Design issues and challenges in clinical trials with a surgical and non-surgical comparison

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Abstract

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Conducting surgical trials is essential to establish evidence based practice and inform health policy, particularly in the face of economic pressures. Randomised controlled trials (RCT) evaluating surgical interventions can be difficult to design and conduct, especially when including a non-surgical comparison. Only around half of initiated surgical trials reach their recruitment target, and failure to recruit is cited as the most frequent reason for premature closure of surgical RCTs.

The aim of the thesis was to gain a greater understanding of the main methodological challenges to the design and conduct of trials that directly compare surgical and non-surgical interventions, explore potential solutions, and provide guidance for use in future studies.

The work contained in the thesis purposefully used several different methodologies; a systematic review, case study, qualitative evidence synthesis and two qualitative interview studies. This approach provided insight from different perspectives in order to more fully understand the challenges involved in this type of trial, and therefore contribute to the design of future trials.

Several methodological challenges were identified in these types of trials related to; difficulty implementing blinding, recruitment difficulties, complexity of intervention content and delivery, imbalance in timing of follow-up, non-compliance with treatment allocation, and differential loss to follow-up. The dichotomy between several aspects of the surgical and non-surgical interventions, for example, level of invasiveness, risk, and perceived mechanism of effect, were seen to contribute to strong preferences of both patients and clinicians, making recruitment particularly challenging. The potential benefits of undertaking pre-trial qualitative research to identify potential issues of patients' and clinicians' treatment preferences in these types of trials, was also identified.

Several methodological issues were identified in this thesis that have the potential to impact on the design, conduct and analysis of these types of trials. If not adequately addressed, these issues may introduce significant bias and threaten the viability of the trial, and also the validity of the results. Consideration of these specific challenges should be made in the planning and design of future studies to optimise trial conduct.

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Contents

Chapter 1 1

Introduction 2

Randomised controlled trials 2

Application of evidence based care to surgery 4

The challenge of designing clinical trials 6

Pilot and feasibility studies 11

Choice of comparator 12

Thesis aims and objectives 15

Structure of the thesis 16

Chapter 2 18

Introduction 19

Objectives 20

Method 20

Results 25

Eligibility 26

Identification 26

Screening 26

Included 26

Discussion 53

Limitations 58

Summary of findings 59

Chapter 3 61

Introduction 62

Objectives 63

Methods 64

Inclusion Criteria 66
Exclusion Criteria 66
Results 68
Allocation 72
Discussion 82
Limitations 86
Summary of findings 87
Chapter 4 88
Introduction 89
Objectives 90
Methods 91
Findings 99
Eligibility 100
Identification 100
Screening 100
Included 100
Themes 114
Discussion 137
Implications for practice 143
Limitations 143
Summary of results 145
Chapter 5 146
Introduction 147
Objectives 148
Methods 149
Discussion 165
Chapter 6 171

Introduction 172
Aim 173
Methods 173
Results 176
Discussion 184
Limitations 188
Summary of results 188
Chapter 7 190
Introduction 191
Overview of thesis findings 192
Recommendations for research practice 202
Inclusion Criteria 248
Exclusion Criteria 248

List of tables

Table 1: PICOT format for developing a research question [52, 53] (adapted from Bandholm et al, 2017)[51] 7
Table 2: Key differences between trials with explanatory and pragmatic attitudes (from Zwarenstein et al.) [61] 9
Table 3: Challenges to the planning and conduct of RCTs comparing surgical interventions with different types of comparator (modified from Ergina et al, 2009) [15] ... 14
Table 4: Study inclusion and exclusion criteria 21
Table 5: Summary of included studies 27
Table 6: Summary of general trial studies 42
Table 7: Summary on the data on trial recruitment, non-compliance and loss to follow-up. 46
Table 8: Assessment of each risk of bias item presented as a % across all studies (n = 90) 47
Table 9: Factors reported to affect the design and conduct of surgical versus non-surgical studies 49
Table 10: Inclusion and exclusion criteria for the ACL SNNAP trial 66
Table 11: Screening data and number of patients randomised by site during the 12 month pilot phase 70
Table 12: Reasons for patient ineligibility 71
Table 13: Reasons eligible patients decline trial participation 75
Table 14: Time in weeks for patients in ACL SNNAP trial who have received treatment (31st Jan, 2019) 77
Table 15: Time in weeks for patients in ACL SNNAP trial Number awaiting treatment start date (31st Jan, 2019) 78
Table 16: Total number of follow-up questionnaires sent and received (31st January, 2019) 81
Table 17: Seven steps of Noblit and Hare's meta ethnography [234] 92
Table 18: Study inclusion and exclusion criteria using modified PICO [244, 245] 94
Table 19: Definitions of the components of the CERQual approach [252] 98
Table 20: Descriptions of level of confidence in a review finding (CERQual approach) [252] 98

Table 21: Summary of included studies 102
Table 22: Characteristics of studies included in the QES.....104
Table 23: Summary of Qualitative Findings (SoQF) table.....111
Table 24: Final themes, conceptual categories, studies supporting each theme and additional narrative exemplars from the primary studies. 130
Table 25: Six-phase analytic process of thematic analysis [322].....152
Table 26: Characteristics of patients interviewed, include her age, gender, activity at time of injury, time from injury to diagnosis.....156
Table 27: Six-phase analytic process of thematic analysis [322].....175
Table 28: Recommendations for the conduct of RCTs with a surgical and non-surgical comparison.....203

List of figures

Figure 1: Structure of thesis.....17
Figure 2: PRISMA flow diagram of included studies 26
Figure 3: Participant flow diagram to highlight eligibility in early stage of the trial.....72
Figure 4: Percentage of eligible patients randomised and declining participation by site 76
Figure 5: Participant flow to illustrate number of randomised patients who has undergone treatment in ACL SNNAP study (31st January, 2019).....80
Figure 6: PRISMA flowchart summary of literature search for QES 100
Figure 7: Conceptual model for QES 129
Figure 8: Target against actual recruitment graph ACL SNNAP (March 2017-March 2018).....246

List of abbreviations

ACL	Anterior Cruciate Ligament
ACL SNNAP	Anterior Cruciate Ligament Surgical Necessity in Non Acute Patients
CASP	Critical Appraisal Skills Programme
CONSORT	Consolidated Standards of Reporting Trials
eMERGe	Meta-ethnography reporting guidance
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FDA	Food and Drugs Administration
GRADE CERQual	Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Controlled Trial Register
IQR	Interquartile range
ITT	Intention to treat
KOOS	Knee Injury and Osteoarthritis Outcome Score
LCL	Lateral Collateral Ligament
MCL	Medial Collateral Ligament
NHS	National Health Service
NIHR	National Institute of Health Research
OA	Osteoarthritis
OxKIC	Oxford Knee Injury Cohort
PICO	Population, Intervention, Comparator, Outcome
PRECIS	Pragmatic Explanatory Continuum Indicator Summary
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QES	Qualitative Evidence Synthesis
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SITU	Surgical Intervention Trials Unit
SoQF	Summary of Qualitative Findings
TA	Thematic Analysis
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

Chapter 1

Introduction

Introduction

The aim of this thesis is to gain a greater understanding of the main methodological challenges in the design and conduct of randomised controlled trials (RCT) that directly compare surgical and non-surgical interventions, to explore potential solutions, and to provide guidance for use in future studies.

In this introductory chapter, the background of this thesis is outlined. Firstly, a brief overview of the development of RCTs, the application of evidence based care in surgery and methodological challenges in the conduct of surgical trials is provided. In the latter part of the chapter, the challenges of the trial design process are discussed. The aims and objectives of the thesis are presented, and a brief outline of the methods used is given.

Randomised controlled trials

Randomised Controlled Trials (RCTs) are widely accepted as the most reliable method of determining the effectiveness of different healthcare interventions. A well designed and conducted RCT provides the most rigorous evidence with minimal bias, bias that might otherwise lead to incorrect conclusions or generalisations about the effectiveness of a treatment.[1] Furthermore, pooling all available evidence from RCTs to produce high quality systematic reviews and meta-analyses, are seen to be a fundamental requirement for knowledge generation and support of evidence based decision making.

The evaluation of streptomycin for the treatment of tuberculosis in 1948 marked the conduct of the first randomised clinical trial.[2] Building on earlier work,[3] it was a landmark trial introducing the process of concealed randomisation of patients to generate comparable groups and minimise bias. Since that time, further statistical and methodological developments have occurred to advance clinical trial methodology. For

example, a greater understanding of the need for blinding,[4] advanced statistical methods,[5] novel study designs, introduction of independent monitoring committees, and developments in recommendations for agreed standardised outcomes sets.[6] To provide guidance on protocol development the SPIRIT Statement[7, 8] was introduced in 2013, and uniform standards now exist for the reporting of clinical trials (Consolidated Standards of Reporting Trials [CONSORT]).[9, 10] In addition, to increase transparency in reporting, mandatory registration of clinical trials has now become part of the formal condition of Research Ethics Committee (REC) approval, and a prerequisite for trial publication.[11]

During this time, several developments in the ethical standards for the design and conduct of clinical trials have also occurred,[12] such as, the Nuremberg Code, Declaration of Helsinki,[13] and Belmont report.[14] These have led to mandatory regulations, such as the International Conference on Harmonisation guidelines, Directives of the European Union, and the US Food and Drugs Administration (FDA). As a result, pharmaceutical manufacturers are now required to demonstrate therapeutic safety and efficacy, through RCTs, before drug approval.[3] A similar level of rigorous regulation on the basis of high-quality evidence, however, has not occurred in other areas, such as medical devices and surgery.[15-17]

Over time, the clinical trials landscape has evolved and both the questions being asked and design of trials are becoming increasingly complex. With this increased complexity brings additional challenges in the design and conduct of these trials. Addressing these challenges in terms of theoretical developments and through the consideration of the practical application of methodology in the delivery of trials,[18] will continue to support the generation of reliable evidence to guide clinical practice.

Application of evidence based care to surgery

The application of evidence based care to surgery has, in general, improved over the past decade. [19] However, surgical interventions remain less likely to be investigated using full scale and well-designed RCTs than other fields of medicine.[20] Despite a recent increase in the volume of surgical research (37% in 1999 to 47% in 2009),[19] trials of surgical interventions only account for around 15% of published RCTs in medicine [21] with only 24% of the currently used surgical therapies supported by results of RCTs.[22] More specifically, within the area of orthopaedics, only 20% of procedures are estimated to be supported by at least one low-risk-of-bias randomised controlled trial showing that surgery is superior to a non-operative alternative.[23]

A number of potential obstacles to conducting RCTs in surgery have been discussed.[15, 24-27] As detailed above, the regulatory governance of surgical interventions is not comparable to pharmacological treatments.[3] Many surgical interventions have been in long term use, and new procedures are proposed in clinical practice without the requirement to be subject to a clinical trial.[1] One of the difficulties discussed in the evaluation of surgical procedures is deciding on the most appropriate timing to carry out the evaluation.[28] Development of a surgical procedure can undergo a high level of incremental change, where both the procedure itself and the clinical management of patients may be extensively modified and refined.[20] Recognising the realities of how surgical procedures evolve, the IDEAL (Idea, Development, Exploration, Assessment, and Long-term study) [29-31] framework was developed to provide an integrated pathway approach to the evaluation of surgery and other complex interventions.[32] The framework includes five consecutive stages, with stage-specific optimal research designs and outcomes to evaluate new treatment, from case reports (stage 1), case series and

prospective cohort studies (stage 2a and b), RCTs (stage 3), and then registries (stage 4).[33] However, as treatments become established and stable it may then, become more difficult to initiate a trial when the procedure is widely accepted by both the patient and surgical community, with equipoise difficult to achieve.[1, 34] As described by Buxton's law: "It is always too early [for rigorous evaluation] until, unfortunately, it's suddenly too late".[35]

Equipoise, a state of genuine uncertainty over the most effective treatment, plays an integral part in the conduct of a clinical trial.[36] The principle is that there is no certainty as to whether a patient would be advantaged or disadvantaged if they were to receive any of the interventions under investigation.[37] Ethical issues underlying equipoise, however, are often debated [38] and the concept has shown to raise great difficulties for recruiting clinicians participating in surgical trials.[39] A concept of community equipoise (or "clinical equipoise") is often key to justify evaluation and reflects the collective uncertainty in the clinical community about which treatment is best.[37] Furthermore, clinicians' views about the optimal management of individual patients can mean that equipoise at a clinician level ("individual equipoise") is hard to achieve,[39] leading to difficulties with recruitment.

Surgical trials are also considered difficult to design and conduct, with only around 50% of initiated surgical trials reaching their original recruitment target.[40, 41] Recruitment difficulties are cited as the most frequent reason for premature closure of surgical RCTs.[42] Difficulties with recruitment are especially evident when the interventions being evaluated are markedly different, such as, trials comparing surgical and medical interventions.[23, 43, 44] Low recruitment rates not only have implications for internal and external validity, but may also lead to extended recruitment periods with implications for finance and resources. The potential exists for delaying the introduction of effective

treatment. Substantial amounts of public funds are invested in medical research, for example in 2016/2017, the National Institute of Health Research (NIHR) spent £207 million over their broad range of research programmes.[45] Given these potential negative consequences of incomplete RCTs, improving the design and conduct of such trials evaluating surgery and minimising the risk of failure is a priority.[44]

Methodological and practical challenges in the design and conduct of surgical trials have been discussed.[15, 24] Many of the challenges relate to the complex nature of the interventions being evaluated, which can have implications for the conduct of these types of trials. For example, in contrast to drug treatments, surgical interventions are often difficult to standardise as they usually consist of several interrelated components often (e.g. surgeon expertise, learning curve), many of which can have an important impact on the treatment effect.[15, 46] Implementing blinding of patients, care providers, and outcome assessors, is also challenging because of the nature of the interventions.[47, 48]

Before looking in more detail at trials that compare surgical and non-surgical interventions, the following section provides a general understanding of trial methodology.

The challenge of designing clinical trials

Developing a research question

The design of any type of clinical trial starts with identifying a clinical problem which is formulated into a research question.[49] This is a key stage of the research process. A clear research question will guide the design, conduct and provide a framework for the analysis i.e. to assess whether the intervention is better than (superiority trial), is at least not worse than (non-inferiority), or whether it is equally effective (equivalence trial) as a comparator.[49-51]

The commonly used acronym PICO, introduced in 1995 [52] and later expanded to PICOT,[53] is now a widely recognised strategy for developing research questions. Framing of the research question using this PICOT [52, 53] approach enables key components of a trial to be specified: target Population (P), the Intervention of interest (I), the Comparator intervention (C), key Outcomes (O), and the Time frame (T) over which the outcomes are assessed (Table 1).

The FINER criteria (Feasible, Interesting, Novel, Ethical and Relevant),[54] is also often used to define the desirable properties of a good research question, and suggestions on how to achieve each attribute.

Table 1: PICOT format for developing a research question [52, 53] (adapted from Bandholm et al, 2017)[51]

Letter	Stands for	Meaning
P	Population or population of interest	What patient population or problem are you trying to address?
I	Intervention or issue of interest	What will you do for the patient or problem?
C	Comparison with another intervention/issue	What are the alternatives to your chosen intervention?
O	Outcome of interest	What will be improved for the patient or problem?
T	Time frame	At what time following the intervention do you decide it is doing more good than harm?

For example:
Objective: The trial will investigate whether exercise therapy (Intervention) is more (superiority design and expected direction) effective than arthroscopic partial meniscectomy (Comparison group) in improving the primary outcome, patient reported knee function (Outcome of interest) at 24 month (Time) in middle-aged patients with degenerative meniscal tears (Population).

Trial design

A distinction in trial design is often made between an explanatory (efficacy) and pragmatic (effectiveness) trials.[55] Initially described by Schwartz and Lellouch in 1967,[55]

the terms represent two different approaches to trial design to address two different kinds of problems. Explanatory trials test a hypotheses to determine whether an intervention works in tightly controlled conditions with highly selected patients to achieve optimal efficacy and/or to understand the key mechanism of action.[56] As an explanatory trial aims to discover what components of the intervention 'work', they are more likely to try to constrain and/or measure the interaction, and include a placebo comparison.[57] Efforts are made to minimise all sources of variation, other than the interventions themselves.[58]

In contrast, pragmatic trials are aimed at providing information to inform real world clinical decisions about choice between alternative treatments.[58] Pragmatic trials are more likely to test a complex intervention e.g. surgery, as it would normally be delivered in clinical practice and target patients that are encountered in clinical practice.[58]

Rather than a dichotomy between the two approaches, trials may contain elements from each.[59] Table 2 describes some key differences between the explanatory and pragmatic approaches to trial design, such as, expertise in those delivering treatments, degree of standardisation of intervention protocol.

The development of the PRECIS (Pragmatic Explanatory Continuum Indicator Summary) tool,[59] updated to PRECIS-2 [60] was designed to help support trialists making design choices that are consistent with the intended purpose of their trial.[58]

Table 2: Key differences between trials with explanatory and pragmatic attitudes (from Zwarenstein et al.) [61]

	Explanatory attitude	Pragmatic attitude
Question	Efficacy: can the intervention work?	Effectiveness: does the intervention work when used in normal practice?
Setting	Well resourced, 'ideal' setting	Normal practice
Participants	Highly selected; poorly adherent participants and those with conditions which might dilute the effect are often excluded	Little or no selection beyond the clinical indication of interest
Intervention	Strictly enforced and adherence is monitored closely	Applied flexibility as would be in normal practice
Outcomes	Often short-term surrogates, or process measures	Directly relevant to participants, funders, communities and healthcare practitioners
Relevance to practice	Indirect: little effort is made to match the design of the trial to the decision making needs of those in the usual setting in which the intervention will be implemented	Direct: the trial is designed to meet the needs of those making decisions about treatment options in the setting in which the intervention will be implemented

Controlling bias

Bias refers to any systematic error arising from the design and conduct of a study, which may compromise the validity of the study.[62] The potential for bias can occur at different stages of the research process, and should be considered in the initial planning and study design, data collection, and analysis.[63] A description of the key components of trial design that aim to minimise bias are described below.

Random allocation

The main strength of an RCT, compared to other study designs (such as a cohort or case-control study), is its ability to minimise bias through random allocation of patients to different groups.[62] With random allocation, each participant has an equal probability of

being assigned to any given group, minimising the possibility of selection bias and therefore balances known and unknown confounding factors (e.g. severity of illness, comorbidities), which may affect outcome.[64] Study groups are as similar as possible at the outset, so that investigators can isolate and quantify the effect of the intervention they are studying. Random allocation, however, does not protect RCTs against other types of bias (such as performance bias, detection bias and attrition bias), which also may affect outcome.

Allocation concealment

In addition to random allocation, allocation concealment (e.g. central randomisation by phone or online system) is another key factor in the randomisation process that seeks to minimise selection bias.[65] The process prevents trial personnel and patients from knowing the random allocation sequence until assignment, so that decisions regarding participation are not influenced by this knowledge e.g. exclusion of certain patients based on their prognosis, and potentially introduce bias.[66]

Blinding

Blinding (also known as masking) refers to the practice of preventing patients, healthcare professionals, and those collecting and analysing data, from knowing which groups patients are randomised to.[64] Knowledge of treatment allocation may influence patients' perceptions about treatment and affect outcome, potentially leading to biased results, particularly when there are subjective outcomes.[64] Patients' may be less likely to comply with their allocated intervention, withdraw from the trial without providing outcome data, or seek additional interventions.[67] Knowledge of treatment received could also influence clinicians' management of patients during the trial, e.g. differential use of additional interventions, which can be a source of bias (performance bias).[64, 65, 68] Blinding of

outcome assessors also can help minimise the potential for differential assessment of the outcomes (detection bias) between the groups.[65]

Minimising loss to follow-up

Differential reasons for loss to follow-up following randomisation may also introduce bias (attrition bias).[67] Ideally, all patients who consent to participate in a trials would complete the study and provide outcome data. However, there may be several reasons for loss to follow-up, for example, patients may withdraw or become uncontactable. Approaches to minimise loss to follow-up are essential to prevent serious threats to validity.[67]

Intention-to-treat analysis

Although there are several different analysis approaches to estimate intervention effects, such as, “per protocol” or “treatment received”, most trialists agree that the primary analysis in a RCT should be an intention to treat (ITT) analysis.[65, 69] The ITT approach maintains the benefit of randomisation, i.e. that the intervention groups do not differ systematically with respect to measures and unmeasured prognostic factors.[65]

Pilot and feasibility studies

Given the potential challenges to conducting trials, pilot and feasibility studies, are increasingly seen as a means to explore potential challenges and enable trialists to optimise trial design and conduct.[70, 71] Identifying problems with recruitment, delivery of interventions or retention, ensures that money is not wasted on trials that might otherwise fail.[72] Quantitative methods can be used to assess key study logistics such as eligibility and recruitment. However, increasingly, quantitative and qualitative designs are recognised as being able to make an important contribution to the design of trials.[73-75] The

number of qualitative studies conducted alongside clinical trials is reported to be increasing, however, studies in surgical trials, remain rare.[76]

Studies have addressed aspects such as acceptability of a trial [77, 78] and feasibility of interventions, understanding challenges and optimising recruitment,[39, 79, 80] or exploring outcome measures to be used.[81] The majority of these studies however have been conducted alongside the main trial rather than at a pre-trial stage, where they could have the potential to explore important factors to trial design such as the level of equipoise or preference for treatment, therefore potentially optimising the conduct of the main trial.[82, 83]

Many of the design issues and challenges discussed when conducting surgical trials, can depend on the choice of comparator. This final section outlines the main types of comparisons in surgical trials and highlights how the choice of comparator may result in some of the specific challenges being potentially more problematic.

Choice of comparator

The efficacy or effectiveness of a surgical intervention can be evaluated using a range of different comparisons, as detailed below. The choice of comparator may result in some of the specific challenges being potentially more problematic. Table 3 outlines some potential challenges in the planning and conduct of surgical trials depending on the comparison.[15] Innovative solutions may be required based on the aim of the study.[15]

The 5 main comparisons:[84]

1. **Similar surgical procedures**, for example, the use of reamed or unreamed nails for fixation of tibial fractures.

2. **Substantially different surgical procedures**, for example, open versus laparoscopic hernia repair.
3. **Substantially different interventions**, for example, surgery versus medicine in the treatment of gastroesophageal reflux disease.
4. **Placebo surgery**, for example, arthroscopic debridement versus sham surgery for osteoarthritis.
5. **No surgery (no treatment)**

Table 3: Challenges to the planning and conduct of RCTs comparing surgical interventions with different types of comparator (modified from Ergina et al, 2009) [15]

	Similar surgical procedures (e.g. two-stage v three-stage postpartum perineal repair [85]	Substantially different surgical procedures (e.g. open v minimally invasive procedures [86]	Substantially different interventions Non-surgical treatment (e.g. back surgery v physiotherapy) [87]	Sham (placebo) surgery (e.g. stem cells for Parkinson's disease')[88]	No surgery (no treatment)
Patient reluctance to participate	Unlikely	Likely	Yes	Yes	Yes
Randomisation in operating theatre possible	Yes	Likely	No, because of different health-care providers	Yes	No, because of different health-care providers
Imbalance in surgical expertise	Unlikely	Likely	No, because of different health-care providers	No	No, because of different health-care providers
Poor compliance with allocation (i.e. crossover)	Unlikely	Yes	Yes	Yes	Yes
Contamination (i.e. lack of fidelity)	Yes	Unlikely	No	Unlikely	No

Difficulties with recruitment are especially evident in trials directly comparing surgery and non-surgical interventions.[23, 43, 44] Strong preferences for treatment of both clinicians and patients, can pose a challenge to recruitment where the interventions are markedly different.[89-91] The invasiveness and irreversibility associated with surgery procedures contrasts considerably with that of a non-surgical procedure and is likely contribute to patients reluctance to participate in trials with this type of comparison, making them particularly challenging to conduct.[92]

Understanding and managing potential challenges appropriately is key to the design and conduct of all clinical trials. Methodological challenges in trials that directly compare surgical and non-surgical interventions have not been fully explored.

Thesis aims and objectives

The aim of this thesis is to gain a greater understanding of one area of clinical trial methodology with a focus on surgical intervention evaluation. It is to explore the main methodological challenges to the design and conduct of trials that evaluate surgery using a non-surgical comparator (e.g. physiotherapy, drug treatment), explore potential solutions, and provide guidance for use in future studies.

The work contained in this thesis uses knowledge from quantitative and qualitative research to understand the challenge of conducting randomised controlled trials (RCT) that compare surgery with non-surgical interventions. It purposefully uses different methodologies to provide insight from different perspectives in order to more fully understand the challenges involved in this type of trial and therefore contribute to the design of future trials. The findings from this thesis may be transferable to trials comparing other disparate interventions

Innovation of this thesis:

The innovation of this thesis is to bring together knowledge from a range of quantitative and qualitative methodologies in order to understand the challenges of conducting randomised controlled trials (RCT) that compare surgery with non-surgical interventions.

Structure of the thesis

The structure of this thesis is schematically represented in Figure 1. The thesis consists of two parts:

Firstly, **Chapter 2** reports the findings from a systematic review of trials that identified any reported challenge of conducting randomised controlled trials that compare surgical with non-surgical interventions.

In the second part of the thesis, the specific challenges identified in Chapter 2 were then further explored in 4 chapters outlined below:

Chapter 3 reports the findings from a case study which explored challenges experienced during a multi-centre trial of a surgical versus non-surgical comparison (ACL SNNAP).

Chapter 4 reports findings from a qualitative evidence synthesis which explored the challenges of participating in trials that compare surgery with non-surgical interventions

Chapters 5 and 6 report findings from two qualitative research studies that explored the barriers to conducting a trial comparing surgical and non-surgical interventions for ACL injury, in (a) patients, and (b) clinicians.

Chapter 7 presents the conclusions and implications for future surgical versus non-surgical trials, along with recommendations for future research.

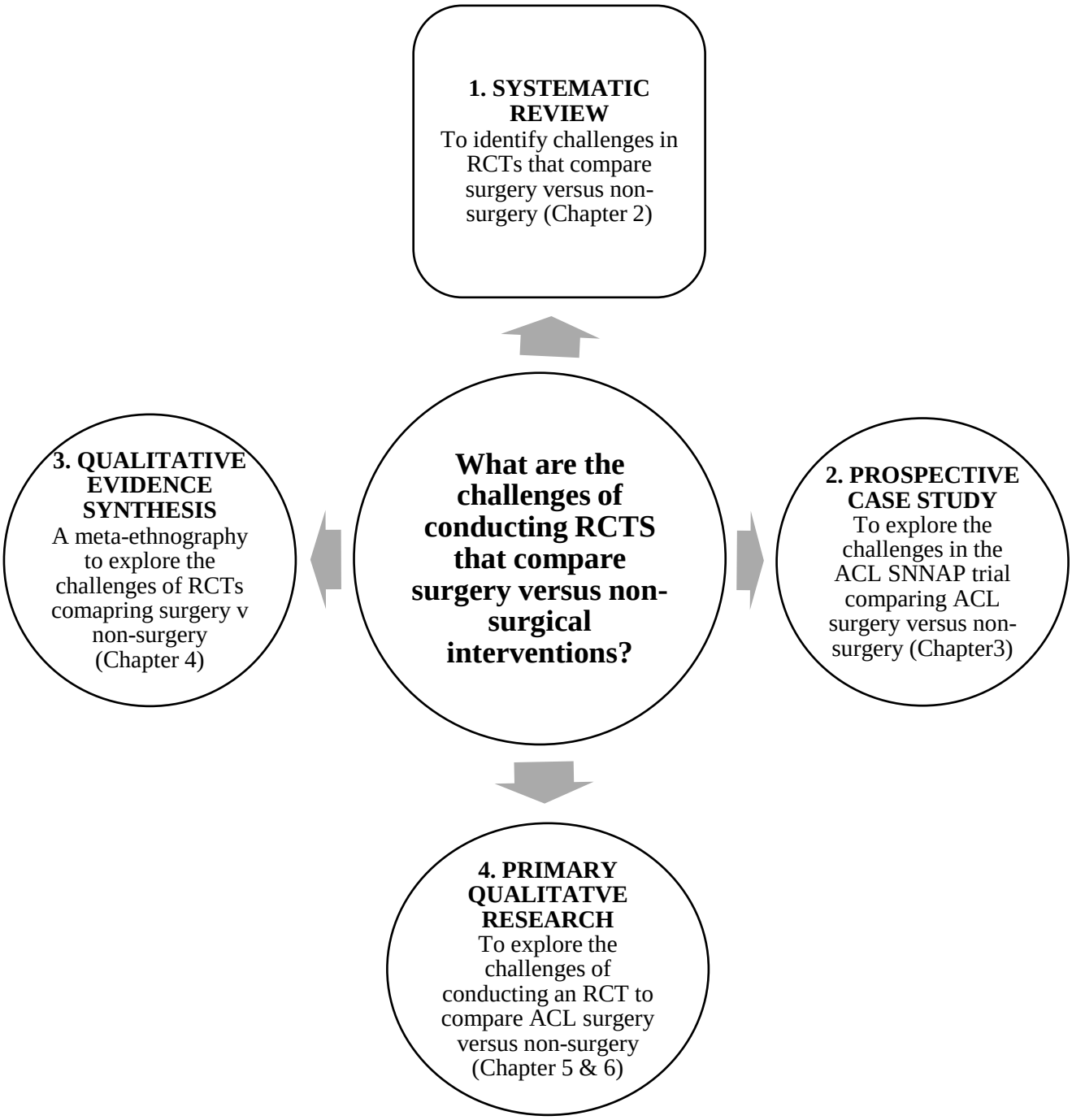


Figure 1: Structure of thesis

Chapter 2

Methodological challenges reported in trials with a surgical and non-surgical comparison: a systematic review

Introduction

As described in Chapter 1, randomised controlled trials (RCT) are considered the most robust research design to determine the effectiveness of interventions, however, conducting trials can be challenging. The process of developing a relevant and worthwhile question, designing the trial to control for bias, recruiting to time and target and minimising loss to follow-up, requires considerable planning and raises several potential challenges. The evaluation of surgery interventions are considered to add additional challenges to those that evaluate pharmacological interventions.[93] Evaluating surgical procedures can be complex, as they consist of several interrelated components (e.g. surgeon expertise, learning curve), which may impact on treatment effect. Only around half of initiated surgical trials reach their original recruitment target and failure to recruit is cited as the most frequent reason for premature closure of surgical RCTs.[42] Difficulties with recruitment are particularly evident when comparing surgical and non-surgical interventions.[43, 44, 94]

Understanding the challenges of trials that compare surgical and non-surgical interventions, which by their nature are starkly contrasting interventions, would enable trial teams to make more effective design choices and facilitate the delivery of such trials. Several reviews have explored reasons for recruitment difficulties in discontinued clinical trials in general [95, 96] and more specifically, surgical trials.[42] For example, overestimating the prevalence of eligible participants and the influence of strong treatment preferences of recruiters and participants were identified as the most frequently reported reasons for recruitment failure.[42, 95, 96] The feasibility of conducting surgical trials with a placebo comparison, have also been explored.[97] Methodological challenges reported in successfully completed trials of *surgical* and *non-surgical* comparisons have not been

systematically explored. With the focus on one clinical speciality, the aim of this study was to conduct a systematic review of published orthopaedic RCTs directly comparing surgical and non-surgical interventions in order to identify any challenges to their design and conduct.

Objectives

The objectives of the review were:

1. To systematically identify relevant published studies of RCTs directly comparing surgical and non-surgical interventions.
2. To describe the characteristics of the published trials of this comparison specifically those related to recruitment, non-compliance with allocated intervention and loss to follow-up.
3. To identify the main areas of risk of bias in trials with this type of comparison.
4. To identify factors affecting the design and conduct of trials with this type of comparison reported in the discussion section of the published studies and summarise the common themes

Method

Study design

A systematic review of orthopaedic trials that directly compared surgical and non-surgical interventions was conducted.

Types of studies

Published reports of randomised controlled trials comparing surgical and non-surgical interventions (e.g. medical treatment or physiotherapy) and qualitative studies that explored experiences of patients and healthcare professionals participating in trials of this

type of comparison were included. The review focused on trials evaluating musculoskeletal or orthopaedic interventions. Details of inclusion and exclusion criteria, based on the PICO ***(P***opulation, ***I***ntervention, ***C***omparator and ***O***utcome) format, are included in Table 4.

Table 4: Study inclusion and exclusion criteria

	Inclusion	**Exclusion**
Population:	Studies evaluating patients with orthopaedic or musculoskeletal pathology.	Studies with participants under 18 years of age.
Intervention:	Studies where at least one treatment arm includes a surgical procedure.	Interventions focusing on other aspects of the surgery such as anaesthesia or pharmacological and adjuvant treatments in surgical patients.
Comparator:	Studies where at least one treatment arm includes a non-surgical intervention (e.g. drug therapy, physiotherapy).	
Outcome:	There was no restriction made based on the outcomes reported in the identified studies.	
Studies:	Peer reviewed journal articles of randomised or quasi randomised trials comparing surgical and non-surgical interventions and qualitative studies exploring trials of this type of comparison published between January 2010 and end of August 2018. Articles in English language, published in any country. No restriction in terms of RCT design or trial purpose (superiority/noninferiority/equivalence).	Case series, observational studies, articles published as abstracts only, editorials, news, or correspondence sections.

Case series, observational studies, articles published as abstracts only, editorials, news, or correspondence sections were excluded. Only articles in English were reviewed. Studies of paediatric trials were also excluded because of the potential for challenges related only to the specific nature of the population being identified.

Search strategy

The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register. An initial search was conducted between January 2010 and December 2015. This search was updated in September 2018. The search strategy is included in Appendix 1.

The titles and abstracts were screened by two reviewers (LD and VT) and all retrieved reports and articles that did not meet the inclusion criteria were excluded. Full text articles were then assessed and discussed with a second reviewer with experience in conducting reviews (JC), to reach agreement on which papers to include.

Data extraction and synthesis

Each paper was uploaded into NVivo 11 (QSR International, Warrington, UK),[98] qualitative data analysis computer software, to manage the data. Data were extracted on the following areas: 1. General trial characteristics; 2. Numerical data on trial recruitment, non-compliance with allocation and loss to follow-up, 3. Risks of bias, and 4.Descriptive data exploring factors affecting the design and conduct of trials reported in the discussion sections of the trial report.

To reduce errors, data was extracted independently by two reviewers (LD and VT) and a single set of data was agreed. A descriptive analysis was undertaken.

1. General trial characteristics

A standardised data extraction form was used to collect information on the general trial characteristics of each study including: details of pathology or condition, type of surgical and non-surgical interventions compared, year of publication, country in which trial was

conducted, number of trial sites (single centre or multi-centre), length of follow-up period, and details of primary outcome.

2. Numerical data on recruitment, non-compliance and loss to follow-up

To explore any specific challenges related to recruitment, non-compliance with treatment allocation and loss to follow-up, descriptive numerical data was extracted related to:

1. Recruitment
    - Target and actual sample size.
    - Screening and randomisation: number of participants who were assessed, eligible, randomised and who declined participation.
    - Length of recruitment period.
2. Non-compliance with treatment allocation (overall and by treatment arm)

Non-compliance included any departure from treatment allocation following randomisation up to collection of primary outcome (or end of study, if primary outcome not reported).

3. Loss to follow-up (overall and by treatment arm)

For the purpose of this study, loss to follow-up included any primary outcome data that were not collected for randomised participants and any data excluded from analysis, for example participants who were randomised and subsequently excluded due to ineligibility (post randomisation exclusions).

3. Risk of bias

To identify the main areas of risk of bias, an assessment of the included studies was conducted using the Cochrane Collaboration's risk of bias tool (Version 1).[99] Appraisal criteria included:

- Sequence generation for randomisation,
- Concealment of allocation,
- Blinding of participants/personnel,
- Blinding of outcome assessment,
- Incomplete outcome data.

Each domain was rated as a 'low', 'high' or an 'unclear' risk of bias. All papers were reviewed by LD. A second reviewer (Ines Rombach) reviewed 20% of the papers, and any disagreements were resolved by discussion or referral to a third reviewer (Jonathan Cook).

4. Descriptive data exploring factors reported to affect the design and conduct of the trials

A thematic analysis of the discussion sections of the published reports was also conducted to identify challenges reported in conducting the trials. Each paper was read to identify the challenges and limitations reported by the authors. Preliminary coding was then undertaken for each study. Specific segments of the data, which had meaning relevant to the research question i.e. identified a specific challenge, were 'coded' and labelled with a phrase that captured the meaning of that data.[100] This data was extracted using NVivo (QSR International, Warrington, UK) [98] software. After initial coding was completed, a list of codes was compiled from all studies and added to an excel spreadsheet table. The full list of codes were organised, through constant comparison, into categories or 'piles' that reflected the key ideas. Data was then added to an excel spreadsheet table and preliminary headings were given to the themes. Thematic maps were also created to explore the patterns and connections between themes.[100] The themes were then discussed with two other reviewers (DB, JC) to ensure that they were

sufficiently clear and comprehensive and reflected the data. The final themes were used to structure the results section.

Results

Ninety studies were included from 239 full text articles screened. Figure 2 outlines the identification of potentially eligible studies and the reasons for exclusion.

As only two qualitative studies were identified, these were not included in this review. A separate review was conducted of qualitative studies and the search was expanded to include all clinical specialities. This review is presented in Chapter 4.

Table 5 provides a summary of the included studies, including condition examined, number of participants, number of trial centres, country, and trial interventions.

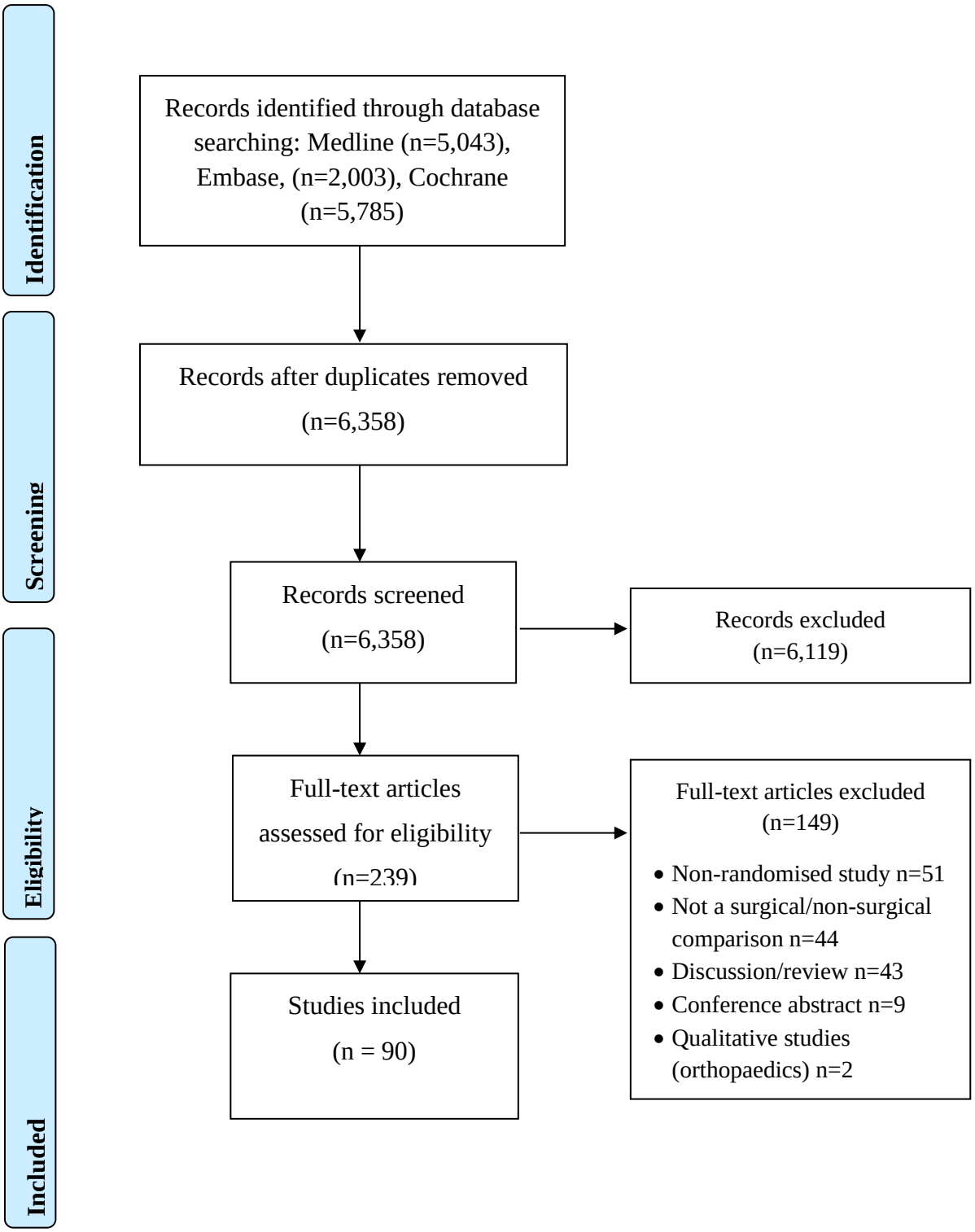


Figure 2: PRISMA flow diagram of included studies

Table 5: Summary of included studies

Trial	Condition	Participants	Centres	Country	Surgical Interventions	Non-surgical Intervention
2018						
Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multicentre randomised controlled trial [101]	Femoroacetabular Impingement Syndrome	348	23	UK	Hip arthroscopy	Individualised hip therapy
Comparison of plate osteosynthesis versus non-operative management for mid-shaft clavicle fractures-A prospective study [102]	Closed clavicle fractures (Robinson type 2B)	69	1	India	Plating	Conservative care: arm pouch, gradual assisted passive movement
Intra-articular distal radius fractures in elderly patients: a randomized prospective study of casting versus volar plating [103]	Intra-articular distal radius fractures	97	1	Spain	Open reduction and internal fixation with volar plate	Closed reduction and plaster immobilization
Arthroscopic surgery or physical therapy for patients with femoroacetabular impingement syndrome [104]	Femoroacetabular Impingement Syndrome	80	1	USA	Arthroscopic hip surgery	Physical Therapy
Comparative study of surgical and conservative treatments for fifth metatarsal base avulsion fractures (type I) in young adults or athletes [105]	Displaced fifth metatarsal base avulsion fractures	46	1	China	Closed reduction and fixation with percutaneous screw	Cast immobilisation
Comparison of surgical or nonsurgical treatment outcomes in patients with thracolumbar fracture with score 4 of TLICS [106]	Thoracolumbar fractures	50	1	Iran	Surgery (PSF pedicular screw, rod)	Nonoperative treatment

Subacromial decompression versus diagnostic arthroscopy for shoulder impingement: a randomised, placebo surgery controlled clinical trial [107]	Shoulder impingement symptoms	210	1	Finland	Arthroscopic subacromial decompression (ASD)/diagnostic arthroscopy	Exercise therapy
Proximal medial gastrocnemius recession and stretching versus stretching as treatment of chronic plantar heel pain [108]	Plantar heel pain	40	1	Norway	Proximal medial gastrocnemius recession	Physical therapy
A randomized controlled trial of arthroscopic capsular release versus hydrodilatation in the treatment of primary frozen shoulder [109]	Idiopathic frozen shoulder	50	1	UK	Arthroscopic capsular release	Hydrodilation
Effect of early surgery vs physical therapy on knee function among patients with nonobstructive meniscal tears. The ESCAPE randomized clinical trial [110]	Meniscal tears	321	9	Netherlands	Arthroscopic partial meniscectomy/	Physical therapy
2017						
Plate fixation compared with nonoperative treatment for displaced midshaft clavicular fractures [111]	Displaced midshaft clavicular fractures	160	16	Netherlands	Open reduction and plate fixation	Non-operative treatment
Posterior cervical transfacet fusion with facetal spacer for the treatment of single-level cervical radiculopathy: A randomized, controlled prospective study [112]	Single-level symptomatic forminal cervical stenosis without cervical myelopathy	119	1	Italy	Posterior cervical tranfacet fusion (PCTF)	Cervical traction technique
Surgery for Type B ankle fracture treatment: a combined randomised and observational study (CROSSBAT) [113]	Closed AO-type 44B1 distal fibula fracture	160	22	Australia, New Zealand	Surgical fixation using plate and screws	Walking boot, full weight bearing

Minimally invasive osteosynthesis with a bridge plate versus a functional brace for humeral shaft fractures [114]	Displaced humeral shaft fractures	110	1	Brazil	Surgical treatment with a bridge plate	Functional brace
The Clavicle Trial. A multicenter randomized controlled trial comparing operative with nonoperative treatment of displaced midshaft clavicle fractures [115]	Displaced midshaft clavicle fractures	302	20	UK	Open Reduction Internal Fixation/	Non-operative management: Sling immobilisation
Prolonged physiotherapy versus early surgical intervention in patients with lumbar disc herniation: Short-term outcomes of clinical randomized trial [116]	Lumbar disk herniation	60	1	Egypt	Early discectomy	Medically and prolonged physiotherapy
Prospective randomised trial of non-operative versus operative management of olecranon fractures in the elderly [117]	Isolated stable displaced fractures of the olecranon	19	2	UK	Tension band wiring or plate	Collar and cuff and supervised physiotherapy after 2 weeks
Conservative management equally effective to new suture anchor technique for acute mallet finger deformity: A prospective randomized clinical trial [118]	Acute Wehbe-Schneider type I A-B and II A-B mallet fingers	29	1	Turkey	Suture anchor technique	Conservative treatment
Six month outcomes from a randomised controlled trial of minimally invasive SI joint fusion with triangular titanium implants vs conservative management [119]	Chronic sacroiliac (SI) joint pain	109	9	Europe: Belgium, Germany, Italy, Sweden	Minimally invasive sacroiliac joint fusion (SIJF)	Optimization of medical therapy, individualised physical therapy
Treatment of displaced midshaft clavicle fractures: figure-of-eight harness versus anterior plate osteosynthesis [120]	Displace midshaft clavicle fractures	117	2	Brazil	Anteriorinferior plate osteosynthesis	Figure of eight harness

Arthroscopic subacromial decompression for subacromial should pain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial [121]	Subacromial shoulder pain	313	32	UK	Arthroscopic subacromial decompression (ASD)/Investigational arthroscopy	No treatment
2016						
Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up [122]	Degenerative meniscal tear	140	2	Norway	Arthroscopic partial meniscectomy	Exercise therapy
Comparison of open acromioplasty, arthroscopic acromioplasty ad physiotherapy in patients with subacromial impingement syndrome: a prospective randomised study [123]	Sub acromial impingement syndrome	87	1	Sweden	Arthroscopic subacromial decompression (ASD)/Open acromioplasty	Physiotherapy
Percutaneous vertebroplasty versus conservative treatment in aged patients with acute osteoporotic vertebral compression fractures	Osteoporotic vertebral compression fractures	135	1	China	Percutaneous vertebroplasty	Conservative therapy
A prospective, randomized, multicentre, open-label clinical trial comparing intradiscal biacuplasty to conventional medical management for discogenic lumbar back pain [124]	Lumbar discogenic pain	67	9	Canada	Intradiscal biacuplasty	Conventional medical management
A prospective randomized trial comparing surgical and nonsurgical treatments of acute achilles tendon ruptures [125]	Achilles tendon ruptures	60	1	Finland	End to end open repair	Cast immobilization followed by functional orthosis

Comparison of clinical and radiologic outcomes between non-operative and operative treatment in 5th metatarsal base fractures (Zone 1) [126]	5th Metatarsal base fractures (Zone 1)	18	1	South Korea	Open Reduction Internal Fixation	Short leg cast
A small group Whiplash-Associated-Disorders (WAD) patients with central neck pain and movement induced stabbing pain, the painful segment determined by mechanical provocation: [127]	Whiplash associated disorders	49	1	Sweden	Cervical fusion surgery	Multimodal rehabilitation
A minimally invasive fixation technique for selected patients with fifth metacarpal neck fracture [128]	Fifth metacarpal neck fracture	24	1	Turkey	Minimally invasive surgical fixation	Splinting
MILD is an effective treatment for lumbar spinal stenosis with neurogenic claudication: MiDAS ENCORE Randomized controlled Trial [129]	Lumbar Spinal Stenosis	302	26	USA	Lumbar decompression (MILD procedure)	Lumbar interlaminar epidural steroid injections
The curative efficacy of arthroscopic therapy in treating anterior cruciate ligament rupture with secondary osteoarthritis [130]	Anterior cruciate ligament rupture secondary OA	68	1	China	ACL reconstruction, OA debridement & functional rehabilitation training	Drug therapies, early functional rehabilitation
2015						
Surgical vs Nonsurgical Treatment of Adults With Displaced Fractures of the Proximal Humerus: The PROFHER Randomized Clinical Trial [131]	Displaced fractures of the proximal humerus involving the surgical neck	250	32	UK	Internal fracture fixation / hemiarthroplasty	Sling and active rehabilitation
Surgery versus nonsurgical treatment of lumbar spinal stenosis: a randomized trial [132]	Lumber spine stenosis	169	2	USA	Surgical decompression	Physical therapy

Which is better to multiple rib fractures, surgical treatment or conservative treatment? [133]	Multiple rib fractures	164	1	China	Open reduction internal fixation	Conservative treatment
Comparing surgical repair with conservative treatment for degenerative rotator cuff tears: a randomised controlled trial [134]	Degenerative, non-traumatic full thickness rotator cuff tears	56	3	Netherlands	Surgery	Conservative treatment
Conservative Treatment Versus Arthroscopic Assisted Screw Fixation of Scaphoid Waist Fractures – A randomised Trial with Minimum 4 Year follow Up [135]	Acute non- or minimally displaced scaphoid waist fractures	45	1	Sweden	Arthroscopic assisted screw fixation	Conservative treatment with a cast
Surgical treatment of displaced middle-third clavicular fractures: A prospective, randomized trial in a working compensation population [136]	Displaced middle-third clavicular fractures	76	1	Chile	Open reduction and internal fixation (ORIF)	Conservative treatment
Conservative treatment has comparable outcome with bouquet pinning of little finger metacarpal neck fractures: a multicentre randomized controlled study of 85 patients [137]	Little finger metacarpal neck fractures	85	3	Norway	Closed reduction and bouquet pinning	Conservative treatment without reduction
Multicenter Randomized Clinical Trial of Nonoperative Versus Operative Treatment of Acute Acromio-Clavicular Joint Dislocation [138]	Acute acromio-clavicular (AC) joint dislocations	83	11	Canada	Hook plate fixation	Non operative treatment
A Randomized, Controlled Trial of Total Knee Replacement [139]	Moderate to severe Osteoarthritis who were eligible for a unilateral total knee replacement	100	2	Denmark	Total knee replacement followed by 12 wks. of nonsurgical treatment	12 weeks of non-surgical treatment

Sacroiliac Joint Fusion Using Triangular Titanium Implants vs. Non-Surgical Management: Six-Month Outcomes from a Prospective Randomized Controlled Trial [140]	Chronic sacroiliac (SI) joint pain	158	19	USA	SI joint fusion	Non-surgical management
Manual physical therapy versus surgery for carpal tunnel syndrome: A randomised parallel-group trial [141]	Carpal tunnel syndrome	120	1	Spain	Open or endoscopic decompression and release of carpal tunnel	Physical therapy
2014						
Operative versus non-operative treatment for closed, displaced, intra-articular fractures of the calcaneus: randomised controlled trial [142]	Acute displaced, intra-articular fractures of the calcaneus	151	22	UK	Open reduction and internal fixation	Non operative treatment
Percutaneous vertebroplasty compared with conservative treatment in patients with chronic painful osteoporotic spinal fractures [143]	Chronic painful osteoporotic compression fractures	96	1	China	Percutaneous vertebroplasty	Conservative treatment
Knee arthroscopic surgery is beneficial to middle-aged patients with meniscal symptoms: A prospective, randomised, single-blinded study [144]	Meniscal symptoms	150	1	Sweden	Knee arthroscopy	Exercise programme
Treatment of non-traumatic rotator cuff tears: A randomised controlled trial with one-year clinical results [145]	Non traumatic tears of the supraspinatus tendon	180	3	Finland	Acromioplasty/rotator cuff repair, acromioplasty and physiotherapy	Physiotherapy
Recompression in new levels after percutaneous vertebroplasty and kyphoplasty compared with conservative treatment [146]	Osteoporotic vertebral compression fracture	290	1	China	Percutaneous vertebroplasty, kyphoplasty	Conservative treatment

The treatment of displaced intra-articular distal radius fractures in elderly patients [147]	AO type C distal radial fracture	185	12	Germany	ORIF	Closed reposition and casting
Outcomes and complications of fractures of distal radius (AO type B and C): volar plating versus nonoperative treatment [148]	Distal radius fractures (AO type B and C)	64	1	India	Volar plating	Closed manipulation above elbow plaster of Paris cast application
2013						
Surgery versus Physical Therapy for a Meniscal Tear and Osteoarthritis [149] MeTeOR trial	Meniscal tear and Osteoarthritis	351	7	USA	Surgery and postoperative physical therapy	Standardised physical therapy (with the option to cross over to surgery at the discretion of the patient and surgeon)
Open Reduction and Plate Fixation Versus Non operative Treatment for Displaced Midshaft Clavicular Fractures A Multicenter, Randomized, Controlled Trial [150]	Displaced midshaft clavicular fractures	200	3	UK	Open reduction and plate fixation	Non operative treatment
Operative Versus Non operative Treatment of Displaced Intra-Articular Calcaneal Fractures A Prospective, Randomized, Controlled Multicenter Trial [151]	Intra-articular calcaneal fracture	82	5	Sweden	Open reduction internal fixation	Non operative treatment
Surgical versus nonsurgical treatment of cervical radiculopathy [152]	Cervical radiculopathy	68	3	Sweden	Anterior cervical decompression and fusion combined with structured physiotherapy	Structured physiotherapy
A prospective study comparing conservative with operative treatment in patients with a floating shoulder including assessment of the prognostic value of the glenopolar angle [153]	Floating shoulder - fracture of the clavicle and neck of the scapula	25	1	India	Fixation	Conservative treatment

A comparative study of meniscectomy and nonoperative treatment for degenerative horizontal tears of the medial meniscus [154]	Degenerative horizontal tear of the posterior horn of the medial meniscus	108	1	Korea	Arthroscopic meniscectomy	Non operative treatment
Prospective randomized controlled trial of operative rib fixation in traumatic flail chest [155]	Flail chest injury fractured ribs	46	1	Australia	Operative fixation	Best practice mechanical ventilator management
Does laminoplasty really improve neurological status in patients with cervical spinal cord injury without bone and disc injury? A prospective study about neurological recovery and early complications [156]	Cervical spinal cord injury	25	1	Japan	Laminoplasty	Rehabilitation
Stable surgical repair with accelerated rehabilitation versus nonsurgical treatment for acute Achilles tendon ruptures: a randomized controlled study [157]	Acute achilles tendon rupture	100	1	Sweden	Surgical	Non-surgical treatment
Operative vs conservative treatment of traumatic patellar dislocation: Results of a prospective randomized controlled clinical trial [158]	Patella dislocation	24	6	Germany	Operative	Conservative
2012						
Sling compared with plate osteosynthesis for treatment of displaced midshaft clavicular fractures: a randomized clinical trial [159]	Displaced midshaft clavicular fractures	32	1	Finland	Plate osteosynthesis	Sling c
Treatment of trigger finger: randomized clinical trial comparing the methods of corticosteroid injection, percutaneous release and open surgery [160]	Trigger finger	150	1	Brazil	Percutaneous release and open surgery	Corticosteroid injection

Operative versus nonoperative treatment of unstable lateral malleolar fractures: a randomized multicenter trial [161]	Unstable lateral malleolar fractures	81	6	Canada	Open reduction and internal fixation and	Non-operative treatment
Surgical treatment with an angular stable plate for complex displaced proximal humeral fractures in elderly patients: a randomized controlled trial [162]	Displaced, unstable three or four part proximal humerus fracture	50	1	Canada	Open reduction Internal fixation	Non-operative treatment including closed reduction if displaced.
Shoulder adhesive capsulitis: manipulation and arthroscopic arthrolysis or intra-articular steroid injections? [163]	Idiopathic adhesive shoulder capsulitis	46	1	Italy	Manipulation and arthroscopic arthrolysis	Intra-articular steroid injections
Hemiarthroplasty for humeral four-part fractures for patients 65 years and older: a randomized controlled trial [164]	Four part fractures of the proximal humerus	50	1	Netherlands	Hemiarthroplasty	Non operative
Result of percutaneous disc decompression using nucleoplasty in Thailand: a randomized controlled trial [165]	Radicular or axial low back pain secondary to contained herniated discs	64	1	Thailand	Nuceoplasty	Conservative treatment
Treatment of unstable intraarticular fracture of distal radius: POP casting with external fixation [166]	Unstable intraarticular fracture of distal radius	60	1	Pakistan	External fixation/	Above-elbow Plaster of Paris
Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: A 12-month randomized follow up, controlled trial [167]	Vertebral fractures	125	1	Spain	Vertebroplasty	Conservative

2011						
Sanders type II calcaneum fractures–surgical or conservative treatment? A prospective randomized trial [168]	Sanders type II calcaneum fractures	30	1	India	Operative	Non operative
Hemiarthroplasty versus nonoperative treatment of displaced 4-part proximal humeral fractures in elderly patients: a randomized controlled trial [169]	Four part fractures of the proximal humerus	55	1	Sweden	Hemiarthroplasty	Non operative treatment
Surgical versus nonsurgical treatment of selected patients with discogenic low back pain: a small-sized randomized trial [170]	Discogenic low back pain	41	1	Japan	Anterior discectomy versus	Exercise
Operative compared to non-operative treatment of displaced intra-articular calcaneal fractures [171]	Displaced intra-articular calcaneal fractures	72	1	Iran	Open reduction and rigid internal fixation	closed reduction and cast immobilization
Comparison between operative and nonoperative treatment methods in the management of comminuted fractures of the clavicle [172]	Comminuted fractures of the clavicle	60	1	Iran	Open reduction and internal fixation	Closed treatment
Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: Two year follow-up of randomised study [173]	Chronic low back pain	173	5	Norway	Disc prosthesis	Rehabilitation
Operative versus non-operative treatment of acute rupture of tendo Achilles: a prospective randomised evaluation of functional outcome [174]	Acute achilles tendon rupture	80	1	UK	Operative repair using an open technique	Non operative treatment in cast

Conservative versus surgical management of Pipkin type I fractures associated with posteriordislocation of the hip: a randomised controlled trial [175]	Pipkin type 1 fractures (hip)	16	1	China	Closed reduction followed with fragment excision	Closed reduction
Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial [176]	Acute vertebral compression fractures	300	21	Austria, Belgium, France Germany, Italy, Sweden, Netherlands, UK	Balloon kyphoplasty	Non-surgical treatment
A prospective randomized trial comparing nonoperative treatment with volar locking plate fixation for displaced and unstable distal radial fractures in patients sixty-five years of age and older [177]	Displaced and unstable distal radial fractures	73	1	Austria	Volar locking plate fixation	Nonoperative treatment
Comparative prospective randomized study comparing conservative treatment and percutaneous disk decompression for treatment of intervertebral disk herniation [178]	Intervertebral disk herniation	31	1	Greece	Percutaneous disk decompression	Conservative treatment
Randomized prospective study about the traumatic patellar dislocation: The conservative treatment and the medial patellofemoral ligament reconstruction with patellar tendon-a minimum 2-year follow-up [179]	Patella dislocation	41	1	Brazil	Reconstruction of the medial patellofemoral ligament	Non operative treatment

Internal fixation versus nonoperative treatment of displaced 3-part proximal humeral fractures in elderly patients: a randomized controlled trial [180]	Three part fractures of the proximal humerus	60	1	Sweden	Locking plate	Immobilisation and physiotherapy
Vertebral body reconstruction system B-Twin® versus corset following non-osteoporotic thoracic and lumbar fracture. Functional and radiological outcome at 12 month follow-up in a prospective randomized series of 50 patients [181]	Non-osteoporotic thoracic and lumbar fracture	50	1	Italy	B-Twin spacer (vertebral body reconstruction technique)	Corset
2010						
A Randomized Trial of Treatment for Acute Anterior Cruciate Ligament Tears [182, 183]	Acute anterior cruciate ligament tears	121	2	Sweden	Structured rehabilitation plus early ACL reconstruction	Structured rehabilitation with the option of later ACL reconstruction if needed
Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial [184]	Osteoporotic vertebral compression fractures	202	6	Belgium	Percutaneous vertebroplasty	Conservative treatment
Twelve-months follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with percutaneous vertebroplasty: a clinical randomized study [185]	Acute or sub-acute osteoporotic vertebral fractures	50	1	Denmark	Percutaneous vertebroplasty	Conservative treatment
Acute achilles tendon rupture: a randomized, controlled study comparing surgical and nonsurgical treatments using validated outcome measures [186]	Acute achilles tendon rupture	97	1	Sweden	Surgical treatment	Nonsurgical treatments

Manipulation or microdiskectomy for sciatica? A prospective randomized clinical study [187]	Lumbar disc herniation	40	1	Canada	Manipulation	Microdiskectomy
Comparison between surgery and physiotherapy in the treatment of small and medium-sized tears of the rotator cuff: A randomised controlled study of 103 patients with one-year follow-up [188]	Small and medium sized full thickness tears of the rotator cuff	103	1	Norway	Operative treatment	Physiotherapy
Operative versus nonoperative treatment of acute Achilles tendon ruptures: a multicenter randomized trial using accelerated functional rehabilitation [189]	Acute achilles tendon rupture	144	2	Canada	Operative treatment	Non operative treatment
Plasma disc decompression for contained cervical disc herniation: a randomized, controlled trial [190]	Cervical disc herniation	120	1	Italy	Plasma disc decompression (Coblation SpineWand device)	Conservative care

1. General trial characteristics

Table 6 provides a summary of general trial characteristics, including condition examined, type of non-surgical intervention, year of publication and region trial conducted. Over half of the studies were conducted in Europe (n=51/90; 57%). The majority of the studies were of a single centre RCTs (n=56; 62%), compared with 34 (38%) multi-centre studies. Forty-four (49%) of the studies were trials of fracture management.

The non-surgical interventions included in the trials varied greatly and ranged from those involving a single modality, such as the provision of a device e.g. brace or splint or the administration of a drug (with minimal ongoing input from a health professional), to interventions that involved a package of care (e.g. progressive individualised exercise programs that may have been combined with the use of splinting, braces). Most of the studies compared surgery with an intervention that included a physiotherapy or exercise component (Table 6). In two studies,[156, 165] it was difficult to determine the content of the conservative intervention as there was minimal intervention description. The primary outcome was reported in 66/90 studies (73%), with the majority being subjective outcomes (n=45; 68%).

Table 6: Summary of general trial studies

Characteristic	Total (N=90)	(%)
Condition		
Disk Herniation	4	4%
Acromioclavicular joint dislocations	1	1%
Adhesive Capsulitis	2	2%
Carpal Tunnel Syndrome	1	1%
Cervical radiculopathy	1	1%
Femoroacetabular Impingement Syndrome	2	2%
Fracture	44	49%
Ligament injury	7	8%
Low back Pain	3	3%
Lumbar discogenic pain	1	1%
Mallet fingers	1	1%
Meniscal injury	5	6%
Patella Dislocation	2	2%
Planter Heel Pain	1	1%
Rotator cuff tears	3	3%
Sacroiliac joint pain	2	2%
Severe Knee Osteoarthritis	1	1%
Spinal Cord Injury	1	1%
Stenosis	3	3%
Subacromial shoulder pain	3	3%
Trigger finger	1	1%
Whiplash	1	1%
Non-surgical intervention		
Conservative management/ non-surgical management	2	2%
Current best practice mechanical ventilator management	1	1%
Drug intervention	7	8%
Elevation, ice, graduated weight bearing	1	1%
Hydrodilatation & standardised physiotherapy	1	1%
Immobilisation with Cast/Brace/Sling plus physiotherapy	29	32%
Immobilisation with Cast/Brace/Splint	12	13%
Manual physical therapy	2	2%
Minimal treatment intervention: daily walking an stretching	1	1%
Multimodal intervention (including physiotherapy)	8	9%
No treatment (specialist reassessment)	1	1%
Physiotherapy and cognitive intervention	1	1%
Physiotherapy/Exercise	21	23%
Spinal traction	2	2%

Year of publication	N	%
2018	10	11
2017	11	12
2016	10	11
2015	11	12
2014	7	8
2013	10	11
2012	9	10
2011	14	15
2010	8	9

Region	N	%
Africa	1	1
America	5	6
Asia	20	22
Canada	6	7
Europe	51	57
South America	5	6

2. Numerical data on recruitment, non-compliance and loss to follow-up

Table 7 provides as summary on the data on trial recruitment, non-compliance and loss to follow-up.

a. Recruitment

- **Target and actual sample size.**

Only sixty two (69%) of the studies reported a target sample size. The recruitment target was not met in ten (16%) of these studies.[107, 117, 123, 132, 134, 147, 158, 167, 187, 189] The target sample size was recalculated in two additional studies; the initial plan to stratify according to activity level was abandoned because of low recruitment of subjects with moderate activity levels in one study [182] and an error in sample size calculation was the reason reported in the other study.[111]

- **Screening and randomisation**

Only 60% of the studies (n=54) reported the overall number of patients screened, and number of people excluded for not meeting the inclusion criteria (median 30% IQR 4,64% range 0-96%). Details specifying the reasons for ineligibility were not routinely reported.

The number of eligible patients who declined participation was only reported in 52% of studies (n=47). Of the patients eligible to participate, a median of 32% (IQR 15,54%, range 1-74%) declined. On average, the percentage of eligible patients declining participating was higher in the multi-centre studies (median 48% IQR 21,58% range 1-74%), than in single-centre studies (median 23% IQR 12,35% range 4-55%). The level of detail recorded for reasons why eligible patients declined participation varied between trials.

The average number of patients recruited and randomised overall was 82 (IQR 50,150 range 16-351). On average, more patients were recruited in the multi-centre trials (median 159 IQR 89,208 range 65-351), than in the single centre studies (median 60 IQR 46,97 range 16-290).

- **Length of recruitment period**

A similar length of recruitment period was reported in both single centre (median 36 months IQR 23,48 range 5-120) and multi-centre studies (median 37 months IQR 31,47 range 11-102). However, on average, the number of patients recruited in the multi-centre studies was almost twice as many as in the single centre studies (Table 7). The reason for recruitment taking almost five years in one single centre study, was reported to be due to the low incidence of the pathology (four part fracture of proximal humerus).[164] In three studies, recruitment was stopped early because of much lower than expected recruitment

rates and limited resources.[123, 132, 147] One further study recruitment was stopped early because of a high rate of complications in the surgical arm.[117]

b. Non-compliance with treatment allocation

More than half of the studies (n=55; 61%) reported a degree of non-compliance with treatment allocation i.e. any departure from treatment allocation following randomisation. The average amount of non-compliance was only 3% (IQR 0,8% range 0-38%), there were some trials where level of non-compliance was more problematic and was reported to be over 20%.[104, 112, 121, 127, 132, 147, 187] There were also differences in the percentage of non-compliance between treatment arms, with greater levels of non-compliance in the non-surgical treatment arm (median 3% IQR 0,12% range 0-70%) compared to the surgical arm (median 0% IQR 0,5% range 0-32%).

A number of studies included a crossover component in their design. One study included a formal option for cross over to surgery in the non-surgical group, if chosen by the participant, provided pre specified criteria were met.[182] In two other studies,[124, 140] cross-over to surgery was also permitted after the 6 month primary outcome period. Seven additional studies reported that patients in the non-surgical group were informed that they could 'cross over' to surgery if there was no improvement, or if the indication for surgery arose.[107, 110, 111, 132, 144, 149, 167] Conversion to surgery, in cases of significant loss of reduction of fracture, was permitted in the protocol of two additional studies.[147, 161]

c. Loss to follow-up

Length of follow-up was similar in both the single and multi-centre studies with an average follow-up period of 12 months. Sixty four (71%) studies reported having some missing primary outcome data (median 9% IQR 0,14% range 0-37%), and differences in percentage of loss to follow-up was similar between treatment arms; surgical 8 % (IRQ

0,14% range 0-36%) and non-surgical intervention 8% (IQR 0,15% range 0-38%). Differences however existed in the amount of missing data between single (median 5% IQR 0, 13% range 0-37%) and multi-centre studies (median 11% IQR 8, 14% range 0-23%).

Table 7: Summary on the data on trial recruitment, non-compliance and loss to follow-up.

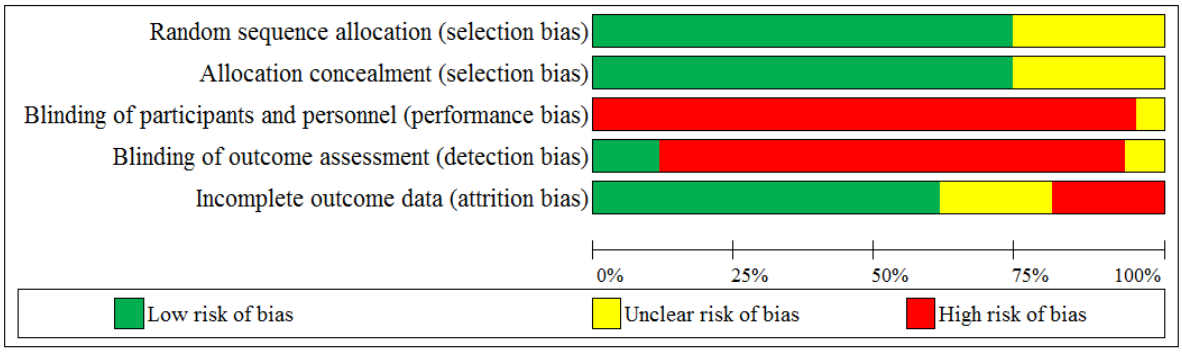
	All studies (N= 90)	**Single-centre studies (n= 56)**	**Multi-centre studies (n= 34)**
Number of sites	1 (1, 3), 1-32	1	6 (3, 18), 2-32
Number of participants recruited	82 (50, 150), 16-351	60 (46, 97), 16-290	159 (89, 208), 65-351
Length of recruitment	36 months (25, 48), 5-120	36 months (23, 48), 5-120	37 months (31, 47), 11-102
Length of follow-up	12 months (12, 24), 2-52	12 months (12, 24), 2-52	12 months (12, 24), 3-24
% screened patients excluded	30% (4-64%), 0-95%	19% (4, 40%), 0-70%	49% (5, 75%), 0-91%
% eligible refused	32% (15%-54%) 1-74%	23% (12, 35%), 4-55%	48% (21, 58%), 1-74%
Non-compliance with treatment allocation	3% (0%-8%) 0-38%	0% (0%-5%) 0-38%	6% (2%-11%) 0-29%
▪ Surgical arm	0% (0%-5%), 0-32%	0% (0%-2%), 0-32%	3% (0%-7%), 0-32%
▪ Non-surgery arm	3% (0%-12%), 0-70%	0% (0%-10%), 0-70%	6% (2%-14%), 0-57%
Loss to follow-up	9% (0-14%), 0-37%	5% (0-13%),0-37%	11% (8-14%), 0-23%
▪ Surgical arm	8 % (0, 14%), 0-36%	1% (0-11%), 0-36%	11% (8-14%), 0-28%
▪ Non-surgical arm	8% (0, 15%), 0-38%	2% (0-14%), 0-38%	10% (7-16%), 0-27%

Median (interquartile range, range)

3. Risk of bias

An assessment of the risk of bias was conducted for all studies. A summary of the results is included below in Table 8. Blinding patients to treatment allocation was not possible given the nature of the interventions. However, because of the subjective and self-reported nature of the outcomes, the majority of studies were assessed as having a potential high risk of bias. Blinding of outcome assessment was 'unclear' in a number of studies or not performed, as assessors were aware of treatment assignment, and was therefore judged as a high risk of bias.

Table 8: Assessment of each risk of bias item presented as a % across all studies (n = 90)



4. Descriptive data exploring factors reported to affect the design and conduct of studies

Factors affecting the design and conduct of trials with this type of comparison, reported in the discussion section of the published studies were coded and summarised into six themes (Table 9), and detailed below.

Difficulty implementing blinding (intervention/outcome assessment)

Blinding patients to treatment allocation was described as not possible given the nature of the interventions being evaluated.[101, 104, 107, 108, 111, 113, 115, 117, 119, 121, 125, 129, 131, 141, 145, 149, 155,

[159, 191, 192] Studies described how patients may have been affected by their knowledge of treatment assignment, especially as subjective outcome measures were used, leading to bias and a potentially exaggerated treatment effect.[107, 119, 121, 131, 176, 178, 184, 191] Although, both treatments were acknowledged to have a potential placebo effect, surgery was considered to have greater placebo effects compared with non-surgical interventions.[122, 139] The inclusion of a sham or placebo group was considered in some trials; [101, 139, 149] However, ethical and logistical difficulties were discussed as reasons for this not to be feasible. One study described the challenges of implementing blinding of outcome assessment because of practical challenges, such as staff availability and resources.[157]

2. Recruitment difficulties

Recruitment difficulties were discussed in 15 studies.[104, 111, 122, 123, 125, 132, 134, 137, 142, 147, 149, 152, 159, 164, 173] Problems with recruitment were described in some trials to result in not reaching target sample size,[123, 132] early closure [147] or unequal numbers of participants in treatment arms, making interpretation of outcome difficult.[111, 134, 147]

Recruitment difficulties were described as being due to three factors: patients' treatment preference, clinician preference and staffing issues. Details are described below.

a. Patients' treatment preference

Patients' preference for particular treatments was described as a barrier to participation that made recruitment challenging.[125, 132, 134, 137, 149, 152, 173] The strength of particular treatment preferences varied depending on the particular trial.

Table 9: Factors reported to affect the design and conduct of surgical versus non-surgical studies

	Theme
1.	**Difficulty implementing blinding (intervention/outcome assessment)**
	a. Nature of interventions compared.
	b. Practical challenges related to blinding of outcome assessment
2.	**Recruitment difficulties**
	a. Patients' treatment preference.
	b. Clinicians' treatment preference.
	c. Staffing issues influencing recruitment.
3.	**Complexity of intervention content and delivery**
	a. Standardisation of intervention.
	• Variation between sites in delivery of interventions.
	• Individual differences in clinical presentation.
	b. Clinician experience / learning curve.
	c. Insufficient evidence to guide decision making on content of intervention.
4.	**Timing of assessments**
	a. Differential delays in receiving trial intervention e.g. hospital waiting lists.
	b. Variation in time to effect for the different interventions.
5.	**Non-compliance with allocated treatment intervention**
	a. Potential for crossover has asymmetry i.e. crossover could not occur in the surgical arm once the surgery had been performed
6.	**Differential loss to follow-up**
	a. Potential for differential loss to follow-up.
	b. Potential for imbalance in patients excluded (post-randomisation exclusions based on surgical findings).

Strong preference for surgical treatment was reported in some trials as creating difficulty with recruitment.[132, 134, 152, 173] Having previously undergone conservative treatment or being referred specifically for surgical treatment, were described as factors influencing patients' preference towards surgical treatment.[134, 152, 173] Other studies reported difficulties with recruitment either because patients had a baseline preference for non-surgical treatment [137] or a preference for one of the treatments on offer.[149] The trial not being able to recruit particular patient groups was discussed (for example patients with the worst symptoms not agreeing to participate).[152, 159] A statement from the national health board indicating that 'surgical treatment may provide no benefit for this patient group' was reported in one study to have a positive impact on recruitment.[144]

b. Clinician preference

Clinicians' preference for particular treatments was also described as a potential factor influencing recruitment. Studies described how an evaluation by an orthopaedic surgeon, to confirm eligibility prior to participation, might result in selective enrolment and therefore slow recruitment.[104, 149] Patients varying presentation of a pathology or injury was reported to affect clinicians' decision making regarding treatment and trial participation.[101, 118, 142] Availability of new scientific evidence, during a lengthy recruitment period, was also considered in one study to influence clinicians' views in favour of surgical treatment, resulting in a subsequent reduction in recruitment.[111]

c. Staffing issues influencing recruitment

Issues with staffing and funding constraints, was also reported to be challenging in a number of multi-centre studies and was described to contribute to variability in performance between recruiting sites.[113, 142]

3. Complexity of intervention content and delivery

A number of factors were discussed in relation to intervention content and delivery. Although several studies described the interventions as being highly standardised and delivered on the basis of a defined protocol,[104, 106-108, 122, 123, 131, 139, 142, 145, 149, 151, 157, 161, 162, 173, 182] in other trials variation in patient presentation meant that the intervention would have to be adapted to individual characteristics.[119, 188] For example type of exercises, frequency and duration of treatment individually adjusted according to the clinical findings and patients' response to treatment.[188] In other cases, variation between sites in the delivery of interventions, such as the type of surgical implants, content of non-surgical care was reported to potentially affect outcome.[111, 119, 136, 176] Clinician experience was also discussed as a factor that could potentially affect patient outcome.[134, 137, 142, 173]

Complex interventions consisting of separate components (for example, surgery and post-operative rehabilitation or multimodal non-surgical treatments) was considered in some trials to potentially affect outcome, or make it difficult to ascertain the mechanism of effect.[113, 121, 139, 157, 173]

Insufficient evidence available to guide decision making on intervention content, particularly in relation to the non-surgical interventions e.g. frequency and dose of therapy, was also challenging and could potentially lead to biased comparisons.[108, 140, 141, 144]

4. Timing of assessments

Differential delays in patients receiving trial interventions, for example due to hospital waiting lists, was highlighted in a number of studies as having the potential to affect interpretation of outcome.[101, 121, 145, 184] One study indicated that additional follow-up

assessments were included in the trial design for patients who had significant delays waiting for surgery to enable appropriate comparisons.[121]

Decisions around appropriate outcome assessment time points was also viewed as challenging. Timing of follow up was considered to potentially favour one intervention over the other, as time to effect could be different for each of the interventions being evaluated.[101, 135, 174, 186] For example, comparisons made at time points shortly after non-surgically treated patients had their plaster cast removed were considered to favour results of the surgical patients.[135, 174] Several studies also discussed the limited follow-up period and indicated that longer term follow up may have revealed differences between treatment groups in progression of arthritis, recurrence rate, or requirement for further treatments.[101, 136, 142, 145, 146, 162, 174, 177, 179, 186, 188, 191]

5. Non-compliance with allocated treatment intervention

Non-compliance with treatment allocation was discussed in several studies as potentially introducing bias [104, 115, 121-123, 127, 131, 132, 140, 144, 145, 147, 149, 152, 167] and presenting difficulties with interpretation of outcome.[123, 132, 140, 147, 152, 173] Non-compliance was described as mainly occurring in the non-surgical group, with patients subsequently receiving surgical treatment. In one study, this was associated with severity of fracture.[147] Non-compliance also occurred in the surgical group in some trials; patients assigned to surgery either improved while waiting and did not proceed with surgery, or changed their mind about undergoing surgery post randomisation.[121, 131] This, however, was considered to reflect what might occur in real-life clinical practice. Some trials reported a variation between sites in the proportion of patients who did not comply with their allocated intervention.[149, 173]

A number of the studies described how they included a crossover to surgery component in the study design for participants who did not benefit from non-surgical management. Without this option, it was considered to be more challenging to recruit participants, especially to trials of established practice.[140, 149] To account for crossovers, one study indicated that an additional outcome measure was included *a priori*, as a secondary analysis, however, acknowledged that this analysis was vulnerable to bias as the treatment assignments were not blinded.[149] A greater understanding of clinical pathways to surgery and reasons for crossover was also suggested as important in the conduct of these types of trials.[104]

6. Differential loss to follow-up

The potential for differential loss to follow-up to influence outcome was discussed.[107, 111, 135, 144, 145, 159] Woltz et al (2017)[111] considered whether patients are less likely to return to the hospital for follow-up after non-surgical care than after surgery.

A number of studies reported loss to follow-up through the exclusion of participants based on surgical findings (e.g. identification of pathology that would have made the patient ineligible), without comparable exclusions in the non-surgical group.[107, 135, 145] This high number of exclusions among the surgical participants was primarily attributed to unexpectedly poor sensitivity of the methods for confirming diagnosis e.g. magnetic resonance arthrography,[107] lack of objective diagnostic tools [108], or limitations in existing diagnosis classification.[164]

Discussion

This systematic review has shown that in trials that compare surgical and non-surgical interventions there are issues related to recruitment, non-compliance and loss to follow-up. It has also identified several methodological challenges encountered in the design and

conduct of successfully completed orthopaedic trials that directly compared surgical and non-surgical interventions. The review incorporated quantitative and descriptive data from the discussion of trial reports to understand the challenges involved in this type of trial. Understanding the challenges of such comparisons would enable trial teams to make more effective design choices and benefit the delivery of such trials.

The inability to blind patients and investigators to their treatment allocation, due to the nature of the interventions evaluated, was discussed as creating several challenges to the conduct of these types of trials. Patients' knowledge of interventions could potentially influence outcome and introduce bias, particularly in trials utilising subjective outcome measures. Unlike trials where patients are blinded to the allocated intervention, marked differences between the interventions has the potential to influence how interventions are perceived by patients and affect their behaviour during the trial. Patients' may be less likely to comply with their allocated intervention, withdraw from trial without providing outcome data, or seek additional interventions.[67] For example, previous studies have described how patients' prior strength of preference for surgery was a reason why patients randomised to non-surgical treatment chose to crossover from non-surgical management to surgery [87, 193] or withdraw from the trial and undergo surgery. [194]

This review highlights difficulties with recruitment. Several of the studies were characterised with lengthy recruitment periods, having implications for funding and trial resources. Slow recruitment led to several trials not reaching recruitment target or the early closure of some trials. Multi-centre studies were seen to recruit, on average, almost twice the number of patients over similar recruitment periods than single centre studies, however, they had greater levels of eligible patients declining participation than in the single centre studies. Levels of non-compliance and loss to follow-up were also higher in the multi-centre studies, compared with single centre studies. The involvement of

multiple sites is often required to ensure that there is sufficient availability of the patient population to be able recruit to time and target, and can also provide a better basis for the subsequent generalisation of findings.[195] However, the findings of this review suggests that although the inclusion of additional sites enables trials to reach greater recruitment targets over similar recruitment periods, it adds additional complexity to the conduct of these studies.

It was not always possible to understand in full the reasons for recruitment problems in these trials, as screening data i.e. reasons for patient non-eligibility and non-consent, was only documented in around half of the reports. Where the data was collected, it was not clear in the majority of studies as to what was defined as a 'screened' patient, and this may have resulted, in part, in the large variance in these numbers. Details specifying the reasons for ineligibility or why eligible patients declined participation were also not routinely reported, making it difficult to understand any reasons for difficulty. Collection of trial screening data has the potential to identify reasons why eligible patients decline participation or key eligibility criteria that are problematic.[196-198] This information would inform more effective trial conduct, particularly in trials with type of comparison where there are such challenges to recruitment.

The findings of this review suggest that patients' treatment preference created difficulties with recruitment in a number of the trials. Strength of preference for particular treatments varied between the trials, with some trials describing difficulties because of strong preference for surgery,[101, 102, 113, 122, 132, 134, 149, 152, 173, 182, 184, 189] whereas in other trials preference for non-surgical interventions was more evident.[104, 115, 137-139, 157, 177, 187] The different conditions or pathologies evaluated and range of interventions compared are likely to contribute to variation in patients' preference between trials. Stark differences between the interventions in these types of trials, compared to trials of similar

comparisons (e.g. two different surgical procedures), are likely to have a greater influence on how the different interventions are perceived by patients and influence decisions regarding trial participation.[199] Understanding reasons for the strength of patients' preference for particular treatment, would identify potential issues specific to a particular trial comparison that may affect recruitment. This could offer opportunities to address potential issues, such as developing targeted patient information, and strategies to support recruiting teams.

Clinicians' views on treatments were also identified as potentially influencing the level of patient participation, acting as a barrier to trial recruitment. Recruitment to trials with starkly different comparators has the potential to be more problematic than in trials of similar comparisons (e.g. two surgical comparisons). Particularly as these inherently involve at least two different clinical specialities. Previous studies have identified that trials with such diverse comparators, demonstrate evidence of the most severe recruitment difficulties compared to other types of comparison (for example, two surgical procedures).[23, 43, 200] It is no surprise that clinicians, who are responsible for recruiting, hold a priori preferences for a particular intervention. Their preferences are embedded in experience of treating the patient group, which influences their preference towards particular treatments.[39] In trials where patients were evaluated by clinical specialists to confirm eligibility prior to participation, this was considered as having the potential to generate selective enrolment.[104, 149] The structure of the treatment pathway within orthopaedics makes it more likely to be a challenge in trials of this speciality. Unlike other clinical specialities, where diagnosis often precedes a referral to a specialist (e.g. oncology), orthopaedic surgeons play a central role in diagnosing orthopaedic conditions and therefore confirming eligibility for trial participation.[201] Alternative approaches to recruitment, such as involving the research nurse,[202] or other members of the research

team, changing the order in which patients meet clinicians or holding joint clinics with recruiting clinicians have been suggested.[203-205]

The findings of this review demonstrate that the complexity of both the surgical and non-surgical interventions (for example, physiotherapy, medical management) exacerbated the challenge of designing, conducting and analysing trials of this type of comparison. Both interventions potentially involve several interacting components that could be a source of bias and could therefore have an effect on outcome. For example, the varying skill and experience of clinicians,[15, 195] particularly when conducting multi-centre studies.[134, 137, 142, 173] The findings of this review indicate that in some cases, deciding on the content of the interventions was challenging because of insufficient evidence available to support decision making.[108, 140, 141, 144] Decisions made on intervention content may not only affect patients' willingness to participate in a trial, but also have implications for the implementation of findings in practice.

In contrast to trials evaluating two surgical procedures, varying content could also potentially mean that the timing of follow-up to favoured one intervention, this could introduce bias. For example, comparisons made at time points shortly after non-surgically treated patients had their plaster cast removed were considered to favour results of surgical patients.[135, 174]

The findings of this review demonstrate that there was a level of non-compliance with treatment allocation ("crossover") in orthopaedic trials comparing surgical and non-surgery. The overall levels of non-compliance were low (median 3% IQR 0,8% range 0-38%), and were comparable to the findings reported previously by Adewuyi et al (2015) in trials with surgical versus non-surgical comparison from all surgical clinical specialities [84] (median 4 % 0, 6% 0-10%). The findings of this review however indicate

that there were a number of trials where reported levels of non-compliance were more than 20%.[104, 112, 121, 127, 132, 147, 187] Further research to explore reasons for high levels of non-compliance in these types of trials would be useful. An imbalance in the degree of non-compliance between treatment arms was also seen, with a greater percentage of non-compliance in the non-surgical arm. Asymmetry between the treatment arms, in particular due to the fact that crossover can only occur in one direction (towards surgery) can further complicate the interpretation of trial findings. Although there is no agreement about when crossover is considered to threaten or invalidate the results of a trial, [206] it has the potential to confound the interpretation of outcome. [84, 87]

Levels of loss to follow-up reported in this review were slightly lower (median 9% IQR 0-14% range 0-37%) than reported previously by Adewuyi et al (2015) (median 14% IQR 6,17 range 0-46).[84] The surgical versus non-surgical trials included in that review however, were from a range of clinical specialities, rather than only orthopaedics, which may explain the differences.[84] There was no differential loss to follow-up identified. A number of the studies however, discussed the potential for differential loss to follow-up to influence outcome.[107, 111, 135, 144, 145, 159] For example, patients may be less likely to return to hospital for follow-up after non-surgical care than after surgery.[111] Studies also reported loss to follow-up through the exclusion of patients based on surgical findings (e.g. identification of pathology that would have made the patient ineligible).[107, 135, 145] As comparable exclusions are not possible in the non-surgical arm this can introduce bias.

Limitations

There are some limitations to this review. Only published trials from one clinical speciality, orthopaedic or musculoskeletal, were included, and this may limit the generalisability of the results. In addition, the majority of trials were of fracture

management. Whilst the findings of this review are specific to trials of orthopaedic or musculoskeletal interventions, it highlights more general issues that may be transferable to other trials with such diverse comparisons in other clinical specialities.

The quality of the reporting in the published study, may also have limited the information available. As there is often limited space to report in peer reviewed publications, not all of the challenges the trial team experienced may have been reported. The initial aim of this review was to include qualitative studies that explored challenges to the design and conduct of these types of trials. However, only two studies were identified related to an orthopaedic speciality, and it was therefore decided to conduct a separate review of qualitative studies and expand the review to include all clinical specialities. This review is presented in Chapter 4.

Summary of findings

The aim of this chapter was to conduct a systematic review to identify the challenges of conducting randomised controlled trials that compare surgical with non-surgical interventions. Difficulties with recruitment were evident with lengthy recruitment periods, early closure of some studies and a number of trials not reaching recruitment target. Several methodological challenges were identified related to; recruitment difficulties, difficulties implementing blinding, complexity of intervention content and delivery, timing of assessments, non-compliance with allocated treatment intervention and potential for differential loss to follow-up. Several of the challenges with this type of comparison were more evident in the multi-centre studies. Although the conduct of multi-centre studies enabled trials to reach greater recruitment targets over similar recruitment periods, they also experienced greater percentage of numbers of eligible patients declining to participate, imbalance in non-compliance with treatment allocation and

greater percentage of loss to follow up than the single centre studies. Whilst not all trials experienced each of these challenges, the review highlights that the issues are common to trials that compare surgical and non-surgical interventions. If not adequately addressed, these issues may introduce significant bias and threaten the viability of the trial, and also the validity of the trial results. Consideration of these specific challenges should be made in the planning and design of future studies to optimise trial conduct.

Chapter 3

Exploring challenges in trials with a surgical and non-surgical comparison: a case study of the ACL SNNAP trial

Introduction

The systematic review described in Chapter 2 identified specific challenges in the design and conduct of trials that directly compare surgical and non-surgical interventions. Difficulties with recruitment were evident with lengthy recruitment periods, early closure of some studies and a number of trials not reaching recruitment target.[107, 117, 123, 132, 134, 147, 158, 164, 167, 187, 189] Additional challenges were identified related to the diverse nature of the interventions being evaluated, which if not adequately addressed, may introduce significant bias and threaten the validity of the results in these types of trials. For example, the inability to blind patients and investigators to treatment allocation, complexity in the content and delivery of interventions, choice of timing of outcome assessments to potentially favour one intervention, potential for imbalance in non-compliance with allocated intervention, and differential loss to follow-up. Although not all trials experienced each of these challenges, the review highlighted how common these issues can be in trials with this type of comparison.

The findings of the review in Chapter 2 also identified that several of the challenges with this type of comparison were more evident in the multi-centre studies. Studies with multiple trial sites recruited, on average, almost twice the number of patients of single centre studies over similar recruitment periods. However, multi-centre trials experienced a greater percentage of eligible patients declining to participate, imbalance in non-compliance with treatment allocation and greater percentage of loss to follow up. Inclusion of multiple sites in the conduct of trials is often required to ensure that there is sufficient availability of the patient population to be able recruit to time and target, and to provide a better basis for the subsequent generalisation of findings.[195] Large variation in

recruitment rates at participating sites in multi-centre centres, however, is often reported.[197, 203]

The ability to identify and understand key factors for recruitment difficulties and reasons for non-compliance in trials with such contrasting interventions would be beneficial to facilitate the successful completion and delivery of such trials. Case studies are often used in exploratory research to provide an in-depth investigation of one particular individual, group, time-period or event.[207] A case study approach can involve a range of qualitative and quantitative research methods to investigate underlying principles of an occurrence within a real-life context. The aim of this case study was to explore the challenges experienced during the conduct of a multi-centre trial, which exemplified a surgical and non-surgical comparison, and provide insight into the implications for future trials.

Objectives

The objectives of the study were to:

1. To identify and understand any key factors limiting accrual (i.e. reasons for ineligibility and non-consent) during the 12 month pilot phase.
2. To identify any potential challenges with the timing/delivery of the different interventions.
3. To explore and understand any differences between treatment arms in levels of non-compliance (departures from random allocation).
4. To explore and understand reasons for any differential loss to follow-up between treatment arms.
5. To suggest options and solutions for the above issues.

Methods

Data to address these objectives were collected from the National Institute of Health Research (NIHR) funded ACL Surgery Necessity in Non Acute Patients trial (ACL SNNAP).

Ethics approval

Approval to conduct the ACL SNNAP trial was granted by the South Central - Oxford C Research Ethics Committee (Reference No. 16/SC/0502) on 25th October, 2016.

Overview of ACL SNNAP trial

The ACL SNNAP trial is a pragmatic NIHR HTA funded multi-centre trial comparing a strategy of non-surgical (rehabilitation) and surgical management (reconstruction) options for patients with a symptomatic non-acute anterior cruciate ligament (ACL) deficient knee (ACL SNNAP trial).[208] The trial design incorporates the option for later ACL reconstruction in the non-surgical arm, only if required.

Rupture of the anterior cruciate ligament of the knee, is a common sporting injury and is most frequently seen in young and physically active individuals.[209] Current management of ACL deficiency includes both reconstructive surgery and non-surgical treatments (rehabilitation) but there remains uncertainty which management is superior.[210, 211] Much of the current evidence base is limited in methodological quality, being based on a number of retrospective case-control and cohort studies and only one randomised controlled trial.[182, 212]

The pilot phase of the trial was conducted over a 12 month period (1st March 2017 to 28th February 2018), at 16 NHS secondary care hospitals.

The primary outcome for the ACL SNNAP trial is the Knee Injury and Osteoarthritis Outcomes Score (KOOS4),[213] a validated patient reported outcome measure, at 18 months post randomisation.

Data collection and analysis

Prospective data from the ACL SNNAP trial was collected on the following:

1. **Recruitment**

   i. Overall recruitment against target

   ii. Recruitment rate at participating sites

   iii. Reasons for patient ineligibility

   iv. Reasons eligible patients declined participation

2. **Time from randomisation to start of treatment**

   i. Time from randomisation to start of treatment by treatment arm

   ii. Time from randomisation to date of data lock by treatment arm

3. **Non-compliance with allocated intervention**

4. **Loss to follow-up**

Recruitment and screening data (reasons for ineligibility and why eligible patients declined participation) were collected during the pilot phase of the trial. The pilot phase of the trial was conducted over a 12 month period (1st March 2017 to 28th February 2018), at 16 NHS secondary care hospitals. The process of patient identification, eligibility assessment and recruitment is detailed in the recruitment process flowchart.

Patient screening and recruitment data was collected on a screening form (Appendix 2), which were entered by research teams at participating sites on to a Web-based electronic data capture (EDC) system. The bespoke electronic system was developed in

collaboration with Fr3dom Limited, healthcare software developers (http://www.fr3dom.net/index.html), to maximise data collection and consistency of data across all sites.

The form captured information on eligible patients who agreed to participate, as well as documenting reasons for non-inclusion to the study (i.e. reasons patients were ineligible, or declined to participate). To capture the specific reasons for ineligibility, the trial exclusion criteria (Table 10) were listed on the screening form and included a free text option and the ability to indicate more than one reason for ineligibility.

Table 10: Inclusion and exclusion criteria for the ACL SNNAP trial

Inclusion Criteria
1. Participant is willing and able to give informed consent for participation in the study. 2. Male or Female, aged 18 years or above 3. Symptomatic ACL deficiency (instability-episodes of frank giving way or feeling unstable) with ACL deficiency confirmed using clinical assessment and MRI scan.

Exclusion Criteria
Patients were excluded if they were; 1. Less than 4 months since injury, 2. Have had previous knee surgery (other than diagnostic arthroscopy) to index knee, concomitant severe injury to contra-lateral knee, 3. Have meniscal pathology considered sufficiently symptomatic to require surgery i.e. locked knee, large bucket handle cartilage tear. 4. Have knee joint status of grade 3 or 4 on the Kellgren and Lawrence scale [214] 5. Have grade 3 Medial Collateral Ligament (MCL)/Lateral Collateral Ligament (LCL) injury, associated Posterior Cruciate Ligament (PCL)/Posterolateral Corner (PLC) injury 6. Have inflammatory arthropathy. 7. Pregnant. Pregnancy is checked for before receiving an MRI scan.

For eligible patients who declined participation, four options were available for completion; preference for physiotherapy, preference for surgery, no reason stated, and a free text 'other' tick box.

In cases where the reason for ineligibility or declining participation were entered in the free text option, the data was collated and categorised and the listed reasons were subsequently reviewed and discussed with the Trial Statistician (Beverly Shirkey) and Chief Investigator (David Beard), until consensus was gained on reason stated.

Teams at recruiting sites also entered treatment forms (rehabilitation and operation forms) onto the EDC system to indicate the start of treatment.

Any patient departures from random allocation (non-compliance) were also entered on the EDC system at local sites. Non-compliance included any departure from treatment allocation following randomisation e.g. decisions not to undergo surgery for surgery patients or decision to have surgery in the rehabilitation arm before undergoing three months of rehabilitation.

Follow-up questionnaires were sent out directly to participants via e-mail at 6, 12 and 18 months post randomisation, data was captured on the EDC system when completed. For the purpose of this study, loss to follow-up included any primary outcome data not collected after the initial attempt to obtain the data (i.e. initial e-mail questionnaire, follow up reminder email at 1 day, 1 week and 1 month later and 2 text message reminders), at any of the three follow-up time points (6, 12 or 18 months).

For the analysis, data was downloaded from the EDC system, collated in an Excel spreadsheet and summarised using descriptive statistics.

Screening data were monitored, and challenges discussed by the Trial Management Group (DB, BAS, HF, LD, CA). Regular teleconference calls with participating sites

were made by the team (DB, LD, CA) to discuss progress and challenges. Trial process and challenges were also discussed at Trial Steering Committee meetings (26th July, 2017, 24 Jan and 4th Oct, 2018) and with the funding body at end of first phase of the internal pilot (18th August, 2018).

Results

1. Recruitment

i. Recruitment against target

Difficulties with recruitment were identified during the pilot phase of the trial with 77 (82%) of the target 94 patients randomised over the 12 month period (Appendix 3). Figure 3 provides an overview of the number of patients assessed for eligibility, those who were ineligible, and declined to participate.

ii. Recruitment rate at participating sites

The recruitment rate at the sites was lower than anticipated. Overall only three sites achieved the target recruitment rate of one patient randomised per month. The variation in the recruitment rates between sites is detailed in Table 11. The percentage of eligible patients randomised ranged between 0-100% between the sites.

iii. Reasons for patient ineligibility

During the pilot phase of the study (1st March 2017 to 28th February 2018), 475 patients were assessed for eligibility of which 456 satisfied all inclusion criteria. Of these potentially eligible patients, 277 (61%) were ineligible because of the presence of one or more exclusion criteria. The main reasons reported for ineligibility were: undergoing prior knee surgery (n=69; 25%), having associated meniscal pathology requiring surgery

(n=55; 20%), being less than 4 months since injury (n=43; 16%), and having grade 3 MCL, LCL injury (n=23; 8%), as shown in Figure 3 and Table 12. below.

Table 11: Screening data and number of patients randomised by site during the 12 month pilot phase

Site	Months open to recruit (n)	Patients screened (n)	Eligible (n)	% of screened eligible	Randomised	% of eligible randomised	Monthly recruitment rate
1	12	12	11	92%	5	45%	0.4
2	12	11	5	45%	3	60%	0.3
3	12	55	8	15%	1	13%	0.1
4	11	33	24	73%	19	79%	1.7
5	10	104	30	29%	22	73%	2.2
6	10	33	8	24%	1	13%	0.1
7	10	115	34	30%	12	35%	1.2
8	10	5	4	80%	1	25%	0.1
9	9	14	14	100%	2	14%	0.2
10	9	4	3	75%	2	67%	0.2
11	8	49	14	29%	0	0%	0
12	7	22	12	55%	3	25%	0.4
13	5	8	4	63%	4	100%	0.8
14	4	9	7	78%	1	14%	0.3
15	2	1	1	100%	1	100%	0.5
16	1	0	0	-	0	-	0
		475	**179**	**38%**	**77**	**43%**	

Table 12: Reasons for patient ineligibility

Reason for patient ineligibility (exclusion criteria)	**N = 277**	**%**
Undergoing previous knee surgery	69	25
Associated meniscal pathology requiring surgery	55	20
Less than 4 months since injury	43	16
Other*	40	14
Two or more reasons	32	12
Grade 3 MCL/LCL injury	23	8
Knee joint status grade 3/4 KL scale	11	4
Inflammatory arthropathy	4	1

*included in Appendix 4

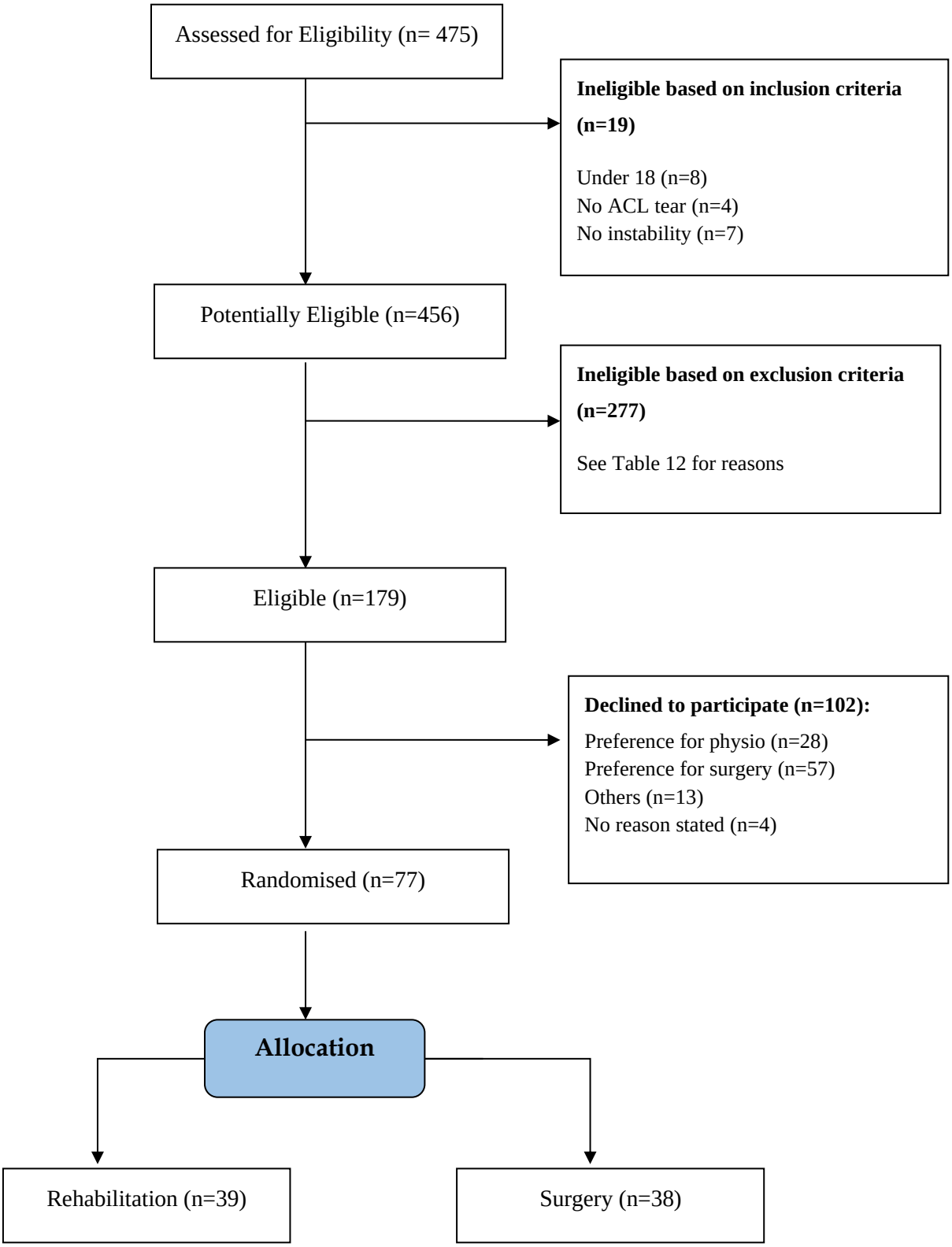


Figure 3: Participant flow diagram to highlight eligibility in early stage of the trial

The reasons reported for ineligibility were monitored by the trial team and discussed with local teams at participating sites to understand and difficulties with recruitment. The 3 main reasons identified are detailed below and modifications made by the trial team to the eligibility criteria.

1. Previous knee surgery

Patients who had previously undergone a primary ACL reconstruction on their index knee were identified as the reason for a high number of exclusions due to prior surgery. Changes were made to the eligibility criteria in the amendment to the trial protocol (November, 2017), to clarify details around the criteria related to previous knee surgery. It was specified that patients who have undergone primary ACL reconstruction on the index knee were not eligible for inclusion (Appendix 5).

2. Associated meniscus pathology requiring surgery

The exclusion criteria 'associated meniscal injuries requiring surgery', was identified in this trial as one of the main reasons for ineligibility. The protocol specified that only certain patients presenting with associated meniscal injuries, considered by the recruiting clinician as significant enough to require more immediate surgery (i.e. locked knee or complex cartilage tears producing mechanical symptoms), would be excluded. However, large variation was observed between sites in the number of patients excluded for this reason. Discussion with recruiting clinicians identified differences in interpretation and application of this criteria. As there is no clear consensus in the management of meniscal injuries,[215] this also potentially contributed to the variation between recruiting teams in the interpretation and implementation of this criteria and the high proportion of patients excluded. An amendment made to the trial protocol (November, 2017) provided greater clarity to the criteria around associated pathology (Appendix 5).

3. Less than 4 months since injury

Exploring reasons for the exclusion of potentially eligible patients, identified differences in the treatment pathway across participating sites that were impacting on accrual rates. It became evident that the criteria specifying time frame since injury of (greater than four months), was problematic for some sites. This specified time frame, identified through feasibility work (Appendix 6), was set to reflect NHS practice at the time of the funding application. Since that time NHS practice had changed, with the introduction of acute knee clinics at some hospitals resulting in patients being seen earlier following their knee injury. An amendment was made to the eligibility criteria in the trial protocol (November, 2017) to modify the time since injury exclusion criteria (Appendix 5). This enabled sites to screen and approach patients through A&E and acute knee clinics, increasing the number of potentially eligible patients considered for the trial.

iv. Reasons eligible patients declined participation (overall and by site)

During the pilot phase of the study, 102 out of 179 (57%) eligible patients that were approached to participate declined (Figure 3 and Table 13). The majority of patients who declined had a preference for surgery (n=57; 56%). A further 28 (27%) patients had a preference for physiotherapy. Other reasons reported for eligible patients declining participation are summarised in Table 13.

There was also variation between recruiting sites in the number of eligible patients declining participation (range 24% - 100%), as shown in Figure 4.

Table 13: Reasons eligible patients decline trial participation

	N = 102	%
Preference for surgery	57	56
Preference for physiotherapy	28	27
Other*	13	13
No reason stated	4	4

* Patient referred for surgery from clinic (n=3), previous conservative treatment, preference for surgery (n=1), moving out of area/treatment closer to home (n=2), no response/did not attend clinic appointment (n=3), non-English speaker (n=2), surgery seen to be more suitable (n=1), no current functional instability symptoms (n=1).

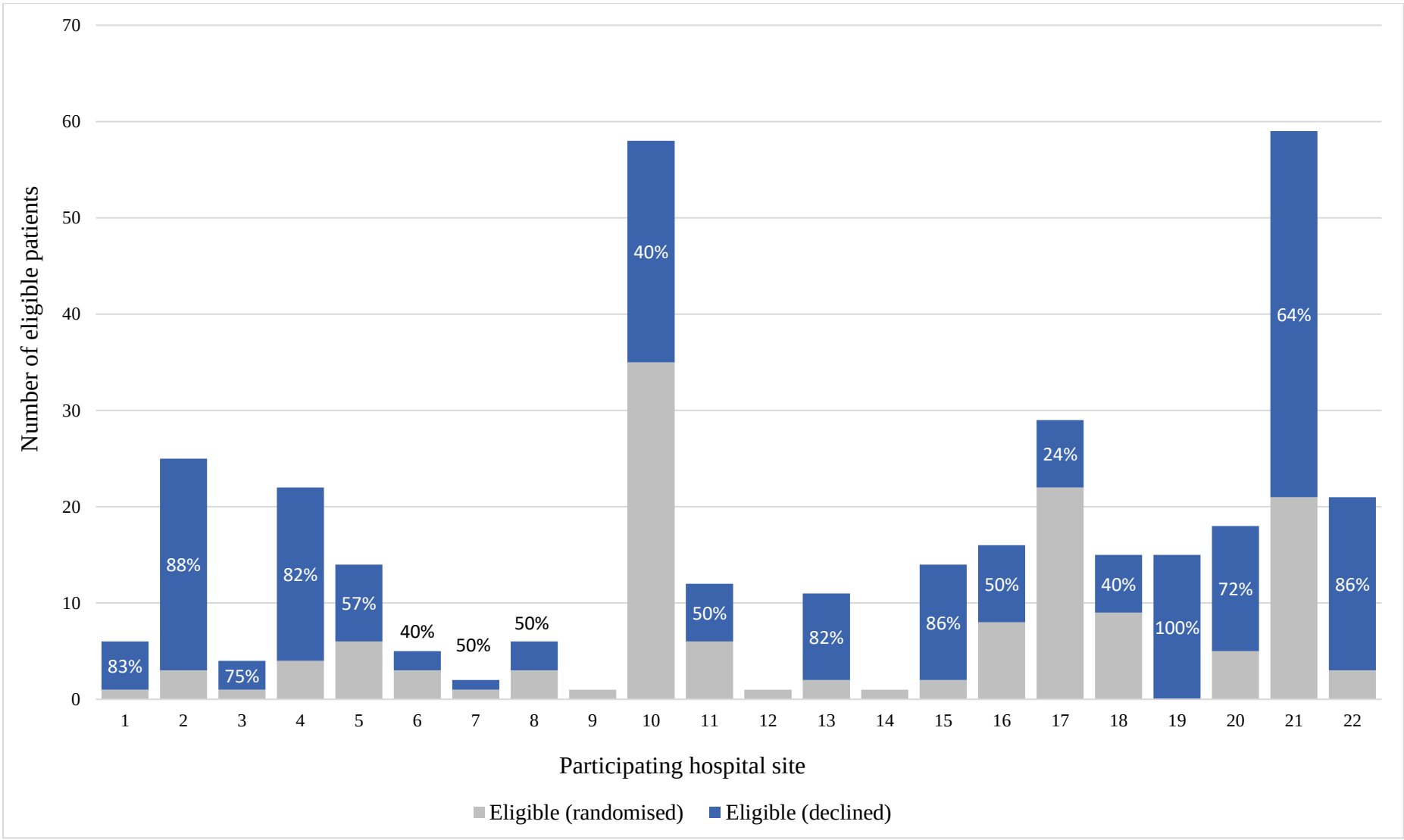


Figure 4: Percentage of eligible patients randomised and declining participation by site

2. Time from randomisation to start of treatment

Differences in the length of time from randomisation to the start of treatment were observed between the rehabilitation and surgical groups. The length of time to the start of treatment was greater for the patients who had undergone treatment in the surgical arm (14 weeks) than that of the patients in the rehabilitation group (3 weeks) (Table 14).

Table 14: Time in weeks for patients in ACL SNNAP trial who have received treatment (31st Jan, 2019)

	Rehab (n=67)	**Surgery (n=56)**
Median	3	14
IQR	2,5	9,19
Range	0-57	2-36

Values are number of weeks

The differences in waiting times, however, were seen to reflect those observed in clinical practice and identified in the prior feasibility work. On average, all patients who had received their intervention to date (31st Jan, 2019), were within the pre-specified time frame of 18 weeks. This time frame was indicated to sites during site feasibility assessment in order to standardise timing of delivery of intervention. There were some patients in both groups who received treatment after this time frame. Additional pressures on hospital waiting lists due to seasonal 'winter pressures' on elective surgery procedures, and patients' decisions to postpone surgery (e.g. work, social commitments) extended these times in some cases.

The trial is ongoing and a number of patients had outstanding treatment start dates at the time of the data lock (31st Jan, 2019). For patients waiting treatment, to date, the times

were similar in both groups (Table 15). One patient in the surgical group however, has reached the end of the follow-up time point without undergoing treatment.

Table 15: Time in weeks for patients in ACL SNNAP trial Number awaiting treatment start date (31st Jan, 2019)

	Rehab (n=34*)	**Surgery (n=47*)**
Median	15.5	19
IQR	10,24	9.5,24
Range	2-67	2-78**

* excluding cancelled surgery in surgery arm or had surgery in rehab arm
** one patient has reached 18 month time point (primary outcome) without undergoing treatment
Values are number of weeks

3. Non-compliance with allocated intervention

There was some evidence of non-compliance with treatment allocation in both treatment arms, at the time of the data lock (31st January, 2019). Figure 5 provides an overview of the number of randomised patients who has undergone treatment. In this trial, the option for patients in the rehabilitation arm to subsequently undergo surgery if there was no improvement in symptoms, was an integral design aspect of the study. At the time of the trial data lock (31st January, 2019) six patients of the 109 randomised to the rehabilitation arm had, somewhat prematurely, opted to undergo surgery before undergoing 3 months of rehabilitation. One other patient had withdrawn, as they had a preference for surgery.

In comparison, of the 114 patients randomised to the surgery group, 9 patients had made a decision not to proceed with surgery (3 cancelled surgery because of work commitments, 3 cancelled op date not rebooked and 3 opted not to undergo surgery). One patient subsequently requested to undergo surgery after the preliminary decline. One other patient did not undergo ACL reconstruction at the time of operation (clinician

decision) and underwent another procedure because of associated pathology and one patient had reached the final follow-up time point without undergoing an intervention.

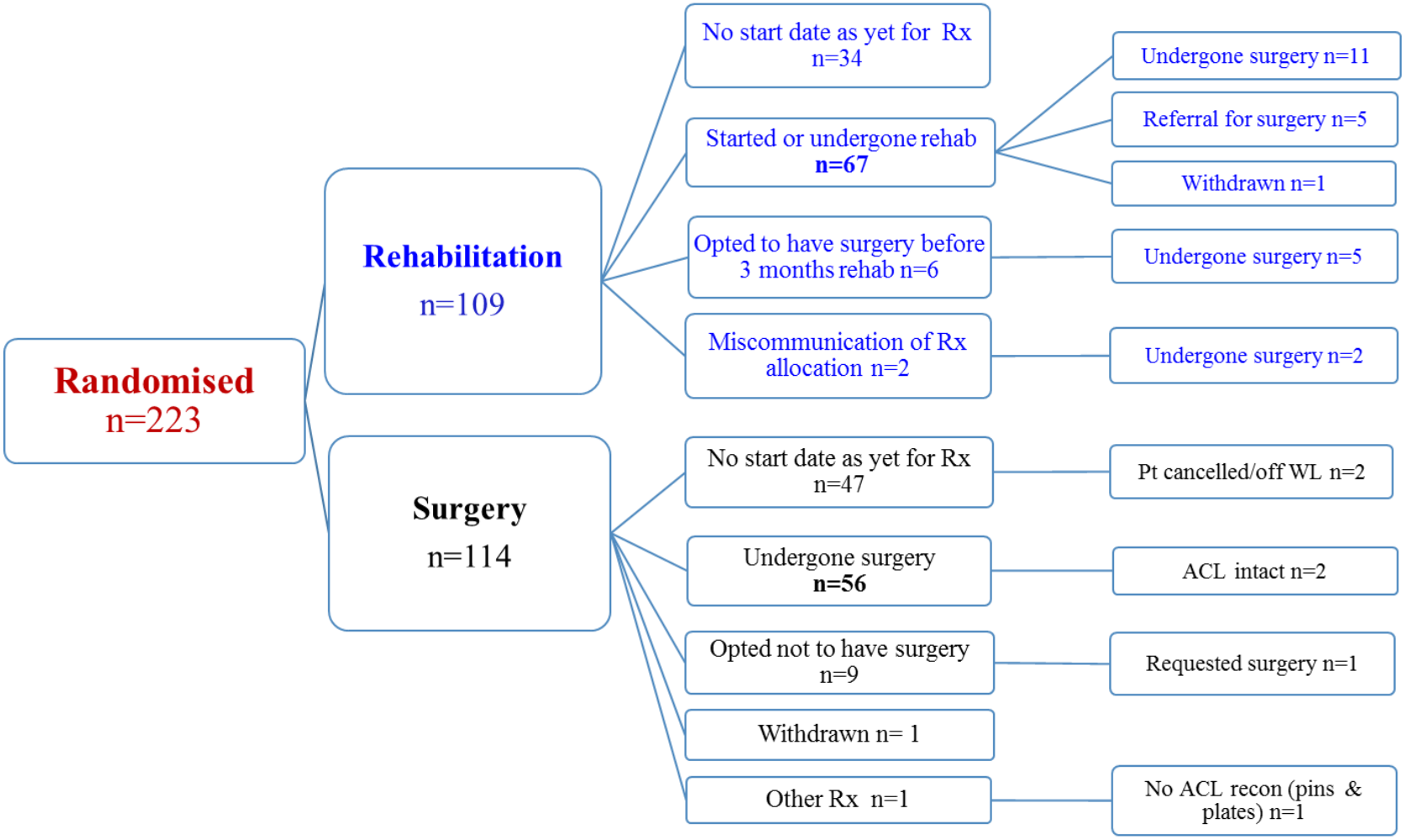


Figure 5: Participant flow to illustrate number of randomised patients who has undergone treatment in ACL SNNAP study (31st January, 2019)

4. Loss to follow-up

Overall there were difficulties with loss to follow-up with greater than 50% of the questionnaires not returned at each of the follow-up time points (at the time of the data lock, 31st January, 2019) [Table 16]. There was also some evidence of differential loss to follow-up between the treatment groups, with the response rate in the surgical arm being greater (Table 16).

Table 16: Total number of follow-up questionnaires sent and received (31st January, 2019)

Questionnaire	Reached Time point N	Received overall N (%)	Surgery arm	Rehab arm
6 months	138	62 (45%)	35/68 (51%)	27/70 (39%)
12 months	65	15 (23%)	11/31 (35%)	4/34 (12%)
18 months	19	6 (32%)	3/9 (33%)	3/10 (30%)

Potential difficulties with overall follow-up was expected by the trial team as the population is a young and geographically mobile population.

Reasons patients had not returned their questionnaires were collected from responses made on follow-up phone calls. The responses suggested that misunderstanding of the follow-up process contributed to the reduced response rate. Some patients indicated that they thought that they did not have to complete the questionnaire as they had not yet undergone treatment (delay to intervention), or in some cases patients in the rehabilitation arm who had undergone surgery indicated that they thought they were no longer part of the study because of their change in management.

Discussion

The aim of this case study was to explore any challenges experienced during a multi-centre trial with features of surgical versus non-surgical comparison in order to provide insight and help design future trials. Key factors related to trial eligibility criteria and strength of patients' preference for particular treatments were identified as creating difficulties with recruitment. Aspects relating to the delivery of the trial interventions, compliance with treatment allocation and differential loss to follow-up were also identified as having potential implications for the interpretation of outcome in trials with such diverse comparisons.

Recruitment difficulties were observed in this trial example, with variation between participating sites the number of eligible patients, recruitment rates and patients declining participation. Differences in clinicians' application of trial eligibility criteria has been identified in previous studies as creating a challenge to trial recruitment, contributing to marked differences between trial sites in eligibility and recruitment numbers.[216-218] Clinician decision making in the management of associated pathology, was identified in this example, as one factor potentially impacting on the number of patients considered eligible for the study. Unlike trials comparing similar interventions (two surgical procedures), any associated pathology in trials with this type of comparison, would not be managed in the same way. As a result, this may lead to variation between clinicians in decision making around trial eligibility criteria, and willingness to consider patients appropriate to approach to participate [219] potentially affecting recruitment. Analysing reasons for ineligibility in a feasibility trial of surgical and non-surgical treatment of oesophageal squamous cell cancer by Blazeby et al (2014),[203] also identified marked variation in the proportion of eligible patients between sites. Differences between sites in

local staging investigations to assess tumour length, were identified as contributing to these differences. Collection and analysis of screening data on patients considered for trial participation, therefore, can be particularly valuable in trials of this type of comparison. Identifying potential problems and variation in the interpretation and application of eligibility criteria could facilitate improvements with recruitment.[196, 220]

In this trial case study, patient preference towards surgery was the main reason eligible patients declined participation. Patients' preference for particular interventions has the potential to be more problematic in these types of trials compared to trials of similar comparisons (e.g. two surgical interventions) because of the marked differences between the interventions. The findings of this study, however, are in contrast to the reasons eligible patients declined participation in the only other trial comparing these management options for ACL deficiency.[221] The majority of patients in the study by Frobell et al, (2010) had a preference for non-surgical treatment rather than a preference for surgical intervention as seen here in this work.[221] However, patients in the trial by Frobell et al (2010) were approached at an earlier stage of the injury presentation and therefore patients may have perceived more value to an initial non operative approach. Trial participation was also seen by patients who had strong preference for surgery as a means to bypass waiting lists, which also may have influenced participation.[193, 221] The findings highlight the potential influence of other factors, such as time since injury, influencing patients' preference for treatment and trial participation. Exploring the extent and balance of patients' preference for treatment and understanding the potential influence of treatment/trial pathways, particularly in trials where the interventions being evaluated are so diverse, could enable issues in a specific trial to be identified and addressed. These issues should be explored early on in the design and preparation of the trial.

Differences in delays in patients receiving treatment between treatment arms, for example due to waiting lists, were identified in this study as having potential implications for the interpretation of outcome in trials of this type. The influence of factors such as waiting lists, however, may depend on the nature of the comparisons in a trial. For example, delays in receiving treatment are likely to be more problematic in trials which involve an elective surgical procedures, due to waiting lists, compared to trials of more acute pathology (e.g. trauma). Delays in patients receiving treatments could also be said to reflect clinical practice and increase the applicability of the findings. However, differential delays between groups, particularly when lengthy delays do not allow for an adequate follow-up period, have the potential to cause problems with interpretation of results.

The potential for substantial post-randomisation delays in receiving treatment have also been identified in trials comparing two surgical interventions.[222-224] However, practical differences in the delivery of the interventions in trials with a surgical versus non-surgical comparisons, such as, different clinical specialities or departments with different pathways and waiting lists, may result in imbalanced and problematic delays.[102, 121, 145, 184] Potential solutions in trial design in previous studies have involved the inclusion of additional follow-up assessments for patients who had significant delays waiting for surgery to enable appropriate comparisons.[121, 222] The impact of alternative follow-up timings on patient outcomes have been explored in trials of surgical comparisons,[224] where similar results were observed with the different follow-up timings.[224] Further studies to explore the effect of delays in receiving an intervention within trials of surgical and non-surgical comparisons would be useful. Potential factors influencing the timing of follow up, such as waiting lists, need to be considered in trials of this type of comparison to ensure interpretable results.

The findings of the systematic review in Chapter 2 identified that departures from random allocation (non-compliance) are common in trials of this type of comparison. Non-compliance could potentially result in an imbalance between treatment arms, as crossover can only occur in one direction (towards surgery) resulting in interpretation complexities.[206] In ACL SNNAP there was a legitimate option in the rehabilitation arm to undergo subsequent surgery as part of the design and it may be different in trials where there is no such option. ACL SNNAP raised other forms of non-compliance. In the surgical group, a clinical decision was made for one patient to undergo a different procedure and in two cases the surgical procedure was deemed unnecessary as no ligament tear was identified following surgical access. As these findings only apply to the management of the surgical patients, decisions on how these patients are managed in the analysis of the study has potential to introduce bias. Previous studies have reported excluding participants based on surgical findings, without comparable exclusions in the non-surgical groups, resulting in imbalanced distribution of participants between groups.[107, 135, 145] Decisions made on how cases of non-compliance are managed has the potential to introduce significant bias and threaten the validity of trial results, and therefore should again be considered in the design and planning of these types of trials.

In this trial example (ACL SNNAP), there was evidence of differential loss to follow-up between the treatment groups, with a greater percentage of loss to follow-up from the non-surgical group. This difference is comparable to the surgical versus non-surgical comparison in a review of orthopaedic trials by Herman et al (2009).[225] These findings were different to those of the review presented in Chapter 2, where the loss to follow-up between the treatment groups was very similar. Details of the surgical versus non-surgery trials evaluated in the review by Herman et al (2009) [225] were not included, making it

difficult to review any potential reasons for any differences, such as length of follow-up periods.[226]

Potential reasons for differential loss to follow-up in trials with this type of comparison have been discussed in other studies. For example, patients may be less likely to return to hospital for follow-up after non-surgical care than after surgery,[111] or patients randomised to non-surgical treatment who go on to have surgery might be more likely to withdraw.[194] In ACL SNNAP, patients who had not yet received treatment or patients in the rehabilitation arm who had undergone surgical treatment were considered to be less likely to complete their follow-up questionnaire. Exploring reasons for loss to follow-up in trials with this type of comparison could help to identify and understand reasons for potential differential loss to follow-up. Specific strategies could then be developed to improve retention.

Limitations

There are some limitations to this case study. The nature of a case study is that it draws on a specific example, in this case an orthopaedic trial comparing a surgical and non-surgical intervention, and this may limit its applicability. Nevertheless, it does highlight potential challenges that may impact on recruitment and trial conduct in trials with this type of comparison that should be considered at the trial development stage. In addition, it demonstrates the benefits of conducting pilot and feasibility studies to explore potential challenges in preparation for an RCT,[70] and optimise trial conduct.[71]

Lastly, the issue of innovation versus maturity of current practice should be considered. This particular trial example is of a comparison of two well established interventions, both of which may be acceptable. The level of maturity of an intervention may influence

patients' and clinicians' views of treatment and trial participation. The findings may have been different if the comparison included a novel intervention.

A case study is often criticised for its dependency on a single case exploration, making it difficult to generalise to other areas.[207] However, this approach enabled an in-depth investigation into the potential challenges, using prospectively collected data within a real-life context of a trial of this types of comparison.[207]

Summary of findings

The aim of this case study was to explore any challenges experienced during a multi-centre trial, which exemplified a surgical and non-surgical comparison, and provide insight into the implications for future trials. The intention was a more penetrating investigation of some aspects highlighted by the systematic review Chapter 2.

Key factors related to trial eligibility criteria and strength of patients' preference for a particular treatment were identified as factors limiting accrual. Additional factors for trials with such diverse comparators related to the delivery of the trial interventions, potential for differential delays in patients receiving interventions, non-compliance with randomised allocation, and differential loss to follow-up.

The findings of this study highlight the potential benefits of collecting screening data in trials with such diverse comparisons. Potential difficulties with implementation of eligibility criteria and strong patient preferences for treatment could be identified and strategies implemented to improve recruitment.

Consideration of these specific challenges should be made in the planning and design of future studies to optimise trial conduct.

Chapter 4

Exploring methodological challenges in trials with a surgical and non-surgical comparison: a qualitative evidence synthesis using meta-ethnography

Introduction

The case study of a multi-centre trial comparing surgical and non-surgical interventions presented in Chapter 3 identified key factors related to trial eligibility criteria and patients' preference for treatment, which resulted in difficulties with recruitment. Aspects relating to the delivery of the trial interventions, compliance with treatment allocation and differential loss to follow-up were also identified as having potential implications for the interpretation of outcome in trials with such diverse comparisons.

Variation between participating sites was also observed between sites in the number of eligible patients, recruitment rates and number of eligible patients declining participation. The findings highlight the potential complexity of conducting multi-centre trials of this type of comparison as variation in clinician decision making regarding trial eligibility criteria and differences between aspects of treatments pathways between sites (e.g. waiting lists), could result in additional challenges. As discussed in Chapter 3 the inclusion of multiple sites is often required in trials to ensure that there is sufficient availability of the patient population to be able to recruit to time and target, and also to provide a better basis for the subsequent generalisation of findings.[195] However, large variation in recruitment rates between participating sites in multi-centre studies are often reported.[197] Exploring the reasons for the challenges reported in the conduct of these types of trials could support trial teams in improving the design and delivery of such trials.

Qualitative research has been used to understand challenges in the conduct of difficult randomised controlled trials (RCTs), such as those in surgery, and inform the development of strategies to improve the design and conduct of trials.[82, 219, 227] Syntheses of qualitative studies, such as meta-ethnographies, can increase our understanding of the complex process of heath care and improve the experience and quality of care, provide

evidence of the acceptability, feasibility, and appropriateness of interventions or services [228, 229] and can illuminate people's experience of illness and healthcare.[230]

Several reviewers have applied this method to increase the understanding the challenges of recruitment to trials.[219, 231-233] These studies provided important insights into the complexities of recruitment. However, at the present time, no review has been conducted to understand the challenges of conducting trials with surgical and non-surgical intervention comparators. The aim of this review was to conduct a qualitative evidence synthesis of studies that explored the experiences of patients and healthcare professionals participating in trials comparing surgical and non-surgical interventions and to identify challenges to their design and conduct.

Objectives

The objectives of the review were:

1. To systematically identify relevant qualitative research that explores patients and clinicians experiences of participating in trials with a surgical and non-surgical comparison.
2. To conduct a qualitative evidence synthesis to explore factors that can affect the design and conduct of trials with a surgical and non-surgical comparison.
3. Develop a conceptual framework to increase our understanding of factors influencing the design and conduct of surgical trials with a non-surgical comparison.

Methods

Phase 1: selecting meta-ethnography and getting started

A qualitative evidence synthesis using meta-ethnography [234] was conducted. Appendix 7 shows the recent 'eMERGe' meta-ethnography reporting guidance that was used to guide this report.[235] Several methods for synthesising qualitative data exist [236] such as meta-ethnography,[234] thematic synthesis [237] and critical interpretative synthesis.[238] Studies range from those aiming at describing qualitative findings to more interpretative studies aimed at generating theory. Unlike quantitative analysis (e.g. meta-analysis) which aims to evaluate or estimate the magnitude of the effect of interventions by statistically pooling numerical data, qualitative evidence synthesis (QES) is exploratory in nature, expanding the understanding of the studied topic through integration of multiple inter related qualitative studies.[239] A QES aims to go beyond the method of both narrative and systematic literature reviews, which summarise a field of research, and involves a re-conceptualizing of findings and to interpret them in order to create new insights beyond those attained from individual studies.[240] The synthesis process follows a fine balance between preserving the integrity of the meaning of included studies but at the same time to go beyond simple descriptions of findings.[239]

Noblit and Hare [234] describe a seven step process to meta-ethnography, which start with formulating a research idea through to expressing the findings of the research (Table 17). The stages outlined are not discrete but form part of an iterative research process. This interpretative approach to knowledge synthesis, proposed by Noblit and Hare, 1988 [234] was considered the most appropriate method for this review to enable the development of a new conceptual understanding of the primary studies, whilst preserving the interpretative properties of the primary data.[236] The analysis involves a process of identifying the key ideas or "concepts" from the primary qualitative studies, abstracting

these concepts into conceptual categories, further abstracting categories into themes and finally developing a line of argument. The line of argument refers to building up a picture of all the aspects of the synthesised parts using a short paragraph, diagram or conceptual model.[236] Central to this approach of synthesising qualitative research is developing a conceptual understanding through the process of constant comparison and abstraction rather than alternative approaches which describe the findings.[234]

Phase 2: deciding what is relevant

This stage of the review involved systematically searching, screening and appraising potential studies to decide which to include in the synthesis.

Table 17: Seven steps of Noblit and Hare's meta ethnography [234]

Seven steps of Noblit and Hare's meta ethnography[234]
1. **Getting started**
2. **Deciding what is relevant**
3. **Reading the studies**
4. **Determining how the studies are related**
5. **Translating the studies into one another**
6. **Synthesising translations**
7. **Expressing the synthesis**

Consensus on whether you need to search for, and include, all available studies to undertake a 'good' qualitative synthesis has not be reached.[241, 242] In their original text on meta-ethnography Noblit and Hare [234] do not advocate an extensive literature search when conducting a review. Unlike a quantitative review, a qualitative synthesis does not aim to summarise the available body of evidence, but provide a conceptual and

interpretative contribution. Although the number of qualitative studies conducted alongside clinical trials is reported to be increasing, studies in surgical trials compared with other areas such as behavioural trials, remain rare.[76] A systematic search of the literature was therefore conducted, to be able to identify the studies published in the area and identify any gaps in knowledge. This approach has been successfully conducted with others reviews.[230, 243]

Published reports of qualitative studies that explored experiences of patients and healthcare professionals participating in RCTs with a surgical and non-surgical comparison were included. Details of the inclusion and exclusion criteria are included in Table 18. Perspectives of both patients and clinicians were included. Pilot, feasibility and mixed methods studies that included a qualitative method of data collection e.g. interviews and analysis and where the qualitative component was clearly identifiable and could be extracted were also included. Studies of paediatric trials were excluded because of the potential for challenges related only to the specific nature of the population being identified. Only articles in English were reviewed because of limited resources to provide translation services.

Search process

Searching for qualitative research related to RCTs can be challenging because the qualitative work may be embedded in the wider trial making it difficult to identify.[244] Therefore an iterative approach was taken combining several strategies.

To help develop the search strategy, an initial search for any existing qualitative evidence synthesis related to challenges in conducting clinical trials was conducted using terms developed by Booth (2016) [244] (see Appendix 8).

Table 18: Study inclusion and exclusion criteria using modified PICO [244, 245]

Inclusion	Exclusion
Patient/Population:	
Peer reviewed journal articles and conference papers published anytime up to end of February 2018.	Unpublished dissertations, book chapters, papers or conference abstracts without corresponding full text articles.
Patients or health care professionals (clinicians) stakeholder views participating in RCTs with a surgical and non-surgical comparison.	Studies with participants under 18 years of age.
Articles in English language, published in any country.	
Intervention:	
RCTs with a surgical and non-surgical comparison	
Comparison:	
Randomised controlled trials that have a surgical and non-surgical comparison e.g. physiotherapy, drugs, medical management.	
Outcomes:	
Challenges related to the design and conduct of RCTs with a surgical and non-surgical comparison such as recruitment, retention, compliance with treatment allocation.	
Studies:	
Qualitative studies (or mixed methods studies containing substantial qualitative components that can make a contribution to the meta synthesis). As an operational definition data collected were in the form of semi structured interviews, focus groups, open ended evaluation forms including free text responses, observational field notes, or reflective journals. Papers should report some form of thematic or inductive analysis.	Studies of recruitment into surgical studies that are not randomised controlled trials.
	No qualitative analysis undertaken or primarily quantitative data reported. This includes questionnaire data.

The search strategy for the synthesis is detailed in Appendix 8. The following databases were searched up to the end of February, 2018: Medical Literature Analysis and Retrieval System Online (MEDLINE), and the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register, CINAHL, Embase and PsycINFO.

Electronic bibliographic database searches used a combination of medical subject headings (MESH) and free text. To increase the likelihood of identifying all suitable qualitative studies the reference lists of included studies and the qualitative evidence synthesis identified in the initial search [91, 219, 233] were also searched for further potential studies.

Selecting primary studies

One reviewer (LD) screened the titles and abstracts and articles that did not meet the inclusion criteria were excluded. Full text articles were then assessed and discussed with a researcher with experience in QES, Francine Toye (FT), to reach agreement on which papers to appraise for inclusion.

Quality appraisal

Despite ongoing debate about how, or whether, to assess the quality of qualitative research, [246-248] a growing number of researchers are appraising studies for the purpose of QES.[249] There are now many suggested frameworks for appraising the quality of qualitative research, although there is no consensus on what makes a study 'good'. [246-248]

Quality appraisal of the studies was carried out by two reviewers (LD and IO) using the Critical Appraisal Skills Programme (CASP) checklist [250] (Appendix 9). Individual assessments were compared and any areas of discrepancy were resolved through discussion.

Phase 3 and 4: Reading included studies and determining how studies are related

Each paper was read thoroughly to identify, describe and list the concepts. This is not a discrete stage of the process and reading of the papers continued throughout. The identified ideas or concepts from the primary studies are the raw data of the meta-

ethnography. The concept of first- and second-order constructs by Schutz [251] are often used in meta-ethnography studies to distinguish the data used.[247] First order constructs are defined as the participants' 'common sense' interpretations in their own words, whereas, second order constructs are the researchers' interpretations of the first order constructs. In meta-ethnography, the 'data' are second order constructs which are further abstracted to develop third order constructs (reviewers' interpretations of second order constructs) which are the themes and findings of the QES.[242] All full text articles were imported into NVivo 11 (QSR International, Warrington, UK),[98] the computer software used to manage the data. Using this software, all conceptual findings identified within the original papers were coded. Concepts from all included studies were then added to an excel spreadsheet table.

Two reviewers (LD and IO) discussed the concepts and in cases where it was agreed that there was no clear concept articulated i.e. 'no central idea pulling the description together',[242] in the original source material, the data was excluded. However, this did not mean that the whole study was rejected in its entirety.

Data on study characteristics was extracted: setting, aim, sample and methods of data collected and analysis. This provided contextual information to allow the reviewers and readers to examine the relevance of each study and to determine how each study was related to each other and the overall study aims.

Phases 5 and 6: Translating studies and synthesising translations

Translating studies into each other involves determining the relationship among the second order concepts from across the studies through constantly comparing and discussing concepts with a second reviewer (IO). The data was gradually organised into

conceptual categories that reflected the key ideas or concepts. Figure 3 (Appendix 10), shows an example of how, using thematic maps, second order constructs were compared to identify similarities and differences between them and organise them into further abstracted conceptual categories with shared meaning. The conceptual categories were then compared and discussed with a second reviewer (IO) to develop the final themes. Once a description of the conceptual categories were agreed and they were discussed with the wider team (DB and FT) to develop the themes.

Phase 7: Expressing the synthesis

The final stage of a meta-ethnography involves expressing the synthesis findings. The line-of-argument approach [234] was utilised to build a picture and integrate the themes to derive new insights. A diagram was constructed to develop and refine the line of argument that reflected the final interpretation. The findings were also summarised, using the GRADE CERqual approach to determining confidence in review findings, in the Summary of Qualitative Findings (SoQF) table.[252]

Confidence in review findings – GRADE CERQual

The 'Confidence in the Evidence from Reviews of Qualitative research' (GRADE-CERQual) approach has been developed to provide a structured method for assessing confidence in the evidence from a QES, and this framework used for this review.[253] GRADE-CERQual (CERQual) involves an assessment of each individual review finding in terms of four components: 1. Methodological limitations; 2 Coherence (consistency across primary studies), 3 Adequacy of data (the degree of richness and quantity of data supporting the review finding); 4 Relevance (Table 19).

In relation to QES, a review finding can be defined as an analytic output (e.g. theme, category, thematic framework, theory or contribution to theory), based on data from primary studies and describes a phenomenon or an aspect of a phenomenon.

Table 19: Definitions of the components of the CERQual approach [252]

Component	Definition
Methodological limitations	The extent to which there are concerns about the design or conduct of the primary studies that contributed evidence to an individual review finding.
Coherence	An assessment of how clear and cogent the fit is between the data from the primary studies and a review finding that synthesises that data. By 'cogent', it is meant how well supported or compelling.
Adequacy of data	An overall determination of the degree of richness and quantity of data supporting a review finding.
Relevance	The extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context (perspective or population, phenomenon of interest, setting) specified in the review question.

The assessments of the four components collectively contribute to an overall assessment of whether the findings from the qualitative evidence synthesis provide a reasonable representation of the phenomenon of interest. The overall confidence in each review finding is then reported as high, moderate, low, or very low confidence (Table 20).

Table 20: Descriptions of level of confidence in a review finding (CERQual approach) [252]

Level	Definition
High confidence	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest.
Moderate confidence	It is likely that the review finding is a reasonable representation of the phenomenon of interest.
Low confidence	It is possible that the review finding is a reasonable representation of the phenomenon of interest.
Very low confidence	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

The overall CERQual assessment of confidence in each individual review finding was discussed between LD and IO and any discrepancies resolved by discussion with FT. The summary of each review finding and indicators of confidence in each review finding are included in the findings below.

Findings

Outcome of study selection

In total, 4,339 titles, 3,692 abstracts, and 49 full texts of potentially relevant studies were screened (Figure 6). Of the 49 potential studies, 23 did not meet the study aims and were excluded. Reasons for excluding the studies included, not a surgery/non-surgery comparison, (n=14) [254-267] conference abstract only (n=4), [268-271] protocol/methods paper (n=5).[73, 272-275] Twenty six studies [39, 80, 89, 90, 193, 203-205, 217, 218, 276-291] were included in the review. Twenty one studies (21 /26) explored experiences within or associated with the context of a single RCT, [89, 90, 193, 203-205, 217, 276-287, 289, 290] whilst 5/26 studies provided a synthesis of results from multiple RCTs.[39, 80, 218, 288, 291] A summary of literature search and outcome is presented in the PRISMA flowchart diagram Figure 6.[292]

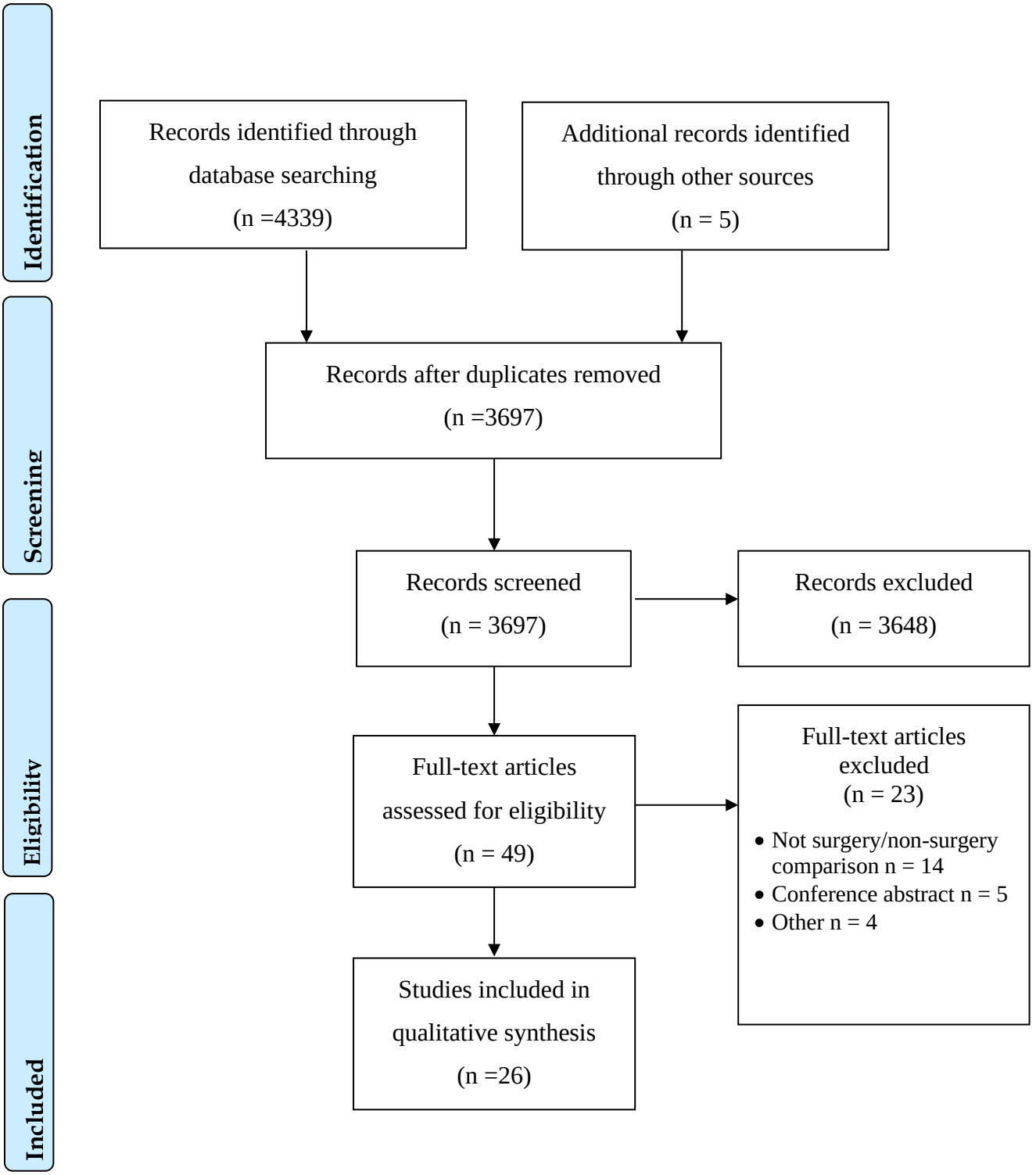


Figure 6: PRISMA flowchart summary of literature search for QES

Characteristics of included studies

Table 21 provides an overview of the 26 included studies included and Table 22 provides details of the characteristics of the studies [39, 80, 89, 90, 193, 203-205, 217, 218, 276-291] including author, year of publication, country, study aim, sample size, data collection, analytic approach and participants. The studies explored the experience of patients and healthcare professionals. Eleven of the 26 studies included experiences of both patients and healthcare professionals, six included experiences of healthcare professionals only and nine explored the experience of patients only. The majority of trials were conducted in the UK (24/26), and Oncology was the most frequently explored clinical speciality (20/26). The focus of the majority of the studies (24/26) were related to the challenges of recruitment,[39, 80, 89, 90, 203-205, 217, 273, 276-281, 283-291] however, two studies explored reasons for non-compliance to treatment allocation (i.e. why patients crossed over from being randomised to the non-surgical arm to surgical management) following randomisation.[193, 293]

Quality appraisal

The outcome of the quality appraisal of all the 26 included papers and indicators of confidence in each review findings are shown in Appendix 9.

Concepts and themes

Eighty five concepts were identified from the 26 studies. 17 of the 85 concepts did not fit the analysis. The excluded concepts were related to aspects of the individual trials or the process of randomisation in general, rather than specifically a surgical versus non-surgical comparison. The 68 remaining concepts explored the phenomenon of interest and were organised into 9 conceptual categories and then into five themes:

Table 21: Summary of included studies

Characteristics of studies	Number of studies n=26
Country:	
UK	24 39, 80, 89, 90, 203-205, 217, 218, 277-291
Sweden/Finland/Iceland	2 193, 276
Perspective:	
Healthcare professionals only	6 204, 205, 218, 280, 281, 291, 294
Patients only	9 90, 193, 279, 282, 284-287, 290
Healthcare professionals and patients	11 39, 80, 89, 203, 276-278, 283, 288, 289
Speciality area:	
Oncology	20 39, 80, 89, 90, 203-205, 217, 218, 276, 279, 286, 288, 291
Orthopaedics	7 39, 193, 281-283, 289, 290
Urology	2 280, 284
Ophthalmology	1 285
Obstetrics	1 287
Ear, Nose, Throat (ENT)	2 277, 278
Types of comparison:	
Surgery versus no active intervention	1 276
Surgery versus medical management**	13 80, 203-205, 217, 218, 279, 280, 285, 287, 288, 291
Surgery versus deferred surgery**	2 277, 278
Surgery versus medical management versus active monitoring**	5 80, 89, 90, 218, 286, 291
Surgery versus physiotherapy/exercise component**	5 193, 281-283, 289
Surgery versus placebo versus active monitoring	1 39
Surgery versus closed contact casting	1 290
Surgery versus medical management versus no active intervention	1 284
Data collection:	
Qualitative interviews only	16 193, 204, 218, 276-284, 286, 287, 290, 291
Mixed qualitative methods**	5 39, 203, 205, 217, 283, 288
Focus groups	1 285
Audio recordings of recruitment appointments	4 80, 89, 90, 289

* Includes more than one paper reporting on the same trial

**Mixed qualitative methods, interviews combined with the following: audio recordings of recruitment appointments, focus groups

Five main themes were abstracted from the data:

1. Radical choice between treatments,

2. Patients' discomfort with randomisation: best treatment for me as an individual,

3. Challenge of equipoise: Patients' *a priori* preferences for treatment,

4. Challenge of equipoise: Clinicians' *a priori* preferences for treatment, and

5. Imbalanced presentation of interventions.

The themes are discussed below and illustrated with narrative exemplars from the primary studies. Table 24 provides a summary of the themes, including the conceptual categories, studies supporting each theme and additional narrative exemplars from the primary studies

Table 22: Characteristics of studies included in the QES

Reference (Study, country)	Study aim/objectives	Stage of trial	Sample	Interventions	Data collection and analysis
1. Bill-Axelson et al (2009) [276] (Sweden, Finland, Iceland)	To understand attitudes to the randomization process among patients and clinicians in the hope of rendering the process more acceptable for these stakeholders in future.	2-8 years following randomisation	Nine patients with early prostate cancer (n=9 [5 participants and 4 non-participants) and randomizing clinicians (n=5)	Radical prostatectomy/watchful waiting	Semi-structured interviews Content analysis
2. Blazeby et al (2014) [203] (United Kingdom)	To determine the feasibility of a main trial of chemotherapy and surgery vs definitive chemoradiotherapy for localised oesophageal squamous cell carcinoma (SCC).	Pre-trial (Feasibility)	26 paired audio-recordings of surgery and oncology appointments and 14 in-depth patient interviews.	Neoadjuvant treatment and surgery/definitive chemoradiotherapy	Audio-recordings of surgery and oncology appointments and in-depth patient interviews. Conversation analysis Thematic analysis
3. Hamilton et al (2013) [217] (United Kingdom)	To investigate whether it was feasible to undertake a multicentre, RCT comparing disease-free survival and voice outcomes between laser surgery and radiotherapy and particularly factors affecting recruitment and data collection.	Pre-trial (Feasibility)	Surgeons (n=3) and recruiters (n=3)	Endoscopic excision/Radiotherapy	Semi-structured interviews/focus groups/audio-recordings of recruitment encounters Content and thematic analysis

4. McSweeney, et al. (2017) [278] (United Kingdom)	To assess the practicality of the proposed internal pilot and full scale trial.	Pre-trial (Feasibility)	Participants (n=48), ear, nose and throat (ENT) consultants, 1 ET trainee (registrar), research nurses (n=6), nurse practitioners (n=4), trial manager (n=2)	Tonsillectomy/deferred surgery as conservative management option	In-depth interviews Framework analysis
5. McSweeney (2017).[277] (United Kingdom)	To determine the impact of recurrent sore throats and tonsillitis in adults and stakeholder views of treatment pathways.	Pre-trial (Feasibility)	Patients (n=15), General Practitioners (n=11), 9 ENT consultants, 1 specialist registrar, 6 research nurses, 4 nurse practitioners, 2 trial managers (n=22)	Tonsillectomy/non-surgical management	In-depth interviews Framework analysis
6. Mills et al (2011) [90] (United Kingdom)	To explore how patients' treatment preferences were expressed and justified during recruitment to a randomised controlled trial (RCT) and how they influenced participation and treatment decisions.	Main trial (Recruitment)	Participants with localized prostate cancer (n=93)	Radical prostatectomy/ radical conformal radiotherapy/active monitoring	Audio-recordings
7. Moynihan, C., et al. (2012) (United Kingdom)	To illuminate problems in the context of randomization to a randomized controlled trial comparing selective bladder preservation against surgery in muscle invasive bladder cancer	Pre-trial (Feasibility)	Patients (n=24)	Radical surgery (cystectomy) following neo-adjuvant chemotherapy/ selective bladder preservation where definitive treatment (radiotherapy or cystectomy) was decided based on response to neo-adjuvant chemotherapy	Semi-structured interviews Framework analysis

8. Paramasivan et al (2011) [205] (United Kingdom)	To explore reasons for low recruitment and attempt to improve recruitment rates by implementing changes suggested by qualitative findings.	Pre-trial (Feasibility)	Healthcare professionals (n=9)	Radical surgery (cystectomy) following neo-adjuvant chemotherapy/selective bladder preservation where definitive treatment (radiotherapy or cystectomy) was decided based on response to neo-adjuvant chemotherapy	Audio-recordings Semi-structured interviews Conversation analysis Thematic analysis
9. Skea, Z. C., et al. (2017) [280] (United Kingdom)	To explore trial site staff's perceptions regarding barriers and facilitators to local recruitment. To identify trial-specific modifiable factors that could enhance the facilitators and remove the barriers to recruitment.	Main trial (Recruitment)	Members of staff from 4 trial sites (n=11) Co-applicant (n=1), Principal Investigators (n=3) Consultant Urologist (n=1), Research Nurses (n=5), Research Assistant (n=1)	Extracorporeal shockwave lithotripsy/ureteroscopic stone retrieval (via surgery)	Semi-structured interviews Thematic analysis using Framework approach
10. Strong et al (2016) [204] (United Kingdom)	To explore how teamwork influences recruitment to a multicentre randomised controlled trial (RCT) involving interventions delivered by different clinical specialties.	Main trial (Recruitment)	Healthcare professionals (n=21)	Surgical (oesophagostomy)/definitive chemoradiotherapy)	Semi-structured interviews Thematic analysis
11. Thorstensson (2009) [193] (Sweden)	To understand patients' views about treatment after acute ACL injury, and to explore why patients crossed over from the training only to the surgical and training treatment arm despite consenting to participate in a trial comparing the two treatments.	Main trial	Patients (n=34)	Arthroscopic surgical reconstruction followed by physiotherapist supervised outpatient training (exercise)/supervised training only.	In-depth interviews Framework approach

12. Zeibland et al (2007) [281] (United Kingdom)	To explore their understanding of the trial purpose and how this understanding had influenced their recruitment procedures and interpretation of the results.	Completion of study	Participating surgeons (n=11)	Intensive functional rehabilitation programme (FRP) with spinal fusion surgery for treatment of chronic low back pain	In-depth interviews Thematic analysis
13. Wade et al (2009) [89] (United Kingdom)	To open the "black box" of what goes on during informed consent appointments in a large multi-centre RCT (ProtecT).	Feasibility and main study	Recruitment appointments (n=23) 12 recruitment staff	Radical prostatectomy, radical conformal radiotherapy and active monitoring	Audio-recordings Thematic, content and conversation analysis
14. Minns Lowe (2017) [293] (United Kingdom)	To explore why participants recruited within UKUFF (The United Kingdom Rotator Cuff Tear Trial) did not remain within their allocated treatment arm, and explored crossover and decisions about having/declining surgery from the perspective of trial participants.	During study	Participants (n=18)	Arthroscopic rotator cuff repair surgery/open/mini-open rotator cuff repair surgery/Rest then Exercise (RtE)	Semi structured interviews Interpretative Phenomenological Analysis (IPA)
15. Griffin et al (2016) [283] (United Kingdom)	To understand how to optimise recruitment in a future full RCT of this question. Feasibility study comparing surgery and non-operative care for hip impingement.	Feasibility	Trial Management Group (n = 10) and clinicians (n = 21) RCT consultations recorded (n = 87)	Arthroscopic surgery/physiotherapy	Audio-recordings In depth semi-structured interviews Thematic analysis
16. Brookes 2003 [284] (United Kingdom)	To examine the impact of including a 'no active intervention' arm (called conservative management) in a RCT comparing treatments (including surgery) for men with lower urinary tract symptoms related to benign prostatic enlargement.	Main trial	Participants (n=22) Non participants (n=11)	Transurethral resection of the prostate (TURP)/no active intervention (conservative treatment)/non-contact laser therapy.	In-depth semi structured interviews Thematic analysis

17. Leighton 2012 [285] (United Kingdom)	To examine the attitudes of patients, who presented with advanced glaucoma in at least one eye, to participation in a randomised prospective trial comparing primary medical treatment with primary surgical treatment for advanced glaucoma.	Pre-trial	5 focus groups (between 4-8 participants)	Primary medical treatment/primary surgical treatment	Focus groups Thematic analysis
18. Mills 2003 [286] (United Kingdom)	To explore patients' perceptions of randomization and understand the reasons for consenting or refusing randomization within a controversial trial of treatments for localized prostate cancer.	Main trial	Participants in ProtecT study with localized prostate cancer (n=21)	Radical prostatectomy,/radical conformal radiotherapy/ active monitoring	In-depth interviews Constant comparison
19. Lie, M., et al. (2012) [287] (United Kingdom)	To provide insights into two strands of understanding; firstly, women's experience of participating in research about abortion and secondly, their experience of participating in a randomised preference trial, thus having implications for the design and conduct of termination of pregnancy clinical trials.	Main trial	Participants (n=30)	Medical/surgical termination of pregnancy	Semi-structured interviews

20. Rooshenas et al (2016) [39] (United Kingdom)	To investigate how clinicians conveyed equipoise during recruitment appointments in ongoing RCTs, with the view to identify practices that supported or hindered equipoise communication.	Main trial	Pragmatic UK based RCTs (n=6) Clinicians recruiting to the RCTs (n=16) Appointments in which these clinicians presented the RCT to trial eligible patients (n=105) 2 trials included a surgical/non-surgical comparison	Trial 1: Arthroscopy with surgical manipulation/Arthroscopy alone/Active monitoring with specialist reassessment Trial 2: Neoadjuvant treatment and surgery/definitive non-surgical treatment	In-depth interviews Audio-recordings Thematic and content analysis
21. Paramasivan et al (2015) [288] (United Kingdom)	To systematically investigate, quantify and qualitatively explore the imbalances in the presentation of treatments to patients.	Pre-trial (Feasibility)	RCTs (n=2) 1 trial included in this review Recruitment appointments (n=26) patients (n=16) Staff (n=20)	Chemotherapy plus surgery or radiotherapy	Semi structured interviews Audio-recordings
22. Realpe 2016 [289] (United Kingdom)	To investigate the conduct of recruitment consultations that led to participants agreeing to participate in the pilot trial of arthroscopic surgery for hip impingement compared with non-operative care.	Pre-trial (Feasibility)	Consultations (n=92) Participants (n=60_ (n=34 diagnostic, n=58 recruitment consultations)	Arthroscopic surgery/non-operative care.	Audio recordings Thematic and conversational analysis
23. Keene 2016 [290](United Kingdom)	To investigate patients' experiences of living with a fractured ankle and experiences of being in the trial.	Main trial	Study participants (n=36)	Closed contact casting/Open Reduction Internal fixation (ORIF)	Interviews
24. Mills et al (2014) [80] (United Kingdom)	To investigate how RCT recruiters reacted to patients' treatment preferences and to identify key strategies to improve informed decision making and trial recruitment.	Main trial (Recruitment)	RCTs (n=3) 2 trials within this Recruitment appointments (n=103) participants (n=96)	Trial 1: Surgical and non-surgical treatment for cancer Trial 2: Surgery/radiotherapy/active monitoring	Audio recordings

25. Donovan et al (2014) [218] (United Kingdom)	To understand the recruitment process from the perspective of recruiters actively recruiting RCT participants in six pragmatic RCTs and to identify opportunities for interventions to improve recruitment.	Feasibility and main trial	RCTs (n=6) 3 trials included in this review Trial 1: Doctors (n=3) Trial 2: Doctors (n=13)/nurses (n=10) Trial 3: Doctors (n=8)/nurses (n=3)	Trial 1: Surgery/radiotherapy Trial 2: Surgery/radiotherapy/active monitoring Trial 3: (Chemotherapy) surgery/radiotherapy	In-depth Interview Content and thematic analysis
26. Donovan et al (2014) [291] (United Kingdom)	To investigate how doctors considered and experienced the concept of equipoise while recruiting patients to RCTs.	Feasibility and main trial	RCTs (n=6) 3 trials included in this review Trial 1: Doctors and nurses (n=6) Trial 2: Doctors and nurses (n=20) Trial 3 Doctors (n=8)	Trial 1: Laser surgery/radiotherapy Trial 2: Surgery/radiotherapy/monitoring Trial 3: : (Chemotherapy) surgery/radiotherapy	In-depth Interview Content and thematic analysis

Table 23: Summary of Qualitative Findings (SoQF) table

Review Finding	**Studies Contributing to the Review Finding**	**Assessment of Methodological Limitations** (details of CASP checklist included in Appendix 9)	**Assessment of Relevance**	**Assessment of Coherence**	**Assessment of Adequacy**	**Overall CERQual assessment of Confidence**	**Explanation of judgement**
1. Radical choice between treatments	13/26 studies [90, 193, 203, 205, 217, 277, 280, 282-285, 287, 290]	Minor methodological concerns (not clear in a number of studies whether the relationship between the researcher and participants was adequately considered)	Moderate concerns. All included studies were exploring issues related to trials where there was a surgical and non-surgical comparison. Some of the concepts in some studies were related to aspects of the individual trials and did not fit the analysis.	Moderate concerns. Overall the majority of studies included in this review are oncology studies conducted in the UK, however a range of studies from different specialities contributed to this finding. Data consistent within and across all studies. Data reflects the variation in the types of interventions compared in the different studies and highlights differing views depending on the comparison.	Moderate concerns about adequacy (13 studies contributed to this review finding providing moderately rich data overall).	Moderate confidence	The finding was graded as moderate confidence because of minor concerns regarding methodological limitations and moderate concerns regarding adequacy, relevance and coherence.

2. Patients' discomfort with randomisation: best treatment for me as an individual	7/26 studies [90, 203, 276, 279, 283, 285, 295]	Minor methodological concerns (not clear in a number of studies whether the relationship between the researcher and participants was adequately considered)	Moderate concerns. All included studies were exploring issues related to trials where there was a surgical and non-surgical comparison. Some of the concepts in some studies were related to aspects of the individual trials and did not fit the analysis.	Moderate concerns. Overall the majority of studies that contributed to this finding were oncology studies conducted in the UK. Data was well supported by the details in the underlying studies.	Moderate concerns about adequacy (7 studies contributed to this review finding providing moderately rich data overall).	Moderate confidence	The finding was graded as moderate confidence because of minor concerns regarding methodological limitations and moderate concerns regarding adequacy, relevance and coherence.
3. Challenge of equipoise: Clinicians' a priori preferences for treatment	6/26 studies [39, 217, 218, 276, 283, 291]	Minor methodological concerns (not clear in a number of studies whether the relationship between the researcher and participants was adequately considered)	Moderate concerns. All included studies were exploring issues related to trials where there was a surgical and non-surgical comparison. Some concepts in some studies were related to aspects of the individual trials and did not fit the analysis.	Moderate concerns. Overall the majority of studies that contributed to this finding were oncology and orthopaedic studies conducted in the UK. Data was consistent within and across all studies.	Moderate concerns about adequacy (6 studies contributed to this review finding providing moderately rich data overall).	Moderate confidence	The finding was graded as moderate confidence because of minor concerns regarding methodological limitations and moderate concerns regarding adequacy, relevance and coherence.

4. Imbalanced presentation of interventions	9/26 studies [39, 203-205, 280, 283, 288, 289, 291]	Minor methodological concerns (not clear in a number of studies whether the relationship between the researcher and participants was adequately considered)	Moderate concerns. All included studies were exploring issues related to trials where there was a surgical and non-surgical comparison. Some concepts in some studies were related to aspects of the individual trials and did not fit the analysis.	Moderate concerns. Overall the majority of studies that contributed to this finding were oncology studies conducted in the UK. Data was well supported by the details in the underlying studies.	Moderate concerns about adequacy (9 studies contributed to this review finding providing moderately rich data overall).	Moderate confidence	The finding was graded as moderate confidence because of minor concerns regarding methodological limitations and moderate concerns regarding adequacy relevance and coherence.
5. Challenge of equipoise: Patients' a priori preferences for treatment	8/26 studies [80, 89, 203, 205, 217, 218, 276, 283]	Minor methodological concerns (not clear in a number of studies whether the relationship between the researcher and participants was adequately considered)	Moderate concerns. All included studies were exploring issues related to trials where there was a surgical and non-surgical comparison. Some concepts in some studies were related to aspects of the individual trials and did not fit the analysis.	Moderate concerns. Overall the majority of studies that contributed to this finding were oncology studies conducted in the UK. Data was well supported by the details in the underlying studies.	Moderate concerns about adequacy (8 studies contributed to this review finding providing moderately rich data overall).	Moderate confidence	The finding was graded as moderate confidence because of minor concerns regarding methodological limitations and moderate concerns regarding adequacy relevance and coherence.

Themes

1. 'Radical choice' between treatments

In contrast to trials with very similar treatment arms (e.g. two surgical procedures), clinicians described how they found it challenging to recruit to trials with a surgical and non-surgical comparison as they felt that patients had a strong preference for a particular treatment, largely because they saw the decision as a 'radical choice' between the two treatments.[205, 279]

> *The other trials that I work on that are randomised are usually working say between two different types of chemotherapy (…) and no, I haven't had problems with patients going into studies like that. I think it's the fact that it is sort of the radical choice if you like, surgery-no bladder, bladder preservation keep your bladder (Nurse, Recruiter).*[205]

Similarly patients described these marked differences between the interventions in these types of trials as having an impact on their views and decision making regarding treatments.

> *I felt that they [clinicians] were very keen … to say, 'It doesn't matter which method you have, it'll be fine; that's why it's OK to have a random trial because the medical's like this and the surgical's like this and really there's no difference between the two', however, I always kind of felt myself there is a difference between the two; sort of obviously, physically, and secondly, psychologically. I think it does have an impact (Patient).*[287]

Some patients expressed clear preference towards one treatment or the other and clinicians' described this strength of patients' preference for particular treatments as a major challenge to recruitment in trials with this type of comparison.[205, 217, 280, 283]

Clinicians indicated that although some patients accepted that treatments could potentially provide an equally effective outcome, the physical and psychological differences of undergoing a particular treatment, influenced patients' views towards treatments and trial participation.[205, 280]

> *Either people want it [the cancer/bladder] out desperately, don't want to talk about anything unless it's out, they want rid of it. Or the group of patients that really doesn't pander to the idea of a big operation and want to hang on to their bladder, they want to be normal. And so I find a lot of patients come along, even if they haven't been influenced by somebody else, even if the trial has been put to them beautifully, they usually have some kind of preference based on what happens to them rather than on the effects or the efficacy of the treatment, and I think that's the biggest problem from the patient's point of view (Oncologist, Recruiter).*[205]

There were four factors related to differences between interventions compared in these types of trials that seemed to influence patients' preferences for treatment:

a. Level of invasiveness – surgery cannot be undone

Clinicians felt that differences in the degree of invasiveness between the surgical and non-surgical interventions influenced patients' preferences for treatment, making the recruitment discussion challenging. Some patients declined trial participation as they felt if the same results could be potentially achieved without an operation, it was preferable to start with the non-surgical treatment. Surgery could be considered later as an option if there was no improvement with non-surgical management.[193, 279]

> ....Oncologist: *Ok. What, in particular puts you off the surgery?* Patient: *I don't think I'm particularly worried about surgery, as such,... - if the [non-surgical option] can do the same thing without the cutting that's my only reason, really [in picking it]. Oncologist: Ok. That's fair enough'.* [288]

You can't undo surgery, but if you have training and don't get well you can always have surgery (Patient).[193]

Preference for the less-invasive option was linked to some patients' anxiety about surgery, [80, 280, 283, 285, 293] with surgery viewed as the point of last resort.[283, 285]

> *A lot of patients seem a lot keener on the lithotripsy because obviously it's a much less invasive procedure… we do always say to them, "Well, look. If you have these…you can have up to three treatments … three treatments and if all three of those fail then you will end up having (surgery) anyway", but generally patients are much keener to try the less invasive procedure first, which is understandable (Research Assistant).*[280]

b. Level of potential risk: Is surgery worth the risks?

Differences in the level of potential risk associated with surgery compared to non-surgical treatment, and the implications of those risks,[285, 293] influenced patients' preference towards particular treatments in trials with this type of comparison.

> *Patient: I'm definitely veering towards the monitoring side of things, because why have all those additional complications, the potential for them… I've got a good quality of life and I would like it to continue..... Research nurse: So what would be your worry with surgery? Patient:…With surgery there could be complications… the catheter and impotence.* [80]

Patients' views of the potential risk of undergoing surgery and implications of the risks varied depending on the condition or injury being evaluated. Greater duration or severity of symptoms was discussed by patients as influencing their views towards more invasive treatments, affecting their willingness to participate in a trial.[277, 278, 280, 283]

> *..I'd be anxious to have the surgery sooner because I've been suffering since I was young...to wait even more and to miss more time off work, no I really think it's time that they come out (Patient).* [277]

Some patients considered the potential risks associated with surgery to be 'worth it' if it enabled the patient to continue with an activity that was important to them. [193]

> *I imagine the risk of OA increases with surgery. It might be worth the risk if you think you'll have an additional 10 years with football, because it's a long period of your life. If you have OA later, you might be prepared to deal with it, because you had 10 more years with football (Patient).* [193]

Differences in the overall strength of patients' preference for either surgical or non-surgical interventions varied between the trials. For example, the potential risk of blindness from glaucoma surgery (although seen to be low), was identified as a factor underlying strength of patients' preference for non-surgical treatment in a feasibility study for a trial evaluating surgical or medical management for advanced glaucoma.[285]

> *'I think it's difficult to explain to people that maybe surgery is better, because you could lose your eyesight… in the operation. I don't know whether that's happened a lot or not. But if you're still on the drops, and your eyesight's going gradually, it might be years before you end up in the same situation that the operation [might create immediately], you know…' (Patient).*[285]

c. Mechanism of effect is clear with surgical treatment

Comparing interventions with fundamentally different treatment mechanisms also influenced patients' and clinicians' willingness to participate in trials with a surgical and non-surgical comparison. Clinicians described how they felt patients were more accepting of the surgical option as they could intuitively understand the effects of surgery, the mechanism of something being repaired or removed. Patients described surgery as providing a cure or 'fixing' a problem,[283, 288] and viewed surgery as providing a definite treatment, a sense of finality of having received or undergone the treatment.[290]

> *''Surgery rids the prostate and therefore rids the cancer. I would be worried about it spreading if I had active monitoring' (Patient).*[90]

> *..it's the best way really to get you on your feet quickly because it's so fixed and you can't do damage you know following the op….life's too short to spend months and months and months around the house worrying about whether or not the bone has knitted properly but I've no idea it that is the case…Yes, a quick fix. The way surgeons you know are always saying I fixed you up. You'll be fine now (Patient).* [290]

Non-surgical treatment was not always viewed by patients with as much confidence in being able to provide a definitive treatment to their problem. Some patients viewed non-surgical care as a "provisional solution or as a first step treatment plan" [283] because it was not clear by what mechanism non-surgical treatment alone could repair the damage, correct, provide a 'fix' or 'cure'.[203, 283]

> *Physio may improve a bit but I can't see how physio can resolve the problem if it is hip impingement. I, it can tear again if I get active, and if I've got arthritis, I don't see how it can get better (Patient).*[283]

Some patients indicated that they would be uncomfortable with the uncertainty linked to undergoing non-surgical treatment i.e. whether the injury was healing or whether they were wasting time before the problem was resolved with surgery.[290]

Patients' lack of confidence in non-surgical treatment being able to provide a definitive treatment not only affected patients' willingness to participate in a trial, but was also identified as the reason why some patients randomised to the non-surgical arm did not comply with their treatment allocation, and subsequently underwent surgery.[193, 293] Some patients randomised to non-surgical treatment, considered whether undergoing subsequent surgery would provide a cure, or enable better levels of function to reach full potential, as highlighted in the example below.[193, 293]

Training was good, it helped me cope at home, to get stronger and dare more. But I reached the line where I felt good but not 100%. I have been somewhat better, but I want to achieve the last bit. It may get worse as well, they've told me that, even though the chances are quite good. 90–95% get well from surgery, that's quite a lot (Patient, pre-surgery group).[193]

d. Disparity between treatment pathways

Marked differences between aspects of the treatment pathways in trials with this type of comparison also influenced patients' views towards treatments. Unlike trials of similar comparison (e.g. two surgical procedures), where interventions are delivered by the same clinical speciality with for example similar waiting times for procedures, level of patients input, patients viewed practical or logistical differences between the trial arms as influencing their decisions around willingness to participate. For example, a more complex treatment process or longer waiting times before being able to start treatment influenced patients' views towards treatments.[205, 217, 280, 293]

Unfortunately, in this facility, sometimes the surgical option is not as quick as…the lithotripsy option. You can see that actually influencing people's decisions, which they can have the earliest (Research nurse). [280]

With some trial comparisons, patients viewed surgical treatment as more convenient, whereas the non-surgical treatment was seen as more involved, required more effort or impractical for example because of socioeconomic factors e.g. time off work.[39, 217, 283, 293]

'[The patient] was with his daughter and… said, very clearly, ''I'm not having radiotherapy'' because of the travelling every day, because of his family… he wanted something that was in and out…' (Recruiter). [217]

Because you have to be out work and in crutches, and it would have implications for me for childcare if I have it, I don't know how immobile you'd be. (Patient).[283]

2. Patients′ discomfort with randomisation: best treatment for me as an individual?

This theme describes how, although patients accepted the importance of research, they expressed discomfort in how decisions about their individual treatment were left to chance through randomisation, particularly when there were such differences between the treatment comparisons. Some patients' indicated that they felt individual factors such as age and extent of problem should be considered in decision making about the best treatment for them as an individual, and felt that a particular treatment would be more suitable than the other.[283, 286]

> *I think it ought to be dependent on your particular situation rather than on a 50: 50 toss of a coin which way you went. I'm sure some issues, and some hip injuries, are probably more suited to one route rather than other (Patient).* [283]

> *Well I think [random treatment allocation] is quite dodgy. You'd have thought that when you come down to a particular individual their particular circumstance like their age, like the extent of the cancer, like the degree of dispersion of the cancer, like the level of the PSA [prostate-specific antigen], I mean all those individual factors you'd have thought would have some impact on the decision over the treatment…. Wouldn't you want to identify with the doctor the best treatment for you as an individual? (Patient).* [286]

Although some patients found the uncertainty between the different treatments made it easier to decide whether to participate, [287] others felt uncomfortable with the loss of 'control' over decision making and the departure from a more traditional doctor patient relationship.

> *In my head you've now firmed everything up … by electing to stay in the study I'm not in control. I've always been in control of everything and that is why I wish to opt out of the study and go for regular monitoring. I don't think at this stage I need [further*

information] cos I have made up my mind. I'm quite happy that it's monitoring.'' (Patient). [90]

Patients questioned the need for randomisation and how the trial undermined the role of the clinician.[283, 286]

'*I just do what (my consultant) says and that's it.' 'I would sooner rely on what (my consultant) is telling me. Therefore that's the route I'm going down, I'm not interested in pros and cons, I'm relying on him to do, err. I'm just interested in, he's the expert, he's the one I'll put my faith in.'(Patient).* [285]

3. Challenge of equipoise: Patients' a priori preferences for treatment

This theme describes clinicians' challenge of being able to reconcile patients' a priori views so that they would consider trial participation.[205, 217, 280, 283] Clinicians' considered this more challenging in trials where interventions are markedly different to each other and where there is potential for patients to have strong preferences for particular interventions.

'Yeah, and the other thing we're up against… is that patients have this absolute fixation… they have a fixation that somehow laser's magic right? And I can't debunk that however much I try' (Surgeon 1, interview). [217]

Some recruiting clinicians were reluctant or found it uncomfortable to challenge patients' expressed preferences for treatment and would accept them without further exploration of whether or not they were based on accurate information.[39, 80, 89, 205, 217, 280, 291]

(Challenging patient's preferences) depends very much on the patient. If I feel that they're the sort of person who could cope with the uncertainty, then I'll say to them, 'we're not going to know unless research is done'…… if they absolutely want the bladder removed, you're not going to be able to sway them, and I don't think it would be ethical to try to be honest. If they're adamant, no they want it

> *over with, they want it out, they want it gone, then I don't think it's ethical to push, because if it wasn't the trial, they wouldn't be having radiotherapy pushed on them anyway, and I don't feel it's ethical to push them any further (Nurse, Recruiter).(Paramasivan 2011)*

Challenging patients' preferences for treatment was viewed by some clinicians as potentially coercive,[39] particularly with the elevated risks associated with surgery compared with non-surgical treatment. Some clinicians felt that patients may be 'rushed into' a surgical procedure because of participation in the trial.

> *There are significant risks in people who undertake surgery compared to those that don't, that's where it is awkward because these two treatments are so very different (Clinician).* [283]

Some clinicians felt that if patients had previously had some form of non-surgical management e.g. physiotherapy, this might contribute to patients reluctance in some cases to undergo further conservative care.[193, 282, 283]

> *Patients come when [they have] already had a course of physiotherapy, that is patients have often come [after] non-operative treatments, and they look at you as if you are mad if you say 'I want to send you back to physiotherapy for more treatment'.* [283]

Exploring individual views about the trial or treatment process and tailoring the information provided to address patient concerns was discussed as a potential strategy to help balance patients' views about treatments, and enable patients to make an informed choice regarding trial participation.[80, 89, 90, 276, 283]

> *''In this situation it's important to make them understand that the alternatives are equivalent and if a patient preferred surgery I stressed the risks with surgery. The point is to get the patient neutral, not until then is he fully informed and at the same level as current knowledge'.* [276]

4. Challenge of equipoise: Clinicians′ a priori preferences for treatment

Clinicians' conflict between their willingness to participate and support research and their own individual preferences towards certain treatments for particular patients was regarded as a barrier to trial recruitment. The influence of strong clinical speciality convictions was especially evident in this type of trial comparison.

Clinicians could justify participation through a sense of community equipoise, that is, the collective uncertainty in the clinical community about which treatment is best, due to lack of robust evidence. [39, 291] However, their views about the optimal management of patients on an individual level ("individual equipoise") sometimes made it difficult to recruit certain individuals.

> *I've not found it [equipoise] personally difficult in concept, because I've been absolutely convinced that we don't know which is the best treatment and although surgery may be a better procedure for cancer cure it has such a high impact that a small number of people might benefit and it's quite a few who are paying a heavy price to get that. So I've not really had any difficulty in that. I think where it's got difficult, I would say is, in a group of patients that intuitively I feel might do better with active treatment. I know intellectually there's no evidence about treatment in particular sub-groups, but ... there's little sub groups where I've found it more difficult than others, and that's inevitable, I think (Clinician).* [218]

Clinicians' strong preferences for particular treatments or in relation to specific patient groups were described in the studies as contributing to the lack of eligible participants. Patient related factors such as severity of symptoms, age and specific disease presentation influenced the development of clinicians' preferences for treatment.[39, 217, 218, 276, 283, 291]

> *"My bias is that in a younger person, [intervention 1] probably is a better treatment … Rather than putting them into trial, I think what I'd like to do is give them [intervention 1] up-front." (Clinician).* [218]

Some clinicians viewed the balance of current evidence to favour one treatment over another, or their clinical experience influenced their strong preferences for certain treatments. [39, 283] This was regarded as more problematic in RCTs evaluating treatments that were already established in clinical practice where clinicians had developed strong views about particular treatments.[39, 288]

> *I spent 20 years learning how to treat patients with certain problems and I've gradually learned over the years which ones I can help and which ones I'm less effective in helping (Surgeon).* [283]

> *It is the case though that historically because we've had such a strong surgical lead to the MDT (Multi-Disciplinary Team meeting), we've got a long history of surgery for that group of patients (…) I think that it's not because we think surgery is better, it's just that we've more experience and that it's been a gold standard here for so long. (Oncologist).* [288]

Targeted training and support for recruiting clinicians, which was delivered in a number of the trials increased clinicians' levels of confidence and comfort with equipoise and ability to recruit.[291] Clinicians described how they were more aware of potential prejudices and how they felt more comfortable to challenge their own assumptions.[218]

> *I found the [training] meeting [about trial] fascinating. Because you don't realise all the prejudices that you do have until you talk to other people about it and you talk about a trial like this and you realise that you are making lots of assumptions, and the main assumption is that as a surgeon you're doing good. Do you know what I mean? If you get rid of something you're doing some good. But you've got to critically evaluate that. It's hard. It's hard to be honest and say, ''I'm doing all this work, slaving away and actually, have I achieved anything?'' (Clinician).*[218]

5. Imbalanced presentation of interventions

Clinicians' presentation of the surgical and non-surgical interventions during the recruitment discussion was described as being imbalanced, influencing patients' views towards treatments and willingness to participate in a trial. There was also a sense that varying involvement and enthusiasm towards the trial by the different clinical specialities influenced patients' expectations and preferences towards particular treatments.

The terminology that clinicians used to describe treatments was considered to be loaded with meaning or imbalanced and this affected how patients viewed the treatments.[39, 205, 283, 288] For example in trials comparing surgery and radiotherapy, surgery was described by clinicians using definitive terms such as 'cure', 'kills the cancer', 'gold standard', 'physically removes' or 'cuts it away' whereas radiotherapy was described more tentatively as ' having a chance of killing the tumour', 'tries to kill it', 'shrinks the tumour', 'may be able to treat the tumour' or as an option for those who did not want an operation.[39, 205, 288] Clinicians' descriptors of treatment influenced patients' interpretations, not only on the likelihood of effectiveness, but also on the acceptability of the treatment process. Where the surgical process was described as 'nice and simple',[217] a quicker answer to your health problem [39] compared with non-surgery treatment being 'a bit more labour intensive', 'a bit further for you to travel'.[217]

> *Clinician: [after describing definite beneficial effects of treatment x]: However, if you use [treatment y], well, potentially you can get the health benefits that you want, but it does require a lot of input from you.*
>
> *Patient: Looking at what you told us, [treatment x] would be the best option for me, because it's a quick answer to my health problems.*[39]

Variable 'buy in' from the clinicians from the different clinical specialities involved in the trial, led some recruiting teams to discuss whether both treatments were presented with equal enthusiasm.[204] Differences in the level of engagement with the study, with some clinicians very committed and others "indifferent" or even "antagonist to it", created difficulties as patients developed strong preferences for one arm or the other.[205, 280]

> *Some people, urologists especially, in some centres are not behind the trial at all, and will not put patients in towards it, so some centres I know haven't recruited because there's a problem with the urologist. Clinicians in general are doing what they think is best, so surgeons are very defensive of cystectomy because they've done lots of them, and they think that that's the best thing to do, and some of them haven't accepted that the best thing to do is put patients into SPARE [Selective bladder Preservation Against Radical Excision (cystectomy) in muscle invasive bladder cancer] (Investigator).* [205]

Some trial teams felt that the order in which patients saw clinicians would create imbalance and influence expectations and the development of preferences towards treatments. [204, 205]

> *I think the main problem of the trial was who saw them first. If the oncologist saw them first then they would be able to lay out their stall first – with the pluses and the minuses and then if they were seen again – in a few days' time by the surgeons then foremost in their mind would be what the oncologist had to offer and we (as surgeons) would then have to, in inverted commas, compete with that. Whereas, if it happened the other way round we would then at least get our information across on a blank canvas. I think that's the difficult thing with two very different treatments with two very different side-effect and complication profiles (Consultant surgeon).* [204]
>
> *Depends who's spoken (laughs lightly) to them first, I mean if the surgeons have spoken to them first, they generally think that surgery is the best option because*

> *it's been discussed by a surgeon and to a surgeon that is the best option. If they've spoken to an oncologist or myself, if they speak to me, they tend to be more open-minded about it, because I present both sides. It's quite difficult to get people onto a trial saying, 'hey let's see if it's alright to not have surgery', when the surgeons are saying, 'well I'd have surgery'. It's not that (surgeon) is anti-trial or anything else, because he's not... he's very pro trials, but his fundamental belief is that if you've got a bladder cancer you should have your bladder taken out (Nurse, Recruiter).* [205]

Studies in which recruitment discussions were audio recorded described how surgery was often presented at greater length and more favourably than either choosing conservative care or participating in an RCT.[203, 283, 289] Clinicians described the challenge of presenting a treatment arm that is not as familiar to them.[203, 281, 283].

Several studies explored ways to create a more balanced approach to recruitment, for example: changing the order that the treatments are presented; having combined clinical speciality consultations or multi-disciplinary team meetings to reduce professional barriers; considering another member of the research team, better placed to introduce the study to potential patients.[204, 289]

> *P13: You almost want the patients informed and consented and entered into the trial by a non-oncologist and non-surgeons. You want somebody who knows about both treatments, very well and in detail, knows about potential complications but also is removed from the frontline, so that they can impart as much information as possible in an unbiased way. (Consultant surgeon).* [204]

Other trials redrafted patient information sheets or advice given to recruiters to provide information in a more balanced way.[205, 289]

Conceptual model

The final phase of a meta-ethnographic analysis is to develop a model or line of argument that is abstracted from, but more than the sum of, the themes (Figure 7). [234] Four reviewers (LD, FT, JC, DB), discussed the abstracted themes and developed a model that made sense of the final themes.

The model highlights the potential challenge for both patients and clinicians to achieve a position of equipoise in these types of trials where the intervention comparators can be so diverse. The model details the potential factors influencing patients' and clinicians' *a priori* preferences for treatment. The model illustrates, depending on the particular interventions being evaluated, how there could be potential for imbalance in how the interventions are viewed, which could lead to recruitment difficulties.

The model highlights the potential complexity in the development of a patients' preference for one treatment or another. The model demonstrates how the interventions compared could be perceived by patients as a 'radical choice', potentially leading to strong treatment preferences for one intervention or another. The model also illustrates how clinicians' *a priori* preferences may contribute to an imbalanced presentation of the trial interventions, potentially contributing patients' preferences towards treatments.

Finally, the potential complexity underlying patients a priori preferences detailed in this model can also help to understand the potential challenge it can be for clinicians' in discussing trial participation with patients in these types of trials.

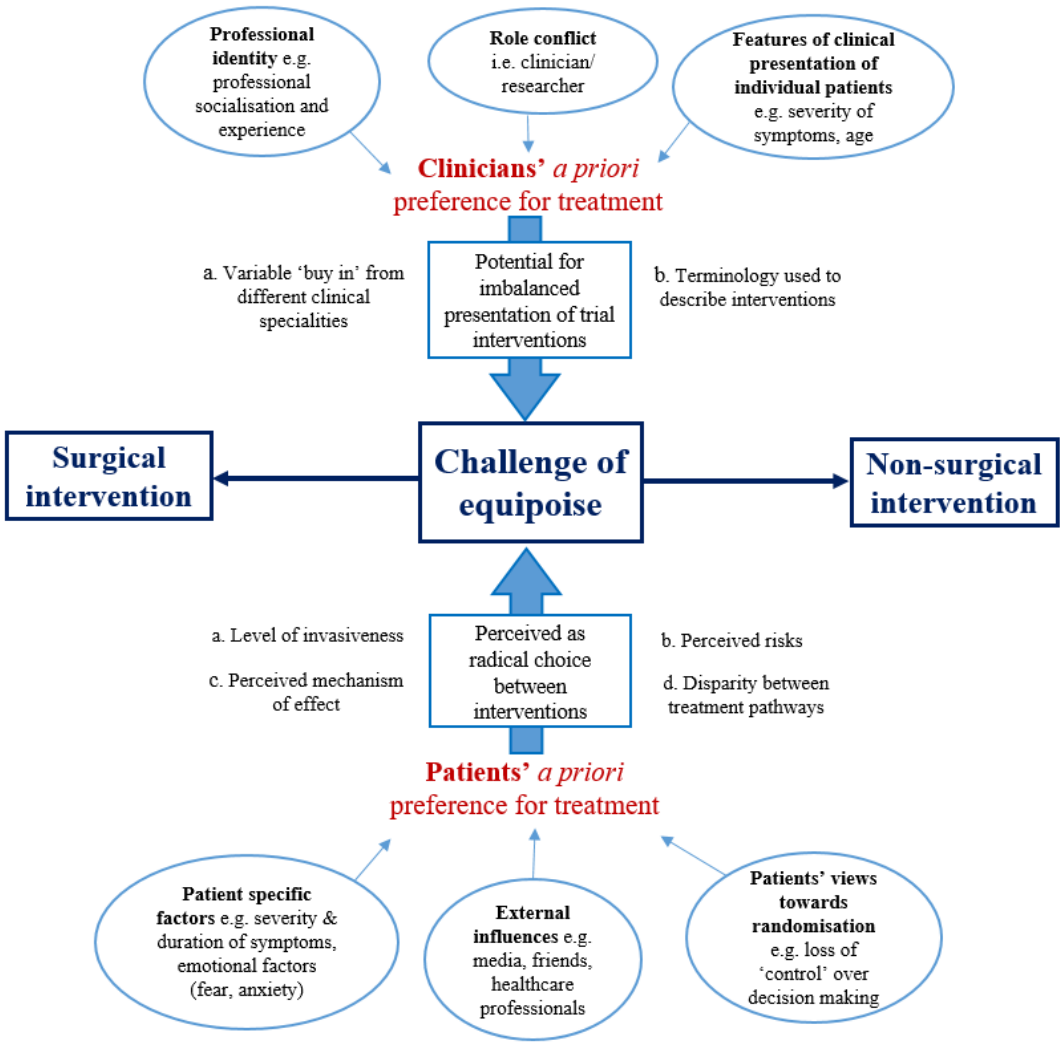


Figure 7: Conceptual model for QES

Table 24: Final themes, conceptual categories, studies supporting each theme and additional narrative exemplars from the primary studies.

Theme	Examples of narrative from primary study chosen to illustrate conceptual category
1. Radical choice between treatments. Primary studies supporting this category:[90, 193, 203, 205, 217, 277, 280, 282-285, 287, 290]	*It's a very difficult decision and there isn't a right and a wrong answer and some people have very clear ideas about what they want to do, whether it should be an operation, they want to have it cut out. Other people, the thought of the operation is just so frightening they opt for the radiotherapy treatment. But for us, we don't know which of these treatments is - is better (Oncologist).*[288] *So having chemo and radiotherapy, there's no guarantee with any of it, but in my mind, you're just trying to shrink the tumour and there is no guarantee that you will do it with that, but with surgery you're physically cutting it out (Patient).*[288] *Surgery for most people has got to be the last option, now if they can sort it out with physio, and after 12 months of physio doesn't work, OK let's do the surgery, I think that's acceptable to me, I won't have a problem with that, it is information that I'd like to have (Patient).*[283] *Thing is, when you've got (some sight), even if you've lost a little sight, you've got something. But if the operation wasn't successful, you might end up with nothing' (Patient).*[285] *If they have the symptoms the same as somebody else and the other person's having surgery to correct it, the person who's having physio would think 'how can it be corrected without the surgery?' (Patient).*[283] *"My shoulder had improved, I thought shall I go (for surgery) and I thought…the surgery will fix it…I wanted a cure because I knew somebody who had surgery and it cured it completely" (Patient).*[282]

	'If you come in with a tumour… but you've got more than a ninety percent chance of curing this whatever we do, ninety five if it's really small… you've got a life, you've got kids to manage, you've got a job to manage and you've got all the rest of it to manage, what are you going to choose?' (Surgeon).{Hamilton, 2013 #145.
2. Patients' discomfort with randomisation: best treatment for me as an individual. Primary studies supporting this category:[90, 203, 276, 279, 283, 285, 295]	*I don't necessarily agree [that clinicians don't know the best treatment]. One would be more suitable to one patient and something else to another…. I'm not really in favour of it [randomization]. I can understand why you would rather have it randomized, so that nothing else affects it, but I think all patients are probably different and that difference, the state of their health and so on, is different (Patient).* [286] *"(...) but the only thing I don't understand is when you are pulled out of the computer.. .that's when the problem started (I withdrew) 'you will be picked out at random' was what they said...and I had no more control.. .I got out." (Patient).* [279] *What he said it was either the knife or the radiotherapy or this wait and see business, which would be, if I would agree, by computer random choice and I said, "Well, yes" because I've got in back of my mind that whoever's programmed that computer has got to have some kind of medical knowledge because obviously someone whose got a very large cancer, which could cause death straight away or within a few months, I can't imagine his name being down on a wait-and-see basis. What I'm trying to say, there's got to be a level somewhere where they can say, "Yes, we'll wait," "No, we can't wait." I'm hopin', I'm puttin' me faith in it (Patient).* [285] *I understood that [treatments were equally effective], but I just find it difficult to deal with a random approach to anything. To feel that this very important decision, which is genuinely a decision about the possibility of life or death at some point in the future, being down to chance, I find that difficult to accept. I ought to be able to do better than that. I ought to work it out, the one that is most*

	appropriate for me. I think, well, one of the three is going to be better than the other two for me (Patient).[286] *Interviewer: Did he explain why treatment was randomized? Mr. Williams: Well, yeah, because I mean they didn't know enough about it and so they obviously wanted so many people to agree and wanted an even number as possible, I suppose, of people. Obviously in research they want to compare each one, don't they. But I thought, well, I want the one that is suitable for me.*[286] *It is not ethical if it's random [. . .] It makes you wonder 50 : 50 if you're just going to be put in one or the other without looking at how your symptoms are or how you are, it sounds worrying (Patient).*[283]
3. Challenge of equipoise: Patients' a priori preferences for treatment. Primary studies supporting this category:[80, 89, 203, 205, 217, 218, 276, 283]	*'Research nurse: Have you had a chance to look through the literature you were given in the clinic about the different treatment options?* *Patient: Yeah I did....I mean I'd like to go for [minimally invasive surgical option].* *Research nurse: Okay that's fine. I'll let [recruiter's] secretary know that'.*[80] *Patient: Because from what I can gather it's not that bad, it hasn't spread anywhere else. So the chances are this, this [non-surgical option] could cure it. Oncologist: That's absolutely right Patient: You know if it had gone anywhere else I'd, I would have said straightaway well go for that [surgical option]…. Oncologist: Yep, yeah I understand that it's a worrying time isn't it. So you would rather go for the [non-surgical option]? Patient: I think that's the best thing to do. Oncologist: Yep ok, that's absolutely fine….I think that's the right thing to do actually'.*[80]
4. Challenge of equipoise: Clinicians' a priori preferences for treatment	*Hmm, I have to say, I mean being honest, with the more elderly patients with more co-morbidities, diabetes, I tend to go straight for [procedure x] on those patients (in routine practice). Hmm, just*

Primary studies supporting this category:[39, 217, 218, 276, 283, 291]	*because they've got a limited life expectancy. In the younger patients I get with the less co-morbidities, I certainly have a preference for [procedure y] (Clinician).*[39] *The literature by and large shows 80% of the people get good results, as far as symptoms go with surgical treatment. There is no evidence anywhere that conservative treatment will work (Clinician).*[283] *"I wouldn't be involved with the trial because it wouldn't be ethical if I had a strong view that this wasn't right … But, there are a subset of younger men with more aggressive tumours where I find that really quite difficult."(Clinician).*[291] *I think the radiotherapists should believe in radiotherapy and I think surgeons believe in surgery. And I think that's probably pretty normal actually. To tell you the truth, I believe in surgery because I'm a surgeon. And I think what we'll find out from the study is whether the radiotherapy treats as well as we do (Clinician).*[291] *As far I am concerned, there isn't a position of equipoise for consent on this, because there is enough data in the literature, which admittedly, isn't high-quality data, particularly with cam impingement, we get good results with surgery in terms of symptom relief (Clinician).*[283] *There's a proportion of patients who will say to me, ''What do you think doctor?'' And in that situation, I think my gut feeling is important. I always tell them. I wouldn't have become a surgeon if I thought another form of therapy was the best form of therapy, would I? So my preference does matter to some patients but, you know, it's important for them in my opinion to also go and talk to the radiotherapist who, presumably, will be more passionate about their treatment (Clinician).*[218]
5. Imbalanced presentation of interventions.	*I think the main problem of the trial was who saw them first. If the oncologist saw them first then they would be able to lay out their stall first – with the pluses and the minuses and then if they were seen*

Primary studies supporting this category:[39, 203-205, 280, 283, 288, 289, 291]	*again – in a few days' time by the surgeons then foremost in their mind would be what the oncologist had to offer and we (as surgeons) would then have to, in inverted commas, compete with that. Whereas, if it happened the other way round we would then at least get our information across on a blank canvas. I think that's the difficult thing with two very different treatments with two very different side-effect and complication profiles (Surgeon).*[204] *'So you come in, you go to theatre, you have your operation, you come back to the ward, you wake up and then you toddle off home and you're all done. And that's nice and simple… Sounds great, doesn't it?'* *'The radiotherapy which you discuss with doctor X is a bit more intensive, that's a bit more, you know, labour intensive. So you'd have to go into X hospital for that, which is a bit further for you to travel. But you would be going over there every day for six weeks, but you're only there about fifteen twenty minutes, so it's quite quick so although it sounds a lot, six weeks of treatment' (Recruiter, recruitment appointment).*[217] *You almost want the patients informed and consented and entered into the trial by a non-oncologist and non-surgeons. You want somebody who knows about both treatments, very well and in detail, knows about potential complications but also is removed from the frontline, so that they can impart as much information as possible in an unbiased way (Surgeon).*[204] *In my view the patient gets a bias towards surgery from the start (...) The patient tends to hang on to the first thing, so even if the patient gets to a radiotherapist (...) they quite often say, "oh yes, I'll have surgery" even if they get to the radiotherapist. By the time they get to me for what is supposed to be the pros and cons and the discussions around randomisation, they quite often have things set in their mind (Oncologist, Recruiter).* [205]

	Some of my colleagues in the unit would want to operate on absolutely everything they had the opportunity to operate on, and so might not emphasise the chemoradiotherapy bit quite as strongly. (Surgeon). [204] *But of course the surgeon is obviously more biased to surgery and the oncologist is biased to that treatment. I think subconsciously the way they talk to them… It may be something even more subtle than in words that they are saying. (Research nurse).* [204] *Clinician: The first is [treatment x] to remove the cancer to give us the chance of cure.* *Clinician [later]: [Treatment y] is designed to shrink down the tumour and try and kill it off.* *Patient relative: The thing that's worrying me if she has [treatment y if that doesn't take it away but if she has [treatment x] then it's gone.*[39] *There was someone who used to work here who used to say 'well I can cut away your tumour or they can shrink it with radiotherapy', so the word you use matters a lot because 'shrink' gives the impression that you're not going to get rid of it, whereas to cut it out means you've taken it away, gives you the impression that you're definitely cured (Oncologist).*[288] *I normally talk about the fact that we need to do chemotherapy ... and that the surgery is the 'gold standard' way of managing the cancer and that there is a possibility of the selective bladder preservation possibly being an alternative, but we need to confirm that in the trial and that's why we're doing a trial (Oncologist, Recruiter). They're either having the 'gold standard' treatment or an experimental treatment (Nurse, Recruiter).*[205] *We have a large trial portfolio and we try to have 'buy-in' from the whole team to a clinical trial so the clinical trials that we do are agreed by the whole team then, not done in isolation. And the MDT decision will be to offer a clinical trial. That's one of the reasons why we've been very successful in*

	terms of actually putting people into trials because there is 'buy-in' from the whole team to do clinical research. So, I think it was an MDT decision that they were eligible for the study and we went from there. (Oncologist).[204] *We can certainly stir up and reinforce a patient's bias very easily with a throw away comment like the aim of the surgery is to cut out your cancer and that could ruin everything from the point of view of a balanced randomised trial (Surgeon).*[288]

Discussion

1. The aim of this QES was to identify, and synthesise findings from qualitative studies exploring the challenges in the design and conduct of trials directly comparing surgical and non-surgical interventions. Five main themes related to challenges to these types of were identified: 1. Radical choice between treatments; 2. Patients' discomfort with randomisation: best treatment for me as an individual; 3. Challenge of equipoise: Patients' a priori preferences for treatment.4. Challenge of equipoise: Clinicians' *a priori* preferences for treatment

and 5. Imbalanced presentation of interventions.

The findings of this review suggest that the marked differences between treatments compared in these types of trials can be viewed by patients as a 'radical choice', influencing decisions regarding trial participation. Differences between treatments in the level of invasiveness, level of potential risk, perceived mechanism of effect and disparity between the treatment pathways, influenced patients' views towards particular treatments, making recruitment challenging. Patients' treatment preferences are one of the main challenges to recruitment in clinical trials[15] and is known to be particularly problematic in trials comparing surgical and non-surgical interventions.[23, 43, 44] In the context of RCTs, the development of patients' preferences is known to be complex.[199, 218] Bower et al, (2005) [199] in their conceptual model of the development of preferences in randomised trials, define preference as the "difference in the perceived desirability of two (or more) interventions within an RCT". The concepts of *utility* ' a measure of satisfaction gained from the consumption of a good or service, such as health care [296] and *attitude* 'a disposition to respond favourably or unfavourably to an object, person, institution or event' [297] were central to their model.[199] Bower et al conceptualise patients as having a

particular ‘strength’ of preference from a ‘slight preference which has little substantive importance, through to large preferences which have a major influence on behaviour’.[199] The findings of this review highlight factors identified as contributing to the strength of patients’ preference for particular interventions, in trials with this type of comparison.

The marked contrast between the invasiveness and irreversibility associated with the surgical and non-surgical procedures were seen to contribute to patients’ reluctance to participate in trials with this type of comparison. Previous studies have discussed how surgical procedures can raise particular emotions (e.g. fear, anxiety), and surgical interventions can be associated with particularly high negative value.[92, 199] The importance of considering emotional influences on patient decision making in trials was discussed by Bower et al (2005),[199] and can be particularly salient in trials of this type of comparison, where the magnitude of difference between the interventions is so great. The findings of this review suggest that to some patients, surgery is viewed as a ‘point of last resort’ or, as also discussed by Sibai et al, 2012, [92] the option to consider if there are no improvements with non-surgical care. The potential for patients’ preferences for treatments to be dynamic has been discussed in previous studies, and decision making on trial participation may depend on when patient is approached.[199, 298]

The difference in the level of potential risk associated with surgery compared to non-surgical interventions was also identified as influencing patients’ preference towards treatments. Specific factors, however, such as, a patients’ particular diagnosis/condition, duration and severity of symptoms, were also seen to affect patients’ perception of risk associated with treatments. Previous studies have discussed the importance of considering potential participants’ health state (life-threatening conditions, long-term conditions), and trajectory of their condition (established or recently diagnosed conditions) during

recruitment to clinical trials.[233, 298] For example, a trial of two surgical procedures, urethrotomy and urethroplasty, for recurrent urethral stricture by Whybrow et al (2017),[298] found that patients decisions regarding willingness to participate was seen to be related to a patients' symptom progression. Patients either felt the condition was *'*too slight to consider a serious operation or too severe not too*'*.[298] In this trial one of the treatments was more invasive and viewed by patients as potentially being curative, whereas the other procedure was relatively straightforward operation but considered more as symptom palliation.[298] Whybrow et al (2017) considered that there may only be a 'particular window of opportunity in which patients would be willing to accept either procedure'. Understanding the strength of patients' preference for particular interventions, and factors underpinning any preferences, prior to trial conduct, could provide valuable information to trial teams. Exploring patients' views towards treatments could enable issues specific to a particular trial to be identified and addressed.

The findings of this review also indicate that explanations of a condition or injury as a mechanical problem with a mechanical fix were seen to be understood more intuitively by patients and influenced strength of patients' preference towards surgery. Surgery was viewed by patients as providing a definitive treatment to the problem, whereas patients' expressed difficulty in understanding how a non-surgical intervention could achieve a similar outcome. Patients' lack of confidence in the expected effectiveness of non-surgical treatments compared to surgery, has also been highlighted in studies exploring reasons for treatment choices made in routine clinical practice.[299, 300] Ensuring that both surgical and non-surgical interventions are understood and viewed by patients as comparative, despite the differences between them in mechanism of effect, is important

because of the potential impact on patients' views towards treatments and trial participation.

In this review, disparity between the treatment pathways of the surgical and non-surgical interventions also contributed to patients' views towards the different treatments. A more complex treatment process, differences in level of patient input, timing of when patients would receive the intervention, and socioeconomic factors for example, time off work were seen to contribute to patients' views towards treatments and trial participation. As discussed by Bower et al (2005), 'process issues' [301-303] such as financial cost of personal convenience may be equally important to patients when making decisions regarding trial participation.[199] Unlike trials of similar comparisons (e.g., two surgical procedures), aspects of the interventions are more likely to be markedly different in these types of trials, potentially influencing patients views.

The marked differences in the interventions compared in these types of trials resulted in some patients being reluctant to leave decision about their individual treatment to chance through randomisation. Previous studies have demonstrated patients can find the concept of randomisation challenging.[304, 305] As with trials of other types of comparisons (e.g. two surgical procedures), patients were seen to be uncomfortable with the loss of 'control' over decision making and the departure from a more traditional doctor patient undermining the role of the clinician. The findings of this review suggest that patients in these types of trials considered that individual differences in symptom presentation, age, or previous non-surgical care would impact on decisions made over their treatment, making one option more suitable than the other.

Discussing trial participation with potential patients who have strong preferences for treatment was discussed in this review as a challenging for recruiting clinicians in these

types of trials. Patients' treatment preferences are often considered a 'barrier' to recruitment.[199, 306, 307] However, exploring patients' preferences is increasingly being recognised as an integral part of the information exchange necessary for informed decision making about treatments and trial participation.[90] Exploring patients' treatment preferences and providing evidence-based information has been shown to improve levels of informed decision making and facilitate participation.[90] Communicating trial information for example, randomisation, equipoise, to potential patients can be challenging,[91, 304] particularly when there are such 'radical' differences between the interventions.[218, 291] Training recruiting clinicians to explore patients' treatment preferences has shown to facilitate recruitment in trials with such diverse comparisons.[90, 308, 309] Understanding factors underpinning patients preferences for treatments and providing trial specific training for recruiting staff,[203-205] may help to ensure a more balanced approach to recruitment in these types of trials and facilitate recruitment.

The findings of this review highlight the potential conflict clinicians can have in their role as a clinician and participating in research. Clinicians' strong preferences for treatment are a well-recognised challenge to the conduct of clinical trials, potentially having a detrimental impact on recruitment.[91, 95, 310] The additional influence of strong clinical speciality convictions were identified in this review as being especially evident in trials with this type of comparison. Professional preferences of the different specialities involved in these types of trials, may result in more complex issues concerning social roles, power and authority influencing recruitment.[311] Clinicians' experience, knowledge, and views on available evidence, both RCT and non RCT, influenced preferences towards treatments and were seen to affect their position of equipoise. These finding reflect those of previous studies,[312, 313] where the difficulties clinicians can experience in a dual role of

clinical care and research are discussed. Ingrained values, skills and knowledge that clinicians' develop over time through 'intensive professional socialisation',[313] are considered to make it difficult for clinicians to totally separate from the care and welfare of patients when involved in research.[312, 313] In this review, clinicians' preference for treatment was seen to be potentially more influential where trials challenged established treatments, which may reflect the potential for stronger professional views towards the treatment of a patient population to develop over time through experience. Understanding clinicians' perspectives at a pre-trial stage could identify equipoise issues and help develop effective and targeted training to support recruitment and engagement from all specialities.

The findings of this review suggest that the way treatments are discussed, and the terminology used by recruiting clinicians in these types of trials has the potential to be imbalanced, contributing to patients views towards treatment and trial participation. As trials evaluating surgical versus non-surgical interventions typically involve more than one clinical speciality, the difficulties were seen to be potentially more problematic. The potential for asymmetry in clinicians' delivery of information about surgical and non-surgical treatments to patients has also been identified in studies of clinical practice.[201, 314, 315] A study by Hudak et al (2013) of orthopaedic surgery consultations, showed that when surgeons discussed surgery versus non-surgical options, surgery was portrayed as having a 'special, privileged status relative to other options'.[201] The structure of surgeons' treatment recommendations were seen to potentially shape patients' expectations, whether for surgery or some alternative.

Implications for practice

The conceptual model (Figure 7) details the specific factors, related to the diverse nature of the surgical and non-surgical comparison, which were seen to influence patients' and clinicians' views and make recruitment challenging in trials with this type of comparison. Trialists may wish to consider exploring through qualitative feasibility studies the extent of preference for treatments, before they start recruitment, to enable issues specific to a particular trial to be identified and addressed. Exploring patients' views of treatments and reasons for decision making could be hugely beneficial to help understand the patient group and range of influences on the development of particular preferences. Similarly, exploring clinicians' views on the context in which the trial will be conducted and the range of patients typically seen could identify and help understand factors underpinning clinicians' preference for treatment and potential difficulties with equipoise. Developing and providing trial specific training, to support recruiting clinicians, could also prove beneficial in improving communication of trial information where the interventions being compared are so diverse and help facilitate recruitment.

Limitations

There are some limitations to this review. Only published literature was included, other sources such as unpublished dissertations were not included. Similarly, studies not published in the English language were excluded, meaning that relevant publications may have been omitted. There is also a discrepancy in the dates of the search strategy between the systematic review (January 2010 – 2015 [updated to September, 2018) reported in Chapter 2 and that used in the QES (up to February, 2018). As only two qualitative studies were identified in the initial search of the systematic review, the search was

expanded in the QES to maximise the potential inclusion of studies. In addition to including all clinical specialities, rather than the inclusion of only orthopaedic trials in the systematic review, the time period was also expanded. The different years included in the search strategies, however, means that there are some papers included in the QES that are commenting on trials that are not included in the systematic review.

The majority of the trials were of elective surgery and therefore some of the aspects may not be applicable to the trials in the more acute setting such as fracture management, where there may be differences in the consent process. In addition, as outlined in the summary of included studies table (Table 21), the majority of the studies were from an oncology speciality and set in trials conducted in the UK. Several of the papers discussed findings from the same trial, limiting the number of different trials included. However, a range of specialties and comparisons were included which provided a valuable in-depth insight into expectancies, beyond that of the individual studies.

The majority of the published literature were of studies that explored challenges to recruitment in trials of this type of comparison. Further research could be conducted to explore areas identified as challenging in these types of trials where knowledge is lacking, such as, non-compliance and reasons for differential loss to follow-up. Finally, there is no agreed way to determine confidence in QES findings which are an interpretation based on abstraction. Further studies to explore the utility of GRADE CERqual for conceptual reviews such as meta-ethnography would be useful.

Summary of results

Conducting surgical trials is essential to establish evidence based practice and inform health policy, particularly in the face of economic pressures. Randomised controlled trials in surgery can be difficult to design and conduct, especially when including a non-surgical comparison. Specific factors related to the diverse nature of the surgical and non-surgical comparison were identified in this review as influencing patients' and clinicians' views and making recruitment challenging. Five main themes were identified: 1. Radical choice between treatments; 2. Patients' discomfort with randomisation: best treatment for me as an individual; 3. Challenge of equipoise: Patients' a priori preferences for treatment; 4. Challenge of equipoise: Clinicians' a priori preferences for treatment and 5. Imbalanced presentation of interventions.

The review highlights the value of qualitative studies in identifying and understanding these challenges from the experiences of the patients and clinicians involved. Understanding the challenges of such comparisons can be hugely beneficial and learning from the experience of others will enable trial teams to make more efficient considered design choices and benefit the delivery of such trials.

Chapter 5

Patients' treatment preference – ACL injury: a qualitative interview study

Introduction

The findings of the systematic review and case study described in Chapters 2 and 3, identified that patients' strong preferences for treatments can create pose a significant barrier to recruitment to trials where the interventions being evaluated are markedly different. The development of patients' preferences for particular treatments is complex.[291] In the context of a randomised controlled trials (RCTs), there can often be a dichotomy between patients' strong preference for one treatment or another depending on the trial comparison, making recruitment particularly challenging.[199, 218, 291] The findings of the qualitative evidence synthesis in Chapter 4 identified how stark differences in the level of invasiveness, potential risks, disparity between treatments pathways and views on perceived mechanism of effect, between interventions in trials with a surgical and non-surgical comparison, influenced patients' treatment preferences, making recruitment challenging.[205, 279, 285, 290]

Understanding the reasons underpinning patients' preferences for particular treatments and the strength of preference could offer opportunities to address issues by developing targeted patient information and strategies to support recruiting teams, with the view to improve recruitment and optimise trial conduct.[82, 83, 316] Qualitative research with its emphasis on meaning, context and process, is an ideal means of exploratory work to enhance understanding of aspects such as patients preferences, and in doing so contribute to improvements in trial design.[73] Qualitative research is increasingly used to understand challenges and improve the conduct of difficult RCTs such as those in surgery.[76] The majority of these studies however have been conducted alongside the main trial rather than at a pre-trial stage, where they could have the potential to explore important factors

to trial design such as the level of equipoise or preference for treatment that may be problematic in a trial.[82]

One area where there remains uncertainty in the evidence base to guide practice is the management of anterior cruciate ligament injuries. Rupture of the anterior cruciate ligament (ACL) of the knee, is a common sporting injury and is most frequently seen in young and physically active individuals.[209] Current management of this injury includes both reconstructive surgery and non-surgical treatments (physiotherapy), however, there remains uncertainty in which management option is superior.[210, 211] Much of the current evidence base is limited in methodological quality being based on a number of retrospective case-control and only one RCT by Frobell et al.[182, 183] As a result, large variation in the management of this patient group has been demonstrated in the UK.[317, 318] The RCT conducted by Frobel et al [182, 183] in Scandinavia demonstrated the feasibility of conducting an RCT with this patient group. However, difficulties in recruiting patients to the trial where there was a surgical and non-surgical treatment arm was reported.[193, 221] Exploring patients' views on both surgical and non-surgical treatment options for this injury, could provide valuable information on patients' preferences for treatment that may be problematic in a future trial. The aim of this study therefore was to explore factors underpinning patients' preference for surgical and non-surgical treatments for the management of ACL injuries that might have an impact on recruitment to a trial.

Objectives

The objectives of the study were:

1. To explore patients' experience of ACL injury and views on surgical and non-surgical approaches to the management of the injury.

2. To explore patients' treatment preferences.
3. To explore factors that may impact on trial recruitment

Methods

Study design

A qualitative research study was conducted using thematic analysis.

Ethics approval

Ethics approval to conduct this study was granted by the Wales Research Ethics Committee 7 (Reference No. 14/WA/1108).

Sample

This qualitative study was embedded in a single centre prospective cohort study, the Oxford Knee Injury Cohort (OxKIC): Understanding Knee Injuries and the Best Treatment Options for NHS patients. The aim of the cohort study was to explore the treatment decision-making process for patients with ACL injuries, and examine factors that can predict poor outcome, to inform and improve patient care and service delivery. An overview of the OxKIC cohort is provided in Appendix 11.

The OxKIC cohort was based at the Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Foundation Trust. The sample was a convenience sample of patients referred to the Acute Knee Outpatient Clinic at the Nuffield Orthopaedic Centre, following any acute knee injury involving the anterior cruciate ligament and/or meniscal injuries.

Clinical management of all participants entering the cohort study followed usual practice and pathways at the Oxford University Hospitals NHS Foundation Trust Oxford. Both physiotherapy and surgery were delivered as standard treatment options. The sample was therefore relevant to the research aim to understand factors underpinning patients' preference for surgical and non-surgical treatments.

Recruitment

Patients were recruited to the OxKIC cohort study and had the option to agree to participate in the interview component of the study. Patients who met the inclusion criteria for the cohort study received a Participant Information Leaflet (PIL) with their clinic appointment letter or at their clinic appointment. This included a detailed explanation about the cohort study including the details of the additional qualitative interview study. Patients were approached directly by either SK, LD, PL, MM regarding participating in the OxKIC study. Patients with knee injuries that did not include the ACL or where the level of associated pathology resulted in the requirement for more immediate surgery e.g. locked knee, large bucket handle or complex cartilage tear producing mechanical symptoms, were not approached.

Written consent was obtained from all patients who agreed to participate (Appendix 12). Patients who indicated on the consent form that they agreed to be contacted regarding an interview were sent an email by LD to arrange a suitable time and location.

Data collection

Data was collected by semi-structured interviews. A topic guide (Appendix 13) outlined the questions and areas to be explored during the interview. It was designed as a prompt to encourage participants to talk freely and allow exploration of issues raised by patients.

The questions were iteratively modified as the study progressed to enable exploration of emerging themes in later interviews. This modification of questions is part of an iterative qualitative research process.[319] Sampling continued until no new information or insights were gained from the interviews.[320] Interviews were conducted face to face at the Nuffield Orthopaedic Centre or over the phone depending on patients' preference. The interviews were digitally audio recorded, transcribed verbatim and anonymised. The interview duration ranged from 26 and 53 minutes. Transcripts were compared with audio recordings to ensure accuracy.

The following data was also collected in a baseline questionnaire, in order to provide some numerical baseline characteristics to describe the sample.

- Time since injury and how the injury occurred.
- The Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire,[213] a validated patient reported outcome used with this patient group. A self-reported outcome measure is derived from 4 of 5 subscales; pain, symptoms, difficulty in sports and recreational activities, knee related quality of life with scores ranging from 0 – 100, a higher score indicating better health.
- Tegner Activity Scale [321] an activity level scale, graded from 1 (low activity levels) to 10 (professional level).

Analysis

An approach to thematic analysis (TA) developed by Braun and Clarke, 2006 [322] was used to collect and analyse the data (Table 25). Thematic analysis is a qualitative research method that can be applied across a range of theoretical and epistemological approaches. It is a widely used method for "identifying, analysing, and reporting patterns (themes)

within data".[322] Many versions of TA exist,[323-327] which vary in terms of analytic procedures and guiding philosophy. Other approaches to qualitative research, such as interpretative phenomenological analysis [328] and grounded theory [329] offer theoretical frameworks which inform the methods of data collection and analyses. In contrast, the approach to TA developed by Braun and Clarke, 2006 [322] is characterised by independence from any particular epistemological and ontological base and can be used within most theoretical frameworks. It is this 'flexibility' which partly makes it distinct from other qualitative analyses.[100]

The six-phase analytic process described by Braun and Clarke (2006) [322] (Table 25) are detailed below. However, as the process of qualitative research is not linear but iterative and recursive, the process involved moving back and forth between the different phases.

Table 25: Six-phase analytic process of thematic analysis [322]

Phase	Description
1. Familiarisation with the data	Transcribing data, reading and rereading the data, noting down initial ideas
2. Generation of initial codes	Coding interesting features of the data systematically across the entire data set, collating data relevant to each code
3. Search for themes	Collating codes into potential themes, gathering all data relevant to each potential theme
4. Review of themes	Checking if the themes work in relation to the coded extracts and the entire data set, generating a thematic map
5. Defining and naming themes	Ongoing analysis for refining the specifics of each theme and generating clear definitions and names for each theme
6. Producing the report	The final opportunity for analysis. Selection of vivid compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a report of the analysis.

Familiarisation with the data and coding (phase 1-2)

The audio recordings of each interview were transcribed, and each transcript was read thoroughly several times to become familiar with the data. Throughout this process, initial thoughts and ideas about the data were generated and recorded.

All transcripts were imported into NVivo (QSR International, Warrington, UK),[98] the computer software used to manage the data. Preliminary coding was then undertaken for each transcript. Specific segments of the dataset, which had meaning relevant to the research question,[100] were 'coded' and labelled with a phrase that captured the meaning of that data. An example of the coding is included in Appendix 14. After initial coding was completed, a list of codes was compiled from all transcripts and added to an excel spreadsheet table.

Development of themes (phase 3)

The full list of codes was organised, through constant comparison, into categories or 'piles' with shared meaning. This was an active process of developing pattern formation across the dataset to create provisional themes. The provisional themes each had a core idea or concept underpinning the theme, known as a central organising concept.[330] Thematic maps were also created to explore the patterns and connections between themes.[100]

Review and defining themes (phases 4-5)

The provisional themes were then refined by reviewing the coded data extracts for each theme to consider whether they were sufficiently clear and comprehensive reflected the data.[322] Two reviewers (FT and DB) also reviewed the coded extracts to determine

whether the themes were sufficiently clear and comprehensive. The analytic process continued until final themes were defined and named.

Producing the report (phase 6)

The final phase of the process involved writing the report of the findings. Exemplars of the narrative were then chosen to illustrate each of the themes and these are presented in the results section below.

Demonstrating research rigour

To demonstrate rigour is to show "the degree to which the study's findings are authentic and the interpretations credible".[331] However, there are no accepted consensus about the standards by which such research should be assessed.[332]

Strategies used in this study to establish rigour are detailed below:

i. The provision of a transparent and clear description of the research process from initial outline, through the development of methods and reporting of findings.[333] A clear account of the process of data collection and analysis is important to enable others to consider whether the interpretation made is adequately supported by the data.[334]

ii. Evidence of reflexivity is an important element of qualitative research because it enables researchers to consider the (inevitable) impact that they have, through their own characteristics and experiences, on data collection and analysis.[335] It is considered important for the researcher to recognise any personal a priori ideas and to reflect on potential influences.[336] The standpoint from which the researcher carried out the analysis for this study was primarily as a physiotherapist and

clinical trials manager with a strong interest in the design and conduct of RCTs of complex interventions.

iii. In order to determine whether the themes are sufficiently clear and comprehensive, review of the coding and interpretation by another researcher is advocated.[337] For this, FT, an experienced qualitative researcher and social scientist and DB, Chief Investigator of the ACL SNNAP, reviewed the themes to ensure that they reflected the data, and discussed alternative interpretations and suggestions about the organisation of themes. The aim of this process is not to prescribe 'the singular true account', but to ensure the credibility of the final account.[338]

iv. To enable the reader to make judgements about whether the final themes are true to participants' accounts, 'rich and thick' verbatim extracts from participants have been included in the results section as exemplars of the narrative.[339] The extracts selected as exemplars were chosen on the basis of that they represented the 'most articulate expression' of that theme.[340]

Results

Fifteen patients with Anterior Cruciate Ligament (ACL) injury were interviewed. The characteristics of the patients interviewed are detailed in the table below (Table 2). The age range of participants was 21-57 years. The patients were an active population with a Tegner activity level score ranging from 3-10 (a score of 5 indicates participation in recreational sports to a score of 9 indicating participation in competitive sport on a nonprofessional level). The patients KOOS score indicated that the main problems (lower scores on KOOS) experienced by the patients in this study were related to sport and recreational activities (KOOS Sport/Rec) and quality of life (KOOS QOL), as detailed in

the table below. Ten of the fifteen patients were female. Ten patients were interviewed face-to-face and five interviewed over the phone.

Table 26: Characteristics of patients interviewed, include her age, gender, activity at time of injury, time from injury to diagnosis.

Participant	Gender	Age	Activity at time of injury	Tegner activity level	Time from injury to diagnosis (weeks)	KOOS Pain	KOOS Symptom	KOOS ADL	KOOS Sport/Rec	KOOS QOL
KS015	F	57	Skiing	6	4	58	64	85	40	50
KS005	F	41	Skiing	6	4	14	57	24	0	0
KS039	M	41	Football	9	5	78	50	90	45	44
KS049	M	34	Cricket	7	4	53	39	47	0	13
KS001	F	26	Netball	7	9	47	79	54	0	38
KS014	F	40	Netball	7	4	44	64	52	0	6
KS060	M	30	Rugby	10	16	86	61	99	90	69
KS152	M	21	American Football	9	6	72	71	81	35	31
KS122	F	23	Rugby	9	13	36	61	63	10	13
KS137	F	21	Netball	7	5	67	46	79	25	19
KS141	F	29	Skiing	6	6	50	46	66	25	25
KS148	M	25	Football	7	4	39	50	46	0	19
KS139	F	53	Skiing	4	10	78	57	90	75	50
KS177	F	29	Skiing	3	4	56	58	71	0	19
KS112	F	33	Netball	7	6	78	58	93	45	38

Data was coded into four themes that underpinned patients' treatment preference:

1. Implications of the diagnosis,

2. Surgery considered by 'everyone' as the best means of returning to being active,

3. Surgery intuitively understood as providing a 'fix' to the problem, and

4. I'll try the least invasive first, but surgery is always an option.

The themes are discussed below and illustrated with narrative exemplars.

1. Implications of the diagnosis

This theme describes how a diagnosis of an ACL tear, influenced patients' views on prognosis and their decision about treatment. It could also have a strong emotional impact. For some the implications of the diagnosis were positive, while others were

negative. Several patients considered the diagnosis of an ACL injury to imply the need for surgical treatment, regardless of their current symptom presentation or their previous level of activity/sport.

> *Once I was told it was going to be an ACL I was still trying to get my head round it, I knew I had to have it fixed it is just my way, my sporting way. I have to be put back right again (KS039).*
>
> *So when he said ACL my heart just sank instantly because all I could think in my brain was, you are going to have to have surgery (KS177).*

Patients also indicated that being given a diagnosis was important because it helped them acknowledge their injury and enabled them to move forward and start to deal with the implications, consider options and make decisions.

> *Just having a diagnosis really helped because I was okay, right, I know what the problem is with my knee I can sort of go away and understand what this means…. (KS152).*

Hearing the diagnosis however, could create feelings of shock as it was a 'bad sign', and could escalate patients' views on the severity of the problem. Patients who were aware of this type of injury, expressed that they had 'feared' or 'hoped' that it was not an ACL injury. Some felt that an alternative diagnosis, such as meniscal tear, would have more positive implications for recovery, not require a surgical intervention, or imply a more immediate return to activities than with an ACL injury.

> *I had really got my hopes up that it was a dislocated kneecap or something slightly less extreme, because I know that you can have meniscal tears and they can heal on their own. I was hoping it was a strain or a partial tear… (KS137).*
>
> *I didn't know that you don't have to have surgery on an ACL until I spoke to the consultant. Up to that point in my brain it was MCL no surgery quick recovery,*

ACL, surgery long recovery and that was pretty much all that was in my brain (KS177).

*So I was still holding out any hope that if [*the ACL ligament] *hadn't gone I could start doing physio and rehab to try and get back to playing at the varsity match. (KS001)*

The diagnosis evoked strong emotions in some patients who had not previously heard of the injury. Hearing that you had 'completely ruptured your ACL', resulted in feeling of 'shock' and uncertainty as to what the implications of the injury were.

On hearing the diagnosis, mentally I went into meltdown thinking, what does this mean…does it mean that I will never be able to walk, you know all sorts of stupid things (KS015)

Awareness of their diagnosis instantly influenced patients' thoughts on prognosis, which in the majority of cases was seen to have a negative impact related to their sporting career; the 'end of my football career'; a 'career limiting injury'. It also created thoughts of uncertainty about how it would affect the future, in terms of sporting lifestyle, potential for further injuries and the development of osteoarthritis.

Because you know if you rupture it you will never play at that level again and you know it is a career limiting injury and then you start thinking…..oh god I'm going to have a meniscal injury with it, I am going to increase my chances of medial OA, am I going to have a knee replacement, that sort of thing (KS060).

.....at the time I could walk fine, it was more how's this going to affect me, cold winters will I feel it, a friend of mine is now in his 60s and he didn't have the operation 20 years ago and it affects him greatly….would it affect me when I'm older, will it affect my sporting lifestyle (KS039).

Awareness of the particular diagnosis also inferred a trajectory of a long recovery, regardless of the treatment decision.

Of course I knew straight away 12 months, a minimum 12 months and obviously the higher level you play the more you put yourself under strain and the longer the physio takes……I was aware of what it entailed which is why I guess it hits you so hard when someone tells you it is that, it all goes through your mind very quickly (KS039).

2. Surgery considered by 'everyone' as the best means of returning to being active

Patients described the strong influence of friends, family, healthcare professionals and the media towards recommending surgical treatment as the best means of returning to activities that were important to them. Patients indicated how 'everyone', they spoke to had views on the injury and opinions on treatment. Strong recommendations towards the perceived benefits of surgery influenced patients' views and decisions about treatment, often before they attended their clinic appointment.

…it was a tough one, sort of everyone I had spoken to, my rugby coach, she had ACL surgery and she plays rugby for England, so she was like have surgery… by the time I had got to the appointment I was thinking I am having surgery. So in my mind it was surgery, there wasn't really an option not too (KS122).

Positive experiences of friends who had an 'amazing recovery' following surgery and were back to sporting activities, influenced patients' preferences towards surgery.

I saw it as a long path, but I did see it as a way to get back to Rugby and I know people who have had an ACL and they have had the surgery and they have gone back to like normal sort of sporting stuff. So I don't so maybe in ideal world it was sort of other people were doing it so… (KS122).

Patients' views on surgical treatment were reinforced and justified by their awareness of professional athletes often seen to be having surgery following this particular injury.

> *… it just felt like it would be the thing that worked and again if you see professional athletes having it done and it clearly shows that is the best route to go down if you are wanting to be more active (KS137).*

In addition, clinicians were described as indicating surgery as the only means of being able to return to particular activities. Some patients felt that physiotherapy was encouraged for people who weren't going to be as active or were prepared to become less active.

> *…all those people who were prepared to become less active would go down the conservative route, and I did not really feel that sort of adequately described me (KS005).*

> *It just seemed that the physio route was more encouraged for people who weren't going to be as active or weren't necessarily in my stage of life, that was my impression at the very least, it might have been my own biases coming through!, yes that is what I thought (KS137).*

Following treatment discussions with clinicians, other patients felt that surgery was inevitable and the only solution to 'fix' the problem of their injury.

> *you can either have the surgery now and recover once or have surgery later and recover twice that was the impression I kind of got….surgery is the failsafe almost, so you know exercise will work well but the surgery is the best thing to do to fix the issue straight away was the impression I got (KS177).*

Some patients reflected on the negative experiences of people they knew who did not undergo the surgery, and 'didn't play rugby again', or 'never felt strong enough', to support their views towards undergoing surgical management.

> *Her sister who hasn't [had the operation] still has a bit of meniscal damage and her knee often locks even during matches……and its constantly a problem during high competitive matches when she is a bit tired and lands funny or not quite control or balance (KS001).*

Information sourced on the internet about the injury was also described by patients, regardless of their own preferences for treatment, to imply that surgery was 'what happened' following an ACL injury, or was expressed positively as the means to returning to an active lifestyle.

> *It just seemed the more and more I read about it [on the internet], the more it seemed that if I was going to lead an active lifestyle in the way that I wanted to, surgery was going to be the way to do that. Despite the setback for about a year or six months I was going to be able to go back to trust both of my knees and physio didn't seem to be an option that was going to work for me in that kind of thing (KS137).*

In contrast, some patients indicated that it was difficult to find information on the outcomes of conservative treatment as an alternative way to manage this injury. Examples of where people had returned to activities without undergoing surgery, were described as difficult to find, influencing patients' thoughts towards treatments.

> *…Wikipedia, Knee Guru and I also looked at [internet] forums that were specific to the activities I undertake, to see whether [other people] were able to carry on doing things irrespective of route or whatever route they took. It is very difficult to find stuff about the conservative route (KS005).*

Information available that described non-surgical treatment, implied considerable restrictions on the type of activities patients would be able to do, such as, straight line activities, for example, swimming and cycling. This was expressed as having negative implications for patients in terms of the ability to return to activities that were important to them, not just competitively but in terms of social contact and identity.

> *....the conservative route I say would place considerable restrictions on what I would be able to do…I would need to be holding back for the rest of my life and would have to constantly think about whether I could or could not do something*

and not be able to join in with friends that sort of thing….That was quite significant because as a single person fairly dependant on the friends for social contact that sort of thing…..these activities are very important to me (KS005)

3. Surgery intuitively understood as providing a 'fix' to the problem

Surgical and non-surgical treatments were not viewed by the majority of patients as potentially being able to provide an equivalent outcome. Patients viewed surgery as a means of providing a 'fix' to the problem that the injury had caused. The operation was viewed as providing mechanical stability in the knee and therefore reassurance.

The surgery that they offer is the reassurance that a mechanical knee which has been tested on the table. It is never going to be the same as it was but you know there is something there holding it together (KS060).

Surgery was seen to restore strength and stability in the knee by means of repairing something that had been broken. The majority of patients considered that by having surgery the tear would be repaired, a mechanical action providing a definitive treatment. A number of patients viewed surgery as the means to the knee being normal again, while others were aware the knee was never going to be the same again, highlighting patients varying expectations of treatment.

I didn't see surgery as a magic cure, as in have the surgery and everything will be wonderful. I was aware that things perhaps were never going to be quite the same again but I did think that it would give me a lot better chance of getting back to those sorts of things [activities] (KS005).

Although patients described how physiotherapy could 'strengthen' the knee, concern was expressed as to whether adequate stability would be achieved. Several patients described how it didn't seem intuitive that you could return to activities without the ligament in place, particularly in activities which required pivoting, change of direction movements.

I didn't really think much about not having the surgery,… I knew strengthening it was an option if you didn't have it reconstructed, but just to get back to playing netball where it is stop start and so much forward pressure of the thigh over the shin without an ACL, it didn't seem very intuitive that you could get back to playing without having something there (KS001).

I had it clear set in my mind that I would have to have surgery just because of my age, the lifestyle I live and also with my job I didn't believe that I would ever be able to get the stability I needed to fulfil to the maximum abilities (KS149).

In addition to this physical stability, the surgery was described as increasing a patients' confidence and trust in the knee. Patients considered that if the ACL had been 'fixed' it was less likely to 'give way' and become unstable and they felt less vulnerable to further injury.

Because it does play a little bit on your subconscious because you know well so I didn't go for the surgery so maybe everything is not there so maybe it could happen again (instability) (KS049).

I can't imagine doing a year of physio, obviously it does things, but I think I would always be worrying about my knee constantly regardless of how much physio I was doing….I think that you can feel something has happened after the surgery. So I wonder in a way it is like a placebo effect making you feel like it is better to a certain extent, I don't know (KS137).

4. I'll try the least invasive first, but surgery is always an option

For some patients it was preferable to do everything possible to avoid surgery or at least to try the least invasive option first. Surgery however, was always considered to be an option if patients were unable to return to sport or activities that were important to them.

I'm of the opinion if you can do it without going under the knife then so be it ……I would try the physio as best I could to make sure it worked and only if that wasn't working would I consider a surgical option ….and I knew surgery would set me back a short term before it took me forward so I had all of that in my mind…….. I thought I would try the least invasive one first please (KS139).

If I do reach a point where I'm unable to do the things that I would like to do, purely because is such a huge part of my life,…. that is alright we can have surgery at some point then, but I am in no rush and I want to give this a try. If I don't have to have surgery then that is great, no one loves or has casual surgery (KS141).

Some patients viewed an initial non-surgical approach as a potential way to enable a quicker return to work or sport. Others described the potential implications of 'lost time' if the non-surgical treatment was taken first and was not effective. Some felt that physiotherapy would be a waste of time and that it would delay return to sport, or create concern over the risk of secondary damage.

There is a possibility that they [different treatments] would offer the similar or same outcome but if I did the physio now and in 2 months now the instability still exists then in my head I have wasted 2 months essentially… if I went for surgery option… I know straight away that there is a 92% of getting back to where I want to, whereas with the physio 50:50 and then we would still then have to wait and see if there was enough stability in the joint (KS049).

Cost of time it would take if you go down the conservative route, there is risk of further damage down the line and sort of feeling that that there is potential for me to end up settling for a less satisfactory end result (KS005).

Knowing that you could undergo surgery if there was no improvement following non-surgical treatment, however, was described as reassuring.

Basically I wanted to get back to [sport] it as soon as possible and figured if there is a chance of it being better by January then I might as well go for it and see what happens and if it is not then I get surgery anyway and I have only lost 4 months so I might as well really (KS152).

So I just wanted to give it [physio] a try, because [the clinician] said, you know even if you decide in 2 years we'll do it then and I thought that is fine, I'll make that decision if it hurts and if it doesn't work as well as I want it to, if I start falling over loads at netball I will think about it again that was good to know that I could come back it is not like you have to know now that was really useful (KS014).

Discussion

The aim of this study was to identify factors underpinning patients' preference for surgical and non-surgical treatments, which may impact of the ability to recruit to a future trial with these comparisons. Exploring patients' views on surgical and non-surgical treatment options identified strong preferences for particular treatments and provided a greater understanding of factors underpinning patients' preference. Overall patients viewed surgery more positively than a non-surgical, physiotherapy approach. A number of patients however, did express a preference for an initial non-surgical approach, knowing that the option of surgery could be considered if there was no improvement.

Four key factors underpinning patients' treatment preference were identified; 1. Implications of the diagnosis, 2. Surgery considered by 'everyone' as the best means of returning to being active, 3. Surgery intuitively understood as providing a 'fix' to the problem 4. I'll try the least invasive first, but surgery is always an option. Whilst these findings are specific to this particular example, they highlight the potential benefit of exploring patients' views of treatments at the development stage of trials with very different treatment arms. In addition, they identify general issues, underpinning patient

preferences, which may be transferable to other trials with a surgical and non-surgical comparison.

Receiving a diagnosis of an ACL injury, was identified in this example as influencing patients' views on prognosis and preference for particular treatments. The findings of this review suggest that regardless of the patients' current symptom presentation in this study, diagnosis of an ACL injury implied surgical treatment. A number of patients did express a preference for an initial non-surgical approach, however, it was indicated that a surgical intervention would be considered, if there was no improvement. Returning to activities, regardless of activity level prior to injury or whether they were participating competitively or socially, was expressed as important, influencing decisions regarding treatment. The findings reflect those of other studies of this patient group, where ACL reconstruction was perceived as the only choice for a possible return to sports at the pre-injury level and non-surgical treatment was understood as accepting loss of normal functioning.[341] Exploring patients' views towards treatments identified that patients viewed surgery more positively than a non-surgical, physiotherapy approach and may provide some early indication to trial teams of the potential for treatment preference to pose a challenge to recruitment in a future trial. Qualitative studies, conducted at a pre-trial stage could be used to explore patients' understanding of a particular diagnosis or condition to be evaluated in a trial, to help trialists understand patients' views towards treatments.

External influences, such as friends, family healthcare professionals and the media, were identified in this example to contribute significantly to the overall strength of patients' preference for surgical treatment. The pathology, ACL rupture, is a common sporting injury,[209] with both treatments well established in clinical practice. The injury has

coverage in the media, with high profile sports people commonly undergoing surgical intervention for the injury. Unlike other clinical specialities, where a diagnosis often precedes a referral to a specialist e.g. oncology, in the majority of cases within orthopaedics, surgeons not only play a central role in diagnosing orthopaedic conditions such as an ACL injury, but also in discussing and recommending a range of treatments other than surgery. [201] Although current successful management of ACL deficiency includes both surgical and non-surgical treatments, patients expressed difficulty in finding positive examples of people returning to sport following non-surgical treatment, influencing decision making. The influence of these external factors however, are likely to be very trial specific, and vary depending on factors such as the particular condition, nature of the trial comparison, the treatment pathway or how patients are recruited. For example, trials evaluating a novel intervention, previous patient experience may not have such an influence, as with other more well established treatments.[199] Exploring and understanding the potential impact and influence of the wider social context on patients' knowledge development and decision making about treatments,[199] could help trial teams develop and provide patients with more balanced information to potential participants.

Surgical treatment was identified in this example, as being more intuitively understood by patients as a means of 'repairing' the injury. It was seen to provide mechanical stability, and as a result reassurance and confidence to return to activities. Whereas, non-surgical treatment was not viewed by patients with as much confidence in being able to provide a definitive treatment to their problem. The findings reflect those of the qualitative evidence synthesis discussed in Chapter 4, where the mechanism of something being repaired or removed, provided patients with a sense of finality of having received or undergone treatment.[290] The perception that an intervention has the potential to result in a

more favourable outcome, has been particularly problematic in recruitment to trials evaluating surgery and non-surgical interventions.[104, 132, 134, 152, 173] Negative views on the expected effectiveness of non-surgical treatments has also been demonstrated in studies of other pathologies in clinical practice, with strong patient preference for surgical treatment.[299, 342] Providing balanced information, addressing patients' views towards treatments, to ensure potential patients are fully informed about the treatments, could be beneficial in helping make decisions regarding trial participation.

The findings of this review identified that although some patients considered it preferable to start with a non-invasive approach to treatment, undergoing surgery was always discussed as a subsequent option by patients in this study. No improvement in symptoms or not being able to return to sport or activities were reasons for considering surgery. These findings reflect those of the qualitative evidence synthesis presented in Chapter 4, which explored the experiences of patients and healthcare professionals participating in these trials with divergent treatments in other clinical areas. As discussed in Chapter 4, surgical interventions can evoke negative emotions, making some patients more inclined to favour the less invasive procedure with lowest risk.[217, 314] The findings of the review also indicated that patients with more severe symptoms or those whose symptoms progressed, were more likely to consider undergoing surgical treatment.[277, 284] As suggested by Whybrow et al (2017), patients' decisions regarding willingness to consider trial participation may be related to a 'trajectory of worsening symptoms'.[298]

The inclusion of a clear route back to undergo a surgical intervention has been identified in previous qualitative studies as affecting patients' willingness to be randomised to trials with this type of comparison.[193, 277] Several studies have also made decisions to include this option as a design component, because of the perceived potential challenge to

recruitment.[140, 182, 343] Inclusion of this formal option for subsequent surgery may be a beneficial design consideration in a trials including these intervention comparisons.

Limitations

The findings of this study relate to a particular exemplar of musculoskeletal injury in a specific clinic in a single hospital where surgical and non-surgical treatment options are available as routine treatments. However we have highlighted barriers to trial recruitment that may be transferable outside this context.

The study included patients who agreed to be interviewed, and it would have been useful to explore the experience of those who did not respond to the participant invitation. This limitation is applicable to all research. More women agreed to participate than men and further research to explore difference in men's experience would be useful.

We did not recruit participants directly from the trial. Patients' preferences for certain treatments are multi-factorial and may change over time as a result of interaction with recruitment staff.[90] However, our focus was on identifying and understanding factors underpinning any existing preferences for treatment that occur prior to recruitment that may influence the ability to recruit. The patients interviewed in this study provide some insight into whether patients' preferences for treatment exist and understanding of the factors underpinning preferences that may impact on the ability to recruit to a subsequent trial.[90] The patients were recruited from a clinic that was representative of a type of clinic where patients would potentially be recruited during a subsequent trial. However, the cohort provided a convenience sample of a particular group of patients with acute ACL injury from a specific knee clinic at a single hospital and therefore limits the findings.

Further research to explore difference in patients' views of the wider patient population (e.g. different hospitals, stage of presentation) would be beneficial.

Summary of findings

Exploring patients' views on both surgical and non-surgical treatments highlights the strength of preference that can exist for particular treatments. The study provided a greater understanding of factors influencing the development of preferences and the potential implications for recruitment to a trial evaluating these interventions. In this chapter, four key factors underpinning patients' treatment preference were identified; 1.Implications of the diagnosis 2. Surgery the best means of returning to be 'active' 3. Surgery intuitively understood as proving a 'fix' to the problem 4. Least invasive first, but surgery is always an option. Although trialists cannot anticipate all the potential challenges prior to the start of recruitment, this study highlights the potential benefit of exploring patients' views of treatments in trials with diverse comparisons. Before the trial begins, trialists may wish to consider exploring the extent and balance of preference for treatments, particularly in trials where the interventions being evaluated are markedly different, to enable issues to a particular trial to be identified and addressed.

Chapter 6

Clinician equipoise: a qualitative interview study

Introduction

The findings discussed in Chapter 3 demonstrate that patients and clinicians can have strong preferences for treatment and this can pose a challenge to recruitment, adherence to treatment allocation and ultimately the success of a trial with a surgical and non-surgical comparison.[89-91, 217, 281, 291, 344] Clinicians' views on treatment can influence the level of patient participation [345] and act as a barrier to trial recruitment.[218, 291]

As discussed in Chapter 1, the ability to adopt a position of equipoise and a willingness to accept that there is genuine uncertainty over the most effective treatment [36 31] plays an integral part in conducting a clinical trial. The principle is that there is no certainty as to whether a patient would be advantaged or disadvantaged if they were to receive any of the interventions under investigation.[37] The concept of community equipoise (or "clinical equipoise") reflects the collective uncertainty in the clinical community about which treatment is best, which is crucial for informing the design of clinical trials.[37] Ethical issues underlying equipoise however are often debated [38] and the concept has been shown to raise great difficulties for recruiting clinicians,[39] especially when the interventions being evaluated are very different, such as a surgical and non-surgical comparison. Clinicians' views about the optimal management of individual patients can result in equipoise at a clinician level ("individual equipoise") being hard to achieve.[39]

As outlined in Chapter 4, qualitative research is used to understand challenges to recruitment in challenging randomised controlled trials (RCTs) and inform the development of strategies to improve recruitment.[219 39, 83, 205, 275] The majority of these studies however have been conducted alongside a main trial rather than at a pre-trial stage, where they could have the potential to explore other aspects such as the level of

equipoise or preference for treatment.[82, 83] Exploring clinician views on recruiting patients to a proposed trial could identify potential barriers to conducting a trial comparing surgical and non-surgical interventions.[82, 83]

Aim

The aim of this study was to explore clinicians' views on recruiting patients to a proposed orthopaedic trial with a surgical and non-surgical comparison and to identify potential challenges to recruitment.

Methods

Study design

A qualitative research study was conducted using semi structured interviews.

Ethics approval

Ethics approval to conduct this study was granted by the Wales Research Ethics Committee 7 (Reference No. 14/WA/1108).

Purposive sample

A trial assessing the management of anterior cruciate ligament (ACL) deficiency,[208] which exemplified a surgical and non-surgical comparison, was chosen to provide a purposive sample for the qualitative study.

Rupture of the anterior cruciate ligament of the knee is a common sporting injury and is most frequently seen in young and physically active individuals.[209] Current successful management of ACL deficiency includes both reconstructive surgery and non-surgical treatments (physiotherapy) but there remains uncertainty which management is

superior.[210, 211] Much of the current evidence is limited in methodological quality, consisting of a number of retrospective case-control and cohort studies and only one randomised controlled trial.[182, 212]

Orthopaedic knee surgeons and specialist lower limb physiotherapists from eight NHS hospital trusts who had expressed an interest in participating in a proposed trial of ACL deficiency management (NIHR HTA 14/140/63), through a previous survey of practice feasibility work (Appendix 6), were invited to participate. In cases where the specialist lower limb physiotherapist was no longer working as part of the team in the assessment and management of this patient group, alternative contact details were provided and the clinician was invited to participate. All clinicians were experienced in the management of ACL injuries. This group were chosen as they are currently managing patients with this injury and would be the most likely to participate in a future trial.

Recruitment

Participants were purposively sampled to ensure that a range of clinicians form across all the eight NHS hospital trusts were included. Clinicians who had expressed an interest in participating in a proposed trial of ACL deficiency management (NIHR HTA 14/140/63), through prior feasibility work, were contacted via e-mail. Clinicians who agreed to participate were sent a short synopsis of the proposed trial and an information sheet was sent to all clinicians prior to the interview (Appendix 15). This provided an overview of the aims, inclusion exclusion criteria and study design. The interview was arranged at the clinicians' place of work at a convenient time. Written consent was obtained from all clinicians who agreed to participate.

Data collection

Data was collected by semi-structured interviews. A topic guide (Appendix 16) was developed which outlined the questions and areas to be explored during the interview. It was designed as a prompt to encourage participants to talk freely and allow exploration of issues raised by participants. The questions were iteratively modified as the study progressed to enable exploration of emerging themes in later interviews.[319]

All interviews with participants were conducted face to face. Interviews were held at the clinicians' place of work and were digitally audio recorded, transcribed verbatim and anonymised. Transcripts were compared with audio recordings to ensure accuracy.

Analysis

The methods for qualitative thematic analysis have been described in detail in Chapter 5. A summary of the six-phase analytic process is summarised below in Table 27.[322]

Table 27: Six-phase analytic process of thematic analysis [322]

Phase	Description
1. Familiarisation with the data	Transcribing data, reading and rereading the data, noting down initial ideas
2. Generation of initial codes	Coding interesting features of the data systematically across the entire data set, collating data relevant to each code
3. Search for themes	Collating codes into potential themes, gathering all data relevant to each potential theme
4. Review of themes	Checking if the themes work in relation to the coded extracts and the entire data set, generating a thematic map
5. Defining and naming themes	Ongoing analysis for refining the specifics of each theme and generating clear definitions and names for each theme
6. Producing the report	The final opportunity for analysis. Selection of vivid compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a report of the analysis.

Demonstrating research rigour

The methods for demonstrating research rigour have been described in Chapter 5.

Results

Sixteen clinicians from eight NHS hospital trusts were approached and 12 clinicians were interviewed in total, (6 surgeons and 6 physiotherapists), from six NHS hospital trusts. The clinicians were experienced orthopaedic knee surgeons and specialist lower limb physiotherapists who work together managing patients with ACL deficiency. All clinicians were interviewed individually apart from one site where the clinicians were interviewed together. Three themes were identified that highlight the challenge of recruitment for clinicians to trials where the interventions compared are very different;

(a) Clinician equipoise for specific patients,

(b) Self-acknowledged clinician bias, and

(c) Lack of patient equipoise.

These themes are explained in the following section with narrative exemplar. There was no indication that themes were different for physiotherapists and surgeons.

a. Clinician equipoise for specific patients

This theme describes how being in a position of equipoise for certain patient groups with specific characteristics (age, activity level and time since injury) may be difficult. All clinicians interviewed expressed strong support for a proposed trial of ACL deficiency management and considered it an important research question. The majority of the

clinicians discussed the study in relation to limited evidence and could see its value in relation to the NHS patient population.

All clinicians indicated that they would be happy to randomise patients to the proposed trial. However, when talking more specifically about certain patients or patient subgroups who were eligible for the study, some were more uncomfortable about the possibility of not offering a particular treatment or about recruiting certain patients to the trial. This discomfort was underpinned by concerns about age and activity levels, and was particularly evident when considering young active patients hoping to return to sports such as football. Clinicians discussed being uncomfortable with not offering surgical treatment to this patient group.

> *Yes to summarise that, I think . . . there would be certain groups of patients with high pivoting activity levels that we might feel uncomfortable not operating and I realise that could be a biased view . . . (laughter) quite. . . quite biased yeah, but that is the honest answer (Surgeon).*
>
> *I think that it is an important question to answer but I think it is going to be difficult. I think most ACL surgeons have reached a point in their decision making that if you have a young active patient wanting to go back to sport it is very difficult to discuss non operative treatment. I think that most people now have got the view that ACL reconstruction is the best way forward for most of those patients (Surgeon).*

In contrast, some clinicians described being in a position of equipoise as easier for certain patients.

> *They are the ones that would tend to be more polarised [young active /older not so active] . . . and I would agree with them feeling polarised . . . it is that group in the middle . . . in their 30s not playing that regularly, it is not clear cut, they would be the group that would be more easy to feel in equipoise and persuade them to enter a trial, I think (Surgeon).*

There were mixed feelings regarding equipoise related to a person's age, some clinicians thought that it was not necessarily age but functional level that should be considered.

> *I think there are set ideas at the moment that if you are kind of forty plus you are much less likely to have this (operation) done, if you are under forty you are much more likely to have it done . . . but this sort of pseudo too old too young needs to be shifted to one side and I don't think it is the primary or should be the primary reason for it, it should be function (Physiotherapist).*

> *More difficult would be . . . the fifty year old skiing lady who I feel quite strongly . . . should be managed conservatively first of all. I would be, I would feel less appropriate to start presenting them with an equipoise choice (Surgeon).*

Clinicians' perceptions of patient priorities related to age and 'stage in life' was also expressed by many of the clinicians as a reason for recommending surgery with certain patients.

> *We are more likely to recruit the 35 year old who getting back to football is less of a priority in their life than the 21 year old* (Surgeon).

> *Classically someone who is in their first or second year at university, they have got two more years left at university and want to play for their university football team because that is where their social life is. Whereas people in their 30s who are in the workhouse of their career, they have many other priorities that they are looking at doing and the thought of not having an operation if they have got family and got other things going on, they are happier to wait 6 months* (Surgeon).

Some clinicians were aware that this would potentially influence their decision to recruit patients to the trial and therefore the generalisability of trial findings.

> *Whilst things are changing there is still a significant feeling out there that at least 70 percent will need surgery whatever happens. . . that will skew your line of people getting into it (Surgeon).*

Real risk that you will end up with a patient group where we naturally even now go 'well it is your choice' rather than a more active patient who we encourage strongly to have an ACL reconstruction (Surgeon).

Some clinicians indicated that equipoise would be difficult if patients had sustained the injury more than four months previously. At this stage the presenting symptoms would predominately be instability rather than a combination of pain, swelling and instability at the more acute stage and therefore would be more likely to recommend surgery in these cases.

I would struggle with equipoise with certain patients groups actually, perhaps even more so with these chronic ones . . . Because they have only sought referral because they have got instability and if a lot of those people who play football or rugby have tried to get back not realising what their injury was and then of course we are all worried about secondary injury to the knee (Surgeon).

The reason that some clinicians expressed difficulty in adopting a position of equipoise for certain patients was because they considered these patients as potentially at a greater risk of secondary damage and subsequent development of osteoarthritis (OA) to the knee. Many of the clinicians discussed this with specific reference to the current evidence.

The Frobell study [182, 183] is a level 1 RCT . . . . [rather than] lower level evidence, but there is some consistent evidence to suggest that if your knee keeps giving way then that isn't a good thing. If you delay an ACL reconstruction the chance of secondary meniscal chondral pathology in pretty much all studies is consistently higher, you do secondary damage as time progresses and there does seem to be a highly consistent correlation between the amount of secondary damage and the risk of radiographic OA years later . . . . what I tend to say to patients is don't let your knee give way again you can either do that by downgrading your level of activity or restabilising your knee surgically (Surgeon).

In terms of the Australian and the US evidence base if you leave people with ACL [deficiency] they will irreversibly trash their meniscal and chondral surfaces and get arthritis quicker and you need to fix all these young people, it is contra to what the Scandinavian stuff that tells us it is not necessarily the case (Surgeon).

b. Self-acknowledged clinician bias

Clinicians were aware that the way they frame or present information about treatment may influence patient choice and thoughts about treatment. In some cases the clinicians anticipated that this might be done inadvertently. However, there was also a sense that in some cases they steered certain patients towards a particular treatment.

We all know that if you try, you can talk through the risks and benefits of non-operative treatment and surgical treatment in lots of different ways depending on whether you personally as the surgeon want, think the operation is a good idea or not so yeah you can emphasise the terrible risks of surgery or you can gloss over them almost and completely change the emphasis of your discussion and sometimes you probably do that unwittingly (Surgeon).

Yes, well equally so, but there will be quite a few patients that come through that actually will be driven by the surgeon as well . . . .I'll freely admit that …if I have a guy who is a semi-professional footballer I am going to steer towards surgery (Surgeon).

Despite indicating that they would be happy to discuss the trial and randomise participants to it, in some cases clinicians' did not seem to be aware of the possible impact phrasing would have on patients' thoughts about treatment.

I'd be happy to randomise the young ones as long as they are happy with that, the patients, so I's say look if you push me to make decision I think you are heading towards surgery, but if you are willing it is perfectly reasonable not to have surgery and if you are not sure about it we are running trial that I am happy to put you in to. So even if I felt that they were more of a surgical candidate, as long

as they feel unsure about it and they are perfectly okay to then go into the trial (Surgeon).

Others questioned whether or not it should be the clinicians recruiting patients to the trial. They were aware however of the potential challenge with this because of the requirement for a clinician to make a diagnosis.

It is probably best to approach these patients before they have a detailed discussion with the surgeon. Recruitment done by someone completely separate with no particular bias towards one particular treatment or the other (Surgeon).

….you have to make the diagnosis first, somebody has to make the diagnosis of ACL injury and not talk about treatment pretty much (laughter). It was easier with [name of another trial], because the diagnosis of an arthritic knee is much more straightforward and is usually made before the patient gets to clinic. Whereas typically an ACL injury is not diagnosed until a consultant has laid hands on the patient. (Surgeon)

When the clinicians discussed the treatments in general they were not expressed in equivalent terms or considered to provide equivalent outcome. Surgery was considered as a means to getting back to sport or providing the 'fix', and preventing your knee from giving way.

At the other end you have got the 45 year old occasional sports person or female skier that does it that doesn't play any twisting or turning sport who I would say look we could fix it you have ruptured it but actually there is no rush to make that decision and we will see how you go first go down the physio route (Surgeon).

It would be reasonable to either have an ACL reconstruction and stabilise your knee or just be careful and make sure your knee doesn't give way by carrying on with straight line sports (Surgeon).

c. Lack of patient equipoise

Clinicians felt that patients would come to a clinic appointment with certain preconceived ideas about an ACL injury and treatments available. There was a sense that, although some might prefer a conservative approach, others would have stronger preference towards surgical treatment.

> *Quite a lot of patients they do come with you know, when I express to them that it is not a clear cut decision most of them actually make a decision fairly quickly that actually they really not keen to have surgery they definitely want to push with physiotherapy first or you know, I think I need an operation because I am really keen to play football at a high level and I just know that is what footballers have done (Surgeon).*
>
> *There is that perception out there that if your ACL goes you can't ski and you can't play with your kids and it is trying to break down some of those perceptions (Surgeon).*

Some clinicians felt that many patients did not see physiotherapy as a definitive treatment, with patients' decisions around treatment hinging on whether or not to have surgery, rather than an active choice for physiotherapy. Clinicians considered that patients viewed surgery as a means of fixing a problem, whereas with a physiotherapy approach there would always be the uncertainty of 'will it be good enough'.

> *Potentially or it might just be the fact that they (patients) may think the only way to do it is to solve the problem . . . with the operation. The patients that I have seen that are deficient, most of their treatment has been a conversation around should they or shouldn't they [have an operation] and they are still thinking that they may well, as opposed to this [physiotherapy] is definitive treatment, I would say (Physiotherapist).*
>
> *Yeah, well it is that big uncertainty; if they don't have it done is the knee going to be good enough. Lots of people I don't think like possibly like to live with*

uncertainty, personality type may not want to live with uncertainty. I think a lot, I don't know and maybe it is my bias I think a lot of people want to get on with things and they think if I'm going to have to have it done I'll have it now (Physiotherapist).

Clinicians felt that as this is a fairly common sporting injury with high media profile, this preference was highly influenced by various sources; patients' social environment, and experiences of family, friends.

Well, I guess it probably applies to the groups that I have talked about you tend to get these 18/19 year old footballers and they know that Michael Owen had an operation when he did it and therefore they should have an operation when they do it and they are fairly clear cut in their minds and perhaps they are right (Surgeon).

A patient will say 'my mate had it done', 'I must have a patella tendon graft or a hamstring graft' and I'm going to need surgery because I'll never get back to it [sport] because the club has a therapist and has said to them, you will need surgery (Surgeon).

In addition, they recognised the impact of information available through social media and the internet.

It is hard … if they come in as we said with that preconceived 'I need an operation' and there is so much out there on the internet they can go away and do all the research (Surgeon).

*We have some websites that we recommend. We try and keep people off google and Wikipedia and all that sort of stuff but we have some recommended websites which are on the back of our ACL protocol, knee guru is one of them, ACL reconstruct I think is another (*Physiotherapist).

Clinicians also described how previous treatment received and advice from health care providers, especially if the patient had been referred from elsewhere on the treatment

pathway e.g. referral clinics, could highly influence patients choices and make it difficult to discuss and recruit to the trial.

> *The only problem here would be patient expectation. So if someone has been told they need to see me because they need an operation, then it is then difficult to have the conversation because even though I am the specialist, if someone has been told they should have an operation it is very hard to then turn that round into we are not sure about this operation (Surgeon).*
>
> *It is interesting when they come to us, especially if they come from somebody else . . . if somebody has already told them you are going to need an operation, and I am going to send you to the person who is going to do your operation and sort your knee out, then we are a bit stuffed on that one (Surgeon).*

Some clinicians also considered the implications of patients' treatment preferences on potential drop-out from the trial.

> *There will always be some people who for various preconceptions will not want to be part of it (the trial) because they will want a particular treatment and I suppose the risk for the trial is that if we recruit them then they will drop out if they are not recruited to their preferred arm (Surgeon).*

Discussion

Randomised controlled trials that compare a surgical and non-surgical intervention can be challenging to conduct and many struggle with recruitment.[205, 217] Strong treatment preferences of both clinicians and patients can pose a challenge to recruitment, adherence to treatment allocation and ultimately the success of a trial. In this example, exploring clinicians' views on recruiting patients to a proposed trial highlight the difficulties in adopting a position of personal equipoise when the interventions being compared are diverse and delivered by different healthcare professionals. Three main areas were identified that highlight the potential challenge of recruitment for clinicians; (a) Clinician

equipoise for specific patients, (b) Self-acknowledged clinician bias and (c) Lack of patient equipoise. Whilst the findings are specific to this particular example, they highlight more general issues that are transferable to other trials with a surgical and non-surgical comparison.

Despite overall strong support for the proposed trial, it was clearly identified in this example that there were certain sub groups of patients for which clinicians would find difficulty in adopting a position of full personal equipoise and allowing approach to participate. Reluctance to recruit particular patients who fit trial eligibility criteria has been shown to result in patients not being approached to participate, impacting on recruitment and patients' autonomy to consider trial participation.[39, 205, 217, 219, 291, 346] Clinicians' misunderstanding of the trial design for example, trial aims and nature of comparison, has also been identified as having the potential to adversely affect recruitment.[281]

As seen in this study, in cases where clinicians are responsible for recruiting, preconceived personal preferences associated with an intervention are likely to be present. As highlighted in Chapter 4, strong clinician preferences are also likely to be more prominent when interventions being evaluated are delivered by different specialities.[291, 346-350] Differences in clinical judgement regarding potentially eligible patients, highlight the underlying conflict clinicians can often have in their roles as a clinician and researcher that is, 'the clash between the clinical mandate to act in the individual patient's best interests (beneficence) while causing no harm (non-maleficence), with the scientific mandate to pursue knowledge with appropriate rigor'.[313, 351] As discussed in Chapter 4, ingrained values, skills and knowledge that clinicians' develop over time through 'intensive professional socialisation',[313] can make it difficult for

clinicians to totally separate the care and welfare of patients to that of clinical research.[312, 313] Taking into account the knowledge and experience of clinicians', it could be argued that it may be unethical to suggest that clinicians should maintain equipoise over and above clinical practice in the decision making over individual patients. Alternative approaches to randomisation may be required in cases where issues with equipoise make recruitment particularly problematic. The findings of this study highlight the possible benefits of pre-trial qualitative studies to identify patients or sub groups of patients that recruiting clinicians could have difficulty approaching. In addition, exploring and understanding reasons underpinning potential issues with equipoise that may be problematic in the conduct of a trial, can enable these issues to be carefully considered in the planning of a trial.

Potential for clinician bias towards particular interventions led clinicians, in this example, to question whether it should be the respective healthcare professionals (that is, surgeons and physiotherapists) recruiting to a trial with a surgical and non-surgical comparison. Previous qualitative studies of trials with similar diverse comparisons highlight these difficulties.[203, 291] As discussed in Chapter 4, despite clinicians' intentions to conceal or suspend personal inclinations or beliefs, clinicians with treatment preferences or less balanced views can often undermine patient equipoise through presenting patients imbalanced descriptions about trial treatments, offering treatment recommendations, or making clear predictions about trial outcomes.[79, 89-91, 204, 344] Patients' reasons for declining trial participation have also been shown to be based on their interpretations of clinicians' treatment preference.[217, 286] Alternative approaches to recruitment, such as involving the research nurse,[202] or other member of the research team, changing the order in which patients meet clinicians or holding joint clinics with recruiting clinicians have

been explored or suggested.[203-205] However, as highlighted in this example, clinical knowledge required to make a diagnosis and to decide if a patient is suitable to undergo each of the interventions, and the complexity of the treatment pathway can make alternative approaches challenging to implement.

Potential for patients to have strong preference towards surgical treatment was also considered by clinicians (in this example) to pose a challenge to recruitment. With trials that compare a surgical and non-surgical approach there can be a dichotomy between strong preference for one treatment or another, making recruitment particularly challenging.[199, 218, 291] The findings of the qualitative evidence synthesis presented in Chapter 4 and of the patient interview study discussed in Chapter 5, highlight the many factors can contribute to the development of patients' preferences with this type of comparison. For example, the level of invasiveness of the surgical option, differences in level of risk, logistical differences in terms of what each treatment entails, and views on the perceived mechanism of effect.

In this ACL trial example, negative beliefs of patients about the efficacy of the non-surgical treatment was viewed by clinicians to pose a challenge to recruitment. The findings reflect those discussed in Chapter 5, exploring factors underpinning patients' preference for surgical and non-surgical treatments for ACL injury. Surgical and non-surgical treatments were not viewed by the majority of patients as potentially being able to provide equivalent outcome. Surgery was intuitively understood by patients as providing a 'fix' to the problem, whereas patients expressed concern as to whether the adequate stability would be achieved with non-surgical treatment and whether they would be able to return to activities that were important to them. Ensuring that the interventions being evaluated are viewed as comparative and acceptable by both patients and clinicians

because of the potential negative impact on recruitment, has been highlighted in other trials with a surgical and non-surgical comparison.[282] The strength of patients' preference for particular interventions and underlying reasons for them, however, will not always be clear to the trial team until the start of recruitment. Future qualitative studies at a pre-trial stage could be used to explore patients' views of treatments and reasons for decision making, prior to recruitment, to better understand the target patient population.

Limitations

The findings of this study relate to a specific example of a proposed trial comparing a surgical and non-surgical intervention and therefore may limit its applicability to other trials. Nevertheless, it does highlight general issues related to equipoise that are transferable to other trials with a surgical and non-surgical comparison. This study included clinicians who had expressed an interest in participating in a proposed trial following prior feasibility work. The study therefore does not represent views of all clinicians managing patients with this injury or clinicians who may have been interested in participating in this proposed trial but did not participate in the feasibility work. However, it does highlight the views of clinicians' who were likely to participate, from six different hospital sites, and therefore understand factors that may impact on the ability to recruit to a subsequent trial. At one of the sites the clinicians were interviewed together because of time difficulties, which may have influenced the interview.

Summary of results

Exploring clinician views on recruiting patients to a proposed trial with a surgical and non-surgical comparison highlight the difficulties clinicians' have in adopting a position of equipoise when the interventions being compared are diverse and delivered by

different healthcare professionals. In this chapter, three main areas were identified that highlight the challenge of recruitment for clinicians: 1. Clinician equipoise for specific patients, 2. Self-acknowledged clinician bias and 3. Lack of patient equipoise. Trialists may wish to consider the use of pre-trial qualitative studies to identify and address equipoise issues especially in trials with markedly different interventions.

Chapter 7

Discussion

Introduction

The aim of this thesis was to gain a greater understanding of the main methodological challenges to the design and conduct of trials that directly compare surgical and non-surgical interventions, explore potential solutions, and provide guidance for use in future studies. The work contained in the thesis purposefully used different methodologies to provide insight from different perspectives in order to more fully understand the challenges involved in this type of trial and therefore contribute to the design of future trials.

The thesis was conducted in two parts. Firstly, Chapter 2 reported the findings from a systematic review of trials in order to identify any reported challenge of conducting randomised controlled trials that compare surgical with non-surgical interventions. In the second part of the thesis, the specific challenges identified in Chapter 2, namely, difficulty implementing blinding, recruitment difficulties, complexity of intervention content and delivery, imbalance in timing of follow-up, non-compliance with treatment allocation, and differential loss to follow-up, were then further explored in four separate studies. Chapter 3 described the findings from a case study that explored the challenges experienced during a multi-centre trial, which exemplified a surgical and non-surgical comparison (ACL SNNAP). Chapter 4 reported the findings from a qualitative evidence synthesis which explored the challenges of participating in trials that compare surgery with non-surgical interventions. Chapters 5 and 6 reported the findings from two qualitative research studies that explored the barriers to conducting a trial comparing surgical and non-surgical interventions for ACL injury, in (a) patients, and (b) clinicians.

This final chapter will bring together the findings of each of the chapters, discuss the implications of these findings in order to provide insight and help design future trials of this type of comparison. Possibilities for future research will also be presented. The findings from this thesis have important considerations for trialists who design and conduct trials that directly compare surgical and non-surgical interventions.

Overview of thesis findings

Several methodological challenges to the design and conduct of trials that directly compare surgical and non-surgical interventions were identified in this thesis; difficulty implementing blinding, recruitment difficulties, complexity of intervention content and delivery, imbalance in timing of follow-up, non-compliance with treatment allocation, and differential loss to follow-up. The implications of these findings to the design and conduct of these types of trials are discussed in the following section.

Challenges and potential solutions

Difficulty implementing blinding

The inability to implement blinding in these types of trials, because of the nature of the interventions being compared, was identified in Chapter 2 as creating a challenge to the conduct of these types of trials. Blinding of patients and participating clinicians to treatment allocation is one of the key components of trial design that aim to minimise bias in the conduct of RCTs, and therefore could have implications for the conduct of these types of trials. As discussed in the introduction to this thesis, patients' knowledge of treatment allocation may influence patients' perceptions about treatment and affect outcome, potentially leading to biased results, particularly when there are subjective outcomes.[64] Patients' may also be less likely to comply with their allocated intervention,

withdraw from the trial without providing outcome data, or seek additional interventions.[67] Knowledge of treatment received could also influence clinicians' management of patients during the trial, for example, differential use of additional interventions, which can be a source of bias.[64, 65, 68]

In these types of trials, where it is impossible to implement blinding of patients and practitioners and there is potential for strong preferences of patients and clinicians, it could be said that undertaking pilot and feasibility work should be an essential component in the planning of these trials. The inclusion of objective outcome measures and blinded outcome assessment should be considered in these types of trials to help reduce the potential for bias.[65]

Recruitment difficulties

Difficulties with recruitment were identified in this thesis as one of the main challenges to the conduct of trials that directly compare surgical and non-surgical interventions. The findings of the systematic review presented in Chapter 2 identified problems with lengthy recruitment periods, early closure of some studies and a number of trials not reaching recruitment target in trials of this type of comparison. The findings support previous studies that highlight the challenge of recruiting to surgical trials,[41, 352] particularly those with a non-surgical comparison.[23, 43, 44] Low recruitment can not only have implications for the internal and external validity of a trial, but may also lead to extended recruitment periods with implications for finance and resources. The potential exists for research findings to be missed or delaying the introduction of effective treatment. Given the potential negative consequences of incomplete trials, understanding reasons for difficulties to improve the design and conduct of these types of trials and minimise the risk of failure is therefore a priority.[44]

The findings of this thesis adds to our understanding of the potential reasons for difficulties with recruitment to trials with this type of comparison. The conceptual model presented in Chapter 4, highlights the complex interplay of patient and clinician factors that can affect the recruitment process in trials of this type of trial comparison. The dichotomy between several aspects of the surgical and non-surgical interventions, for example level of invasiveness, risk, and perceived mechanism of effect, evaluated in trials of this comparison were seen to contribute to strong treatment preferences of both patients and clinicians. Patients' and clinicians' treatment preferences have been recognised as a key factor contributing to recruitment difficulties in surgical trials.[91, 95, 199, 306, 310, 353] The specific factors identified in this thesis as influencing patients' and clinicians' treatment preferences in trials with this type of comparators are discussed below.

Chapter 4 and 5 show that the invasiveness and irreversibility associated with surgical procedures has the potential to raise negative emotions such as fear, anxiety,[92, 199] and affect patients' views towards treatments and trial participation.[80, 193, 280, 288] Some patients viewed surgery as the 'point of last resort, or an option to consider if there were no improvements with non-surgical care.[92, 283, 285] The emotional aspect of decision making has been discussed as a factor contributing to patients' reluctance to consider trial participation in any trial that involves a surgical comparator.[92, 199] The magnitude of difference in the invasiveness and irreversibility between the surgical and non-surgical interventions, however, may make emotional factors particularly salient in these types of trials.[92, 199] This emotional impact has implications for recruitment to these types of trials, and should be considered when setting recruitment projections for this type of trial

comparison. For example, conducting pilot studies with collection of detailed screening to inform the setting of recruitment targets.

Differences in the level of potential risk between the interventions compared in these types of trials, was also identified as an important factor influencing patients' preference towards treatments. Patients' views on the potential risk of undergoing surgery and the implications of the risks, however, were seen to vary depending on specific factors, such as, a patients' diagnosis, duration or severity of symptoms. For example, patients with more severe symptoms or with greater symptom duration were seen to be more likely to consider surgical intervention. The findings of this thesis support those of previous studies that have discussed the importance of considering potential participants' health state (life-threatening conditions, long-term conditions), and trajectory of their condition (established or recently diagnosed conditions) during recruitment to clinical trials.[233, 298] Exploring views of the specific patient population through pre-trial qualitative studies, could identify factors that may influence recruitment.

The findings of this thesis also highlight that surgery was seen to be understood more intuitively by patients as providing a mechanical 'fix' or 'cure' to a mechanical problem, influencing views towards the particular treatments. In Chapter 4, 5 and 6, surgery was discussed as being viewed by patients as providing a definitive treatment to a problem, whereas patients' expressed difficulty in understanding the mechanism by which non-surgical interventions could achieve similar outcomes. Patients' lack of confidence in the expected effectiveness of non-surgical treatments compared to surgery, has also been identified in studies exploring reasons for treatment choices made in routine clinical practice.[299, 300] Ensuring that both surgical and non-surgical interventions are understood and viewed by patients as comparative, despite the differences between them in

mechanism of effect, is important because of the potential impact on patients' views towards treatments and trial participation. Providing balanced information, addressing patients' views towards treatments, to ensure potential patients are fully informed about treatments, could be beneficial in helping patients make decisions regarding trial participation.

Disparity between the content of the interventions and treatment pathway of the surgical and non-surgical interventions were also identified as potentially contributing to patients' views and preferences towards the different treatments. Differences between the types of interventions in factors such as, level of patient input (whether they were passive or active interventions), timing of when patients would receive the intervention (for example, waiting lists), and socioeconomic factors (for example, time required off work) were seen to contribute to patients' views towards treatments and trial participation.

The findings of the systematic review in Chapter 2, demonstrate that patients' strength of preference for either surgical or non-surgical treatments can vary between the different trial comparisons. Such variability between trials, reflects the potential complexity in the development of patients' preferences in these types of trials. The findings of the patient interview study in Chapter 5, however, highlights how exploring the extent and balance of patients preferences for treatment, could enable trial specific issues related to a particular pathology and treatments to be identified. Understanding reasons underpinning patients' preferences for particular treatments and the strength of preference could offer opportunities to address issues by developing targeted patient information and strategies to support recruiting teams, with the view to improve recruitment and optimise trial conduct.[82, 83, 316] Qualitative research with its emphasis on meaning, context and process, is an ideal means of exploratory work to enhance understanding of aspects such as patient

preference and clinician equipoise, and in doing so contribute to improvements in trial design.[73]

Discussing trial participation with potential patients was also seen to be particularly challenging for recruiting clinicians in trials of this type of comparison. The stark differences between the interventions and potential for patients to have strong a prior preferences for treatment, was considered by clinicians to make the process more difficult than for example trials of two similar surgical procedures.[218, 291] The qualitative evidence synthesis (QES) presented in Chapter 4, described how challenging patients' preferences for treatment was viewed by some clinicians as potentially coercive,[39] particularly with the elevated risks associated with surgery compared with non-surgical treatment. Some clinicians felt that patients may be 'rushed into' a surgical procedure because of participation in the trial.[283] It could be argued that in cases where strong preferences for treatment exist, patients should not be approached to participate and should receive their treatment of choice.[90, 354] However, studies have shown that exploration of patients' initial views about treatments are sometimes based on misunderstanding of scientific evidence.[90] Exploring patients' preferences and proving patients with evidence based information, therefore could be seen as an important and integral part of the information exchange necessary to enable patients to make informed decisions not only about trial participation, but also about their own care.[90]

The findings of this thesis highlight the conflict clinicians can have in their role as a clinician and participating in research. As discussed in Chapter 4, clinicians' strong preferences for treatment are a well-recognised challenge to the conduct of surgical trials, potentially having a detrimental impact on recruitment.[91, 95, 310] The additional influence of strong clinical speciality convictions were identified in this thesis as being evident in

trials with this type of comparison. Reluctance by clinicians to recruit particular patients who fit trial eligibility criteria has been shown to result in patients not being approached to participate and impacting on recruitment and patients' autonomy to consider trial participation.[39, 205, 216, 217, 219, 281, 291, 346] Variation between participating sites in the number of eligible patients, recruitment rates and patients declining participation was observed in the case study example of a trial presented in Chapter 3. As discussed in Chapter 4, ingrained values, skills and knowledge that clinicians' develop over time through 'intensive professional socialisation',[313] can make it difficult for clinicians to totally separate the care and welfare of patients to that of clinical research.[312, 313] Taking into account the knowledge and experience of clinicians', it could be argued that it may be unethical to suggest that clinicians should maintain equipoise over and above clinical practice in the decision making over individual patients. Alternative approaches to randomisation may be required in cases where issues with equipoise make recruitment particularly problematic.

The qualitative studies presented in Chapter 6 highlight the potential benefit of exploring clinicians' views on treatments in trials with such diverse comparisons. Pre-trial studies have the potential to identify patients or sub groups of patients that recruiting clinicians could have difficulty approaching and understand factors underpinning equipoise issues. Understanding these issues could help develop effective and targeted training to support recruitment and engagement from all specialities.

Complexity of intervention content and delivery

The findings of this thesis highlight how the complexity of both the surgical and non-surgical interventions being compared can create additional challenges to the design, conduct and analysis of trials with this type of comparison. Depending on the

interventions being compared, both interventions potentially involve several interacting components (for example, the varying skill and experience of clinicians) [30, 195] that could be a source of bias and could therefore have an effect on outcome. As discussed in the systematic review in Chapter 2, these factors may be particularly problematic when conducting multi-centre studies.[134, 137, 142, 173] Evaluating interventions with such different components also raises questions in how intervention fidelity, that is, the extent to which an intervention's core components might be achieved in these types of trials.[355] As discussed in Chapter 2, intervention content was not well reported in the trials included in the review making it difficult to explore in these trials. The challenges around complexities of the trials interventions, such as standardisation and fidelity, were not explored in depth in this thesis, but would provide an interesting area for further research.

Imbalance in timing of follow-up outcome assessments

Selecting the appropriate timing of follow-up assessment was also identified in this thesis as being a potential challenge in trials of this type of comparison. The varying content of the surgical and non-surgical interventions, such as, a one off surgical intervention compared to an exercise intervention conducted over several months, was identified as having the potential to favour one intervention. The time to effect for the different trial interventions may differ and the choice of timing of the outcome assessment may therefore introduce bias.

Differential delays in patients receiving trial intervention, for example, due to hospital waiting lists, between treatment arms were also identified as having potential implications for the interpretation of outcome in trials of this type. This was considered to be potentially more problematic in trials that involve elective procedures than to trials of more acute pathology (for example, trauma).

Potential factors influencing the timing of follow-up, such as the content of the different interventions and impact of waiting lists, need to be considered when decisions are made on the choice of timing of outcome assessment in these types of trials to ensure interpretable results. Understanding the time to effect of different interventions could help decision making in the choice of timing for outcome assessment in these types of trials. Further work could explore the potential for differences in outcome assessment based on the timing of assessment.

Imbalance in non-compliance with allocated treatment intervention

The potential for differences between intervention groups in departures from random allocation (non-compliance), was also identified in this thesis as a potential challenge to the conduct of these types of trials.[84, 87, 206] Compared with trials of similar procedures (for example, two surgical procedures), non-compliance could potentially result in an imbalance between treatment arms in these trials, as crossover can only occur in one direction (towards surgery) resulting in complexities with interpretation.[206] Non-compliance was identified as being particularly problematic (greater than 20%) in some of the trials [104, 112, 121, 127, 132, 147, 187] included in the systematic review presented in Chapter 2. This may related to factors specific to the trial comparison, such as strength of patient and clinician preferences. Further qualitative research could explore reasons for non-compliance and increase our understanding of factors that make non-compliance more problematic with certain trial comparisons.

The potential for other forms of non-compliance in trials with this type of comparison were also identified in this thesis. For example, in the surgical group, clinical decisions made to undergo a different procedure or surgery deemed unnecessary of impossible after gaining surgical access. As discussed in Chapter 3, decisions made on how cases on non-

compliance are manged has the potential to introduce significant bias and threaten the validity of trial results, and therefore should be considered in the design and planning of these types of trials.

Differential loss to follow-up

The findings of this thesis highlight the potential for differential loss to follow-up in these types of trials, which may introduce bias [67] and result in difficulties with interpretation of the results. The findings of Chapter 2 highlight how common loss to follow-up can be in these types of trials, with 71% of studies reported some missing data, and the percentage of loss to follow-up higher in the multi-centre studies. Differences in loss to follow-up between intervention groups were not observed in the review of published studies presented in Chapter 2. However, the findings of the case study, identified a greater percentage of loss to follow-up in the non-surgical than surgical group. These differences may reflect that the published studies reflect the final figures on retention and do not include what was undertaken in resources and time to obtain the retention figures.

Potential reasons for differences between treatment groups in loss to follow-up were discussed. Future studies could explore reasons and increase our understanding for loss to follow-up in these types of trials.

Strengths and limitations

This is the first study to fully explore the methodological challenges that directly compare surgical and non-surgical interventions. The work contained in the thesis uses knowledge from quantitative and qualitative research to understand the challenge of conducting randomised trials of this type of comparison. The thesis purposefully used different methodologies to provide insight from different perspectives in order to more fully

understand the challenges involved in this type of trial and therefore contribute to the design of future trials. Practical considerations for the conduct of trials with this type of comparison are discussed below.

The limitations of this research have been discussed in detail in each chapter and centre mainly around potential concerns regarding generalisability. Apart from the qualitative evidence synthesis presented in Chapter 4, which included studies from a range of clinical specialities, the findings of the other studies relate primarily from one area of health care (Orthopaedics). However, the findings highlight general issues that may be transferable to other trials in comparing disparate interventions. Where available, evidence to support the findings have been presented from other clinical areas. Further research therefore may be required to investigate specific clinical areas.

Recommendations for research practice

Several methodological issues were identified in this thesis that have the potential to impact on the design, conduct and analysis of these types of trials. If not adequately addressed, these issues may introduce significant bias and threaten the viability of the trial, and also the validity of the results. Consideration of these specific challenges should be made in the planning and design of future studies to optimise trial conduct.

Recommendations and guidance for the conduct of trials with a surgical and non-surgical comparison, based on the findings from this thesis summarised in Table 28 below.

Table 28: Recommendations for the conduct of RCTs with a surgical and non-surgical comparison

Potential challenges (findings from thesis)		Recommendations and guidance based on findings from thesis
1. Difficulties with recruitment	a. Potential for patients' preference for a particular treatment to affect recruitment.	1. Conduct pre-trial qualitative studies to explore and understand the extent and balance of patients' preferences for the interventions being compared. 2. Conduct a review of the treatment pathways and consider the potential impact of factors, such as, the referral process and previous non-surgical treatment on recruitment. 3. Provide balanced patient information, addressing patients' views towards treatments, e.g. details to explain mechanism of effect of both interventions. 4. Consider the terminology that will be used to describe the intervention comparators and how this may potentially influence patients' perceptions of the interventions. 5. Collect detailed screening data during pilot/feasibility stage to: a. Understand reasons for non-eligibility/non consent to identify and address potential issues affecting recruitment. b. Inform the choice of realistic recruitment targets for main trial. 6. Provide education and training of and strategies to support recruiting teams to explore patients' preference for treatment, with the view to improve recruitment and optimise trial conduct.

2. Difficulties with recruitment (continued)	b. Potential for clinicians' preference for a particular treatment to affect recruitment.	1. Conduct pre-trial qualitative studies to explore and understand clinicians' (all specialities involved) views towards the trial and intervention comparators. a. To identify patients or sub groups of patients that recruiting clinicians could have difficulty approaching because of preference for a particular treatment and understand factors underpinning equipoise issues. b. To identify any other concerns/issues that clinicians may have with the proposed eligibility criteria in relation to the specific patient population e.g. potential differences in interpretation of criteria. 2. Provide education and training to support recruitment and engagement from all clinical specialities involved. Discuss the findings of feasibility stage with recruiting teams to highlight potential challenges. 3. Collect detailed screening data during pilot/feasibility stage to: a. Identify potential difficulties with recruiting teams in the application and interpretation of the eligibility criteria. b. Identify potential difficulties with recruiting teams in randomising eligible patients.
2. Complexity of intervention	a. Potential for variation in the content and the delivery of	

content and delivery	interventions e.g. level of clinical expertise, to impact on trial outcome.	1. Ensure that the interventions and expertise of clinicians delivering interventions are clearly described in both treatment arms to enable interpretation of the study and generalisation of the results.
3. Imbalance between treatment arms in timing of follow-up.	a. Potential for differences in the content of interventions and treatment pathways to impact on the interpretation of the trial outcome	1. Conduct a review of the treatment pathways to identify any potential for differential delays between intervention arms e.g. due to hospital waiting lists, that may affect interpretation of outcome. 2. Consider whether the time to effect for the different trial interventions may differ e.g. a one off surgical intervention compared with an intervention delivered over several months. Discussion of appropriate assessment time points to prevent potential bias in outcome assessment.
4. Imbalance in non-compliance with allocated treatment intervention	a. Potential for non-compliance between treatment arms to be asymmetrical i.e. non-compliance could not occur in the surgical arm once surgery has been performed. b. Potential for patients' strong preferences for	1. Consider whether the strength of patients' preference for particular interventions could potentially impact on the level of non-compliance with treatment allocation. If so, consider the inclusion of a cross-over component in trial design. 2. Detail in protocol decisions made on how patients randomised to surgery are managed and analysed if there is non-compliance with treatment allocation based on surgical findings e.g. clinical decision made to undergo a different procedure or surgery deemed unnecessary or impossible after gaining surgical access.

	particular treatments to affect compliance with treatment allocation. c. Potential for imbalance between treatment arms in non-compliance due to surgical findings.	
5. Differential loss to follow-up	a. Potential for change in a patient's treatment allocation e.g. non-compliance or delay in receiving allocation intervention, to affect patients' perception of necessity to complete follow-up.	1. Provide clear information regarding follow-up to patients and recruiting teams throughout the study period i.e. importance of all patients, regardless of any possible change in management, to complete follow up. 2. Explore potential reasons for loss to follow-up at the pilot stage and approaches to minimise loss to follow-up.

Future research

This thesis has identified several challenges in the conduct of trials with a surgical and non-surgical comparison. The findings have also highlighted several areas of potential future research.

Difficulties with recruitment have been discussed throughout the chapters of this thesis as being a potential challenge the conduct of trials with this type of comparison. The qualitative studies reported in Chapter 5 and 6' highlight the potential benefit of exploring both patients' and clinicians' views of treatments in trials with such diverse comparisons. This feasibility work could enable issues to a particular trial to be identified and addressed through, for example, targeted education and training of recruiting teams or the provision of more balanced patient information. Future research could aim assess the impact of implementing such interventions on the conduct of these types of trials.

As discussed in Chapter 2, the complexity of both the surgical and non-surgical interventions contributed to the challenge of designing, conducting and analysing trials of this type of comparison. Both interventions potentially involve several interacting components, for example, varying skill and experience of clinicians, which could be a source of bias and affect outcome. Future research could consider how we standardise and subsequently monitor interventions in these types of trials where the interventions are diverse and delivered by different specialities.

As outlined in Chapter 2, differences in the content of surgical and non-surgical interventions, for example, a one off surgical procedure compared to an intervention delivered over several months, and treatment pathways has the potential to impact on the interpretation of the trial outcome. Understanding the time to effect of different

interventions could help inform decision making in the choice of timing for outcome assessment in these types of trials. Further work could explore, using cohort studies, the potential variation in the trajectories of time to effect for different interventions and help inform the inclusion of appropriate outcome assessment time points.

As identified in Chapter 2, the degree of non-compliance to treatment allocation varied greatly between the trials. There were a number of trials where the reported levels of were more than 20%,[104, 112, 121, 127, 132, 147, 187] potentially resulting in difficulties with interpretation of outcome. Future research could aim to examine the factors that contribute to the variation in non-compliance between the trials. In addition, further qualitative research exploring reasons for high levels of non-compliance would be beneficial to increase our understanding of why it can be more problematic with particular intervention comparators.

The potential for differential loss to follow-up was also identified in this thesis as a potential challenge in the conduct of these types of trials. Some potential reasons for differences in retention between treatment arms were discussed in Chapter 3, however, they were not explored in depth in this thesis. This is an interesting area for potential future research and has been the focus of a recent Priority Setting Partnership (PSP).[356] One area identified that would be particularly relevant to trials of this type of comparison would be to understanding how a participant's ongoing experience of a trial can affect retention.[356]

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Appendix 1: Search strategy for systematic review (Chapter 2)

Cochrane search terms
#1 (surgery or surgical or operative or arthroscopy or laparoscopy or endoscopy or transplantation or scopy):ti,ab,kw (Word variations have been searched) #2 (non-surgical or nonsurgical or nonoperative or non-operative or conservative or physical therapy or physiotherapy):ti,ab,kw (Word variations have been searched) #3 (clinical trial or randomsied clinical trial or RCT or randomised controlled trial or randomisation):ti,ab,kw (Word variations have been searched) #4 (review or animal or stimulation):ti,ab,kw (Word variations have been searched) #5 (dental or anaesthesia or prevention):ti,ab,kw (Word variations have been searched) #6 (#1 and #2) and #3 not #4 not #5
Ovid EMBASE
~"((((clinical trial).ti,ab OR (randomized controlled trial).ti,ab OR (randomisation).ti,ab OR (rct).ti,ab OR (random allocation).ti,ab OR (randomly allocated).ti,ab OR (allocated randomly).ti,ab OR (Randomized controlled trial).ti,ab OR (Controlled clinical trial).ti,ab OR "RANDOMIZED CONTROLLED TRIAL (TOPIC)"/ OR (randomized controlled trial).ti,ab OR (clinical trial).ti,ab OR "CLINICAL TRIAL (TOPIC)"/) AND ((surgery).ti,ab OR (surgical).ti,ab OR (operative).ti,ab OR (arthroscopy).ti,ab OR (endoscopy).ti,ab OR (transplantation).ti,ab OR (laparoscopy).ti,ab OR (non-surgical).ti,ab)) AND ((nonsurgical).ti,ab OR (conservative).ti,ab OR (physical therapy).ti,ab OR (physiotherapy).ti,ab OR (non-operative).ti,ab OR (nonoperative).ti,ab)) NOT ("META ANALYSIS"/ OR (review).ti,ab OR (animal).ti,ab OR (prevention).ti,ab OR (preoperative).ti,ab OR (pre-operative).ti,ab OR (post-operative).ti,ab OR (postoperative).ti,ab OR (case report).ti,ab OR (case study).ti,ab)"

Appendix 2: Screening form ACL SNNAP trial (Chapter 3)

ACL SNNAP Screening / Randomisation Form

Instructions for completion:

- This form is to be completed for all participants with a knee injury considered potentially eligible to participate in the study.
- When completed, please enter the data onto the ACL SNNAP database.

Site Name:

Section 1 – Eligibility and Consent

Inclusion criteria

- Male or Female, aged 18 years or above
- Symptomatic ACL deficiency (instability-episodes of frank giving way or feeling unstable) with ACL deficiency confirmed using clinical assessment and MRI scan.

Date of MRI scan D D / M O N / Y Y Y Y

Exclusion Criteria

- Less than 4 months since injury
- Previous knee surgery (other than diagnostic arthroscopy) to index knee concomitant severe injury to contra-lateral knee
- Meniscal pathology considered sufficiently symptomatic to require surgery i.e. locked knee, large bucket handle cartilage tear.
- Knee joint status of grade 3 or 4 on the Kellgren and Lawrence scale
- Grade 3 MCL/LCL injury, associated PCL/PLC injury
- Inflammatory arthropathy
- Pregnancy.

Please review the study inclusion and exclusion criteria above and answer the following question:

1. Is the patient eligible to participate in the study? Yes ☐ No ☐ If no, please tick the reason/s below:

Exclusion Criteria

Less than 4 months since injury	☐
Previous knee surgery (other than diagnostic arthroscopy) to index knee concomitant severe injury to contra-lateral knee	☐
Meniscal pathology considered sufficiently symptomatic to require surgery i.e. locked knee, large bucket handle cartilage tear.	☐
Knee joint status of grade 3 or 4 on the Kellgren and Lawrence scale	☐
Grade 3 MCL/LCL injury, associated PCL/PLC injury	☐
Inflammatory arthropathy	☐
Pregnancy	☐
Other (if other, please indicate below)	☐

ACL SNNAP_PreRandomisationForm_V2.0_19Dec2016

2. Did the patient consent to participate? Yes ☐ No ☐ If no please state reason below:

Patient stated preference for physiotherapy ☐

Patient stated preference for surgery ☐

No reason stated ☐

Other (if other, please indicate below) ☐

Study Number A C L _ _

Section 2 – Demographics (this section is only be completed for patients who consent to participate in the study. A study number will be created by the database once a patient is randomised)

First name:

Surname:

Address:

Postcode:

E-mail:

Alternative e-mail:

Telephone number:

Gender: Male ☐ Female ☐

Date of Birth: D D M O N Y Y Y Y

NHS / CHI No:

GP name:

GP Address:

1. Which knee is injured? Right ☐ Left ☐

2. How did you injure your knee?

3. When did the knee injury occur? (i.e. can you give your best estimate of when you ruptured your ligament in approx. months) ☐☐☐ Months

Appendix 3: Recruitment graph ACL SNNAP trial (Chapter 3)

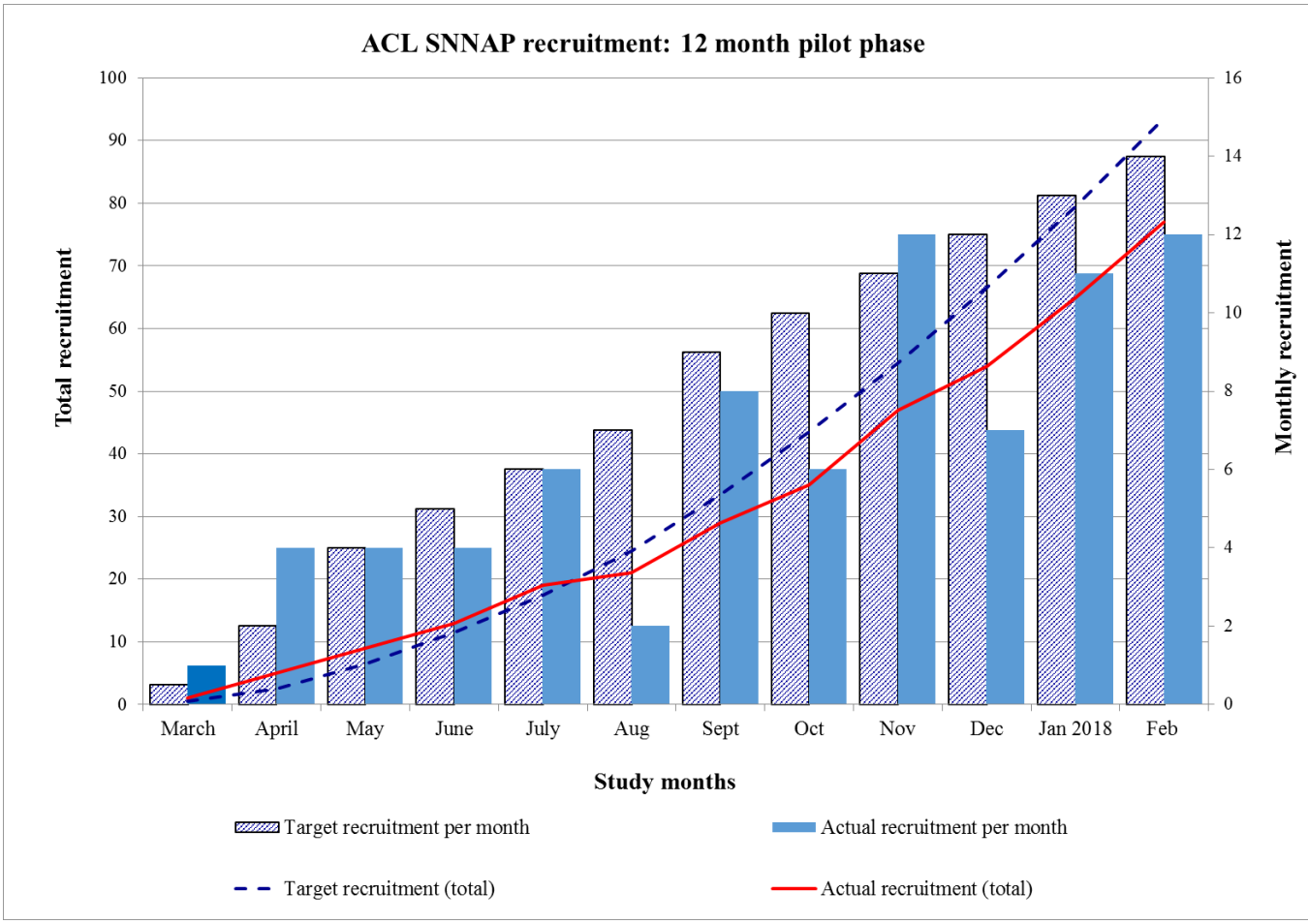


Figure 8: Target against actual recruitment graph ACL SNNAP (March 2017-March 2018)

Appendix 4: Table of other reasons for ineligibility ACL SNNAP (Chapter 3)

'Other' reasons for ineligibility	Number (N)
Clinician preference for conservative treatment due to other health problems	2
Clinician preference for conservative treatment	8
Clinician preference for surgery	2
Complex knee injury, clinician preference for surgery	2
Patient moving away from area	3
Not for surgery	1
Other complex/medical pathologies present	6
Partial tear	1
Participating in another study	2
Patient did not attend appointment	2
No treatment required at present	1
Changes in employment	1
Symptoms improved	1
Previously non-compliant with treatment	1
Long standing injury, listed for surgery	1
Patient started physiotherapy	1
Clinician states patient ineligible	1
Not suitable for surgical option.	1
Patient preference for surgery	1
Other/Blank form	2
Total	**40**

Appendix 5. Revised eligibility criteria ACL SNNAP (Chapter 3)

Inclusion Criteria
1. Participant is willing and able to give informed consent for participation in the study. 2. Male or Female, aged 18 years or above 3. Symptomatic ACL deficiency of the native ligament* (instability-episodes of frank giving way or feeling unstable) with ACL deficiency (either partial or complete tear) confirmed using clinical assessment and MRI scan.
* Patients who have undergone primary ACL reconstruction on the index knee were not eligible for inclusion.

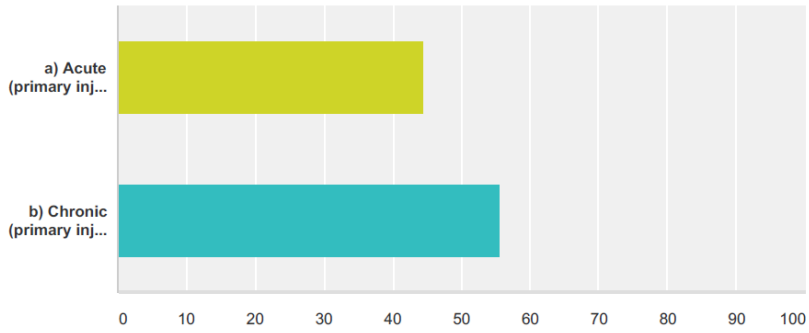
Exclusion Criteria
8. Patients in the acute phase of primary ACL injury i.e. they had not recovered from any acute symptoms relating to their initial ACL injury*. 9. Have had previous knee surgery (other than diagnostic arthroscopy or partial meniscectomy) to the index knee, concomitant severe injury to the contra-lateral knee, 10. Have meniscal pathology with characteristics that indicate immediate surgery. i.e. locked knee, large bucket handle or complex cartilage tear producing mechanical symptoms. 11. Have knee joint status of grade 3 or 4 on the Kellgren and Lawrence scale [1], 12. Have grade 3 Medial Collateral Ligament (MCL)/Lateral Collateral Ligament (LCL) injury, associated Posterior Cruciate Ligament (PCL)/Posterolateral Corner (PLC) injury 13. Have inflammatory arthropathy. 14. Is pregnant. Pregnancy is checked for before receiving an MRI scan.
*= Patients with pre-existing ACL deficiency presenting with acute symptoms (from a recent instability episode) can be considered for inclusion.

Appendix 6. Feasibility work ACL SNNAP (Chapter 3)

Example of surgeon questionnaire feasibility work for ACL SNNAP trial

Q2 What percentage of these patients are:

Answered: 21 Skipped: 1



Answer Choices	Average Number	Total Number	Responses
a) Acute (primary injury occurred LESS than 4 months previously)	45	935	21
b) Chronic (primary injury occurred MORE than 4 months ago)	55	1,165	21
Total Respondents: 21			

#	a) Acute (primary injury occurred LESS than 4 months previously)	Date
1	70	10/5/2014 1:26 PM
2	50	9/22/2014 1:40 PM
3	10	9/11/2014 2:05 PM
4	30	9/9/2014 4:21 AM
5	100	9/5/2014 7:41 AM
6	25	9/2/2014 11:27 AM
7	50	9/2/2014 12:34 AM
8	10	8/30/2014 1:53 PM
9	90	8/29/2014 9:47 AM
10	40	8/29/2014 9:47 AM
11	35	8/29/2014 5:14 AM
12	50	8/27/2014 11:26 PM
13	30	8/27/2014 3:45 PM
14	50	8/27/2014 2:20 PM
15	50	8/27/2014 12:35 PM
16	40	8/27/2014 6:52 AM
17	70	8/27/2014 4:57 AM
18	10	8/27/2014 1:46 AM
19	25	8/27/2014 1:08 AM

Appendix 7. 'eMERGe' meta-ethnography reporting guidelines (Chapter 4)

Guidelines for reporting Meta-Ethnography

			REPORTED ON PAGE
PHASE 1: Selecting meta-ethnography and getting started			
1	Rationale and context for the meta-ethnography	Describe the gap in research or knowledge to be filled by the meta-ethnography, and the wider context of the meta-ethnography	70
2	Aim(s) of the meta-ethnography	Describe the meta-ethnography aim(s)	71
3	Focus of the meta-ethnography	Describe the meta-ethnography review question(s) (or objectives)	71
4	Rationale for using meta-ethnography	Explain why meta-ethnography was considered the most appropriate qualitative synthesis methodology	71
PHASE 2: Deciding what is relevant			
5	Search strategy	Describe the rationale for the literature search strategy	73
6	Search processes	Describe how the literature searching was carried out and by whom	75
7	Selecting primary studies	Describe the process of study screening and selection, and who was involved	75
8	Outcome of study selection	Describe the results of study searches and screening	79
PHASE 3: Reading included studies			
9	Reading and data extraction approach	Describe the reading and data extraction method and processes	76
10	Presenting characteristics of included studies	Describe characteristics of the included studies	84
PHASE 4: Determining how studies are related			
11	Process for determining how studies are related	Describe the methods and processes for determining how the included studies are related	76
12	Outcome of relating studies	Describe how studies relate to each other	90
PHASE 5: Translating studies into one another			
13	Process of translating studies	Describe the methods of translation	77
14	Outcome of translation	Describe the interpretive findings of the translation.	93

PHASE 6: Synthesizing translations			
15	Synthesis process	Describe the methods used to develop overarching concepts (“synthesised translations”)	77
16	Outcome of synthesis process	Describe the new theory, conceptual framework, model, configuration, or interpretation of data developed from the synthesis	108
PHASE 7: expressing the synthesis			
17	Summary of findings	Summarize the main interpretive findings of the translation and synthesis and compare them to existing literature	116
18	Strengths, limitations, and reflexivity	Reflect on and describe the strengths and limitations of the synthesis	122
19	Recommendations and conclusions	Describe the implications of the synthesis	123

Appendix 8. Search strategy for QES (Chapter 4)

Example search strategies:

1. Identifying existing qualitative evidence synthesis (QES)

Example search syntax for MEDLINE	
Qualitative free-text terms	((("meta ethnography" OR "meta ethnographic") OR ("meta synthesis") OR (synthesis AND ("qualitative literature" OR "qualitative research")) OR ("critical interpretive synthesis") OR ("systematic review" AND ("qualitative research" OR "qualitative literature" OR "qualitative studies")) OR ("thematic synthesis" OR "framework synthesis") OR ("realist review" OR "realist synthesis") OR ((("qualitative systematic review" OR "qualitative evidence synthesis")) OR ("qualitative systematic reviews" OR "qualitative evidence syntheses")) OR (("quality assessment" OR "critical appraisal") AND ("qualitative research" OR "qualitative literature" OR "qualitative studies")) OR (("literature search" OR "literature searching" OR "literature searches") AND ("qualitative research" OR "qualitative literature" OR "qualitative studies")) OR (Noblit AND Hare)) OR ("meta narrative" OR "meta narratives" OR "narrative synthesis") OR ("realist reviews" OR "meta study" OR "meta method" OR "meta triangulation")) OR (CERQUAL OR CONQUAL).
Randomised controlled trials free-text terms	((((((trial[Title]) OR randomly[Title/Abstract]) OR "clinical trials") OR placebo[Title/Abstract]) OR randomized[Title/Abstract]) OR controlled clinical trial) OR Randomized controlled trial

2. QES search strategy

Example search syntax for MEDLINE
(((“semi-structured”[TIAB] OR semistructured[TIAB] OR unstructured[TIAB] OR informal[TIAB] OR “in-depth”[TIAB] OR indepth[TIAB] OR “face-to-face”[TIAB] OR structured[TIAB] OR guide[TIAB] OR guides[TIAB]) AND (interview*[TIAB] OR discussion*[TIAB] OR questionnaire*[TIAB])) OR (“focus group”[TIAB] OR “focus

groups”[TIAB] OR qualitative[TIAB] OR ethnograph*[TIAB] OR fieldwork[TIAB] OR “field work”[TIAB] OR “key informant”[TIAB])) OR “interviews as topic”[Mesh] OR “focus groups”[Mesh] OR narration[Mesh] OR qualitative research[Mesh] OR "personal narratives as topic"[Mesh] OR (theme[TIAB] OR thematic[TIAB]) OR "ethnological research"[TIAB] OR phenomenol*[TIAB] OR "grounded theory"[TIAB] OR "grounded study"[TIAB] OR "grounded studies"[TIAB]OR "grounded research"[TIAB] OR "grounded analysis"[TIAB] OR "grounded analyses"[TIAB] OR "life story"[TIAB] OR "life stories"[TIAB] OR emic[TIAB] OR etic[TIAB] OR hermeneutics[TIAB] OR heuristic*[TIAB] OR semiotic[TIAB] OR "data saturation"[TIAB] OR "participant observation"[TIAB] OR "action research"[TIAB] OR "cooperative inquiry"[TIAB] OR "co-operative inquiry"[TIAB] OR "field study"[TIAB] OR "field studies"[TIAB] OR "field research"[TIAB] OR "theoretical sample"[TIAB] OR "theoretical samples"[TIAB] OR "theoretical sampling"[TIAB] OR "purposive sampling"[TIAB] "purposive sample"[TIAB] "purposive samples"[TIAB] OR "lived experience"[TIAB] OR "lived experiences""purposive sampling"[TIAB] OR "content analysis"[TIAB] OR discourse[TIAB] OR "narrative analysis"[TIAB] OR heidegger*[TIAB] OR colaizzi[TIAB] OR spiegelberg[TIAB] OR "van manen*"[TIAB] OR "van kaam"[TIAB] OR "merleau ponty"[TIAB] OR husserl*[TIAB] OR Foucault[TIAB] or Corbin[TIAB] OR Strauss[TIAB] OR Glaser[TIAB]
Randomized controlled trial.pt. OR Controlled clinical trial.pt. OR Randomized.ab. OR Clinical trials as topic OR Randomly.ab. OR Trial.ti.

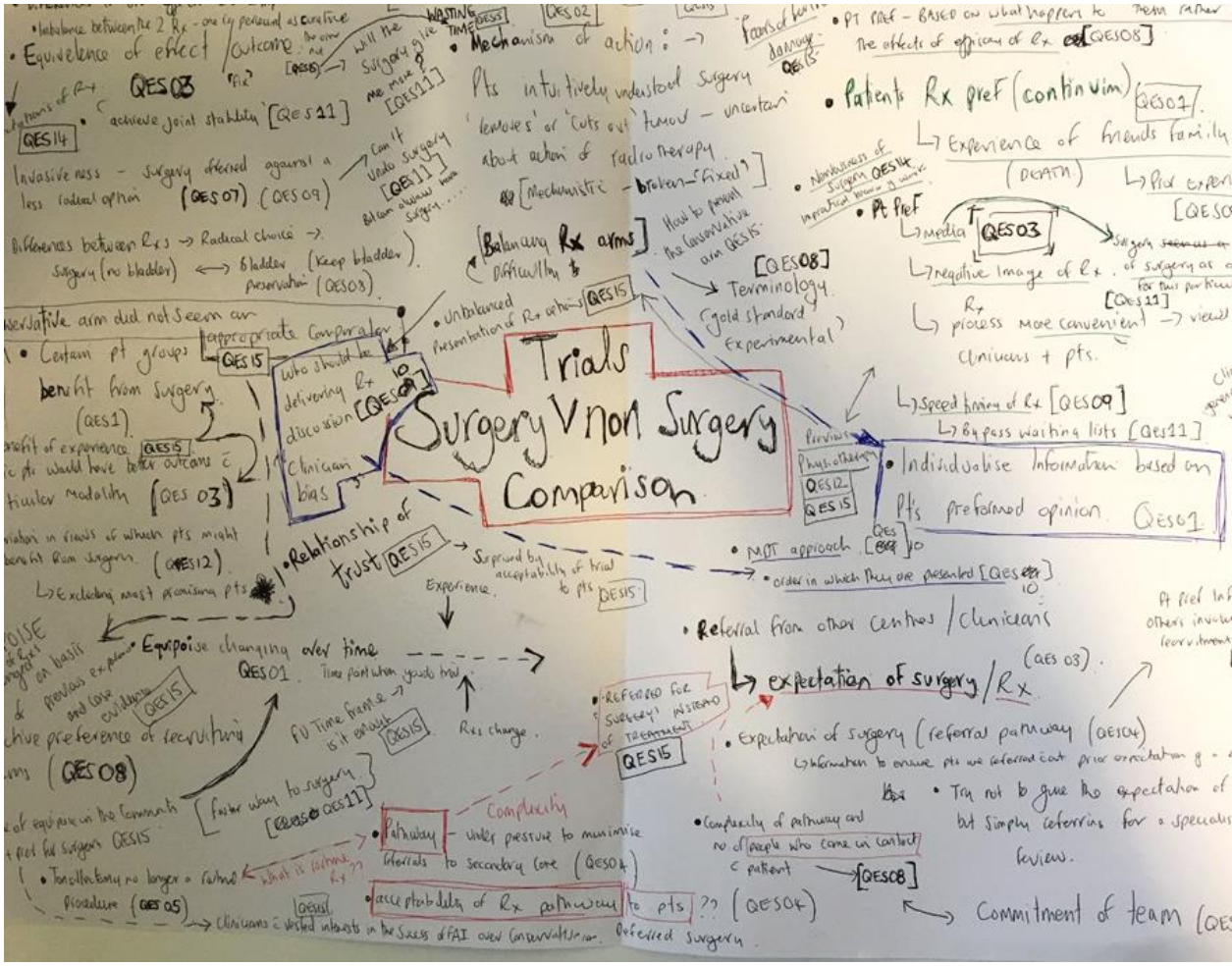
Appendix 9. Critical Appraisal Skills Programme (CASP) checklist (Chapter 4)

Q1. Was there a clear statement of the aims of the research?
Q2. Is qualitative methodology appropriate?
Q3. Was the research design appropriate to address the aims of the research?
Q4. Was the recruitment strategy appropriate to the aims of the research?
Q5. Was the data collected in a way that addressed the research issue?
Q6. Has the relationship between researcher and participants been adequately considered?
Q7. Have ethical issues been taken into consideration?
Q8. Was the data analysis sufficiently rigorous?
Q9. Is there a clear statement of findings?
Q10. How valuable is the research?

1=No, 2=Can't tell from details in paper, 3=Yes.

Reference (Study, country)	Q1.	Q2.	Q3.	Q4.	Q5.	Q6.	Q7.	Q8.	Q9.	Q10.
1. Bill-Axelson et al (2009) [276]	3	3	3	3	3	2	2	3	3	3
2. Blazeby et al (2014) [203]	3	3	3	3	3	2	2	3	3	3
3. Hamilton et al (2013) [217]	3	3	3	3	3	2	2	3	3	3
4. McSweeney, et al. (2017) [277]	3	3	3	3	3	2	2	3	3	3
5. McSweeney (2017).[278]	3	3	3	3	3	2	2	3	3	3
6. Mills et al (2011) [90]	3	3	3	3	3	2	2	3	3	3
7. Moynihan, C., et al. (2012) [271]	3	3	3	3	3	2	2	3	3	3
8. Paramasivan et al (2011) [205]	3	3	3	3	3	2	2	3	3	3
9. Skea, Z. C., et al. (2017) [280]	3	3	3	3	3	3	2	3	3	3
10. Strong et al (2016) [204]	3	3	3	3	3	2	2	3	3	3
11. Thorstensson (2009) [193]	3	3	3	3	3	2	2	3	3	3
12. Ziebland et al (2007) [281]	3	3	3	3	3	2	2	3	3	3
13. Wade et al (2009) [89]	3	3	3	3	3	2	2	3	3	3
14. Minns Lowe (2017) [293]	3	3	3	3	3	2	3	3	3	3
15. Griffin et al (2016) [283]	3	3	3	3	3	2	2	3	3	3
16. Brookes 2003 [284]	3	3	3	3	3	2	2	3	3	3
17. Leighton 2012 [285]	3	3	3	3	3	2	2	3	3	3
18. Mills 2003 [286]	3	3	3	3	3	2	2	3	3	3
19. Lie, M., et al. (2012) [287]	3	3	3	3	3	3	3	3	3	3
20. Rooshenas et al (2016) [39]	3	3	3	3	3	3	2	3	3	3
21. Paramasivan et al (2015) [288]	3	3	3	3	3	2	3	3	3	3
22. Realpe 2016 [289]	3	3	3	3	3	2	3	3	3	2
23. Keene 2016 [290]	3	3	3	3	3	2	2	2	3	2
24. Mills et al (2014) [80]	3	3	3	3	3	2	3	3	3	3
25. Donovan et al (2014) [291]	3	3	3	3	3	2	2	3	3	3
26. Donovan et al (2014) [218]	3	3	3	3	3	2	3	3	3	3

Appendix 10: Thematic maps QES (Chapter 4)



Appendix 11. Summary of OxKIC cohort (Chapter 5)

Study Title	**The Oxford Knee Injury Cohort: Understanding Knee Injuries and The Best Treatment Options for NHS patients**	
Internal ref. no. / short title	OxKIC Oxford Knee Injury Cohort	
Study Design	Cohort study	
Study Participants	Patients with anterior cruciate ligament (ACL) and/or meniscal injuries	
Planned Sample Size	234 Qualitative sub study – approximately 20 patients and 20 healthcare professionals will be recruited to this aspect of the study.	
Planned Study Period	July 2014 – March 2021	
	Objectives	**Endpoints**
Primary	To investigate whether ACL reconstruction leads to a greater improvement in self-reported pain and function than participants following a rehabilitation pathway only.	Change from baseline to 2 years in the mean value of four of five subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS4).
Secondary	To assess the other potential baseline risk factors including: change of patient reported quality of life, activity levels, productivity loss and baseline clinical assessment findings. To explore the expectations and treatment preferences of participants and their experience of the interventions. **Nested cohort** To assess the predictive value of new serum and urine biomarkers, an ultrasound assessment of the suprapatellar recess synovium (joint lining) of the main outcome changes.	• Tegner Activity Scale • Visual Analog Scale for Pain • Health economics assessment • Semi-structured interviews • Correlations between serum, urine, synovial levels of markers, ultrasound of synovium assessment score and synovitis histology score. • Association between baseline serum and synovial biomarker levels, ultrasound synovium assessment score and change of the KOOS4 score.

Appendix 12. Consent form OxKIC Cohort (Chapter 5)

Consent Form
Oxford Knee Injury Cohort - OxKIC
(REC: Wales REC 7; REC Reference: 14/WA/1108)

	Please INITIAL in the boxes if you agree
1. I confirm that I have read and understood the information sheet dated: ……/……/…… Version*:* ……for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or my legal rights being affected.	☐
3. I agree to complete ongoing questionnaires regarding my knee for the duration of the study.	☐
4. I understand that I might be asked to participate in focus groups or interviews during the study.	☐
5. I understand the interview will be audio-recorded but data will be kept confidential.	☐
6. I agree to the use of anonymised quotes in reports and publications and to pass anonymised data on to other organisations where appropriate.	☐
7. I understand that responsible members of the OxKIC research team may look at relevant sections of my medical notes and data collected, during the study. I give permission for these individuals to have access to my records.	☐
8. I understand that data collected during the study may be looked at by authorised individuals from the University of Oxford and Oxford University NHS Trust where it is relevant to my taking part in this research. I permit these individuals access to my research records.	☐
9. I agree to take part in the above study.	☐

Appendix 13. Topic guide patient interviews (Chapter 5)

Interview to take place at a time convenient to the participant being interviewed.

Introduction

- Obtain consent
- Introduce self and research question
- Allow time to read the information sheet.
- Explain need to record interview
- Written consent obtained prior to interview

Please remember that any answers are anonymous and confidential. The only people who have access to your answers are the research team working on this study. As you know we are recording the interview today, but you can ask for the tape recorder to be switched off at any point. If tell me anything that you don't wish to be included in the final recording then please let me know and we can discuss it at the end. Most importantly – Please remember that there are NO right or wrong answers to the questions. What we are most interested in is your experiences and opinions. First I will be asking some questions about your injury.

1. Today we are mainly talking about your knee injury but it helps to put your injury into perspective if I know a bit more about you in terms of for example work/sporting interests.

2. How did you injure your knee?

3. Did you know anything about this type of injury before you experienced it yourself?

4. What can you tell me about the treatment options that were discussed at your initial appointment?

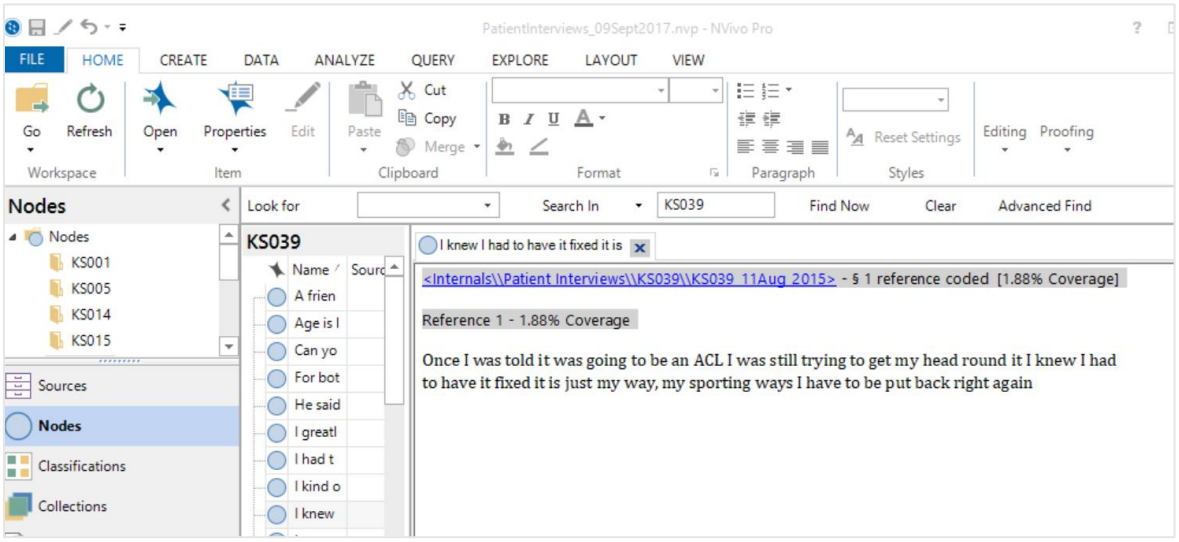
5. Did you know anything about the types of treatment for this injury before you experienced it yourself? Explain.

6. What do/did you think about the treatment options you have? Do you consider any advantages and disadvantages of a particular treatment?

Closing Questions

- Thank them for their time
- Any final comments they would like to make?

Appendix 14. Example of coded patient interviews using NVivo (Chapter 6)



Appendix 15. Overview of ACL SNNAP trial (Chapter 6)

Comparison of the clinical and cost effectiveness of two management strategies for non-acute Anterior Cruciate Ligament (ACL) injury: rehabilitation versus surgical Reconstruction

The ACL SNNAP Trial: ACL Surgery Necessity in Non Acute Patients





Background and Rationale

Rupture of the Anterior Cruciate Ligament (ACL) is common but the resulting disability can be variable. Some patients recover and cope fine without their ACL whilst others do not and continue to have episodes of knee instability/giving way affecting day to day activities, work and recreation. It is often thought that these patients require surgery (ACL reconstruction) to stabilise the knee. In the NHS it is estimated at least 14,000 primary ACL reconstructions are performed each year (annual incidence 13.5 per 100, 000 UK - Jameson et al, 2012) but based on Swedish Registry data the frequency may be much greater (possibly up to 40,000 pa). Based on the conservative estimates the costs of ACLR to the NHS will be approximately £60 million for 2015 (each operation and post op care = £3800).

The variability, i.e. the effect of the injury being neither consistent nor predictable, means that clinical management varies from surgeon to surgeon and from hospital to hospital. Some surgeons feel that patients should *always* undergo surgery (ACL reconstruction), and as soon as possible after being diagnosed. The rationale is that by not surgically stabilising an unstable knee, the knee might continue to buckle and give way which potentially causes further internal damage (of the cartilage) and can affect long term outcome. Conversely some surgeons feel that a period of rehabilitation (exercises) should *always* be prescribed as it may be possible to avoid an operation altogether. Indeed, recent work in Scandinavia (Frobell et al 2013) has shown (albeit in more recently injured patients than would be seen in the NHS) that a period of rehabilitation can reduce the number of surgical reconstructions by 50% without compromising outcome. Unfortunately, because these patients were recently injured (acute) the results cannot be extrapolated to the NHS where it is commonplace for 4-12 months to have passed since initial injury and the initiation of a clinical management plan. The delay introduces an

element of screening and self-selection. Those patients that are likely to "cope" without their ligament and benefit from remedial exercises are likely to be already doing so and will not present to secondary care.

Overall, the picture of management for the non-acute ACL deficient knee is confusing with limited and conflicting evidence for efficacy. In addition, the costs to the health service are not insubstantial. The benefits for either management approach are uncertain and therefore a new study is required to discover the best treatment option.

We propose to carry out a randomised controlled trial with the following aim;

> **To determine, in patients with non-acute (greater than 4 months since injury) Anterior Cruciate Ligament Deficiency (ACLD), whether non-surgical treatment (with the option for later ACL reconstruction if required) is more effective than surgical ACL reconstruction (as measured by the Knee Injury and Osteoarthritis Outcome Score [KOOS4] at 18 months from randomisation).**

In terms of impact and cost implications, the results of this trial are far reaching. If, as suspected, a period of rehabilitation is not necessary for patients with a chronic condition and all patients should undergo ACLR as soon as possible then £2.8 million per annum could be saved by forgoing unnecessary rehabilitation. However, if patients do benefit from remedial exercises (in a similar manner to those acute patients in the Scandinavian study) then this could reduce the number of operative procedures. Between £1.6 and 27 million pa could be saved in surgical costs (depending on the reduced frequency of reconstruction - see table below).

Secondary objectives will include investigation of complications (need for operation [in the rehab group] or re-operation [in the surgery group]), return to sport/activity, patient satisfaction, and the cost implications of these management options for patients and employers as well as healthcare providers.

Study Design

Multi-centre superiority randomised controlled trial, parallel group two arm design with 1:1 allocation ratio.

- **Sample Size:** 320 patients recruited from approx. 20 NHS orthopaedic units (with defined experience/volume).
- **Population**: Patients with unilateral symptomatic (unstable) ACL deficient knee.
    - Greater than 4 months since initial injury.
    - Complete ACL tear confirmed by clinical assessment and/or MRI scan.
- **Interventions**: Non-surgical management (rehabilitation) or surgical management (reconstruction).
- **Outcome:** Knee Injury and Osteoarthritis Outcome Score (KOOS) at 18 months.

Inclusion Criteria: Patients >18yrs with symptomatic ACL deficiency confirmed by clinical assessment and/or MRI scan.

Excluded Criteria: Less than 4 months since injury, previous knee surgery to study (index) knee (except diagnostic arthroscopy), meniscal pathology sufficiently symptomatic to require surgery i.e. locked knee, large bucket handle tear, knee joint status arthritic (grade 2 KL scale, grade 3 MCL/LCL injury, PCL/PLC injury, inflammatory arthropathy.

Further information:

If you would be interested in finding out more about the proposed study please contact Loretta Davies at Oxford University on 01865 737210 or loretta.davies@ndorms.ox.ac.uk. The study:

- will be centrally managed by the Surgical Intervention Trials Unit (SITU), Oxford with the support of the Oxford Clinical Trials Unit (OCTRU). Application to the Clinical Research Network (CRN) will be made to support the study locally.
- is supported by British Association for Surgery of the Knee (BASK), National Ligament Registry (NLR), Public and Patient Involvement and has the potential to further develop the evidence base, inform standards of care and change practice for ACL deficiency management.

STUDY FLOW DIAGRAM

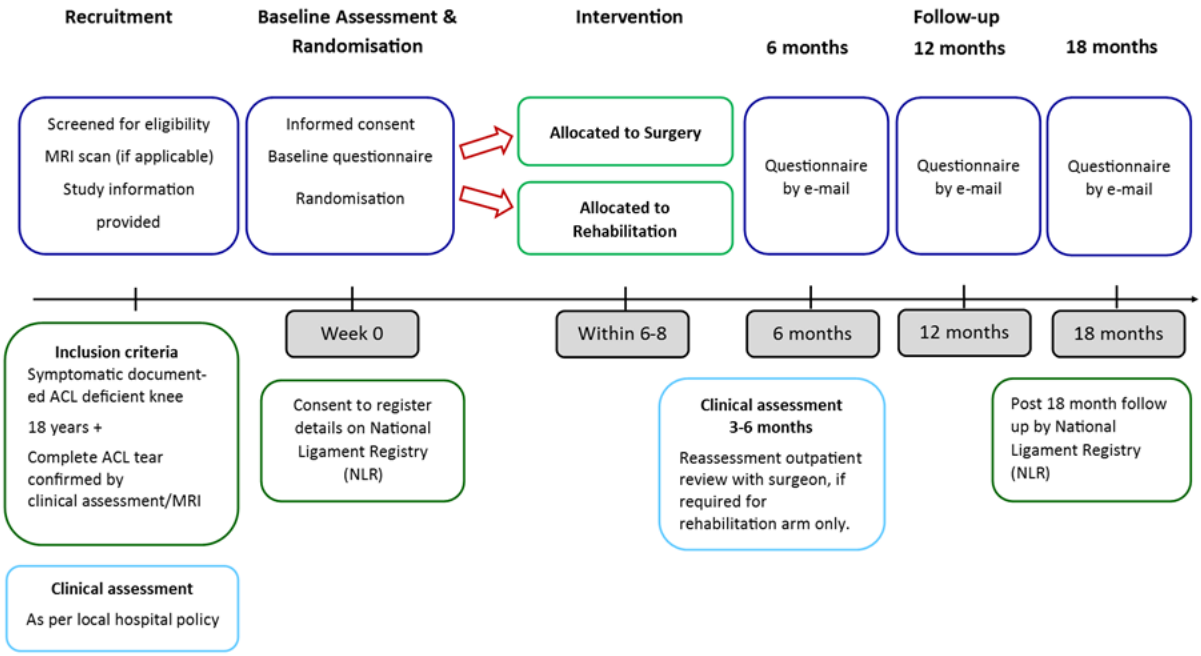


Figure 1. Study Flow Chart

Appendix 16. Topic guide clinician interviews (Chapter 6)

Aim

To explore clinicians'' views on recruiting patients to a proposed trial with a surgical and non-surgical comparison and identify potential challenges to recruitment.

A. Current patient management at hospital. (current patient pathway)

1. What is the current patient pathway for patients following ACL injury at this hospital (e.g. acute knee clinic, referred to physio)?

B. Presentation of the proposed study

Introduce the proposed study (copy of proposal previously sent to participant)

1. What are/were your thoughts on this proposed study of ACL deficiency management? (explore), do they think there is a need for an RCT with this population)

2. Based on the information you have to date, would you be happy to participate in (and recruit patients to)? (explore why– yes and no)

3. Do you think your colleagues (other PIs and recruiters) would you be happy to participate in and recruit patients to? (explore why– yes and no)

4. Are the eligibility criteria for the RCT clear?

5. Are there any reasons why you think it would be difficult to recruit patients to this study? – (resources, patient pathway (availability of patients meeting criteria in your clinics)?

6. Patient preference for a particular treatment has been seen to be a barrier to recruitment in some surgical trials.

    a. Do you think it will be a problem for this study?

7. How easy do you think it will be to respond to patient preference? (do you feel that you would be able to explore or challenge their preference? why, why not? what do you feel would help with this?

Closing Questions

- Thank them for their time
- Any final comments they would like to make?