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Patient Recruitment in a Challenging Surgical Trial: Issues and Possible Solutions

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Contents

Table of Figures

Acknowledgements

I dedicate this work to my children, Paulina and Gregory, so that they can learn from my struggles.

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Declaration

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree.

The work presented (including data generated and data analysis) was carried out by the author except in the cases outlined below and in **Chapter 3**:

- Collaboration with Mr S Brydges, eLab, the University of Warwick, to develop an online tool for eliciting expert opinions
- Collaboration with Dr L Locock, Health Expeiences Research Group, University of Oxford, to develop patient interview schedule
- Collaboration with Dr A Adams, Warwick Medical School, to develop a patient decision making analysis framework (**Chapter 3.3**)
- Collaboration with Dr N Parsons, Warwick Medical School, to develop statistical models for combined expert opinions analysis and expression of clinical equipoise level

Parts of this thesis have been published by the author (**Appendix I**).

- Parsons N, **Kulikov Y**, Girling A, Griffin D. A statistical framework for quantifying clinical equipoise for individual cases during randomized controlled surgical trials. Trials. 2011 Dec 13;12:258.

Abstract

Randomised Controlled Trials (RCTs) are regarded as a 'gold standard' technique to evaluate and compare clinical interventions. Strict ethical criteria dictate the participation of humans in clinical research, based on informed consent, voluntary decision making and putting patients' interests first.

Demand for RCTs in Trauma and Orthopaedics is high, but patient recruitment continues to pose a significant challenge, especially when the treatments being compared are obviously different. Lack of blinding, treatment preference and negative perception of random allocation to interventions are among the obstacles which need to be considered.

Based on review and analysis of current knowledge, an attempt is made to develop a new recruitment process that incorporates high ethical standards and provision of the best possible clinical care for an individual patient. By integrating the principle of clinical equipoise, modern technology and statistical concepts, such as subjective probability, the Patient Eligibility Assessment through Clinical Equipoise (PEACE) framework has been introduced. This provides an alternative that could be used in trials where the fixed eligibility criteria approach is likely to fail. It was tested involving 77 real clinical cases from a national multi-centre trauma RCT, which compared contrasting treatments.

A new trial recruitment approach aiming to avoid direct contact between a patient and a treating clinician was rolled out in the same trial. The feedback was collected from both the clinicians and the patients involved. Thematic analysis of 23 semi-structured interviews improved understanding of the various factors influencing patients' decision about trial participation. Further typological analysis provided a valuable insight into the different attitudes that patients adopted when faced with the dilemma. In particular, that many are positive towards research involvement, but not comfortable with randomisation based on fixed eligibility criteria.

According to these results, a new model for patient recruitment is suggested, which could be researched and tested in future trials.

Abbreviations and glossary

Attitude – a psychological tendency that is expressed by evaluating a particular entity with some degree of favor or disfavor.

Attribute – a factor that affects a decision or choice.

Cochrane Collaboration – the internationally recognised independent non-profit organisation formed to present healthcare research evidence in systematic way. Freely accessible online systematic reviews are published through **Cochrane Library**.

Cue – a stimulus or an attribute expressed by a subject, that prompts and/or influences a decision formation.

CUP [Collective Uncertainty Project] – an independent research project set up within the UK Heel Fracture Trial in order to develop and test a methodological framework that can assess and compare level of uncertainty in expert opinions about a clinical case in real time.

Equipoise – in clinical research: genuine uncertainty whether one intervention (treatment, procedure etc.) is beneficial when compared to other intervention(s). Can be described as:

> **Clinical or collective** – shared between clinicians in the expert medical community
>
> **Individual** – related to one person (clinician, patient etc.)
>
> **Theoretical** – in description of individual, because some degree of preference is highly likely

Effective – same as individual, but in addition to direct intervention effects, takes into account all attributes that influence a decision, such as personal values, social responsibility etc.

Expert belief – expected likelihood or forecast of a certain outcome from an expert.

Grounded theory – open-minded approach to qualitative data without pre-formulated hypothesis.

Implicit assumption - an assumption that includes the underlying agreements or statements made in the development of a logical argument, course of action, decision, or judgment that are not explicitly voiced nor necessarily understood by the decision maker. Often, these assumptions are made based on personal life experiences, and are not consciously apparent in the decision making environment. These assumptions can be the source of apparent paradoxes, misunderstandings and resistance to change in human behaviour or decision making.

Paradigm shift – change of core assumptions and views shared by scientific communities. Introduced in 1962 in the landmark book about the history of science 'The Structure of Scientific Revolutions' by Thomas S. Kuhn.

PEACE [Patient Eligibility Assessment through Clinical Equipoise] – the new concept and methodological framework for patient eligibility assessment in an RCT. Developed during the CUP (see above).

PTIV [Patient Trial Information Video] – as part of the new approach to patient recruitment to RCTs.

Randomisation – in clinical research: allocating patients via random assignment to an investigated intervention or control.

RCT [Randomised Controlled Trial] – type of clinical research to compare interventions.

Strong expert vote – an opinion (outcome prognosis) expressed by an expert in one or two categories only for a clinical case assessment within the PEACE concept.

Statistical inference – a procedure used to draw conclusions from datasets arising from experiments.

Utility –value of a choice attribute to a decision maker, depending on its probability.

Verstehen – the concept of understanding a phenomenon in its context.

Chapter 1 Review of theory and practice of patient recruitment in challenging surgical trials

Understanding the patient recruitment process in challenging surgical trials is the subject of this study. A trial is considered challenging when substantially different procedures are being compared (such as open versus minimally invasive, or operative versus non-operative interventions, for example physiotherapy) (Ergina, Cook et al. 2009). My aim is to explore existing and novel strategies to modify the process of patient involvement as trial subjects. These changes need to take into account the ethical and methodological concerns of all involved parties (patients, clinicians and researchers), in order to improve the integrity of the trial.

This chapter starts with an overview of the methodological fundamentals of clinical trials (**1.1**) and attempts to review the theoretical and ethical basis of patient involvement in clinical trials (**1.2**). It then looks at issues surrounding random treatment allocation and patient recruitment specific to surgical trials (**1.3**). Finally, the effects of clinical research on patients as subjects to both research and clinical care are uncovered (**1.4-5**).

A systematic approach was adopted for the literature search across several relevant platforms (PubMed, MEDLINE, PsycINFO, EMBASE, CINAHL

etc., see **Appendix L** for a Search Strategy example), but no formal systematic review was completed. This allowed some freedom in paper selection and inclusion according to the research question and subject relevance.

The chapter is summarised (**1.6**) to formulate a list of research questions that are grouped together for ease of future reference.

1.1 Methodological fundamentals of a clinical trial

Medical research aims to increase knowledge in order to advance medical practice. Research methods differ depending on the problem to be investigated and the research discipline involved. In order to evaluate the effectiveness and safety of an intervention in clinical practice, such as a drug, an investigation or a surgical procedure, an experimental study needs to be performed. This can be contrasted with an observational study, where the investigator observes, describes, analyses and interprets an existing or pre-existing setting but does nothing to influence events. Both such experimental and observational types of studies come under the umbrella of clinical research; this generally involves humans, who may often be ill or in distress, as research subjects. This calls for high ethical standards and scrutiny, which have to be considered and enforced, when any such research is designed and undertaken. In the UK, Ethics Committees represent an internationally established and regulated system (World Medical Association 2008) that oversee all research involving humans. They monitor the safety, rights and welfare of participants.

The aim of an experimental study is to assess differences in observed outcomes that are a direct consequence of the relative efficacy of the interventions being compared, rather than being affected by a multitude of other (confounding) factors, such as the age, gender or the physiological and clinical background of the subjects. It follows that patient allocation

to the tested interventions needs to be controlled, in order to achieve comparable groups of individuals who should ideally reflect the study population. Such controlled experimental studies of clinical practice are usually called 'clinical trials'. This term is now used much more commonly than an alternative term 'experimental trial' to reflect high ethical standards and commitment to the best possible patient care (Gauch 2008).

A number of factors need to be controlled in a clinical trial to ensure a fair comparison of interventions. First of all, criteria for selecting subjects for a study have to be defined. These are called 'eligibility criteria'. They define the characteristics a subject must have in order to be eligible for trial participation. Apart from demographics, these might include definition of a disease/condition and various other elements, such as background health or mental status.

Delivery of the experimental intervention itself also needs to be specified. The test intervention is often compared to a control (standard or placebo) intervention using a chosen measure, preferably a validated score, which is specific to the researched condition. Use of a control group is one of the signature characteristics of a clinical trial. Without a rational direct comparison, an experimental study is extremely vulnerable to error. The patients' responses may be influenced by a researcher's enthusiasm and (even unconscious) reassurance, the placebo effect and other psychological factors. Historical controls are usually unreliable, due to environmental and

welfare changes, general care advances, stage of diagnosis and multiple other factors that evolve or change over time.

Bias is another major concern when assessing or interpreting the findings of a clinical trial. 'Bias is a systematic distortion of a result due to a factor not allowed for in the design of the study' (Smith and Smith 2003, p. 33). Randomisation and blinding are the classical techniques used to alleviate bias. Random allocation gives all eligible patients the same chance of receiving either of the compared interventions. It is independent of a patient's characteristics, preference or of the clinician's opinion. The Cochrane methodology review confirms that, when trials are non-randomised, it is impossible to predict the magnitude or direction of possible selection biases (Odgaard-Jensen, Vist et al. 2011). This leads to the distortion of treatment effects, often presenting them as more significant or sometimes even as a reversal of the 'true' direction of the effect (e.g. from harmful to beneficial or vice versa).

The goal of blinding is to keep trial participants and researchers ignorant, and therefore not susceptible to conscious or unconscious bias or influence, by concealing the type of intervention allocated to each participant. Trials can be single-blind when only the patient is unaware of an allocated intervention, double-blind when the investigator does not know either, or triple-blind when even the data monitoring body or study statistician are not allowed to know. Trials where interventions are not concealed are known as open trials.

The very features of Randomised Control Trials (RCTs) described above (placebo control, randomisation and blinding), are seen as essential by the research community, but can be viewed as foreign to the principles of clinical care if they are not justified by medical benefits to patients (Miller and Brody 2003). This gives rise to inherent and on-going conflicts for clinicians between therapeutic obligations to provide the best possible care for current patients and clinical research responsibilities to improve care continuously for the benefit of future patients. This issue is reviewed in the next part of this chapter.

1.2 Ethical basis of patient recruitment to an RCT

Randomised Controlled Trials (RCTs) became a gold standard technique for evaluating new drugs and treatment regimes in clinical medicine following publication of the landmark RCT of streptomycin for pulmonary tuberculosis in 1948 (Medical Research Council). In a RCT patients are assigned on a random basis to the various treatments being compared; this causes prognostic variables to be randomly distributed across the trial intervention groups, so that no treatment is biased through patient selection. This brings reliability and scientific integrity to research findings and makes these trials very attractive to clinical scientists. However, this very principle of randomisation took the dilemma of the clinician's ethical obligations to a new level. On the one hand there is an obligation to provide the best possible care for an individual patient and on the other hand there is a responsibility to society and future patients to continuously improve the quality of care. This was described by Adams (1989, pp. 449-50) as a distinction between 'action-aims' and 'outcome-aims' as follows:

"We can say that I was doing the best for my patients as an action-aim insofar as I am disposed to do (now) what I think is best for my (present) patients. I have it as an outcome-aim insofar as I am disposed to try (now) to bring it about that I do (in the rest of my career) the best for my (present and future) patients".

These ethical considerations led to the development of the equipoise

principle. This states that genuine uncertainty about the relative merits of different treatments to be compared must be present before a patient is offered the opportunity to take part in clinical research (Fried 1974). The equipoise principle puts the individual patient first. It does not allow clinicians to compromise their patients' interests even for the sake of greater potential benefits to other patients. This principle was later reinforced in the Declaration of Helsinki (Association 2008).

Individual equipoise, however, proved to be an "overwhelmingly fragile" concept and was referred to by Freedman as theoretical equipoise (1987). Even though it may not be known which treatment is better, most individual patients tend to have preferences, which may be more or less rational. In comparing potential arms of a RCT, each person will make comparisons which are unique depending on personal values, such as risks versus benefits, attitude to risk taking and innovations. This comparison between options will lead to equipoise at different points for different people even when they have the same knowledge of the case or subject (Veatch 2006).

In addition, individual equipoise is subject to change for a number of reasons. These reasons may include peer pressure, results of imperfect studies and the influence of advertising. So Freedman proposed that clinical equipoise (also known as collective equipoise) should be used as a justification for inviting patients to participate in RCTs. He defined clinical

equipoise as "honest, professional disagreement among expert clinicians about the preferred treatment" p.144, (Freedman 1987, p. 144). He argued that collective equipoise should override the individual clinician's lack of individual equipoise to allow him/her to enter patients in the trial even when clinicians hold their own preferences.

It has to be noted here that there has been little discussion of what counts as knowledge when applied to uncertainty (Ashcroft 1999). Many feel that uncertainty needs clearer definition if a concept of clinical equipoise is to be applied to the ethical judgement of research (Paradis 2006). Yet Freedman's argument remains very strong and at present it is still accepted by society that collective equipoise is required before a clinical trial can be approved (Chard and Lilford 1998).

Currently, in order to recruit patients into human trials ethically, reasonable and/or substantial uncertainty (Peto and Baigent 1998) between expert clinicians about compared treatments (i.e. clinical equipoise) needs to be established. Once established, a case needs to be presented to an Ethics Committee. Sometimes it is presented as informal information (e.g. opinions of local clinicians), sometimes as semi-formal information (e.g. evidence of diversity in practice across institutions/clinicians or different opinions in the literature), at other times as formal information by specific measurement of expert belief, although this is very rare (Freedman and Spiegelhalter 1992; Lilford 1994). Ethics Committees represent society with

a diverse mix of clinicians, scientists, people trained in ethics and law, lay members etc. In particular, they judge whether trial participants could be disadvantaged, if allocated to one or another intervention being compared in a trial. If a proposed trial is ethically approved, this uncertainty about a treatment or procedure choice needs to be explained to a potential trial participant. In addition, a patient has to be informed about the nature, significance, implications and risks of the suggested interventions, so that an informed choice can be made about proposed trial participation. When all necessary research and clinical information is given and sufficiently understood, patients themselves need to reach effective equipoise (Chard and Lilford 1998). This is the point in the decision process where the expected utilities of both treatment options are the same in patients' minds. In other words, this is the point where the pros and cons of different intervention options, from a patient perspective, are too close to hold an obvious preference towards one or another option. At this point their trial consent is regarded as freely obtained.

In spite of all that has been stated in the previous paragraph, the principle of clinical equipoise does not remain unchallenged. This is mainly due to difficulties with the practical application of this principle in clinical trials (Weijer and Miller 2003). Traditionally, physicians tend to express disregard or denial of uncertainty when faced with the treatment of an individual patient, even when there is no evidence to prove any difference between two treatments (Katz 1984). This remains the case even when clinical

equipoise has been demonstrated and accepted by clinicians at the start of a trial. There are possibly a number of explanations for this phenomenon. These explanations may include apparent emotional ties which clinicians develop with a standard treatment, especially if they have had some good results and this treatment has been presented as the best choice by them. It is difficult to disagree with Paradis when he states that "often in medicine, we do not know what it is that we do not know. We have a tendency to equate reason, observation, and past experience with knowledge and with certainty." (Paradis 2006, p. 62).

Some authors are suspicious of the very fact that the principle of equipoise requirement includes commitment to the traditional account of physicians' therapeutic obligations. They believe that this makes it erroneous in theory and practice. They argue that "clinical research, by virtue of being aimed at producing generalizable knowledge, adopting methods foreign to medical care (e.g., randomization, masked treatment assignment, and the use of placebo controls), and including procedures that carry risks to research participants that are not justified by medical benefits to them, should be understood as governed by ethical norms distinctive from those that apply to clinical medicine."(Miller 2006, p. 59). According to them "clinical research, including treatment trials, would be impossible if it were held to the ethical standard of promoting the medical best interests of patients that governs therapeutic medicine," (Miller 2003, p. 165). They propose a 'difference position' which views the clinician's activity as being divided

into three activities distinct in their nature and goals, namely therapeutic care, clinical research and public health (Brody 2006). They argue these three activities require different ethical approaches.

This view is criticised by other opponents of clinical equipoise on the basis that it denies clinical trial participants the privileges and protections of the traditional therapeutic relationship (Chiong 2006). Although the "difference position" comes with a proposition of a safeguard framework aimed to prevent patient exploitation (Miller and Brody 2003; Buchanan and Miller 2005), it appears that a principle of non-exploitation can be interpreted in different ways to support different views. Chiong argues that both clinical research and therapeutic medicine should follow the same therapeutic ethical framework of the "similarity position". It follows that clinical research should continuously search for alternative and improved study designs to minimise ethical research compromises, such as blinding, extra investigations and placebo procedures. These all carry attendant risks to patients even when these risks are minor.

The "similarity position" fits perfectly with the clinical equipoise principle. However, the equipoise application is criticised by Chiong also for rigidly disallowing clinicians from facing the question of compromises in patient care justified by the potential benefits to third parties. However his proposal that "the therapeutic obligation can be discharged by providing good enough treatment" (p. 37), reflects one of the clinical equipoise followers'

interpretations that the clinician's obligation "does not require the provision of the best possible care, rather it requires the provision of competent care" (Miller and Weijer 2003, p.115). Both statements expose a degree of compromise to clinical care provision that is felt necessary with the currently available RCT methodology.

The theoretical premise for this study is the contention that "equipoise exists if well-designed studies have yet to answer the question as to which of two interventions are to be preferred for a particular population of patients" (Halpern 2006, p. 2). The principle of clinical equipoise reflects the high ethical standards of clinical research expected by society and has been accepted widely as a trigger for setting up a trial and benchmark for ethical approval. However, it fails to be transferred into the practice of clinical trials. This is because individual equipoise is a fragile and unreliable concept that is usually not present when a patient is recruited to a trial by a clinician. The offer of a random allocation to a treatment is usually based on clinical equipoise demonstrated when a trial is suggested and set up. This randomisation issue and other methodological difficulties related to challenging surgical RCTs are discussed in the following sections.

1.3 RCTs for surgical interventions

It is generally accepted that there is a place for RCTs in modern surgical practice. As evidence for this assertion, it would probably be sufficient to recall examples of surgical practice where less rigorously evaluated procedures have been found to be ineffective: gastric freezing for a bleeding peptic ulcer, carotid body denervation for bronchial asthma, prophylactic portacaval shunt to prevent oesophageal variceal bleeding, nephropexy for visceroptosis, removal of a chronically inflamed appendix and periarterial sympathectomy or internal mammary arterial ligation to improve angina symptoms (Cobb, Thomas et al. 1959; Baum 1981; Salzman 1985). Moreover, there is a shocking list of surgical procedures that became parts of standard practice before being proven ineffective: routine tonsillectomy, routine circumcision, repeated cesarean delivery, internal-thoracic-artery ligation, jejunoilial bypass for morbid obesity, laparotomy for tuberculous peritonitis or pelvic inflammatory disease, adrenalectomy for essential hypertension, and extracranial or intracranial bypass for carotid-artery occlusion (Freeman, Vawter et al. 1999)

However, there are at least two more arguments exposing an increasing need for high quality evaluation of differences between treatments. First, with improvements in various aspects of healthcare, the risk of biased estimation of treatment effects between particular procedures in observational studies is higher than ever (Boutron, Ravaud et al. 2007).

Surgery is a part of a complex intervention where the wider context of the surgical team and pre-operative and post-operative care are important. A multitude of confounding factors, such as the availability of appropriate equipment, treatment delays, staffing issues, physiotherapy regime and so on, all play their part and can affect the eventual outcome.

In a recent example concerning trauma surgery, only a meta-analysis of RCTs, comparing the use of intramedullary nails with extramedullary implants for extracapsular hip fractures, showed significantly more peri- and post-operative complications associated with intramedullary devices (Parker and Handoll 2008).

Secondly, the tremendous diversity in practice patterns at the present time across institutions, coupled with the continuously increasing range of available interventions, suggests a rather low level of agreement between clinicians about the value of those interventions (Halpern 2006). Patient demands, pathology itself and treatment indications change with time. Surgical treatments are usually less standardised: one surgeon may carry out a procedure differently from another and have a different level of skill and experience, even when the intervention has the same 'label'.

Randomised Controlled Trials (RCTs) are recognised as representing the highest level of published evidence, either on their own or as part of systematic reviews, and are used to inform decisions regarding all areas of clinical care (Centre for Evidence-Based Medicine, University of Oxford,

www.cebm.net). In the UK, the National Institute for Health Research (NIHR) is the main public funder of clinical trials (www.netscc.ac.uk). RCTs are regarded as the gold standard methodology in clinical trials. In particular the pragmatic randomised control trial design (discussed later), is the mainstream for studies supported by its Health Technology Assessment Programme. Clinical Trials Units (CTU) are seen as central to the overall vision of expanding the number and volume of clinical trials in the UK, so in 2008 the CTU Support Funding was introduced. Major independent research organisations, some of them charitable, such as Arthritis Research UK, fund clinical research with the expectation that an RCT will be the appropriate methodology to answer important research questions regarding efficacy and effectiveness for a test intervention. These factors to a large extent explain the recent surge of the RCT as the most favoured clinical trial design in surgery.

However, it is important to understand that rigid application of available RCT methodology is certainly not a panacea that will provide answers to all the clinical research questions that need answering (Senn 2013). Particularly in surgical applications, RCT efficiency in proving definitive answers to many research questions is more debatable. There is ongoing argument about the reliability and the limits of RCTs in surgical practice (Abel and Koch 1999), and even their scientific value. In particular, this critique concerns the applicability of group probabilities derived from large trials to subgroups with different disease and background characteristics

or to individual patients (Sleigh 1997; Herman 1998). It is not uncommon that a particular research question remains unanswered even after a careful methodological review of the results of several RCTs dealing with the same question. For example, in the case of very common distal radius fractures, 117 patient management questions were identified by expert evidence reviewers. Evidence from 114 related RCTs covered 31 of these research questions to some extent, but only five provided sufficient evidence to judge effectiveness and to compare particular interventions (Handoll and Madhok 2003).

Available evidence from the Cochrane Library indicates that currently surgical RCTs systematically fail to produce meaningful advice about procedure choices. The Cochrane Collaboration is the internationally recognised independent non-profit organisation formed to present healthcare research evidence in a systematic way. Treatment reviews usually include randomised and quasi-randomised trials. For example, in a wide-ranging review of internal fixation implants for intracapsular hip fractures in adults, 30 studies involving 6334 participants (6339 fractures) were analysed but no clear conclusions could be reached on the choice of implant from the available evidence within randomised trials (Parker and Stockton 2001).

In order to improve the chances of detecting a difference between interventions, natural variability between research subjects needs to be

deliberately decreased. This can be achieved by introduction of extensive and restrictive controls of trial eligibility and intervention delivery. This principle is used in exploratory or explanatory trials of new interventions that aim to answer the question 'can this work?', not 'will it work?' (Lilford, Braunholtz et al. 2004). An exploratory trial gives freedom to refine a new procedure in the early development stages and to assess the impact and safety of the procedure. Such a trial seeks to assess whether an intervention can work under favourable conditions, i.e. treatment efficacy. Those patients who are expected to be most suited to the treatment are enrolled and usually treated by surgeons with considerable related expertise. However, generalisability of results for a target population in wider clinical practice suffers.

To answer the 'will it work?' question a pragmatic trial design is used. It seeks to inform clinical decision making by evaluating an intervention in a realistic clinical setting. Pragmatic RCTs follow the principle of larger and simpler trial design with the widest possible entry criteria to allow more clinicians and patients with different prior beliefs and values to participate (Lilford, Braunholtz et al. 2004). Usually these are large multi-centre trials, so that legitimate variations in clinical practice and expertise levels, which are representative of the clinical community in which the intervention is used, can be incorporated into the evaluation. It follows that the pragmatic trial design is beneficial when a technique is to be introduced in common practice or a more established surgical intervention is being researched, due

to the complex nature of such an intervention.

In real life, however, many surgical trials display some characteristics that reflect more than one type or are poorly reported, defying easy categorisation (Cook 2009). Paradoxically, it often happens that the search for consensus between many experts prior to a larger trial leads to complex eligibility criteria. The known prognostic factors, which influence pre-set eligibility criteria at the start of a trial, are not necessarily the most important ones or the ones that a clinician regards as important in a specific case (Abel and Koch 1999). More complex eligibility criteria are more open to interpretation by a clinician, who makes an individual decision about a patient's trial eligibility. This is one of the common criticisms of RCTs, that they themselves introduce a selection bias.

In addition, patient recruitment in modern randomised trials of invasive treatments remains low, in the order of 30% of eligible patients or lower even in well-designed trials (Buchbinder, Osborne et al. 2008; Weinstein, Lurie et al. 2008). This is the case in spite of numerous methodological advances in recent years and results in an even smaller proportion out of an already small number of eligible patients being randomised; so applicability of the results to the more general patient population may be problematic.

The challenge to recruit the targeted number of patients even in excellent surgical RCTs can be demonstrated by the example of the MRC spine stabilisation trial. It was calculated that a sample size of 133 subjects

would be required in each of three treatment groups that were compared: spinal fusion, flexible stabilisation and intensive rehabilitation programme (Fairbank, Frost et al. 2005). This seemed a realistic target considering that the trial was set up in 15 UK hospitals and that about 1000 lumbar fusions were performed in England per year at the time. Both surgeon and patient had to be in individual equipoise for a patient to be eligible for the trial. This appears to ignore Freedman's principle of 'theoretical equipoise', which is shown to be inherently fragile, difficult to attain and impossible to maintain (Freedman 1987), but it redefines a challenge of the practical application of 'clinical equipoise'. After 6.5 years (June 1996 to February 2002) 349 patients were randomised in two groups: two surgical options became a single spinal stabilisation surgery group. It looks as if some lessons have been learned. The recent Spine Patient Outcome Research Trial (SPORT) employed an innovative design. It recruited in both randomised (501 participants) and observational (743 participants) cohorts from 13 spine clinics in 11 US states (Weinstein, Lurie et al. 2008). Even with these flexible arrangements, 747 patients declined to participate in the study. This represents 25% recruitment to the randomised cohort, a percentage which is similar to recruitment levels in other challenging surgical RCTs.

The complexity and specific issues of surgical trials are not a new phenomenon and have been discussed over the years (Love 1975; Stirrat, Farrow et al. 1992; McCulloch, Taylor et al. 2002; Boutron, Tubach et al.

2003; Ergina, Cook et al. 2009). Blinding is usually impossible for a number of reasons. Scars are difficult to conceal, especially when procedures are obviously different. Lack of blinding makes a patient's individual preference especially high (Paramasivan, Huddart et al. 2011) and the surgeon's preference has to be disclosed, if present, to a patient on request. A patient has to consent to surgery, so having a good enough reason to perform a procedure and trust in one's ability to improve or sort out a problem is of paramount importance. It is a surgeon who is going to perform an invasive procedure, in contrast to a drug prescription, and a surgeon's skill and experience can differ even with regard to individual procedures in the same subspecialty. The 'learning curve' effect, i.e. gaining experience in performing a new procedure, needs to be accounted for, as necessary. On the other hand, surgical innovations do not require formal approval through clinical trials, in contrast with the stringent procedures of a new drug approval. With the continual evolution of technology and marketing forces, they often become established, common practice and even popular and in demand before being compared properly to alternative procedures, so patient recruitment becomes even more challenging (Ergina, Cook et al. 2009). A complex of procedures for a structured evaluation of every new surgical intervention or modification is still at the recommendation stage (McCulloch, Altman et al. 2009).

A number of solutions to improve surgical trial design have been suggested over the last fifteen years. A paper entitled 'Framework for Design and

Evaluation of Complex Interventions to Improve Health' (Campbell, Fitzpatrick et al. 2000) proposed sequential phases of developing such RCTs, that included modelling, an exploratory trial and integration of quantitative and qualitative methods. Two significant books have been published recently on Bayesian methods in Clinical Trials (Spiegelhalter, Abrams et al. 2004; Berry 2011). Yet the proposed solutions struggle to find a way into mainstream surgical research and structured methodological advice specific to surgical trials is not easily available. The National Health Service (NHS) Research and Development Methodology Programme has introduced some interesting methodological developments during the past decade which could provide opportunities for imaginative trial design solutions. Unfortunately, however, these have now simply been archived (http://webarchive.nationalarchives.gov.uk/20040308042406/publichealth.bham.ac.uk/nccrm/). The MRC ConDuCT (Medical Research Council Collaboration and innovation for Difficult or Complex randomised controlled Trials) Hub was created in Bristol in April 2009, but the financial support and available resources were limited initially. This has now developed into ConDuCT II, as part of MRC's Network of Hubs for Trials Methodology Research, with a particular focus on the needs of RCTs in surgery. This move created an extensive nationwide resource aimed at research and educational support for clinical investigators.

Hopefully there will be more support and research into methodological options available to investigators in explaining and offering a random

allocation to a treatment. The offer is triggered by pre-set eligibility criteria, which are based on clinical equipoise demonstrated prior to the start of a trial, but may not correlate with individual equipoise, when the actual patient is recruited. Jenkins and colleagues report that, during discussions with patients about randomisation into a trial, clinical oncologists expressed uncertainty about treatment decisions in virtually all of the consultations. That was in spite of the fact that only in 14.6% of consultations was the uncertainty expressed as personal; more commonly, only general uncertainty was expressed (Jenkins, Fallowfield et al. 1999). We are not aware of such studies in surgical RCTs, but it has been suggested that surgeons are even less inclined to uncertainty (McCulloch, Taylor et al. 2002). It is part of the surgeons' ethos to believe in themselves and their surgical skills: some believe that uncertainty is antithetical to surgical training (Rudicel and Esdaile 1985). Surgeons are trained to make decisions in the presence of limited evidence: they seem to be less tolerant of uncertainty than in other medical specialties (McCulloch, Kaul et al. 2005). At the same time, it is a common practice to discuss difficult cases when the treatment choice is not obvious. Even though surgeons may (and probably will) have a treatment preference for a given patient, they will have different levels of confidence about efficacy and may not be certain that their preference is correct (Weijer, Shapiro et al. 2000). Having discussed the 'surgeon factor' in a RCT, patients' involvement is examined next.

1.4 Patients in surgical RCTs

Randomised controlled trials rely on hundreds or thousands of patients giving their consent to participate. Consent or refusal to participate in such trials is adequately informed only if patients understand two key elements in addition to the description of what will happen to them in their particular trial. These two key elements are, first, that participants will be allocated randomly to treatment arms, and second, that at the start of the trial there are no convincing grounds for supposing that any patient would be advantaged or disadvantaged by being allocated to one treatment arm rather than another.

Examination of assumptions held by members of the public when invited to participate in a hypothetical RCT exposed a large mismatch with the assumptions underlying the trial design. Most participants found it unacceptable to suggest allocating treatments at random; furthermore, the scientific benefits of randomisations were not recognised. Around half the participants had difficulty in accepting that a clinician could be completely uncertain about which of the treatments was better. This extensive in-depth work from the NHS Research and Development Health Technology Assessment (R&D HTA) Programme "suggests that many potential trial participants may have difficulty understanding and remembering trial information that conforms to current best practice in its descriptions of randomisation and equipoise" (Robinson, Kerr et al. 2005, p. iv). Several

authors have found that those who refuse to take part in RCTs know less overall about the subject of a trial than those who consent to participate (Leach, Hilton et al. 1999; Lovegrove, Rumsey et al. 2000; Fleissig, Jenkins et al. 2001). In research into participants' understanding of equipoise, it is awareness of this uncertainty that is assessed most often, rather than understanding of the term equipoise itself.

Some authors hold the view that the central ethical problem in clinical research designs is the process of informed consent, rather than the tension between individual and collective ethics (Pullman and Wang 2001). It is therefore important for a good quality clinical trial not only that current evidence is presented as fairly and as clearly as possible, but also that patients understand that judgement about possible treatment outcomes in an individual case can vary between investigators (Lilford 2003). The possible effects of individual preferences on the patient recruitment process can be limited by having consent and randomisation moderated by a third party (Lilford, Braunholtz et al. 2004) or by pre-randomisation (Adamson, Cockayne et al. 2006).

Pre-randomisation implies that the consenting process is primarily about a proposed intervention, rather than a proposed research that is viewed as associated and secondary to the intervention. To allow this, a patient is randomised at the point of eligibility assessment. When suggested originally to improve patient recruitment in challenging RCTs (Zelen 1979), the

full research consent was only obtained from participants who were pre-allocated the experimental intervention. Control treatment was regarded as the best standard care, so availability of the experimental intervention was not mentioned. Permission for research follow up and data collection could be asked separately. This was called the single consent method. The double consent method was introduced later (Zelen 1990), where retrospective consent was sought from participants pre-allocated to any intervention group, which allowed all participants an option to refuse and 'crossover' to an alternative procedure. Both pre-randomisation techniques were used successfully over the years across different medical specialties and scenarios with acceptable crossover rates (Adamson, Cockayne et al. 2006). The most well known in Trauma and Orthopaedics is the RCT of arthroscopy for osteoarthritis of the knee (Chang, Falconer et al. 1990). It claimed a six-fold increase in patient recruitment and had a high impact on clinical practice resulting in dramatic reduction of arthroscopic procedures, which were demonstrated to be ineffective. However, the issue of retrospective consent remains controversial both ethically and legally. Some argue that this makes pre-randomisation completely unacceptable (Marquis 1986), but mostly a cautious approach is adopted at the discretion of the Research Ethics Committees (Schellings, Kessels et al. 2009).

The most effective available way of improving understanding in the informed consent process for prospective research participants appears to be having a study team member or a neutral educator spend more time

talking one-on-one with them (Flory and Emanuel 2004). At the same time, some studies demonstrate that the use of visual aids improves the ability to remember facts and risks associated with treatments, beyond a verbal presentation alone: this is particularly true of surgical treatments (Moseley, Wiggins et al. 2006). However, these studies disagree on the question of whether video groups were more willing to participate in a trial (Fureman, Meyers et al. 1997; Weston, Hannah et al. 1997).

The latest Cochrane review of the audio-visual presentation of information for informed consent for participation in clinical trials (Ryan, Prictor et al. 2008) demonstrated weak evidence that the intervention may have limited positive effects on the quality of information disclosed, and may increase patients' willingness to participate in the short-term. The authors of the review encourage investigators to continue to explore innovative methods of providing information to potential trial participants.

Qualitative techniques are increasingly included in medical and health research to help in the interpretation of quantitative results or the understanding of trials (Snowdon, Garcia et al. 1997; Featherstone and Donovan 1998). In the controversial ProtecT (prostate testing for cancer and treatment) trial comparing surgery, radiotherapy and monitoring, changes to the content and delivery of study information according to the results of the parallel qualitative study of the process of recruitment increased recruitment rates from 40% to 70% (Donovan, Mills et al.

2002). However, the decision making process about trial participation is more complex than a rational assessment of available information. This is discussed in the next section.

1.5 Patient decision making process about trial participation

Decision making is the process of selecting one of multiple options based on their true or perceived utility. In other words, decision makers must weigh up the probability and compare possible outcomes at different points in time. Economists and psychologists have long studied how people make choices that can lead to rewards or punishments of different amounts at different times with different probabilities (Kenji and Shalden 2012). This leads to the development of economic and psychological models of the decision making process. Economic models such as 'Rational Choice Theory' imply a tendency to maximise benefits and minimise the costs. This theory uses utilities that represent a patient's subjective value for choice attributes, such as a health state or a treatment characteristic (Schacter, Gilbert et al. 2011). Psychological models take into account the more emotional aspects of decision-making, assessing people's attitudes in different circumstances. Attitudes are defined as a psychological tendency that is expressed by evaluating a particular entity with some degree of favour or disfavour. Modern neurophysiological data accord with psychological models of decision-making (Eagly and Chaiken 1993).

It appears that decision making is a combination of reasoning and emotional processes which can be rational or irrational, and often influenced by implicit assumptions. The value of different attributes

changes depending on circumstances and personal attitudes. Therefore modern decision making models tend to be tailored to an area of interest and take into account both economic and psychological factors.

Investigations of views about clinical trials have suggested that both lay people and clinicians may hold views about trial treatments even without being given any substantive information about them: the default assumption seems not to be one of equipoise (Appelbaum, Roth et al. 1987). It is suggested (Robinson, Kerr et al. 2005) that patients' prior knowledge and expectations about the normal sequence of events in a consultation may make it hard for them to process an unexpected invitation to enter a trial. Once they have made the necessary switch, they are likely to attempt to make sense of why the trial is being conducted in a particular way, for example why treatments are allocated at random. However readable and clear the trial information, if it merely describes what will happen without offering explanations that connect with patients' existing knowledge and beliefs, patients may come up with their own, incorrect, interpretations (Featherstone and Donovan 1998; Featherstone and Donovan 2002). Their consent or refusal to participate in the trial may thus not be genuinely informed.

Greater disclosure about treatment options and the clinical trial itself seems to prompt people to either select one of the treatments or refuse randomisation (Edwards, Lilford et al. 1998; Wragg, Robinson et al. 2000).

Surveys found that people were often unwilling to participate in randomised trials even when they held a positive attitude towards research in general (Fallowfield, Jenkins et al. 1998; Purdy, Finkelstein et al. 2000; Fleissig, Jenkins et al. 2001). The patient's level of uncertainty is not defined simply by probabilities of outcomes, but also by how they value those outcomes (Dudley 1986). In other words, where a treatment has well-known side effects, the point of equipoise is not 'no effect' but an effect big enough to compensate for its perceived disadvantage. This point is defined by decision analysis as that where the expected utilities of both treatment options are the same (Lilford and Thornton 1992). It was later called 'effective equipoise' (Chard and Lilford 1998).

It has been argued that it is the equipoise of the subjects, and not that of clinicians or researchers, that is morally significant because they are the ones who are subjected to the effects of a clinical trial (Veatch 2002). Whoever we choose to refer to in a clinical trial, equipoise at present is understood as "inherently a subjective concept based on idiosyncratic evaluative judgments about the projected benefits and harms of alternatives, as well as personal value orientations toward risk-taking and optimism about innovation" (Veatch 2006, p. 56). There are so many variables to consider for each individual which are normally well beyond the expertise or knowledge of a clinician or investigator: cultural background, economic, legal, religious, familial and aesthetic interests are just some of them. If researchers do not know how the patient will assess the expected benefits and harms of the

treatments, how can they know when the patient would be more or less equally poised between treatments and thus more inclined to volunteer? Furthermore, not only might some subjects choose to enter trials when they have a preference for one treatment arm, they may have that preference at a point of their decision process that is quite different from that of clinicians and investigators.

1.6 Summary and research questions

This final part of this introduction chapter aims to summarise the evidence presented, leading to formulation of research questions. The questions are grouped together for ease of reference.

Despite increasing numbers of surgical RCTs, and financial investment in them, their efficiency in answering research questions and their ability to influence surgical practice remains low. This could be explained by a lack of methodological rigour and poor patient recruitment. Poor recruitment reduces trial power and the applicability of results to the general patient population, especially at a subgroup level. Obstacles for efficient patient recruitment may well include the following: an individual surgeon's lack of equipoise, the ethical obligation to provide the best possible treatment, and the requirement to admit in front of a patient insufficient knowledge to determine the best choice of intervention. This is coupled with a patient's understandable reluctance to accept random allocation to a treatment when substantially different procedures are being compared (such as open versus minimally invasive, or operative versus non-operative interventions, for example physiotherapy). The reluctance is likely to be even greater when surgical innovations are involved, especially when they are already available outside the trial (Ergina, Cook et al. 2009). For both parties, detachment from decision making about a choice of treatment seems to be rather uncomfortable and damaging for the surgeon-patient relationship (Fung

and Lore 2002). This 'surgeon' issue cannot be ignored in the same way as clinicians are in drug trials simply because surgeons are integral to surgical interventions.

Strict and complex pre-set eligibility criteria are often necessary with current trial set ups; but this is at odds with pragmatic trial principles by further reducing the numbers of trial participants. The distinction from the explanatory trial becomes blurred, further reducing the applicability of results to standard surgical practice or policies. The application of pre-set fixed trial eligibility criteria often fails to transfer the principle of clinical equipoise to the process of patient recruitment into a trial. This creates inherent conflict between a clinician's therapeutic obligation to provide the best possible care for an individual patient and their clinical research responsibility to society to maximise trial participation for the benefit of many future patients. This is because often either a patient or a recruiting clinician, or neither, are in individual equipoise about a treatment choice, especially when compared interventions are obviously different and the involved parties feel unable to express their opinion and/or preference. The dilemma leads to the first research question of this study:

1) *Is it possible to develop a methodology that integrates/transfers the principle of Clinical Equipoise into a clinical trial recruitment process?*

Legally enforced ethical regulations dictate that trial participation should be voluntary and based on informed consent. Some factors affecting a patient's

effective equipoise, such as treatment preference and poor understanding of the principles behind random treatment allocation, are known to prevent patients from enrolling.

The process of informed consent is central to the ethical and legal acceptability of any research that involves humans. When trial information is presented by a clinician, patients hold certain assumptions and expectations about a consultation, which may lead to difficulties in providing unbiased explanation about treatment options. Trial introduction by a third party and pre-randomisation have been used previously to limit the exposure of an individual clinician's opinion and/or preference. In addition, the use of patient information videos has been shown to enhance understanding and to provide reassurance for patients invited to take part in clinical trials.

As mentioned already, it can be difficult for a treating clinician to provide impartial advice about treatment options in the context of a clinical trial. A patient has the right to know a surgeon's personal opinion and judgement. Also, consenting to clinical research can be a rather time-consuming process, yet it is crucial to informed decision making by a patient about trial participation. This motivates the next research question:

2) *How to achieve clear, impartial and consistent delivery of trial information to patients in the context of a challenging surgical trial, when the compared interventions are obviously different?*

When innovations are introduced, it is a good research practice to understand the experience of recipients/users. "Researchers should assess systematically the effects of different intervention components and delivery characteristics, and should involve consumers in intervention development" (Ryan, Prictor et al. 2008, online CD003717).

Usually, patients do not expect a clinical trial to be a part of their clinical care. Factors leading to 'effective equipoise' sufficient for their agreement to participate are poorly understood. There is limited systematic analysis of patient experience data available directly from surgical trials (Mills, Donovan et al. 2003; Paramasivan, Huddart et al. 2011; Leighton, Lonsdale et al. 2012) and none to my knowledge from trauma and orthopaedic trials. More specific knowledge about patients' response within different types of clinical studies may help individual researchers and trial design teams to choose an approach that promotes better-informed and more rational decisions about taking part. This leads to the final research question to be answered:

3) *What is the patient perspective on the recruitment process in a challenging surgical trial, when the best current advice as well as innovative approaches to the principles of patient participation are integrated?*

It is my intention in the remainder of this thesis to provide answers to the proposed research questions and to suggest further work and development on the basis of the research which I have carried out. A challenging trauma

trial is described in **Chapter 2** as an appropriate setting to test and explore some of the ideas and solutions proposed elsewhere in this study. The study design is complex, multi-faceted and uses both qualitative and quantitative methods. An overview of the research methods used throughout this study is given in **Chapter 3**, including a more detailed description of the qualitative methodology and the study population. The research process is explained and results are described over the course of three chapters (**Chapters 4, 5 and 6**), before combining all the relevant outcomes from the different studies into some conclusions in **Chapter 7**.

Chapter 2 The UK Heel Fracture Trial (UK HeFT)

The research questions posed in the previous chapter assume development and introduction of a new trial recruitment methodology based not only on a solid theoretical background, but also through better understanding of a surgical trial population. This chapter describes a trauma trial that provided a test setting for the methodology that was going to be developed during the course of this study. This is in line with modern principles of translational research that theoretical and methodological developments are tested for practical application whenever possible and at the earliest opportunity. In addition, this approach allows direct user feedback both from clinicians and patients.

The UK Heel Fracture Trial (UK HeFT), in which I was closely involved, provided both the opportunity and the stimulus for my research project into patient recruitment. Its aim was to compare operative and non-operative treatment of displaced intra-articular calcaneal (heel bone) fractures. The intervention arm involved a modern surgical procedure performed within three weeks of the injury, by surgeons trained and experienced in the technique. The control arm was treated with analgesia and elevation to control pain and swelling. This was followed by early mobilisation and standardised physiotherapy regime, the same for both treatment arms. It was not clear from earlier evidence whether the possibility of improved

results after surgery (Sanders 2000) justified the risk of frequent and serious complications, reported by other studies (Folk, Starr et al. 1999; Howard, Buckley et al. 2003). Such contrasting trial interventions presented a challenge to patient recruitment, as discussed in the previous chapter.

At the time it started in 2007, the UK HeFT was the largest national trauma trial designed according to current methodological advice. It was compliant with modern regulations and recommendations on the best clinical research practice. The study was set up as a multi-centre, two-arm, parallel group, assessor-blind randomised controlled trial (ISRCTN 37188541). It was designed as a pragmatic trial and all the participating surgeons were recognised as foot and ankle or trauma specialists. The Chief Investigator had overall responsibility for the conduct of the trial and had fiscal control over grant funds. He also headed the central trial office. The central trial office team included a trial co-ordinator, statisticians and co-investigators. Each trial centre had an expert surgeon designated as a Principal Investigator, with responsibility for local trial conduct and leadership. They were supported by Research Assistants, who facilitated patient recruitment and paperwork processing. The primary outcome was based on the injury-specific patient-reported outcome score at two years after injury. The Kerr-Atkins was a validated, reliable, patient-derived outcome instrument for pain and function following calcaneal fracture, accepted by surgeons working in the area (Kerr, Prothero et al. 1996). However, since participants were inevitably aware of the trial arm to which they were

allocated, the possibility of 'preference' bias or a surgical placebo effect had to be accounted for in patients' reports. Secondary outcomes included risk of complications, potential differences in quality of life, stiffness and deformity of the hindfoot, gait and foot pressure patterns.

All patients in participating trial centres diagnosed with calcaneal fractures during the trial recruitment period were assessed for trial eligibility according to pre-set fixed eligibility criteria. Patients were eligible if they were at least 18 years old and able to give informed consent with a recent (less than 3 weeks) closed, intra-articular, displaced (sub-talar joint posterior facet displacement of at least 2 mm) calcaneal fracture. They were excluded if they had very severe deformity of the hindfoot (described in subjective terms as 'fibula impingement'), other serious lower limb injuries (which the local investigator judged would be likely to influence outcome of the calcaneal fracture at two years), would be unfit for surgery (e.g. due to severe cardiac impairment), suffered from peripheral vascular disease, or would be unable to adhere to trial procedures or to complete questionnaires.

A novel recruitment process was introduced that confined the clinician's role to assessing eligibility and grading fracture severity before seeing a patient. Specially trained research associates (nurses or physiotherapists) then approached eligible patients about the possibility of participation in the trial. A patient trial information video was used to ensure a complete,

standardised and balanced explanation of the trial. Patients had the option of watching the video in the presence of a research associate, who would be able to clarify any immediate queries or concerns. A compact DVD player was then left with patients for at least a 24 hour period to enable them watch it again as necessary on their own or with friends or relatives. A research assistant then returned to assist with any further questions and enquires about the patient's decision whether to accept an invitation to enter the trial. This process was researched as part of my study and it is described in more detail in **Chapter 5**.

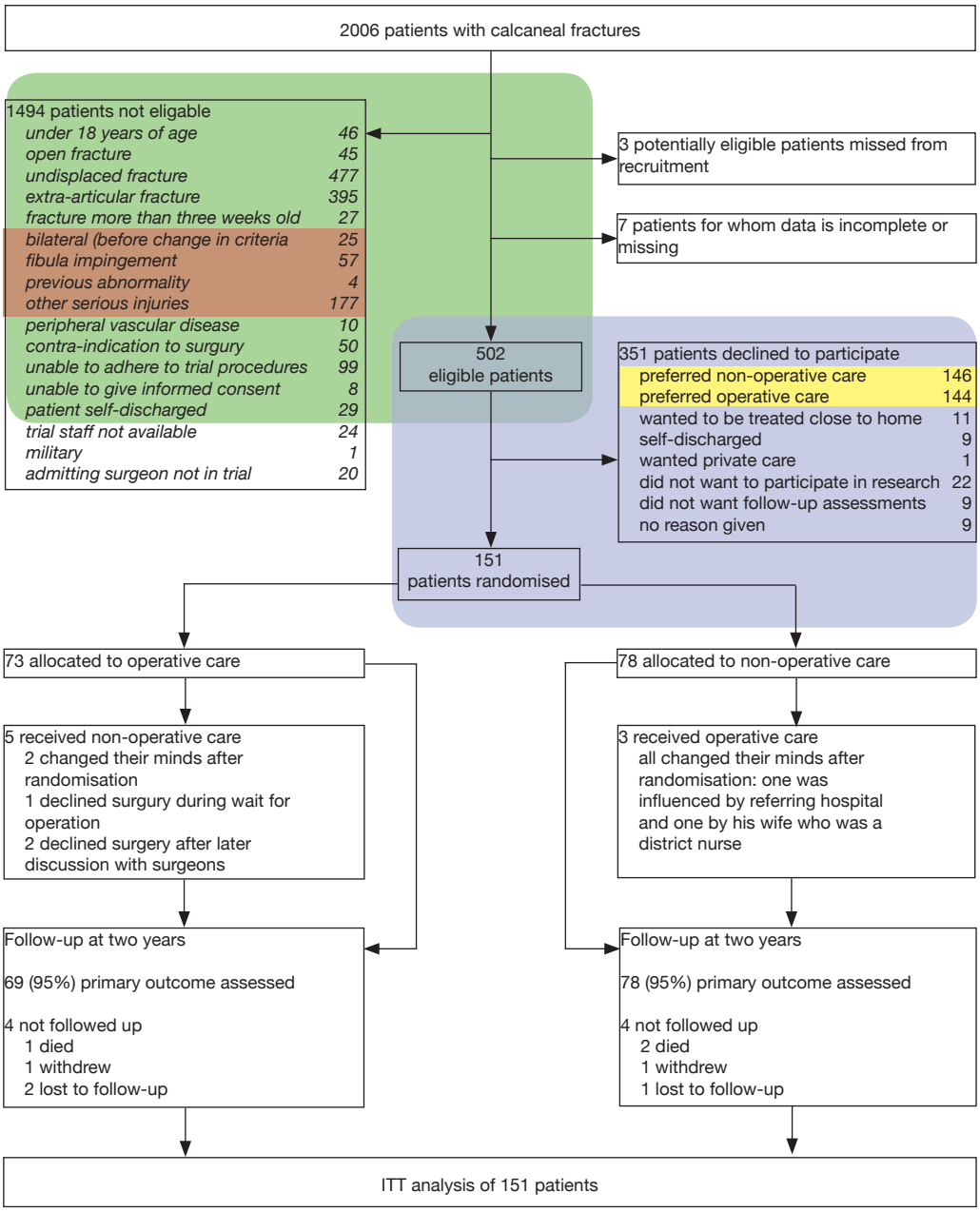
Participants were recruited from patients presenting to 22 collaborating hospitals in the UK (**Appendix A**) during the period January 2007 to December 2009 to achieve a recruitment target of 150 participants. The patient screening process was audited continuously at every centre. A Principal Investigators and Research Assistants network was co-ordinated by the Trial Central Office. Regular educational and networking events were organised to stimulate peer review and exchange experience about the patient recruitment process, in addition to trial site monitoring.

Patients who consented to take part in the trial were randomised on a 1:1 basis to receive operative or non-operative care. Mixed clinical and questionnaire follow up was arranged at six weeks, then 6, 12, 18 and 24 months. At the final two year follow up appointments, participants were assessed by a single independent physiotherapist, who was unaware

of treatment allocation. Heel width and hindfoot ranges of movement (dorsiflexion, plantarflexion, inversions and eversion) were measured in comparison with the other side and gait was assessed. During examination, participants were asked to wear thin socks to obscure surgical scars and not to disclose the treatment they had received.

A trial flow diagram (**Fig. 2.1**) demonstrates the trial profile and stages of the trial recruitment process researched in the context of this study. These stages include identifying eligible patients, presenting trial information according to the informed consent principle and then managing patient decision making about trial participation. Of 502 eligible patients identified in this trial according to pre-set fixed eligibility criteria, only 151 (30%) agreed to take part. The most common reason for declining, by a significant margin, was a preference towards either operative or non-operative care, which was evenly balanced (144:146).

Statistical analysis of patient demographic data for the trial (**Appendix B**) showed that the injury tended to occur in younger men and in older rather than younger women. Even when they were eligible, younger men and middle-aged women were more likely to refuse to enter the trial. This caused some concern that women and younger men might be under-represented in the trial, although this was considered when interpreting the trial results. Overall there were four times more men presenting with the injury considered eligible for the trial, which was expected. The



Light green area – trial eligibility assessment stage researched in the context of the PEACE methodological framework (**Chapter 4**). Brown coloured box – patient groups adding up to 263 patients, many of whom would have been assessed for trial eligibility on an individual basis if the PEACE framework was used, rather than excluded according to pre-set criteria (**Chapter 4.4**).

Violet area – trial recruitment stage researched in the context of the PTIV recruitment approach (**Chapter 5**). Yellow coloured box – two groups adding up to 290 patients who were mostly positive towards research, but not able to accept the randomisation offer in its current form (**Chapter 6**).

Figure 2.1. The UK HeFT patient throughput.

proportion refusing to enter the trial was similar: 72% for women and 68% for men. This is in line with recent high-quality challenging interventional trials (Buchbinder, Osborne et al. 2008; Weinstein, Lurie et al. 2008), when treatment arms are significantly different. Taking into account the limitations outlined above, after two years no beneficial symptomatic or functional advantage of operative treatment was identified, compared to non-operative care in patients with typical displaced intra-articular fractures of the calcaneus. At the same time, the risk of complications was confirmed to be higher after surgery.

Having outlined the context of my research and the particular trial it was tested in, I am now in a position to describe the study design in the next chapter.

Chapter 3 Study design and methodology

The patient recruitment process into surgical RCTs, which is the subject of this study, can be divided into three consecutive phases: identification of eligible patients, invitation to take part in a trial based on the principle of informed consent and the decision process by a subject about trial participation. The three research questions posed in **chapter 1.6** reflect these three phases. The approach taken to research the three distinctive issues inevitably had to involve mixed methods. This presented a significant challenge, because I had to find a way to acquire new knowledge and balance between different subjects (methodological development and qualitative reflection) with different theoretical backgrounds (experimental and observational). In addition, I had to find a way to develop collaborations that did not exist in my institution. However, it was felt important to adopt the mixed methods approach not only because the research issues to be addressed were linked as parts of the same process, but also because the feedback and reflection from stakeholders, in particular subjects, of proposed innovations could enrich and strengthen an argument to transfer these innovations in future practice. This attempt to design a transferable methodological research project is explained next, starting with the first research question:

1) *Is it possible to develop a methodology that integrates/transfers the principle of Clinical Equipoise into a clinical trial recruitment process?*

The principle of Clinical Equipoise is used to justify the proposal of a clinical trial, but is substituted by the application of trial eligibility criteria when a patient's eligibility is assessed. It has been demonstrated in **chapter 1.2 & 1.3** that although pre-set eligibility criteria reflect the clinical equipoise present at the start of a trial in relation to the relevant patient population, it often falls short of being affirmed in relation to an individual patient assessment. This may lead to lower confidence that the patient in question would not be disadvantaged through random allocation to interventions compared in the trial. Currently however, there is no methodological alternative available to assess patient eligibility for a RCT, other than an application of the pre-set fixed eligibility criteria. Once the eligibility criteria are met, the patient has to be offered trial participation, which assumes random allocation to the intervention arms even when a patient and/or a treating clinician are not equipoised about the choice. It follows that to answer the first research question of this study about the randomisation offer, it is necessary to suggest and develop a methodological framework that incorporates expression of clinical equipoise at the stage of identification of eligible patients for a RCT. Research into novel methodologies is often complex and typically requires a multi-disciplinary approach. This work is no exception. At different stages it involved collaborating with, amongst others, an IT specialist and a statistician. Methods used to develop a new framework for patient trial eligibility assessment through quantifying and demonstrating levels of clinical equipoise in real time for an individual patient are described later in this chapter (**3.1**).

The second research question concerns trial information delivery to patients, based on the principle of informed consent:

2) *How to achieve clear, impartial and consistent delivery of trial information to patients in the context of a challenging surgical trial, when the compared interventions are obviously different?*

The methodological improvement in order to provide consistent and clear presentation of research and clinical information to eligible patients is outlined(**3.2**).

Both new methodological developments were tested during the challenging trauma trial which was described in **chapter 2**. The aim was to assess the potential benefits, practicalities and relevance to similar trials that may be undertaken in different fields in the future. When innovations are introduced, it is good research practice to understand the experience of recipients/users. "Researchers should assess systematically the effects of different intervention components and delivery characteristics, and should involve consumers in intervention development" (Ryan, Prictor et al. 2008, online CD003717). This principle links to the final research question:

3) *What is the patient perspective on the recruitment process in a challenging surgical trial, when the best current advice as well as innovative approaches to the principles of patient participation are integrated?*

This research question, that seeks an understanding and meaning of

patients' experiences of the trial recruitment process, merits the application of qualitative methods. There was a rather limited expertise of qualitative research available in our department, so I had to look for help and assistance from experienced qualitative researchers pro-actively. This eventually led to effective collaboration and supervision arrangements, as described in the final part of the chapter (**3.3**). The choice of the qualitative approach allowed me to study the wider influences which shaped patients' decision making about participation in a trial comparing invasive and non-invasive treatment. After all, it is a patient's voluntary participation that is at the centre of a trial's success or failure. Better understanding of patient motivations towards clinical research participation may help to shape both current and future methodological modifications.

3.1 A new methodological framework development

I aim to describe consecutive the steps taken, in order to develop a new methodological framework for trial eligibility assessment. The framework is designed to be easily understood by clinicians and implemented in real time during the course of a trial. This process brought together a number of research methods across different disciplines. Their complementary and complex relationship is illustrated in **Figure 3.1**, accompanied by an explanation in the text.

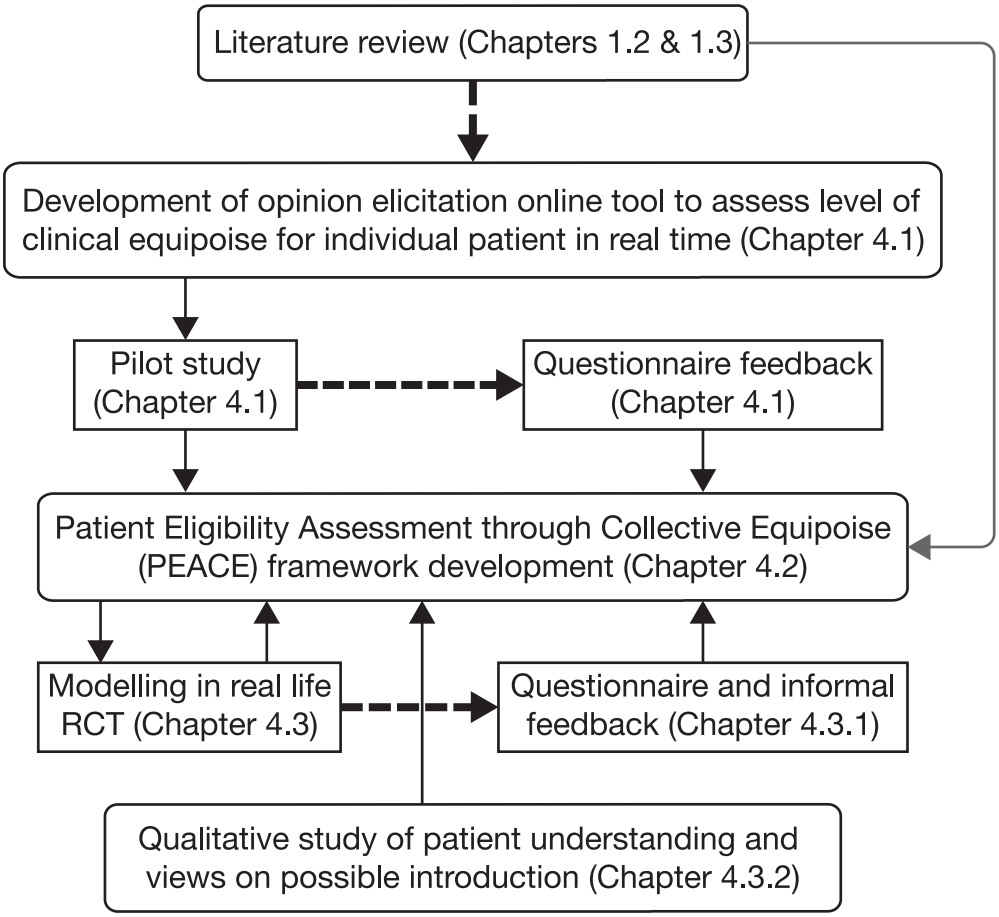


Figure 3.1. Methods used to develop a new methodological framework.

The literature review in **chapter 1.2** indicates that Clinical Equipoise as the basis for setting up a clinical trial is usually demonstrated by a failure of consensus between experts about the effectiveness of an experimental intervention compared to a control. This is usually caused by the lack of knowledge that enables experts to forecast the outcome of a proposed intervention. A "measure of a state of knowledge" (Jaynes and Bretthorst 2003) can be demonstrated using the concept of Bayesian subjective probability. Bayesian methods allow one to quantify the level of an expert's individual uncertainty or confidence about the effectiveness of an intervention. When experts' opinions are combined, or pooled, it is safe to assume that for most patients in a trial population, the experts should fail to reach an agreement in presence of clinical equipoise, which is necessary for a patient to be recruited ethically. This concept provides a platform from which to develop ideas in the challenging trial setting.

An expert treatment prognosis can be viewed as a Bayesian prior which is assigned to a specific hypothesis; it is personal and varies with an individual's knowledge and expertise. However, turning informally expressed ideas into a mathematical prior distribution is perhaps one of the most difficult aspects of Bayesian analysis (Spiegelhalter, Abrams et al. 2004). There are five widely used approaches: (i) elicitation of subjective opinion, (ii) summarising past evidence, (iii) default priors, (iv) 'robust' priors and (v) estimation of priors using hierarchical models. There is no such thing as a correct prior or method of determination, but option (i)

is the most suitable to elicit and quantify the collective subjective opinion from a panel of experts in real time. It has the advantage of being dynamic and flexible, because knowledge and preferences can change during the course of a trial. This may happen, for example, on the publication of related research, or as individual and collective clinical experience accumulates amongst experts.

Development of an online tool for opinion elicitation has been the first step to bring the Clinical Equipoise assessment in real time. Previously, elicitation of subjective opinion in surgical settings has been achieved by collecting opinions through a questionnaire survey (Young, Harrison et al. 2004) or by a series of scenario-based specialist interviews (Lilford 1994). Both methods are time and labour intensive and could only be used to support a justification to start clinical research. An alternative technique, which involves the collection of subjective judgements in relation to clinical decision making, allows participants to distribute 100 points between bins that reflect their 'weight of belief' in a range of available outcome options (Parmar, Spiegelhalter et al. 1994; Parmar, Griffiths et al. 2001). This technique was used to develop a novel web-based tool for the collection and measurement of specialist beliefs about a specific clinical case (**Chapter 4.1**). The technical implementation was achieved in collaboration with Mr S Brydges, eLab, the University of Warwick. Freely available software (Adobe Flash Player, MSDN Microsoft Data tables) and the University of Warwick web-based platforms (Warwick Forums, SiteBuilder) were used. The

tool was then tested in a pilot study. A questionnaire, as well as informal feedback, was used to assess expert perception and usability of the tool. I was interested in technical issues, format, clinical information sufficiency and ultimately whether I had the experts' support to take the study further. Accordingly, a combination of closed (choice of categories) and open questions was used to guide responses (**Appendix K**). The questionnaire was designed in an easy to read one page format with spaces for comments (Boynton and Greenhalgh 2004). It was posted to surgeons' secretaries upon completion of the pilot study.

Once the voting data for a case are obtained, two potential approaches to pooling the opinions are available, (i) a parametric model based on a Beta distribution and (ii) a nonparametric model based on estimated means and standard deviations. Statistical models of expert opinions were developed in collaboration with Dr N Parsons, Medical Research Statistician, Statistics and Epidemiology, Warwick Medical School. An **Opinion Elicitation Course** was attended (CRiSM: Centre for Research in Statistical Methodology, 13/04/2011, University of Warwick). Subjective logic principles (Jøsang 1997) were used to develop a statistical model that allowed us to measure and visually present a level of clinical equipoise for an individual clinical case. The formal statistical methods necessary to implement the model, which are outside the scope of this thesis, are described in detail elsewhere (Parsons, Kulikov et al. 2011) (see **Appendix I**). The focus here is on the underlying conceptual framework

and interpretation of clinical equipoise levels (**Chapter 4.2**). In particular, decisions about trial eligibility depend on the application of decision rules. There is little research available on this subject, other than a stand-alone ground-breaking paper where collective equipoise levels sufficient for initiating a clinical trial were estimated (Johnson, Lilford et al. 1991). This ethometric study with the general public investigated how much collective equipoise can be disturbed before potential trial subjects deem it to be unethical. Their findings suggested that "trials are perceived as unethical when equipoise is disturbed beyond 70:30. In other words, when 70 per cent of experts favour treatment A, then 50 per cent of subjects would prefer that treatment A be administered rather than subjected to critical assessment." When 80% of experts favour one treatment, less than 3% of the lay public would consider human trials morally justifiable. Based on these estimates, decision rules were suggested and this complemented the development of the Patient Eligibility Assessment through Clinical Equipoise (PEACE) methodological framework.

To test the new methodology, the PEACE framework was introduced as an independent research project called 'Collective Uncertainty Project' within the UK HeFT (**Chapter 4.3**). The aim was for real clinical cases to be assessed in real time by an expert panel consisting of principal investigators in the context of a challenging trauma trial, but without interfering with the clinical management or the trial course itself. This was achieved by asking eligible patients to consent to the use of their clinical data at least 6

weeks after the injury, when a decision about trial participation was made and a treatment course was initiated. The use of ethical approval was kept separate from the main trial (**Appendix C**). This had the additional advantage of approaching both patients who agreed to take part in the UK HeFT and those who did not. Surgeons who were involved in case assessments as part of the expert panel were asked for their feedback informally and via questionnaires (**4.3.1**). On this occasion the questionnaire design was more complex (**Appendix G**). Although anonymous, some background information was requested from experts to reflect levels of specialist surgical and research experience. Data examples were given and the choice of categories included an open element to stimulate reflection of the study involvement experience.

Finally, patient understanding and views about the possible introduction of the new framework in future trials were researched, as part of the qualitative study (using semi-structured interviews), which is described later in this chapter (**3.3**).

3.2 Methodological improvement to patient recruitment approach

To answer the second research question, concerning trial information delivery to patients , the new trial recruitment approach is suggested that aims to avoid direct contact between a patient and a treating clinician until a decision about trial participation is made (**Chapter 5**). This is to prevent possible disclosure of likely treatment preference by a surgeon, so that a set of standardised unbiased trial information is presented to every potential participant. The sequence of steps undertaken to introduce and test such methodological development is illustrated in **Figure 3.2**.

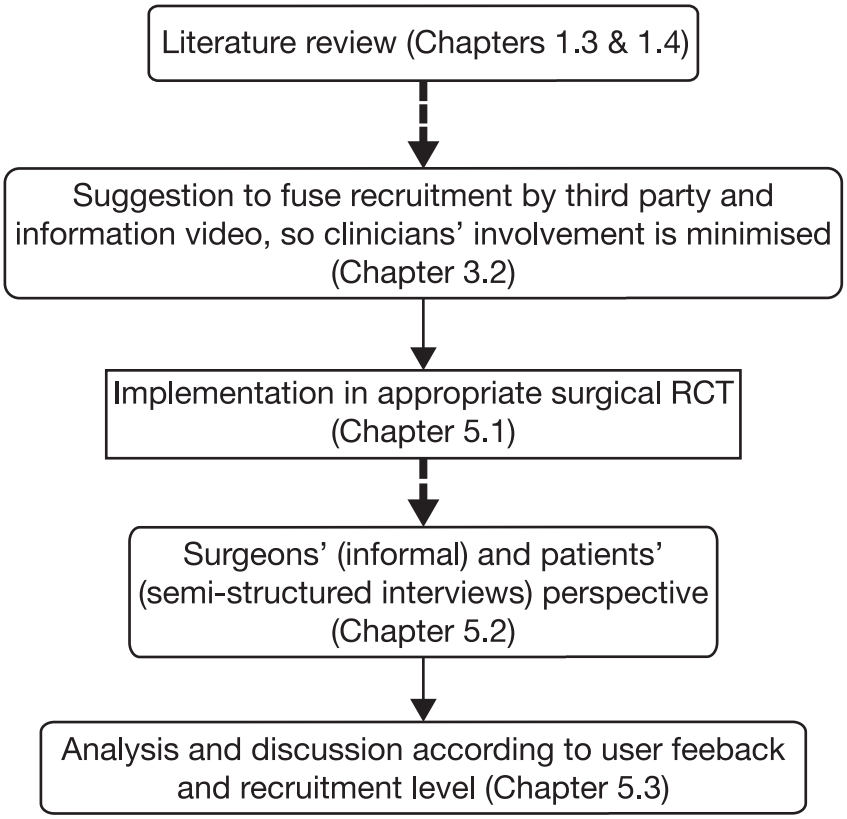


Figure 3.2. New patient recruitment approach development.

The approach was based on developing and recording an audio-visual presentation of trial information, supplemented by one-to-one personal support from a research team. The video was to become the main source of research and clinical information for an eligible patient. This methodological improvement is effectively a combination of two methods that have been shown previously to improve understanding and reduce bias during the consent process for a clinical trial (**chapter 1.4**). On this basis, it was approved both by the Ethics and the Trial Steering Committees to be introduced in the challenging surgical trial described in the **chapter 2**.

The format of the Patient Trial Information Video (PTIV) was discussed with the UK HeFT set-up team. It was decided that it should be in the form of an expert explaining the injury and the trial using appropriate illustrations. The Chief Investigator of the UK HeFT (Damian Griffin, Professor of Trauma and Orthopaedic Surgery) drafted a script based on recommendations by the National Research Ethics Service on informed consent and essential information that needed to be provided to patients invited to take part in clinical research. The video was filmed, processed and edited by the Warwick Medical School Audio-Visual Team. The video was distributed to the Trial Steering Committee (including non-medical members), collaborating Principal Investigators (surgeons) and physiotherapists involved in trial planning. Comments were collected, the script re-drafted and the video filmed again accordingly. After a repeat circulation, new editing touches were applied. Finally, the video

was introduced and discussed with the first three patients eligible for the UK HeFT by the Chief Investigator himself and the Trial Co-ordinator. Patients' comments were analysed by the trial set-up team and final editing touches were applied. A CD with the final version of the PTIV is attached.

Research Assistants involved in every trial centre were trained by the UK HeFT Head Office based at Warwick Medical School to approach and introduce eligible patients to the video and then assist with all patient queries.

Clinicians' reaction was uniformly positive in every trial centre from the outset and remained so for the duration of the trial. Therefore, the formal exploration of their views and feedback was not felt necessary. On the other hand, patients' views as subjects of the trial recruitment process were researched (**Chapter 5.2**), as part of the qualitative study described next. These data proved crucial in illuminating strengths and weaknesses of the proposed approach (**Chapter 5.3**).

3.3 Patient experience of recruitment to a trauma trial

'Qualitative investigations can thus be used to elucidate challenges to recruitment in trials with very different treatment arms, but require sufficient time to be undertaken successfully.' (Paramasivan, Huddart et al. 2011, p.1)

As mentioned already in this chapter, it is of vital importance to learn about the impact of the suggested new trial interventions on patients, as subjects of those interventions. The Patient Trial Information Video (PTIV) based recruitment approach was introduced directly in the challenging surgical RCT (**Chapter 5.1**), while the new framework for trial eligibility assessment was researched as an independent project integrated within the same trial (**Chapter 4.3**). In this way, both interventions became a part of patient's experience in the surgical RCT with very different treatment arms (**Chapter 2**).

There are rather limited data available directly from such trials about factors that influence patient decisions about participation, as highlighted by the literature review in **Chapter 1.5**. This led to the third research question concerning gaining further insight into the patient perspective of the trial recruitment process.

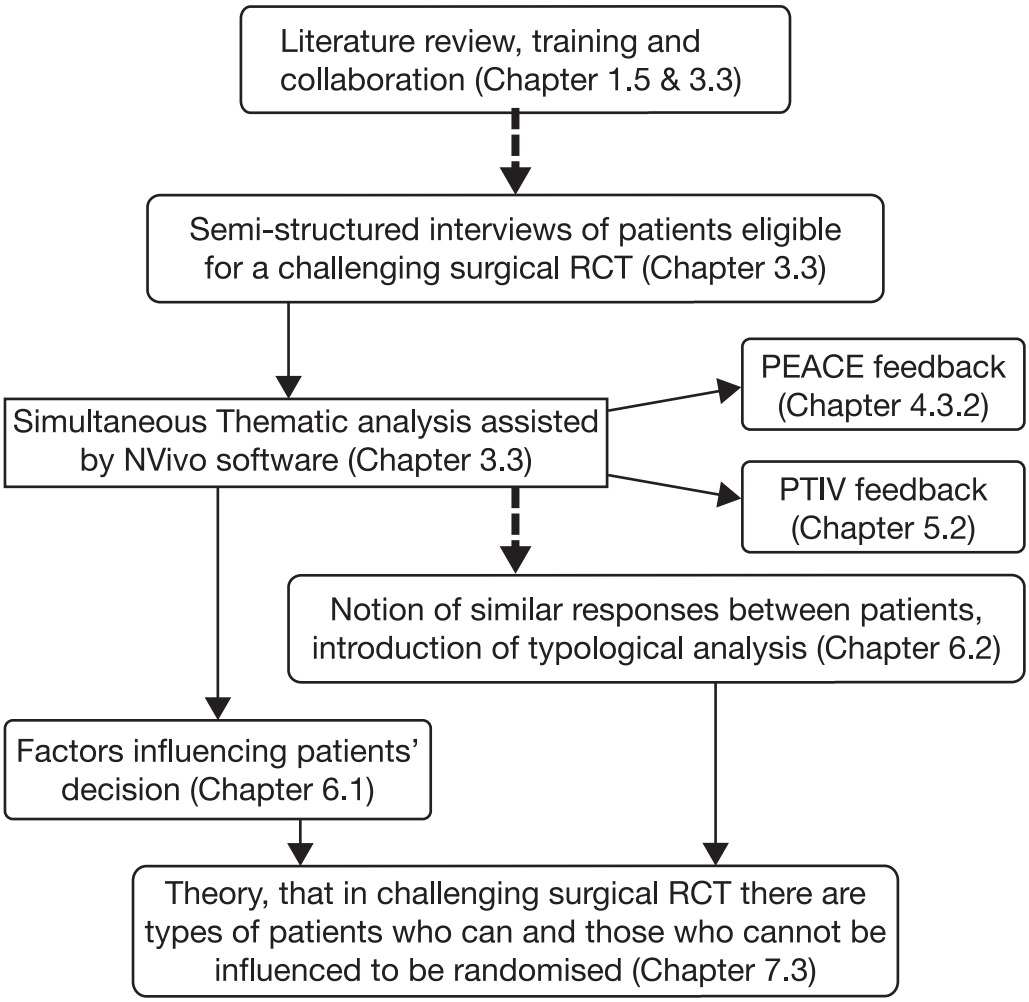


Figure 3.3. Patient decision making process about trial participation

The research question dictated the choice of theory and methods applied to answer it, as illustrated in **Figure 3.3**. The aim was to understand the experience of being approached about participation in the clinical trial from the perspective of the patients who had been through this situation in the UK Heel Fracture Trial. This is in line with the Verstehen approach (Holloway and Wheeler 2010), which assumes a reflective reconstruction of particular situations that these patients found themselves in and

interpretation of the decision-making process about research participation, with attention to factors which affected or which could modify this process. With this approach it is crucial to interpret a phenomenon from the perspective of the people affected by it, as it is constructed by those people.

Phenomenological methods could not be used, however, because it was important to uncover a multitude of factors that led to either a positive or a negative decision for different patients, even though they were in a similar context. Phenomenology suggests a holistic perspective to life experiences, so that the researched phenomenon is explored by means of extracting common themes (essential structures or essences) that go beyond individual cases, rather than focusing on the narratives of each participant (Holloway and Wheeler 2010).

Grounded Theory, on the other hand, starts with a careful search for any emerging themes and topics from every individual account, which are coded and analysed right from the start and which guide ongoing data collection. Through data comparison, initial concepts or even hypotheses are formed, which inform and guide the further research process. The systematic generation of a new theory is guided purely by emerging data, rather than by testing a pre-conceived hypothesis. (Glaser and Strauss 1967; Green and Thorogood 2009).

Thematic analysis of content (Adams and Preiss 1960) combines the open-minded approach of grounded theory with the phenomenological principle

of identifying common themes. This method emphasises organisation of the narrative data through a structured process. Although it starts with minimally organised rich data interpretation and coding, the end aim is to identify common patterns (themes) within data through constant comparison and re-evaluation (Braun and Clarke 2006). The researcher is pro-active in data interpretation and analysis, which is in line with my efforts to understand patient trial experience, specifically in response to current and proposed recruitment interventions, as this may affect their future use and development. The phases of thematic analysis followed in this study are described later.

Ethical approval was sought and obtained for this study (**Appendix E**).

Subjects were recruited in a single centre, which was one of the largest UK HeFT centres - the University Hospital of Coventry and Warwickshire (UHCW). All 47 patients who agreed to provide their data for the Collective Uncertainty Project, introduced earlier (**3.1**) were invited to interviews. Patient information sheets presented as an invitation letter with separate reply slips (**Appendix F**) and pre-paid return envelopes were posted. After two weeks, telephone calls and email reminders followed. Options to be interviewed either at one of two local hospital sites or at home were offered.

Individual stories of a decision making process about the trial participation were of prime interest. For this reason it was felt that group patient

interviews, where shared experiences are explored, would not be appropriate. A semi-structured interview format made it possible to set an agenda for personalised data extraction, while allowing sufficient flexibility for patients' responses to determine the information which was provided and themes which were discussed. Structured interviews would not have allowed patients to develop their own narrative of the events, while unstructured interviews on the other hand may not have covered certain topics of interest, such as more specific feedback about introduced and proposed new methodologies from this study. In addition, unstructured interviews do not allow direct comparison of data between patients. This would have prevented a typological analysis that developed into an important part of this study as described later.

My experience as a clinician in the same specialty provided the background in the development of theoretical sensitivity in order to categorise significant and less important topics to be covered in the interviews. On the other hand, there was a risk that interviewees could view me as another member of a clinical team, rather than an independent researcher, and modify their responses accordingly.

Analysing Qualitative Interviews Training Course was attended (26-27/02/2008, Health Experience Research Group, the University of Oxford). The interview schedule was developed in collaboration with the course providers, when common research interests were uncovered

(**Appendix D**). The schedule had three distinct parts. The initial narrative component was prompted at the start of interviews. Patients were asked how their injury occurred and what happened to them until the moment a treatment decision was made. Topics of special interest for an interviewer included the way they were approached about taking part in a clinical trial and what influenced their decision about participation and/or treatment. They were left free to develop their stories, only occasionally being interrupted for clarification or more in-depth explanation of a new, interesting or important theme. This aimed to reveal the issues and topics that mattered most to patients when making a decision about trial participation. The intention was also to allow interviewees to express themselves, to relax and find their comfort zone during the interview, thus enabling them to bring back memories of the event that had happened up to two years previously.

This retrospective recollection of events that happened a considerable time prior to an interview relied on the patient's memory and their verbal report of those memories. This can be viewed as a potential weakness of the selected approach. However, this time lapse may have clarified truly important issues that really mattered for many of the interviewees.

The initial narrative part was followed by showing and discussing the PTIV. For some patients this refreshed not only memories of the video itself, but also of the trial recruitment process in general. Patients were

free to interrupt the video to make comments and raise queries, or to leave these until after the viewing was complete. Some important topics, such as 'clarity of information' in the video, were prompted if not commented on spontaneously. Being a trainee orthopaedic surgeon and part of the trial set-up team helped me to appreciate the difference between the intended impact of the provided trial information and patients' interpretation.

Finally, the PEACE results for a patient's own calcaneal fracture were shown. This was a completely new experience, so time was taken to explain result diagrams and to answer queries. The interviewees were then asked to imagine that these results were available at an earlier stage and used as a basis for inviting them to take part in the trial. Their reaction, and in particular the way that this would influence their decision, was recorded.

As a first step, two interviews were conducted with an experienced interviewer-researcher from the Health Experience Research Group, University of Oxford. This allowed practical interviewing experience to be gained and adjustments to the interview schedule to be made. Other interviews were conducted independently by myself, seven of them in patients' homes. The shortest interview was 25 minutes in duration and the longest took over an hour.

Interviews were recorded with an Olympus digital voice recorder VN-5500PC. Hand written notes of thoughts and ideas occurring during interviews were also taken. Two interviews were transcribed by the Health

Experience Research Group, one by myself and the other by a transcriber registered with the University of Warwick.

Thematic analysis (Guest, MacQueen et al. 2012) starts with getting familiar with the data and generating initial codes. I was familiar with the data, because I interviewed all participants and recorded my initial impressions, for example the emotional context, in research notebooks. Coding is the primary process for developing themes from the raw data prior to interpretation. It recognises important and meaningful parts of a narrative from the subject's point of view. This is often reflected in labelling codes with the terminology used by participants. To generate codes, I listened to interview audio recordings while reading through transcripts and I used notes taken during interviews. I used QSR NVivo 8 software that facilitated the interview data management and the coding of emerging topics.

As the coding progressed simultaneously with the data collection (interviews), codes were grouped into common themes. They were revised and re-grouped as further data emerged, evolving as a cyclical process of constant data comparison. Eventually, a number of themes formed an outcome of coding for analytic reflection. At this stage the themes related to the research question were reviewed and refined, looking for connections and formation of coherent patterns. These patterns are described and explained in the relevant **chapters 4.3.2, 5.2** and **6.1**. The qualitative research supervisor (Dr Ann Adams, Warwick Medical School)

continuously monitored and cross-checked the data analysis at all stages.

When analysing interviews it became apparent that some patients had broadly similar responses and attitudes towards the invitation to take part in the RCT. After discussion with the supervisor, the typological analysis (Holloway and Wheeler 2010) was applied in view of this emerging picture. Understanding and anticipating certain response patterns from potential trial participants may help to improve the trial recruitment process, especially with a view to developing a new methodology application. A psychological model of clinical decision-making as a classification process (**Fig. 3.4**) was adapted from work by Adams et al. (2008) to facilitate a structured approach to the analysis of interview data that relates to a patient's decision-making process.

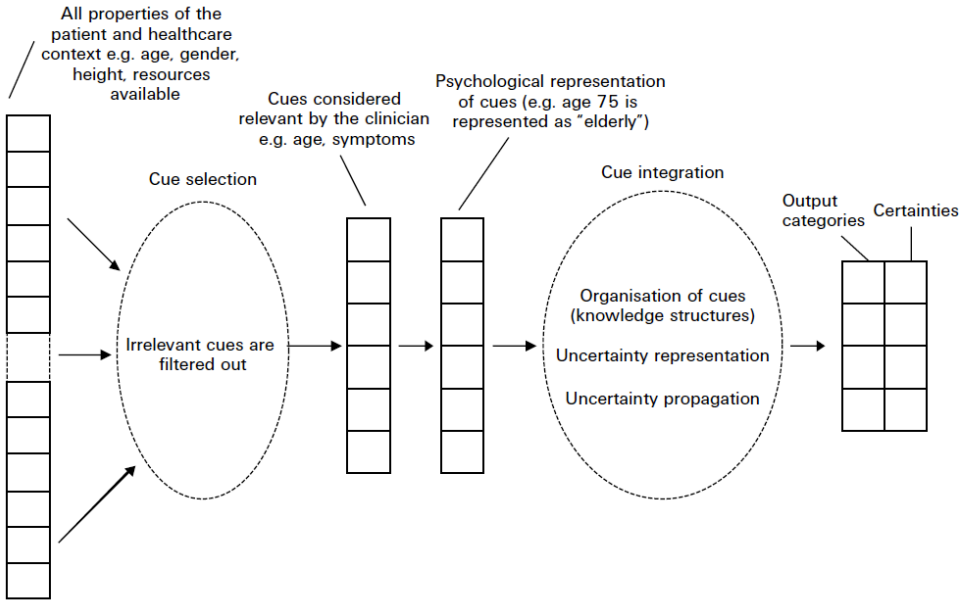


Figure 3.4. A psychological model of clinical decision making as a classification process. (Adams et al., 2008)

Buckingham and Adams (2000) analysed a multitude of clinical decision-making theories that were confined to different discipline contexts. The underlying similarities were identified and allowed the development of a unifying framework for interpreting decisions across different clinical domains. In particular, nursing and medical clinical decision processes could be analysed and compared directly. My interview data suggested that the UK HeFT patients were put in a similar position to clinicians making decisions when invited to take part in the trial and given a lot of clinical information about the choice of two very different treatments for their injury.

The components of the Buckingham & Adams framework were transferred into a master table (**Table 3.1**) to adapt it for analysis of the patient decision making process. The table was populated from every interview according to patients' responses (**Appendix H**). The first column called 'Patient and context attributes' listed the interviewee characteristics with identifier. The next two columns ('Cue selection' and 'Relevant cues') presented factors that influenced their decision process, from a selection of key factors to those more broadly supporting the decision. Next came the emotional context in the 'Psychological representation of cues' column as described by patients and how they weighed or conceptualised the relevant factors. Different sources of information and knowledge, such as prior experience, media and online resources, other people's opinions, including family and friends, were listed in the 'Cue integration' column.

Patient and context attributes	Cue selection	Relevant cues	Psychological representation of cues	Cue integration	Potential outcomes (risk assessment)	Certainties	Outcomes Happy?
CH019 – female, 18-40, unemployed	- I did ask if I could be part of the trial, but just be the operation side but they wouldn't let me.	- they're just given your name or something. They weren't given a lot of information and then they just said operation or non-operation, so that for me was one of the things I didn't understand.	- I didn't want then, after having that on for so long and all the pain and everything, I didn't want to end up having to have an operation anyway - I think I knew straightaway. - I knew at the time it was a new thing and they really, really wanted people to... So I did feel in a way that I was kind of letting them down. - To us, it wasn't a fine balance. It was completely the operation – no doubt about it.	- the way I looked at it is that if something is broke, it needs fixing - Because they'd said the heel was shattered, I didn't feel as though just having a plaster cast on was going to sort it	- Because of the arthritis... R: ...The bones the way they are, the heel changing shape... R2: ...The heel would be out of shape and deformed, so we wanted her to get back to as normal as possible. It doesn't matter about a bit of pain does it to start with, or being cut open? R: No.	- at the time I don't think it was confusing but I was certain that I wanted to have the operation. - there are going to be people that hate operations and dread having one and would prefer to have the opposite way	- no trial - surgery - very happy.. He's a very good surgeon. Well, after the operation I mean everything kind of healed really well. I was walking and I could move my foot and all of that. He was quite proud as well.

Table 3.1. A patient decision making analysis framework about clinical trial participation. (Illustrated with the case from chapter 6.2.2, shortened version)

The 'Potential outcomes' column identified patient expectations and concerns about the possible effects of either the experimental or control interventions. The next column 'Certainties' described background beliefs upon which a decision was based. Finally, the actual decision about whether to join the trial was stated in 'Outcomes' column together with the patient's reflection about it, after having experienced a chosen treatment.

This structured approach allowed direct comparison between interviews, and in particular, identification of recurrent themes. This is different however from the thematic analysis described earlier, aiming to identify the important decision making components that influence a patient's decision (concerns etc reflected in the themes). The use of the model organises these themes to clarify the decision making process. In turn, this leads to better understanding of the mechanisms for patients' decision making, such as factors and potential outcomes that are most influential in shaping the decisions they make. This should help to recognise the type of patient response in future similar trials in order to anticipate and target better their information needs and how best to approach them about the issue of trial participation, with the aim of improving recruitment.

Responses were compared and those showing similar patterns were grouped together to form a separate table for each emerging type of patient stance. This material was cross checked by, and discussed with, the qualitative research supervisor. One example of tabularised

interview material for patient types presented by more than one patient is demonstrated in **Appendix H**. All patient types with quotes are described in detail in **Chapter 6.2**.

Having outlined in this chapter the methods used to approach the research questions posed in **chapter 1**, it is now possible to describe how these methods were used to attempt to answer these questions. The next chapter explains in some detail how deconstructing the ethical and theoretical basis of clinical research helps to build a novel methodological framework for patient recruitment that may become a valuable alternative to current standard approaches in the difficult environment of challenging surgical trials.

Chapter 4 Study A: Development of the PEACE methodological framework

This chapter describes the development of a new methodological framework for patient eligibility assessment in a challenging surgical trial to address the first research question from **Chapter 1.6**:

Is it possible to develop a methodology that integrates/transfers the principle of Clinical Equipoise into a clinical trial recruitment process?

The framework is based on elements of standard clinical care, where for instance a clinician considers treatment options for a case and undertakes risk assessment about the suitability of one or another treatment. If a case is difficult and there is no clear evidence in favour of one or another treatment, it is good clinical practice to discuss and listen to one's peers before making a final decision, or indeed agree a collective treatment decision with colleagues. The proposition of this study is that every potentially eligible case for a challenging surgical trial should be treated in this way. This proposition is adopted firstly because the main reason for instigating a clinical trial is the lack of definitive evidence in favour of one or another treatment, and secondly because fixed pre-set eligibility criteria are an inadequate basis for complex clinical decision making. The challenge is then to develop a feasible system to assess clinical cases in real time during the course of a trial.

The clinical decision making system described in the following sections combines statistical methods, in order to elicit and assess opinions, and modern on-line technology to allow immediate transfer of assessment data to the trial management team. The formal statistical methods necessary to implement the clinical decision making system were developed collaboratively with Dr Nick Parsons (Statistics and Epidemiology, Warwick Medical School) and are outside the scope of this thesis. The focus here is on the underlying conceptual framework and interpretation, rather than details of the implementation which are described in detail elsewhere (Parsons, Kulikov et al. 2011).

Three stages of the methodological framework development formed the Collective Uncertainty Project and were outlined in Chapter 3: (i) online tool, (ii) statistical model and (iii) proof of principle test within a real trauma trial. These are now described in detail in this chapter. This was complemented by end-user (surgeon) feedback and analysis of the reactions and understanding from patients' perspective as research subjects (4.3.1 and 4.3.2). The hypothesis for the Collective Uncertainty Project (CUP) is that clinical cases from a trial can be assessed online by a panel of experts in order to provide the data necessary to quantify the level of confidence or equipoise about treatment choice.

4.1 Methods to elicit and quantify clinical equipoise

A web based tool was developed for collecting treatment outcome prognoses from clinicians for specific clinical cases. A dedicated CUP webpage (http://www.warwick.ac.uk/go/heft/cup) was set up, using the University of Warwick Sitebuilder software (IT services, University of Warwick, UK) for building webpages on the University virtual platform. It had a link to enable a member of a trial research team to submit clinical data, including images such as Xrays and CT, to the CUP team. Data were published in an anonymised manner on a password protected voting page (**Fig. 4.1**). Participating clinicians were alerted to a new case by email or SMS via a secure Warwick University online forum. Emails contained web links to the published cases and an invitation extended to examine the available data and estimate outcome probabilities for contrasting interventions. Outcome probabilities provided estimates of expert opinion on whether a patient would get better or worse by various degrees if the procedure in question were applied.

When selected, case web links opened relevant case voting pages. Clinicians were asked to enter their usernames and passwords in order to access the published clinical data. Each voting page was an 'image gallery', which allowed clinicians to see the thumbnails at a glance, and zoom into the detail with a single click as necessary. The right hand column presented relevant patient data, such as age, occupation and the circumstances leading to the injury.

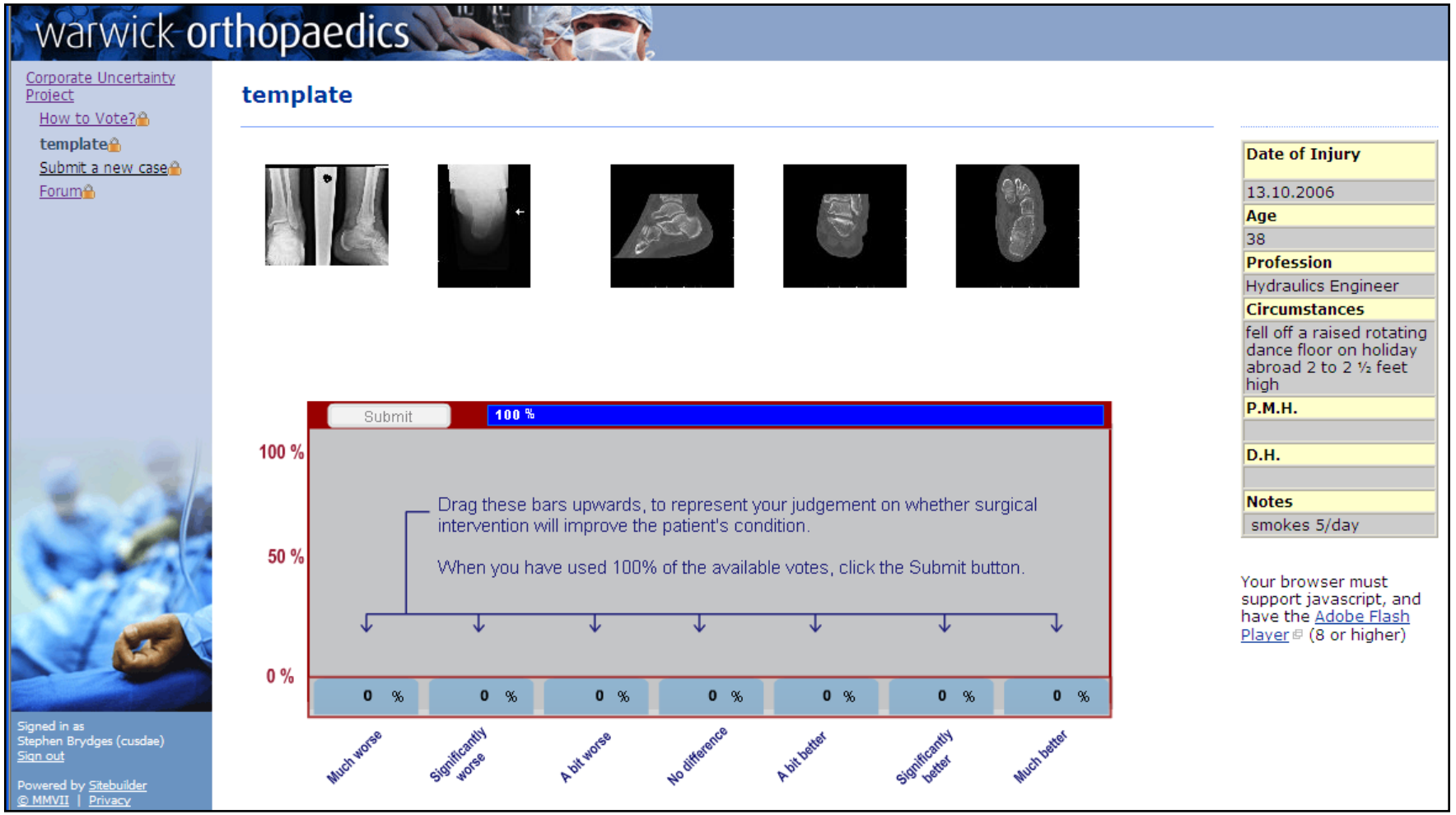


Figure 4.1. Collective Uncertainty Project (CUP) voting webpage (template).

After assessing the clinical data available for a given patient, the clinician was able to scroll down to an interactive voting scale, featuring bars (initially set at zero) above each of seven outcome categories indicating whether after surgical intervention the patient's condition would get *"much worse"* (1), *"significantly worse"* (2), *"a bit worse"* (3), *"no difference"* (4), *"a bit better"* (5), *"significantly better"* (6) or *"much better"* (7). Each outcome prognosis bar could be dragged with a left-click of the mouse to a desired percentage, which was then reported numerically over the bar. It was important and intentional that clinicians were asked to give an honest outcome prognosis, rather than simply to express their personal preference for one or another treatment. This was done specifically to reduce preference bias. Once the assessment reached a total of 100% (reflected in a digital window in the upper left corner of the scale) the submit button allowed the data to be sent to the trial lead for analysis (**Fig. 4.2**).

Once submitted, the votes were stored online within FormsBuilder. This is an add-on tool to Sitebuilder, that enables creation and maintenance of different types of online forms to facilitate interactive features, such as remote data submission by website users (**Fig. 4.3**). At any time the CUP team could download the submitted votes in Excel format for more detailed statistical analysis.

Initially the system was tested in a pilot study by seven Orthopaedic surgeons from five UK hospitals. Ten retrospective calcaneal (heel bone) fracture cases were selected and adjusted to represent typical variability.

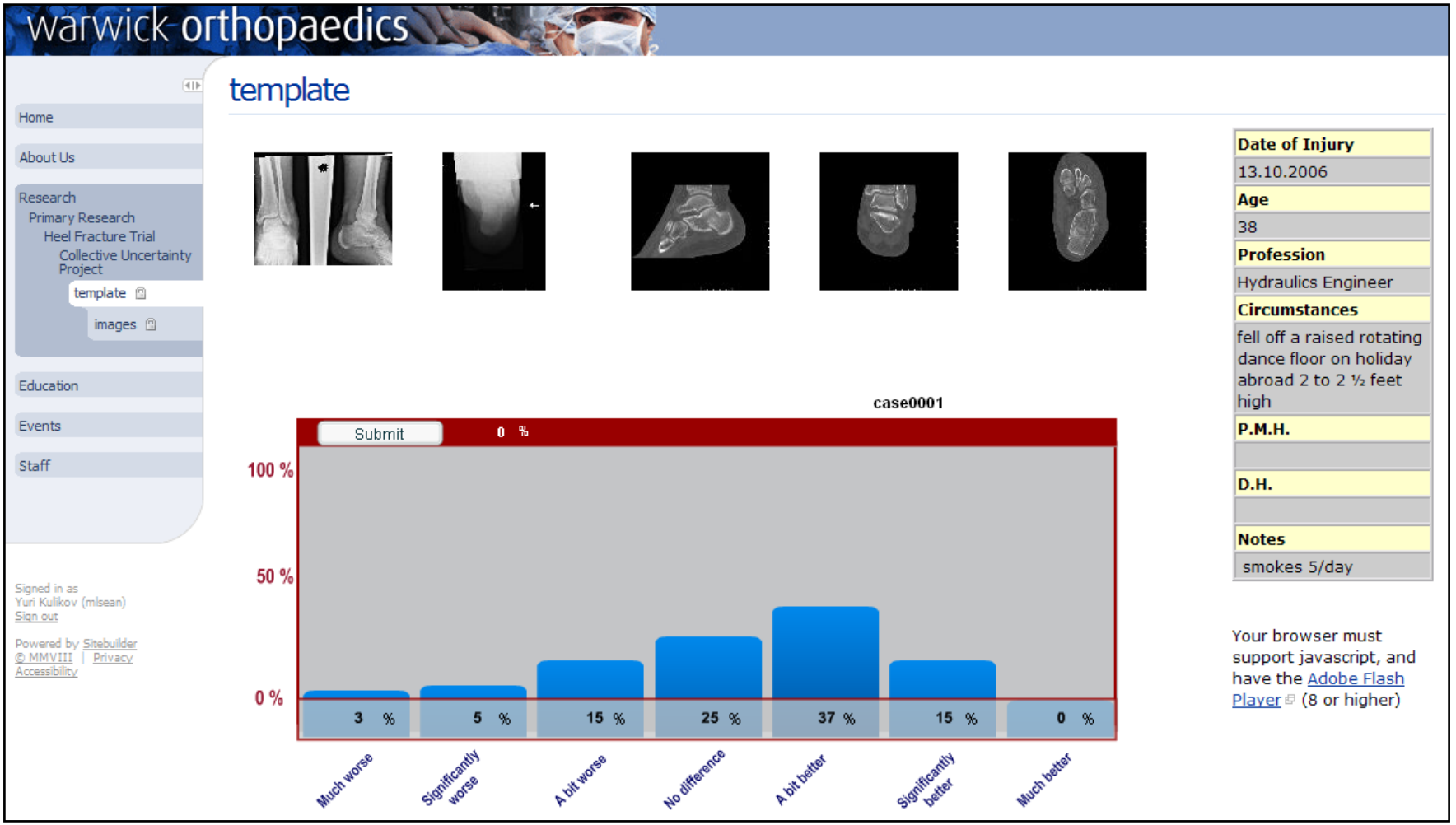


Figure 4.2. CUP voting page: case outcome prognosis ready for submission.

The surgeons followed the instructions on the website with online and telephone technical support available; no specific training was given. When voting on all ten cases was completed, surgeons were asked to fill in an evaluation questionnaire (**Appendix K**). The available clinical information was found sufficient and the whole process user friendly by all participating surgeons. Voting on a single case never took longer than 5 minutes. All surgeons responded and were willing to participate in further research on the subject.

FormsBuilder

Done

Query Criteria

Filter

Start Date 07/02/2006

End Date 07/03/2007

Apply Filters

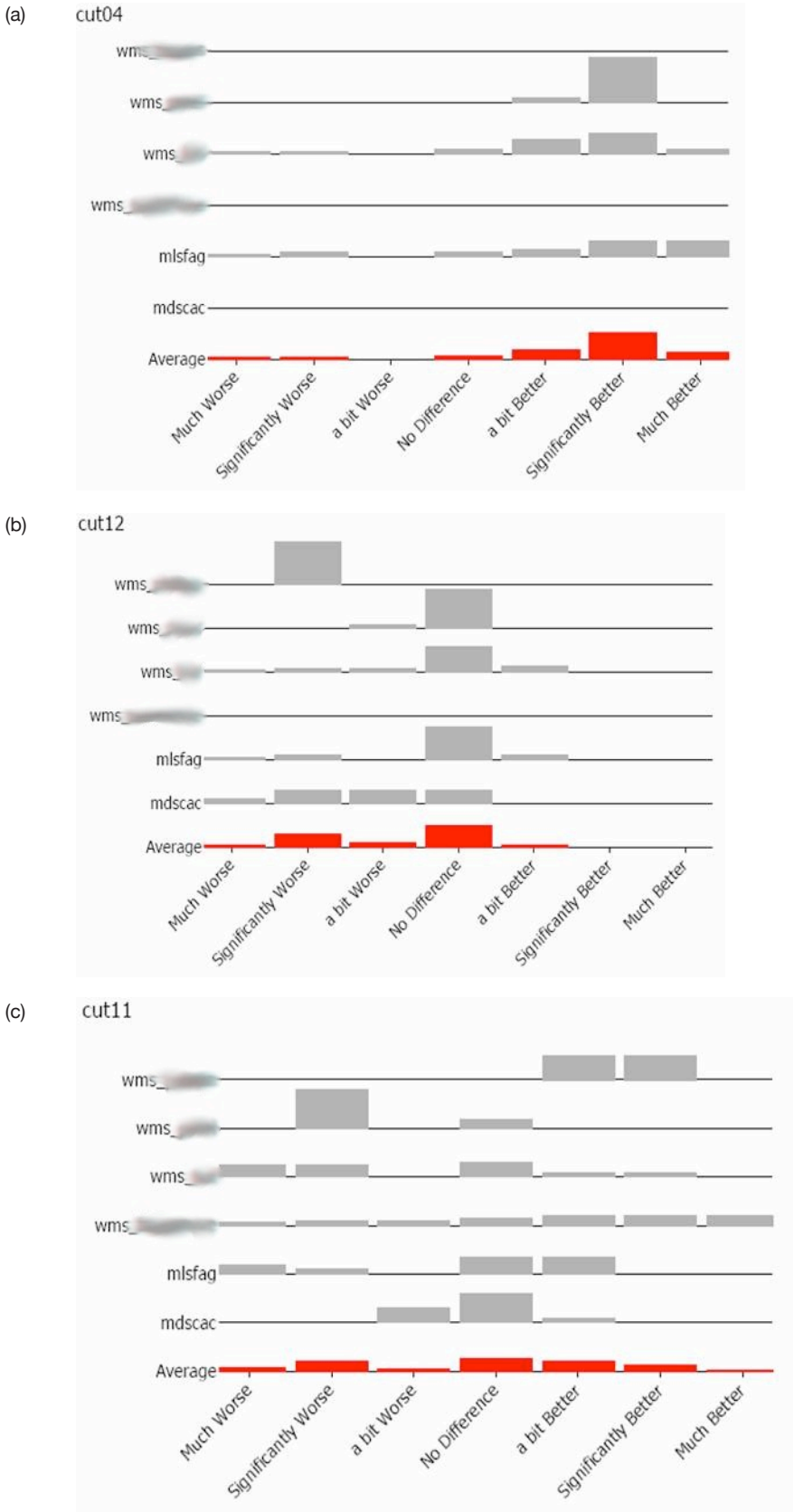
List of Submissions

Submission time	Case number	much worse	significantly worse	a bit worse	no difference	a bit better	significantly better	much better	Uni ID no	usercode	user name	user email
06/03/2007 12:06	helpvote	0	22	15	20	43	0	0	0370679	cusdae	Stephen Brydges	Stephen.Brydges@warwick.ac.uk
06/03/2007 10:50	case0001	18	32	39	11	0	0	0	0370679			
05/03/2007 17:52	case0001	44	44	12	0	0	0	0	0370679			
22/11/2006 17:57	cut19	2	3	3	8	30	33	21				
22/11/2006 17:55	cut_06	5	7	8	12	25	33	10				
22/11/2006 17:54	cut11	5	6	7	10	27	29	16				
13/11/2006 17:40	cut16	0	0	0	0	30	70	0				
13/11/2006 17:39	cut14	0	0	0	100	0	0	0				
13/11/2006 17:38	cut10	0	0	0	10	0	90	0				
13/11/2006 17:37	cut19	0	0	0	0	100	0	0				
13/11/2006 17:36	cut11	0	80	0	20	0	0	0				
13/11/2006 17:35	cut_06	0	0	50	50	0	0	0				
13/11/2006 17:33	cut12	0	0	10	90	0	0	0				

Figure 4.3. Submitted votes in FormsBuilder.

Borrowing from the concept of subjective logic (Jøsang 1997; Jøsang 2001), a pooled expert opinion can be thought of as comprising three distinctive aspects: *belief*, *disbelief* and *uncertainty*. *Belief* represents the tendency of experts to expect a particular treatment to perform better for a particular patient (case); this manifested itself in the tendency for the experts to drag bars up in the higher (Right) end categories of the voting scale (**Fig. 4.4a**). Conversely, the level of *disbelief* is equated with the tendency for a particular patient to do worse with the given procedure; this manifested itself in the tendency for the experts to score cases in the lower (Left) end categories of the voting scale (**Fig. 4.4b**). The *uncertainty* associated with the *belief* and *disbelief* represents the spread of the data across the opinion range (**Fig. 4.4c**)

The pooled collective opinion as a combination of *belief*, *disbelief* and uncertainty can be mapped on a ternary plot that displays these characteristics in a manner that allows them to be compared to decision rules that partition the opinion space. A ternary plot is a plot for displaying three variables which sum to a constant; in our case *belief*, *disbelief* and *uncertainty*. It graphically depicts the ratios of the three variables for each case as positions in an equilateral triangle, thus allowing patient cases to be compared and contrasted simply in a two-dimensional diagram. This ability to visualise and compare collective expert opinions about different cases is at the heart of the Patient Eligibility Assessment through Collective Equipoise (PEACE) described next (**chapter 4.2**). Once completed, the



(a) consensus about better outcome after operative treatment, (b) Consensus about no better or worse outcome after operative treatment and (c) Uncertainty (equipoise) about outcome after operative treatment.

Figure 4.4. Opinions about three cases expressed by surgeons in the pilot study.

feedback about the level of uncertainty and advice about trial eligibility is emailed back to the submitting trial team. The assessment process from case submission by a trial team to a feedback email (**Fig. 4.5**) can be completed within a 48 hour time frame.

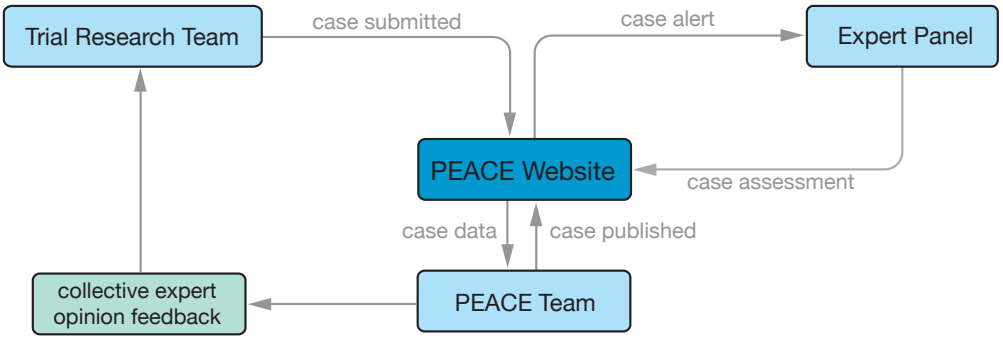


Figure 4.5. Web-based assessment of a clinical case by a virtual expert panel.

4.2 Patient Eligibility Assessment through Collective Equipoise (PEACE)

In the previous section, methodology was described that showed how to elicit and pool expert opinions concerning a clinical case in real time. The focus in this section is to explain the underlying conceptual framework for analysis and interpretation of clinical equipoise levels based on pooled opinions. In particular, it will examine how decisions about trial eligibility can be made dependent on the level of clinical equipoise. The process may superficially appear complex, but it is in reality rather simple and easy to explain to clinicians in lay terms. The remainder of this section provides a more formal (technical) description of the important components of the Patient Eligibility Assessment through Clinical Equipoise (PEACE) process for those familiar with recruitment processes and decision making in this setting. The following sub-section (**4.2.1**) provides a lay summary that puts the process in a wider context and as such may appeal more to a clinical audience.

The PEACE process is outlined schematically in Figure 4.6 using examples of expert clinical assessments in three selected clinical cases. To express a pooled opinion mathematically, a distribution curve can be fitted to pooled data for each case marked i, ii and iii to estimate parameters that characterise the fit using concepts of belief, disbelief and uncertainty, according to the principles of subjective logic (Jøsang 1997). Belief

represents the tendency of a clinical expert to expect a trial intervention to work better, while disbelief represents the tendency of an expert to expect a trial intervention to do worse for a patient. The uncertainty associated with the belief and disbelief is expressed by the expert through the spread of the data between belief and disbelief. For example, in cases presented in Figure 4.6, the scores of some experts are concentrated around one category, while other experts spread out their prognosis between several categories. When a distribution curve is fitted to several expert opinions in the same case, it becomes a collective expert opinion for this clinical case. It is expressed in the same way as scores from individual experts through *uncertainty* spread in different categories between *belief* and *disbelief*.

Values informing a distribution curve can then be mapped as a dot onto a ternary plot (opinion space) that represents belief, disbelief and uncertainty as positions in an equilateral triangle, where each corner of the triangle represents the highest level of belief (positive outcome), disbelief (negative outcome) and the level of uncertainty, that together constitute a pooled expert opinion. The pooled opinions representing greater levels of belief and greater levels of disbelief are mapped towards the right-hand and left-hand corners of the triangle respectively, while a higher level of uncertainty will move an opinion towards the uncertainty apex (**Fig. 4.6**). A detailed statistical methodology that allows this way of quantifying the level of clinical equipoise from voting data for a panel of experts for an individual clinical case has been published (Parsons, Kulikov et al. 2011) (**Appendix I**).

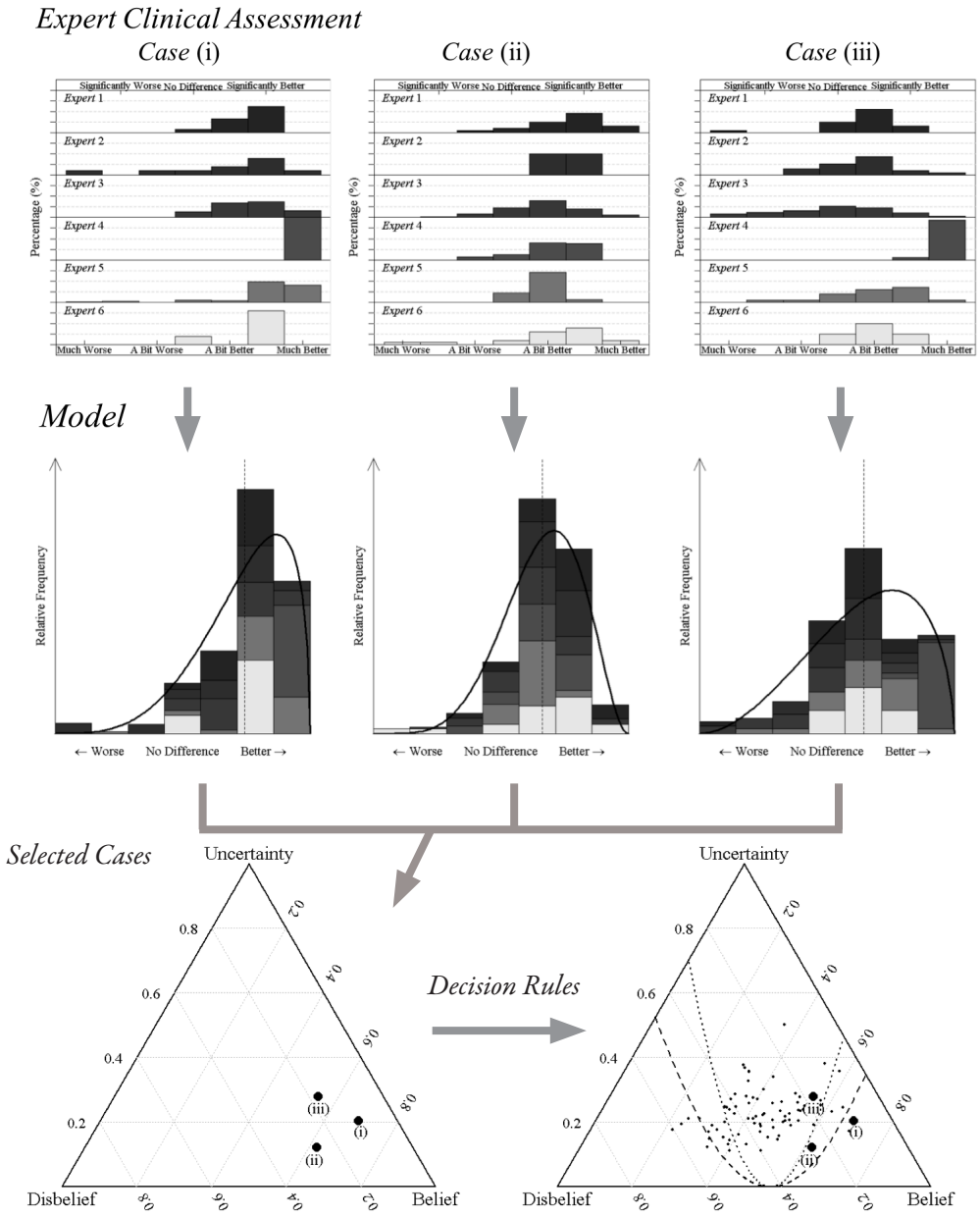


Figure 4.6. Expert opinions analysis - schematic illustration for three real life calcaneal (heel bone) fracture cases (UK Heel Fracture Trial).

When several cases are mapped on the opinion space, their level of equipoise can be compared and/or assessed against provisionally agreed decision rules. Decision rules represent the level of clinical equipoise between clinicians that deems a clinical case eligible for a trial. They can then be imposed onto the opinion space, shown as interrupted and dotted curves in **Fig. 4.6**. Patient eligibility for a trial is then dependent on the opinion dot position in relation to a decision rule line or lines. The framework is designed as an open platform, so decision rules can be discussed and applied according to the needs of a specific clinical trial. However, in this work a baseline 80:20/70:30 eligibility decision rule is proposed according to the work by Johnson et al. (1991), described in **chapter 3.1**.

Feedback from the pilot study, described earlier in this chapter, indicated an agreement between surgeons that they would consider operative treatment only if it is likely to make a patient better. Based on these findings it was determined that the point of equipoise was located slightly to the right of the centre point of the assessment scale towards belief between no difference and a bit better. The 70:30 and 80:20 equipoise distribution lines have been superimposed on the opinion space accordingly, shifted to the right from the no difference point between outcomes in the middle (**Fig. 4.6**). Collective opinion dots appearing inside the 70:30 zone, such as case (**iii**), are considered as cases ethically acceptable by the public for the trial, because collectively experts give less than a 70% chance of either

improved or worse outcome if one or another treatment is chosen. Cases mapped outside the 80:20 zone, such as case (**i**), indicate too high a level of agreement between experts about likely outcome for a treatment to be ethically randomized into a trial and therefore were deemed not eligible.

The limits of equipoise obtained by opinion surveys are generally not precise, cannot be clearly translated into a probability and depend on various factors such as the level of emotional attachment to the subject of the research and individual variations in approaching uncertainty. For these reasons, a zone between the 70:30 and 80:20 decision rules on the opinion space was viewed as a 'buffer zone' reflecting an "order of magnitude, rather than a precise cut-off limit" (Johnson, Lilford et al. 1991, p. 33). Exhaustive permutation resampling aided decision making for those cases in the buffer zone, such as case (**ii**); the statistical process outlined above was repeated for every possible combination of experts in the panel, who expressed an opinion on that case. The results of this process can be visualised as a cloud of smaller dots on the opinion space, representing possible collective opinions based on real expert votes. In order to decide eligibility for cases mapped in the buffer zone, the number of possible opinion dots in the eligible zone inside 70:30 and the not-eligible zone outside 80:20 can be compared. If relatively more combinations of expert opinions are mapped to inside the 70:30 rule, then the case is deemed eligible for a trial. If on the other hand more opinions are mapped to outside the 80:20 rule, then the case for inclusion in a trial cannot be ethically justified.

4.2.1 PEACE: a lay summary

In summary, the PEACE framework allows one to collect opinions from a group of experts about a clinical case in real time. Opinions for each case are pooled using simple rules and processed through the application of statistical methods (i.e. fitting a model distribution and estimating a number of parameter attributes that characterise the expert opinions for the case), resulting in a collective opinion that can be mapped onto an *opinion space*. The results of the pooling are estimates that represent the belief, *disbelief* and *uncertainty* that the intervention will be effective for each case. These three attributes are scaled so that they sum to one, in the same way that probabilities do; this ensures that for instance as our *belief* in the effectiveness of a treatment increases, then our *disbelief* and/or *uncertainty* must decrease. The simplest graphical way to represent three quantities that vary in this way is what is known as a ternary plot (see **Figure 4.6**). A ternary plot allows one to plot three values in a natural manner for each case such that an increasing value for each attribute results in the plotted point moving towards the apex of the triangle representing that attribute. The results of many cases for a single study can be plotted in such a way, showing the full range of expert opinions on each case in the study (**Fig. 4.7**). Decisions about whether or not to include individual cases in a trial can be made based on the plotted position on the ternary plot, in this case called opinion space. A decision rule should be decided on before a study begins; these may be based on previously published work or be completely new ideas. Rules are

superimposed graphically on the *opinion space*, effectively dividing the space up into a number of regions which guide the user as to the appropriate decision for the case; (i) recruit the case into the study and randomize, (ii) allocate to the test treatment or (iii) allocate to the control treatment. Application of the Patient Eligibility Assessment through Clinical Equipoise (PEACE) process was tested in the context of a real life trauma trial comparing operative and non-operative treatment after heel fracture. This is described in the following section.

4.3 Modelling the PEACE framework in a challenging trauma trial

The PEACE methodological framework was introduced as an independent research project within the UK Heel Fracture Trial (UK HeFT), which compared operative and non-operative treatment for displaced fractures of the calcaneal (heel) bone across 22 hospitals in England and Wales (**Chapter 3**). The project had a separate ethical approval and a consent form, in addition to the main trial (**Appendix C**). This allowed inclusion of both those patients who took part in the UK Heel Fracture Trial and those who declined, as soon as the patient met the trial eligibility criteria. To avoid interference with the clinical course, patients were asked permission to use their data at the 6 weeks follow-up clinic or later.

The instruction presented to surgeons was the same as in the pilot study: "Drag these bars upwards, to represent your judgement on whether surgical intervention will improve the patient's condition" (**Fig 4.1**). The UK HeFT compared operative and non-operative treatment, where surgery was seen as potentially beneficial unless risks were overwhelming or the potential for improvement was small compared to the risks. Therefore 'belief' that surgery can make a patient better implies intention to do surgery, while 'disbelief' implies the intention to avoid a surgical intervention, in other words to choose a conservative option.

Patients who met pre-set trial eligibility criteria and were initially approached

by a member of the research team about the possibility of participating in a trial were seen by a member of the research team at the six week follow up clinic or later. They were then asked permission for their anonymised clinical details to be distributed among a panel of expert clinicians for an opinion regarding the effectiveness of the proposed treatment; they were assured that this was a separate matter and in no way influenced already initiated treatment. Clinical data including X-ray and CT scan images from consented patients were made available on a secure website managed by eLab at the University of Warwick, and all panel members were alerted by email and optional text message to the posting of a new patient and asked to offer their personal opinion about the likely prognosis of the proposed treatments. The expert assessment panel included 12 surgeons from nine hospitals. All surgeons were foot and ankle specialists and acted as principal investigators in their individual trial centres.

Three trial centres agreed to submit their patients' data to the Collective Uncertainty Project. Seventy-seven calcaneal fractures in 70 patients were assessed during three years of the UK HeFT. On average six surgeons voted in each case (minimum three and maximum nine). Collective opinion dots for all cases mapped on the opinion space. Their position was assessed against the 80:20/70:30 eligibility decision rule superimposed on the opinion space, as described earlier in **4.2**. Collective opinion dots for all seventy-seven fractures can be seen in **Figure 4.7** and are explained below.

Cases located in the eligible zone inside the 70:30 rule are shown as black opinion dots. Their location suggests that sufficient uncertainty between experts has been demonstrated to justify their eligibility for trial participation. They make up 74% (57) of all assessed cases.

Collective opinion dots outside the 80:20 rule zone are shown in red. Their position indicates that the panel experts reached consensus about likely treatment outcomes for 7 (9.1%) cases : two in favour of operative treatment (located towards the lower right corner of the opinion space) , while five other cases were seen as certain to produce poor results with surgery (located towards the lower left corner of the opinion space).

Finally, for 13 cases located in the buffer zone between 70:30 and 80:20 rule lines (yellow dots) exhaustive permutation resampling had to be performed, as described earlier in **4.2**. After the number of dots inside the 70:30 and outside the 80:20 zones was compared out of the cloud of possible collective opinions for each case, eight of them were added to the eligible pool. This makes up 84.4% of patients from the three UK HeFT centres invited to the trial participation according to pre-set fixed eligibility criteria, for whom clinical equipoise was confirmed.

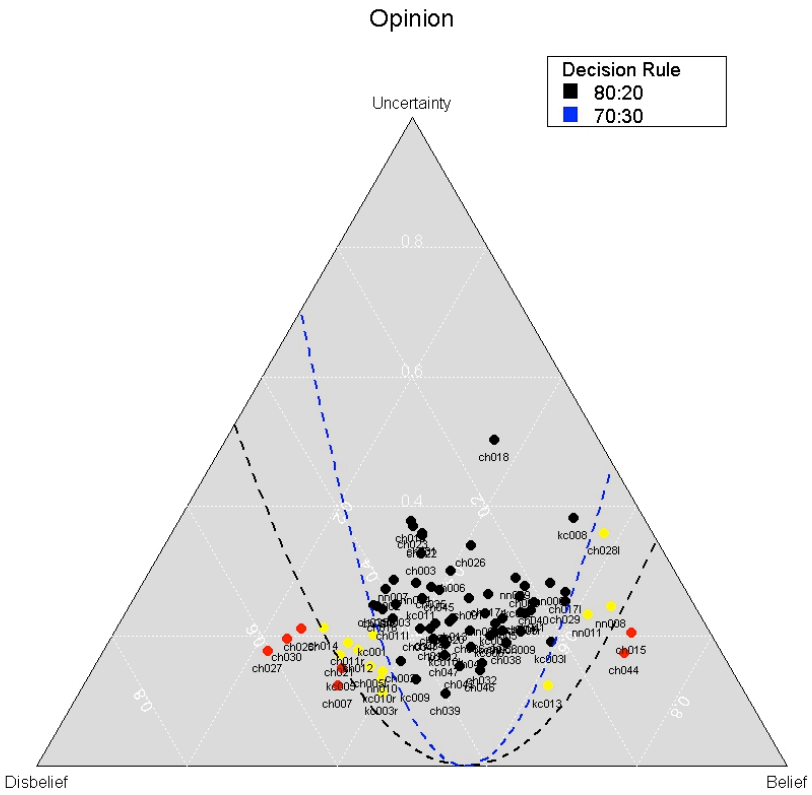


Figure 4.7. The PEACE opinion space for the Collective Uncertainty Project.

4.3.1 Surgeon feedback

A feedback survey from surgeons collected data informally during the research project and then formally via questionnaires (**Appendix G**) when the patient recruitment and the voting on all cases had been completed. Eleven out of our 12 panellists returned their feedback forms. Ten of them indicated that this was a low research time methodology, meaning that little time and effort was required for case assessment. All eleven offered support for introducing the framework in surgical RCTs, even if in challenging ones only. In cases where consensus about treatment outcomes was present between surgeons, five of our experts would still offer random treatment allocation within a clinical trial context, four would choose a treatment according to consensus, while two would leave the final decision to the treating surgeon.

Informal feedback revealed difference in interpretation of the treatment prognosis by two surgeons who provided consistently 'strong' opinions for assessed cases. Opinions were viewed as 'strong' if all 100% of possible votes were allocated to one or two neighbouring categories on the treatment outcome scale (**Fig. 4.2**). This highlighted the necessity of clear explanation and instructions to experts about the scale usage.

4.3.2 Patient feedback

Patient feedback about the PEACE concept was collected formally during the final part of patients' interviews (**chapter 3.3**). All twenty two patients who agreed for an interview were from the Collective Uncertainty Project database. This means that at some point prior to the interview they all consented for their anonymous clinical data to be used for a study about comparing expert opinions. It seemed only fair and logical to give participants some form of feedback. The aim was to learn about their understanding and views about possible introduction of the framework in future similar trials.

Towards the end of interviews, I suggested to participants that they should see the study results in the form of bar charts with combined surgeons' votes for their own calcaneal fracture. They were all interested to see these:

> *"if you had several surgeons looking at those X-Rays and then giving you that result, I think it would be better"* (CH003, 46 year old male, manual worker)

For many, looking at the charts helped with understanding the need for a trial and presented a more balanced view of surgeons:

> *"But it also shows you if these are surgeons that they're not all pushing for 'Oh it would have been better if I'd have operated'."* (CH018, 76 year old male, retired)

This was more in line with how many participants imagined that random allocation to a treatment during a trial would occur:

> **Respondent**: *"Yes and how does the computer decide?"*
>
> **Interviewer**: "Completely random."
>
> **Respondent**: *"But with the computer you must put some information in to say 'this is what the X-Ray is showing at the moment' and then entering it and it makes the decision of the best, so self-healing or...?"* (CH026, 42 year old female, manual labourer)

Seeing the chart settled doubts for those patients:

> *"when I looked at it then [during the trial] one of the questions I asked the next day was quite a simple question really, which is - there must be a ratio where an op is the only way forward and how would you get to that point, in a one to ten scenario where anything from seven and above is an op and anything below seven is a non-op. That's where I was struggling in my head to get to, because I couldn't get that answer."* (CH020, 43 year old male, office worker)

The idea and the theory behind the charts were easily understood:

> **Respondent 2:** *"Yes, I find it very interesting."*
>
> **Respondent 1:** *"I understand that, yes."*

Respondent 2: *"It's understandable and very interesting."*

Respondent 1: *"It is, because it shows you there's a mixture of opinions."* (CH018, 76 year old male, retired, and his spouse)

This was the case even with those who usually struggle to understand charts:

Respondent: *"I don't really understand charts anyway."*

Interviewer: *"But you found you could understand this one?"*

Respondent: *"Yes."* (CH036, 25 year old male, skilled self-employed)

This young man found an interesting and correct way of interpreting the chart he saw:

"Yes, it does look very clear now. I mean like, you know, I mean to me like there's a lot more surgeons who are really saying it makes it a bit better, but it swings in roundabouts really, doesn't it?" (CH036, 25 year old male, skilled self-employed)

Yet more detailed interpretation of charts was often misguided, for example, concerning strong votes:

Respondent 1: *"If this was presented to me now, I would say 'I won't have surgery.' If that was presented to me now that's what I'd say; 'I'm not*

having surgery because this man seems to know that I'll probably get worse.' These are just..."

Respondent 2: *"...Sitting on the fence."*

Respondent 1: *"Yes, they're just on the fence. This man is quite confident that I'll get worse."* (CH023, 47 year old male, skilled self-employed, and his spouse)

Although seeing opinions from different surgeons helped to explain uncertainty about a treatment choice and there was general support for it to be used in future trials, many patients felt that advice and guidance from the treating surgeon would be essential:

"I'd still have to discuss it and I'd take the lead from the surgeon that was dealing with me, or the consultant that was dealing with me at the time without a doubt, but it would have definitely helped yes" (46 year old male, skilled)

They felt that such results would be better interpreted and presented by a clinician, rather than given to them directly:

"I mean it is good information but reassurance and what-not doesn't really, you know...to me like people who just think that this is basically a bit of paper and the results. You know, you don't really get reassurance from it do you? To me, to look at that it looks fairly clear, but it's just obviously

that it is like just mixed feelings isn't it?.. I think talking about hearing it from a surgeon is more sort of reassurance than just seeing it on a graph, because obviously the surgeon is going to be doing the work with you isn't he, whereas the graph isn't? So yes, I think to have the surgeon talking to you would be a lot better really." (CH036, 25 year old male, skilled self-employed)

The surgical panel reached a consensus about the treatment of choice for six patients who were interviewed. Four of them did not join the trial. Interestingly, all of them were treated according to the panel recommendation and were very pleased about their decision:

"I'd have gone with them; it's three against one isn't it?" (CH027, 55 year old female, skilled)

Does this mean that surgeons often would find a way to communicate their preference even in the context of RCTs? As one of those patients indicated:

"He explained to me that the fracture was this long, and had it been a bit longer they might have done surgery but he, you know, he thought well, I'd be alright and they ought to leave it, that's fine." (CH027, 55 year old female, skilled)

The other two were randomised and, again, had their treatment allocated in line with the panel recommendation. One of them, a 76 year old retired

lady, was still comfortable with random treatment allocation after seeing the surgeons' opinions. Another patient in a similar situation, a 40 year old academic, was taken aback by the discrepancy between the information he was given when he joined the trial and the results of the surgeons' votes, where they agreed about the preferred treatment option unanimously:

> *"I would think, I would expect that [er] the part of it was that the doctor at least has some doubts about which [er] which treatment to choose ... Of course, the doctor is very experienced and qualified to have his opinion, right, but ethically I think if you are in the trial and you are shown the video which says the doctors are not sure, then this means your doctor is not sure."*(CH015, 40 year old male, academic)

He asked a lot of questions and concluded:

> *"I realise it's not realistic to only take people in the trial where the doctor is completely putting his hands up and saying, [er] "I am, I have no clue." Right? "But [er] it's fifty-fifty." But at least we should discount the, those cases where the doctor is sure about that treatment."* (CH015, 40 year old male, academic)

His conclusion echoed the opinion of most of the other interviewed patients, that randomisation should not be offered when consensus about a choice of procedure is present between experts.

In the next, concluding, part, results of all three stages of the PEACE methodological framework development will be discussed.

4.4 Discussion

The PEACE framework demonstrated a reliable correlation between the levels of uncertainty and consensus about treatment choice for cases assessed during a real life multi-centre clinical trial. Most cases were mapped safely in the eligible zone in line with pre-set eligibility criteria (84.4% match in the UK HeFT population), while a small number were highlighted when consensus about a treatment choice was present between experts. The suggested approach to elicit, pool and quantify expert opinions in order to estimate the level of clinical equipoise was based on a strong ethical background of clinical research and seemed to work well in practice. It is visually simple to understand and easy to use, as evidenced by our expert feedback. The framework is designed as an open platform to be adaptable to a variety of clinical research scenarios. Careful attention and thorough discussion of the question posed to panellists and decision rules to be applied are required before the start of recruitment. Ideally, this should be piloted prior to the commencement of the main trial. It needs to be made clear to clinicians that they are being asked to provide an honest prognosis of possible outcomes, if treated in their own hands, rather than simply expressing a treatment preference.

Patients also had good understanding and a positive outlook on the PEACE concept. Charts with combined opinions from different surgeons about their own injury, which is the corner stone of the Patient Eligibility

Assessment through the Clinical Equipoise, were in line with their own expectations about clinical research and helped with understanding why it was necessary for their kind of injury. There was little doubt from a patient point of view that it is unethical to offer a random treatment allocation in the presence of consensus about a treatment choice between experts. Future use of the PEACE concept in future trials was widely supported. Presentation of assessment results by the treating clinician was favoured by patients in terms of clinical quality assurance. It is also desirable because patients oversimplified and misinterpreted voting results when viewing and attempting to analyse themselves.

It is reassuring that the group of eligible patients identified by the PEACE methodology largely overlaps with patients eligible according to standard fixed pre-set eligibility criteria. It is significant, however, that for a small number of patients there is a clear consensus between experts about one or another treatment being likely to lead to a better outcome. This confirms a concern that most patients involved in the trial expressed in their interviews in **Chapter 7** about random treatment allocation. Fixed pre-set eligibility criteria cannot replicate or replace expert judgement, and it is unethical to offer randomisation in the absence of clinical equipoise. It follows that the PEACE framework offers protection for patients in cases when there is a consensus between experts about a treatment that is likely to lead to a better outcome, even when factors affecting this judgement are not yet known or not expressed in currently available evidence. It is still possible

to research these factors and investigate whether they indeed lead to an expected outcome if patients are offered participation in a study as part of a comprehensive cohort design (Torgerson and Sibbald 1998).

At the same time, what the PEACE methodology can offer is simplified inclusion criteria for the trial eligibility assessment. In the case of the UK HeFT it was clear that severely displaced and comminuted fractures could not be entered into the trial. What was far from clear was how to describe the extent of injury that should not be included. After extensive debates between specialist surgeons involved in the trial design: "Calcaneal fracture with severe deformity, with the lateral wall of calcaneus impinging on the fibula" was agreed as an exclusion criterion. Those who are involved in Orthopaedic Trauma management can readily recognise that this definition is open to interpretation. This came up again and again when Principal Investigators were briefed on patient recruitment: 'what exactly do you mean by this..?' On several occasions during the course of a trial, surgeons called the head office asking about a particular case. If simplified PEACE criteria were used in the UK HeFT, at least 57 more patients excluded with 'fibula impingement' as well as many from other excluded categories marked in the brown box in **Figure 2.1** would have been assessed for trial eligibility. The additional number of eligible patients under PEACE would have more than compensated for the small number of patients for whom a consensus about treatment choice, expressed by the expert panel, would have resulted in their exclusion from the trial (**Fig. 4.8**).

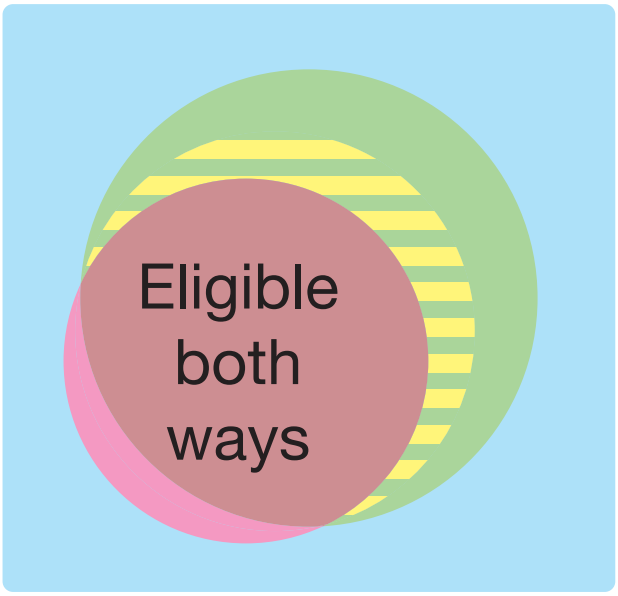


Figure 4.8. Overlap of patient cohorts meeting simplified PEACE criteria for trial eligibility assessment and those eligible according to standard fixed pre-set eligibility criteria in a clinical trial.

Having described the successful design and testing of the PEACE framework, in the next chapter the new approach to trial patient recruitment is described and researched.

Chapter 5 Study B: Patient Trial Information Video (PTIV) recruitment approach

> *"I think it depends on how you word things sometimes doesn't it? It's how you deliver the message, you know."* – a patient eligible for the UK HeFT (CH043).

This chapter describes a new approach to patient recruitment in a trial that combines a standardised audio-visual presentation of the trial information with one-to-one personal support, in order to address the challenge posed in the second research question (**chapter 1.6**):

> *How to achieve clear, impartial and consistent delivery of trial information to patients in the context of a challenging surgical trial, when the compared interventions are obviously different?*

Apart from identifying eligible patients, a treating clinician is not involved in the proposed trial recruitment process. In fact the clinician specifically avoids personal contact with possible trial participants in order to avoid disclosure of their likely personal treatment preference while patients decide about trial involvement. Feedback from both parties is explored (**5.2**), especially considering the question of whether the surgeon's initial absence is notable and significant.

Delivery of clear, comprehensive and impartial information during the recruitment process is a considerable challenge in a clinical trial involving obviously different procedures (Paramasivan, Huddart et al. 2011). It is difficult for recruiters to avoid constant use of 'loaded' specialised terminology when talking to a patient. Often a recruitment pathway is complicated, involving not only different people, but even different specialties; so effective communication is of paramount importance. Finally, expression of treatment preferences, both by potential participants and by trial staff, is an issue.

For the UK HeFT, a new method for approaching eligible patients to inform and invite them to participate was developed, combining a Patient Trial Information Video (PTIV) with availability of a dedicated study team member to deal with any patients' queries and concerns. This combination was designed to provide consistently high quality of disclosed information, strengthened by an individual approach to improve understanding. The aim was to exclude a treating surgeon from initial patient contact in order to avoid a possible treatment preference disclosure, as described in the **UK Heel Fracture Trial Manual** v2.1May08 (p. 10):

> " 3.2 Role of the Principal Investigator
>
> We have prepared a DVD in which the Chief Investigator explains the injury the patient has sustained and the possible treatment options, together with advantages and disadvantages of each method. This is

intended to enable you to take a step back from the process of informing the patient about treatment options, so that you are not put in the position of having to remain neutral when you might have an opinion as to which treatment could be better for that patient.

Once the information process is completed, the research associate will obtain informed consent to join the trial, and you will only have to take consent for surgery in the normal way if that is the treatment to which the patient is randomised. At this point, please make sure you do not re-visit the question of which treatment option might be best; simply obtain consent for the surgery."

5.1 The PTIV approach to recruitment in a trauma trial

The initial PTIV script was drafted according to the Information Sheets & Consent Forms Guidance for Researchers and Reviewers (version 3.2 May 2007) published and regularly updated by the National Research Ethics Service. The script fully reflected the information disclosed in the UK HeFT Patient Information Sheet. This was reviewed and discussed with the Trial Steering Committee members, including those who had not received formal medical training., Principal Investigators and Research Physiotherapists involved in the trial set up were also involved in the discussion. The video was filmed with the Chief Investigator explaining the trial with model and visual demonstrations of relevant points. The aim of the process was to present an eligible patient with clear and comprehensive information about the trial, including a balanced, unbiased view about two treatment options. Special attention was paid to avoid confusion through potentially 'scary' specialised wording and phrasing (Donovan, Mills et al. 2002). Once the patient recruitment started, several eligible patients were approached by the Chief Investigator and the Trial Co-ordinator and informal feedback about the video was collected. Final editing touches were applied at that point and the video content was not changed again through the rest of the recruitment period. A CD with the final PTIV version is attached. Both initial and final copies of the video were supplied to the Research Ethics Committee involved.

A dedicated Trial Recruitment Research Associate was employed and trained for each trial centre. This Associate acted as a contact person to address any possible patient queries and/or concerns, including involvement of a treating surgeon or other trial staff as necessary during the recruitment period. The surgeon was excluded from direct interaction with a patient during the trial recruitment process, unless a patient specifically wanted to meet his/her surgeon before making a decision about trial participation. As the trial expanded, adding more centres across the UK, extra training sessions were organised where the recruitment pathway was discussed and 'tips' were provided by lead recruiters.

5.2 Surgeon and patient feedback

All surgeons were very supportive of the suggested recruitment pathway from the outset. It was seen by them as liberating from the trial routine and it defined them as decision makers about trial eligibility. Nobody raised objections or declined to take part because of the PTIV approach, so no need was felt for formal feedback.

On the other hand, patient feedback was collected formally as part of the qualitative study (**Chapter 3.3** and **6**) to explore effects of the new methodology on its recipients. Patients were interviewed a considerable time (one to two years) after the trial participation was offered to them, in line with the intention that feedback should have minimal or zero impact on a clinical or trial course. On the one hand, this had the advantage that, on initial recollection, patients remembered what was most important and significant for them during the trial recruitment process. However, they often struggled to remember further details and impressions, so the PTIV was shown again during interviews after the initial recollection was prompted.

At the outset I expected to learn patient views about the clarity of the information provided and the possible impact of the surgeon's absence during the trial recruitment process. Another important issue was whether the choice of compared treatments was evenly balanced from the patients' perspective and so whether the video could be used effectively as a decision

aid about trial participation. Two additional aspects about the approach emerged from the data. One was that the PTIV potentially could be an important information source in managing patient expectation during the recovery period. The other was a more general concern about appropriate timing and the environment for the clinical study invitation. All these issues are presented and discussed below.

5.2.1 Clarity and understanding of trial information

In this section, I am going to look at the reaction of patients when asked whether the trial information was clear and easy to understand. I shall quote (in italics) from responses which patients provided.

Overall, patients' reaction to the audio-visual presentation about the trial was positive:

> *"That video is much better than reading about it. With him talking to you and giving that explanation for everything – what happens and everything; it's much better. You can understand that much better. All the leaflets in the world don't put things over as clearly as somebody on a video or talking to you"* (CH018, 76 year old male, retired)

Some comments seemed to respond directly to guidelines and recommendations published by the National Research Ethics Committee

about giving impartial information and allowing patients time to decide without any pressure:

> *"it was good that was, because it wasn't like you telling us and the way he did it – that DVD, you could watch it and you could listen to it and you could decide yourself without someone else there trying to influence you."* (CH019, 28 year old female, unemployed)

The clarity of the presented trial information was universally recognised as one of the main video features:

> *"It's clear, yes. It's as clear as day."* (CH035, 39 year old male, manual labourer)

> *"It's short, it's clear and it tells you about how you can leave it naturally to heal and how you can have the operation. It gives the advantages and disadvantages."* (CH026, 42 year old female, manual labourer)

> *"It can't be any clearer, can it? It can't get any clearer. No, no. That's quite good that, I thought."* (CH022, 75 year old male, retired)

> *"It's very well done isn't it? It's very explanatory. It clearly defines the definition between op and non-op."* (CH020, 43 year old male, office worker)

For most patients the PTIV improved their injury understanding, as

explained by one interviewee:

> *"The DVD was really helpful. It made me understand more about the actual injury because up to that point, I didn't understand what had actually happened. I knew I'd fractured my heel and that's as much as I knew, but when I watched the DVD, you know...the impact side of it and things like that, I understood then".* (CH020, 43 year old male, office worker)

The fact that the trial information and especially treatments were explained by a senior medical specialist did not go unnoticed:

> *"He introduces himself even beforehand talking about the injury. That's very helpful that he introduces himself as a medical professor."* (CH015, 40 year old male, academic)

Patients appreciated the effort and quality of information provided:

> *"He's a good communicator for sure. He's had to say what he said."* (CH043, 52 year old male, manual labourer)

> *"The presentation was good. Obviously it was calm, reassuring, professional and the surgeon thing giving you a lot of information, which I suppose if you hadn't have had that trial it would have just been a fact sheet I'd imagine that would have just been given over, or not even that."* (CH021, 46 year old male, skilled)

The PTIV appeared to achieve the main purpose to explain why the study was set:

> *"It was very useful yes, because it explained exactly what the dilemma is and the pros and cons of treatment and obviously the dilemma the surgeons and the doctors have got of what is the best treatment."* (CH032, 60 year old male, skilled self-employed)

The above quotes demonstrate that the PTIV provided clear, concise information about the trial, that was easily understood by patients.

5.2.2 Was the surgeon missed?

One crucial and central question to be addressed was about the surgeon, and whether his/her presence was missed during the trial recruitment process.

Only two out of 22 patients specifically requested to see a treating surgeon before a decision about trial participation was made:

> *"Well, I'm not gonna make my mind up instantly; I'd like professional advice from a surgeon or something like that."* (CH022, 75 year old male, retired)

One of those two was the only patient in the interviewed group who misunderstood the trial concept:

> **Interviewer**: *"But have you been aware that actually, [Name: 0:47:02] or the specialist who didn't know that at the time had actually seen your X-Rays and knew about you and that he actually made the decision that you were a suitable candidate for this study?"*
>
> **Respondent**: *"No. I wasn't aware, no."*
>
> **Interviewer**: *"Because obviously it's not the person who is showing you the DVD. It's the specialist who decides if the person is suitable for the study and then you're approached about the study."*
>
> **Respondent**: *"OK. That makes sense."*
>
> **Interviewer**: *"Would that make a difference if you knew?"*
>
> **Respondent**: *"Yes."* (CH026, 42 year old female, manual labourer)

From these patient quotes we can conclude that in at least some of the cases, the patients needed a personal contact with the specialist in charge of their care as soon as the question about possible treatment options was raised. This issue is discussed further in **chapter 7.2**, when combined with selected statistical trial data.

5.2.3 Operative vs non-operative treatment options balance

In this section, I shall look at patients' reported views about the choice of operative and non-operative solutions presented to them.

It was reassuring to learn that all but three out of 22 interviewees agreed that a balanced view about compared treatments was presented, as intended by the trial team:

> *"he [Professor presenting in the video] wasn't just sort of trying to push you for non-operation, or push you either way"* (CH018, 76 year old male, retired)

> *"He gives the cons and the benefits of it"* (CH026, 42 year old female, manual labourer)

There was strong evidence that the other three patients were actively looking for and 'picking out' information that comforted and accorded with their treatment preference, despite the extra effort taken by the trial team to present a balanced view. It is interesting that these patients could describe the video as being both in favour and against operative treatment. That in itself confirms that the factual information presented was evenly balanced:

> *"If I didn't know what I wanted to do before I watched that, I'd certainly pick an operation after watching it anyway.. It said it was a very fine balance to which you had... To us, it wasn't a fine balance. It was completely*

the operation – no doubt about it." (CH019, 28 year old female, unemployed)

With that, we can compare the following reaction:

"Obviously they're trying to veer you towards surgery because that's his job." (CH039, 42 year old male, skilled)

and likewise this:

"If he was a sales rep he would do well because I thought he was selling the operation side of it". (CH038, 41 year old male, skilled)

Prior beliefs had a strong influence on interpretation:

"Some people really do like to have the operation done; but for me, that was just confirming that I didn't want to have it done'; 'I think what puts a lot of people off is when he turns round and says 'The skin might not marry up properly', you know. Women and men are vain like, you know." (CH030, 50 year old male, manual labourer)

Even in the situation when information about a procedure choice appeared evenly balanced to most patients, some of them had a strong preference bias and would pick out information to support their view.

5.2.4 PTIV as a decision aid

In this section, I explore how good a decision aid the PTIV was when patients faced an invitation to become the subjects of clinical research while under medical care. For many patients the PTIV was undoubtedly a good decision aid as they considered trial participation:

> **Interviewer**: *"And did it help you in your decision?"*
>
> **Respondent**: *"Oh, totally yes, immediately. Immediately yes, there's no doubt about it."* (CH043, 52 year old male, manual labourer)

For some patients the video presentation was sufficient for them to make a decision that they wished to join the trial:

> *"You know, I understood exactly what he was saying. That's basically why we joined wasn't it?"* (CH018, 76 year old male, retired)

It was interesting to hear comments by a patient who for some reason was not shown the video during the recruitment process:

> *"Yes, I would have liked to have seen that before, I must admit – yes, just... But no, it's helped me clear up my own thinking, if you like, seeing that."* (CH007, 76 year old female, retired)

The video was certainly thought-provoking:

"The DVD would make you ask further questions of whoever you were dealing with." (CH014, 68 year old female, retired)

Many patients having experienced the injury first hand agreed with the information retrospectively at the time of interview:

"He's right about a few things.. when I saw it again and not so much today, well and today, it's talked a lot of common sense." (CH046, 49 year old male, professional)

The PTIV is seen as a valuable and reliable decision aid.

5.2.5 Possible additional value of the PTIV

In this section I present an interesting observation about the opportunity patients had of seeing the PTIV much later, after their treatment had been concluded.

After seeing the video again long after the injury incident in the calm environment of a research interview , three interviewees emphasised the value of seeing the video again:

"Maybe if I didn't know what this was about I would want, I would want to watch this film twice or to read the transcript." (CH015, 40 year old male, university academic)

"You're hurting, you're injured, you watch the DVD and that was all in hospital. You've had a lot going on through your mind and you come home and you've forgotten all about that DVD. I think if somebody could watch it again after sort of twelve months then that man has told you that it's going to hurt, that your foot might be deformed and he's probably forgotten that he's told you it might be deformed. I'd forgotten that. I'd forgotten most of that DVD. That's why I asked, is it the same DVD that I was shown. I couldn't remember it and I can remember most films, or whatever I watch, but I think because of your injury you tend to blot a lot of stuff out and you're shown it in hospital. You're in unfamiliar surroundings. You do the trial. You know what it's about. You're not stupid. You understand it, but I think to be shown it again eight or twelve months down the line you think 'Oh crikey, he did say there would be some pain. I forgot about that. I forgot he told me I'd have a bit of pain. I forgot he said that.' Then probably after fifteen months I wouldn't have gone down to the doctor and said 'It's still hurting.' That man told me it would hurt. It probably could still hurt and I'd suffer with arthritis. I'd forgotten about that." (CH023, 47 year old male, skilled self-employed)

The same 47 year old man quoted above expressed some preference to see a living person, rather than a video image:

"The most important was somebody coming to talk to you – not the DVD but somebody actually physically standing there talking to you and saying

what it was about.. Literature I don't read. I'll look at it and I'll put it down. I don't. That's a good idea with the DVD because I do sit and watch it, although my mind can wander a little bit because it's sort of a television, but if somebody is stood there talking to you then you've got to listen to what they say because they can ask you a question so you tend to listen to people a bit better and that was the best way for me". (CH023, 47 year old male, skilled self-employed)

However, this same man was quite happy with having a Research Assistant as a contact person and joined the trial.

5.2.6 Time and place

This section looks at some questions about when and where the approach to patients should take place and how they should be invited to take part in the trial. Commonly concerns were expressed about timing and environment when being approached by research team:

"I was sat down in the waiting part – not the waiting part, the actual private part and shown a DVD. I can always remember though thinking, 'This isn't the time to see it'.. I think that a copy of that should be given to the patient to look at in their own time, rather than immediately after. Like I said before, there are a lot of things in your mind where you've injured yourself and not only about the injury but the repercussions of it and then

to be shown that as well, I think it's a bit too much at the time for me." (CH043, 52 year old male, manual labourer)

The timing issue however may not be directly related to the PTIV; this patient actually had a good impression of the presentation overall:

"It's just that I find it a bit frightening to hear that sort of thing sometimes and particularly when I was shown it straight after having the injury in the first place, but otherwise it was very good, yes." (CH043, 52 year old male, manual labourer)

This is discussed further in **chapter 6.1.2.** The PTIV aside, it was a common experience for patients to be given too much factual information in the context of the clinical research, when patients were expecting more encouragement and/or reassurance from the medical profession at the time of injury and hospital admission:

"I understood what he meant by that, you know, so I suppose the language which is to the patient is important just to make them understand it a little bit better perhaps, or to make them feel more at ease because that didn't make me feel at ease particularly.. Even now it doesn't really with some of the words he uses. I know he's got to use them, because he's actually stating the fact just a little bit too black and white for me. You know, perhaps it could be smoothed off a bit for some people because some people are frightened of that aren't they? You know, like I say, you don't only think

about what's happened to your body, although that's important, but you do think about the repercussions of it." (CH043, 52 year old male, manual labourer)

To four interviewees, all male with different levels of education, one of them retired, the video was seen as rather too direct:

Respondent: *"...when I first saw it, it didn't sort of give me any inspiration to sort of do the trial straightaway, so maybe you'd bring that in. You know, you go into someone's face. You could say 'Well, this is what possibly could have happened with the result of what you've done."*

Interviewer: *"It's a bit straight on is it?"*

Respondent: *"It's straight on and you think, 'Oh.'"* (CH046, 49 year old male, professional)

For those four, both the images and the words were upsetting, discouraging them from participation in the trial:

"You see what frightened me, when I saw that video that this young lady showed me of somebody else's operation, there were screws all in it, all the way around it, to hold it in a shape. I thought 'Blimey , with that all in, you never get that out if anything goes wrong." (CH022, 75 year old male, retired)

"There are a lot of words he uses, right? They frighten you, really. He says 'This is a serious injury'. First of all you're thinking, 'Oh god,' you know 'Is it?' Now he's talking about deformities and all of that sort of thing and I think the language that he uses, although he's obviously got to tell you what's what, it's a bit intimidating." (CH043, 52 year old male, manual labourer)

One of these men, and another retired lady, took the information very personally:

"When I first saw that like, I thought, 'Is that me?'.. the DVD says my heel bone is broken into several places, so straightaway you've got bloody hell fire, scared. The biggest thing I wanted to do was see the CT scan to see how bad it was, so straightaway it put a bit of a fear into people. You know, it could have say, compromised a broken heel bone, which could be like this or like this, yes?" (CH046, 49 year old male, professional)

So there was considerable concern not only about timing and place, but also about the volume and level of detail of research information provided.

5.3 Discussion

The PTIV recruitment approach possibly helped to recruit more trial centres for the UK HeFT, because surgeons told us they were attracted by the fact that they would not need to go through the explanation of the trial and consent with a patient.

The video provided consistently high quality trial information delivery that was fully compliant with current regulations and recommendations. Many, but not all (19 out of 22), patients thought that the treatment advice was impartial and balanced. However, emotional response varied greatly between participants. One of them described it in this way:

> *"For some people I think it's a good thing and for some people I think it might frighten them a bit, make them a bit nervous."* (CH043, 52 year old male, manual labourer)

The PTIV approach succeeded in replacing a treating surgeon during the trial recruitment process. Very few patients (2 out of 22) specifically requested to see their surgeon and only one patient (and this was one of those two) misunderstood the trial concept.

Even though carefully selected to provide a necessary minimum for sufficient understanding, the factual information was overwhelming, troubling and difficult to remember at the time of injury. Watching the video again in different, calm and relaxed settings during research

interviews confirmed the value of the information provided about the injury. This could have helped some of the patients during the recovery period.

At the time of injury, a combination of a high quality information video and an independent research assistant perhaps failed to produce assurance about quality of care, usually provided by a clinician. This was the case even though the research assistants were specifically selected to represent a particular healthcare profession (physiotherapy or nursing). It has been argued recently that it is of paramount importance to place the emphasis on the intention to provide the best possible care in a research context, in particular giving reassurance that random allocation to a treatment would not disadvantage a participant (Leighton, Lonsdale et al. 2012). This is based on emerging evidence that even with a pragmatic approach, the clinical research environment and governance tends to improve the overall level of care provided for participants.

I have demonstrated in this chapter that the patients in the HEFT trial reacted, on the whole, very positively to the new procedures adopted for the trial information presentation and delivery. In the following chapter, I shall go on to discuss the factors that influenced a patient's decision about participation in the trial.

Chapter 6 Study C: Deciding about trial participation – what makes a difference?

This chapter looks at the content that emerged from the UK HeFT patient interview narratives in response to the third research question (**chapter 1.6**):

> *What is the patient perspective of the recruitment process in a challenging surgical trial, when the best current advice as well as innovative approaches to the principles of patient participation are integrated?*

Twenty-two patients from one trial centre (**chapter 3.3**) consented and were formally interviewed. In addition, one patient refused to come to the hospital for an interview, but was willing to provide information over the telephone immediately: the interview notes were therefore recorded impromptu in a research notebook.

The sample of patients appear to have similar demographic variation to the wider HeFT patient population (**Table 6.1**), including 15 patients who declined trial participation. The only obvious deficiency was under-representation of younger patients. It was particularly difficult to get them to attend an interview. Two young male patients initially agreed to be interviewed, but never arrived for an appointment, even after attempts were made to re-schedule.

Table 6.1. Demographic variation of the interviewed cohort (n=23)

Social status	n	*Age groups*			*Sex (M:F)*
		18-40	*41-60*	*Over 60*	
Unemployed/Retired	*5*	*(1)*		*2 (2)*	*2:3*
Manual labour	*5*	*(1)*	*(4)*		*3:2*
Single parent/ Housewife	*2*	1	*(1)*		*1:1*
Office work	*1*		*(1)*		*1:0*
Skilled	*4*		*(4)*		*3:1*
Self-employed	*3*	1	2		*3:0*
Professional/Academia	*3*		*2 (1)*		*2:1*

Patient numbers who refused to participate in the UK HeFT are in (brackets).

The patient sample (**Table 6.1**) was sufficient for a number of themes to be described by different interviewees. This helped to achieve a better understanding of patients' true inner feelings and beliefs. No new themes emerged in the last few interviews, so it was felt that the point of data saturation was achieved.

Content-rich interview data allowed insight into the patient decision making process about trial participation and identified factors that had a significant influence on patients' decisions about trial participation (**6.1**). Further, a typological analysis identified certain types of patients whom trialists face in a challenging surgical trial, defined by their emotional response, attitude and which factors they consider in order to make a final decision (**6.2**).

6.1 Factors influencing patients' decisions about trial participation

Several attributes emerged as important for orthopaedic trauma patients when faced with an invitation to take part and when provided with information about the clinical trial and treatment choice: social and economic factors, environment and timing of invitation, balancing pros and cons of taking part, external sources of decision support and prior treatment advice. Patients' perception of these factors is presented in this section.

6.1.1 Social and economic factors

Social and economic concerns were mostly reported as adding to general injury stress, rather than having a direct impact on trial participation decisions:

> *"Obviously at the time I was suffering from major trauma, so you've got a number of things going through your head and not just the injury. How long am I going to be off work? I've got to sort my mortgage out. The wife's two hours drive away."* (CH021, 46 year old male, skilled)

Only one interviewed patient, a 43 year old single father of small children, was directly affected by his social responsibilities. He hurried home at the

first opportunity to attend to his childcare responsibilities and was happy to be interviewed, but only over the phone. Only taking impromptu summary notes was possible (**chapter 3.3**), so no direct quote is available from this interview.

6.1.2 Environment and timing of invitation to participate

Factors described below echo strongly experiences discussed already in chapter **5.2.6**, when the PTIV approach experiences where discussed. Half of the 23 interviewees felt that their ability to understand and process the trial information was affected, sometimes significantly, by pain, strong painkillers and injury stress:

Interviewer: ..do you remember who actually spoke to you about the trial itself?

> **Respondent**: "No, because they'd got me on morphine."
>
> **Interviewer**: *"Do you know what sort of information you'd been given?"*
>
> **Respondent**: *"I don't know because my mind was... It was elsewhere."*
>
> (CH003, 46 year old male, manual labourer)

This raised questions about appropriate timing of the trial invitation:

Respondent: *"You're not really ready to listen at the time. It doesn't sink in quite when you've just had the accident. It doesn't really sink in does it? You know, because you're not really ready to expect..."*

Interviewer: *"...Why do you think it doesn't quite sink in?"*

Respondent: *"Because you're still in a bit of pain and shock, you know, and you just don't realise exactly what is what."* (CH007, 76 year old female, retired)

Information about the trial, even though generally well understood once it was processed, seemed overwhelming on initial contact and introduction:

"The only thing I thought that perhaps maybe puts people off doing the research is it seemed that as soon as it was confirmed that it was a heel fracture the people were there with the DVD and because you're there getting drugs and you're in shock that this has happened to you and then somebody is shoving a DVD in front of you and saying, 'Come and be part of this.'.. because if you're having drugs and you're a bit here and there, I don't think you're taking in what they're saying to you anyway." (CH033, 43 year old female, professional)

Even those who do not have a fear of hospitals found the hospital experience and environment rather distressing:

"I'm out of my environment... And don't forget this was a shock.. lying in

a bed, foot up, what's going to happen? .. you don't really need someone to come and say to you, 'Would you be part of our trial as well?' .. You go through a lot, don't you, while you're lying there." (CH027, 55 year old female, skilled)

It appears that many patients look for psychological support and reassurance that they are in the right place and in safe hands to make them better, which the trial invitation fails to provide:

"I suppose that doesn't give you a confidence boost at the time when you're lying there with a broken heel and they don't know which way to go and which is the best way. I can remember that quite clearly." (CH021, 46 year old male, skilled)

Three patients felt uncomfortable about not having any guidance or advice in the process of deciding on a preference for one treatment rather than another:

"I know we're a free society and with the freedom of information act you've got a lot more open now, but sometimes it could be a blessing not to tell them everything. Is that good or bad?" (CH039, 43 year old male, skilled)

They and other patients refused to believe (quite rightly) that their treating surgeons do not have a treatment preference. Their spontaneously proposed solution was that more targeted treatment advice should be provided, even in the absence of an obviously better choice. This seems

similar to the pre-randomisation concept (Zelen 1990):

> *"You know, not bully them into it, but rather than giving them the choice when in the surgeons' own minds they know that this operation needs doing.. So really they should say 'Look, we are advising you' and not saying 'you've got to have it,' but 'we are advising you to have this operation.'"* (CH030, 50 year old male, manual labourer)

One patient was rather distressed by the absence of a surgeon's recommendation and this may have contributed to the trial concept misunderstanding:

> *"On my injury I had to make a personal decision of whether I was going to have a plaster or an operation and I still don't understand up to this day now why. I had the operation by having to make that decision.. I spent two days being really upset while the swelling was coming down and thinking it over in my mind."*(CH026, 42 year old female, manual labourer)

6.1.3 'Trade off' process – balancing pros and cons

Even though the trial information presented seemingly a balanced view about treatment options, there was strong evidence of a 'trade off' process according to a patient's own perception of risk and benefits for both treatments:

"I think having my foot set in a cast in my mind's eye would be less restrictive, but with the surgery I thought that it would achieve more movement." (CH038, 41 year old male, skilled)

Understandably, the prospect of an invasive procedure with significant scarring raised a lot of anxiety for many:

Respondent: *"...they haven't given me much incentive to have the operation if they're telling me about this skin thing. It's not so much for a bloke, but from a female's point of view like I say, with swimming or anything.. if they would have said to me 'Listen, we can operate on you today and you're going to be out of here in two days time. You'll be on crutches for a week and then that's you mended,' I couldn't see... What was I going to say?"*

Interviewer: *Clear benefit?*

Respondent: "*Yes. I couldn't see the benefit I would gain out of having the operation because I'm on crutches for the same amount of time, plus the fact of what does he say, a five percent chance of an infection?"* (CH030, 50 year old male, manual labourer)

Some patients had a more positive attitude to surgery:

"The way I looked at it is that if something is broke, it needs fixing." (CH019, 28 year old female, unemployed)

From the UK HeFT results we know that there were almost equal numbers of patients who did not want (n=144) and who wanted (n=146) to have surgery among those who refused to take part in the trial (Chapter 2, Fig. 2.1). Only two patients were completely passive about the trial participation:

> *"I left it entirely up to them. They're the ones that sort of knew better really what they wanted me to do, so I was quite willing to do whatever they required me to do."* (CH007, 76 year old female, retired)

They were both female, one 76 year old retired lady and the other 28 year old young mother. Their decision to take part in the trial was easy:

> *"'We're doing these trials. Would you like to take part?' and I just said 'Yes, okay that will be fine. I don't mind.'"* (CH004, 28 year old female, unemployed)

However, the older lady achieved this effectively through denial of the choice given to her whether to take part or not:

> *"I didn't have a choice as such. I left it more or less to their discretion what they did with me. I wouldn't say I said, 'I'll choose this', or 'I'll choose that.' I left it to their discretion."* (CH007, 76 year old female, retired)

6.1.4 Sources of decision support

At least a third of the patients interviewed found making a decision about the trial and/or treatment choice straightforward, once all the information was given to them. One in three stated that people they knew (family, friends, colleagues etc.) had a significant influence and effect on their final decision.

Four patients felt that it was necessary to obtain external third party information in addition to what was provided for them. None of them were happy with the random treatment allocation, although they were positive towards clinical research. They offered to take part, but with their own treatment choice:

> *"You're going to read up on it, Google it, Internet it, see what feedback people have had already if they've done it before, so it's not like I haven't just said, no I don't want to do it. I've like, researched it in a small sense."* (CH039, 42 year old male, skilled)

Apart from online searches, they would look and listen to any other available information sources and those are unlikely to be evidence-based:

> *"I watched this DVD and obviously I'd got Internet access there and I started doing a bit of my own research and my next door neighbour here; he's a nurse and I spoke to [Name] and one or two other things. The*

boss did the same break funnily enough...'. 'by Wednesday I was almost getting an expert, you know. I started to learn a lot about the foot all of a sudden, so I mean I'm glad I had access to it and I mean I started to learn." (CH021, 46 year old male, skilled)

6.1.5 Prior treatment advice

Despite the best efforts in our trial recruitment centre to prevent any advice about a treatment choice until a potentially eligible patient had been assessed for trial eligibility, two patients reported being advised about the extent of their injury and possible treatment in the Emergency Department:

"He [in A&E] said 'No, you've got a fracture of the heel,' and he said 'We'll probably operate on it tomorrow...' I'm lying there on the Monday evening thinking that I'm going to be operated on the next day." (CH021, 46 year old male, skilled)

"I can't think of her name, some doctor. She came to have a look and she said that it looked like I'd shattered my heel bone, explained to me that it was probably one of the worst breaks you can do." (CH038, 41 year old male, skilled)

Both those patients declined random treatment allocation in preference for operative treatment. This is a well known factor, which is both important

and significant. I shall pick it up later when I discuss the findings of my study and make recommendations for future practice.

6.2 Patient attitudes

Thematic analysis revealed similar responses to the trial participation offer among some patients. Typological analysis was introduced (chapter 3.3) and resulting patient types according to their response and attitude towards the invitation to take part in a challenging trauma trial are presented in the diagram (**Figure 6.2**).

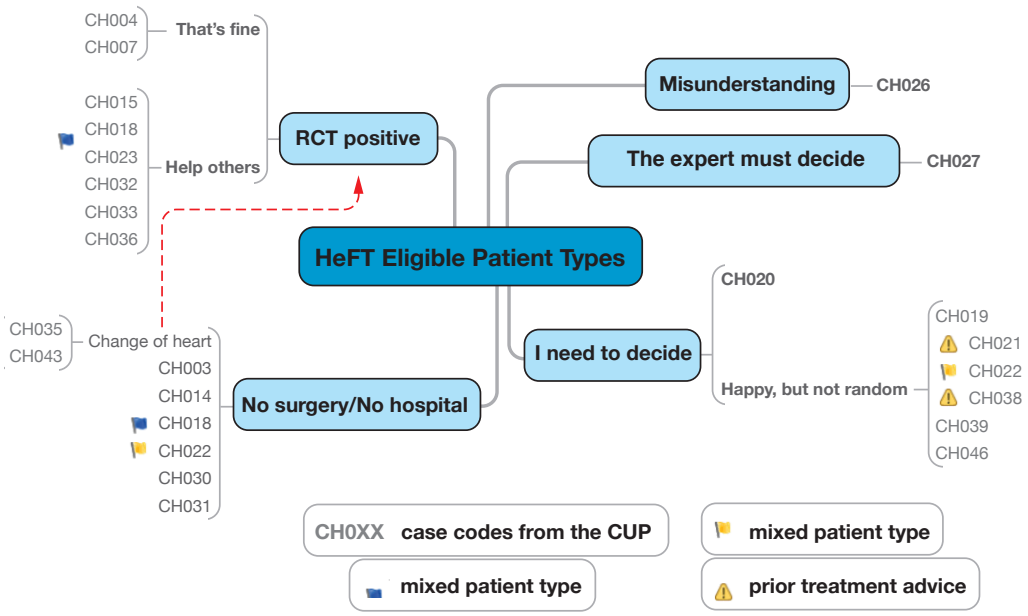


Figure 6.2. HeFT Eligible Patient Types diagram.

Each patient type will now be discussed separately.

6.2.1 RCT positive

First of all it was interesting to see what makes patients agree to the clinical trial in the RCT positive group (**Fig. 6.2, Appendix H.1**). This group included eight out of 23 interviewees.

6.2.1.1 In equipoise – 'that's fine'

The interview data confirmed that individual equipoise about treatment options is rare even among trial participants. Only two patients who did not engage in the pros and cons "trade off" process between two trial treatments were in equipoise. One was a 28 year old single mother, who summarised her feelings as follows:

> *"It was explained to me that it was just trials. I could opt out. I wouldn't be treated any differently and she had to make a phone call to see if it was operative or non-operative and it was just like a stab in the dark really to which one I got, so I was like 'Okay then that's fine'."* (CH004, 28 year old female, unemployed)

The other one of those two patients, a 76 year old retired lady, did not even engage in trying to understand the trial concept and process:

> *"I knew that they would keep an eye on what happened. I realised that,*

you know...but I didn't know exactly what was going to happen and how it would proceed." (CH007, 76 year old female, retired)

Her decision was based on complete trust in professionals who provided her medical care and a willingness to help others:

"They're the ones that sort of knew better really what they wanted me to do, so I was quite willing to do whatever they required me to do.. the main reason was I thought if I could help anybody else in the same circumstances then I was willing." (CH007, 76 year old female, retired)

One more patient, a 40 year old university academic, was completely comfortable with the concept of the RCT, despite having some preference towards one of the trial treatments:

"Maybe because I am a scientist doing research myself, or maybe just because, [er] because everybody knows how important medical research is. .. I was having difficulty coming up with a reason why I shouldn't do this." (CH015, 40 year old, academic)

6.2.1.2 Social responsibility – 'help others'

For the other six interviewees in the RCT positive group it was overwhelmingly a sense of social responsibility that made them join:

"If I can help you to help people then I'm doing my bit.. You have to, to help people out and to sort out the best procedures." (CH023, 47 year old male, skilled self-employed)

One of them, a 25 year old self-employed mechanic, linked this responsibility directly with NHS service:

"Just take part and give something back to the NHS and help other people out for the future really" (CH036, 25 year old male, self-employed)

These five patients agreed to participate in the trial even though they were not comfortable with the trial concept of random treatment allocation and had a degree of preference for one treatment. Some of them hoped to avoid an operation:

"I think fortunately for me they decided not to operate" (CH032, 60 year old male, skilled self-employed)

At the same time others wanted an operative treatment to be allocated:

"I was sort of inclined, on the basis of what I knew, that I am, that maybe I should have that operation." (CH015, 40 year old male, academic)

When patients discussed or mentioned eventual treatment outcomes, it seems that their level of satisfaction depended on their initial treatment preference. So patients allocated randomly to a treatment had second

thoughts if the treatment was not in line with their wishes or feelings even though those may have been subconscious. On the other hand, patients who chose their treatment themselves (described in the next section **6.2.2**) were all happy with the choice, even when the outcome did not sound very good.

6.2.2 I need to decide

Another sizable (7/23) and heterogeneous group of interviewed patients (**Fig. 6.2, Appendix H.2**) were not able to give up responsibility for a decision that would affect their future life:

> *"I didn't want them to make that decision for me, because if they made the wrong decision I couldn't live with that, whereas if I've made that decision then it's down to me."* (CH038, 41 year old male, skilled)

They were negative about the randomisation process:

> *"I think that's what maybe put some people off staying in the programme because it's a bit like roulette isn't it?"* (CH039, 42 year old male, skilled)

Six out of seven of these patients, however, were positively proactive about taking part in research if randomisation could be removed:

> *"I was happy to do it, but I didn't want the choice taken away from me.*

I still wanted to have the final choice of surgery or...if it was offered." (CH021, 46 year old male, skilled)

"I did ask if I could be part of the trial, but just be the operation side but they wouldn't let me." (CH019, 28 year old female, unemployed)

None of them really appreciated or understood the value of random treatment allocation. As the same young lady explained:

"let me just make a choice and still be part of the trial, I don't see how that made any difference whatsoever." (CH019, 28 year old female, unemployed)

They were taken aback when confronted with the currently recommended explanation of a trial that clinicians did not know which was the better treatment for them:

"Somebody comes up and says 'We're doing a trial,' and why they're doing a trial and 'We don't know which is the best way to proceed with this,' and you're thinking 'Well hold on a second'." (CH021, 46 year old male, skilled)

In the situation when a clinician 'did not know' and could not provide some guidance or advice, they would seek additional information using a variety of alternative sources before making any decision:

"You're going to read up on it, Google it, Internet it, see what feedback people have had already if they've done it before, so it's not like I haven't just said, no I don't want to do it. I've like, researched it in a small sense." (CH039, 42 year old male, skilled)

Despite the trial information delivering a message that two treatment options offered to trial participants were finely matched, when a patient's own 'research' was applied, the balance was lost:

"To us, it wasn't a fine balance. It was completely [one treatment option] – no doubt about it." (CH019, 28 year old female, unemployed)

To some extent, these patients felt that they would be disadvantaged by not being allocated their preferred treatment:

"If I had [another treatment option] I might have disadvantaged myself." (CH046, 49 year old male, professional)

Their top priority was to make what seemed the best choice in their situation:

"To find out what the best way for me and to proceed with it if it was offered." (CH021, 46 year old male, skilled)

Once they made their choice, these patients were committed to the best possible treatment outcome:

"I think it's the nature of the animal, so if you want to sit on your arse and do nothing, or if you want to try and get back to how you were." (CH038, 41 year old male, skilled)

It appeared that taking part in research as it was offered was not seen in this group as an option that assured the best quality of care:

"You just feel as though if you do enter the programme you might be railroaded towards going down what they want, rather than what you want, so once you enter these terms it's all very well saying you can just opt out when you want, but there's always a bit of pressure." (CH039, 42 year old male, skilled)

It must be noted that two patients from this group had prior advice about a possible choice of treatment from a health professional before they were approached by a specialist group about trial participation (marked with caution triangle in **Fig. 6.2**). They chose their treatment accordingly.

6.2.3 Negative attitudes to invasive treatment and/or hospital

The third large (8/23) group of patients (**Fig. 6.2, Appendix H.3**) shared a negative attitude and concern about invasive treatments:

"I just don't want an operation if I can avoid it." (CH014, 68 year old female, retired)

They also had a low opinion of hospitals in general :

> *"I just hate hospitals like, you know. I just wanted to get out, as a lot of people do."* (CH030, 50 year old male, manual labourer)

This man, as indeed others in the group, still engaged in the 'trade off' decision process, but it was heavily biased against operative treatment:

> *"It didn't give me much incentive to have the operation to be honest with you and maybe that's because I wanted to get out of hospital as soon as I could."* (CH030, 50 year old male, manual labourer)

Interestingly, this was the most fluid group, with many of them relying on advice from others to support their feelings:

> *"I was offered plaster or an operation and he didn't really go into the operation side much because he said he'd looked at my face and he could see the thought of an operation was no, horror."* (CH014, 68 year old female, retired)

These patients were most susceptible to change their opinion under external influence:

> *"It was an easy decision not to have it but my wife talked me into it and my family saying it would be for the best, so I got it done."* (CH018, 76 year old male, retired)

This 76 year old man (marked in two categories with a blue flag in **Fig. 6.2**) joined the trial after discussion with his family. Another 75 year old man (marked in two categories with a yellow flag in **Fig. 6.2**) really wanted to help and would be happy to:

> *"Get in your trial, if you can just tell, not have an operation, just tell..."* (CH022, 75 year old male, retired)

Two patients, had a 'change of heart' (**Fig. 6.2**) during the interview. Both were manual workers (39 and 52 year old men) for whom the heel fracture was potentially a career changing event. When questioned what their advice would be to others towards the end they gave an encouraging message about joining the trials and would have joined themselves:

> *"From what you've told me this evening and from what I've seen on there, it's very interesting because it's personal to me. I've had this injury and it's not a common injury, so I think that anyone that's been offered the chance to take part in a study – not necessarily to have surgery, because that's a very personal thing, but anyone that wants to take part in helping to find out more information, or definitive information even about this should do it. Why not?"* (CH043, 52 year old male, manual labour)

6.2.4 'Don't give me choices' : the expert must decide

One patient (a 55 year old female hairdresser) could not face responsibility for a decision about her treatment or trial participation (**Fig. 6.2**):

> *"I couldn't afford to make the wrong decision. I wasn't prepared to make that decision."* (CH027, 55 year old female, skilled)

She was determined to get the best option and expected experts to provide it for her:

> *"I would rather somebody who's a consultant or is, you know, knows this field [um] to make the decision for me."* (CH027, 55 year old female, skilled)

She felt strongly that the trial was an experiment rather than provision of the best possible care: 'Not on me', she said, and was extremely concerned about the possibility of making the wrong choice:

> *"Don't give me choices because I might make the wrong one."* (CH027, 55 year old female, skilled)

She responded to this dilemma by ignoring the research team's plea for participation:

> *"If I broke my arm next week and you came to me again I'd probably say, 'No, I don't want to.'"* (CH027, 55 year old female, skilled)

6.2.5 Misunderstanding of the clinical trial concept

Only one patient, a 42 year old female manual labourer, completely misunderstood the concept of a clinical trial (**Fig.6.2**):

> *"On my injury I had to make a personal decision of whether I was going to have a plaster or an operation and I still don't understand up to this day now why. I had the operation by having to make that decision."* (CH026, 42 year old female, manual labour)

This misunderstanding brought her to the position where she had to make an important, but inappropriately difficult, decision that she was not qualified or prepared for. This led to a significant distress:

> *"I had a decision to make of whether to have it put in plaster and wait and see how quickly it healed itself; the bones, or to have an operation and I spent two days being really upset while the swelling was coming down and thinking it over in my mind."* (CH026, 42 year old female, manual labour)

Consequently, she was desperately looking for the sort of specialist advice and support that she had come to the hospital to receive in the first place. She did not see this offered in the context of the HeFT recruitment procedure:

> *"I wanted to see my specialist first about the injuries and talk about that*

first and then afterwards you don't mind, because you know you've seen someone. You feel at ease don't you? You're focused and then you're willing to listen about what this survey is and how you can help other people as well." (CH026, 42 year old female, manual labour)

6.3 Discussion

The interviewed patient cohort matches the UK HeFT patient population closely. Not only does it have good demographic variation (**Chapter 4, Table 4.1**), there is also a similar proportion (around one third) of patients who agreed to take part in the trial. The remaining two thirds of patients are split evenly into groups who chose operative or non-operative treatment. These were the same proportions as in the actual trial. In addition, no new themes (codes) were created when analysing the last few interviews. This data saturation suggests that the patient sample was at least close to the maximum variation of the UK HeFT patient population.

It is reassuring that only one of 23 interviewees completely misunderstood the trial concept, because the literature review (**Chapter 1.5**) suggests that a significant proportion of patients is at risk of making an incorrect interpretation of trial information in surgery. This reflects positively on the chosen method of trial information delivery to patients, which included the Patient Trial Information Video. However, the timing of the trial invitation together with the apparent failure of the research team to provide assurance about the quality of care provided for the patients appear to be major themes, even for patients who agreed to take part in the trial. The conscious decision in the trial design to avoid initial contact with a treating surgeon, replacing it with the PTIV approach, may have contributed to this.

The study confirms that most patients apply a 'trade off' process to their

decision making about clinical research participation to the extent that some needed additional independent sources of information. They 'researched it in a small sense' before making a final decision. Moreover, the majority of patients quite correctly assume that surgeons themselves are likely to have a treatment preference to some extent when they assess a patient and his or her injury. It is difficult not to notice that, as a result, for most people a choice between two very different treatments is not equal. Only two out of 23 interviewed patients confirmed individual equipoise about treatment options and did not use the 'trade off' approach. This means that many who agreed to the trial compromised under the weight of social responsibility they felt, rather than being in equipoise. It is not surprising then to learn that the majority felt disadvantaged if they had been randomly allocated a treatment choice which in their eyes was second best, and were unable to compromise. This majority of patients form two large typological groups.

One group is characterised by a more emotional, negative response to interventional forms of treatment and hospitals in general. Their views range from dislike to fear. This is a more fluid group of subjects, susceptible to different forms of external influence and often willing to take advice or accept an explanation. This is demonstrated by two patients. They both start being concerned about and willing to avoid an operation, yet one of them eventually decides to join the trial after discussion with his family, while the other is willing to join if his choice to avoid surgery is respected.

Hence the two patients eventually ended up in two different typological groups. The other two patients from the same initial group converted to the randomised trial participation group during the course of the interview, as they realised the importance and better understood the background of the clinical research.

Patients in the other group take a more rational and pro-active approach in finding the difference between the two proposed treatments, as applied to their individual circumstances. They are committed to the best possible treatment outcome and are positive about participation in research, but without the desire to have random treatment allocation. This is because they want to take responsibility for a decision that may affect their life, rather than give it up to random allocation by chance, which has negative social associations reminiscent of playing roulette. Sometimes there is a direct association with previous experience or knowledge, as demonstrated in two cases who had received prior medical advice before being approached by the trial team. Another patient made a decision based on his previous experience of a serious leg injury that needed surgical treatment.

There is a small number of patients who are initially negative to invasive treatments, but can potentially be converted to randomised trial participation. But there is a much larger number of patients willing to take part, but refusing random treatment allocation on grounds of rationality. Only one patient was directly negative about the trial or research

participation in general. Taking into account one other patient who misunderstood the trial information, and those who did not actively express willingness to take part without randomisation, there are still at least 70% (16/23) patients who could provide valuable research data as described above, as opposed to the 35% (8/23) who actually took part from this group. This is a significant amount of potential clinical data that is ignored with a 'randomised only' Clinical Trials design.

Demand for more targeted treatment information supports the argument in favour of the pre-randomisation approach (Zelen 1990) to patient recruitment in a challenging surgical trial. One of the patients suggested this spontaneously:

> *"Well maybe if they said 'We want to track your progress and we believe this will be an option, a better option,' then it might be you'd get more people being guided or advised to go down the operation route and you'd probably get a better feedback..."* (CH039, 42 year old male, skilled)

Better understanding of the factors that influence patients' decisions about trial participation may indicate areas of the trial recruitment process to be researched further and optimised. In particular, this may inform optimal usage of the novel trial methodology proposed in this study. This is attempted in the next chapter.

Chapter 7 Conclusions

This chapter summarises the study results which answer the research questions set out in **chapter 1.6**. Each research question is stated prior to providing a summary outlining the results described in earlier chapters. The questions cover the whole process of patient recruitment in a challenging surgical RCT, looking at ethical issues, effectiveness and integrity. Perspectives of stakeholders and currently available methodological advice are taken into account. Combination of proposed methodological developments tested in the context of the real life surgical RCT and the patient feedback leads to better understanding of trial recruitment components and their effects on patient decision about trial participation. As the outcomes of each study presented in this thesis are analysed, concerns and areas for further development and research are identified.

In the final part of this chapter, the results of the quantitative and qualitative studies are combined in order to suggest a possible model for future usage of the methodological framework. The model adds to the methodological portfolio available to researchers when considering options for designing an appropriate recruitment process for a specific trial. This new model is a suggestion only at this stage; clearly the practicality and usefulness will only really be tested by implementation in a real-life setting, which should be the subject of future research.

7.1 Study A: PEACE methodological framework

Is it possible to develop a methodology that integrates/transfers the principle of Clinical Equipoise into a clinical trial recruitment process?

A new methodology was developed to determine levels of clinical equipoise for patients in a clinical trial, allowing identification of patients eligible for randomisation **(Chapter 4**). The Patient Eligibility Assessment through Clinical Equipoise (PEACE) framework can be implemented in real time during a trial. It uses modern technology to distribute clinical data for expert assessments on line and state-of-the-art statistical tools to pool and compare collective data. This approach allows one to integrate the core principles of clinical research, such as clinical equipoise and randomisation, in a clinical trial recruitment process.

The PEACE framework adds to the methodological portfolio of trial designs that are available to researchers undertaking challenging surgical trials, particularly those comparing contrasting procedures, where patient recruitment is expected to be difficult. Often the comparison is between higher risk operative interventions and safer, but arguably less effective, conservative measures. There are examples of trials when a traditional fixed eligibility criteria approach simply fails; up until now no methodological alternative has been available in these settings. Examples of such failures include the endoscopic anti-reflux procedures (EARPs) trial (Eckardt, Pinnow et al. 2009), where 134 patients were interviewed,

but only 13 (10%) were successfully recruited. In addition, there were virtually no patient referrals from 50 collaborating private practices and 23 hospitals. The authors blamed the scepticism of the referring physicians and strict selection criteria for this failure. The situation was even worse for MIMOSA, the mixed urinary incontinence (MUI) medical or surgical approach trial (Brubaker, Moalli et al. 2009), where 1198 subjects were screened and approached for study enrolment, but only 27 consented to randomisation. The Early Randomized Surgical Epilepsy Trial (ERSET) (Engel, McDermott et al. 2012) was also stopped prematurely due to much slower than expected patient accrual.

There are two main reasons why the PEACE framework has the potential to improve recruitment in such challenging surgical trials. First, it allows for simpler initial entrance criteria, so more patients would be considered for a trial than with conventional fixed entry criteria (**Chapter 4.4**). Secondly, every potential trial participant is assessed by an expert panel. This is in line with patient expectations from a clinical consultation; that is, to get the best possible advice on the appropriate treatment (**Chapter 1.4**). Expert panel assessment with the option of personal involvement in such an assessment will also likely encourage more sceptical clinicians to take part or refer patients.

As outlined in **Chapter 1.4**, the theoretical basis of the PEACE framework is a recognition that randomised clinical trials are ethical and necessary in

the presence of clinical equipoise. When clinical equipoise exists, it should be difficult to decide on the best treatment or procedure for a patient in most cases. It is accepted as good clinical practice to discuss such cases with several experts before a final decision is made. The PEACE framework aims to identify cases where experts agree about a better outcome for one or another treatment for a patient; in these cases it follows that randomisation becomes unethical and the patient cannot be recruited into the study. It is significant that for some cases recognised as eligible by the fixed eligibility criteria used in the UK HeFT, experts agreed that one or another treatment option was likely to produce a better outcome. It can be argued that these instances indicate that the framework would give patients reassurance that their cases are individually assessed in order to provide the best treatment choice. Conversely, when no consensus about likely treatment outcome has been demonstrated, a clinician would have more confidence that random treatment allocation would not disadvantage their patient even when they may have an individual preference. Similarly, patients offered randomisation would be reassured that opinion across a panel of experts was such that there was no agreement on the best treatment in their particular case. The panel assessment results were easy to interpret and simple enough to be explained to both patients and clinicians (**Chapter 4.3**). Both groups were positive about introducing the new concept in future trials.

The current methodological framework is flexible and open source, so

that it can be adjusted to the needs and specifics of a given trial. Most importantly, for consensus about an intervention choice to be considered, the following factors need to be discussed before implementation and decided by the trial team: a) the questions posed to experts (**Chapter 4.3**); b) the clinical information to be submitted; c) the decision rules for case eligibility or otherwise. Once agreed, the rules need to be accepted by all Principal Investigators and trial centres involved in a study prior to the commencement. I think that the work by Johnson et al. (1991), as used in this study (**Chapter 4.2**), is a good starting point. It is strongly advisable to test the chosen rules in a pilot study, using hypothetical cases and a putative panel of experts if necessary (**Chapter 4.1**).

The expert panel choice is crucial and needs to involve well known and respected specialists in a given area, although votes in all cases must be anonymous. Experts need to be clear how patient trial eligibility is decided and understand that a treatment choice in each case depends on them, in order to increase the level of expert involvement. Experience from the Collective Uncertainty Project (**Chapter 4.3**) suggests that at least four experts need to express their opinion in order to make a case valid for eligibility assessment; however it is clear that a higher number of experts make an analysis more powerful. From the UK HeFT experience, a panel of somewhere between 10 and 20 experts should provide a sustainable number of votes per case over what is often a considerable period of time required for trial recruitment. Expert votes need to be monitored

by the research team and may be questioned, for example concerning the use of overwhelmingly strong votes (e.g. 100% in favour of one or other treatment) or possible bias. It is important for a treating clinician to be able to express their opinion as part of the panel, so that they are directly involved in the clinical decision for their patient and able to compare their vote with the other panellists. PEACE is designed to be 'time light' for the expert clinicians involved; this is achieved, however, through extra work and effort required from the research team.

7.1.1 Concerns and areas for future research/development.

Although tested in the context of a real-life RCT, the PEACE framework was not actually used in the trial recruitment process. Rather, it provided valuable data to guide further developments, so that it can be used in future trials. The web based tool for expert opinion elicitation was constructed from several freely available software blocks (**Chapter 3.1**). This demonstrated that it is feasible, even on a limited budget. It worked well, but had occasional glitches due to factors out of the control of the research team, such as software or system updates. It is imperative and a legal necessity due to data protection issues that the software and patient data should be secure, stable and under the full control of the study research team. If the system developed for UK HeFT were to be used elsewhere, the clinical data input and assessment could be simplified, for example through

compatibility with hospital digital imaging systems, such as picture archiving and communication systems (PACS), and the development of dedicated applications compatible with portable digital devices, such as Tablet PCs.

Currently, statistical modelling is implemented in a high level statistical software package (R Developmental Core Team 2013), but for widespread use by clinicians and clinical trialists a more user friendly point-and-click Graphical User Interface (GUI) would be preferable. It would require a considerable amount of initial (one-off) additional work by programmers to develop such a system.

7.2 Study B: PTIV trial recruitment approach.

How to achieve clear, impartial and consistent delivery of trial information to patients in the context of a challenging surgical trial, when the compared interventions are obviously different?

A new approach to patient recruitment was successfully introduced in a challenging trauma trial (**Chapter 5**): a Patient Trial Information Video (PTIV) supported by a dedicated specially trained study team member to assist with any patient's queries and concerns. The information video and introduction of the trial information moderated by a third party are the two powerful tools known to improve the informed consent process in RCTs (**Chapter 1.4**). They were combined in order to exclude a treating surgeon from initial patient contact, so that a possible disclosure of a likely treatment preference by the surgeon was prevented. This allowed a consistently high standard of trial information delivery to eligible patients and minimised involvement of the clinical team in the research process. The latter proved to be attractive to clinicians involved as Principal Investigators (**Chapter 5.2**) and may have a positive effect on increasing the number of clinicians and centres willing to take part in future trials. Dedicated Research Assistants are now routinely used to approach eligible patients about trial participation in all RCTs set up by the Trauma and Orthopaedics Department in Warwick Medical School.

However, an attempt to exclude the treating clinician from the recruitment

process until a decision about trial participation was made sometimes led to failure to provide sufficient psychological support and assurance, which should be a part of the clinical care provided for a patient in pain and distress. A small proportion of patients were rather upset about not being able to see a treating surgeon early on admission (**Chapter 5.2.2**). In addition, it appears that neither surgeon exclusion nor impartial delivery of clear and high quality trial information managed to improve the level of patient acceptance of randomisation, and consequently of trial participation, as had been hoped. This is in agreement with the previously stated opinion that it is the patient's 'effective equipoise' that is pivotal to any decision about trial participation (Chard and Lilford 1998). Therefore, it is not effective or advisable to limit the surgeon-patient interaction either with the PTIV or possibly with any other trial recruitment approach.

Most previous efforts to improve patient recruitment were concentrated around improvement of quality and understanding of the trial information. Yet reviews of the most effective ways to increase understanding disagreed about their effect on patients' willingness to participate in the actual RCTs (**Chapter 1.4**). This conclusion has been confirmed in the current research.

7.2.1 Concerns and areas for future research/development

The patient feedback (**Chapter 5.2**) should be considered when developing trial video material in the future. Although it is evident that there is significant individual variation in the interpretation of the video, potential participants/lay persons can be involved at earlier stages of production. Different formats could also be considered, for example, including patients with the same condition or from similar clinical trials in the presentation.

Finally, an interesting feature of the Patient Trial Information Video was expressed in the patient interviews. This is the value of being able to watch the video during the lengthy recovery period after the injury (**Chapter 5.2.5**). This could be exploited and researched further, in order to improve retention of trial information and manage patient expectations.

7.3 Study C: Decision process about trial participation.

What is the patient perspective of the recruitment process in a challenging surgical trial, when the best current advice as well as innovative approaches to the principles of patient participation are integrated?

A qualitative study was designed (**Chapter 3.3**) and analysis was performed of significant and emerging themes concerning patients invited to participate in a national multicentre trauma RCT comparing operative versus non-operative treatment (**Chapter 6.1**). Emerging data indicated similar patterns of response to the invitation to take part in the trial, which prompted typological analysis of patients' attitudes in the decision making process about trial participation (**Chapter 6.2**).

The feedback obtained from patients during the three years of the UK HeFT was illuminating. It provided evidence that could be valuable for the design of similar trials in the future.

At the present time, clinical research is not usually expected by patients to be an integral part of clinical care (Robinson, Kerr et al. 2005). Yet trialists assume an informed rational approach from subjects to the decision about committing to a research process, in particular random allocation to an intervention group. Possibly, this stems from the ethical responsibility to provide all important information about the compared interventions and the research process, in order to ensure informed consent or refusal to participate (**Chapter 1.4**).

This study confirms previous reports that most patients struggle to understand and retain trial information, especially in the hospital environment, where they may be affected by medication and have difficulty coping with change in their condition (**Chapter 6.1**). Although some of them are happy to consider all possible information about a treatment choice, most found the sheer volume and type of information provided overwhelming. In particular, patients are very uncomfortable with uncertainty about a treatment choice, as presented in current RCT designs. In a pragmatic clinical consultation scenario, a clinician is expected to provide an individual assessment and expert advice, which needs to balance carefully the advantages, risks and availability of alternative treatments. Patients with newly diagnosed conditions or injuries, often in pain and distress, request some psychological support and reassurance of the best clinical care as part of good standard clinical practice. It appears that the current trial recruitment process interferes with, and may even exclude, this clinical decision making process, by the application of fixed eligibility criteria. Even patients who agreed to take part in the UK HeFT mostly did it due to a sense of social responsibility, rather than being comfortably in equipoise about a treatment choice.

A surprising alternative suggestion to reduce research process interference in the clinical care process was uncovered. This came up spontaneously from several interviewees from the UK HeFT (**Chapter 6.1.2**). Patients were rather uncomfortable with the idea of accepting two very different

interventions as being equally good, yet not knowing which one they were going to have. They were desperate for some form of guidance and reassurance from their surgeon that one or another treatment was a good choice for them, even where there was no evidence to support which one was better.

This is suggestive of pre-randomisation (**Chapter 1.4**), where an eligible patient is randomly allocated to one of the compared treatments before being approached for potential recruitment (Zelen 1990). This technique was used successfully (83% recruitment rate) in a previous significant large trial of calcaneal fractures in Canada (Buckley, Tough et al. 2002). Pre-randomisation was considered for the UK HeFT, but later dropped because a patient is randomised without a consent, which is difficult to justify ethically.

The typological analysis (**Chapter 6.2**) highlighted the different approaches patients adopted to deal with this additional stress. While some were passive or even intimidated by the clinical and research data provided, others pro-actively took charge of the clinical decision making process. Using available external sources of information and their own judgement, they usually preferred and chose one treatment or the other. The treatment preference was the main reason for non-participation in the UK HeFT, despite most of the participants being positive towards clinical research. However, this undoubtedly subjective and biased approach produced evenly

split and similar patient groups (146 preferred operative and 144 non-operative care, **Fig. 3.1**), closely resembling those obtained from random treatment allocation. These groups represent a significant number of patients (83% of 351 who refused to take part in the UK HeFT) who are committed to the best treatment outcome, yet are ignored by researchers, unless an inclusive trial design is used (Torgerson and Sibbald 1998).

In addition, most of those excluded from the research analysis due to treatment preference appear to have a specific psychological profile. They are pro-active about the decisions leading to their treatment choice and committed to the best possible outcome for the chosen treatment. These subgroups of patients (**Fig. 6.2**) can be seen in the light of a new theory of patient attitudes in the surgical trial. This highlights that certain types of patients are not and cannot be included within the current recruitment approach, affecting the generalizability of the results. This may be viewed as a selection bias secondary to, or even caused by, current methodological approaches to patient recruitment. In turn, this may contribute to failure to spot a difference between treatment outcomes, or indeed even to erroneous inferences for the whole trial.

7.3.1 Concerns and areas for future research/development

A major limitation of this work is that the above results concern a single trial centre in a single orthopaedic trauma RCT, albeit a multi-centre study. This was my first experience of qualitative research, although I had support and guidance from senior qualitative researchers. In order to make stronger and wider inferences, the results would need to be replicated in the setting of other challenging surgical RCTs.

7.4 Mixed methods – research success story

Arguably the most significant outcome of this research project is the development of the novel methodological framework for Patient Eligibility Assessment through Clinical Equipoise (PEACE), that was successfully tested during a real clinical trial (**Chapter 4**). It is, however, the qualitative study of patient experiences in this trial (**Chapter 6**) that can guide the future use of the new framework. This is because it is the patient's 'effective equipoise' that matters in the trial recruitment process (Chard and Lilford 1998).

7.4.1 Model for future use

The UK Heel Fracture Trial (UK HeFT), that provided a setting and platform for the current research, is a typical example of a challenging surgical RCT that is the subject of this research (**Chapter 2**). Contrasting operative and non-operative treatments have been compared, so patient recruitment was expected to be difficult. The trial recruitment process was set up according to the latest methodological advice, including introduction of a novel combination of two powerful tools known to improve the informed consent process in RCTs: a trial information video and availability of a dedicated research team member to address patient's concerns (**Chapter 3**). These measures, however, failed to improve the level of trial

recruitment. It was low, but comparable to other similar trials (**Chapter 2**).

As highlighted earlier (**7.3**), patients found the suggestion of random allocation to a treatment group disruptive to the expected pattern of normal clinical care. What they expect is expert advice, discussion with the treating clinician and support to make the best possible choice of treatment. This expectation helps to explain the success of the pre-randomisation approach used in previous similar trials (Chang, Falconer et al. 1990; Buckley, Tough et al. 2002); in this methodology an eligible patient is allocated to one of the interventions to be compared prior to being approached about trial participation. The consultation process that follows then resembles a standard clinical situation, when a pre-allocated (proposed in standard practice) intervention is offered, although in the context of research participation. The control (alternative in standard practice) intervention is described as an equal and available alternative, should the patient have a strong preference and decide to decline the pre-allocated treatment. Indeed, such an approach was spontaneously suggested by some patient interviewees from the UK HeFT.

The major obstacle that prevents a wider use of pre-randomisation is the ethical concern about the lack of consent when the research process (i.e. pre-randomisation) has been initiated (**Chapter 1.4**). However, if the PEACE framework was introduced, this ethical issue would be eliminated. This is because pre-randomisation at the point of trial eligibility assessment

can happen after a prospective patient is approached by a clinical team initially and alerted about an ongoing study. Permission for their clinical data to be assessed by an expert panel would be sought in the context of a consultation process to identify an optimal intervention, if sufficient agreement between experts is present. A treating clinician can engage in the panel assessment of a case. In this way, the initial decision by a patient to engage in the research process (expert panel assessment) is not associated directly with the dilemma of random allocation to the compared interventions, which is often viewed negatively by patients. Rather, they allow the expert panel to determine a more appropriate intervention when possible or random allocation, if no consensus is reached. Pending the panel's decision, a period of time is available for a patient to consider and prepare to face uncertainty and a possibility of different outcomes.

It is my aim to set up a follow up study that would involve the PEACE framework linked to the pre-randomisation approach in the trial recruitment process, according to the model described above. Close collaboration with specialists and/or researchers in statistics and information technology would be essential for success of the future projects. I hope to overcome justifiable scepticism from the research community, funding bodies and ethical committees through a series of engaging publications, arising from data acquired already. Positive and encouraging feedback from both experts and patients in the UK HeFT is a powerful driving force for this task.

A larger pool of patients approached about possible trial participation (**Fig.4.8, Chapter 4.4**) and improved patients' experience of research involvement may appeal to the wider concept of larger, simpler trial designs, so that they become integral, rather than disruptive, to normal clinical practice. The data acquired then guides the trial until the research objective is achieved or shown to be not worth pursuing (Weijer, Shapiro et al. 2000).

A weakness of this study is that the main conclusions and recommendations are based on evidence collected from a single, albeit multi-centre, RCT. Potentially, due to some unknown or unforeseen reasons, these data may have misled us and provided a poor evidence base on which to make recommendations. The effectiveness of the PEACE framework in identifying eligible patients and eventually improving trial recruitment rates is yet to be proven. In particular, it has not yet been proven whether the process of Patient Eligibility Assessment through Clinical Equipoise will meet patients' primary expectation and demand for the best possible care and interventions applicable to their case. So it may be that until the methods developed here can be shown to be useful in at least one other study, it is likely that there will be scepticism within the research community and limited take-up or buy-in.

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Appendix A

UK HeFT collaborating hospitals

Addenbrooke's University Hospital, Cambridge

Arrowe Park Hospital, Wirral

Aintree University Hospital, Liverpool

Birmingham Heartlands Hospital

University Hospital Wales, Cardiff

Cheltenham General Hospital

Gloucester Royal Hospital

James Cook University Hospital, Middlesbrough

King's College Hospital, London

Leeds General Infirmary

Leicester Royal Infirmary

Musgrove Park Hospital, Taunton

Northern General Hospital, Sheffield

Norfolk & Norwich University Hospital

Royal Bolton Hospital

Royal Devon & Exeter Hospital

Royal Liverpool Hospital

Royal Victoria Hospital, Belfast

Selly Oak Hospital, Birmingham

Ulster Hospital, Belfast

University Hospital Coventry & Warwickshire

Wrexham Maelor Hospital

Appendix B

Statistical analysis of the UK HeFT patient demographic data

UK Heel Fracture Trial: Statistical Summary (25–Feb–2011)

Data Screening

The Centre Patient Log at the end of recruitment has background data on 1325 individuals.

All the background information is available for the 152 enrolled individuals. Of the 1173 non-enrolled individuals, four have invalid Gender and have been omitted for simplicity, leaving 1321 individuals in the following analysis. Also, nineteen non-enrolled individuals had unknown dates of birth (DoB); given the distribution of the known ages (see for example Figure 1) it seems very likely that these individuals were elderly. The previous statistical summary (31–Aug–2010) omitted these nineteen subjects; the current analysis includes them with a conventional DoB 22–Dec–1922, possibly giving a more accurate picture of the overall age distribution of the non-enrolled subjects, though not of the specific ages of some of the oldest individuals.

The 1321 individuals may be classified according to *enrollment status*, defined as

1. Enrolled (152 patients)
2. Eligible but refused (331 patients)
3. Ineligible with bilateral fractures (60 patients):
   32 during 2007 when bilateral fractures automatically implied ineligibility,
   28 from January 2008.
4. Ineligible without bilateral fractures (778 patients).

Apart from the specific issues raised above concerning DoB and occasional missing Gender, which only affect non-enrolled individuals, the data quality appears excellent—for example, gender is compatible with name (when given).

Drop-out Rate

A total of 132 out of 152 enrolled individuals (87%) completed the 6-month form. For individuals enrolled in 2007, 2008 and 2009 the proportions were 26/33 (79%), 50/61 (82%) and 56/58 (96%) respectively. Note that early in the trial, some subjects withdrew shortly after randomization, or were found to be ineligible (e.g. by being outside the 3 week limit since injury).

The final 24-month form has so far been completed by 92 individuals enrolled on the trial. Of these, 76 (83%) have completed all four forms (6-, 12-, 18- and 24-month), and 10 (11%) had not completed the 6-month form.

Everyone recruited by the end of January 2009 should have completed the 24-month form by now; 89/99 (90%) have done so. Of the 10 who have not completed the 24-month form, 5 did not complete any of the forms.

Everyone (53/53) recruited after January 2009 has completed at least the 12-month form, compared to 82/99 = 83% of those recruited up to the end of January 2009. If the current pattern continues, then we can expect at least 90% (137) of the 152 enrolled individuals to complete the 24-month form, and about 85% to have completed all four forms.

Data Summary

The following tables summarise number of patients by *gender*, *age* on admission, and *status*.

		Age (decade)										
	Status	< 20	20–	30–	40–	50–	60–	70–	80–	90–	100–	**Total**
Female	Enrolled	1	3	5	3	4	4	4	0	0	0	24
	Refused	2	11	11	11	14	7	3	2	0	0	61
	Bilateral	1	5	5	1	0	0	0	0	0	0	12
	Ineligible	14	24	27	27	26	32	31	23	3	0	207
	Total	18	43	48	42	44	43	38	25	3	0	**304**

		Age (decade)										
	Status	< 20	20–	30–	40–	50–	60–	70–	80–	90–	100–	**Total**
Male	Enrolled	2	17	29	28	19	24	8	1	0	0	128
	Refused	6	47	47	69	48	37	10	5	0	1	270
	Bilateral	2	14	13	8	4	3	3	1	0	0	48
	Ineligible	41	160	131	93	59	54	17	12	2	2	571
	Total	51	238	220	198	130	118	48	19	2	3	**1017**

Thus out of 304 women, 85 (28%) were eligible for entry to the trial, and 24 (8%) were enrolled; whereas out of 1017 men, 398 (39%) were eligible, and 127 (13%) were enrolled. The proportion of eligible individuals refusing to be entered into the trial is similar at 61/85 (72%) for women and 270/398 (68%) for men.

Representativeness of Data

An important feature of the current data in the Centre Patient Log is that the injury tends to occur in younger men and in older rather than younger women, yet younger men and older women are more likely to be ineligible, and possibly less likely to be enrolled, as shown in the following tables.

		Status			
	Age	Enrolled	Refused	Bilateral	Ineligible
Female	50+	12	26	0	115
	< 50	12	35	12	92

		Status			
	Age	Enrolled	Refused	Bilateral	Ineligible
Male	50+	52	101	11	146
	< 50	76	169	37	425

Thus women and younger men in particular may be underrepresented in the trial; any such patterns will of course be considered when interpreting the trial results.

More detail on these patterns can be seen in Figures 1 & 2 (on the next two pages).

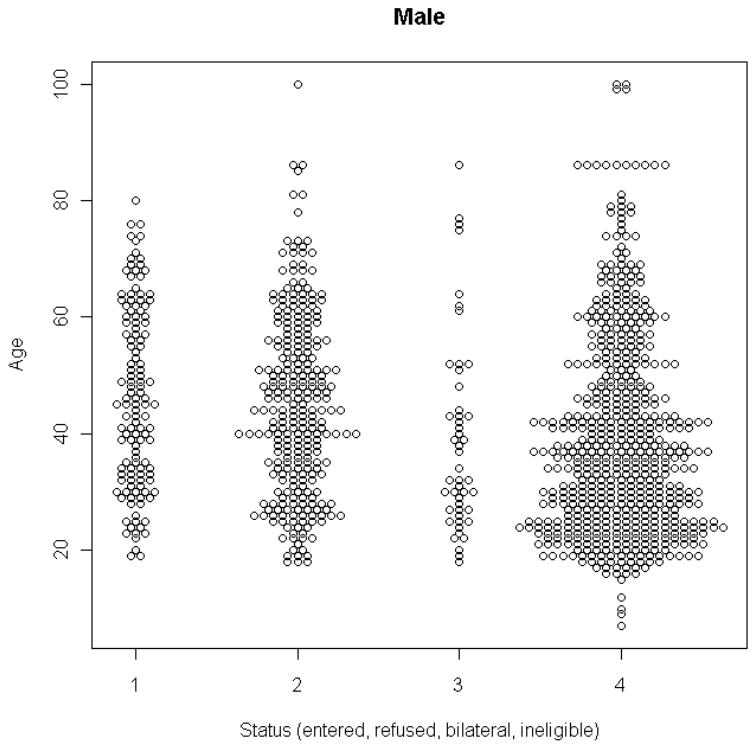


Figure 1: Age by enrollment status (Males)

Figure 1 suggests that younger men are rather more likely than older men to be ineligible for entry to the trial (in many cases because of alcohol, drug or psychological problems). Other than that, the age distribution for men is broadly similar across all four categories.

Note that all but one of the ages around 86 correspond to males given the conventional DoB 22–Dec–1922, however the five ages around 100 look unusual but seem to be genuine.

Female Enrollment

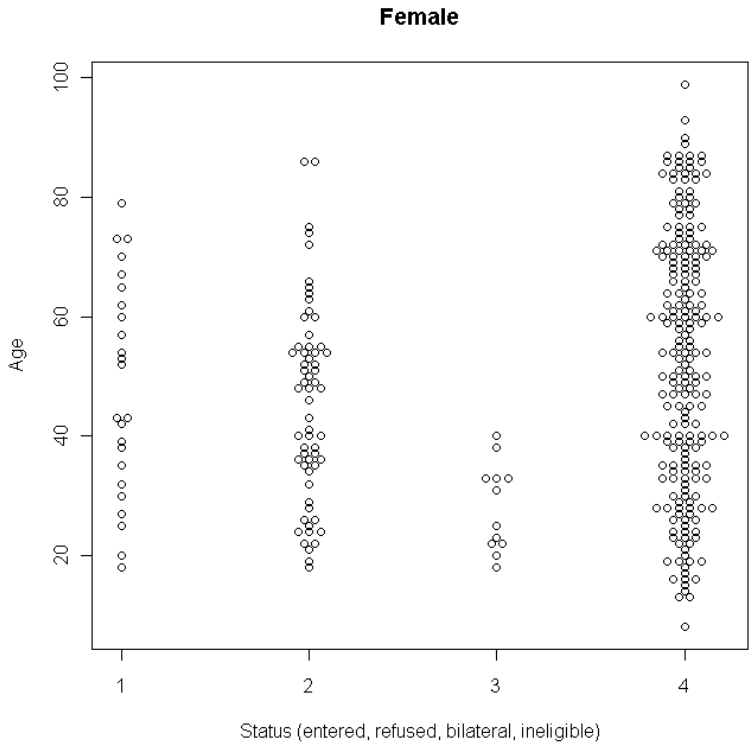


Figure 2: Age by enrollment status (Females)

Figure 2 shows considerable differences in the age distributions. Compared to the men, older women are less likely to be eligible for the trial, and middle-aged women are perhaps more likely to refuse to be entered even if eligible. Also, of ineligible females, bilateral fractures are more common in younger women.

Effect of Including Bilateral Fractures

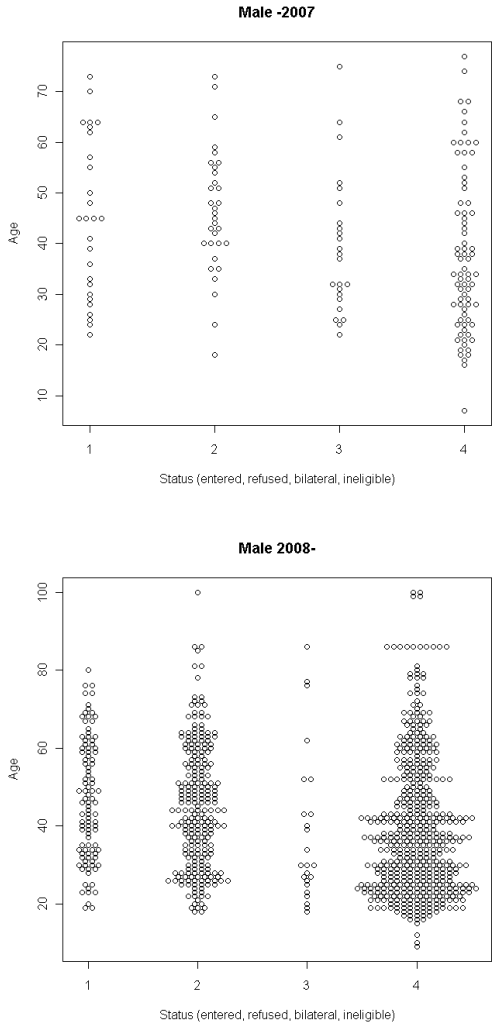


Figure 3: Enrollment split at January 2008

Figure 3 plots enrollment status for males up to the end of 2007, and from January 2008 onwards (when patients with bilateral fractures were no longer automatically excluded). The plots show that the age distributions are similar, but that many patients with bilateral fractures became eligible for the trial. Corresponding plots for females have been omitted, as the data are too sparse.

J. E. H. Shaw (Statistician)

Appendix C

Collective Uncertainty Project ethics amendment

National Research Ethics Service

Oxfordshire REC A
2nd Floor, Astral House
Chaucer Business Park
Granville Way
Bicester
OX26 4JT

Tel: 01869 604077
Fax: 01869 604055

30 May 2007

Professor Damian Griffin
Professor of Trauma and Orthopaedic Surgery
Clinical Sciences Research Institute
Clifford Bridge Road
Coventry
CV2 2DX

Dear Professor Griffin,

Study title: **Uk Heel Fracture Trial**
REC reference: **06/Q1604/58**

Amendment number: **4**
Amendment date: **15 May 2007**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 23 May 2007.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	Final (relevant pages)	01 November 2006
Corporate Uncertainty Project workflow	1.0	15 May 2007
PIS/CF Corporate Uncertainty	1.0	
Notice of Substantial Amendment (non-CTIMPs)	4	15 May 2007

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

06/Q1604/58:	Please quote this number on all correspondence

Yours sincerely,

Mr Gordon Riddell
Committee Co-ordinator

E-mail: oethicscommitteea@nhs.net

Enclosures List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: *Professor Steven Thornton, University Hospitals Coventry and Warwickshire NHS Trust*

Oxfordshire REC A

Attendance at Sub-Committee of the REC meeting on 23 May 2007

Name	*Profession*	*Capacity*
Ms Sara Owen	Medical Ethicist / Alternate Vice-Chair	Lay
Dr Brian Shine	Hospital Consultant / Chair	Expert

Also in attendance:

Name	*Position (or reason for attending)*
Mr Gordon Riddell	Committee Co-ordinator

Appendix D

Collective Uncertainty Project patient interview schedule

Preamble:

I'm interested to know about how and why you were invited to take part in the UK Heel Fracture Trial, what sort of trial it was, what kind of information you were given, what you decided and why, what it was like taking part, and how you feel about it now looking back. I'd like you to tell me your story/what happened in your case with as much detail as possible. Then I may have some extra questions if you haven't already covered them in what you say.

Prompts:

Recruitment, information and consent

How did you first hear about the trial (i.e. A&E, nurse on ward, admitting doctor…?)

Who approached you? What did they say/how did they communicate? Why do you think they approached you?

What information were you given? How well written was it? What did you think of DVD? Was it what you needed?

What did you understand about the trial? What was it testing for?

Did you feel that you understood about the trial and the treatments involved?

Do you think the Research Associate who talked to you understood it?

What did the Research Associate /doctor say about the treatments being compared?

Did they talk about uncertainty?

Did you feel that you were able to ask all the questions that occurred to you and were they answered fully?

Why did you decide to take part/not take part? Probe for main and subsidiary reasons. If not, could your decision be different if it was a drug trial?

How easy did you find it to make up your mind?

Did members of your family or your friends influence your decision about whether to participate? How?

Did you feel put under any pressure either way? Gratefulness / social desirability / attention - Did you feel that the Research Associate /doctor was hoping that you would agree to participate?

Were you hoping that you'd be allocated to one group rather than the other(s)? If so, did you discuss this with the Research Associate / doctor?

Do you have any sense that there is a moral duty to take part in research? (Role of faith?)

Did you know much about trials and research beforehand? Media reports?

In trials people may use a lot of technical terms – words like randomisation, control groups, placebo, intervention, blind or double-blind. Did you feel you were given enough explanation of terms like this? Are there things now you feel you didn't understand or wish you'd known more about?

What's your understanding of what randomisation is and why it's needed?

Taking part

How did you feel when you learnt which group you had been allocated to?

What was it like taking part in the trial? What did it involve for you?

Did you ever think about dropping out (or why did you drop out?)

Do you think you got 'better' treatment as a result of being in the trial? What kind of extra or better things?

Did you have someone you could contact if you were uncertain about anything?

Were you ever unsure about what to do, e.g. on holiday?

Were there any side effects for you?

Any implications for personal/family relationships?

Afterwards

Are you having any long-term follow-up? How is this organised?

Are you glad you took part or do you have any regrets?

Do you know who funded the trial? Does it matter to you where the money for a trial comes from?

What are your feelings about the way trials are organised?

Is there anything you'd want to say to NHS professionals about the conduct of trials?

And to policy-makers? Do you think that more should be done to raise public awareness about taking part in clinical research as a treatment process?

What would you say to anyone else thinking about whether to take part in a trial?

PTIV - Show the DVD with pause for any comments along the way. Then

give time to reflect.

Uncertainty - You may remember that we did a study about uncertainty. Your injury was assessed by several surgeons specialising in foot and ankle trauma across the UK. This is a diagram demonstrating their opinions (explain a diagram). Is it easy to understand?

Do you think it could be helpful to you at this stage? In what way? Would uncertainty diagram help in your decision at the time?

Appendix E

Ethical Approval for the CUP patient interviews

NHS
National Research Ethics Service

Oxfordshire REC A
2nd Floor, Astral House
Chaucer Business Park
Granville Way
Bicester
OX26 4JT

Tel: 01869 604077
Fax: 01869 604055

20 March 2009

Prof Damian Griffin
Professor of Trauma and Orthopaedic Surgery
Clinical Sciences Research Institute
Clifford Bridge Road
Coventry
CV2 2DX

30 MAR 2009

Dear Professor Griffin

Study title:	**Uk Heel Fracture Trial**
REC reference:	**06/Q1604/58**
Amendment number:	**Number 8**
Amendment date:	**N/A**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 13 March 2009.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	Number 8	
Participant Consent Form: Patient Interview	2.0	
Patient Reply Slip	1.0	
Protocol	1.0	
Uncertainty Graph (sample)		
Interview Schedules/Topic Guides	1.0	
Covering Letter		18 February 2009
Participant Information Sheet: Patient Interview	1.0	

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

R&D approval

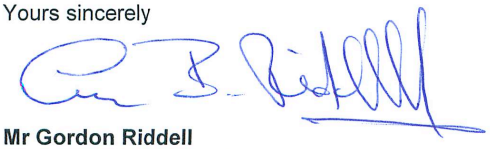
All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

06/Q1604/58:	Please quote this number on all correspondence

Yours sincerely



Mr Gordon Riddell
Committee Co-ordinator

E-mail: scsha.OxfordRECA@nhs.net

Enclosures — List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: — *Prof Steven Thornton*

Appendix F

Patient information/invitation to the interview with reply slip

Corporate Uncertainty Study (Patient Interview)

Hello

My name is Yuri Kulikov. I am a researcher from Warwick Orthopaedics, Warwick Medical School. I would like to invite you to an interview about your experience of the UK Heel Fracture Trial. It does not matter if you agreed to take part in the trial or not. Before you decide if you want to be interviewed or not, I want to tell you why the interview is being held, and what you can expect if you do take part. Please read what I have to say carefully, talk about it with friends or relatives if you wish and feel free to ask me any questions you may have. Please take as much time as you like to decide.

Thanks for reading this.

What is the purpose of the study?

Randomised controlled trial (RCT) is the most reliable method to compare different treatments. However, they are particularly difficult to do when

surgical treatments are studied. The UK Heel Fracture Trial was set up to the best standards for modern clinical trials and also used some new methods which we hope provide better understanding and experience for patients who are invited to take part in the trial.

We hope that information from interviews will help researchers and health professionals to understand what it is like for people to receive an invitation to and/or to take part in a surgical clinical trial . We would like to know if we provided sufficient support and information for you to make an informed decision about taking part in the trial.

Why have I been chosen?

Everybody who agreed to provide their data for our Corporate Uncertainty Study will be invited for an interview. This is partly because it is very important that we hear views of different patients - those who either agreed or not to take part in the trial, those who had an operation or not, those who are happy or not with their experiences etc. Also we have very interesting results from the Corporate Uncertainty Study which we want to share with you during the interview. We want to hear your opinion before we consider using this assessment tool in future.

Do I have to take part?

No. It is entirely up to you to decide whether or not you want to take part. If you decide to take part you will be asked to sign a 'consent form'. You

are still free to withdraw at any time without giving a reason. No questions will be asked if you stop. If you do not take part, or stop taking part, the care you get from your doctors and nurses will not be affected in any way.

What will happen if I take part?

If you complete and send back the enclosed 'reply slip', I will contact you to arrange an interview at a time and place that suits you. We suggest for the interview to take place in your local hospital. You will be paid for the cost of your travel. However, you may choose to be interviewed at home. I will try to answer any questions you may have about the interview or the Corporate Uncertainty Study.

What would the interview be like?

If you agree to take part in the interview you will be given the 'consent form' to sign. You will keep a copy of the consent form. The interview will be audio recorded.

The interview will be a little like a conversation, but I will help you talk about yourself in your own words. I will ask you to talk about your experiences of the UK Heel Fracture Trial. I will ask questions about what happened to you, what your thoughts and feelings have been at different stages, how you have got information, what you have done, and what have been the good and bad parts of the experience.

While people sometimes find it helpful to talk about their story to researchers this research is not the same thing as counselling. However, I can provide you with contacts which can be used to get more help if you want.

How long would the interview take?

The time it takes for an interview varies, depending on how much you have to say, but most interviews last at least an hour. If you would prefer, I can interview you on two different occasions. Remember, if you want to stop the interview at any time, you can do so without giving any reason at all.

What would happen after the interview?

I will label the interview tape with a code number and give it to a typist who will type out everything you said in the interview. The typist signs an agreement to keep everything you say in the interview secret. The tape and the typed up record (transcript), identified only by the code number, would be kept in a secure place at Warwick Orthopaedics.

What you said will be analysed and compared with issues raised by other interviewees. Results will be presented in medical and scientific meetings and published in medical and scientific literature. Your name will not be disclosed in any way. The interviews will not be used for profit or commercial gain.

What if I decide to withdraw after the interview has taken place?

You are free to leave the study at any time. If you decide to leave after an interview has taken place, all tapes, transcripts and typing of your interview will be destroyed.

Who is organising and funding the research?

Warwick Orthopaedics is a research body of the Department of Trauma and Orthopaedics, Warwick Medical School, University of Warwick and sponsors this research.

Contact for further information

I hope that this information sheet has told you what you need to know before deciding whether or not to take part. If you have any queries at all about the project or wish to make a complaint please email Y.I.Kulikov@warwick.ac.uk or telephone Yuri Kulikov on 07725666023 or Professor Damian Griffin on 024 7696 8616.

Notes:

- I am a professional researcher and am paid for my work.

- The study has been approved by Multi Centre Research Ethics Committee for health research (Ref. 06/Q1604/58)

- The Warwick Medical School has a specific insurance policy to protect patients who take part in research. The insurance provides for 'no fault compensation' consistent with that provided through the Association of British Pharmaceutical Industries (ABPI), as well as for legal liability.

Many thanks for reading this information sheet.

Corporate Uncertainty Study – interview reply slip

Please, fill in the relevant options, sign and post back in the pre-paid envelope provided:

☐ Yes, I am happy to be interviewed as part of the above study

☐ I am considering being interviewed, but would like you to address following questions/concerns: (alternatively, email Y.I.Kulikov@warwick.ac.uk or call 07725666023)

☐ I do not want to be interviewed (please, consider contacting Yuri Kulikov, Principal Investigator, or leave your contacts below for him to get in touch before you make a final decision)

Name: Signature:

Date

To arrange the interview you can contact me by:

Email Mobile

Telephone

Thank you!

Collective Uncertainty Project: Final Analysis

Expert questionnaire

Dear Mr. X

Thank you very much again for continuous support of the Uncertainty Project. To complete the data analysis we need to ask you to complete this final questionnaire. All the data provided will be treated as confidential and reported anonymously.

Background information.

1. Specialist register / certificate / FRCS(Orth) year

2. Time in research/academic post years months

3. Research degree (if any)

Appendix G

Surgeon questionnaire about the CUP expert panel participation

Collective Uncertainty Project: Final Analysis

Expert questionnaire

Dear Mr. X

Thank you very much again for continuous support of the Uncertainty Project. To complete the data analysis we need to ask you to complete this final questionnaire. All the data provided will be treated as confidential and reported anonymously.

Background information.

1. Specialist register / certificate / FRCS(Orth) year

2. Time in research/academic post years months

3. Research degree (if any)

Your vote counts.

4. You have been one of the more frequent voters in the project. In your opinion, what are the factors that influenced this?

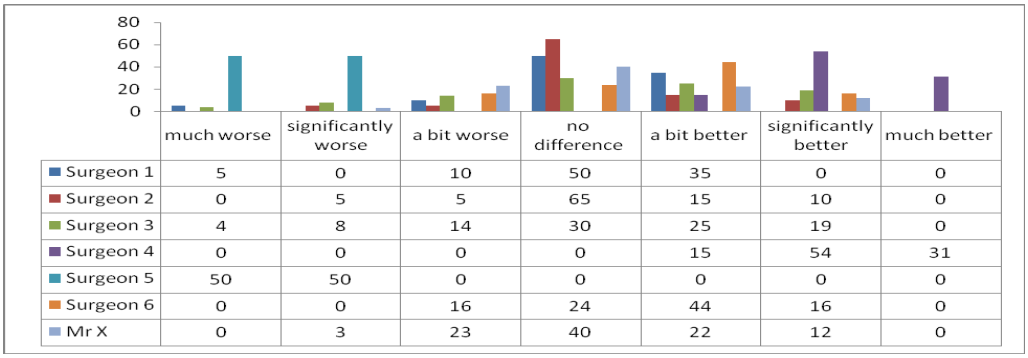
5. Would you agree that this is a "low research time burden" methodology, i.e. little time and effort is necessary to take part?

Yes ☐ No ☐ Other ☐ (please, explain)

6. Would you support this methodology to be adopted in a real life clinical trial?

Yes ☐ No ☐ Other ☐ (please, explain)

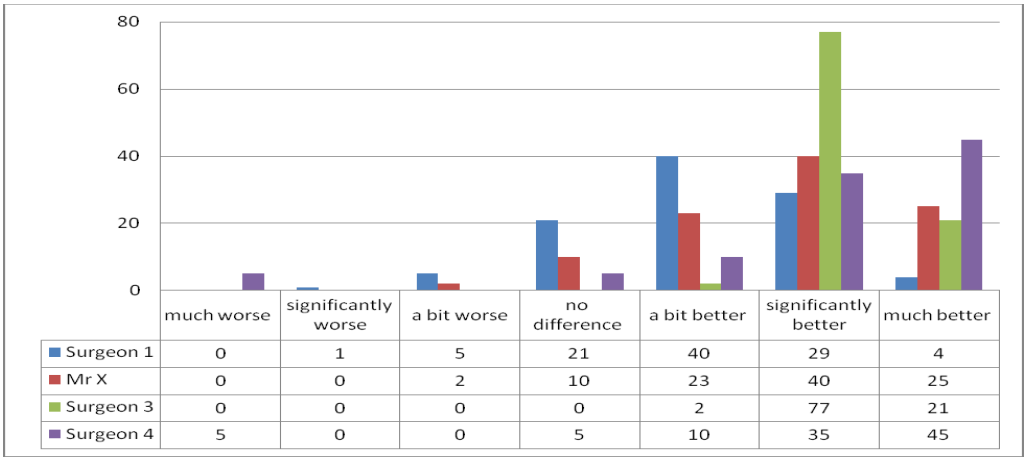
Typical example of your vote with the panel in a case:



	much worse	significantly worse	a bit worse	no difference	a bit better	significantly better	much better
Surgeon 1	5	0	10	50	35	0	0
Surgeon 2	0	5	5	65	15	10	0
Surgeon 3	4	8	14	30	25	19	0
Surgeon 4	0	0	0	0	15	54	31
Surgeon 5	50	50	0	0	0	0	0
Surgeon 6	0	0	16	24	44	16	0
Mr X	0	3	23	40	22	12	0

7. Having seen that surgeons approached voting process differently (meaning percentage distribution rather than expressing different opinions), would you like to comment about this?

Below is a rare example when a patient was eligible for the UK HeFT, but surgeons from the Uncertainty panel recommended operative treatment:



	much worse	significantly worse	a bit worse	no difference	a bit better	significantly better	much better
Surgeon 1	0	1	5	21	40	29	4
Mr X	0	0	2	10	23	40	25
Surgeon 3	0	0	0	0	2	77	21
Surgeon 4	5	0	0	5	10	35	45

8. On the basis of votes in this or similar case, would it be more appropriate

☐ to randomise as usual

☐ to offer treatment according to surgeons' consensus

☐ other (please, explain)

Appendix H

Examples of tabularised interview analysis according to patient types

Table H1 Help others

Patient and context attributes	Cue selection	Relevant cues	Psychological representation of cues	Cue integration	Potential outcomes (risk assessment)	Certainties	Outcomes Happy?
CH023, male, 41-60, skilled self-employed	I think it helps you blokes to sort out the best way to help people and if I can help you to help people then I'm doing my bit.	if you've got no feedback from patients or don't do trials then you just plod along doing what you think is the right way of doing things and probably not. You don't know unless you do trials like this, so I was quite happy to participate on trials like this.	You have to, to help people out and to sort out the best procedures. That's the way I feel anyway and that's what I'd put over to somebody else.	- my reason for saying to my dad to go on the trial was because if the likes of myself... I didn't know at the time then, but if the likes of my dad doesn't help then how do people like you know which is the right way to go about looking after injuries? - to get onto a trial basically because you're helping other people down the line and if they don't do the trial and nobody else does the trial then how do we know what is the correct procedure to fix bones and injuries and everything else? If people won't do the trial then we all sit in the dark and we just plod on how we've been going for years and years and years. How does new technology start if people aren't prepared to do trials?	The Professor said that you might have to have another operation and it was like, 'No I don't want that.' I didn't want to go through that again. Do you know what I mean? So I was quite happy when they said 'you're non-operative', but it would have been nice if I'd have had surgery so I could...like I say, to compare with my dad.	Even if my father hadn't have done it and they'd have come straight to me and said 'We've got a trial,' and this and that and the other, so 'Would you be willing to participate?' then I would if I was offered it again.	Trial yes No surgery It came like I say as non-operative, which in a way I suppose is OK because you haven't got to be cut open or pinned and everything, so... I don't know. I don't know whether it was a good idea or a bad idea, I'm not too sure

Table H2

"I need to decide"

Patient and context attributes	Cue selection	Relevant cues	Psychological representation of cues	Cue integration	Potential outcomes (risk assessment)	Certainties	Outcomes Happy?
CH046 – male, 41-60, professional	- I'll be happy to be part of the trial but I don't want an operation on it - I think if I had an operation I might have disadvantaged myself.	- I'd gone onto the internet to look at research about operations and the success and whatever. - Everyone is different, but she gave me some guidance to go on some sites to look at the sites - Family and friends; I'd gone through a lot of family and friends. - that's what put me off more than anything; not just having one operation, but maybe over time or before it actually gets right, it's having pins in the foot. - There were some horrific sites that put me off. Now, the L shape in the heel where you see it after with the infection and stuff like that, that sort of put me off.	- I would say to people don't rush into anything. Spend a bit of time. Speak to your friends and speak to your family. Think about it. Spend forty-eight hours thinking about it and if there is any other research you can do then speak to some of you guys. - I had to take it seriously. - I think the way the decision was sent to me and you'd come out of hospital, you'd seen that, you'd spoken to the consultant and then at the end of the day the ball was put in your court. It's your decision, so you're going like, 'Well aren't you guys the experts here?'	- No one could actually define what was right and what was wrong, whether operative or non-operative and just having a bit of independent research on it helped me. It probably put me off a lot of things. - 60 percent I wouldn't be part of the trial and 40 percent I may be part of the trial until I'd seen the CT scan, so I based it on some of the stuff I'd seen online to see how bad or how shattered the heel was and when I saw the scan, it was yes, there were fractures there but I personally didn't think it was as bad as what I'd actually seen on websites	- They took into account the risk of infection, the risk of further operations, so I actually made that decision there and then.	- part of the trial is to enhance and make better the services and the rehabilitation - hence why I'm more than happy to support this and if I can help in any way, I'm definitely more than happy to do that.	- no trial - no surgery - Yes, I think I made the right decision. Yes, I mean you never know what's going to happen. - I don't think it will ever be a hundred percent. I used to do a lot of walking, hill walking. I haven't actually tried that, but I have walked for about four or five miles so I can start the walking again and getting back into doing a lot more swimming again and stuff like that now. Yes, so it's not really getting in the way. It's just something I'm living with, with a bit of pain every so often.

Table H3

No surgery/no hospital - negative attitudes to invasive treatment and/or hospital

Patient and context attributes	Cue selection	Relevant cues	Psychological representation of cues	Cue integration	Potential outcomes (risk assessment)	Certainties	Outcomes Happy?
CH030 – Male, 41-60, manual labour	- It didn't give me much incentive to have the operation to be honest with you and maybe that's because I wanted to get out of hospital as soon as I could - I've never once thought, I wish I would have had the operation - I just hate hospitals like, you know. I just wanted to get out, as a lot of people do.	- 'Well what happens if I don't have the operation?' and they said 'Well you're out of hospital today and you'll be on crutches for six weeks and you might have a limp.' So I opted not to have the operation - they kept telling me how mine would mend itself without pins, I mean they said the chances are I'd get arthritis. - she basically said, 'It's entirely up to you.' She said 'I can't tell you to have an operation or not to.' She goes, 'All I can say is you can have the operation if you wish.' You know, so I'm not saying that I didn't get a great deal of information because I probably did and I probably wasn't taking much notice to be honest. - I don't think a computer should tell me if I'm going to have an operation or not. You know, I think that is down to the individual	- I just can't help thinking that if someone says to someone 'Look, you can have the operation or you can't,' that you can or you have a choice, so you either have the operation or you don't, right? Going back to what I said, if someone is scared then they're going to say no every time. - just turning round and saying 'It will benefit you a lot to have this operation' and then it eases everything doesn't it? - sometimes people, if they're given a choice of an operation they might be scared. You know, they're saying 'Well you can have this operation or you can't, but we advise you to have it.' But if people are scared they'll say 'Well, he's not telling me I've got to have it,' so they'll say 'I won't have it.'	- if I'm truthful with you, it didn't make sense about the operation - I didn't think there was any point of having the operation `when the outcome they said would be the same, apart from I'd be in hospital longer. I know with some people, if it's bad they have to have the operation, but I think I was given the choice because it was a straight split, you know.	- I'd have a scar. The scar might not marry up properly and there's a chance of infection and I'd be on crutches for six weeks - Then you've got the infection thing where he says then you might have to have another operation	- there is a girl I know. Well, she used to work where I work and she broke her heel and you can see the scar. She didn't get an infection but you can see the scar, but she has got a limp. It's not a bad limp, you know, and I haven't got a bad limp whatsoever but maybe that's just luck. - When they turn round and say you know, 'The outcome might be the same,' then people like me are just going to turn round and say 'I'm out of here now!'	- They said it had mended perfectly because they told me it was a straight crack and to be fair, I aint had no problems with it since. They said I might get a limp but I haven't got a limp, so I opted not to have the operation and that's why.

Appendix I

Parsons et al. Trials 2011, 12:258
http://www.trialsjournal.com/content/12/1/258

TRIALS

METHODOLOGY Open Access

A statistical framework for quantifying clinical equipoise for individual cases during randomized controlled surgical trials

Nicholas R Parsons[1*], Yuri Kulikov[1], Alan Girling[2] and Damian Griffin[1]

Abstract

Background: Randomised controlled trials are being increasingly used to evaluate new surgical interventions. There are a number of problematic methodological issues specific to surgical trials, the most important being identifying whether patients are eligible for recruitment into the trial. This is in part due to the diversity in practice patterns across institutions and the enormous range of available interventions that often leads to a low level of agreement between clinicians about both the value and the appropriate choice of intervention. We argue that a clinician should offer patients the option of recruitment into a trial, even if the clinician is not individually in a position of equipoise, if there is collective (clinical) equipoise amongst the wider clinical community about the effectiveness of a proposed intervention (the clinical equipoise principle). We show how this process can work using data collected from an ongoing trial of a surgical intervention.

Results: We describe a statistical framework for the assessment of uncertainty prior to patient recruitment to a clinical trial using a panel of expert clinical assessors and techniques for eliciting, pooling and modelling of expert opinions. The methodology is illustrated using example data from the UK Heel Fracture Trial. The statistical modelling provided results that were clear and simple to present to clinicians and showed how decisions regarding recruitment were influenced by both the collective opinion of the expert panel and the type of decision rule selected.

Conclusions: The statistical framework presented has potential to identify eligible patients and assist in the simplification of eligibility criteria which might encourage greater participation in clinical trials evaluating surgical interventions.

Keywords: Equipoise, Randomised controlled trial, Surgery, Statistical model

1 Background

There is an increasing demand for randomised controlled trials (RCTs) in surgery to provide high quality evaluation of new interventions; we use the word intervention synonymously with treatment, procedure or surgical procedure. In a background of ever evolving and improving healthcare, differences between interventions for the same condition are often small, substantially increasing the risk of biased estimation of treatment effects in simple (uncontrolled) observational studies of the interventions [1]. The need for the kind of high level evidence provided by RCTs for surgical interventions is clear [2], although a number of methodological issues have been raised for surgical trials [1,3]. One of the most important issues being recruitment, and specifically identifying whether patients are eligible for entry into a trial.

The existing tremendous diversity in practice patterns across institutions coupled with an ever increasing range of available interventions suggests a low level of agreement between clinicians about both the value of many interventions and the appropriate choice of intervention [4]. A present or imminent controversy in the expert medical community about a choice between interventions is called clinical (or collective) equipoise. Equipoise

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Full list of author information is available at the end of the article

is the point where we are equally poised in our beliefs about the potential benefits of a particular intervention [5]; i.e. is intervention A better than intervention B. Clinical equipoise is present "if there is genuine uncertainty within the expert medical community - not necessarily on the part of the individual investigator - about the preferred treatment" [5]. In many cases the only way to resolve collective uncertainty about the optimum intervention choice is to undertake a clinical trial. Individual equipoise relates to a single clinician, i.e. the position where he or she has no preference amongst a range of available treatments. It is subject to change for a host of reasons, including peer pressure, the results of potentially imperfect studies and the influence of advertising. Freedman [5] argues that global clinical equipoise should override the individual clinician's lack of equipoise. Clinicians should subsume their personal views and recruit patients into a trial, even if not individually in a position of equipoise themselves. This view is implicitly accepted by society in the form of ethics committees, which must ensure that the treatments being compared are reasonable options before trial participants are sought. Often, for a treatment that is not completely novel, this is demonstrated by the presence of clinical equipoise in an expert and/or wider medical community. Once ethics committee permission has been granted, it then becomes an individual clinician's decision whether the offer of entry into the trial is appropriate for an individual patient [6]. Unfortunately, the varied preferences expressed (which may be rational, anecdotal or irrational) between individual institutions and between individual surgeons within and between institutions often make patient recruitment to trials very challenging.

Statistically the level of individual uncertainty about the effectiveness of an intervention can be quantified by a (subjective) probability, which is assigned to a specific hypothesis and is personal and varies with an individual's knowledge and expertise. "A measure of a state of knowledge" [7] is provided by the Bayesian concept of subjective probability. The process of expert evaluation about the effectiveness of a proposed intervention in an RCT is synonymous with elicitation of a Bayesian prior; i.e. a statement of knowledge prior to performing an experiment or trial usually stated in the form of a probability density. There are a number of approaches to turning informally expressed ideas into a mathematical prior distribution, with no consensus as to the optimal method of determination for a process that is usually problem specific [8]. We choose to elicit the subjective opinion of a panel of experts as a basis for decision making regarding the eligibility of a patient for recruitment to an RCT [9]. This has the advantage of being dynamic and flexible, in the sense that it is quite feasible that opinions will change during the course of a trial, for example with the publication of related research [8], or as experience accumulates amongst clinicians as to how best to undertake a surgical procedure.

Methods for formal measurement of clinical uncertainty, as a prelude to a clinical trial have been suggested previously [10] and measures of surgeon's equipoise in the setting of surgical trials have also been reported [11]. However, we develop these ideas further, using techniques for eliciting subjective judgements before a trial [12-14] and introduce a novel framework for decision making regarding recruitment to an RCT that we hope will be easily understood by clinicians and implemented in real time during the course of a trial. It is particularly challenging recruiting patients to trials comparing operative to non-operative treatments or a standard against a new but popular well-marketed treatment. Therefore we develop a statistical framework to model clinical equipoise (Section 3), using a parametric and a nonparametric approach, for data collected from a clinical trial comparing conservative and operative treatment for displaced fractures of the calcaneus. The results of applying the models are reported in Sections 3.7-10 and we draw conclusions in Section 4.

2 Methods

Using available web design tools a method was developed to capture the opinions of clinicians in real time for individual patients (cases) in an ongoing RCT. It comprised of a virtual expert panel giving their opinion about the effectiveness of a proposed treatment for individual patients based on online clinical details; the individual assessments were then synthesized and fed back electronically to the lead clinical investigator. This process is described in greater detail below.

Patients who met the initial trial inclusion criteria were identified and approached by a member of the research team to alert them to the possibility of participating in a trial. They were then asked permission for their anonymized clinical details to be distributed among a panel of experts/clinicians for an opinion regarding the effectiveness of the proposed treatment. Clinical data from consented patients were made available on a secure website managed by eLab at the University of Warwick, and all panel experts/clinicians were alerted by email and text message (if requested) to the posting of a new patient and asked to offer their personal opinion on the likely success of the proposed treatments. The assessment scale is described in more detail for the specific example of the UK Heel Fracture Trial. Initially the system was tested in a pilot study with seven surgeons from five UK hospitals. Ten retrospective calcaneal fracture cases were selected to represent typical variability. The surgeons followed the

instructions on the website with online and telephone technical support available; no specific training was given. When voting on all ten cases was completed, surgeons were asked to fill in an evaluation questionnaire. Voting on a single case never took longer than 5 minutes and the available clinical information was found sufficient and the whole process user friendly by all participating surgeons.

After the successful pilot study the system was introduced as an independent component of the UK Heel Fracture Trial, which compared conservative and operative treatment for displaced fractures of the calcaneus. The study had separate ethical approval and a consent form, in addition to the main trial. This allowed inclusion both of those patients who took part in the UK Heel Fracture Trial and those who declined, as soon as the patient met the trial eligibility criteria. To avoid interference with the clinical course, patients were asked permission to use their data at the 6 weeks follow-up clinic or later. Their anonymous clinical data including X-rays and CT images were posted to a secure website. The expert assessment panel included 12 surgeons from 9 hospitals. All surgeons were foot and ankle specialists and acted as principal investigators in their individual trial centres.

After assessing the clinical data available for a given patient, the surgeon was able to scroll down to an interactive scale, featuring bars (initially set at zero) above each of seven outcome categories indicating whether after surgical intervention the patient would get "*much worse*" (1), "*significantly worse*" (2), "*a bit worse*" (3), "*no difference*" (4), "*a bit better*" (5), "*significantly better*" (6) or "*much better*" (7). A left-click of the mouse and a drag allowed each outcome prognosis bar to be set to a desired percentage, which was reported numerically over the bar. Once the assessment summed to 100% (reflected in a digital window in the upper left corner of the scale) the submit button allowed the data to be sent to the trial lead for analysis. The UK Heel Fracture Trial compared operative (surgical) and non-operative (conservative) treatment. Surgical techniques are becoming widespread for calcaneal fracture, but do have associated risks, therefore it was important for the clinician to assess the improvement potential relative to the risks for this procedure. Belief, in the context we describe here, that surgery can make a patient better implies intention to do surgery, while disbelief implies intention to avoid surgical intervention, hence to choose the conservative option. The question posed to the expert panel can and should be tailored to the specific trial. For the UK Heel Fracture Trial the experts were asked to compare operative (surgical) and non-operative (conservative) treatment, which although strongly contrasting treatment options may vary in the exact detail of the constituent components. For studies with less contrasting treatment options (e.g. two types of surgery) the question to experts may simply be whether the test intervention would be better or worse for a patient, compared to a control (standard) intervention.

Table 1 shows four examples of data elicited from between 4 and 6 clinical experts, not necessarily the same individuals labelled as 1 to 6, who provided their opinions on the effectiveness of surgical compared to non-surgical intervention after fracture of the calcaneus. As expected there are clear differences in the both the locations and shapes of the individual distributions for a number of these cases and indeed a number of clear similarities for other cases. For instance, the opinions of the clinicians vary widely for case 1; clinical expert 3 is reasonably confident that the patient will improve significantly after treatment whereas for expert 4 the most likely outcome of treatment is that the condition of the patient will be unchanged. There is much clearer

Table 1 Assessment of the likely effectiveness of surgical intervention after fracture of the calcaneus for four example cases and up to six clinical experts

Case	Assessment	Clinical Expert					
		1	2	3	4	5	6
Case 1	Much Worse	5	5	0	0	0	0
	Significantly Worse	5	5	0	0	5	9
	A Bit Worse	10	25	5	15	10	21
	No Difference	20	50	5	59	30	36
	A Bit Better	30	15	15	25	45	23
	Significantly Better	20	0	70	1	10	11
	Much Better	10	0	5	0	0	0
Case 2	Much Worse	0	0	0	0	0	-
	Significantly Worse	0	0	2	0	0	-
	A Bit Worse	10	0	4	10	5	-
	No Difference	15	10	12	13	20	-
	A Bit Better	40	40	32	35	45	-
	Significantly Better	30	50	48	40	30	-
	Much Better	5	0	2	2	0	-
Case 3	Much Worse	10	10	5	5	-	-
	Significantly Worse	10	20	10	15	-	-
	A Bit Worse	15	30	10	20	-	-
	No Difference	20	20	15	20	-	-
	A Bit Better	20	10	30	20	-	-
	Significantly Better	15	10	20	15	-	-
	Much Better	10	0	10	5	-	-
Case 4	Much Worse	20	5	40	10	20	-
	Significantly Worse	60	85	50	80	70	-
	A Bit Worse	15	10	10	5	5	-
	No Difference	5	0	0	5	5	-
	A Bit Better	0	0	0	0	0	-
	Significantly Better	0	0	0	0	0	-
	Much Better	0	0	0	0	0	-

agreement for case 4 where all the experts expect the patient to worsen significantly after treatment. How do we use these data to decide whether a patient (case) is eligible for recruitment to a clinical trial? We propose two approaches here to model the opinions obtained from each expert clinician, a parametric model based on a Beta distribution (Section 3.2) and a nonparametric model based on estimated means and standard deviations (Section 3.3) that characterise expert opinions using concepts of *belief, disbelief* and *uncertainty*. The *belief, disbelief* and *uncertainty* are visualized using a ternary plot that displays these characteristics in a manner that allows them to be compared to decision rules that partition the opinion space. Finally, resampling methods are used to draw inferences concerning the sufficiency of evidence from the clinical experts to patient eligibility for recruitment

3 Results and Discussion

3.1 Expert opinion

An opinion regarding the effectiveness of a procedure can be thought of as comprising of three distinctive aspects; *belief, disbelief* and *uncertainty*. *Belief* represents the tendency of an expert to expect a particular treatment to perform better than an alternative (control intervention) for a particular patient (case); i.e. the tendency for the experts to score cases in the higher end categories of the rating scale of Table 1. Conversely, the level of *disbelief* is equated with the tendency for an intervention to have a worse outcome as compared to a control intervention; i.e. the tendency for the experts to score cases in the lower end categories of the rating scale. The *uncertainty* associated with the *belief* and *disbelief* represents the spread of the data across the opinion range; i.e. all the scores might be concentrated in the central category (no difference) or be spread equally between all categories in Table 1 - we would have equal *belief* in these two scenarios but a maximum difference in *uncertainty*.

Borrowing from the notation of subjective logic [15,16], we label the *belief, disbelief* and *uncertainty* associated with an opinion for expert i as b_i, d_i and u_i, and apply the constraint that

$$b_i + d_i + u_i = 1 \text{ and } \{b_i, d_i, u_i\} \in [0, 1]^3 \quad (1)$$

where the triplet $\pi_i = \{b_i, d_i, u_i\}$ is described as the opinion of expert i. Intuitively it makes sense that there should be a constraint on these characteristics, as expressed in (1), as clearly when we have a maximum level of *belief* in a procedure we must necessarily have zero *disbelief* and *uncertainty*. Similarly, when there is a maximum level of *uncertainty* there clearly must be zero levels of *belief* and *disbelief*. The constraint that our levels of *belief, disbelief* and *uncertainty* must sum to unity is of course a matter of convenience, in an analogous manner to that in conventional probability where the same constraint is used. It seems reasonable, using statistical arguments, that we should scale our levels of *belief* and *disbelief* about the effectiveness of a procedure by the associated *uncertainty*. That is we are interested in the quantities b/u and d/u, in the same way we might want to normalize a treatment difference in an RCT by the associated standard deviation measuring the spread or uncertainty in the estimated difference to give an effect size. In order to estimate b, d and u, we need to develop a model for the clinical expert assessment data.

3.2 Parametric model

3.2.1 Assessment pooling

The assessment of the likely effectiveness of the intervention x was scored on a discrete valued symmetric scale with descriptive terms selected to imply an even spacing between categories. For our selected example, the seven-category ordinal scale, described in Section 2, was transformed onto the interval [0,1] as follows; $2 \to \frac{3}{14}$, $2 \to \frac{3}{14}$, $3 \to \frac{5}{14}$, $4 \to \frac{7}{14}$, $5 \to \frac{9}{14}$, $6 \to \frac{11}{14}$ and $7 \to \frac{13}{14}$. This retains the implicit spacing of the ordinal scale and centres the new scale at the same point as the original scale. Equivalent arguments can be constructed for ordinal scales with different numbers of categories.

Let x_i, where $0 \le x_i \le 1$, quantify the likely effectiveness of a procedure for individual expert i as part of a panel of n experts. The distribution of x_i is assumed to follow an approximate Beta distribution (Figure 1), a continuous probability distribution defined on the interval (0,1) and parameterized by two positive parameters, denoted by α and β, that modify the shape of the distribution. The Beta distribution is widely used for modelling random probabilities, particularly in the context of Bayesian analysis [17] and has been used to describe not only variability within a population as in a conventional statistical model, but also to describe the subjective degree of *belief* in a Bayesian sense [8]. Expressed mathematically, the probability density function for x_i is

$$f_i(x_i; \alpha_i, \beta_i) = \frac{\Gamma(\alpha_i + \beta_i)}{\Gamma(\alpha_i)\Gamma(\beta_i)} x_i^{\alpha_i - 1}(1 - x_i)^{\beta_i - 1},,$$

where $\Gamma(.)$ is the gamma function and parameters $\alpha_i \ge 1$ and $\beta_i \ge 1$, requiring that the distribution be unimodal or at the extreme case, when $\alpha_i = \beta_I = 1$, uniform. In the surgical trial setting described here, it seems unlikely that for instance a u-shaped distribution for x_i (e.g. $\alpha = 0.5$ and $\beta = 0.5$) would be plausible.

The multiplicative pooled assessment [18,19] of the expert panel is obtained as

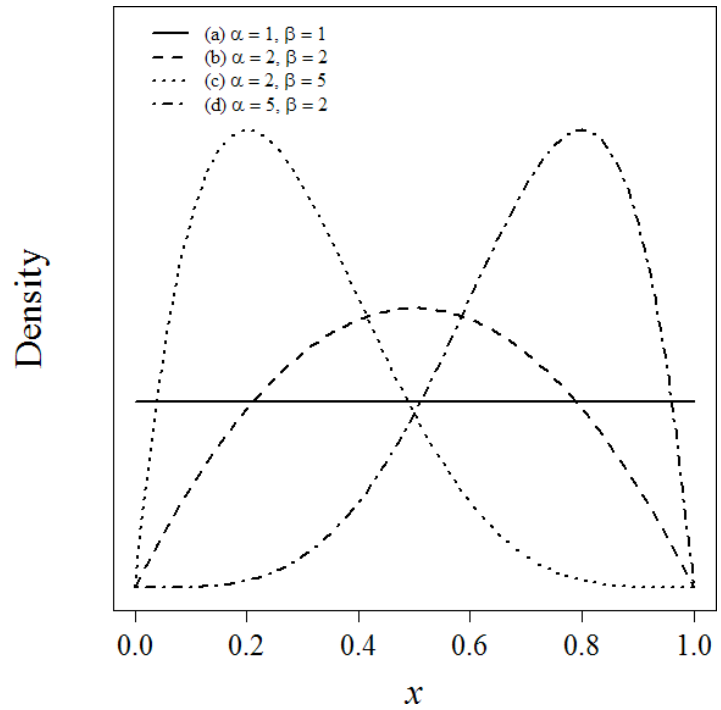

Figure 1 Beta distributions B(α, β) for various values of parameters α and β.

$$f_0(x) = \{\prod_{i=1}^{n} f_i(x_i; \alpha_i, \beta_i)\}^{1/n}$$

where $f_0(x)$ follows a Beta distribution with parameters $\bar{\alpha} = \frac{1}{n}\sum_{i=1}^{n} \alpha_i$ and $\bar{\beta} = \frac{1}{n}\sum_{i=1}^{n} \beta_i$. This provides a pooled assessment that represents the intersection of the beliefs of the expert panel [19].

3.2.2 Opinion model

In order to translate the assessments from the panel of n experts to a collective expert opinion, the measures $\bar{b}/\bar{u}$ and $\bar{d}/\bar{u}$ (Section 3.1), that characterise the pooled opinion, are related to the pooled assessment parameters $\bar{\alpha}$ and $\bar{\beta}$. Equating the level of belief expressed by an expert to the pooled assessments, it is clear that $\bar{\alpha}$ must be proportional to $\bar{b}/\bar{u}$, that is a larger value of $\bar{\alpha}$ represents a greater degree of *belief*; at the extreme as $\bar{\alpha} \to \infty$, then $\bar{b} \to 1$ and $\bar{u} \to 0$, when we have maximum *belief* we must have minimum *uncertainty*. Similarly arguments lead to $\bar{\beta}$ being proportional to $\bar{d}/\bar{u}$; a larger value of $\bar{\beta}$ represents a greater degree of *disbelief*. Although, clearly from example (a) in Figure 1, when the pooled Beta distribution parameter estimates are at their minimum and $\bar{\alpha} = 1$ and $\bar{\beta} = 1$ then there is maximum *uncertainty* ($\bar{u} = 1$) and minimum *belief* and *disbelief*, $\bar{b} = \bar{d} = 0$. Formalizing these arguments leads to the following expressions that satisfy all these conditions

$$\frac{\bar{b}}{\bar{u}} = \bar{\alpha} - 1 \text{ and } \frac{\bar{d}}{\bar{u}} = \bar{\beta} - 1. \quad (2-3)$$

Solving equations (2) and (3), along with the condition that $\bar{b} + \bar{d} + \bar{u} = 1$ (equation 1), yields the following expressions that characterize the relationship between the triplet $\{\bar{b}, \bar{d}, \bar{u}\}$ and the parameters $\bar{\alpha}$ and $\bar{\beta}$,

$$\bar{b} = \frac{\bar{\alpha} - 1}{\bar{\alpha} + \bar{\beta} - 1}, \bar{d} = \frac{\bar{\beta} - 1}{\bar{\alpha} + \bar{\beta} - 1}, \text{ and } \bar{u} = \frac{1}{\bar{\alpha} + \bar{\beta} - 1}; \quad (4-6)$$

where the triplet $\{\bar{b}, \bar{d}, \bar{u}\}$ clearly satisfies $\bar{b} + \bar{d} + \bar{u} = 1$; a more detailed derivation of equations (4)-(6) is provided elsewhere [15,16]. Thus, when $\bar{\alpha} = \bar{\beta} = 1$, $\bar{\pi} = \{0, 0, 1\}$ and the pooled opinion is total *uncertainty* (ignorance); see example (a) in Figure 1. If parameters $\bar{\alpha}$ and $\bar{\beta}$ are greater than unity but equal, we have equal *belief* and *disbelief*; for example (b) in Figure 1 where $\bar{\alpha} = \bar{\beta} = 2$ and $\bar{\pi} = \{\frac{1}{3}, \frac{1}{3}, \frac{1}{3}\}$. As $\bar{\alpha}$ increases relative to $\bar{\beta}$ the *belief* increases and the *uncertainty* decreases and conversely as $\bar{\beta}$ increases relative to $\bar{\alpha}$ the *disbelief* increases and the *uncertainty* decreases; these two scenarios are illustrated in examples (d) and (c) in Figure 1, where $\bar{\alpha} = 5$, $\bar{\beta} = 2$ and $\bar{\pi} = \{\frac{4}{6}, \frac{1}{6}, \frac{1}{6}\}$ and $\bar{\alpha} = 2$, $\bar{\beta} = 5$ and $\bar{\pi} = \{\frac{1}{6}, \frac{4}{6}, \frac{1}{6}\}$.

3.3 Nonparametric model

An alternative nonparametric formulation for *belief, disbelief* and *uncertainty* allows a more general approach to that described in Section 3.2. Defining μ_i and σ_i as the mean and standard deviation of the assessment of the effectiveness of the intervention x_i for expert i, where x_i is in the range [0,1]. Then the *uncertainty* (u_i), *belief* (b_i) and *disbelief* (d_i) associated with an opinion for expert i can be expressed as $u_i = \sigma_i^2 / \mu_i(1 - \mu_i)$, $b_i = \mu_i(1\text{-}u_i)$ and $b_i = d_i = (1\text{-}\mu_i)(1\text{-}u_i)$; as $0 \le x_i \le 1$, then $0 \le u_i \le 1$ and the measures satisfy equation (1). For example using the data from Table 1 for expert 4 from case 3, the weighted mean and standard deviation, based on the transformed seven-category ordinal scale described in Section 3.2.1 $(1/14, 3/14, 5/14, 7/14, 9/14, 11/14, 13/14)$ with weights given by (5,15,20,20,20,15,5), are $\mu = 0.5$ and $\sigma = 0.226$, and so $u = 0.204$ and $b = d = 0.398$. Multiplicative pooling leads directly to estimates for the opinion triplet $\{\bar{b}, \bar{d}, \bar{u}\}$, with weights given by the n^{th} root of the product of the individual expert weights, in an analogous manner to that described in Section 3.2.1 for the parametric model.

In fact the expressions for *uncertainty, belief* and *disbelief* for the Beta model in equations (4)-(6) follow directly from the above expressions for *u, b* and *d*, based on μ and σ, after some rescaling, by noting that the mean and variance of the Beta distribution are $\alpha/(\alpha+\beta)$ and $\alpha\beta/\{(\alpha+\beta)^2\ (\alpha+\beta+1)\}$ respectively.

3.4 Opinion space

As proposed by Jøsang [15], a ternary plot provides a convenient method of representing the triplet of *belief, disbelief* and *uncertainty* that constitute a pooled expert opinion. A ternary plot represents the ratios of the three variables as positions in an equilateral triangle, where each base, or side, of the triangle represents a proportion, with the point of the triangle opposite that base representing a proportion equal to one. As a proportion increases in any one sample, the point representing that sample moves from the base to the opposite point of the triangle. For instance, when $\bar{\alpha} = \bar{\beta} = 1$ (maximum *uncertainty*) the opinion is mapped to the apex of the equilateral triangle, whereas when $\bar{\alpha} = \bar{\beta} = 2$ there is equal *belief, disbelief* and *uncertainty* and the pooled opinion is mapped to the centre of the triangle. The cases representing greater levels of *belief* and greater levels of *disbelief* are mapped towards the right-hand and left-hand vertices of the triangle respectively.

3.5 Decision rules

In order to determine the level of equipoise that should be satisfied for a clinical trial to be considered ethical Johnson *et al*. [20] conducted an ethometric study to investigate how much clinical equipoise can be disturbed before potential trial subjects deem it to be unethical. A series of hypothetical clinical trial scenarios were presented to people from a broad range of societal and geographical groups within the UK. They were asked to specify the level of collective doubt between two treatment modalities that they would accept if casting a vote on an ethics committee. Johnson *et al*. [20] defined the 80:20 rule, that represented the split in equipoise that should be allowed for a trial to be judged to be ethical and recommended its use as an appropriate tool for deciding whether recruitment is ethically justifiable; based on their empirical evidence that less than 3% of subjects questioned thought that a trial should morally be undertaken if equipoise was beyond this point. By way of comparison, an alternative *mean threshold* rule might consider it ethical to recruit patients if the mean clinical effectiveness (μ), estimated as $\alpha/(\alpha+\beta)$ for the Beta distribution, were within predetermined limits. For instance, it might be considered ethical to recruit patients into a trial if the mean clinical effectiveness were in the range $0.4 \le \mu \le 0.7$.

The 80:20 and *mean threshold* equipoise decision rules can be mapped onto the opinion space and visualized on a ternary plot. For the Beta model (Section 3.2), the former rule can be mapped on to the ternary plot by iteratively finding solutions for Beta distribution parameters, α and β, that give estimates for the probability density function equal to 0.2 and 0.8 to the left and right of the central point on the expert rating scale, and for the latter rule by simply solving equations (4)-(6) using the constraint that $\mu(\alpha+\beta)=\alpha$.

3.6 Hypothesis testing

The significance of the estimated pooled opinion ($\bar{\pi}$) is assessed using resampling. For the Beta model for Section 3.2, pooled assessment parameters $\bar{\alpha}^*_m = \frac{1}{n}\sum_{i^* \in S_m} \alpha_{i^*}$ and $\bar{\beta}^*_m = \frac{1}{n}\sum_{i^* \in S_m} \beta_{i^*}$ are estimated for S_m, a set of size n constructed by sampling with replacement from {1,2...n}; for example for the pooled assessment of 5 experts S_m might be {1,2,2,4,1} or {5,3,3,1,1}. This process is repeated many times by random construction of S_m to give empirical bootstrap [21] distributions $\bar{\alpha}^*_1, \bar{\alpha}^*_2, \ldots, \bar{\alpha}^*_M$ and $\bar{\beta}^*_1, \bar{\beta}^*_2, \ldots, \bar{\beta}^*_M$, and thereby $\bar{\pi}^*_1, \bar{\pi}^*_2, \ldots, \bar{\pi}^*_M$. From this empirical distribution, a bootstrap confidence interval for $\bar{\pi}$ is derived for the purpose of hypothesis testing. A similar resampling scheme can also be developed simply for the nonparametric model of Section 3.3.

This resampling methodology represents the variability in opinion that might be obtained for any combination of experts in the panel, including in principle a panel composed entirely of a single expert, and as such represents the full range of possible opinions for the selected population of experts. For the relative small panel of experts in our example, exhaustive permutation resampling [21] is the preferred option, but this may be computational unrealistic for large n where bootstrapping with M = 1000 would be sufficient.

3.7 Beta distribution fitting

The outlined statistical framework is illustrated using the example data introduced in Section 2 (Table 1). We focus here on the Beta model (Section 3.2) as an exemplar, as this fits our data well and is computational slightly more complex to implement than the nonparametric method. Statistical analysis was undertaken in the statistical software package R [22]. Code to replicate the analysis presented here is available on request from the corresponding author.

The parameters of the Beta distribution were estimated for each clinical expert for the four cases shown in Table 1 using the `fitdistr` function available in the MASS [23] library in the statistical software package R [22]. This function estimates parameters for a range of univariate distributions, including the Beta distribution, using maximum-likelihood methods. For the four example cases introduced in Section 2 the pooled parameter estimates were $\bar{\alpha}_1 = 7.11$, $\bar{\alpha}_2 = 9.57$, $\bar{\alpha}_4 = 5.14$, $\bar{\alpha}_4 = 5.14$ and $\bar{\beta}_1 = 5.67$, $\bar{\beta}_2 = 4.71$, $\bar{\beta}_4 = 19.01$, $\bar{\beta}_4 = 19.01$. The fitted distributions for each clinical expert and pooled estimates are shown in Figure 2.

3.8 Opinions

The pooled parameter estimates from the Beta distribution fitting for the four example cases were used to estimates the *belief, disbelief* and *uncertainty* using equations (4)-(6); this gave the following estimates, $\bar{b}_2 = 0.645$, $\bar{b}_2 = 0.645$, $\bar{b}_3 = 0.307$, $\bar{b}_4 = 0.179$, $\bar{d}_2 = 0.279$, $\bar{d}_2 = 0.279$, $\bar{d}_3 = 0.341$, $\bar{d}_4 = 0.778$ and $\bar{u}_2 = 0.075$, $\bar{u}_2 = 0.075$, $\bar{u}_3 = 0.351$, $\bar{u}_4 = 0.043$. Inspection of Figure 2, indicates that there appears to be significant belief for case 2 that the patient will improve after treatment (surgery) and conversely significant disbelief in the effectiveness of the treatment for case for case 4; this is reflected in the large (> 0.6) estimates of b and d for cases 2 and 4 respectively. Also, there is significant uncertainty, seen by the flatness of the curves in Figure 2(c), in the collective opinions of the experts for case 3; this is apparent in the large level of uncertainty for this case, relative to the other cases.

3.9 Decision rules

In order to determine whether an opinion provides sufficient evidence for eligibility for recruitment to a clinical trial, we must first define a decision rule. Here we focus on two rules, the 80:20 [20] and the *mean threshold* rules; although the procedures described here are equally applicable to many more rules that could potentially be defined. The 80:20 and *mean threshold* rules partition the opinion space, visualized by the ternary plot, into regions that determine whether the patient can or cannot ethically be recruited to a trial.

The division lines between the regions for the 80:20 rule were determined iteratively (using an interval search method) by finding estimates of the Beta distribution parameters α and β that exactly divided the probability density 80% and 20% around equipoise, and projecting these estimates into the opinion space using equations (4)-(6). This process was achieved using an implementation of the `uniroot` function in R [22]. After discussion with the clinical experts it became clear that the point of equipoise for the assessment scale described in Section 2 for the 80:20 rule was not located centrally but was in fact located at the division between the '*No difference*' and the '*A bit better*' categories. That is, because surgery was seen to be an active intervention for a condition that required treatment, the point of equipoise was located slightly to the right of the centre point of the assessment scale; which for our definition of the assessment scale is at $^8/_{14}$ rather than at $^1/_2$ on the interval (0, 1). The asymmetry that this implies for the 80:20 decision rule is clear in Figure 3. The *mean threshold* rule divided the opinion space into three

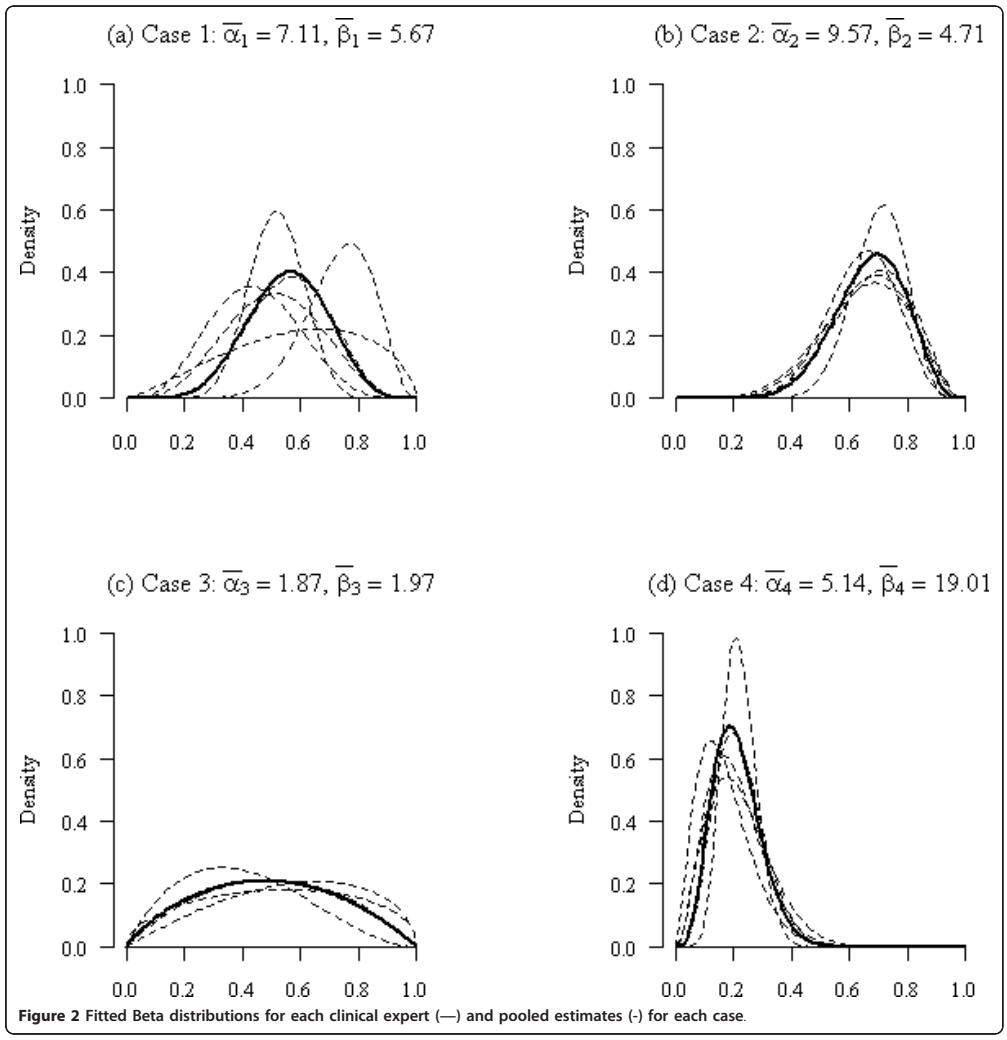

Figure 2 Fitted Beta distributions for each clinical expert (—) and pooled estimates (-) for each case.

distinct regions $\mu < 0.4$, $0.4 \leq \mu \leq 0.7$ and $\mu < 0.7$ characterised by the thresholds 0.4 and 0.7 for the mean, that determined whether the intervention was likely to be effective. The divisions between regions were mapped onto the opinion space by solving equations (4)-(6) using the constraint that $\mu(\alpha+\beta) = \alpha$. For instance for $\mu = 0.7$ and $u = 0$, then $b = 0.7$ and $d = 0.3$ and when $d = 0$ then $u = 3/7$ and $u = 4/7$; these points define the intersections between the upper division boundary with the lower and right edges of the ternary plot in Figure 3.

3.10 Hypothesis testing

The exhaustive permutation test described in Section 3.6 was applied to each of the test cases. This gave 462, 126, 35 and 126 combinations of opinions for the four cases that used respectively 6, 5, 4 and 5 expert clinical assessors. The *belief, disbelief* and *uncertainty* for all the

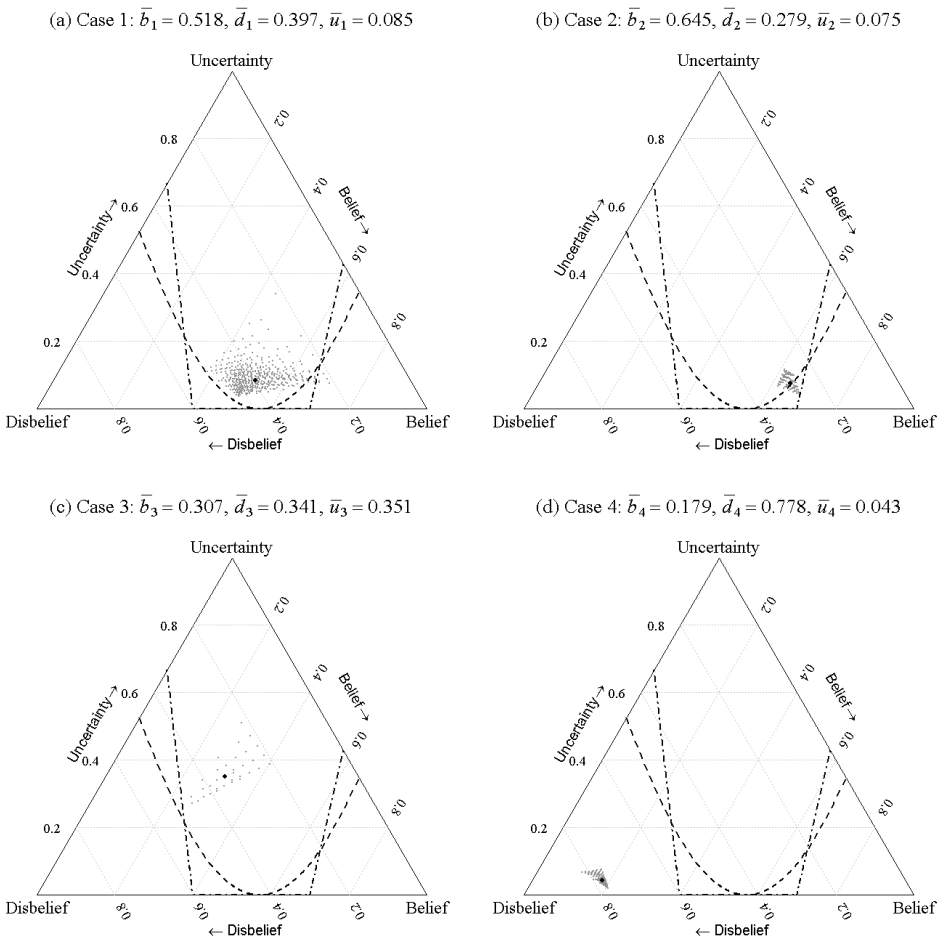

Figure 3 Estimated triplets for all permutations of opinions with the 80:20 (—) and mean (–) decision rules. The best estimate of collective opinion is given by the large symbol (•).

combinations of opinion were estimated for each of the four cases and plotted along with the decision rules in Figure 3.

The 'cloud' of points for each case represents the variability due to the range of opinions expressed by the expert assessors. Where there were considerable differences of opinion, for instance for case 1, there was a much wider spread of points than where there was overall agreement amongst the experts about the likelihood of success of the intervention, for instance for case 2 or 4. It is instructive to look at one particular opinion triplet to more fully understand the meaning of the ternary plots.

For case 1, the opinion triplet π = {0.712,0.211,0.077} located towards the lower right hand vertex of the ternary plot has very high belief and low uncertainty. This is the opinion associated with six replicates of the assessment of clinical expert 3 for case 1 (see Table 1), who had a strong belief that the patient would get significantly better after treatment. If this expert assessor were

indeed representative of the wider population of experts, then it would certainly be unethical for the patient to be recruited to the trial and consequentially the opinion for this potential scenario is located to the right of the 80:20 and *mean threshold* decision rules.

Labelling the regions to the lower right and lower left of the plots to the right and left of the 80:20 and *mean threshold* decision rule partition curves as the 'belief' and 'disbelief' regions, allows us to count the number of opinions falling within these regions for each case and rule; see Table 2. Defining the null hypothesis to be that a case should not be recruited to the trial, Table 2 provides evidence for this hypothesis and suggests appropriate *p*-values based on the 80:20 rule for the four cases to be 0.026 (i.e. 12/462), 0.333, 0.000 and 1.000 and based on the *mean threshold* rule to be 0.011 (i.e. 5/462), 0.000, 0.029 and 1.000. Testing at the 5% level (two-sided) indicates that for the 80:20 rule cases 1 and 3 would be eligible for recruitment and for the *mean threshold* rule cases 1, 2 and 3 would be eligible for recruitment. For this decision making process to have some validity, the decision rule and the significance level would clearly need to be stated before data collection was undertaken.

4 Conclusions

We describe a statistical framework for the assessment of clinical uncertainty, as a prelude to a clinical trial and demonstrate, using data from the UK Heel Fracture Trial, how expert opinions can be pooled, modelled and presented on a ternary plot that represents an opinion space. Individual cases can then be assessed in relation to decision rules mapped onto the opinion space, providing clear and rapid decisions regarding trial eligibility. The methodology has potential to identify eligible patients and assist in the simplification of eligibility criteria which might encourage greater participation in clinical trials.

Methods for the assessment of clinical uncertainty, as a prelude to a clinical trial, have been suggested previously [10,11]. However, the methodology described here is the first attempt at a structured statistical framework to undertake this type of analysis. Beta distributions were fitted to assessments of the likely effectiveness of an intervention elicited from a virtual panel of experts and pooled using methods familiar to exponents of determining expert probabilities [19]. Opinions were expressed using previously suggested [15] definitions of *belief, disbelief* and *uncertainty* that we believe fully characterised the clinical expert assessments. Our analysis restricted the choice of Beta distributions for modelling to unimodal forms ($\alpha \geq 1$ and $\beta \geq 1$). This was not a concern for the examples described here or indeed more widely for other data we have explored in the setting of surgical trials. However, it is in principle possible in other applications that the most likely assessment of clinical effectiveness of an intervention is that a patient would either get *much better* or *much worse* with any other outcome being extremely unlikely. In this setting *belief, disbelief* and *uncertainty* as expressed in equations (4)-(6) would not be defined. For the data presented here the Beta model proved to be the most informative, however where this is not the case the nonparametric methods described, based on estimated means and standard deviations, provide useful alternatives for any distribution on the interval [0,1]. Although the examples described here all use seven point likert type scales for elicitation, the statistical framework introduced would work equally well with any type of ordered categorical assessment scale.

Table 2 Opinion counts by case, decision region and rule, and the total number of opinion combinations available for the exhaustive permutation test

Rule	Region	Case 1	Case 2	Case 3	Case 4
80:20	Belief	12	42	0	0
	Disbelief	0	0	0	126
Mean threshold	Belief	5	0	0	0
	Disbelief	0	0	1	126
Opinion Combinations		462	126	35	126

Expert opinions are pooled here using multiplicative methods [19], as we felt that this best represented clinical equipoise [24] and the views of the experts consulted for the example data; i.e. that all experts opinions were 'correct' and the pooling should represent the consensus based on the intersection of beliefs. However, our view is pragmatic and we see no reason why additive pooling could not be used in preference to multiplicative pooling, particularly if it was felt that the latter method was giving too much weight to the assessment of one or more 'over-confident' individual experts.

We have presented significance tests at the 5% level to assess whether a patient might ethically be recruited to a trial. Our selection of this level for the tests was somewhat arbitrary and clearly this could be set, prior to analysis, at a higher or lower level for a different application or a less formal procedure adopted if necessary. The 80:20 rule [20], which is based on some empirical evidence, was selected as a standard for decision making regarding recruitment. The alternative *mean threshold* rule, as well as being intuitively reasonable, was suggested in part to encourage some debate as to what form the decision rule should take for different cases and in various settings. This is clearly an area that requires additional research.

The focus of this paper has been on developing tools for improving recruitment to trials. For those patients

deemed eligible for recruitment who decide to enter an RCT, it would seem natural to use the expert evidence elicited through this process as a clinical prior, based on subjective opinion, in a formal Bayesian analysis [14].

The methodological framework discussed here has provided additional insight that would otherwise have not been available for the heel fracture trial. Although, clearly this methodology will need to be assessed in future studies to identify whether it can actually deliver improvement in trial recruitment rates. The methodological framework we describe is currently limited to two-arm trials, although we see no reason why this could not be extended to more than two treatment groups. The opinion pooling we describe is appropriate for situations where individual expert opinions may differ to a moderate or large extent, but it is not at all clear that pooling opinions where for instance experts have totally opposing views (100% *belief* or *disbelief* in treatment effectiveness) would be appropriate, as the pooled opinion would in reality represent no individual expert's opinion. Therefore we would recommend the methodology be limited to only those scenarios of the former rather than the latter type. Although we have focussed on surgical trials, we would expect the methodology described here to be applicable to any RCT where recruitment was problematic. The methodology also has clear application in pilot studies where feasibility is being assessed and also potentially as a support tool for inclusive trials where patients are allowed to select an intervention as well as being randomised in a conventional manner [25].

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Authors' contributions
DG, chief investigator for the UK Heel Fracture Trial, and YK developed the original concepts for the study. NP developed the statistical methodology, with input from YK and AG, and wrote the first draft of the paper. All authors contributed to the paper during development and read and approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

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Appendix J

Not used

Appendix K

Evaluated Questionnaire for the Collective Uncertainty Pilot Study

CORPORATE UNCERTAINTY TRIAL (CUT) Feedback Form

Please, delete or cross out as appropriate

- Overall online voting system was: easy/difficult to use.

Comments:

- On average it took … mins to vote on a case.

- Clinical information was sufficient/inadequate.

Comments:

- Extra images were essential/unnecessary.

Movie (MPEG) format – great/not better/could not open

Comments:

- Technical support was

easy/difficult to reach

sufficient/inadequate

Comments:

- Best points:

- Could be improved:

- Did not like:

Appendix L

Example of literature search

Search Strategy

No.	Database	Search term	Info added since	Results
2	MEDLINE – 1950 to date	Informed-Consent#.DE.	unrestricted	27399
4	MEDLINE – 1950 to date	PATIENT-EDUCATION#.DE. OR PATIENT-PARTICIPATION#.DE. OR CONSENT-FORMS#.DE.	unrestricted	58090
5	MEDLINE – 1950 to date	2 OR 4	unrestricted	82139
7	MEDLINE – 1950 to date	Orthopedic-Procedures#.DE. OR Amputation#.W..DE. OR Arthrodesis#.W..DE. OR Arthroplasty#.W..DE. OR Bone-Lengthening#.DE. OR Bone-Transplantation#.DE. OR Diskectomy#.W..DE. OR Fracture-Fixation#.DE. OR Osteotomy#.W..DE.	unrestricted	128600
8	MEDLINE – 1950 to date	5 AND 7	unrestricted	472
9	MEDLINE – 1950 to date	8 AND REVIEW=YES AND LG=EN AND HUMAN=YES	unrestricted	75

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Search Strategy

No.	Database	Search term	Info added since	Results
16	CINAHL (R) – 1982 to date	CONSENT#.W..DE. OR PATIENT-EDUCATION#.DE. OR DECISION-MAKING-PATIENT#.DE. OR HEALTH-KNOWLEDGE#.DE.	unrestricted	42220
19	CINAHL (R) – 1982 to date	Orthopedic-Surgery#.DE. OR Amputation#.W..DE. OR Arthrodesis#.W..DE. OR Arthroplasty#.W..DE. OR Bone-Lengthening#.DE. OR Hip-Surgery#.DE. OR Knee-Surgery#.DE. OR Orthopedic-Prosthesis#.DE.	unrestricted	11909
20	CINAHL (R) – 1982 to date	16 AND 19 AND LG=EN	unrestricted	422
21	CINAHL (R) – 1982 to date	20 NOT rehabilitation	unrestricted	297

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Search Strategy

No.	Database	Search term	Info added since	Results
23	EMBASE – 1974 to date	Informed–Consent#.DE.	unrestricted	15715
25	EMBASE – 1974 to date	PATIENT–INFORMATION#.DE. OR PATIENT–EDUCATION#.DE.	unrestricted	34138
26	EMBASE – 1974 to date	23 OR 25	unrestricted	48373
28	EMBASE – 1974 to date	Orthopedic–Surgery#.DE. OR Amputation#.W..DE. OR Bone–Transplantation#.DE. OR Cartilage–Transplantation#.DE. OR Foot–Surgery#.DE. OR Fracture–Treatment#.DE. OR Hand–Surgery#.DE. OR Joint–Surgery#.DE. OR Osteotomy#.W..DE. OR Periosteum–Transplantation#.DE. OR Prosthesiology#.W..DE. OR Spine–Surgery#.DE. OR Tendon–Surgery#.DE.	unrestricted	154493
29	EMBASE – 1974 to date	26 AND 28 AND LG=EN AND HUMAN=YES	unrestricted	838
32	EMBASE – 1974 to date	29 NOT (rehabilitation OR diabetic OR diabetes)	unrestricted	496
33	EMBASE – 1974 to date	32 AND CLINICAL–TRIAL#	unrestricted	88

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Search Strategy

No.	Database	Search term	Info added since	Results
35	PsycINFO – 1806 to date	INFORMED–CONSENT#.MJ. OR DECISION–MAKING#.MJ. OR HEALTH–KNOWLEDGE#.MJ. OR CLIENT–PARTICIPATION#.MJ.	unrestricted	32341
41	PsycINFO – 1806 to date	SURGICAL–PATIENTS#.DE.	unrestricted	2044
42	PsycINFO – 1806 to date	35 AND 41	unrestricted	27

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