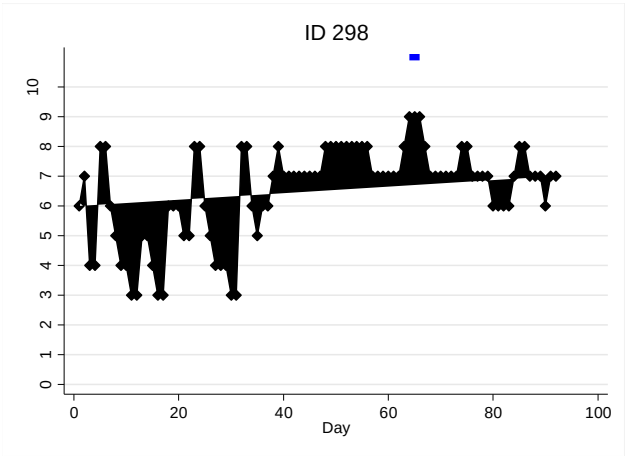
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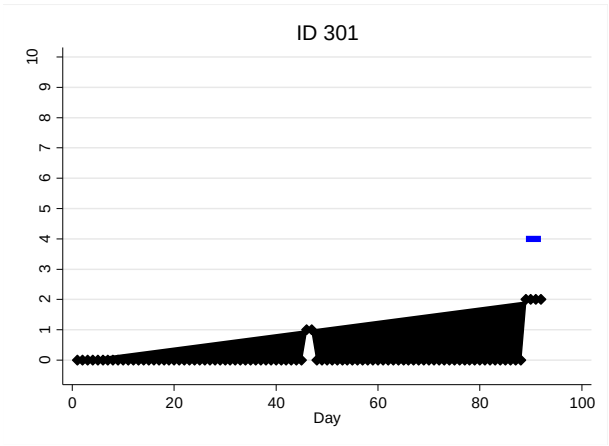
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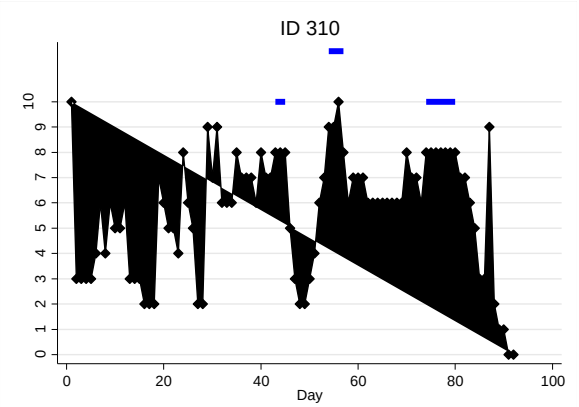
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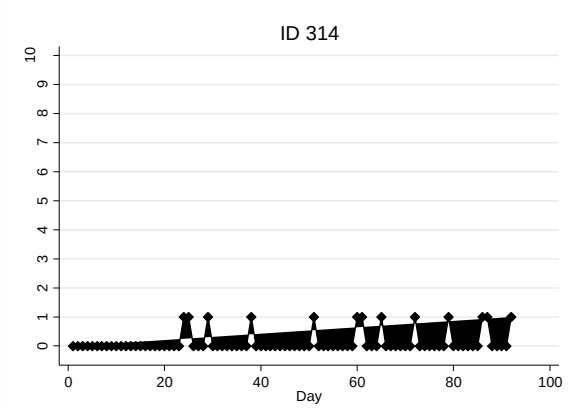
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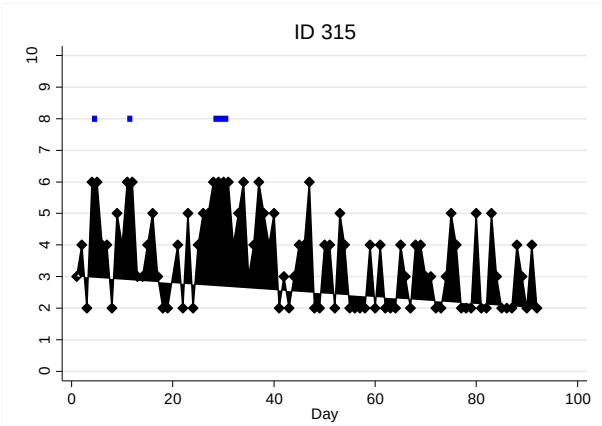
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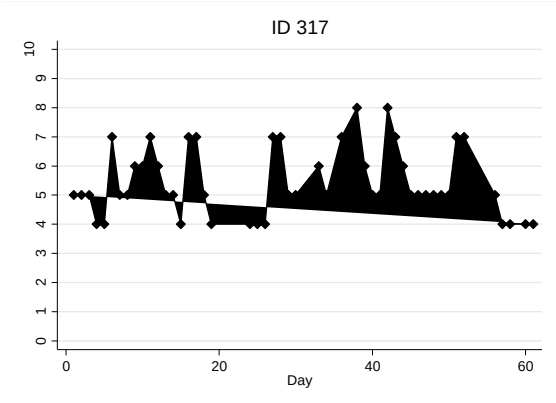
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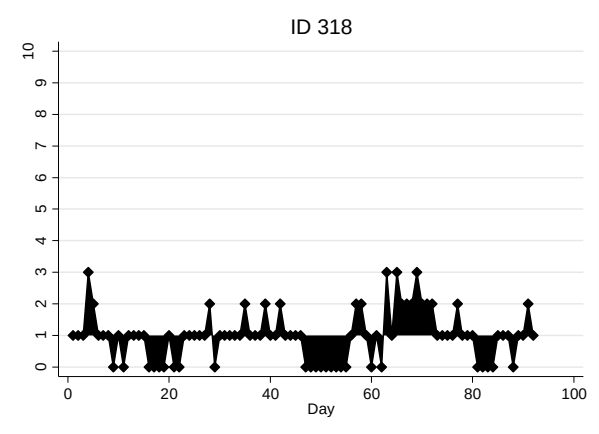
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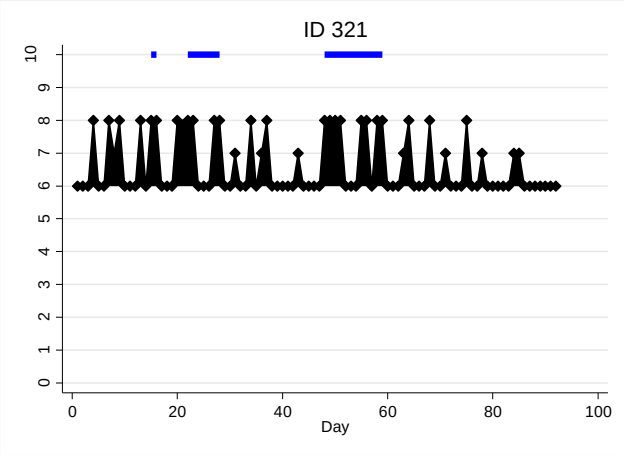
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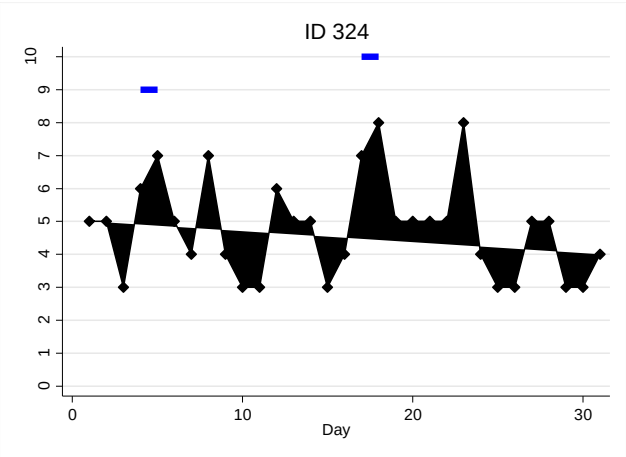
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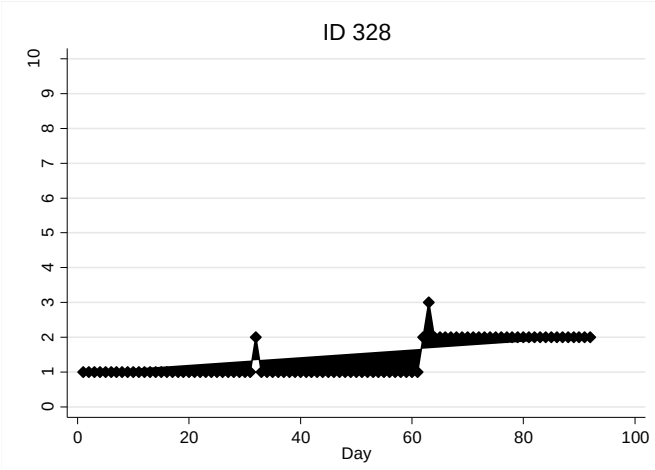
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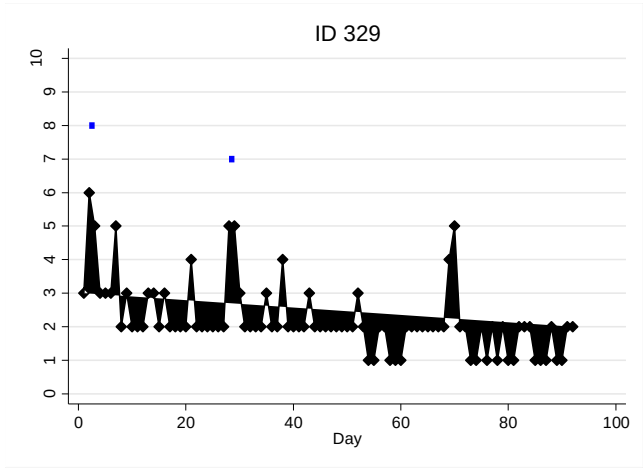
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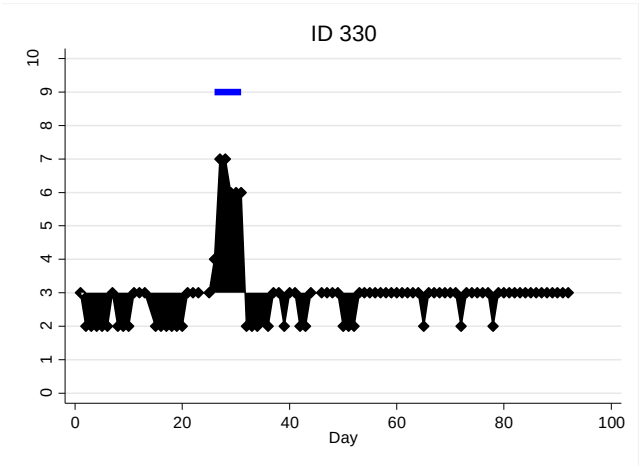
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40
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80
100
Day

Appendix P. Worked example of case-cross over analysis with kneeling for ≥30 as the exposure in the 48 hours prior to a flare (NB. Participants with only unexposed concordant paired observations (Ca-Co-) are not displayed)

Exposure = Kneeling for ≥30 min in the prior 48 hours (n=3 cases, 40 paired observations)

ID of case	Exposure status in case window	Exposure status in control window	Paired observation pattern
148	+	-	+-
148	+	-	+-
148	+	-	+-
148	+	-	+-
315	+	-	+-
315	+	-	+-
315	+	-	+-
315	+	-	+-
315	-	+	-+
315	-	-	--
315	-	-	--
315	-	-	--
315	-	+	-+
315	-	-	--
315	-	-	--
315	-	-	--

209	+	-	+-
209	+	-	+-
209	+	-	+-
209	+	-	+-
165	-	+	-+
165	-	-	--
165	-	-	--
165	-	-	--
298	-	+	-+
298	-	-	--
298	-	-	--
298	-	-	--
330	-	+	-+
330	-	+	-+
330	-	-	--
330	-	+	-+
191	-	+	-+
191	-	-	--
191	-	-	--
191	-	-	--
187	-	+	-+

187	-	-	--
187	-	-	--
187	-	-	--

Appendix Q: Initial mailing pack for qualitative study

GP Practice Details
(i.e. Names of Drs)

Practice Name *Tel:* *XXX*
Practice Address Details *Fax:* *XXX*
Practice Address Details
Practice Address Details
Post-code

Dear Patient,

Knee Osteoarthritis Flare Interview Study

We are writing to see if you would be willing to help with a research study about knee pain. The study is being carried out by this GP practice, together with the Research Institute for Primary Care and Health Sciences at Keele University.

We are interested in getting more information from people who have knee pain due to osteoarthritis. In this research we want to find out:

- How often people have episodes when their knee pain is noticeably worse than the normal day-to-day ups and downs?
- How long does it take for these episodes to settle down?
- Is there anything that brings on these episodes?
- What do people do to manage these episodes?

We hope that our research will give us a clearer understanding of increases in knee pain, sometimes called 'flare-ups', and if we can predict when they might happen and how best to manage them.

We hope that you are able to help with our research and can spare an hour of your time to be interviewed by one of our researchers. Please read the enclosed information sheet about the study and answer the questions on the reply slip if you are happy to take part.

We would be grateful if you could return the reply slip in the envelope provided in the next 2 weeks or as soon as you can. **You do not need a stamp.** If you would like to know more about the study or would rather register your interest via email or telephone contact Dr Emma Parry (Researcher) on e.parry@keele.ac.uk or (01782) 734929 (Mondays and Thursdays).

Thank you very much for your help with this research study

Yours Sincerely
Dr X and partners

Enclosed:
Patient Information Sheet, Pre-paid envelope, Reply slip

Knee Osteoarthritis Flare Interview Study

☐ Yes, I would like to be contacted about this study

☐ No, I do not want to be contacted about this study

Name: .....

Address:.....

.....

Telephone:.....

Please answer the questions below to determine your suitability for taking part in this study by putting a cross in a box, like this: ☒

1. In the **last 12 months** have you had an increase of your knee pain where your pain is worse than normal, has lasted a period of time and may have stopped you from doing your normal activities or meant you had to increase your pain medication)?

   Yes ☐

   No ☐

2. Have you ever had knee replacement surgery?

   Yes ☐

   No ☐

3. What is your date of birth?

☐☐/☐☐/☐☐ *(example: 01/10/59)*

(day) (month) (year)

4. Are you?

Male ☐ Female ☐

Once completed, please return this reply slip using the stamped address envelope provided.

Arthritis Research UK Primary Care Centre
Keele University
Staffordshire
ST5 5BG
01782 734683

working with **Practice name**
Address 1
Address 2
Address 3
GP Name 1
GP Name 2

Information sheet

REC approval date 08/05/2017(v1.4)
IRAS number: 215481

Osteoarthritis Flare Interview Study

You are being invited to take part in a research study. Before you decide to take part, 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.

What is the purpose of the study?

Knee pain, due to osteoarthritis, is a very common problem in this country. It is important that we know more about this pain so that we can help patients manage it.

The aim of this study is to gain insight into patient's experiences when their knee pain is worse than normal or flares up.

What do we mean by a flare-up of knee pain?

A flare-up is an event that:

- causes **an increase in your pain that is beyond normal day-to-day variation that lasts for a period of time**
- comes on suddenly, developing over minutes or hours (rather than a very gradual worsening over days or weeks)

Not everyone is affected in the same way by flare-ups. These are some things that people say they can feel when they have a flare-up. You may experience some, none, or all of these during your flare-ups:

- everyday activities are more difficult or impossible to do
- you need to take (more) painkillers
- limping
- swelling of the joint
- more stiffness of the joint
- pain that disturbs your sleep.

Do I have to take part?

We have written to you as someone who has pain from knee osteoarthritis and we would like to hear your views. *You are, of course, entirely free to choose whether or not to take part*. If you decide to take part, you will be asked to sign a consent form. After giving consent, you are still free to withdraw at any time without giving reason. Your decision to take part in the study, or to withdraw, will not affect any legal rights. If you would like to take part, please return the enclosed reply slip and we will contact you.

What will happen to me if I agree to take part?

If you agree to take part, you will be contacted by telephone to arrange a subsequent face-to-face interview, at a time and place most convenient for you. The interview will last approximately 1 hour and it will focus on increases in your pain above normal, any triggers for the pain, how you manage the pain and how your pain has changed over time. No preparation for the interview is necessary and this is not a test about your knowledge.

We would like to record the interview and will check that this is acceptable to you prior to the interview. The interview will then be transcribed into text by either the interviewer or an external company. No identifiable data will be sent with the recording. Both the recording and the text will be stored in a secure location, only accessed by the research team. Both the recording and the text will contain no personal identifiable information. We will ask if you would like a copy of the transcribed interview for your records. We will store the transcripts securely for 5 years, after which they will be destroyed.

During the interview, you can choose not to answer questions, or to end the interview at any time. You will be asked at the end of the interview if you are still happy to be included in the study. If you decide that you would like to withdraw your consent, your interview will not be used. In order to convey the attitudes and beliefs of participants, we would like to use anonymous direct quotations from the interview. At the interview we will give you a consent form specifically for the use of direct quotations. We would be grateful if you could complete this after your interview.

Any information you give in the interview will not be passed on to anyone else without your permission. If your interview contains comments that might identify a third party (e.g. GP, surgery, hospital), we will ensure that the person or institution cannot be identified in any account or published report of this study.

What will happen to my personal information?

Your GP Practice will keep your name and contact details confidential and will not pass this information to Keele University. Your GP Practice will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from Keele University and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Keele University will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

Keele University is the sponsor for this study based in the United Kingdom. If you agree to take part in this study we will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Keele University will keep identifiable information about you (if you agree to take part in this study), for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information
at https://www.keele.ac.uk/privacynotices/privacynotice-researchparticipants/

What are the possible benefits and risks of taking part?

There are no direct risks relating to medical treatment in this study, nor are there any intended direct medical benefits. There may be an indirect benefit to patients from the insights we gain, but of course, we cannot guarantee this. Occasionally during interviews like these, some people may feel some distress, perhaps a topic may prompt unhappy memories or distressing thoughts. If this happens and you do not wish to discuss this further, the topic will not be followed up again during the interview. The study is not intended to be of any educational benefit.

Who is organising and funding the research, and is it ethical?

This study is part of a programme of work being conducted by the Arthritis Research UK Primary Care Centre at Keele University. It is funded by the National Institute for Health Research and ethical approval has been obtained from the local Research Ethics Committee.

Contact for further information

If you have any questions, or would like further information, about this study please contact our researcher, **Dr Emma Parry** on **01782 734929** (Mondays and Thursdays) or email e.parry@keele.ac.uk or Dr Tracy Nevatte on research.governance@keele.ac.uk.

If you have any questions or concerns about taking part in this research you can also contact the Patient Advice and Liaison Service (PALS). Your local PALS office free phone number for Shropshire is 0800 032 1107. For further information visit their website http://www.pals.nhs.uk/.

Thank you for taking time to read this information leaflet.

Appendix R: Information provided to general practices about the qualitative study

(GP name)
(Address)
(Line 3)
(Postcode)
(Date)

Dear (**insert GP name**),

Knee Osteoarthritis Flare Interview Study

Further to previous discussion, I am writing on behalf of the research team involved in the above study to give you more information.

We intend to contact the patients who are deemed eligible after screening by yourselves to take part in our new research project. The overall aim of the current study is to describe the natural history of exacerbations or flare ups in osteoarthritis from a patients' perspective. We hope the study findings will help support the future prevention, early recognition and effective management of exacerbations as part of overall osteoarthritis management.

Each participant will be invited to take part in a one hour face to face interview after the return of a reply slip with eligibility questions. The interview will explore patients understanding of flare ups in knee osteoarthritis, triggers, predictability, self-management and if their flares have changed over time.

The study has been granted ethical approval and to minimise patient distress we wish to do the following:

a) Network staff will provide your practice with a practice pack containing the study protocol, study contact list, patient information sheet, a copy of letter of approval from REC and R&D, Statement of Research Governance for the Arthritis Research UK Primary Care Centre and Statement of practice agreement.
a) All aspects of the project will be administered from the Centre in the usual way. We will emphasise in the initial mailing pack that patients need to signpost all queries to the Centre, by providing our contact details.
b) We require your input with regards to screening patients who you deem unsuitable to take part.

A member of the Network Staff will contact you shortly to discuss the details of the patient screen.

If you would like any further information about this study please do not hesitate to contact Emma Parry
e.parry@ke

Thank you as ever for your support.

Yours sincerely

Professor Carolyn Chew-Graham
Principal Investigator

Dr Emma Parry
GP Researcher

Knee Osteoarthritis Flare Interview Study

IRAS Number: 215481

We are running a study where we will be interviewing patients with knee osteoarthritis on their understanding and experience of flare-ups of pain.

Study details

- Qualitative interview study using semi-structured interviews.
- We aim to interview approximately 15 patients, male or female aged 45 and over.
- We will explore patients understanding of flare-ups, their health seeking behaviour, triggers for increases in pain and changes in pain over time.

How to get involved

- CRN: West Midlands Research Facilitator will run a search to identify patients aged 45 and over with a consultation for knee osteoarthritis/arthralgia in the past 2 years.
- The search will exclude certain cohorts of patient's e.g. palliative care etc. but the practice clinicians will still be asked to screen the list to remove patients who they believe are unsuitable to be contacted about the study.
- Patient list screening is anticipated to take place in **December 2018/January 2019.**
- Patients may opt to have the interviews at your practice. If this is possible we can pay fees towards the cost of using a room.

What it means for patients

- Patients will be sent information about the study and asked to return a reply slip if they want to take part.
- If they agree to take participate, a one off, 1 hour interview will be arranged at a location of their choosing.

What are the benefits for your practice?

- Reimbursement for assisting with patient identification and screening the patient list.
- Contribute to GP appraisal and revalidation.
- Contribution to evidence base.

We welcome the opportunity to meet with your team to discuss this research study.

If you are interested in the study or would like to find out more please contact:-

Sam Hunt, CRN Research Facilitator samantha.hunt@nihr.ac.uk or 01782 734 892

Dr Emma Parry, GP Researcher e.parry@keele.ac.uk

Appendix S: Consent form for qualitative study

University

Knee Osteoarthritis Flare Interview Study
Patient Consent form
Version 0.2, date 01.11.16
LREC Number: 215481

Title of project: Knee Osteoarthritis Flare Interview Study
Name of researcher: Dr Emma Parry

Please Initial

1. I confirm that I have read and understand the participant information sheet and have had the opportunity to ask questions..... ☐
2. I understand that my participation is voluntary, that I can refuse to answer a question, or withdraw at any time, without giving reason, and without my medical care of legal rights being affected..... ☐
3. I understand that the interview will be recorded and transcribed, and that the recordings will be stored in a secure location, but will bear no personal identifying information. I understand that the recordings and transcripts will be kept for 20 years and after this time will be destroyed..... ☐
4. I understand that transcripts will be archived securely at the Arthritis Research UK Primary Care Centre, Keele University and may be re-used by researchers from the Centre in the future. All such information will be fully anonymised..... ☐
5. I understand that quotations from the interview may be included in reports or publications from this study, but that these will be anonymous and I will not be identifiable..... ☐
6. I agree to take part in the above study..... ☐

Please sign and date on line below:

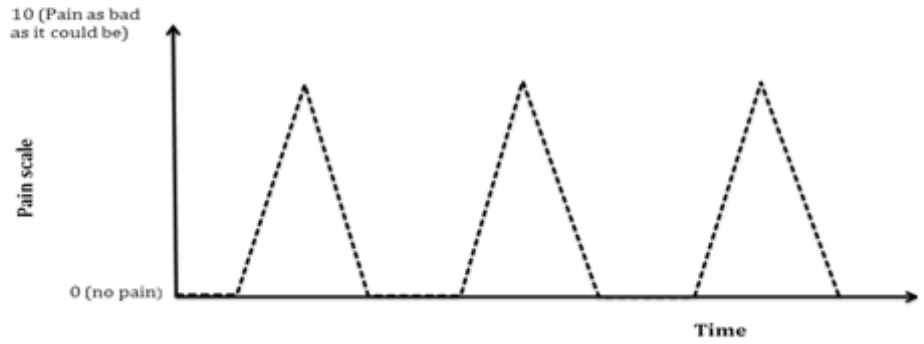
Name of participant	Date	Signature
Name of Researcher	Date	Signature

Study ID

Appendix T: Example pain graphs shown during interview

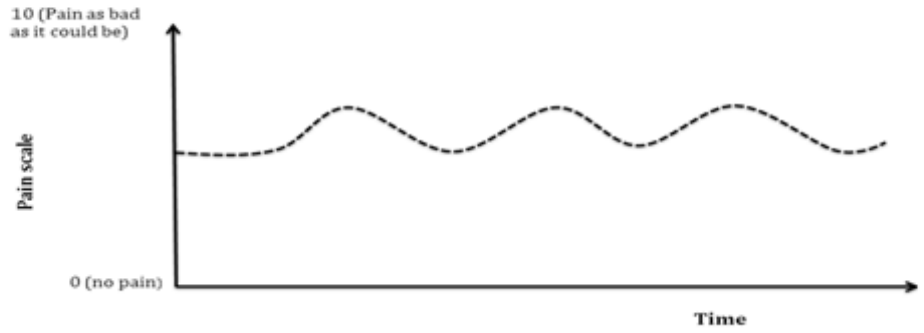
Disease Course Over Time

A



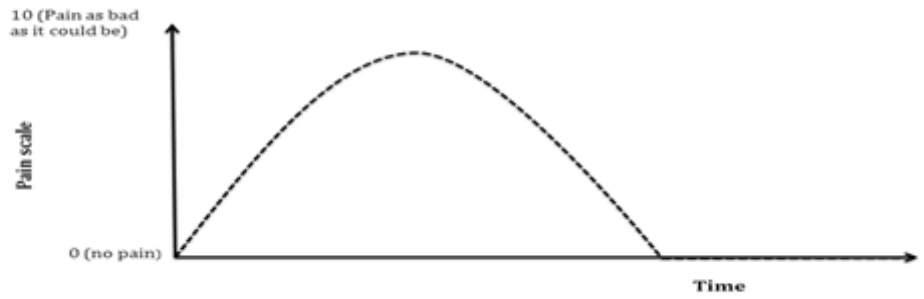
Patients experience flare or increase in pain and return to a background of no pain in between.

B



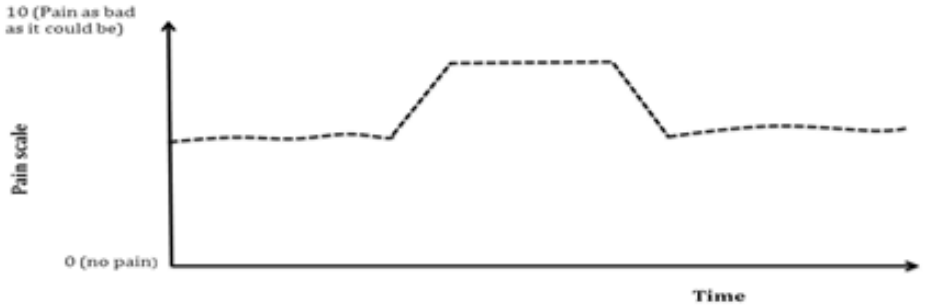
Patients experience flares of pain and return to a background level of pain in between

C



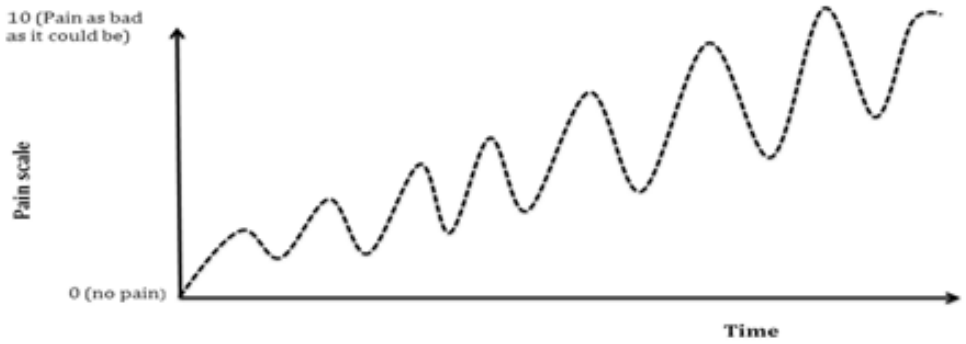
Patients experience an intense a long lasting pain flare and eventually returns to a state of no background pain

D



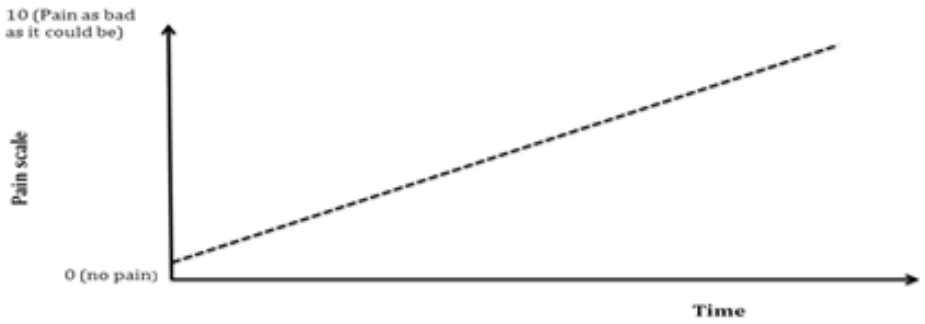
Patients experience a long lasting flare on a background of normal pain

E



Patients experience numerous flares and their background pain increases after each flare.

F



Patients experience a gradual increase in pain over time with no flares

Appendix U: Topic guide

Interview Schedule for qualitative interviews

Modifications in red

1. What do you think the term flare-up means? How would you describe a flare-up?
    a. Does the pain have to be at a certain level for you to think it is a flare-up?
    b. Is the term flare-up something you had heard before this interview? Is it a useful term?

2. Have you ever experienced a flare-up of your knee osteoarthritis?
    a. What was it like?
    b. How long did it/do they last?
    c. How quickly did the pain start?
    d. Did it/do they stop you from doing anything?
    e. Does the way your knee looks change during a flare-up? (e.g. swelling)
    f. How long have you had flare-ups? Do you remember when they started?

3. How often do you tend to get them?
    a. Has this become more or less frequent as time has gone on?

We are interested in finding out what happens with your knee symptoms over time

4. Do you think you would be able to draw me a diagram of time against level of pain to show me how you think your pain symptoms have changed over the past 6 months? Perhaps draw a line for background pain first and then one showing where you may have had flare-ups of pain

How useful do you think it was to draw your diagram? Would this be useful to take to your GP to explain what your pain is like?

(Use the graph as a talking point for the following questions):

5. Can you identify any causes or triggers when you have flare-ups?

6. Can you predict when they will come on?
Are they easier to manage if they are predictable?

7. How do you manage them?
    b. Why do you manage them in this way?
    c. Have you ever consulted your doctor about one?
    d. What would make you consult your doctor about one?
    e. If you wouldn't go to doctors-why? What do you think they would or would not offer you?

Appendix V: Favourable ethical opinion letter for qualitative study

HSC Business Services Organisation

Office for Research Ethics Committees Northern Ireland (ORECNI)

Customer Care & Performance Directorate
Lissue Industrial Estate West
Rathdown Walk
Moira Road
Lisburn
BT28 2RF
Tel: 028 95361400
www.orecni.hscni.net

HSC REC A

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 May 2017

Dr Emma Parry
Primary Care Sciences, Keele University
Keele
Staffordshire
ST5 5BG

Dear Dr Parry

Study title:	**Patient perspectives on flare-ups in Knee Osteoarthritis: An Interview Study**
REC reference:	**17/NI/0091**
Protocol number:	**1.0**
IRAS project ID:	**215481**

The Proportionate Review Sub-committee of the HSC REC A reviewed the above application on 08 May 2017.

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 hra.studyregistration@nhs.net outlining the reasons for your request. 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.

Ethical opinion

On behalf of the Committee, the sub-committee gave a **favourable ethical opinion** of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk 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 management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

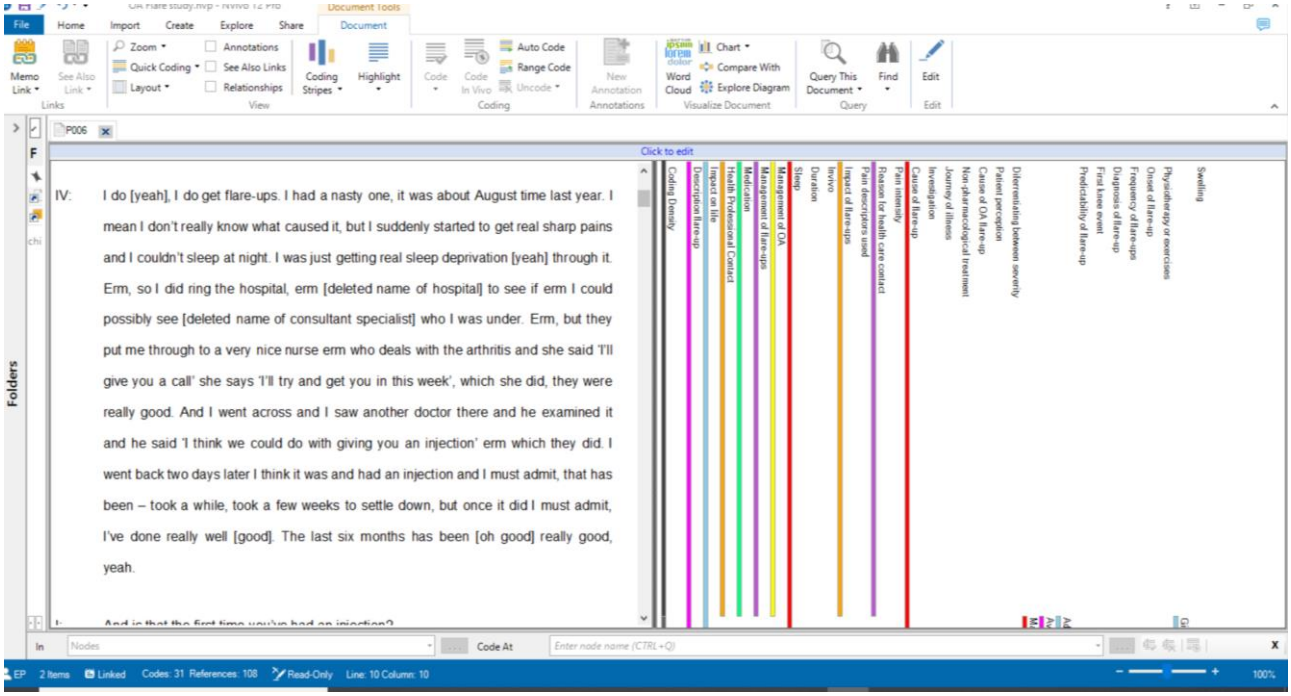
There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

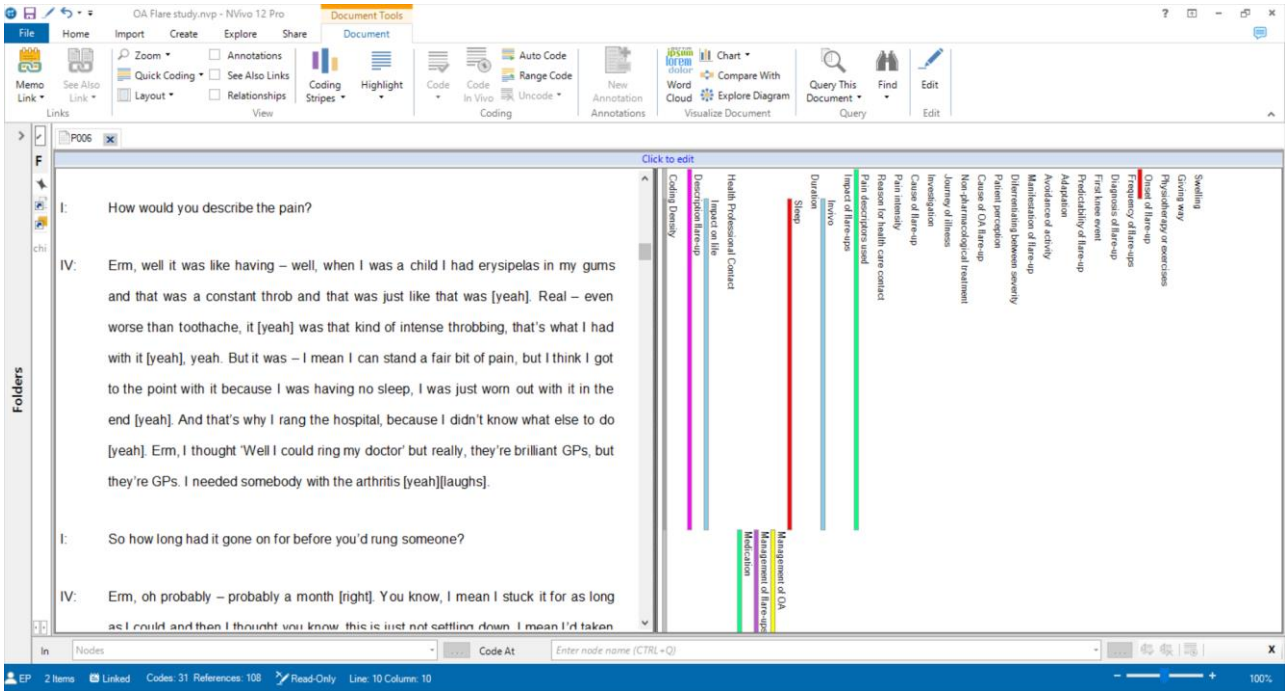
To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

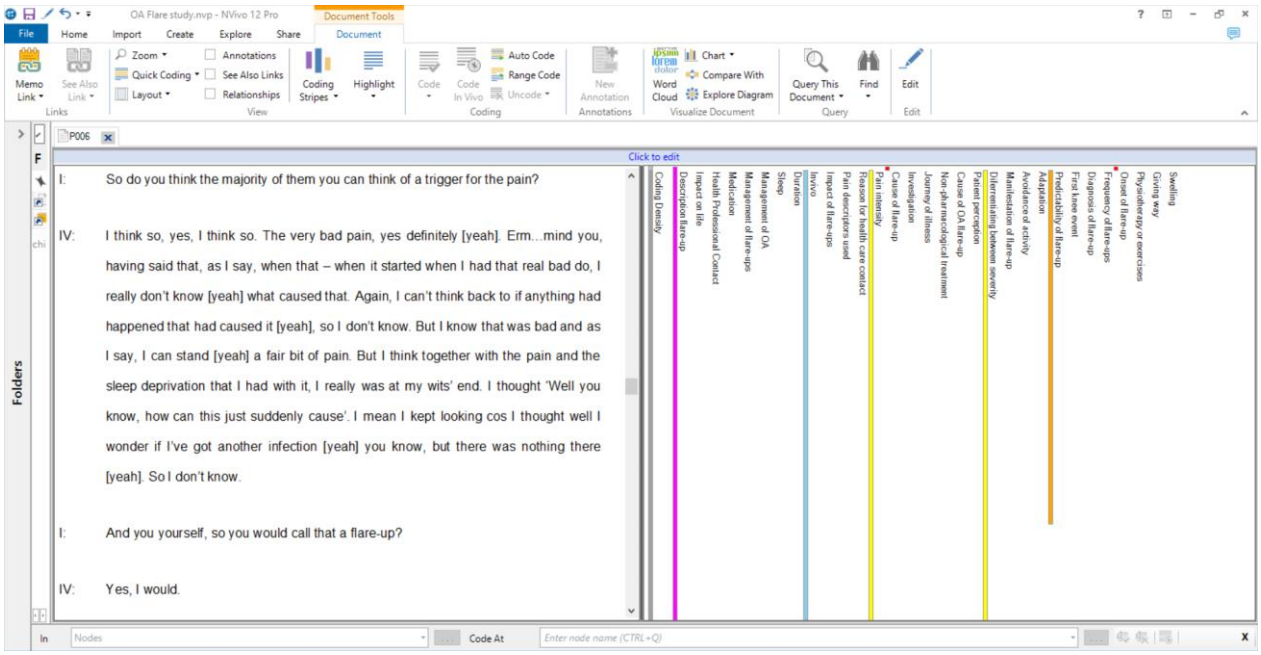
If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

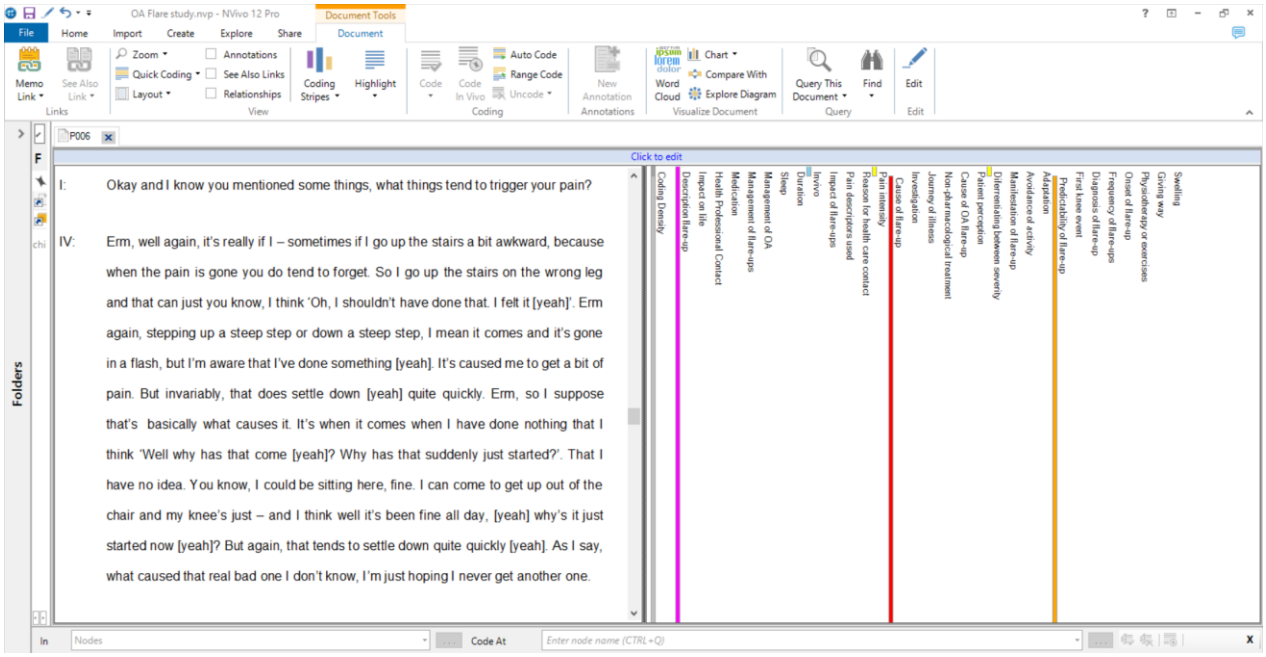
It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Appendix W1: Example of coding in NVIVO






OA Flare study.nvp - NVivo 12 Pro
Document Tools
File
Home
Import
Create
Explore
Share
Document
Folders
P006
Click to edit
I: So do you think the majority of them you can think of a trigger for the pain?
IV: I think so, yes, I think so. The very bad pain, yes definitely [yeah]. Erm...mind you, having said that, as I say, when that – when it started when I had that real bad do, I really don't know [yeah] what caused that. Again, I can't think back to if anything had happened that had caused it [yeah], so I don't know. But I know that was bad and as I say, I can stand [yeah] a fair bit of pain. But I think together with the pain and the sleep deprivation that I had with it, I really was at my wits' end. I thought 'Well you know, how can this just suddenly cause'. I mean I kept looking cos I thought well I wonder if I've got another infection [yeah] you know, but there was nothing there [yeah]. So I don't know.
I: And you yourself, so you would call that a flare-up?
IV: Yes, I would.
Coding Density
Description flare-up
Impact on life
Health Professional Contact
Medication
Management of OA
Management of flare-ups
Sleep
Duration
Invivo
Impact of flare-ups
Pain descripters used
Reason for health care contact
Pain intensity
Cause of flare-up
Investigation
Journey of illness
Non-pharmacological treatment
Cause of OA flare-up
Patient perception
Differentiating between severity
Manifestation of flare-up
Avoidance of activity
Adaptation
Predictability of flare-up
First knee event
Diagnosis of flare-up
Frequency of flare-ups
Onset of flare-up
Physiotherapy or exercises
Giving way
Swelling
Nodes
Code At
Enter node name (CTRL+Q)


OA Flare study.nvp - NVivo 12 Pro
Document Tools
File
Home
Import
Create
Explore
Share
Document
Folders
P006
Click to edit
I: Okay and I know you mentioned some things, what things tend to trigger your pain?
IV: Erm, well again, it's really if I – sometimes if I go up the stairs a bit awkward, because when the pain is gone you do tend to forget. So I go up the stairs on the wrong leg and that can just you know, I think 'Oh, I shouldn't have done that. I felt it [yeah]'. Erm again, stepping up a steep step or down a steep step, I mean it comes and it's gone in a flash, but I'm aware that I've done something [yeah]. It's caused me to get a bit of pain. But invariably, that does settle down [yeah] quite quickly. Erm, so I suppose that's basically what causes it. It's when it comes when I have done nothing that I think 'Well why has that come [yeah]? Why has that suddenly just started?'. That I have no idea. You know, I could be sitting here, fine. I can come to get up out of the chair and my knee's just – and I think well it's been fine all day, [yeah] why's it just started now [yeah]? But again, that tends to settle down quite quickly [yeah]. As I say, what caused that real bad one I don't know, I'm just hoping I never get another one.
Coding Density
Description flare-up
Impact on life
Health Professional Contact
Medication
Management of OA
Management of flare-ups
Sleep
Duration
Invivo
Impact of flare-ups
Pain descripters used
Reason for health care contact
Pain intensity
Cause of flare-up
Investigation
Journey of illness
Non-pharmacological treatment
Cause of OA flare-up
Patient perception
Differentiating between severity
Manifestation of flare-up
Avoidance of activity
Adaptation
Predictability of flare-up
First knee event
Diagnosis of flare-up
Frequency of flare-ups
Onset of flare-up
Physiotherapy or exercises
Giving way
Swelling
Nodes
Code At
Enter node name (CTRL+Q)

Appendix W2: Example coding frame

Overarching theme	Description of theme	Codes	Example of data for code
Experiencing pain: Identifying flares	This theme encompasses how patients describe their pain during a flare, the different components that participants used to understand their flares, for example, in terms of severity, duration, frequency and impact.	Descriptions of pain flares	*"Well it's just like.. like a pumping it's like it's like pumping in my knee. Like real sharp pain. It feels like someone is sticking like a hot pin inside and it's it's phwoar."* **P001 (M, 51)** *"It's got tonnes of knives [right] straight into it [right]."* **P003 (F, 66)**
		Other associated symptoms	*"I just get like the slight swelling underneath the kneecap and at the side but not as much [okay] because at one time it really did swell…"* **P009 (M, 64)** *"Well at that time it was, erm, a matter of swelling [yeah]. Me knee sort of was like a big onion [right] [laughs]. Erm, but the, over the 12 months I got more discomfort when I was walking…"* **P015 (F, 85)**
		Impact	*"Oh no there was a definite difference in that one last year because it stiffened it all. Really did I shouldn't have walked on it really…No just the big one was a flare-up yeah. I think that's fair to say…*No, no. These minor ones I have had them for many years and I can live with it.*"* **P002 (M, 78)**
		Variability of pain intensity	*"Oh no there was a definite difference in that one last year because it stiffened it all. Really did I shouldn't have walked on it really…No just the big one was a flare-up yeah.*

			I think that's fair to say…No, no. These minor ones I have had them for many years and I can live with it.*"* **P002 (M, 78)** *"Sometimes I have some good days and some days I get really bad days as I do totally have pain all from my leg all the way down and plus with my back as well."* **P001 (M, 51)**
		Duration	*"Well with me putting my cream on and my tablets it takes about two to three days…But er.. But sometimes I could be like one or two or three days I'm OK and then it starts flaring up..it starts playing up …and I suffer with it for about a week or a week and half."* **P001 (M, 51)** *"It can last for weeks before it completely settles down. It eases off, but it doesn't go [right]. It can take a couple of months really for it to really settle down [okay]."* **P006 (F, 68)**
		Magnitude of pain intensity	*"Er, well it's stronger, it's not an ache, it's a definite pain and I want to sort of hold it sort of thing for comfort yes."* **P004 (F, 81)**
		Onset of pain	*"…well I think it is starting to do it sort of straight away now whereas when I used to go up the ceilings, it was the next day, it would show up the next day."* **P012 (M, 81)**
		Frequency	"Ooh, about once a month, every couple of months, something like that." **P015 (F, 85)** *[On change in frequency over time]. "No, no they are more regular [yeah]. But as I say, I can honestly say they don't really – I wouldn't say bother me, but I know that they're there and yes I have the pain, but they don't stop me doing anything other than if I have to take it a bit steadier up the stairs or an incline."* **P006 (F, 68)**

		Change over time	*"Erm, well last year I had a bad year with it and it was on and off all the time. But then it did clear up a little bit and I'd – I'd say a week on, a week off…"* **P010 (F, 69)** *"I would think there is very little difference over the years. In fact I feel I am in due to the type of living I mean these last 12, I mean I finished with alcohol a long long time ago I don't have a drop at all 12 years ago. I have never smoked. I feel my health is in better condition now than when I was say 60. And I mean I'm nearly 80 so."* **P002 (M, 78)**
		Patient understanding of flares	*"To me it suggests something that erm it sort of comes out of the blue [yeah] and just sort of suddenly attacks the knee sort of thing you know [okay] yeah, yeah but I've never said I've had a flare-up of my knee, it's not a term I would use truly you know."* **P008 (M, 66)**
		Beliefs on underlying disease process	*"In the knee. But I had never really looked on it as arthritis. I thought it was maybe erm just bone on bone I suppose."* **P002 (M, 78)**
		First flare event	*"But, er, no I have no reason why it should happen at all, as I say I was just walking quite normally in [deleted name of town] down towards [deleted name of department store] and it just suddenly gave way….I had no premonition of it, no pain before, or aches or anything, it just happened totally out of the blue."* **P004 (F, 81)**

Appendix X: Peer reviewed publication: Defining acute flares in knee osteoarthritis: a systematic review

Open access Research

BMJ Open

Defining acute flares in knee osteoarthritis: a systematic review

Emma L Parry, Martin J Thomas, George Peat

To cite: Parry EL, Thomas MJ, Peat G. Defining acute flares in knee osteoarthritis: a systematic review. *BMJ Open* 2018;**8**:e019804. doi:10.1136/bmjopen-2017-019804

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-019804).

Received 27 September 2017
Revised 10 April 2018
Accepted 15 May 2018

Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, UK

Correspondence to
Professor George Peat;
g.m.peat@keele.ac.uk

ABSTRACT

Objective To identify and critically synthesise definitions of acute flares in knee osteoarthritis (OA) reported in the medical literature.

Design Systematic review and narrative synthesis. We searched Medline, EMBASE, Web of science and six other electronic databases (inception to July 2017) for original articles and conference abstracts reporting a definition of acute flare (or synonym) in humans with knee OA. There were no restrictions by language or study design (apart from iatrogenic-induced flare-ups, eg, injection-induced). Data extraction comprised: definition, pain scale used, flare duration or withdrawal period, associated symptoms, definition rationale, terminology (eg, exacerbation or flare), baseline OA severity, age, gender, sample size and study design.

Results Sixty-nine articles were included (46 flare design trials, 17 observational studies, 6 other designs; sample sizes: 15–6085). Domains used to define flares included: worsening of signs and symptoms (61 studies, 27 different measurement tools), specifically increased pain intensity; minimum pain threshold at baseline (44 studies); minimum duration (7 studies, range 8–48 hours); speed of onset (2 studies, defined as 'sudden' or 'quick'); requirement for increased medication (2 studies). No definitions included activity interference.

Conclusions The concept of OA flare appears in the medical literature but most often in the context of flare design trials (pain increases observed after stopping usual treatment). Key domains, used to define acute events in other chronic conditions, appear relevant to OA flare and could provide the basis for consensus on a single, agreed definition of 'naturally occurring' OA flares for research and clinical application.

PROSPERO registration number CRD42014010169.

Strengths and limitations of this study

- ► Identified key domains that are used to define acute events by undertaking a comprehensive synthesis of definitions used in the medical literature.
- ► Broad search strategy covering a wide range of databases including bibliography checks and conference abstracts.
- ► Prospectively registered with an international register of systematic reviews (PROSPERO).
- ► Did not include potential synonyms as search terms ('attack', 'episode', 'fluctuations').
- ► Data extraction was performed by only a single reviewer.

INTRODUCTION

Recurrent acute events or episodes feature in the natural history of many chronic health conditions. The extent to which they characterise the condition varies, as do the presumed pathophysiological mechanisms, and scientific and lay terms used to describe them (eg, an acute exacerbation of chronic obstructive pulmonary disease (COPD) or asthma, an attack of gout or a rheumatoid arthritis flare). With recognition of their importance has come concerted effort to define these phenomena. Definitions for exacerbations or flares currently exist for COPD,[1 2] asthma,[3] systemic lupus erythematosus (SLE)[4] and ankylosing spondylitis (AS)[5] and there are working groups currently trying to define these for rheumatoid arthritis,[6–8] gout[9] and atopic dermatitis/eczema.[10] Despite the different language used, these definitions share some common, core domains: the onset or worsening of symptoms and signs above normal day-to-day variability; speed of onset; duration of sustained worsening and change in medication/healthcare usage.

Osteoarthritis (OA) appears to comprise multiple disease trajectories[11–15] and symptom variability over time and the presence of intermittent pain is well-recognised.[16] Although OA does not typically have the same very obvious acute events as conditions like gout, flares in OA joints are encountered in practice, these phenomena appear in patient literature,[17] have been discussed in expert reviews[18] and are mentioned in 'flare design' trials in OA.[19] These studies induce acute episodes of pain or flare-ups by asking patients to withdraw their usual medication.

In 2009, Marty *et al* proposed scoring criteria for knee OA flares based on nocturnal awakening, knee effusion, morning stiffness and limping,[20] but it is unclear whether this has contributed to a common understanding, shared terminology and criteria. A common definition of OA flare could be important for a number of reasons: (i) to facilitate communication between researchers, (ii) to allow

more direct comparisons between studies on frequencies, determinants and course of events, (iii) to facilitate new insights into novel pathophysiological mechanisms and treatments through valid and homogenous case definitions and (iv) to help clinicians with prompt diagnosis and management.

The aim of this systematic review was to explore the extent to which a concept of OA flare is reported in the medical literature and the prospects for a common, shared definition of these for research and clinical application.

METHODS

This systematic review was registered with PROSPERO registration number CRD42014010169. The review protocol has not been published.

Literature sources and study selection

We searched electronic databases from inception to July 2017; ASSIA, EMBASE, Web of Science, Health Management Information Consortium (HMIC), SPORTDiscus, Medline, CINAHL, PsycINFO, AMED, Ageline, Cochrane Database of Systematic Reviews and Cochrane Controlled Clinical Trials (CENTRAL). The search was developed using previously piloted terms for knee OA and a literature search for common terms used to describe acute events. Searches used combined and/or truncated key terms including: ('KNEE OSTEOARTHRITIS' OR (knee N3 pain) OR (knee N3 arthrosis) OR (knee N3 joint) OR (knee N3 osteoarthritis)) AND (exacerbation OR flare OR (pain AND (diary OR diaries)) OR (pain N3 variab*) OR (pain N3 *) OR (pain N3 *) OR (pain N3 *) OR (pain N3 pattern$) OR (daily N3 pain)). A database search strategy is included in the online supplementary table 1. Reference lists of all included full-text articles retrieved for detailed examination were manually searched.

Studies were included in the final full-text peer-review if they contained a description or definition of an acute exacerbation or flare-up of knee OA in human adults (aged 18 years or over) in the general population, primary care or hospital settings. Studies were included even if their description was not based on clear measurement criteria (eg, stating a 'significant increase in pain' but not the amount of change on a pain score this would equate to). Studies that included a mixed OA population (eg, knee or hip OA) and did not separately report knee-specific findings were included. There were no restrictions on study dates or design. All non-English language articles were translated to identify a flare definition. Theses, dissertations, book chapters and guidelines and animal studies were excluded. Conference abstracts were included if they contained a definition for an OA flare-up. Studies were excluded if the flare was induced by an iatrogenic source, for example, injection-induced flares,[21] as these may have been caused by a different pathophysiological process. Abstracts were included in this study as the main outcome of interest was the definition of flare used and it was decided that including abstracts would ensure a more comprehensive review. For each abstract, a search was conducted to identify a corresponding full-text paper. Where one was found only the full paper was included in the review.

The search and article retrieval was conducted by the first reviewer (ELP). Articles were downloaded into RefWorks bibliography and database manager (RefWorks Copyright 2009). Duplicates were removed and all titles were screened by ELP against inclusion criteria, with the first 20 titles checked by two reviewers (ELP and MJT) for consistency. For qualitative studies, all identified potentially eligible full-text articles were obtained.

All abstracts and then full-text articles were screened by two reviewers (ELP and MJT), with disagreements resolved by consensus adjudicated by a third reviewer (GP). Where articles could not be retrieved or if the flare definition used was not included in the text, contact with authors was made.

The final included articles were checked to ensure results were not duplicated, for example, where different authors were reporting on the same dataset, to reduce bias.[22] For articles containing pooled studies, the original studies were sought and included in the main analysis, where available. No full-text articles were required to be translated.

Data extraction

The following data pertaining to flares were extracted from full-text articles by the first reviewer: definition used for change in pain, pain scale used, duration of flare (for flare design trials we extracted the duration of the withdrawal period for comparison), associated symptoms, rationale behind definition used, terminology used (eg, exacerbation or flare), baseline OA severity, age range, gender, geographical location, number of participants and study design. Missing data were described in the data extraction tables.

Quality assessment of included studies

Our aim was to identify and contrast definitions of flare-ups used in the literature. We were not concerned with the methodological rigour of the studies deriving, evaluating or applying those definitions. However, for studies presenting definitions we sought supporting statements that gave the rationale for the definition.

Data analysis

A narrative synthesis was undertaken guided by the four-stage process of Popay *et al*.[22 23] This approach was chosen as it allowed the words and text in the definitions to be synthesised to summarise findings.[23] The initial data extracted were grouped into drug withdrawal studies ('flare design') and other studies. Frequencies of components included in definitions was tabulated, these included; terminology used, onset/worsening of symptoms; signs/symptoms above day-to-day variability/minimum threshold; speed of onset of symptoms; duration of worsening and change in medication/healthcare usage.

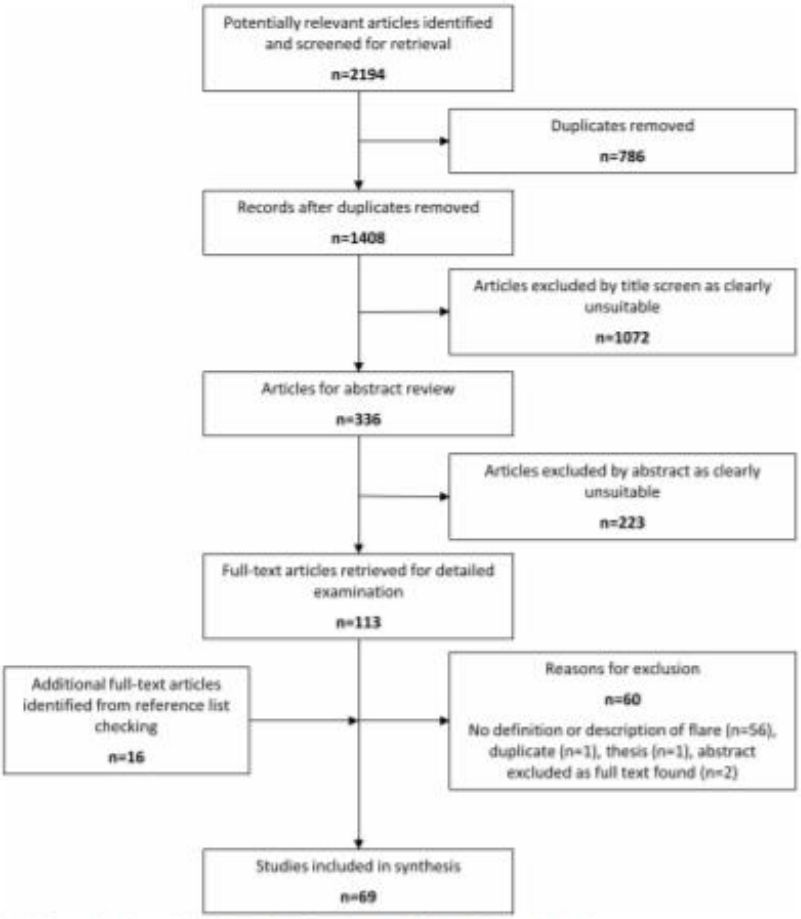


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

This initial tabulation helped identify similarities and differences and allowed themes to emerge. This was done with an inductive-type approach, where possible, that is, without an a priori assumption, and deductively acknowledging that the reviewers were clinicians, that is, they had some background knowledge of the topic of interest. This allowed further examination of the differences of definitions used in drug withdrawal and non-drug withdrawal study designs, and examination of key components of definitions used.

Patient and public involvement

There was no patient or public involvement in this study.

RESULTS

Study selection

The literature search yielded 2194 articles, of which 786 were duplicates (figure 1). After title screening, 336 abstracts were reviewed, 223 were not relevant for the study purpose. One hundred thirteen articles were examined in full, which resulted in a further 60 being excluded. The main reason for exclusion was no definition of flare-up reported in text (n=56). At this stage, a further 16 articles were identified from the reference lists of the retrieved full-text articles resulting in 69 included studies for synthesis.

Study characteristics

Characteristics of the included studies are described in table 1.[20 24–91] The number of participants in each study ranged from 15 to 6085.[20 46] Knee OA was defined by clinical and/or radiological criteria.

Twenty-one included mixed knee and hip OA groups.[24 29 31 37–39 42 45–47 54 55 57–59 63 71 73 75 77] In total, 46 publications used a drug withdrawal RCT design,[24 26–32 34–43 45–53 55–64 75–77 88–91] 4 of which

Table 1 Characteristics of all included studies

First author, year of publication	Setting, geographic location	Participants	Joint	Severity	Study design
Drug withdrawal design studies					
Altman, 2015[29]	Multicentre, recruitment not specified, USA	403 males and females, ≥40 years	Knee and hip	KL grade 2–3	RCT, flare design
Basic 2006[30]	17 medical centres recruiting from community and physician private practice; Canada	216 males and females, 40–85 years	Knee	Radiographic evidence of OA (severity not defined)	RCT, flare design
Baraf, 2011[27]	Primary care, internal medicine, orthopaedic, rheumatology; USA	602 males and females, ≥25 years	Knee	Radiographically mild to moderate (KL grade 1–3)	RCT, flare design
Battisti, 2004[28]	Clinical centres, outpatients; USA	3980 males and females, ≥40 years (age unavailable for Geba 2003 and Weaver 2003)	Knee	ACR functional class rating of I, II or III	RCT, pooled four trials, flare design
Bingham, 2007[25] Bingham, 2011[26]	2×74 outpatient clinics; USA	1207 males and females, ≥40 years	Knee and hip	ARA functional capacity classification I–III	RCT, flare design
Birbara, 2006[31]	Investigative sites; USA	808 males and females, ≥40 years	Knee	ARA functional class, I, II or III	RCT, flare design
Bocanegra, 1998[21]	Clinic; USA	572 males and females, 28–88 years (mean 61–62)	Knee and hip	ARA functional capacity classification I–III	RCT, flare design
Boswell, 2008[32]	50 centres (Europe and Australia)+187 centres (Europe and USA)	1908 males and females, ≥40 years	Knee	KL scale 2 or 3 and ARA class rating of I, II or III	Pooled RCTs (2; one flare design, one non-flare), flare design
Brandt, 2006[33] (pilot studies)	Community; USA	30 males and females, mean age 62 years	Knee	KL≥2	Cohort design, flare design
Case, 2003[34]	Hospital-rheumatology centre; Chicago, USA	82 males and females, 40–75 years	Knee	KL≥1, and clinical criteria (pre-enrolment ambulatory pain); moderate pain by a 5-point Likert scale or increased pain	RCT, flare design
Day, 2000[35]	49 investigative sites in 26 countries	809 males and females, mean age range 62–65 years	Knee and hip	ARA functional class I–III, symptomatic for at least 6 months	RCT, flare design
Ehrich, 1999[36]	Clinical centres; USA	219 males and females, >40 years	Knee	ARA functional class, I, II or III	RCT, flare design
Essex, 2012[38]	Clinical centre; African-American, USA	322 males and females, ≥45 years	Knee	ARA functional capacity classification I–III	RCT, flare design
Essex 2013[39]	Hispanic population, 31 US centres	≥45 years	Knee	ACR criteria, functional capacity classification I–III	RCT, flare design
Gibofsky, 2014[37]	Not specified, USA	305 males and females, 41–90 years	Knee and hip	KL 2–3	RCT, flare design
Gineyts, 2004[40]	Subset of larger study; France	201 males and females, mean age 61–62 years	Knee and hip	ARA I–III	RCT, flare design
Goldberg, 1988[24]	Investigative sites; USA	214 males and females, 40–85 years (mean 64)	Knee and hip	Radiographic evidence of knee OA, not further defined	RCT, flare design
Gottesdiener, 2002[41]	Investigative sites; USA	617 males and females, ≥40 years	Knee	ARA functional class I–III	RCT, flare design
Hochberg, 2011[42]	Centres; USA	1234 males and females, ≥50 years	Knee	ACR functional class I–III	Pooled RCTs (2), flare design
Katz, 2010[43]	Clinical sites; USA	113 males and females, 28–83 years (median 57)	Knee and hip	OA of hip and knee as diagnosed using ACR criteria, no definition of severity	RCT, flare design
Kivitz, 2001[45]	Investigative sites; USA	491 males and females, 28–91 years (mean 58–61)	Knee	Confirmation of OA on weight-bearing radiograph, no definition of severity	RCT, flare design
Kivitz, 2004[44]	Outpatient sites; USA	1042 males and females, ≥40 years	Knee	ACR rating of I–III	RCT, flare design
Leung, 2002[46]	Clinic; USA	677 males and females, ≥40 y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design

Continued

Table 1 Continued

First author, year of publication	Setting, geographic location	Participants	Joint	Severity	Study design
Luyten, 2007[45]	Centres; Belgium	181 males and females, ≥40 years	Knee and hip	ACR functional capacity classification I–III	RCT, flare design
Manicourt, 2005[47]	Outpatient clinic; Belgium	90 males and females, 50–81 years (mean 63–67)	Knee and hip	Clinical and radiographic evidence of OA, severity not defined	RCT, flare design
Marzuca, 2002[48]	Not specified, USA	15 males and females, ≥45 years	Knee	KL 2–3	Observational, flare design
Midtvain, 1989[49]	Investigative sites; USA	139 males and females, mean 65 years	Knee	Radiological evidence of moderate or severe osteoarthritis, not further defined	RCT, flare design
Mendelsohn, 1997[50]	Investigative sites; USA	139 males and females, 21–88 years (mean age 63.3 years)	Knee	Radiological evidence of moderate or severe osteoarthritis, not further defined	RCT, flare design
Moskowitz, 2006[51]	Investigative sites; USA	530 males and females, ≥45 years	Knee	ACR functional capacity classification I-III	RCT, flare design
Pareek, 2009[52]	Multicentre study, India	199 males and females, 40–70 years	Knee	Lequesne criteria, score of 5 and above	RCT, flare design
Pareek, 2010[53]	Hospital; India	220 males and females, 40–70 years	Knee	Clinical and radiological evidence of OA severity not defined	RCT, flare design
Roth, 2004[54]	Physicians private practice or community; USA	326 males and females, 40–85 years	Knee	Radiological evidence of OA, severity not defined	RCT, flare design
Rother, 2007[55]	Outpatient units; Germany	397 males and females, ≥ 40 years	Knee	KL 2–3	RCT, flare design
Schnitzer, 2005[56]	Investigative sites; International (seven countries)	583 males and females, 18–75 years	Knee and hip	Diagnosis based on ACR criteria, severity not defined	RCT, flare design
Scott-Lennox, 2007[57]	Investigative sites; USA	182 males and females, mean age 61 years	Knee	Not defined	RCT, flare design
Silverfield, 2002[58]	Centres; USA	306 males and females, 35–75 years	Knee and hip	Clinical evidence of OA, severity not defined	RCT, flare design
Simon, 2009[59]	Outpatient centres; Canada, USA	775 males and females, 40–85 years	Knee	Clinical and radiological evidence of OA, severity not defined	RCT, flare design
Strand, 2011[60]	Investigative sites; multinational—not specified including USA	875 males and females, 18–80 years	Knee and hip	OA according to ACR criteria and requiring NSAID treatment to control symptoms in the month preceding screening	RCT, flare design
Weaver, 1992[61]	Investigative sites; USA	328 males and females, >50 years	Knee	ACR clinical criteria, diagnostic	RCT, flare design
Wiesenhutter, 2005[62]	Medical centres; USA	526 males and females, 40–89 years	Knee and hip	ARA functional class I, II or III	RCT, flare design
Williams, 2001[63]	Clinical sites; USA	718 males and females, mean age 61–62 years	Knee	ACR clinical and radiographic criteria I–III	RCT, flare design
Wittenberg, 2006[64]	Centres (not specified); Germany	364 males and females, 50 years	Knee	Moderate-to-severe symptomatic OA of the knee according to ACR criteria	RCT, flare design
Yeasted, 2014[65] (poled, abstract)	USA	219 (merged observational), 137 (merged trial) >40 years	Not specified	ACR criteria, diagnostic	Two longitudinal observational studies, placebo arms of two clinical trials
Yocum, 2005[17]	USA, 62 study centres	774 males and females, ≥40 years	Knee or hip	Diagnosis confirmed by XR and clinical symptoms (not further specified)	RCT, flare design
Young, 2014[13] (abstract)	Multicentre	305 males and females, >40 years	Knee or hip	KL 2–3	RCT, flare design
Zhao, 1999[66]	Centre (not specified); USA, Canada	1004 males and females, ≥18 years	Knee	ACR functional capacity classification I-III	RCT, flare design

Continued

Table 1 Continued

First author, year of publication	Setting, geographic location	Participants	Joint	Severity	Study design
Non-drug withdrawal design studies					
Atukorala, 2016[39] (abstract) Atukorala, 2016[40] (abstract)	Not specified, USA+Australia+Sri Lanka	213 males and females,mean age 62 years 345 males and females,mean age 62 years	Knee	Not specified	3-month, web-based longitudinal follow-up study
Bartholdy, 2016[41]	OA outpatient clinic, Denmark	131 males and females, ≥40 years	Knee	Radiographic evidence of OA (severity no defined) and BMI between 20 and 35 kg/m^2	RCT
Bassiouni 2015[42] (abstract)	Not specified, Egypt	60 participants not further specified	Knee	Not specified	Observational
Cibere, 2004[43] Cibere, 2008[44]	Community, Canada	137 males and females,mean age 65 years (43–88) for placebo and 64 years (40–83) for glucosamine group	Knee	KL≥2 on anteroposterior radiograph	RCT
Conrozier 2012[45]	Hospital-rheumatology unit, France	44 males and females, mean age 67.6 years	Knee	Radiographic evidence of knee OA, not further defined	Observational
D'Agostino 2005[47]	Hospital-European multicentre	600 males and females, ≥18 years	Knee	KL grade 1–4	Observational
Erlani, 2014[48] (abstract) Erlani, 2014[49] (abstract) Ferreira, 2016[50] Hunter, 2014[51] (abstract) Makovey, 2015[52] (protocol)	Australia	268 males and females,mean age 62 years 345 males and females, ≥40 years	Knee	ACR criteria, meet at least one, KL≥2	Web-based crossover
Jawad, 2005[53]	GPs in France	3000 (for GP study) males and females	Knee	Not defined	n/a, review of surveys. Definition relates to survey of 3000 French GPs
Marty 2009[55]	Community and hospital, France	6085–641 males and females, mean age 66.4 years (10.9) for flare group, 66.2 years (10.2) no flare group	Knee	OA diagnosis based on ACR criteria, severity not defined	Observational
Murphy, 2015[56]	Community based ,pain clinics USA	45 males and females, 37–83 years	Knee	ACR criteria, severity not defined	Qualitative
Parry, 2017[58]	Community, UK	719 males and females, ≥50 years	Knee	Self-reported knee pain in previous 12months	Observational
Rico 2006[64]	Community, USA	329 males and females, 40–65 years	Knee and hip	Clinical evidence of OA, severity not defined	Nested case-control
Wise 2010[65]	Primary care, hospital, USA	303 males and females, ≥50 years	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment, not further defined	Observational
Zhang 2009[67]	Primary care, hospital, USA	303 males and females, ≥50 years	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment, not further defined	Observational
Zhang 2011[68] (abstract)	Not specified	52 males and females, median age 63 years (50–72 years)	Knee	KL>2	Case-crossover
Zobel 2016[69]	Hospital databases, Australia	297 males and females, >40 years	Knee	ACR criteria, KL≥2 or patello-femoral OA on radiograph	Web-based case-crossover

ACR, Arthritis Center Research; AIA, American Rheumatism Association; GP, general practitioner; KL, Kellgren and Lawrence; RCT, randomised controlled trial.

were pooled studies[28 32 41 62] and 1 used a cohort drug withdrawal design[33] (table 1). The remaining 22 publications included 17 observational studies,[20 25 44 54 65–67 70–72 78 80–85] 3 RCTs,[79 86 87] 1 survey[68] and 1 qualitative interview study.[69] Nine of the included studies were abstracts.[25 44 62 63 72 78 80 81 83] Two abstracts were removed as the corresponding full-text article was available.[69 92] Studies using pooled data or the same dataset were included if they used different definitions of OA flare.[28 44 52 53 62 65 70 71 74]

Rationale given for flare definitions

Six of the included studies gave rationale for the definition used.[29 54 56 69 85 86] None of the definitions was based on a consensus procedure. The studies by Marty *et al*[61] and Scott-Lennox *et al*[66] were the only ones that undertook empirical investigation of flare definitions. The study by Marty *et al*[29] was the only study specifically designed to validate a diagnostic tool for knee OA flares. Potential factors associated with flare-ups were identified, for example, knee swelling and the authors used a logistic regression analysis to assign a weight to each of the items identified. A flare-up score was determined using a general practitioner database and this was then validated using a rheumatologist database. Pain was not included in the final model.

Scott-Lennox *et al*[66] sought to test whether four measures for flare intensity (patient's self-assessment of pain scores, physician's assessment of pain scores, patient's global OA assessment and physician's global OA assessment) could be combined to form a reliable and valid index using data from an RCT using a confirmatory factor analysis. The authors produced three flare intensity groups (low, moderate and severe) and highlighted how these could be used to examine treatment effects.

Cibere *et al*[60] outlined face validity checks. It was specified that the flare definition had been determined by study rheumatologists to be a clinically important change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. The definition used by Murphy *et al*[63] was informed by two studies,[28 53] which used a drug withdrawal design and from the research team's own experience. Ricci *et al*[64] used a combination of data-driven and clinical judgement approaches to establish an agreed cut point. Parry *et al* based their definition on OA flare design studies and flare definitions used in other chronic disease such as back pain and COPD.

Flare definitions in drug withdrawal studies

Terminology used

The majority of publications using a drug withdrawal design used the term 'flare' in their description[24–30 32 33 36–43 45–49 51 53 55–64 74–77 88–91] (n=42; table 2).

One study used the term 'flare-up',[52] two studies referred simply to 'worsening of symptoms'[31 50] and three studies used no specific label.[34 35 73]

Coverage of key components

Onset/worsening of symptoms and signs beyond normal-day-to-day variability: forty-four studies included onset or worsening of signs and symptoms as part of their definition.[24 26–32 34–41 43 45–55 57–64 73–75 77 88–91] All studies included increased pain intensity in their definition. A further two[52 53] specified further signs and symptoms. These included swelling, inflammation, erythema, morning stiffness and nocturnal pain. No studies quantified day-to-day variability.

Twenty-six measurement tools were used to define onset/worsening of symptoms and signs. The most commonly used tools were the Western Ontario and McMaster Universities Arthritis index (WOMAC) Q1 (pain on walking on flat surface) 100 mm Visual Analogue Scale (VAS) (n=9)[29 30 32 38 41 45 59 73 75] and the Investigator Assessment of Disease Status (n=11)[28–30 38 40 45 50 73–75 77] (table 3). Thirty-four studies used only single-item measurement tools,[27–30 32 34–43 45 47 48 50 52 55 56 58 59 61–63 73–77 90 91] five used multiitem[31 46 51 53 60] and five used both single-item and multiitem tools.[24 26 53 88 89]

In addition, the format of global ratings appears to be variable as is use and reporting of the WOMAC.[93] However, despite the exact format of reporting being inconsistent, in general, studies used single items in four areas—pain on activity, pain (not necessarily on activity), physician/investigator global rating and patient global rating.

Temporal characteristics: none of the included drug withdrawal design studies reported a specific time for defining the speed of onset of symptoms. However, they did describe withdrawal or 'washout' periods, whereby after withdrawal of usual medication, participants were given a certain time frame in which to experience 'flare' symptoms in order that they were entered into the study. In total 30 of the studies specified a withdrawal period.[27 30 31 33–36 38–40 43 45–52 56 58 60 61 64 73 74 76 77 88–90]

Four studies specified a time period for minimum duration of symptoms, which ranged from 24 hours to 5 days.[52 53 55 57]

Change in medication or healthcare usage: only one study used increase in medication as part of their definition; 'pain requiring supplemental analgesic medication and/or an increase in non-steroidal anti-inflammatory drug dose'.[57]

Additional domains: thirty-six studies included a minimum threshold, which was usually a minimum level of pain that was required before the participant was considered to have a flare.[24 26 28–31 33 35–38 40–43 45–47 51–53 55 56 58–63 73 75 76 88–91] There was general concordance with the minimum thresholds that different measurement tools used with a few exceptions. A threshold of 40 mm on a 0–100 mm scale was used in 8 of 10 studies using the WOMAC VAS 3.0 Q1 'pain on walking on a flat surface'[29 30 38 41 45 59 73 75] and 4 of 14 studies using the Patient Global Assessment of Disease Status.[29 45 73 75] In studies using various forms of Investigator/Physician Global Assessment, the majority adopted a minimum threshold for a flare of 'fair, poor

Table 2 Definition, terminology and measurement instruments used in all included studies

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Relevance/rationale
Drug withdrawal study design							
Altman[24]	'Flare'	*Pain*: WOMAC Pain subscale (0–100); increase≥15 mm	*Pain*: WOMAC Pain subscale; ≥40 mm	Not specified	Not specified	Not specified	None
Baer 2005[36]	'Flare'	*Pain*: WOMAC LK3.1 Pain subscale (0–20); increase≥2 points and ≥25%	*Pain*: WOMAC Pain score (0–20); ≥6 and ≥1 item rated 'moderate, severe or extreme'	Interval between screening and baseline reassessment unclear	Not specified	Not specified	None
Barel 2011[37]	'Flare'	*Pain* on movement: VAS (0–100 mm); increase≥5 mm	Not specified	1 week washout	Not specified	Not specified	None
Bartlett 2004[38]	'Flare'	Global assessment (investigator): single item, 5-point LK; worsening≥1 point	*Pain*: VAS (0–100 mm); ≥40 mm	Not specified	Not specified	Not specified	None
Bingham 2007[39] Bingham 2011[40]	'Flare'	1. *Pain* waiting on *flat* surface WOMAC VAS 3.0 Q1 (0–100 mm); increase≥15 mm 2. Global assessment of disease status (investigator): single item, 5-point LK; worsening≥1 point	1. *Pain* waiting on *flat* surface ≥40 mm on WOMAC VAS 3.0 Q1 (0–100) 2. Global assessment (investigator): single item, 5-point LK; fair, poor, very poor (acetaminophen users only) 3. Global assessment of disease status (patient): VAS (0–100 mm); ≥40 mm (acetaminophen users only)	Not specified	Not specified	Not specified	None
Bribiesca 2006[36]	'Flare'	1. *Pain* waiting on *flat* surface WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. Global assessment (investigator): single item, 5-point LK; worsening≥1 point	1. *Pain* waiting on *flat* surface WOMAC VAS 3.0 Q1 (0–100); ≥40 mm 2. Global assessment (investigator): single item, 5-point LK; fair, poor or very poor (acetaminophen arm only)	4–15 days washout	Not specified	Not specified	None
Bocanegra 1998[41]	'Worsening of symptoms'	Two out of the following three: 1. Global assessment (physician): single item, 5-point LK; increase≥1 grade 2. Global assessment (patient) patients global assessment (current symptoms and limitation of activity) 5-point LK; increase≥1 grade 3. Composite index: Lequesne OA Severity Index (0–24); increase≥2 points	1. Global assessment (physician): single item, 5-point LK; 'poor/very poor' 2. Global assessment (patient) patients global assessment (current symptoms and limitation of activity) 5-point LK; 'poor/very poor' 3. Composite index: Lequesne OA Severity Index (0–24); ≥7	3–14 days washout	Not specified	Not specified	None
Boswell 2009[42]	'Flare'	1. *Pain* waiting on *flat* surface WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. Global assessment (patient) Patient Global Assessment of Arthritis Condition (PGAC) (unspecified) worsening≥1 point	Not specified	Not specified	Not specified	Not specified	None
Brandt 2006[43] (pilot studies)	'Flare'	Not specified	*Pain*: WOMAC LK Pain subscale (0–20); ≥15 points	Five half-lives of NSAID washout	Not specified	Not specified	None
Case 2003[44]	Not used	1. *Pain* waiting on *flat* surface VAS (0–100 mm); increase≥10 mm 2. Ambulatory pain; 5-point LK; worsening≥1 point	Not specified	14 days washout	Not specified	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/ healthcare use	Rescue/rationale
Day 2000[73]	Not used	1. *Pain* waiting on a flat surface: WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator)*: single item, 5-point LK; worsening≥1 point 3. *Global assessment (patient)*: VAS (0–100 mm); increase≥15 mm (*acetaminophen users only*)	1. *Pain* waiting on a flat surface: WOMAC VAS Q1 (0–100 mm); ≥40 mm 2. *Global Assessment (investigator)*: single item, 5-point LK; 'fair, poor or very poor' 3. *Global Assessment (patient)*: VAS (0–100 mm); ≥40 mm	Longer than five plasma half-lives washout	Not specified	Not specified	None
Ehrich 1999[36]	Not used	*Pain*: VAS (0–100 mm); increase≥15 mm	*Pain*: VAS (0–100 mm); ≥40 mm	Longer than five plasma half-lives washout of NSAID	Not specified	Not specified	None
Esser 2012[38]	'Flare'	1. *Global Assessment (physician)*: 5-point LK; increase≥1 grade 2. *Global Assessment (patient)*: 5-point LK; increase≥1 grade	1. *Global Assessment (physician)*: 5-point LK; 'fair, poor or very poor' 2. *Global Assessment (patient)*: 5-point LK; 'fair, poor or very poor' 3. *Pain*: VAS (0–100 mm); 40–60 mm	48 hours withdrawal	Not specified	Not specified	None
Esser 2013[39]	'Flare'	Not specified	1. *Global Assessment of arthritis (physician)*: Minimum rating of 3 2. *Global Assessment of arthritis (patient)*: Minimum rating of 3 3. *Pain*: VAS (0–100 mm); 40–60 mm	48 hours withdrawal	Not specified	Not specified	None
Gibofsky 2014[37]	'Flare'	*Pain*: WOMAC Pain VAS; increase≥15 mm	*Pain*: WOMAC Pain VAS; ≥40 mm	Not specified	Not specified	Not specified	None
Greyvis 2004[35]	'Flare'	1. *Pain* waiting on a flat surface: WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator)*: 5-point scale; worsening≥1 point	1. *Pain* waiting on a flat surface: WOMAC VAS Q1 (0–100 mm); ≥40 mm	five half-lives of NSAID washout	Not specified	Not specified	None
Goldberg 1988[34]	'Flare'	1. *Pain*: investigator assessed pain grade (none/mild/mod/severe): (i) at rest, (ii) on passive motion, (iii) on palpation, (iv) weight bearing; increase≥1 grade in two items OR increase≥2 grade in one item	Not specified	2–14 days washout until flare	Not specified	Not specified	None
Gottesdiener 2002[40]	'Flare'	1. *Pain on walking*: VAS (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator)*: 5-point LK; increase≥1 point	1. *Pain on walking*: VAS (0–100 mm); ≥40 mm	3–15 days washout	Not specified	Not specified	None
Hochberg 2011[41]	'Flare'	1. *Pain* waiting on a flat surface: WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (patient)*: 5-point LK; worsening≥1 point	1. *Pain* waiting on a flat surface: WOMAC VAS Q1 (0–100 mm); ≥40 mm	Not specified	Not specified	Not specified	None
Katz 2010[42]	'Flare'	Not specified	*Pain*: pain score (0–10) ≥5	Not specified-washout until flare occurred	Not specified	Not specified	None
Kivitz 2001[43]	'Flare'	*Pain*: Patients Assessment of Pain Score (0–10) (unspecified); increase≥2 points	*Pain*: Patients Assessment of Pain Score (0–10) (unspecified); ≥5	Five drug half-lives or 48 hours	Not specified	Not specified	None
Kivitz 2004[44]	'Flare'	1. *Pain on walking*: VAS (0–100 mm); worsening≥15 mm 2. *Global Assessment (investigator)*: 5-point LK; worsening≥1 point	Not specified	NSAID-dependent half-life washout	Not specified	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Leung 2002[43]	'Flare'	1. *Pain on walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator);* 5-point LK; worsening≥1 point	1. *Pain on walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); ≥40 mm 2. *Global Assessment (patient)* (0–100 mm); ≥40 mm (acetaminophen users only) 3. *Global Assessment (investigator);* 5-point LK; 'fair, poor or very poor' (acetaminophen users only)	Determined by drug half-life washout	Not specified	Not specified	None
Luyten 2007[44]	'Flare'	1. *Global Assessment (patient)* 5-point LK; increase≥1 grade 2. *Global Assessment (physician)* 5-point LK; increase≥1 grade 3. Composite definition: Lequesne Osteoarthritis Severity Index (0–24); increase≥2 points	1. *Global Assessment (patient)* 5-point LK; 'fair, poor or very poor' (not on treatment — 'poor or very poor') 2. *Global Assessment (physician)* 5-point LK; 'fair, poor or very poor' 3. (Not on treatment — 'poor or very poor') 4. Composite definition: Lequesne Osteoarthritis Severity Index (0–24) ≥7 5. *Pain:* VAS (0–100 mm); ≥40 mm	2–14 days washout	Not specified	Not specified	None
Manicourt 2009[17]	'Flare'	*Pain when walking on a flat surface:* VAS (0–100 mm); ≥10 mm	Not specified	7–10 days washout	Not specified	Not specified	None
Mazzuca 2002[24]	'Flare'	*Pain on standing:* WOMAC LK Pain Q5 'severe or extreme' after the washout AND decreased after resumption of usual analgesic drugs and/or NSAIDs	Not specified	Drug washout five half-lives	Not specified	Not specified	None
McKenan 1999[45]	'Flare'	Nonmeasurement instrument: increase in pain on motion, swelling, tenderness, redness and/or heat (unspecified if patient/physician/investigator reported)	Not specified	2–14 days washout	Not specified	Not specified	None
Mandelbaum 1997[46]	'Worsening of arthritis condition'	1. *Pain:* Pain scale (0–3) (0=none, 3=severe); worsening score 2. *Global physician's* (0–100); worsening score	Not specified	Up to 14 days washout	Not specified	Not specified	None
Moskowitz 2006[47]	'Flare'	1. *Global assessment (patient)* 5-point LK; increase≥1 grade 2. *Global Assessment (physician)*: 5-point LK; ≥1 grade increase 3. *Composite index:* Lequesne OA Severity Index (0–24); increase≥2 points	1. *Global assessment (patient)* 5-point LK; 'fair, poor or very poor' 2. *Global Assessment (physician):* 5-point LK; 'fair, poor or very poor' 3. Composite index: Lequesne OA Severity Index (0–24); minimum≥7 4. *Pain walking on a flat surface:* VAS (0–100 mm); ≥40 mm	NSAID washout of five half-lives or at least 2 days	Not specified	Not specified	None
Pavelka 2009[48]	'Flare-up'	1. *Pain:* 11-point NRS; increase≥2 points during previous 3–5 days 2. Signs and symptoms suggestive of inflammation, morning stiffness and nocturnal pain interfering with sleep	*Pain:* pain intensity of at least 4 on a 11-point NRS during physical activity for past 24 hours	Placebo washout for 24–48 hours	2–5 days	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Relevance/rationale
Parsek 2010[20]	'Flare'	Flare symptoms noted but not part of definition: morning stiffness, erythema, nocturnal pain and swelling/inflammation	1. *Pain with physical activity*: VAS 0–10; ≥6 2. Composite index: WOMAC total LK; ≥25 3. Composite index: Lequesne OA Severity Index (0–24); ≥5	Not specified	2–5 days	Not specified	None
Roth 2004[18]	'Flare'	*Pain*: WOMAC LK3.1 Pain subscale (0–20); increase≥2points and ≥25%	*Pain*: WOMAC LK3.1 Pain subscale (0–20); score ≥ 'moderate' on at least 1 of the five items; pain score≥6	Washout period of at least 3 days/week pain month	Not specified	Not specified	None
Rother 2007[21]	'Flare'	1. *Pain on walking*: VAS (0–100 mm); increase≥15 mm 2. *Global Assessment (patient)*: 5-point LK; increase≥1 grade	1. *Pain on walking*: VAS (0–100 mm); ≥40 mm 2. *Global Assessment (patient)*: 5-point LK; 3–5	Not specified	Not specified	Not specified	None
Schnitzer 2005[22]	'Flare'	No/not increase in pain	*Pain*: VAS (0–100 mm); ≥40 mm	Not specified	24 hours	Not specified	None
Scott-Lennox 2001[19]	'Flare'	1. *Pain*: VAS (0–100 mm); ≥20 mm 2. *Pain (physician)*: 4-point LK; worsening≥1 point 3. *Global Assessment (patient)*: 4-point LK; worsening≥1 point 4. *Global Assessment (physician)*: 4-point LK; worsening≥1 point	1. *Pain*: VAS (0–100 mm); ≥40 mm at baseline 2. *Pain (physician)*: 4-point LK; ≥2 3. *Global Assessment (patient)*: 4-point LK; ≥2 4. *Global Assessment (physician)*: 4-point LK; worsening≥2	14 days washout	Not specified	Not specified	Confirmatory Factor Analysis
Simon2009[36]	'Flare'	*Pain*: WOMAC LK3.1 Pain subscale; increase≥2and ≥25%	*Pain*: WOMAC LK3.1 Pain subscale; ≥ 'moderate' on ≥1 item	14 days washout	Not specified	Not specified	None
Silverfield 2002[17]	'Flare'	*Pain*: no measurement tool; significant increase	Not specified	Not specified	Not specified	Pain requiring supplemental analgesic medication and/or an increase in NSAID dose	None
Staked 2011[38]	'Flare'	*Global Assessment (patient)*: 5-point LK; increase≥1	1. *Global Assessment (patient)*: 5-point LK; 'fair, poor or very poor' 2. *Pain*: (0–10 NRS); ≥4 but <9 3. *Global Assessment (physician)*: 5-point LK; 'fair, poor or very poor'	14 days washout	Not specified	Not specified	None
Weaver 1995[16]	'Flare'	1. *Global Assessment (physician)*: 5-point Likert; increase≥1 grade 2. *Global Assessment (patient)*: 5-point LK; increase≥1 grade 3. *Pain*: worsening pain on motion and weight bearing	1. *Global Assessment (physician)*: 5-point Likert; ≥2 2. *Global Assessment (patient)*: 5-point LK; ≥2	2–14 days washout	Not specified	Not specified	None
Wesselhoeft 2005[39]	'Flare'	1. *Pain on walking on flat surface*: WOMAC VAS 3.0 Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator)*: 5-point LK; worsening≥1 unit	1. *Pain on walking on flat surface*: WOMAC VAS 3.0 Q1 (0–100 mm); ≥40 mm	Not specified	Not specified	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Williams 2001[40]	'Flare'	1. *Global Assessment (patient)*: 5-point LK; increase≥1 point 2. *Global Assessment (physician)*: 5-point LK; increase≥1 point 3. *Composite index*: Lequesne OA Severity Index (0–24); increase≥2 points	1. *Global Assessment (patient)*: 5-point LK; '(fair), poor or very poor' 2. *Global Assessment (physician)*: 5-point LK; '(fair), poor or very poor' 3. *Composite index*: Lequesne OA Severity Index (0–24); ≥7 4. *Pain*: VAS (0–100 mm); ≥40 mm	2–14 days	Not specified	Not specified	None
Wittenberg 2006[41]	'Flare'	*Pain*: VAS (0–100 mm); increase≥10 mm	*Pain*: VAS (0–100 mm); ≥40 mm	2–7 days washout	Not specified	Not specified	None
Yeasted 2014[42] (pooled, abstract)	'Flare'	*Pain*: 0–10 NRS; increase≥2 points over the mean pain score from the previous 3 days	*Pain*: average daily 0–10 NRS; 4–9	Not specified	Not specified	Not specified	None
Yocum 2000[77]	'Flare'	Disease activity 1. *Global (investigator)* reduction of ≥1 grade 2. *Global Assessment (patient)*: 100 mm VAS; increase of ≥10 mm 3. *Pain: overall assessment (patient)*: 100 mm VAS; ≥35 mm	Not specified	≥3 days washout	Not specified	Not specified	None
Young 2014[43]	'Flare'	(3) *Pain*: WOMAC pain subscale; increase>15 mm	*Pain*: WOMAC Pain subscale>40 mm	Not specified	Not specified	Not specified	None
Zhao 1999[44]	'Flare'	No measurement tool: worsening of signs and symptoms after discontinuation of NSAIDs of analgesics	Not specified	2–7 days washout	Not specified	Not specified	None
Non-drug withdrawal study design							
Atukorala 2016[78] (abstract) Atukorala 2016[79] (abstract)	'Flare'	*Pain*: (10-point NRS); increase≥2 points from the mildest knee OA pain intensity reported at day 0	Not specified	Not specified	Not specified	Not specified	None
Bartholdy 2016[75]	'Flare'	Not specified	*Pain*: (10-point NRS): Pain>5	Not specified	Not specified	Not specified	None
Bassiouni 2015[81] (abstract)	'Flare'	Not specified	*Global Assessment (physician)*: KOFUS≥7	Not specified	Not specified	Not specified	None
Cibere 2004[45] Cibere 2005[47]	'Flare'	1. Patients perception of worsening of symptoms 2. *Pain walking on flat surface*: WOMAC VAS 3.0 Q1 (0–100 mm); increase≥20 mm 3. *Global Assessment (physician)*: 5-point LK; worsening≥1 grade	Not specified	Not specified	Not specified	Not specified	Definition determined by study rheumatologists to be a clinically important change in WOMAC-Ehrich 2000/Bellamy 1998
Conrozier 2012[48]	'Flare'	Fulfilled four following criteria: 1. *Pain*: no measurement tool; 'sudden aggravation of knee pain' 2. Causing nocturnal awakenings 3. Clinical evidence of effusion	Not specified	Sudden aggravation of knee pain, whose beginning was identifiable	Not specified	Not specified	None
D'Agostino 2005[82]	'Flare'	Not specified	*Pain intensity during physical activity*: VAS (0–100 mm); ≥40 mm	Not specified	48 hours	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Erfani 2014[46] abstract) Erfani 2014[47] (abstract) Ferreira 2016[42] Hunter 2014[43] (abstract) Makovey 2015[44] (protocol)	Exacerbation	*Pain*: VAS (0–100 mm); increase≥20 mm from mildest pain score reported at baseline	Not specified	Not specified	Not specified	Not specified	None
Jawad 2005[48]	Exacerbation	*Pain symptoms*: increased morning stiffness, night pain and synovial fluid effusion	Not specified	Not specified	Not specified	Not specified	None
Marty 2009[49]	'Flare'	No measurement tool: morning stiffness>30 min, nocturnal awakening, limping, knee swelling, increased warmth, effusion	Not specified	Not specified	48 hours	Not specified	Regression analysis of cross-sectional data to validate proposed flare criteria
Murphy 2015[50]	'Flare'	1. Investigator definition: inadequate pain relief for an episode of intense pain that is usually brought on by too much activity 2. Participant definitions: described in terms of pain quality, timing (onset and duration), antecedents and consequences 3. *Pain magnitude*: increase in pain or 'intense' or 'severe' level of pain	*Pain*: ≥40 of 100 mm or ≥4 of 10 on NRS	Patients described: 'Quick' or 'sudden'	Patients: 10s to 15 min	Patients: rest or take additional medication	For investigator definition: Battisti 2004, Pareek 2010[8 53] Plus researchers own experience
Parry 2017[40]	'Flare'	*Pain*: recalled worst pain intensity in previous 6 months 0–10 NRS; ≥5	*Pain*: recalled worse pain to be ≥2 points higher than recalled average pain (0–10 NRS) in previous 6 months	Not specified	Not specified	Not specified	Based on previous studies defining knee flares in OA and flares in diseases such as back pain and COPD
Rico 2005[54]	'Flare-up'	*Pain*: self-reported flare severity rating 0–10 NRS; increase≥2 point over usual pain severity	Not specified	Not specified	Not specified	Not specified	Based on statistical analysis and clinical judgement
Wise 2010[70]	'Flare'	Not specified	*Pain*: WOMAC Pain subscale (0–10); score in highest 30% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2009[71]	'Exacerbation or flare'	Not specified	1. Pain: WOMAC pain subscale 0–10 (total score of 50 normalised to a 0–10 scale); score of ≥5, a score corresponding to highest 33% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2011[72] (abstract)	'Exacerbation'	*Pain*: WOMAC Pain score VAS (0–500); increase≥100 units	Not specified	Not specified	Not specified	Not specified	None
Zobel 2016[52]	Exacerbation	*Pain*: 0–10 NRS; increase≥2	Disabling pain	Not specified	8 hours	Not specified	None

COPD, chronic obstructive pulmonary disease; KOFUS, Knee Osteoarthritis Flare-up Score; LK, Likert scale; NSAID, non-steroidal anti-inflammatory drug; NRS, Numerical Rating scale; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3 Summary of number and type of single-item and multiitem measurement tools used

Single-item scales:	
Pain on activity:	WOMAC Q1 3.0 VAS 'pain on walking on a flat surface' (0–100 mm) (n=11) Pain on walking VAS (0–100 mm) (n=5) Pain on movement VAS (0–100 mm); ambulatory pain (5-point Likert); pain with physical activity VAS 11-point scale (n=2)
Pain (not further specified):	Pain VAS (0–100 mm) (n=15) Patients assessment of pain score (0–10); pain scale (0–3); Pain NRS (0–10) (n=11)
Standing knee pain	Item 5 WOMAC pain scale (n=1)
Global rating (physician/investigator)	Investigator Assessment of Disease Status (n=11) Physicians Global Assessment of Arthritis (n=6) Physician Global Assessment of OA (n=2) Physician Global Assessment of Disease Status (n=2); Investigator Assessed Pain Grade; (Physician) Overall Disease Activity (0–100); Physicians Pain Assessment (4-point LK) (n=3)
Global rating (patient)	Patients Global Assessment of Arthritis (n=7) Patient Global Assessment of OA (n=3) Patient Global Assessment of Disease Status (n=4)
Multiple-item scales:	
	Lequesne OA Severity Index (n=5) WOMAC LK3.1 (0–20) (n=3) WOMAC LK Pain subscale (0–25); WOMAC OA Index Questionnaire (n=1); WOMAC knee pain score (0–500) [n=7]; KOFUS (0–14) (n=1)

KOFUS, Knee Osteoarthritis Flare-up Score; LK, Likert scale; N, number of included studies; OA, osteoarthritis; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

or very poor'.[29 30 45 73] The minimum threshold on the Lequesne index (0–10) was either 5[55] or 7.[46 51 60]

Flare definitions in non-withdrawal flare/discontinuation studies

Terminology used

'Flare' was the term most common used in non-withdrawal design studies[20 25 66 67 69 70 78–80 85 87] (n=11) (table 2). One study used the term 'flare-up',[54] eight used 'exacerbation'[44 65 68 72 81–84] (five publications were from the same team) and one referred to both 'exacerbation' and 'flare'.[71] None referred to 'worsening of symptoms' or did not use any specific label.

Coverage of key components

Onset/worsening of symptoms and signs beyond normal day-to-day variability: 16 of 22 studies used onset or worsening of symptoms in their definition.[25 44 54 66 68 69 72 78 81–87 92] Two studies did not use pain intensity as part of its definition.[20 80] Three studies included symptoms other than pain in their definition.[20 66 68] These included nocturnal awakenings, effusion, morning stiffness, night pain, limping and warmth.

The study by Murphy *et al*[69] included an investigator definition of flare and sought to describe patient experience of flares through face-to-face individual interviews. Both investigator and patient definitions included onset/worsening of symptoms and signs; however, there was no differentiation from day-to-day variability.

Seven studies used a measurement tool to define onset of signs and symptoms (table 3). These included the Pain NRS (0–10),[25 54 65 78 85] WOMAC knee pain score VAS (0–500),[72] pain walking on a flat surface (WOMAC),[86 87] Global Assessment of Disease Status (physician) (5-point Likert scale)[86 87] and knee pain VAS not further specified (0–100).[44 81–84]

Temporal characteristics: only one study set a definition for speed of onset, describing this only as 'sudden' with no further specification.[66] Patients in the study by Murphy *et al* used the terms 'quick' and 'sudden' to describe flare onset.[69] Three studies specified a minimum duration of symptoms ranging from 8 to 48 hours.[20 65 67] In the study by Murphy *et al*, patients described duration between 10 s and 15 min.[69]

Change in medication/healthcare usage: no studies used change is medication or healthcare usage as part of their definition. However, in the study by Murphy *et al*, patients reported either taking rest or using additional medication.[69]

Additional domains: two studies defined distribution-based minimum thresholds for flare as the highest 30%[72] or highest 33%[73] of WOMAC Pain subscale scores among participants in the Longitudinal Examination of Arthritis Pain cohort (total score out of 50 was normalised to a 0–10 scale).

DISCUSSION

Flares in OA are recognised in existing clinical guidance[94] and reviews,[95 96] but typically merit little more than a passing mention. Our analysis of the definitions has resulted in the findings of common core domains, which will be useful for developing an agreed consensus

definition for OA flare. From a clinical perspective, a unified definition of a flare could enable clinicians to provide prompt, rationalised and focused treatment. This could also have implications for delivery of self-management strategies involving patients and how episodic management is advocated by clinical guidelines. Our review was motivated by an interest in seeking greater clarity on how these phenomena might be defined by undertaking a broad search strategy, noting that similar efforts have been pursued in other chronic diseases. While we found no current single, agreed definition of OA flare, our review of 69 published studies suggests a number of common domains, which may capture cardinal features. These were: onset/worsening of symptoms and signs, attainment of a minimum symptom threshold during flare, speed of onset/worsening and duration of elevated symptoms/signs. However, we found considerable variation in how these domains have been operationalised for measurement suggesting the need for further conceptual clarification and consensus.

Each potential cardinal feature of OA flare presents different challenges for achieving consensus. The goal of an agreed composite definition is to facilitate both reproducible and comparable research, while enabling more consistent recognition and identification of these phenomena in routine practice. The heterogeneity of OA should also be considered in any definition of a flare-up. Most studies included in our review required an increase in pain over 'usual' or 'baseline' intensity. Although this was measured using a wide range of measurement instruments, several studies selected an increase of 2 or more points on a 0–10 scale providing a possible starting point for consensus. Yet this possible 'signal' is arguably difficult to interpret without also considering the amount of background 'noise', that is, within-person diurnal[97] and day-to-day variability,[98] and the absolute level ('minimum threshold') of pain during a flare. There was general concurrence with the minimum threshold that was adopted, for example, 40 mm on a 0–100 mm scale and this may indicate the potential level of minimally important clinical difference. In the study by Marty *et al*, an increase in pain was not independently associated with flare-up after adjusting for other potential features.[20] However, the studies by Marty *et al*[20] and Scott-Lennox *et al*[96] were the only ones that had attempted to derive and/or validate a prediction model for OA flares. Interestingly, their approaches have not been widely adopted which suggests the complexity of reaching a widely accepted model. Further research on detecting flares over within-person 'normal' variability by collecting frequent repeated measures of pain intensity may be valuable but this approach would not be feasible when identifying flares presenting at the point of care in routine clinical practice. Instead, this may have to rely on the judgement of the patient and/or clinician, the approach used, for example, in defining exacerbations in COPD.[1] A similar consideration surrounds the speed of onset, which was not well defined by studies in our review. Drug withdrawal design studies specified washout periods between 2 and 15 days, but this is unlikely to be synonymous with speed of onset. The remaining studies used terms such as 'sudden' and 'quick'. In COPD, for instance, a judgement around 'acute onset' or 'sudden onset' appears to be acceptable for clinical recommendations, but we would add that the speed of onset of OA flares ought to be considered also in relation to underlying biologically plausible mechanisms. Indeed, presumed aetiology has been argued as a useful feature in defining acute exacerbations in COPD.[99] Minimum duration ranged from 8 hours to 5 days in our review; however, this was not widely reported. COPD definitions refer to a 'sustained worsening' of symptoms,[2] but does not appear to be a feature in other chronic diseases. A minimum duration in OA may help distinguish flares from day-to-day variability. Increase in medication was not found to be a key component in this review despite it being a feature in other chronic diseases such as AS,[5] SLE,[4 100] inflammatory bowel disease and[101] COPD.[1] Interference with function did not emerge strongly from our review as a cardinal feature of OA flare. In other chronic musculoskeletal conditions, such as back pain, interference with function was not shown to be significantly associated with having a flare-up[102] and this domain does not feature in the definitions of exacerbations or flares in diseases such as COPD,[1 2] asthma,[3] AS[5] or SLE.[4]

Our review has several strengths and some weaknesses that deserve attention. We adopted a broad search strategy, covering a wide range of databases, and featuring bibliography checks, contact with authors, inclusion of conference abstracts, no language restrictions and a minimal threshold (any description or definition of flare) for inclusion. Five studies that were included in a similar review by Cross *et al*[103] were not included in this study; four did not contain a clear definition of flare-up, including one which gave a definition of knee OA progression and the final paper by Sands *et al*[104] was not in our search but the original study was.[58] We did not, however, search the grey literature and we did not include some potential synonyms as search terms ('attack', 'episode', 'fluctuations'), although these terms appeared often to relate to comorbidities and other phenomena (eg, episodes of care) and would therefore have been a less efficient search strategy than relying on snowball references. Data extraction was performed by only a single reviewer. Nevertheless, we argue that our review provides a reasonably comprehensive summary of how 'flares' in OA have been described and defined in the medical literature. In comparison with the study by Cross *et al*,[103] our search strategy appeared comprehensive yet efficient—returning 69 included articles compared with 23. We feel that our review expands on the findings of the review by Cross *et al* and adds strength to this important area. The majority of studies describe experimental 'flare design' trials in which flares are induced by drug withdrawal prior to enrolment and randomisation. While intentional or unintentional reduction in usual analgesia may indeed be one trigger for flare, experimentally induced flares

should not be assumed to represent 'naturally occurring' flares. Flare design trials, for example, are unlikely to capture change in management or healthcare usage that may be a common consequence of OA flares—something that is included in flare definitions in other conditions such as AS,[5] SLE,[4 100] inflammatory bowel disease[101] and COPD.[1]

A systematic review such as this cannot hope to resolve the need for a common conception and definition of flares in OA. Definitions for exacerbations of disease states are generally reached through a long process of consensus exercises involving key stakeholders, experts and patients in addition to appraisal of relevant literature from studies using multiple methods.[6 8 105] However, we believe that a consensus definition that is reliable, valid and feasible and widely acceptable both clinically and for research purposes should now be sought. The cardinal features described in this review; onset/worsening of symptoms and signs, attainment of a minimum symptom threshold during flare, speed of onset/worsening and duration of elevated symptoms/signs could help start this discussion. Furthermore, observational studies with repeated measures could give an important insight into the nature of these phenomena.

CONCLUSION

A broad range of ad hoc definitions currently exist in the medical literature. The majority are from drug withdrawal or flare-induced trials rather than 'naturally' occurring flares. The cardinal feature is pain intensity with minimum symptom threshold being another important feature. This review has identified the need to gain consensus on a common definition that can be used for research and clinical application.

Acknowledgements The authors would like to thank Popay *et al* for allowing to use their guidance on the conduct of narrative synthesis in systematic reviews. The authors would also like to thank Jo Jordan and Opeyemi Babatunde for their advice on conducting a systematic review.

Contributors All authors were involved in conception and design of the study, analysis and interpretation of data, drafting the article, critical revision of the article for important intellectual content, final approval of the article. ELP and MJT extracted and synthesised data. ELP assembled the data. GP takes responsibility for the integrity of the work as a whole from inception to finished article.

Funding ELP is funded by a National Institute for Health Research (NIHR) In Practice Fellowship (IPF-2014-08-03). MJT received funding from a NIHR School for Primary Care Research Launching Fellowship and is currently funded by an Integrated Clinical Academic Programme Clinical Lectureship from the NIHR and Health Education England (HEE) (ICA-CL-2016-02-014). This paper presents independent research funded by the Arthritis Research UK Centre in Primary Care grant (Grant Number 18139).

Disclaimer The views expressed in this paper are those of the author(s) and not necessarily those of the NHS, the NIHR, HEE or the Department of Health.

Competing interests GP received consultancy fees from InFirst and Good Relations.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Appendix Y: Peer reviewed publication: Significant pain variability in persons with, or at high risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of cohort data. (No changes have been made to the article presented https://creativecommons.org/licenses/by/4.0/)

Parry et al. BMC Musculoskeletal Disorders (2017) 18:80
DOI 10.1186/s12891-017-1434-3

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Significant pain variability in persons with, or at high risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of cohort data

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Abstract

Background: While knee osteoarthritis (OA) is characterised as a slowly progressive disease, acute flares, episodes of severe pain, and substantial fluctuations in pain intensity appear to be part of the natural history for some patients. We sought to estimate what proportion of symptomatic community-dwelling adults might be affected, and to identify patient and problem characteristics associated with higher risk of such variability in pain.

Methods: We analysed data collected at baseline, 18, 36, 54, and 72 month follow-up of a prospective cohort of symptomatic adults aged over 50 years with current/recent knee pain. At each time point we estimated the proportion of participants reporting 'significant pain variability' (defined as worst pain intensity in the past 6 months ≥5/10 and ≥2 points higher than average pain intensity during the same 6-month period). The associations between significant pain variability and demographic, socioeconomic, lifestyle, clinical, radiographic, and healthcare utilisation factors measured at baseline were estimated by adjusted odds ratios and 95% confidence intervals (aOR; 95%CI) from multivariable discrete-time survival analysis.

Results: Seven hundred and nineteen participants were included in the final analysis. At each time point, 23–32% of participants were classed as reporting significant pain variability. Associated factors included: younger age (aOR (per year): 0.96; 95% CI 0.94, 0.97), higher BMI (per kg/m^2:1.03; 1.01, 1.06), higher WOMAC Pain score (per unit: 1.06; 1.03, 1.10), longer time since onset (e.g. 1–5 years vs < 1 year: 1.79; 1.16, 2.75) and morning stiffness (≤30 min vs none: 1.43; 1.10, 1.85). The models accounting for multiple periods of significant symptom variability found similar associations.

Conclusions: Our findings are consistent with studies showing that, for some patients OA symptoms are significantly variable over time. Future prospective studies on the nature and frequency of flare ups are needed to help determine triggers and their underlying pathophysiology in order to suggest new avenues for effective episode management of OA to complement long-term behaviour change.

Keywords: Knee, Osteoarthritis, Flare, Frequency, Association, Symptom, Variability

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Background

Longitudinal studies of knee osteoarthritis (OA) with repeated measurements over 5-6 years have suggested that symptoms typically follow relatively stable long-term trajectories [1–5]. However, these can mask considerable within-person variability [6–8]. Of particular interest are acute flares and episodes of uncharacteristically severe pain that have been suggested to occur in both the early and advanced stages of OA and which are associated with distress and loss of function, particularly when unpredictable [9].

Flare design trials, in which usual medication is withdrawn with the intention of inducing an acute increase in pain within a specified time period are well established. For example, a recent systematic review identified 33 definite or possible flare design trials evaluating non-steroidal anti-inflammatory drugs (NSAID) [10]. The 'natural occurrence' of such flares has received less attention although there is a growing body of observational research on these phenomena under a variety of labels ("flares", "acute events", "episodes", "exacerbations"). These include studies that have attempted to define an osteoarthritis flare [11, 12], to understand the role of inflammation in these acute events [13, 14], to identify triggers [15] and to describe their impact on productivity [16].

Despite this growing body of research there is an outstanding gap of epidemiological evidence on how common these flare ups may be and the type of patients that are experiencing them. The largest quantitative study by Marty et al. [11] produced a scoring tool to determine those experiencing potential knee OA flare ups but this has not yet been widely adopted clinically or in research. Factors that have been critically important in defining flare ups in other diseases may be important in osteoarthritis. These include worsening of symptoms beyond normal day-to-day variation requiring additional medication [17–19], that is progressive [20] and is clinically significant [21]. Looking at significant symptom variability in osteoarthritis is a starting point.

The aim of our study was to generate a preliminary initial estimate of the frequency of significant symptom variability in a primary care population and assess if there were any risk factors associated with them.

Methods

Design

This was a secondary analysis of prospective observational cohort data from a sample of community-dwelling symptomatic adults – the Clinical Assessment Study of the Knee (CAS(K)).

Study population

Participants were recruited from a two-stage cross-sectional postal survey of all adults ages ≥50 years registered with three general practices in North Staffordshire (irrespective of actual consulting patterns). Respondents reporting pain of any duration in or around the knee within the previous 12 months were invited to attend a research clinic at a local National Health Service Hospital Trust. The study protocol was approved by North Staffordshire Local Research Ethics Committee (project number 1430) and details have been published elsewhere [22, 23]. All participants provided written informed consent to undergo clinical and radiographic assessment. In addition, they were asked for consent to medical record review to assist in excluding pre-existing inflammatory disease. The inclusion criteria for the current analysis were as follows: age ≥50 years, registered with one of the participating general practices at the time of study, responded to both postal questionnaires, consented to further contact, and attended the research clinic. Participants were excluded if they had incomplete baseline radiographs, had not experienced knee pain within the six months prior to clinic attendance, had a pre-existing diagnosis of inflammatory arthropathy in their medical records, or had had a total knee replacement in their most affected knee. Participants who reported total knee replacement (TKR) after baseline and up to 3 years were also excluded. Patients reporting TKR after 3 years were censored at the 3 year time point.

Baseline data collection

All data were planned and gathered prospectively. At baseline, participants underwent a standardized clinical interview and physical examination conducted by one of six research therapists blinded to the findings from radiography, postal questionnaires and medical records.

Participants filled in a brief self-complete questionnaire about their knee symptoms on the day of their clinic attendance.

Plain knee radiographs were obtained on the day of clinic attendance. Three views were taken of each knee: a weight-bearing semi-flexed posteroanterior (PA) view, according to the protocol developed by Buckland-Wright et al. [24], and lateral and skyline views, both in a supine position with the knee flexed to 45°. The tibiofemoral joint was assessed using the PA view and the posterior compartment of the lateral view. The patellofemoral joint was assessed using the skyline and lateral views.

Scoring of plain radiographs

A single reader (a consultant rheumatologist with extensive training in assessing knee radiographs for knee OA), blinded to all other information on participants, scored all films. Films were scored for individual radiographic features, including osteophytes, joint space width, sclerosis, subluxation and chondrocalcinosis. PA and skyline views were assigned a Kellgren and Lawrence (K&L) grade based on these authors' original written descriptions [25]. The

atlas developed by Burnett et al. [26] was used for the lateral view.

For PA, K&L score, skyline K&L score and lateral osteophytes, intra- and inter-reader reliability were assessed in a subsample of 50 participants (100 knees) and found to be very good (κ = 0.81–0.98 and 0.49–0.76, respectively) [27].

Follow-up data collection

Follow up surveys, which included 11-point numerical rating scales (NRS) on current, average and worst knee pain intensity over the past 6 months [28], were mailed to Phase 2 participants at 18 months, 36 months, 54 months and 72 months.

Outcome measure

At baseline and at each follow-up point we classed participants as reporting 'significant pain variability' if their recalled worst pain intensity in the past 6 months was ≥5 out of 10 and at least 2 points higher than recalled average pain intensity in the same 6 month period. To be included in the denominator, individuals had to be 'at risk' during that interval (i.e. average pain intensity <9 out of 10).

This definition was chosen after referring to previous studies of osteoarthritis flares which were described as worsening usual pain [11, 13], within defined limits using equivocal pain scales from flare design trials which set a minimum threshold of 50 mm on a 100 mm visual analogue scale (VAS) [29] and a pain increase of at least 20 mm on a 100 mm VAS or an increase of at least two points on a 10 point scale, from baseline [30, 31]. Definitions used in other musculoskeletal disorders such as lower back pain [32] and non-musculoskeletal conditions such as Chronic Obstructive Pulmonary Disease (COPD) were used [33, 34] where worsening of symptoms is used in addition to requiring different or extra medication. The definitions are all reliant on change and difference in pain.

Putative predictors

Predictors available in the CAS(K) dataset were selected for analysis on the basis of being shown in previous studies to be associated with incidence and progression of knee osteoarthritis [15, 35–39], pain outcomes [15] or acute flare-ups [11] (Table 1).

Statistical analysis

The proportion of participants classed as experiencing significant symptom variability was reported for each time point. For each follow-up time point those experiencing symptom variability at baseline were compared between those followed up and not followed up to identify any differences.

To estimate the association between the putative predictor variables and significant pain variability, we used discrete-time survival analysis. For clinical history/examination and radiographic severity predictors we used information from only one knee per individual, the "index knee": the single painful knee in participants with unilateral knee pain or the most painful knee in

Table 1 Summary of putative predictors and their source

Domain	Indicator
Demographic	Age; gender
Socioeconomic	Employment Status(employed, other); Occupational class[a] (managerial and professional, intermediate, routine and manual)
	Attended further education; Married/cohabiting
Clinical history/Examination	Time since onset of problem (<1 year, 1 to <5 years, 5 to <10 years, 10+ years); Problem started following injury; Bilateral knee pain; Duration of morning stiffness; Knee given way during previous month; Visited a hospital doctor about knee problem; Presence and severity of palpable knee effusion (none, mild, moderate/gross); Nodal symptomatic hand OA
Radiographic Severity	Overall severity of radiographic OA: index knee (none, mild, moderate/severe)[b]
	Compartmental distribution of radiographic OA: index knee (none, isolated TF-J, isolated PF-J, combined PF-J+TF-J)
Lifestyle factors	Body mass index (kg/m^2); Current smoker (Yes/No); Physical activity level[c] : sedentary (Yes/No); moderate (Yes/No); high (Yes/No)
Mental Health	HADS Anxiety and Depression subscale scores scale
Physical function	SF-36 (PF-10 subscale)
Knee-specific pain and functional limitation	WOMAC Pain and Function subscale scores

Hospital Anxiety and Depression scale [54]; OA Osteoarthritis; PF-10 Medical Outcomes Study SF-36 Physical Functioning subscale [55]; SD Standard deviation; WOMAC Western Ontario & McMaster Universities Osteoarthritis Index [56]

[a] Derived from National Socio-economic Classification [57]

[b] Mild = KL2 (PA or skyline view) or grade 1 osteophytes (lateral view); Moderate/severe = KL ≥ 3 (PA or skyline view) or grade 3 osteophytes (lateral view) [58]

[c] Twenty-three physical activity items were originally included. Those that were difficult to quantify were excluded from this analysis for example; 'go out for a walk' and 'go out to work'. We chose 6 items which were then categorised into sedentary ('spend most or all of day in bed or chair'), moderate ('walks of a least a quarter of a mile' and 'walks of two miles') and vigorous physical activity ('play a sport', 'heavy gardening' and 'heavy DIY work at home'). These measures were included if it was reported that they were done on 'all, most or some days'

individuals with bilateral knee pain. Discrete-time hazard survival models become models for dichotomous response when the data have been expanded to person-period data with one observation for each year the person is at risk. For each follow-up time point, we constructed an indicator variable on whether the patient had experienced significant pain variability in the 6 month period or not and estimated the hazard of significant pain variability using logistic discrete-time hazards model. The outcome was right censored at 72 months, which was the last follow-up time. Individuals who were lost to follow-up or withdrew from the study before the period of significant symptom variability was recorded, were also censored. To adjust for changes in proportion reporting significant pain variability over time, we included dummy variables for each follow-up time in all models. Two sets of analyses were conducted. We first modelled the time to first period of significant pain variability, ignoring additional subsequent periods of significant pain variability reported by the participant. We then used multilevel discrete-time survival (frailty) models to take into account recurrent periods of significant pain variability within participants. In the frailty model method, the association between periods of significant pain variability is explicitly modelled as a random-effect term. The frailty model was estimated using logistic discrete-time hazards model with random effects.

The association between each predictor and outcome was estimated and those with P-value <0.20 were selected for inclusion in the multivariable models. Tests of multicollinearity were performed first by pairwise correlations (one variable excluded if correlation coefficient >0.7) and then by variance inflation factor (VIF >5 considered as evidence of collinearity). We used a manual backward elimination procedure to remove variables from the multivariable model until only factors with a P-value <0.05 were retained in the final model. An a priori decision was made to include age and gender in the final models. All analyses were performed using Stata 13 [40].

Results

Eight hundred and nineteen people attended the research clinic, of whom 719 participants were eligible for inclusion for the baseline analysis (54% female; mean age 67.3 (SD 8.5) years; mean BMI 29.3 (SD 5.0) kg/m^2). There was no strong evidence of selective loss to follow-up related to presence of significant pain variability at baseline (Additional file 1 Table S1).

Participants classed as having at least one period of 'significant pain variability'

Between 23 and 32% of participants were estimated to have experienced significant pain variability at each of the five time points (Table 2). Across the entire cohort follow up period 363 (47%) participants reported no periods, 202 (27%) reported one period, 90 (12%) reported two periods, 63 (8%) reported three periods, 30 (4%) reported four periods and 13 (2%) reported five periods of significant pain variability. Table 3 presents the descriptive statistics for participants reporting at least one period of significant pain variability.

Factors associated with time to first period of significant pain variability

Based on the outcome of time to first period of significant symptom variability, baseline measures associated with a higher risk of symptom variability in the adjusted analysis were: younger age (OR (per year): 0.96; 95% CI 0.94, 0.97), higher BMI (per kg/m^2: 1.03; 1.01, 1.06), higher WOMAC knee pain scores (per unit: 1.05; 1.03, 1.10), longer time since onset (e.g. 1–5 years vs < 1 year:

Table 2 Proportion of patients reporting significant pain variability at each time point

	Measurement point				
	Baseline (n = 761)	18 months (n = 679)	36 months (n = 610)	54 months (n = 503)	72 months (n = 410)
Eligible respondents reporting significant pain variability[a]: n (%)	227 (32)	163 (26)	126 (23)	129 (27)	114 (30)
Average pain intensity in past 6 months (0-10NRS)	4.7 (1.7)	4.6 (1.8)	4.5 (1.6)	4.4 (1.5)	4.9 (1.9)
Worst pain intensity in past 6 months (0-10NRS)	7.6 (1.6)	7.5 (1.5)	7.3 (1.5)	7.1 (1.5)	7.6 (1.6)
Eligible respondents reporting no significant pain variability: n (%)	493 (68)	462 (74)	433 (77)	336 (72)	260 (70)
Average pain intensity in past 6 months (0-10NRS)	3.9 (2.3)	3.5 (2.5)	3.9 (2.6)	3.5 (2.7)	3.8 (2.5)
Worst pain intensity in past 6 months (0-10NRS)	4.1 (2.3)	3.7 (2.4)	4.1 (2.6)	3.8 (2.7)	4.1 (2.5)
Ineligible respondents[b]: n (%)	41 (5)	42 (6)	40 (7)	31 (6)	30 (7)
Missing: n (%)	0 (0)	12 (2)	11 (2)	10 (2)	6 (1)

Figures are mean (standard deviation) unless otherwise stated. NRS Numerical Rating Scale
[a]worst pain intensity in past 6 months ≥5 and ≥2 points higher than average pain intensity in past 6 months
[b]average pain intensity in past 6 months ≥ 9/10

Table 3 Comparison of patient baseline characteristics of participants reporting at least one period of significant pain variability potential flare

	Periods of significant pain variability	
	≥1	None
	n = 398	*n* = 363
Female gender	53	56
Age (years): mean (SD)	63.6 (8.2)	67.4 (8.7)
Employed	27	17
Attended full time education after school	17	13
Married/cohabiting	76	68
Current smoker	11	10
Body Mass Index (kg/m^2): mean (SD)	30.0 (5.3)	28.7 (4.8)
Routine/manual occupational class[a]	48	56
PF-10 physical function subscale (0–100): mean (SD)	56.1 (27.9)	58.7 (30.1)
WOMAC knee pain (0–20): mean (SD)	6.5 (4.2)	5.6 (4.3)
WOMAC knee function (0–68): mean (SD)	21.1 (14.3)	18.5 (14.7)
HADS Anxiety (0–21): mean (SD)	6.8 (4.1)	6.3 (4.0)
HADS Depression (0–21): mean (SD)	4.8 (3.4)	4.2 (3.1)
Compartmental distribution of radiographic OA – index knee		
Normal	33	31
Isolated tibiofemoral	5	3
Isolated patellofemoral	23	25
Combined tibiofemoral and patellofemoral	40	41
Overall severity of radiographic OA - index knee		
Normal	33	31
Mild	28	30
Moderate/severe	39	39
Severity of knee effusion – index knee		
None	67	66
Mild	23	23
Moderate/gross	10	11
Nodal symptomatic hand OA	15	18
Previous knee injury		
None	65	71
Unilateral	26	23
Bilateral	9	5
Time since onset of knee problem		
< 12 months	8	16
1 year to < 5 years	36	35
5 years to < 10 years	21	19
≥ 10 years	35	30
Duration of morning stiffness		
None	35	46
≤30 min	60	50
>30 min	6	4

Table 3 Comparison of patient baseline characteristics of participants reporting at least one period of significant pain variability potential flare *(Continued)*

Knee given way during past month	32	27
Seen hospital doctor about knee	27	20
Frequent sedentary activity	11	8
Frequent moderate activity	54	55
Frequent vigorous activity	28	28

Figures are column percentages unless otherwise stated. Hospital Anxiety and Depression scale [54]; OA Osteoarthritis; PF-10 Medical Outcomes Study SF-36 Physical Functioning subscale [55]; SD Standard deviation; WOMAC Western Ontario & McMaster Universities Osteoarthritis Index [56]
[a] Derived from National Socio-economic Classification [57]

1.79; 1.16, 2.75) and morning stiffness (≤30 min vs none: 1.43; 1.10, 1.85) (Table 4).

Factors associated with recurrent periods of significant pain variability

Based on the outcome of recurrent periods of significant symptom variability, i.e. allowing for those experiencing more than one episode, baseline measures associated with a higher risk of potential symptom variability in the adjusted analysis were: younger age (0.94; 0.91, 0.98), higher BMI (1.04; 1.00,1.08), higher WOMAC knee pain scores (1.10; 1.03,1.17), longer time since onset (e.g. 1–5 years vs < 1 year: (2.23; 1.11, 4.46) and morning stiffness (≤30 min vs none: 1.67; 1.07, 2.61) (Table 5).

Discussion

From our study we estimate that between a quarter and a third of adults aged over 50 years with knee pain report significant symptom variability. Such variability was associated with younger age, longer history of knee problem, higher BMI and more severe knee symptoms. Variability was also more common in people reporting previous bilateral knee injury, greater functional limitation, frequent sedentary behaviour and higher anxiety and depression scores at baseline although these associations were not statistically significant after adjusting for covariates.

In the context of previous studies it appears that significant variability in pain affects a large minority of persons with, or at risk, of knee OA but that estimates are sensitive to the definition and period of time and frequency of measurement. Of previous studies employing latent class growth analysis or growth mixture modelling to cohort data with repeated measures of pain only the study by Leffondre et al [41] identified a group of patients characterised by pain variability. Their group of patients with 'highly unstable WOMAC total scores, with abrupt changes or short-term fluctuations' accounted for 18% of the community-dwelling sample of adults aged over 55 years with hip or knee pain. The failure of other studies to extract such a 'fluctuating pain' latent class using similar methodology [2–5], may well reflect the long intervals between re-measurements (typically a year). In studies of low back pain, those with weekly or fortnightly pain measurements classed twice as many patients into a 'fluctuating' trajectory than studies using monthly measurement [42]. It must also be stressed that within trajectory groups that have an average 'stable' trajectory, members of these groups can still experience significant variability in their pain at an individual level. A further source of comparison is Ricci et al.'s [16] estimate from NHANES I data that 38% of US workers aged 40–65 years with arthritis (predominantly hip or knee pain) report 'pain exacerbations'. Like our study, they adopted the same magnitude of increase in pain intensity to define these events (2 or more points on 0-10NRS) although the Ricci study was based on a 2-week recall period.

The extent to which our own, and any of these previous studies, provides insights into the frequency of pain exacerbations or flares is limited by the data available. As noted by Marty [11] and in consensus work for flare definition in other rheumatic diseases [43, 44], flares are probably best thought of as multidimensional constructs. With the data available to us we could not verify the speed of onset, duration, or other features (e.g. swelling, limping) that may be important in distinguishing acute flares from other forms of variability within the natural history of osteoarthritis pain. An important limitation of our study is the potential misclassification bias as a result of recall error. We hypothesise that patients with increased pain closer to the measurement time points may have overestimated their average and worst pain scores whereas those with fewer pain fluctuations or no increase in pain close to the measurement time points are likely to have underestimated their pain scores over the previous 6 months. The overall impact of this on our results is uncertain. In addition, the long period of recall may be particularly prone to 'forward telescoping' where an event is reported more recently than it actually happened [45, 46]. In our analysis we have used the 'average' and 'worst' pain scores taken from the Von Korff pain grade. These were chosen as they were similar but unfortunately not comparable to outcomes used in flare design trials. Flare-ups are identified in drug withdrawal trials by comparing baseline pain scores to worst pain scores. These limitations are only likely to be resolved by prospective studies with frequent repeated measures over clinically relevant time periods incorporating the concept of pain variability

Table 4 Patient baseline characteristics associated with significant pain variability based on discrete-time logit model (first outcome)

		Unadjusted		Adjusted[a]	
	Reference	OR	(95% CI)	aOR	(95% CI)
Male gender	Female	1.15	(0.92, 1.45)	1.22	(0.96, 1.55)
Age (years)	per year	0.96	(0.95, 0.98)	0.96	(0.94, 0.97)
Body mass index (kg/m^2)	per kg/m^2	1.05	(1.03, 1.08)	1.03	(1.01, 1.06)
Occupational class	Managerial/professional				
Intermediate		0.90	(0.56, 1.45)		
Routine and manual		0.76	(0.51, 1.12)		
PF-10 physical function (0–100)	per unit	0.99	(0.99, 0.99)	ns	ns
WOMAC knee pain (0–20)	per unit	1.08	(1.05, 1.11)	1.06	(1.03, 1.10)
WOMAC knee function (0–68)	per unit	1.02	(1.01, 1.03)	mc	mc
Compartmental distribution of radiographic OA[b]	Normal				
Isolated tibiofemoral		1.03	(0.58, 1.81)		
Isolated patellofemoral		0.94	(0.70, 1.28)		
Combined tibiofemoral and patellofemoral		1.06	(0.81, 1.38)		
Overall severity of radiographic OA[b]	Normal				
Mild		0.94	(0.70, 1.25)		
Mod/severe		1.08	(0.82, 1.41)		
HADS anxiety (0–21)	per unit	1.04	(1.01, 1.07)	mc	mc
HADS depression (0–21)	per unit	1.07	(1.03, 1.10)	ns	ns
Previous knee injury	None			ns	ns
Unilateral		1.25	(0.95, 1.64)		
Bilateral		1.82	(1.17, 2.85)		
Time since onset of knee problem[b]	<1 year				
1 year to < 5 years		1.97	(1.29, 3.01)	1.79	(1.16, 2.75)
5 years to < 10 years		1.94	(1.23, 3.05)	1.82	(1.15, 2.89)
≥10 years		2.02	(1.32, 3.08)	1.82	(1.18, 2.82)
Duration of morning stiffness[b]	None				
≤30 min		1.63	(1.28, 2.07)	1.43	(1.10, 1.85)
>30 min		2.26	(1.34, 3.81)	1.44	(0.83, 2.50)
Knee given way during past month[b]	No	1.38	(1.08, 1.77)	ns	ns
Seen hospital doctor about knee[b]	No	1.61	(1.23, 2.10)	ns	ns
Severity of effusion[b]	None				
Mild		0.99	(0.77, 1.30)		
Moderate/gross		1.15	(0.79, 1.67)		
Nodal symptomatic hand OA	No	0.90	(0.66, 1.24)		
Frequent sedentary activity	No	1.59	(1.07, 2.35)		
Frequent moderate activity	No	0.85	(0.68, 1.07)		
Frequent vigorous activity	No	0.88	(0.68, 1.13)		

[a] Adjusted for all other variables; - indicates variables entered but not retained in multivariable model
[b] For index (most problematic) knee
Hospital Anxiety and Depression scale [54]; OA Osteoarthritis; OR Odds ratio; PF-10 Medical Outcomes Study SF-36 Physical Functioning subscale [55]; WOMAC Western Ontario & McMaster Universities Osteoarthritis Index [56]; 95%CI 95% confidence interval
ns Non-significant in multivariable model
mc Variables omitted in the multivariable model due to multi-collinearity

Table 5 Patient baseline characteristics associated with significant pain variability based on discrete-time frailty model (recurrent outcome)

		Unadjusted		Adjusted[a]	
	Reference	OR	(95% CI)	aOR	(95% CI)
Male gender	Female	1.30	(0.86, 1.97)	1.40	(0.93, 2.09)
Age (years)	per year	0.95	(0.92, 0.98)	0.94	(0.91, 0.98)
Body mass index (kg/m^2)	per kg/m^2	1.07	(1.02, 1.12)	1.04	(1.00, 1.08)
Occupational class	Managerial/professional				
Intermediate		0.95	(0.53, 1.70)		
Routine and manual		0.77	(0.49, 1.22)		
PF-10 physical function (0–100)	per unit	0.99	(0.99, 0.99)	ns	ns
WOMAC knee pain (0–20)	per unit	1.12	(1.04, 1.21)	1.10	(1.03, 1.17)
WOMAC knee function (0–68)	per unit	1.03	(1.01, 1.05)	mc	mc
Compartmental distribution of radiographic OA[b]	Normal				
Isolated tibiofemoral		1.05	(0.49, 2.24)		
Isolated patellofemoral		0.93	(0.62, 1.40)		
Combined tibiofemoral and patellofemoral		1.07	(0.75, 1.53)		
Overall severity of radiographic OA[b]	Normal				
Mild		0.93	(0.63, 1.36)		
Mod/severe		1.10	(0.77, 1.57)		
HADS anxiety (0–21)	per unit	1.05	(1.00, 1.10)	mc	mc
HADS depression (0–21)	per unit	1.11	(1.02, 1.21)	ns	ns
Previous knee injury	No			ns	ns
Unilateral		1.27	(0.92, 1.76)		
Bilateral		1.96	(1.02, 3.79)		
Time since onset of knee problem[b]	<1 year				
1 year to < 5 years		2.38	(1.14, 4.97)	2.23	(1.11, 4.46)
5 years to < 10 years		2.32	(1.10, 4.89)	2.20	(1.08, 4.48)
≥10 years		2.40	(1.18, 4.92)	2.11	(1.12, 4.05)
Duration of morning stiffness[b]	None				
≤30 min		2.23	(1.17, 4.23)	1.67	(1.07, 2.61)
>30 min		3.75	(1.16, 12.16)	1.71	(0.73, 3.98)
Knee given way during past month	No	1.42	(1.06, 1.90)	ns	ns
Seen hospital doctor about knee	No	1.89	(1.41, 3.13)	ns	ns
Severity of effusion	None				
Mild		0.99	(0.69, 1.42)		
Moderate/gross		1.18	(0.72, 1.92)		
Nodal symptomatic hand OA	No	0.80	(0.48, 1.35)		
Frequent sedentary activity	No	2.00	(0.96, 4.19)		
Frequent moderate activity	No	0.79	(0.56, 1.13)		
Frequent vigorous activity	No	0.79	(0.51, 1.23)		

[a] Adjusted for all other variables; - indicates variables entered but not retained in multivariable model
[b]relates to index (most problematic) knee
Hospital Anxiety and Depression scale [54]; OA Osteoarthritis; OR Odds ratio; PF-10 Medical Outcomes Study SF-36 Physical Functioning subscale [55]; WOMAC Western Ontario & McMaster Universities Osteoarthritis Index [56]; 95%CI 95% confidence interval
ns Non-significant in final model
mc Variables omitted in the multivariable model due to multi-collinearity

The pattern of associations found in our study is consistent with previous findings for some risk factors but not others. Higher BMI, pain intensity, stiffness, and functional limitation have been found to be associated with flares in previous studies [11, 16]. By contrast, our finding of an increased risk of potential flare with younger age was found by neither Marty nor Ricci which may reflect the duration of data collection. Bouts of heavy physical activity [47], buckling and knee injury [48] and worsening mental health [37] have previously been shown in case-crossover designs to be associated with pain flares. The fact that our study found no association between these factors measured at baseline and episodes of worsened pain occurring months and years later may simply affirm the need to regard these factors as time-varying, proximal triggers. From influential qualitative studies by Gooberman-Hill et al [49] and Hawker et al [9], pain variability is thought to be a particular feature in the early and the advanced stages of osteoarthritis. In our study we found no strong relationship between significant variability in pain and severity of radiographic knee OA suggesting that this may happen across the spectrum of the disease. As noted above, our data do not permit us to explore further the quality or predictability of episodes of severe pain: dimensions identified by patients as critical to their ability to cope [12, 50]. If correct, our finding that younger age, male gender, and BMI are associated with higher risk of significant symptom variability, might imply an important role for joint loading in provoking episodes of severe pain and acute flares.

Conclusion

Up to a third of community-dwelling symptomatic adults recall significant variability in knee pain that includes periods of severe pain. Such variability occurs across the spectrum of radiographic severity of knee osteoarthritis. A larger body of work, as has been done for other diseases such as COPD (Chronic Obstructive Pulmonary Disease), is needed to reliably determine the characteristics of those who experience significant symptom variability, including acute flares [51], to assess burden [52], and to guide prevention [53].

Additional file

Additional file 1: Table S1. Response rates at each follow-up, by presence or absence of significant pain variability at baseline. (DOCX 14 kb)

Abbreviations

BMI: Body mass index; CAS(K): The knee clinical assessment study; COPD: Chronic obstructive pulmonary disease; OA: Osteoarthritis; PA: Postero-anteriorly; PFJ: Patellofemoral joint; SD: Standard deviation; SF-36: 36 item short form health survey; TFJ: Tibiofemoral joint; WOMAC: Western Ontario & McMaster Universities Osteoarthritis Index

Acknowledgements

The authors thank Professor Peter Croft, Professor Elaine Hay, Dr Elaine Thomas, Dr Laurence Wood, Dr Michelle Marshall, June Handy, Professor Krysia Dziedzic, Dr Helen Myers, Dr Ross Wilkie, Dr Rachel Duncan, Dr Jonathan Hill, Charlotte Clements, Professor Chris Buckland-Wright and Professor Iain McCall for their contributions to the design and acquisition of data for the CAS(K) study. We also thank the administrative and health informatics staff at the Arthritis Research UK Primary Care Centre, staff of the participating general practices and Haywood Hospital, especially Dr Jackie Sakhlanvala, Carole Jackson, Julia Myatt and the Radiographers at the Department of Radiography.

Funding

The CAS(K) cohort was supported by the Medical Research Council (Grant G9900322Q), Arthritis Research UK (Grant 18174), and by Support for Science funding secured by North Staffordshire Primary Care Research Consortium for National Health Service support costs. EP is currently funded by a NIHR In-Practice Fellowship and was previously funded by a NIHR Academic Clinical Fellowship. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Availability of data and material

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

The authors contributed to the manuscript as follows: conception and design - GP, EP,RO; analysis and interpretation of data - EP, RO, GP; drafting of the article - EP, GP, RO; final approval - EP, GP, RO. All authors read and approved the final manuscript.

Competing interests

GP has received consultancy fees from InFirst Healthcare Ltd. The authors have no other competing interests to declare.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study involved secondary analysis of anonymised data from the CAS(K) cohort within the cohort objectives approved by North Staffordshire Research Ethics Committee (1430; 03/94; 05/Q2604/72), South Birmingham Research Ethics Committee (06/Q2707/327) and Birmingham East, North, and Solihull Research Ethics Committee (08/H1206/171). All participants provided written consent to take part in the study.

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Received: 11 October 2016 Accepted: 26 January 2017
Published online: 14 February 2017

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Appendix Z: Peer reviewed publication: ‘Acute flare-ups’ in patients with, or at high risk of, knee osteoarthritis: a daily diary study with case crossover analysis

Osteoarthritis and Cartilage 27 (2019) 1124–1128

Osteoarthritis and Cartilage

Brief Report

‘Acute flare-ups’ in patients with, or at high risk of, knee osteoarthritis: a daily diary study with case-crossover analysis

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ARTICLE INFO

Article history:
Received 19 November 2018
Accepted 5 April 2019

Keywords:
Knee
Osteoarthritis
Flare-up

SUMMARY

Objective: To determine the natural history of flare-ups in knee osteoarthritis and their relation to physical exposures.

Design: Adults aged ≥45 years with a recent primary care consultation for knee OA/arthralgia completed a daily pen-and-paper diary for up to three months, including questions on average knee pain intensity, pain descriptors, other symptoms, activity interference, and selected physical exposures (prolonged kneeling, squatting, climbing stairs, ladders, and moving/lifting heavy objects). Informed by a systematic review, flare-ups were defined a priori. We calculated the rate of flare-ups in the sample, described their nature and duration, and estimated their association with physical exposures in the prior 48 h.

Results: 67 participants completed at least one month of diaries, 37 (55%) were female, mean age 62 years (SD 10.6) with a mean body mass index of 24.6 kg/m² (SD 5.1). 30 participants experienced a total of 54 flare-ups (incidence density 1.12 (95%CI 0.80, 1.57) flare-ups/person-days). The median duration of flare-ups was eight days (range: 2–30). During a flare-up participants were more likely to report sharp, throbbing, stabbing, burning pain, swelling, limping, stiffness, being woken by pain, taking more analgesia, and stopping usual activities. Exposure to one or more physical exposure increased the risk of a flare-up in the subsequent 48 h (odds ratio 2.19 (95%CI: 1.22, 4.05)).

Conclusions: Our study with intensive longitudinal data collection suggests acute flare-ups may be experienced by a substantial number of patients. These episodes often last a week or longer, are disruptive, prompt changes in self-management, and may be triggered by high-loading physical activities.

Introduction

Longitudinal studies following patients with symptomatic knee osteoarthritis over several years suggest that non-progressive symptom trajectories are relatively common[1]. However, within these average long-term trajectories, it is well-recognised that patients can experience substantial variability in the presence, nature, and severity of symptoms over time, including episodes of increased pain that may be experienced as acute events[2,3]. These events, particularly when they have an unpredictable, sudden onset, can be distressing for patients and can impact on quality of life, normal activities (including productivity losses[4]) and health service use. Yet unlike other long-term conditions, there is still considerable uncertainty around the nature, definitions, and terminology of these phenomena in osteoarthritis. Classification criteria for flare-ups in knee OA have been proposed but have not been widely adopted[5]. Achieving greater clarity and agreement on these matters is an important goal for research and clinical communities[6], toward which observational research can contribute by gaining insight into the natural history of these phenomena, possible triggers[7], and other proximal and more distal determinants.

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https://doi.org/10.1016/j.joca.2019.04.003
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We sought to describe the natural history of 'flare-ups' in knee OA in a sample of community-dwelling symptomatic adults, using an observational daily diary study. We chose the term 'flare-up' over terms such as 'exacerbation' following workshops with patients and members of the public on their preferred terminology and from more frequently used terminology in the medical literature as found in a recent systematic review[6].

Method

Study design and sample

Adults aged 45 years and over registered at one of two General Practices in the West Midlands, England and with a recorded consultation for knee osteoarthritis or knee pain/arthralgia in the previous two years were mailed a short questionnaire containing items used to describe the sample, judge eligibility for the daily diary study, and provide baseline values of 'what is normal for me' with respect to knee symptoms, activity, and analgesia (adapted from Trappenburg et al.[26]). A standard three-stage mailing procedure was used with non-respondents sent a reminder postcard at two weeks and repeat questionnaire at four weeks. Respondents were eligible for inclusion in the daily diary study if they reported knee symptoms on at least one day in the previous 12 months, provided written informed consent to further contact and indicated their willingness to complete daily diaries for up to three months. Respondents were excluded if they self-reported a diagnosis of inflammatory disease, previous bilateral total knee replacement (TKR) or TKR in the index knee (the worst affected knee) or did not complete baseline knee symptom questions.

Data collection

All eligible, consenting questionnaire respondents were invited to complete three consecutive one-month pen-and-paper diaries. The diaries contained nine items for each day (see Supplementary Data 1) which participants were asked to fill out at the end of the day. Average pain intensity in the previous 24 h was assessed using a 0–10 numerical rating scale (NRS)[9]. We included four single items on other symptoms shown by Marty et al.[5] to be associated with OA flare-ups: stiffness lasting >30 min, swelling, night pain and limping. Participants were also asked about pain quality using a short list of descriptors which included continuous pain descriptors (dull, aching, throbbing), intermittent pain descriptors (sharp, stabbing), and neuropathic-type pain descriptors (burning, numbness, pins and needles)[1,10]. Participants were asked if they had undertaken any of a selected list of physical activities which have previously been linked to onset of knee OA[11]. Participants were also asked about any changes in usual medication (more than normal, less than normal, the same) and whether symptoms had stopped them taking part in usual activities.

The study was approved by the North of Scotland Research Ethics Committee (Reference: 13/NS/0049).

Statistical analysis

Scatterplots were used to visually inspect daily pain intensity scores for each participant. To estimate within-person variability we calculated a Variability Index[12] for each participant based on the average standard deviation of their daily pain intensity scores within half-monthly periods. The periods ranged from 14 to 16 days due to the varying length of the month over the 3 month study period. The standard deviation was chosen as it is the most common measure of variability which averages the absolute deviation of each day's pain intensity from the mean pain over the 14–16 days period thus capturing any pain fluctuations. This method has also been used in a previous study investigating pain variability of patients with fibromyalgia[12]. The 14–16 day periods were chosen based on the number of available data points and to allow for reliable estimation of SD due to the distribution assumptions. The possible values were positive, with zero indicating no variability and a higher number indicating greater variability. Informed by a systematic review of flare-up definitions in the medical literature[6], and considering flare-up definitions used in other conditions[13] we defined a flare-up a priori as: an increase of at least two points from baseline ('normal for me') in average pain intensity in the past 24 h (0–10 NRS) which was sustained for at least two consecutive days. A flare-up was judged to be resolved when pain intensity returned to baseline level for five consecutive days.

We then estimated the proportion of respondents experiencing at least one flare-up during the period of observation, the incidence density with 95%CI of flare-ups for the sample as a whole (expressed as the number of flare-ups per 100 person-days at risk, i.e., denominator excluded days in flare-up and the five days needed for it to be judged 'resolved') using Poisson regression taking into account recurrent events, and the duration of flare-ups (median, interquartile range (IQR)).

The time course of an 'average' flare-up was illustrated by plotting combined group-mean daily pain intensity NRS scores across all first flare-ups, anchored to a common timescale with zero representing the first day of flare-up and extending to seven days prior and 30 days after the flare-up. To describe the nature of flare-ups and their impact on individuals, descriptive statistics (means, SD or proportions) were used to summarise symptoms, change in medication and whether pain had stopped usual activities across all flare-up days and all non-flare-up days, among participants experiencing at least one flare-up. We then used mixed-effect models to estimate the relative frequency (expressed as odds ratios) and severity (expressed as regression coefficients) of symptoms on flare-up vs non-flare-up days accounting for the clustered nature of the observations.

To determine whether exposure to selected physical activities was associated with flare-up onset, we conducted a case-crossover analysis with each individual acting as their own control[14]. Case windows for exposures were defined as the 48 h prior to the first day of a flare-up. For each case we selected up to four matched ambidirectional control windows which were 48-h periods on at-risk days which corresponded with the same days of the week as the case window to remove confounding by variation in physical exposures across days of the week (e.g., weekdays vs weekends). We calculated unadjusted exposure odds ratios (OR) based on the conditional maximum likelihood estimate with 95% mid-P exact confidence intervals using OpenEpi (www.OpenEpi.com).

Analyses were performed using Stata, Version 13 (StataCorp 2013).

Results

Of the 220 out of 330 responders to the baseline questionnaire, 106 (48%) were eligible and were invited to take part in the diary study, consented to further contact, and were mailed the first diary. Reasons for non-eligibility included; inflammatory disease (41), TKR (27), missing/blank Q (22), no recent knee pain (14), withdrew/died/moved (10). Of the 67 (63%) participants who completed at least one monthly diary, 37 (55%) were female, mean age 62 years (SD 10.6) with a mean body mass index of 24.6 kg/m^2 (SD 5.1). Of a possible 5,491 diary days, 4,328 (79%) were fully completed, 1,163 (21%) were partially completed, and 111 (2%) were missed completely. Comparing responders to non-responders ages were similar (mean age 62.2 (SD 10.6) and 61.7 (SD 11.0) respectively)

and there were slightly more females amongst the non-responders (25 (64.1%) non-responders vs 37 (55.2%)).

The median Variability Index across the sample was 0.68 (IQR 0.41, 1.05), and this was higher during non-flare-up days in participants classed as having experienced a flare-up than in those participants who did not experience a flare-up ((median (IQR)): 0.83 (0.51, 1.13) vs 0.52 (0.27, 0.97)).

Over the period of observation 30 participants (45%) were classed as having experienced a total of 54 flare-ups (one flare-up ($n = 16$), two flare-ups ($n = 6$), three flare-ups ($n = 6$), four flare-ups ($n = 2$)) giving an estimated incidence density of 1.12 (95%CI 0.80, 1.57) flare-ups per 100 person-days. Illustrative examples of participants with contrasting variability in daily pain scores are provided in Supplementary Data 2.

Those experiencing a flare-up were slightly more likely to be male (50% vs 40%; proportion difference (95% CI): 10% (−14%, 33%)), have a higher BMI (mean (SD) 25.5 (5) vs 23.9 (6) kg/m^2; mean difference (95% CI): 1.6 (−0.9, 4.1)), and report previous injury (50% vs 42%; proportion difference (95% CI): 8% (−15%, 33%)), although none of these differences were statistically significant given the relatively small numbers of participants in each group.

The median duration for a flare-up was eight days (IQR 3, 23; range 2–30). The 'average' time course shows the sudden onset and relatively quick reduction in pain intensity within 48 h followed by a longish plateau (Fig. 1). Flare-up days compared to non-flare-up days were accompanied by a higher occurrence of knee stiffness (OR 10.9; 95% CI: 7.0, 17.1), limping (12.4; 7.4, 20.8), swelling (14.5; 8.3, 25.4), being woken by pain (7.0; 4.3, 11.2), use of most pain descriptors (but particularly 'throbbing', 'sharp', 'stabbing' pain, and 'numbness'), interference with usual activities (26.5; 3.7, 51.5) and taking more medication than normal (23.9; 13.8, 41.4) (Table I). The above features tended to be at their highest levels during the first two days of a flare-up (data not shown).

For the case-crossover analysis using physical exposures there were 88 cases periods in total and 328 control periods. The number of control periods per case ranged from 1 to 4 (median:2, mean: 2.43 (SD1.12)). Exposure to one or more of the selected physical exposures (prolonged kneeling, lifting/moving heavy objects, climbing several flights of stairs, prolonged squatting, climbing ladders) was associated with increased risk of acute flare-up in the subsequent 48 h (odds ratio 2.19; 95%CI: 1.22, 4.05) (Supplementary Data 3). Exposure to each individual physical activity was positively associated with flare-up onset but estimates lacked precision due to small numbers of discordant pairs.

Discussion

Our study supports the notion that knee OA, for some people, is characterised by intermittent acute or sudden increases in pain with an associated change in pain quality and knee symptoms.

Pain intensity in our study was highly variable for some and stable for others. Although not explored in this study, Schneider et al. found a link between pain variability in OA and depression[15]. Qualitative studies have highlighted the highly variable nature of pain in OA[2] and when unpredictable can be associated with considerable distress[3].

Predictability of pain is important for episode management and patient understanding. Prior to flare-up onset we saw a marked step up in symptoms rather than a gradual onset. This may be partly due to once daily measurement, however, we found that certain activities reported in the 48-h period prior to a flare-up were associated with flare-up onset. Zobel et al. identified that knee buckling and knee injury were triggers for acute events[7]. Physical activity exposures have previously been associated with long term incidence of osteoarthritis[11]. The link we have found may give an insight into short term events and their intrinsic part in how OA develops and progresses. It is possible that these acute events lead to a cumulative insult on the knee joint that eventually leads to disability.

Identifying potential triggers are important in the management of flare-ups in terms of activity avoidance and for earlier and preventative management strategies. Other management strategies that may lead to early termination of a flare-up include recognising the early changes in symptoms, for example knee stiffness, swelling, limping and night pain which have previously been used as part of the criteria for flare-up identification[5].

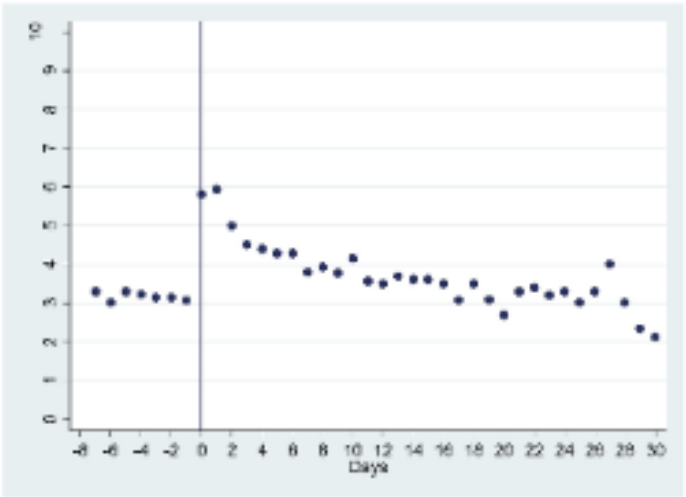

Fig. 1. Time course of an 'average' flare from 7 days prior to 30 days after the onset of a flare (day 0). Points are group-mean pain intensity for all participants' first flares combined.

Table I
Severity and occurrence of symptoms and impact experienced during flare-up days vs. at-risk days among participants experiencing one or more flare-ups (n = 30)

	Flare-up days* (n = 269)	Non-flare-up days† (n = 1958)	Relative frequency/severity on flare-up days vs. non-flare-up days‡
Average knee pain intensity (0–10NRS): mean (SD)	5.4 (1.9)	3.1 (2.0)	2.5 (2.3, 2.6)
Pain descriptors			
Dull	52 (17)	673 (35)	0.4 (0.2, 0.7)
Aching	218 (71)	1122 (59)	6.9 (4.1, 11.6)
Throbbing	95 (32)	301 (16)	18.1 (9.8, 33.3)
Sharp	146 (49)	206 (11)	11.2 (6.8, 18.6)
Stabbing	108 (36)	269 (14)	11.8 (7.2, 19.5)
Burning	73 (24)	171 (9)	6.7 (4.0, 11.1)
Numbness	72 (24)	15 (1)	6.7 (1.9, 23.1)
Pins and needles	1 (<1)	1 (<1)	–
Other	9 (3)	45 (2)	1.3 (0.6, 3.1)
Knee swelling	149 (56)	668 (35)	14.5 (8.3, 25.4)
Limping	191 (64)	804 (42)	12.4 (7.4, 20.8)
Knee stiffness lasting >20 min	178 (68)	505 (26)	10.9 (7.0, 17.1)
Woken at night by knee pain	103 (35)	189 (10)	7.0 (4.3, 11.2)
Taking more medication than usual	94 (34)	181 (12)	23.9 (13.8, 41.4)
Pain stopped usual activities	44 (15)	76 (4)	26.5 (13.7, 51.5)

Figures are n (%) unless otherwise stated.
NRS Numerical rating scale; SD Standard deviation.
* Days during a flare-up (i.e., from start of flare-up to first day when pain returned to 'normal' levels for five consecutive days.
† Excludes flare-up days as well as the five consecutive days after last flare-up day.
‡ From mixed-effect model (logistic for binary and linear for continuous outcome). Results are expressed as odds ratios (95% CI) except average knee pain intensity which is expressed as a regression coefficient (i.e., mean difference) and 95% CI.

In response to flare-ups a third increased usual medication and a small number reported stopping usual activities. Our study did not capture lesser but still problematic interference with activities which may affect quality of life if sustained. We recognise that there may be potential time-varying confounders that could not be controlled in the study, for example, those causing psychosocial stress or a perceived improvement in symptoms, leading to a reduction in medication and increase in activity.

Limitations of the study include the potential for inaccurate recall of average pain scores over the 24-h period and the extent to which participants may have retrospectively filled in diary entries. We also acknowledge the bias that may be introduced by missing data. Our case-crossover analysis was unable to explore individual physical exposures due to small numbers and the use of ambidirectional control windows assumes no strong effect of flare-ups on subsequent exposure levels.

In providing an operational definition of a flare-up we recognise the need for continued empirical work. Sensitivity analyses in larger datasets could usefully explore whether absolute or relative (to baseline) increases in pain are best for defining flare-ups as well as the minimum duration of these.

Conclusion

Our study with intensive longitudinal data collection suggests acute flare-ups may be experienced by a substantial number of patients. These episodes often last a week or longer, are disruptive, prompt changes in self-management, and may be triggered by high-loading physical activities.

Author contributions

All authors were involved in conception and design of the study, analysis and interpretation of data, drafting the article, critical revision of the article for important intellectual content, final approval of the article. GP takes responsibility for the integrity of the work as a whole from inception to finished article.

Competing interest

GP received consultancy fees from InFirst plc and Good Relations plc.

Role of the funding source

The paper presents research funded by Arthritis Research UK [Centre of Excellence award: 18139]. ELP received funding from a National Institute for Health Research (NIHR) In-Practice Fellowship, NIHR Academic Clinical Fellowship and SPCR GP Progression Fellowship.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2019.04.003.

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