1. PROJECT TITLE

HTA Project Number 11/36/37

Full Title Cast treatment versus surgical fixation of fractures of the Scaphoid waist in adults: –a Multi-centre Randomised Controlled Trial

Trial Acronym Scaphoid Waist Internal Fixation for Fractures Trial (SWIFFT)

2. HOW THE PROJECT HAS CHANGED SINCE THE OUTLINE PROPOSAL WAS SUBMITTED

Internal Pilot Study: We will undertake an internal pilot study of the main trial design to check on the feasibility of the study and critically test our recruitment assumptions on the number of eligible patients identified, approached and consented into the trial in the first six months. This will confirm the likely number of participating sites required to achieve our recruitment target. The data from this pilot will be reviewed by the independent Trial Steering Committee (TSC) and Data Monitoring & Ethics Committee (DMEC) to advise the funding body (HTA) on any modifications that are required.

Blocked randomisation for minimally displaced scaphoid fractures: We will stratify the randomisation procedure by presence or not of displacement of a scaphoid fracture which occurs in 20% of cases. We will define displacement as any step less than or equal to 2mm or a gap of >1mm and less than or equal to 2mm as seen on the radiographic views taken at baseline to mimic the common clinical situation as CT scans are not routinely used. We have chosen this magnitude of displacement to avoid compromising surgeon equipoise for non-operative treatment as displacement >2mm is very likely to suggest instability and the need for surgical intervention.

Counter possible bias in completion of the primary outcome: To address the feedback that the primary outcome would be open to bias, we will ensure a consistent approach to recruitment and obtaining informed consent: 1) a specially produced information sheet in collaboration with service users will provide an unbiased account of the study to potential participants; 2) the recruiting clinician will receive training and documentation on obtaining patient consent. In addition we will ask patients at baseline if they have a treatment preference. This will allow us to investigate the interaction between randomised treatment and patients' preferred treatment on the primary outcome.

Five year clinic review: The long-term consequences of cast immobilisation and internal fixation have not been adequately determined in RCTs. After careful consideration and discussion with the trial team, and given the time and resources required to undertake this multi-centre study, we judged that at five years after their original injury all trial participants should be asked to attend a follow-up visit at their participating hospital for a clinical and radiographic follow-up conditional upon the successful conduct of a pilot phase. This follow-up review would be an addendum to the main HTA monograph which would report the results after the one year follow-up. This addendum to our outline application explains the increase in the cost of the study from the outline application (£1,843,075) to the full application (£2,284,683) of which the 5 year review accounts for £384,531.

The timing of the primary outcome measure has been changed to 52 weeks as explained in section 3.9.8b.

3. PLANNED INVESTIGATION

3.1. Null Hypothesis

There is no difference in the Patient Rated Wrist Evaluation (PRWE)[1] score at 52 weeks after injury between adults with a scaphoid waist fracture treated with screw fixation versus plaster cast immobilisation and fixation of only those fractures that fail to unite[2].

3.2. Research Question

We aim to determine the effectiveness and cost-effectiveness of surgical fixation versus plaster cast treatment (with early fixation of 10-12% that fail to unite) of scaphoid waist fractures in adults and to qualitatively investigate patient experiences of their treatment and participation in the trial.

3.3. Research objectives

1. Our primary objective is to determine the effectiveness of surgical fixation versus non-operative plaster cast treatment (with fixation of the 10-12% that do not heal) of scaphoid waist fractures in adults. We will assess outcome using the PRWE (a patient reported outcome measure) at 52 weeks which will be the primary time point. The PRWE will also be assessed at 6, 12 and 26 weeks. The power of the study permits identification of a clinically meaningful difference of 6 points in the PRWE[3].
2. Secondary outcomes will include an assessment of radiological union of the fracture using radiographs and CT scans at 52 weeks; recovery of wrist range and strength, return to work and recreational activities; complications including non-union or malunion, implant problems, avascular necrosis (AVN) and infection.
3. We will conduct a detailed economic analysis to investigate the cost-effectiveness of surgical fixation versus initial immobilisation in a plaster cast.
4. We will explore patient experiences of fracture and its treatment; and will investigate attitudes towards, and experiences of, participating in a surgical, clinical research trial.
5. We will undertake a 5 year clinical review of all trial participants to determine the long-term consequences of cast immobilisation and internal fixation.

3.4. Existing research

Scaphoid fracture is the most common type of wrist (carpal) fracture and is an important public health problem as it affects young active individuals (mean age 29 [2]) in the more productive working years of their lives. These fractures account for 2-7% of all fractures [4]. About 88-90% of these fractures unite when treated initially in a plaster cast. However, 10-12% of the scaphoid fractures do not unite, with a higher incidence (14-50%) in displaced fractures [5-7]. Non-union if untreated almost inevitably leads to arthritis, usually within 5 years [8, 9]. This disables patients at a very young age.

Recent systematic reviews [10-14] have found insufficient evidence from RCTs to inform clinical decisions for scaphoid waist fractures. Eight completed RCTs comparing surgery with non-operative management were included in one review [14]. All were small studies with some flaws in method. It was unclear whether patients who had surgical fixation of undisplaced or minimally displaced scaphoid fractures had better longer term benefit than those treated in a cast. Surgery facilitated early return to previous activity level and function, but was associated with a higher complication rate of between 9 and 22% although the complications were usually minor [2, 15, 16].

The rate of union was reported as being similar with surgical and cast treatment with early fixation of those fractures that failed to unite [2]. Another study [17], too, found similar outcomes at 10 years between surgical and non-surgical treatment groups and no long-term benefits for surgical fixation over non-operative management were identified. This paper recommended that the long-term risks and short-term benefits should be carefully weighed when making a treatment decision. In summary, there is insufficient evidence from small RCTs on scaphoid waist fractures to aid clinical decision making on whether to fix it or treat it in a cast initially.

In spite of insufficient evidence there is a rapidly increasing trend [18] for immediate surgical fixation of these fractures compared to the non-operative method of using a cast for 6 weeks and fixing only those 10- 12% that fail to unite [2]. This current trend to surgically fix both displaced and undisplaced fractures may mainly be attributed to the short-term benefits anticipated with surgery, but concerns remain about lack of evidence on long-term benefits and additional risks from surgery, such as malunion, infection, implant related problems and avascular necrosis (AVN).

Hospital Episode Statistics (HES) for NHS hospitals in England record 1534, 1720 and 2582 acute scaphoid fracture fixations for the three years 2007/8, 2008/9 and 2009/10 respectively. In each of these three years we calculated an expected rate of scaphoid waist fractures of 4140, 4169 and 4197 (population of 51.1, 51.4 and 51.8 million respectively in England in 2007, 8 and 9 and based on a rate of 81 acute scaphoid fractures/million population per year) [19]. We had to estimate this as at present the diagnosis of cases that are not operated or those treated only in the outpatient setting are not recorded in England. The rate of surgery [20] rose very slightly from 37% to 41% from 2007/8 to 2008/9 but then increased sharply to 62% in 2009/10. This trend of increasing intervention rate for these fractures emphasizes the urgent need for this study.

If all acute fractures in England were fixed, this would cost (based on 2011/12 DH Payment by Results (PbR) tariff for Health Resource Group (HRG) HA54Z of £1463.00 and 81/million scaphoid waist fracture rate) £7,206,827. The cost of treatment in a plaster cast (HRG VB02Z, £183) would be £922,272, increasing by £720,683 for surgical fixation of the 10% developing a non-union. The cost difference between the two methods each year would be £5,563,872.

There is little published on patient experiences after a scaphoid fracture; patient interview data will also add to our understanding of the issues pertinent to recruiting participants in surgical, clinical trials [21, 22]. There is also poor information on the economic aspects [23] of this injury and its treatment.

This limitation identified in the current evidence base justifies our intention to carry out an adequately powered multi-centre pragmatic RCT comparing early surgical fixation of all waist fractures with initial non-operative cast treatment for fractures of the waist of the scaphoid bone followed by subsequent fixation of only the small proportion which do not unite.

This study will evaluate whether immediate surgical fixation gives better patient reported outcome compared to initial non-operative treatment and later fixation of only those that fail to unite, include an economic analysis and explore patients' views of their experiences of the two treatment methods. It will investigate cost effectiveness and provide the evidence base for sound clinical decisions for the treatment of this common fracture in young adults.

3.5. Research methods

3.5.1. DESIGN:

A pragmatic multi-centre RCT of surgical fixation vs initial cast immobilisation of acute scaphoid waist fractures followed by fixation of only the 10-12% that fail to unite, with a concomitant economic evaluation. In addition, there is a nested qualitative study to explore the advantages and drawbacks of treatment from the patient's point of view.

3.5.2. SETTING:

JD, SH and the British Society for Surgery of the Hand have obtained agreements to participate from 17 hand surgery units in NHS Hospital Trusts, ensuring wide clinician involvement. The pragmatic design will make findings generalisable. The trial design will involve measures to maximise acceptance of trial results by ensuring competence in treatment provision in both arms of the trial. Surgeons who manage these fractures in the UK will be our main target for dissemination and findings will help these doctors make management decisions informed by good quality evidence.

3.5.3. RANDOMISATION

Patients predominantly presenting in Accident and Emergency (A&E), but also routinely referred from various other sources (e.g. walk-in centre, GP cottage hospital), will be referred to fracture clinics and be considered for inclusion in the study. The research nurse will identify a suitable patient and inform the orthopaedic surgeon who in the fracture clinic will confirm eligibility and invite the patient to consider joining the study. The research nurse or clinician will provide an information sheet and answer any questions. The research nurse or clinician will ask the patient whether they agree to consent at that time or need up to 48 hours to discuss with family or friends and agree on an arrangement with the Research Nurse or clinician to confirm their decision.

When patients have given consent and their baseline forms have been completed, the Research Nurse or recruiting clinician will contact York Trials Unit, either by telephone or via the internet, to access a secure randomisation service. Patients will be randomised to immediate surgical fixation without restricting the type of headless screw used or immobilisation of the wrist in a scaphoid cast or a below elbow cast with the thumb left free [5] thus ensuring treatment concealment and immediate unbiased allocation. The service will record information to identify all participants and their eligibility to reduce inappropriate entry of patients into the trial. Patients will be informed of their allocations as will the clinician managing each patient. As the trial is pragmatic and compares surgery with initial cast treatment, blinding of participants and clinicians to treatment allocation is not possible.

There is evidence from a study of 392 fractures of the waist of the scaphoid that the non-union rate for displaced fractures is 14% compared with 10% for transverse undisplaced fractures [5, 7, 24]. We will therefore stratify the randomisation procedure by presence or not of displacement of a scaphoid fracture [7, 24] which occurs in 20% of cases [7, 24]. We will define displacement as any step of less than or equal to 2mm or a gap greater than 1 mm and less than or equal to 2 mm as seen on the radiographic views taken at baseline to mimic the clinical situation. We will use radiographs[25] rather than a CT scan as the latter is uncommonly used in the initial assessment of scaphoid fractures. We have chosen this magnitude of displacement to avoid compromising surgeon equipoise for non-operative treatment as displacement >2mm suggests significant instability and therefore the need for surgical intervention. Within strata a block allocation sequence of random block sizes will be used to generate the allocation sequence. There are essential X-ray views that must be taken at baseline for comparative purposes that allow for the secondary outcome assessment of bone union at 12 months and the 5 year clinic review. These X-ray views must include the semi 45° prone, semi 45°supine and an elongated scaphoid view e.g. Ziter [26] type view. If these X-ray views are not taken routinely at a participating site we will obtain these X-rays after the patient has consented into the trial and is still in the fracture clinic where there is direct access to the X-ray Department..

3.5.4.INTERNAL PILOT STUDY

We will undertake an internal pilot study of the main trial design from which the data will contribute to the final analysis. The primary reason for this pilot study will be to check our assumptions about recruitment [27] . To do this we will start the trial early at three sites (Leicester, Coventry & Warwick, Middlesbrough) which have a track record of recruiting well into surgical trials. In addition, we shall include a centre (Nottingham) at which the proposed Principal Investigator is not a co-applicant. Then at six months into recruitment we will use the information about number of eligible patients identified, approached and consented into the trial to confirm the likely number of participating sites required to achieve our recruitment target. This will need to be interpreted cautiously, however, as we do not want to over-estimate our ability to do the main trial. The independent TSC and DMEC will review the pilot data and recommend any changes required.

Secondary reasons for undertaking the pilot study will be to inform the practicalities of setting up the trial such as ensuring that: a) the participating sites are provided with enough training and documentation; b) the length of time it takes to consent a patient (including recording reasons given by patients for not taking part) and complete study materials is determined; c) all suitable surgeons at a site are actively taking part in the trial and to find out if not why not; d) eligibility forms are studied for reasons why a surgeon may lack equipoise to recruit an eligible patient potentially due to degree of displacement of the fracture influencing their decision to operate; e) patient adherence to treatment allocation is checked and f) the practicalities of obtaining a CT scan before randomisation, but if not, within 2 weeks of the patient's injury whilst they are still eligible for the trial and before surgery - and to ensure this does not delay the arrangement of surgery beyond the two weeks from when the patient presents to A&E or other point of contact (e.g. walk-in centre, GP cottage hospital).

3.5.5.NESTED QUALITATIVE STUDY.

The clinical research being proposed here will be supplemented by a qualitative investigation of patient experiences of both surgical fixation and plaster cast treatment, providing important patient-centred insight to further guide clinical decision making. Existing evidence about patient experience of wrist fracture recovery is limited [(23),] and an exploration of patient treatment preference is broadly lacking from the literature.

It will also be possible to explore patients' attitudes towards, and experiences of, surgical, clinical research within this nested study. This will contribute to the literature upon clinical trial recruitment and retention, and specifically inform debates about the particular difficulty of recruiting to trials [28-30] where medical and surgical options are compared.

Up to 40 participants will be recruited to take part in this aspect of the research. Participants will be drawn equally from those who have experienced plaster cast treatment and those who have experienced surgical fixation; participants will include both those who are consented to the trial and those who have declined to participate in the main study. At least 10 individuals not involved in the main trial will be interviewed once only to ensure that a range of perspectives on clinical research are collected and will be offered a separate Patient Information Leaflet to explore the purpose of this study and asked to sign a separate consent form before being interviewed. Where it is not possible to obtain written consent due to conducting telephone interviews, verbal consent will be obtained. In such instances of verbal consent, the patient will be asked to make the following statement at the start of the audio-recording: "I understand my participation is voluntary and verbally agree to take part in this interview."

Effort will be made to include interviews with both men and women, with those with dominant and non-dominant side wrist fractures, with those from different occupational groups, and with those with more or less active lifestyles so as to capture a wide range of perspectives upon this wrist fracture and its treatment.

Those who consent to participate into the trial will be interviewed at two time points – immediately after treatment [i.e. within 6 weeks of surgery or plaster application], and approximately 52 weeks after injury to mirror the primary time point in the analysis. At both time points interviews will be semi-structured with open questions used to guide a discussion of a patient's experience of treatment, their opinions about treatment benefits and drawbacks, their reflections upon wrist fracture and recovery, and their attitudes towards participating in clinical research. Initial expectations of treatment, generated in the first interview, will be reflected upon at the follow-up interview. Interviews will be open and flexible so as to allow participants the opportunity to introduce new topics, and managed so as to generate a detailed, personal perspective upon the topic [31].

Interviews will be ideally undertaken face-to-face although, given the geographic spread of participants, it may be more practical to perform some interviews by telephone; it is expected that up to 50% of interviews will be performed in this way. Interviews will be conducted by the researcher and audio-recorded with permission; recordings will be transcribed in full and data handled using the NVivo computer package.

To reflect the exploratory nature of this study, and to ensure that the patient's perspective is at the heart of any insight generated, data analysis will be undertaken inductively following the conventions of the constant comparative

method [32, 33]. This is considered more fully in section 3.9.8.f.

3.6. Planned Interventions

3.6.1. HEALTH TECHNOLOGIES BEING ASSESSED:

3.6.1.a. SURGICAL INTERVENTION

Immediate surgical fixation avoids the need to immobilise the wrist in a cast and is said to accelerate return to function, work and sport [34] but requires the individual to have surgery and be exposed to surgical risks. Surgical treatment will be by percutaneous or open surgical fixation with standard CE marked headless screws generating compression at the fracture site [16, 35, 36] but avoiding the pressure effects of the screw head on articular cartilage. These screws are unlikely to change in the next 5 years, during the recruitment period for this study. The surgical techniques are well described and are now standard [37-39]. We will not restrict the type of common implant used but will record what screw is used. We will not restrict postoperative management as most surgeons at present use some splintage for the first few weeks after surgery.

3.6.1.b. CONTROL TREATMENT

Control treatment is non-operative with immobilisation in a below elbow cast for 6-10 weeks, followed by mobilisation. As no difference has been found in union rate whether the thumb was included in the cast or not [5] we will not specify which below elbow cast should be used, in keeping with the pragmatic study design. However, the type of cast used will be recorded. Early CT will be carried out at the discretion of the treating surgeon if plain radiographs at 6 to 12 weeks raise the suspicion of non-union which we expect in 10- 12% of non-operatively treated cases. If non-union is confirmed on radiographs and/or CT scan, urgent surgical fixation will be performed. The surgical procedure and post-operative care will be similar to the surgical arm of this trial. This is the current standard non-operative pathway [2].

3.6.1.c. REHABILITATION

We will ensure that all patients randomised into the two groups will receive standardised, written physiotherapy advice detailing the exercises they need to perform for rehabilitation following their injury. All patients in both groups will be advised to move their shoulder, elbow and finger joints fully within the limits of their comfort. Those patients treated in a cast will be encouraged to perform range-of-movement exercises at the wrist as soon as their plaster cast is removed at the 6-week follow-up appointment if there are no concerns regarding bone union. Those patients who have the fracture fixed may begin wrist exercises as soon as comfort permits if they do not have a plaster cast or as soon as the cast is removed. In this pragmatic trial, any other rehabilitation input beyond the written information sheet (including a formal referral to physiotherapy) will be left to the discretion of the treating surgeon. However, a record of any additional rehabilitation input (type of input and number of additional appointments) will be noted as part of the 52 week follow-up and this will form part of the trial dataset.

3.7. Planned inclusion/exclusion criteria

We will include all skeletally mature patients aged 16 years old or above and presenting at the participating site within two weeks of their injury with a radiologically confirmed bicortical fracture of the scaphoid waist that does not involve the proximal pole (proximal fifth of the scaphoid). Diagnosis of fracture will be on the standard radiographic views available at each hospital. If the research CT scan is equivocal (i.e. a member of the radiology team cannot confirm that there is a clear bicortical fracture of the scaphoid waist), the patient will remain in the trial as eligibility assessment is based on standard X-ray views taken at baseline.

We will include minimally displaced fractures with less than or equal to 2mm step or gap on any of these views. We will exclude those with >2mm displacement as these are likely to be unstable and their inclusion would challenge surgeon equipoise. We will exclude patients with a concurrent wrist fracture in the opposite limb. We will exclude patients with a trans-scaphoid perilunate dislocation or other injuries in the same limb. We will also exclude the rare patient who lacks mental capacity to comply with treatment or data collection or who are pregnant because of the radiation exposure. We will also exclude patients who are not resident to the trauma catchment area of a participating site.

3.8. Ethical arrangements

In the context of the lack of robust evidence to determine the best treatment for patients with these fractures, the risks are not increased through trial participation. Measures, such as our emphasis on good practice and standardised protocols/care pathways throughout, taken by us are likely to reduce risk and could bring additional benefits. We will emphasise the importance of surgeons performing operations which they undertake on a regular basis with which

they are familiar. We will also stress the importance of competence in non-operative methods. We will adhere to the good clinical research practice guidelines (MRC and Research Governance Framework). The participant information sheet for the study, will be developed with the involvement of service users, and will give a balanced account of the possible benefits and known risks of the interventions. It will state explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. Written informed consent will be obtained from all trial participants. Verbal consent will be obtained from qualitative interview participants when written consent is not feasible.

Ethical approval

An application for ethical approval will be made through the IRAS system in the pre-funding phase. We do not anticipate major ethical concerns with this study. The only potential concern would be the inclusion of patients who lack mental capacity from whom we would be uncertain of obtaining informed consent. This is very rare in young patients presenting with scaphoid fractures and therefore we have decided to exclude these patients from this trial. The local R&D committee of each of the participating hospitals will be approached to approve local involvement in the trial. The trial will be subject to DMEC oversight.

3.9. Primary Research

3.9.1. RISKS AND ANTICIPATED BENEFITS

The percutaneous or open fixation of the scaphoid requires a small surgical incision usually over the scaphoid tuberosity or the front of the wrist. The risks associated with this study are predominantly the risks associated with surgery: infection, bleeding and the very rare risks of damage to the adjacent structures such as nerves, especially the palmar cutaneous branch of the median nerve, blood vessels and tendons. Participants in one group will have surgery and will potentially be at risk from any/all of these complications. However, the evidence available to quantify this surgical risk is limited [2, 40]. There are no data to suggest that the risk of stiffness is greater in one group or another. We believe that the overall risk profile is very small for the two interventions but we intend to document the number of complications in each group as a secondary outcome of this trial. If fixation results in earlier return to function, work and leisure, the risks of surgery may be justified. As only CE marked implants will be used we will not need authorisation from MHRA.

3.9.2. INFORMING POTENTIAL TRIAL PARTICIPANTS OF POSSIBLE BENEFITS AND KNOWN RISKS.

Informed consent will be obtained by the trained local research nurse or clinician using a detailed patient information sheet developed with the help of service users and explaining the risks and benefits clearly. Patients identified with a fracture of the waist of the scaphoid will have their surgery within a fortnight of presentation to A&E or other point of contact (e.g. walk-in centre, cottage hospital) with their wrist injury to allow time for the surgery to be done as immediate as is feasible. In the unlikely event that new information arises during the trial that may affect participants' willingness to take part, this will be reviewed by the TSC for addition to the patient information sheet. A revised consent form will also be completed if necessary. As patients with multiple injuries are excluded we will not need to obtain consent in an emergency where fully informed consent is difficult.

3.9.3. ADVERSE EVENT MANAGEMENT

Adverse events (AE) are defined as any untoward medical occurrence in a clinical trial subject and which do not necessarily have a causal relationship with the treatment. Serious adverse events are defined as any untoward and unexpected medical occurrence that: 1. results in death, 2. is life-threatening, 3. requires hospitalisation or prolongation of existing inpatients´ hospitalisation, 4. results in persistent or significant disability or incapacity, 5. is a congenital anomaly or birth defect, 6. includes any other important medical condition not listed above which may require medical or surgical intervention to prevent one of the outcomes listed.

At participating sites, all SAEs will be entered onto the Serious Adverse Event reporting form for return to the 'SWIFFT' central office within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be determined by the Chief Investigator. SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) within 15 days for a non-life threatening event and within 7 days for a life-threatening event. For non-serious AEs, the central office will be notified within 5 days of the event being known. All such events will be reported to the DMEC at their next meetings. AEs that may be expected with this injury to the wrist that do not need to be reported to the main REC include infection, delayed wound healing, Complex Regional Pain Syndrome, nerve or vessel events, screw related complications, fracture of scaphoid tuberosity, and chondrolysis). There are also adverse events specific to the plaster cast which are expected and do not need reporting to main REC: soft cast / broken cast that leads to movement of wrist, pressure sores, Complex Regional Pain Syndrome, nerve compression, or pain due to tight cast. Movement in a cast is an untoward event as it can mean the fracture is not properly immobilised which can results in failure of the fracture

to unite.

All participants experiencing SAEs and AEs that are unresolved at initial reporting will be reviewed by the Chief Investigator a month later to ensure that adequate action has been taken and progress made to manage the adverse event. Additional reviews at one month intervals will be conducted when necessary until the Chief Investigator decides that no further reporting is required. For the purpose of this trial, we will only record adverse events that are related to the affected wrist and during 12 months follow-up.

The Chief Investigator is being informed by the reviewers of the X-rays/CT scans collected for the study of any abnormalities identified. The Chief Investigator judges whether the abnormality is clinically important and could impact on patient safety (e.g. a protruding screw) and the need to notify the Principal Investigator of the site. Furthermore whether to record this as an AE is considered. No actions or treatments will be discussed between the investigators.

3.9.4. PROPOSED TIME PERIOD FOR RETENTION OF RELEVANT TRIAL DOCUMENTATION.

Essential Trial documentation (i.e. the documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced) is kept with the Trial Master File and Investigator Site Files. The Sponsor will ensure that this documentation will be retained for a minimum of five years after the conclusion of the trial to comply with standards of Good Clinical Practice. Case Report Forms will be used to record all the information required from the protocol. These data will be stored for a minimum of five years after the conclusion of the trial as paper records; and a minimum of 20 years in electronic format in accordance with guidelines on Good Research Practice (MRC Ethics Series, 2000, updated 2005). All paper records will be stored in a secure storage facility or off-site by York Trials Unit. All electronic records will be stored on a password protected server.

3.9.5. PROPOSED ACTION TO COMPLY WITH 'THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004'.

We will specify that only CE marked screws are used in this trial. We will not include screws which are not CE marked and do not therefore require prior authorisation by the UK Competent Authority, the MHRA, under the Medical Devices Regulations 2002.

3.9.6. PROPOSED SAMPLE SIZE

For surgery to justify its increased costs and the exposure to hazards, it must cause greater or quicker improvement in patients' wrist symptoms and function than after non-operative management. We judge, as did the HTA funded DRAFFT trial, that a 6 point improvement in the PRWE in the surgery group (compared to the controls) would be a minimally clinical important difference. We estimate the standard deviation of PRWE at 52 weeks to be 20 points from the PRWE User manual [1]. This figure is reported for distal radius rather than scaphoid fracture and at 6 months. The only published evidence for scaphoid fracture implies a standard deviation in the range of 8 to 10 points [17]; however, this estimate was at a median of ten years after the patient's injury. Hence, to be cautious we have chosen the estimate of standard deviation to be 20, which gives an effect size of 0.3.

We propose to use a superiority design to observe an effect size of 0.3 at 80% power using a 2-sided 5% significance level requiring 350 participants in total. After allowing for 20% attrition we need to recruit and randomise 438 participants (219 surgery and 219 controls). The estimate of attrition should be realistic given that four RCTs (three studies were single centre and one study had two centres) included in a systematic review of the treatment of scaphoid fractures found response rates for completion of patient-reported functional outcomes between 77% and 100% [14].

We have, however, calculated our sample size based on an estimate of a standard deviation of 20 points in the PRWE at six months [1]. We do not have data on the standard deviation of the PWRE at one year which is the primary time point for the analyses. We propose therefore that having followed-up the participants at one year who we recruited into the internal pilot study we will estimate the standard deviation of the PRWE for that group of patients. At this time there should be a sufficient number of participants recruited and followed-up for the purposes of estimating the standard deviation. We do not anticipate that this would lead us to reduce the current sample size but we may need to consider it being increased.

To minimise attrition we will exclude the rare patient in this population who lacks mental capacity and therefore unlikely to either comply with treatment or data collection. Active and systematic follow-up of all randomised participants is then planned at 6 weeks, 12 weeks, 26 weeks, 52 weeks and 5 years. When possible, we will arrange for the questionnaire to be completed when the participant attends the clinic at 6 weeks, 12 weeks, 52 weeks and 5 years. We will monitor the completion of questionnaires at clinics and share retention figures to each trial site

blinded by centre. At 52 weeks there will be a £40 payment for the patient to attend the clinic and we will also cover up to £40 of their travel expenses or more if agreed with the study team. If at 52 weeks we are finding it difficult to arrange the hospital appointment a letter will be sent from the hospital site to the patient along with a leaflet to encourage their attendance. When a patient does attend at 52 weeks a letter will be sent from the hospital site to thank the patient for their attendance and remind the patient of the 5 year review. Other strategies to collect follow-up data on patients who do not return their questionnaire or attend clinics are: to use a participating hospital's Picture Archiving Communication Systems (PACS) for the local area/region to retrieve imaging of patients; access Summary Care Records to view patients' addresses/General Practitioner registered with to help contact them; and ask a patient's General Practitioner whether they have had an operation on their scaphoid fracture.

We will employ a proven postal strategy for the return of questionnaires. This will include the use of reminders after 2 and 4 weeks and the option for completion of an abridged questionnaire (a minimum of the primary outcome and EQ-5D) via telephone after 6 weeks. At 52 weeks only (the primary time-point for the study), in addition to the 6 week telephone call we will write to patients and ask them to complete the PRWE in an attempt to at least retrieve the primary outcome. We will still call the patient to complete the remainder of the questionnaire over the telephone. We will also use the email address that the patient provided us with at baseline or since then to keep in contact with them about their follow-up. At 26 weeks, when the patient does not attend for a hospital appointment, we will include an unconditional incentive payment of £5 to maximize the completion and return of questionnaires. We will also write a newsletter during the trial to keep the participants informed and engaged with the trial and regularly update the trial website to keep patients informed of study progress. A trial 'tagline' will also be placed on postal envelopes to patients that will highlight the importance of patients' involvement in the research. At the five year follow-up participants will receive £80 to attend hospital for their clinic review which should cover time off work, travel and parking costs. Finally, to minimise attrition and bias, as there is randomised evidence in a recent systematic review that the return of postal questionnaires can be improved when patients are included in a prize draw (Brueton et al, 2014)[41] those patients who return the questionnaire at 26 weeks will be able to win an iPad worth £500. When patients attend their hospital clinic appointment at 52 weeks and 5 years they will be entered into prize draws to win an iPad worth £500.

Sampling to the nested qualitative study will be purposive intending to include men and women from different trial sites, of different ages, occupations and leisure/ sporting activities, and those with scaphoid fractures on their dominant and non-dominant sides. We think it is unlikely to need more than 40 participants to reach theoretical saturation.

3.9.7. STATISTICAL ANALYSIS PLAN

A detailed analysis plan will be agreed with the Data Monitoring and Ethics Committee at an early stage of the study, before all of the data has been collected. Any subsequent amendments will be clearly stated and justified. All analyses will be conducted on an intention to treat basis, including all randomised participants in the groups to which they were randomised. Analyses will be conducted in SAS version 9.1 or later or STATA version 11 or later, using 2-sided significance tests at the 5% significance level (unless otherwise stated). The statistician conducting the analyses will remain blind to treatment group until all data summaries and results are finalised.

The flow of participants through each stage of the trial will be presented in a CONSORT [42] diagram. PRWE scores will be summarised descriptively (n, mean, sd, median, interquartile range, minimum and maximum) at each time point by treatment group and overall. PRWE at baseline will be collected for the time before and after injury. This will allow the assessment of patients' wrist functioning when limited by cast immobilisation as well as give an indication to what extent wrist functioning returns to normal levels. Mean pre-injury PRWE scores will be presented in total and for each treatment group and compared descriptively to PRWE scores post-injury at baseline and all other follow-up time points.

Our primary analysis will compare total PRWE scores between treatment groups at 52 weeks using a covariance pattern mixed model incorporating all time points, where effects of interest and baseline covariates are specified as fixed effects, and the correlation of observations within patients over time (random effect) is modelled by a covariance structure. The outcome modelled will be PRWE at 6, 12, 26 and 52 weeks, predicted by treatment group, time, treatment group-by-time interaction and adjusting for age, fracture displacement (undisplaced vs. minimally displaced) and hand dominance. Different covariance patterns for the repeated measurements will be explored, and the most appropriate pattern will be used for the final model. Model assumptions will be checked and if they are in doubt the data will be transformed. The repeated measures mixed model will provide increased statistical power to that used in the sample size calculation which is based on a two sample t-test at 52 weeks. Estimates for the other time points will also be produced from the model.

All secondary outcomes will be summarised descriptively. The following outcomes will be analysed using the same methods as the primary analysis adjusting for the same covariates: pain and disability subscales of the PRWE, physical health and mental health component summaries of the SF-12 and range and grip strength. Where

available, baseline values of the dependent variable will be included as a covariate in the models. The presence of any complication assessed by clinical examination up to 52 weeks will be analysed by logistic regression (sufficient numbers permitting). Complications are being defined as medical, surgical or plaster cast related. The number of patients who experience a complication of a certain type will be summarised by trial arm. Union will be assessed as a percentage (0-100%) and categorised as: total non-union [0%]; slight union [>0-20]; partial union [>20-70]; mostly united [>70-<100]; and complete union [100%]. Summary statistics for union will be presented at each time point by trial arm. Union will be dichotomised into a 'Probably need surgery' group [0-20%] and a 'Probably don't need surgery' group [>20-100%] and analysed using repeated measures logistic regression comparing treatment groups.

Two subgroup analyses will be undertaken: one exploring patient preferences (surgery, plaster cast, no preference) and the second exploring the type of fracture displacement (undisplaced, displaced), and any differential effect of the trial treatments in these subgroups. Each baseline factor (preference or displacement) and its interaction with the randomised treatment group will be added to the primary analysis model. Our expectation is for patients who were randomised to their preferred treatment to have better outcomes, and for surgery to be more effective in patients with displaced fractures. Since the trial is not powered for these subgroup analyses, any inferences will be made with caution.The number of adverse events experienced by each participant and the total number of events overall will be summarised for each treatment group.

3.9.8.PROPOSED OUTCOME MEASURES

3.9.8.a. PATIENT RATED WRIST EVALUATION

The primary outcome measure will be the Patient Rated Wrist Evaluation (a validated assessment of wrist symptoms and function)[3] assessed at 52 weeks. The PRWE will also be assessed at 6, 12, and 26 weeks to note change in pain and function.

The Patient Rated Wrist Evaluation (PRWE) score is a 15-item questionnaire that is completed by the patient. It is a brief, reliable and valid instrument for assessing wrist pain and disability in activities of daily living [3, 43]. Scoring for all the questions is on a 10-point, ordered scale ranging from 'no pain' or 'no difficultly' (0) to 'worst ever pain' or 'unable to do' (10). Two non-overlapping subscales can be generated:: pain and function. In addition to the individual subscale scores, a total score can be computed on a scale of 100 (0 = no disability) where pain and function problems are weighted equally.

PRWE is chosen over other traditional outcome measures as patient reported functional outcomes are favoured when considered for decision making and it allows assessment of wrist symptoms and function. It is a validated and widely researched outcome measure which is used in another HTA funded study.

A potential criticism of the choice of this instrument as the primary outcome is that because the participants will not be blind to treatment allocation this could bias their completion of the questionnaire. This may reflect the pragmatic design of the trial but the knowledge of treatment allocation may maximise the placebo effect and reproduce the "normal" conditions in which a patient would receive their treatment during routine care [44]. Nevertheless, to address this criticism we will have a consistent approach to recruitment and obtain informed consent by providing an unbiased account of the study to eligible participants using an information sheet which will be specially produced in collaboration with service users; and by the Trial Co-ordinator providing the necessary training and documentation on this to participating sites.

To explore the potential effect of patients' knowledge of treatment on the results of the trial as measured by the primary outcome we will take two approaches. First, eligible patients will be asked at baseline if they have any treatment preference. To investigate whether patient preference has any effect on treatment outcomes, patient preference will be included in a subgroup analysis of the primary outcome. An interaction term will also be included between randomised treatment and preferred treatment in the analysis to assess if the effect of treatment is different depending on a patient's prior preference. Second, it is possible that patients' knowledge of treatment results in non-response at follow-up. A logistic regression model will be used to identify predictors of non-response and will include all variables collected at baseline. If any variables are found to be predictive of non-response they will be included in the model specified for the primary analysis.

Short Form 12-item questionnaire (SF-12)

The SF-12 is a 12 item generic measure of physical and mental health completed by a participant, the population norms of which have a mean of 50 and standard deviation of 10; higher scores indicate better health [45]. The SF-12 has previously been used in a surgical trial involving the hand [46]. The rationale for including the SF-12 is that whilst the PWRE asks about how much pain and difficulty the participant has had with their wrist, it is feasible that a delay to return to work and recreational activities could impact on participants' ability to perform other daily activities and their emotional well-being. Therefore the SF-12 will be completed at 6, 12, 26 and 52 weeks and at 5 years to measure the potential wider consequences of a scaphoid fracture to both the participants'

physical and mental health.

3.9.8.b. TIMING OF PRIMARY OUTCOME

Two small randomised trials [2, 16] of patients with fractures of the scaphoid have demonstrated that there is little change in objective and subjective outcome measures between 26 weeks and 1 year. This small change in outcome measures and the importance of early return to work and sport for these young patients could lead to 26 weeks being chosen as the primary time point. A potential criticism of this, however, is that for the 10-12% of patients who are treated initially in cast who do not heal, delayed surgery will be performed at between 6 and 12 weeks. This leaves only 14-20 weeks for healing and recovery to take place which may mean that an assessment at 26 weeks is not valid. Therefore to allow all patients the time to heal from surgery and recover from potential complications then a primary outcome measure time point at 1 year should provide an unbiased assessment. We will incentivise attendance at 12 months by offering recruited patients payment for attendance, facilitate attendance at their convenience and cover their travel and parking costs.

3.9.8.c. BONE UNION

The secondary outcome of bone union [47]will be determined at 52 weeks (primary end point) using a Computed Tomography (CT) scan and plain radiographs comprising posterior-anterior, lateral, semi 45° prone, semi 45°supine views and an elongated scaphoid view e.g. Ziter type view[26]. Our criterion for union will be complete disappearance of the fracture line[5] on radiographs and complete bridging on CT scans from those taken at baseline. We will document and quantify partial union on CT scans. The individual imaging results will not be reported back to study participants or their clinicians. The rationale for using CT to determine non-union is twofold. First there is only poor to moderate inter-observer agreement (range of Kappa from 0.113 to 0.528) between senior clinicians in determining the union of a scaphoid fracture when using plain radiographs [48]. There is also evidence that both intra- and inter-observer agreement for the detection of scaphoid fracture[49] displacement is significantly improved ($p<0.001$) for CT alone and the combination of radiographs and CT than it is for radiographs alone [50]. Second the CT scan permits definition of complete union and partial union [51-53] .

A limitation of this assessment of non-union, however, is that the presence of the screw to fix the fracture will unblind the observer as to whether the patient has had an operation or not. To minimise the potential for this to introduce bias, two radiologists with a minimum of five year's experience as a consultant and a special interest in musculoskeletal radiology will be trained in trial procedures. The radiologists who will be from sites that are not taking part in the trial if possible, will interpret the CT and plain radiographs independent of each other, and will meet to discuss the cases when there is discordance. This review will also permit identification of patients inadvertently included with displacement of >2mm. The number of scaphoid fractures with such displacement is likely to suggest instability and the need for surgical intervention and so the surgeon would lack equipoise to recruit patients with greater displacement.

Malunion [54] will be determined on the 52 week CT scan (ratio of Scaphoid Height to Length ≥ 0.6) in the true longitudinal axis of the scaphoid as this is more accurate in demonstrating the humpback deformity than plain radiographs [55].

3.9.8.d. OBJECTIVE MEASURES

Range of wrist movement

We will measure range of movement of both wrists using a goniometer and grip strength of both hands using a calibrated Jamar dynamometer at baseline, 6, 12 and 52 weeks. Wrist extension, flexion, radial and ulnar deviation will be documented using the standard technique described by the International Federation of Societies for Surgery of the Hand [56].

Grip strength

Grip strength will be measured using a calibrated Jamar Dynamometer[57-60]. This is standard equipment available at most centers. Both hands will be assessed. Three recordings will be done on each side and the maximum of these three readings will be used. The measurement will be done with the subject seated, arm by the side, elbow bent at 90 degrees and the wrist in neutral position for rotation [61]. The second setting will usually be used for all subjects but patients with large hands may occasionally need to use the third setting. This reflects common practice and evidence-based practice in assessing grip strength[62]. Strength will be expressed as % of opposite side to account for normal variation in strength during the day.

Beighton Joint Laxity Score

When undertaking the range of wrist movement and grip strength at baseline we should also record the Beighton Joint Laxity Score. This is a measure of joint mobility and helps to indicate the hypermobility of patients which may lead to proneness to orthopaedic disorders [63]. Patients are asked to complete a series of simple tests which allows a numerical score of 0 to 9 to be given, one point being allocated for the ability to perform each of the tests. For the purpose of this study, the thumb count for the injured wrist will be excluded to prevent pain and discomfort to the patient that could also further displace the fracture. This assessment, therefore, will give a score out of 8 rather than 9.

Return to work and recreational activities

This will be established through patient self-report when completing the postal questionnaire at follow-up using standard questions about number of days off work and ability to perform usual activities when at work and when performing unpaid recreational activities.

Complications

Infection will be defined as for the "Surgical Site Infection" audit [64], delayed wound healing will be defined as any wound that has not healed by two weeks. Complex Regional Pain Syndrome is defined after surgery as puffy painful swelling of the whole hand restricting full tuck of the fingers at 2 weeks, nerve (hypoaesthesia or numbness in the territory of the palmar cutaneous branch of the median nerve, superficial division of the radial nerve or the median nerve) or vessel events (large (>2 cm) haematoma in the line of the radial artery), and screw related complications (protrusion of either end into the adjacent joint, fracture or bending of the screw, a radiolucent halo around all parts of the screw > 1mm, screw backing out or moving). Additional complications including nerve injury, implant problems, degenerative change [65], AVN and infection (up to 26 weeks) will also be recorded.

3.9.8.e. COST EFFECTIVENESS ANALYSIS

The economic evaluation will assess the relative cost-effectiveness of surgical fixation compared with plaster cast treatment. Costs and health outcomes associated with the interventions will be collected during the 1-year trial period. These costs and outcomes will be extrapolated and modeled over a longer time horizon than captured by the trial (e.g. lifetime of the patient) if this is appropriate given the results of the trial. The additional data from the 5-year follow-up review on the long-term consequences of cast immobilisation and internal fixation, which are not adequately captured in RCTs, will be used to update the model results once available.

Detailed information will be collected on the costs of surgical fixation, including time in surgery, drugs and hospital bed usage, and the costs associated with plaster cast treatment. The impact of the two treatments on subsequent morbidity costs will be assessed. The use of hospital readmissions, outpatient attendances, general practice, community and personal health services will be collected during the various follow-up points through administered questionnaires. These resource use data will be multiplied by appropriate unit costs obtained from the NHS Reference Costs databases [66], the Personal Social Services Research Unit [67], the British National Formulary [68], and other published literature. The primary perspective of the analysis will be that of the NHS and Personal Social Services, consistent with that used by the National Institute for Health and Clinical Excellence [69]. However, given that surgical fixation avoids the need to immobilise the wrist in a cast and accelerates return to normal function, days lost from work and normal activities, and private expenditures related to treatment will also be recorded and these costs will be included in a secondary analysis.

Health outcomes will be expressed in terms of the quality-adjusted life year (QALY), which captures the impact of treatment on both mortality and morbidity by 'weighting' each period of follow-up time by the value corresponding to the QoL (using the EQ-5D [70] during that period [71]. The EQ-5D will be administered at baseline, 6, 12, 26, and 52 weeks follow-up, and also at the 5-year follow-up review using questionnaires. The EQ-5D 'profiles' generated for each patient, at each follow-up point, will be valued using a set of estimated preferences based on the UK population [72]. These scores will be converted into QALYs using area under the curve analysis [73]. A review of the literature will be conducted to establish whether it is possible to make links between the short term outcomes measured in the trial and longer term health-related QoL.

The results of the trial will provide an unbiased estimate of the relative treatment effect of surgical fixation compared with plaster casts. However, it is unlikely to provide all the evidence relevant to the decision on whether surgical treatment represents a cost-effective option to the NHS. Therefore, a decision-analytic model will be developed to extrapolate the effects of the interventions over a longer time horizon and incorporate other relevant evidence on the interventions, identified through a review of the literature. The precise structure of the model will be developed during the project in collaboration with clinical colleagues but it is likely to be based around the long-term consequences of wrist arthritis. Once the data becomes available, outcomes from the 5- year follow-up will be used to inform the long-term consequences. Cost and QALY data will be synthesised to generate an incremental cost effectiveness ratio (ICER), which is defined as the ratio of the mean difference in costs to the mean difference in QALYs between treatments. In order to characterise the uncertainty in the data, probabilistic sensitivity analyses will be conducted and the potential value of further research in this area assessed [74]. The uncertainty will be presented using a cost-effectiveness acceptability curve which shows the probability of surgical fixation being more cost-effective than plaster casts conditional on a maximum value being attached to an additional unit of health outcome [75]. Multivariable regression analyses will be used to assess heterogeneity in costs, QALYs and cost effectiveness. The economic analysis will also apply imputation techniques to address the statistical issues related to the presence of missing data [76].

The 5-year follow-up review will facilitate an additional analysis that examines the relationship between outcomes reported at 1 year and 5 years. If considered appropriate, structural equation modeling [77] will be used to determine the factors that predict outcomes at 5 years and to assess the predictive performance of outcomes at 1-year. This may also be used to assess the cost-effectiveness of following patients up at 5 years post-surgery in general practice.

In summary, the economic analysis will consist of the following:

1) A within trial analysis with total costs and EQ-5D scores presented for both intervention groups.
2) Extrapolation of mean health-related quality of life and cost estimates observed during the 1-year trial period over time
3) Calculation of mean differences in total costs and QALYs between the interventions, and ICER for surgical fixation to give the incremental cost per QALY gained.
4) Update the model and ICER results based on the data from the 5-year follow-up review
5) Examine the relationship between outcomes reported at 1 and 5 years to assess the predictive performance of outcomes at 1-year.

3.9.8.f. QUALITATIVE STUDY OF PATIENT EXPERIENCE

The qualitative data collected in the nested study will be used to generate a model (or models) which reflect patient experiences of wrist fracture and treatment, and which identify difficulties and advantages of the different treatment options. Such models are likely to focus upon personal and lifestyle attributes as well as physical recovery, and to incorporate a range of non-clinical factors which are not routinely considered in clinical interactions. Insight into participation in a clinical trial will also be generated.

Following the conventions of the constant comparative method [32, 33] data analysis will be carried out alongside data collection, with interviews transcribed and analysed in batches before further data are collected. In this way, the process is iterative with models and theories developed from 'within' the interviews rather than from existing theory or clinical practice] and tested or refined in the collection of more data.

All interviews will be 'coded' independently by the researcher with a second team member ensuring consistency and validity of the coding process. Coded interviews will be reviewed to identify key ideas and themes so that models of patient experience might be constructed. These models will be further tested and *constantly* refined as new data are considered. Data collection, and analysis, ceases when no new themes or ideas are present in the interview data, and when the model of patient experience is stable and no longer growing or evolving. This point is known as data saturation [78], previous research suggests that this is often reached with as few as 10-13 interviews [79] – we propose up to 40 interviews here to include at least 15 from each treatment arm to enable data saturation.

Within this study we would expect to generate up to 4 interrelated models of patient experience: i) reporting patients' experiences of wrist fracture, its impact upon their lifestyle, everyday functioning and their recovery; ii) reporting the benefits and difficulties associated with surgical fixation; iii) reporting the benefits and difficulties associated with plaster cast treatment and, iv) reporting experiences and attitudes towards involvement in surgical, clinical research.

3.9.8.g FIVE YEAR CLINIC REVIEW

The long-term consequences of cast immobilisation and internal fixation have not been adequately determined in RCTs. Therefore at five years after their original injury, all trial participants will be asked to attend a follow-up visit at their participating hospital for a clinical and radiographic follow-up. When possible an unbiased independent orthopaedic surgeon who was not involved in the treatment phase of the study will perform the clinical examination. This will include inspection and evaluation of scar sensibility when applicable, palpation for tenderness, measurement of joint movement with a goniometer, as well as measurement of grip strength and pinch strength [17].

Participants will also be asked to complete a questionnaire asking about perceived hand problems (e.g. weakness of wrist, reduced range of movement) as well as the primary outcome measure, the PRWE and EQ-5D. The radiographic examination will include standardized images of both wrist joints and scaphoid images of the injured wrist comprising posterior-anterior, lateral, semi 45° prone, semi 45°supine views and an elongated scaphoid view e.g. Ziter[26] type view.. We will also obtain a CT scan to investigate for osteoarthritis, its severity and changes around the implant [17]. Radiographs and CT scan will be assessed for union of the fracture, osteoarthritic changes, avascular necrosis, implant status and the shape of the scaphoid [65]. Osteoarthritis will be graded as 1 (a normal joint), 2 (narrowing of the joint space), 3 (osteophytes), 4 (narrowing and osteophytes), or 5 (narrowing, osteophytes, and subchondral sclerosis) [80] .

We shall assess the feasibility of a five year review by undertaking an internal pilot study. For this we would follow-up the participants who were recruited at the four sites into the internal pilot study at five years. Based on our recruitment assumptions, during this time it should be feasible to recruit one patient/month at each of the four sites and therefore at the end of the six months we should have recruited around 24 trial participants. Our main study is designed to detect an effect size of 0.3 at 80% power using 5% significance level, which would require following-up 350 participants at 1 year. If there is a further 20% attrition rate at 5 years of the 350 patients followed-up at 1 year then a final sample size at the end of the proposed long term follow-up period of 280 would provide power of 70% to detect an effect size of 0.3 using 5% significance level. This estimate of attrition and power to detect a difference for a 5 year long term follow-up study has been considered acceptable by the DMEC and TSC for the analogous HTA funded surgical trial of treatment for fractures of the proximal humerus. In short, for the pilot five year review to be considered feasible we would need to follow-up a minimum of 64% of the 24 patients recruited into the trial during its early phase. Therefore the internal pilot study of the five year review would comprise of: following up the six months of participants recruited into the pilot; allow for three months to complete the follow-up of these participants (at the end of this period we would report to the independent members of the TSC and DMEC the proportion of patients who complete the five year review who would then recommend to the HTA whether we should continue); and if the HTA, who make the final decision, declines to continue the review then a further three months would be needed to do the analyses of the data that has been completed and write an addendum to the main HTA monograph.

To maximise the success of the five year review we shall do the following. First, for a young population it should be an effective strategy to collect their mobile number and email address at baseline to check at five years their address details. Should there be problems contacting the participant we will ask their General Practitioner for their address. The participant will have consented for us to do this when recruited into the trial. Second, we would keep in contact with patients through an annual newsletter and incentivise attendance at five year follow-up by offering payment for attendance, facilitate attendance at their convenience and cover their travel and parking costs. In addition we have allocated an extra 9 months to allow us time to contact and follow-up as many of the patients recruited to this study as possible. Third, a previous study has shown that with many telephone calls and letters, as well as using the NHS tracking system, it is feasible to encourage patients to attend such a follow-up clinic [65]. In this study, at a mean of 93 months, 71 of 88 (81%) patients with a fracture of the scaphoid who were randomised to Herbert screw fixation or below-elbow plaster cast immobilisation were successfully followed-up.

3.9.8.g. BLINDING

The patients cannot be blind to their treatment. The treating surgeons will, of course, not be blind to the treatment, but will take no part in the postoperative subjective assessment of patients. The functional outcome data will be collected and entered onto the trial central database via postal questionnaire by a research assistant who will be blind to the treatment allocation. The statistical analysis will also be performed blind. We will mitigate against bias by ensuring that all radiographs and CT scans are assessed by independent senior radiologists and researcher.

3.10. RESEARCH GOVERNANCE

3.10.1.a. QUALITY CONTROL

The University Hospitals of Leicester NHS Trust has agreed to be the lead sponsor for this project. This study will be fully compliant with the Research Governance Framework and MRC Good Clinical Practice Guidance. If a patient wishes to *complain* formally, they will be advised to do this through NHS Complaints Procedure. If a patient is *harmed* and this is due to someone's negligence then they may have grounds for legal action or compensation against the Sponsor (in respect of harm arising out of participation in the trial) or the NHS (in respect of any harm which has resulted from the treatment received).

We will institute a rigorous programme of quality control. The day-to-day management of the trial will be the responsibility of the Trial Co-ordinator based at York Trials Unit who will be supported by administrative staff and regular meeting with the Trial Management Group and will ensure adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by YTU to ensure integrity of randomisation, study entry procedures and data collection. The YTU has a quality assurance manager who will monitor this trial by conducting regular (yearly or more if deemed necessary) inspections of the Trial Master File. Written reports will be produced for the TSC and DMEC informing them of any corrective action that is required.

4. PROJECT TIMETABLE AND MILESTONES

4.1. Patient recruitment and expected recruitment rates

We envisage for the main trial a 4.5 year study but in addition include a 5 year review. The main recruitment period for the trial will be for 30 (24+6 for slower recruitment) months and patients followed up at 6, 12, 26 and 52 weeks.

17 NHS hand units, accounting for 7.6 million population have agreed to participate. The rate of scaphoid waist fractures is 80-161/million/year (the latter in the military) providing a minimum of 608 fractures/year. Previous small studies [2, 16] had a recruitment rate of 83% and attrition of 8%. However, based on our experience of large, multi-centre trials a pragmatic estimate of 40% recruitment and 20% attrition will need identification of 1095 patients to have 350 patients completed by trial end. We would therefore need to recruit for a minimum of 2 years identifying 11 patients a week and recruiting 4 or 5 patients a week which we consider feasible. The results of the internal pilot study will inform the need to set up more than the 17 sites considered necessary to meet our recruitment target.

4.2. Project Plan

The proposed start date of the trial is 01/04/13 for which the duration is 54 months. There are four key milestones to the trial:

First, there is the recruitment of patients into the trial. This will commence early in month 4 with the internal pilot study and should be complete in month 36.

Second, there is the qualitative study in which we will commence recruitment of patients from month 4 onwards. It is envisaged that we will include a sample of patients in the qualitative study from throughout the recruitment phase of the trial, a further twelve months to complete the data collection at 52 week follow-up, and a further six months to complete the analysis.

Third, during months 49 to 54, after completion of trial follow-up and data cleaning, the effectiveness and health economic analysis (within trial analysis and extrapolation from short term to 5 year outcomes) will be undertaken.

Fourth the HTA monograph will be complete in month 54.

In addition to the trial, we propose to undertake a 5 year clinic review of trial participants for which the duration is an additional 54 months. Data will be collected for our cohort of patients from month 64 to 105.

During months 106 and 108 the effectiveness and health economic analyses (to update the model and examine relationships between outcomes at 1 and 5 years) will be undertaken and an addendum to the HTA monograph completed.

Time period (month)	Activity
1 – 3	Complete local R&D approval and set up for 4 sites
4 – 6	Initiate early recruitment (internal pilot study at 4 sites and continue R&D approval for other sites)
7 – 36	Main recruitment for trial
37 – 48	Complete final 12 month follow-up
49 – 54	Analysis and write up of main HTA monograph
55 – 63	Preparation for 5 year clinic review
64 – 96	Conduct 5 year clinic review
64-69	*Internal pilot follow-up for 5 year review*
70-72	*Three months to follow-up the last participant to be followed-up for the internal pilot*
73-75	*If internal pilot is unsuccessful, to complete analysis and write up the report*
97 - 105	Allow 9 months to complete clinics and prepare analysis
106 – 108	Complete analysis and write HTA addendum monograph

5. EXPERTISE

Our multi-disciplinary team which includes service users, clinicians and health service researchers has already fostered a strong research network of collaborating centres for clinical trials in orthopaedic surgery and contributes to the collective research endeavour in the NHS. Qualitative researchers within our units supervised by PL will run the qualitative study.

British Society for Surgery of the Hand (BSSH) has contributed to the development of this proposal and fully supports it. The Patient Liaison Group Lay Chairman, Mr Nick Welch, of the British Orthopaedic Association will represent patients on the TSC ensuring service user involvement from inception through to completion of the project. Service users will contribute to the development of the trial protocol such as the patient information documentation and consent process for trial participation.

The lead applicant (JD) is an internationally recognised expert in scaphoid injuries having published widely [2, 5, 7, 24, 47, 48, 65, 81-97] on the subject and has conducted a smaller prospective randomised study on this injury which has helped design this study. JD will be the CI and chair the Trial Management Group, overseeing every aspect of this trial from design, and conduct to report and dissemination of findings.

Clinicians in the team have a special interest in outcomes after upper limb trauma and other disorders affecting the upper extremity and have published widely on this theme. SH has published on scaphoid fractures, and written the Map of Medicine pathway for scaphoid fractures and will represent the BSSH research committee on the Trial Management Group. AR MC SH will provide expert clinical and trial advice at each stage of the study. SB will oversee the supervision of the Trial Co-ordinator having experience of ProFHER. DT is expert in trial design and economic assessment as are GR and CM. NT, JT, CH will provide statistical oversight, draw up the analysis plan and staff at the YTU will conduct the initial analyses. SB, JD will write the HTA report.

AR is Chief Investigator for the ProFHER Trial (HTA project 06/404/53; grant £1.49 million) and is co-Investigator of the DRAFFT Trial (HTA project 08/116/97; grant £1.6 million), both UK wide multicentre trials of upper limb fractures. DT and SB are grant holders for the ProFHER Trial. DT is Chair of TSC for DRAFFT. AR and SB are grant holders for 'Evidence synthesis on frozen shoulders' which assessed upper limb function after treatment of a common shoulder condition (HTA project 09/13/02; grant £195,909).

PL will provide specialist expertise in qualitative research and will oversee the management of the nested qualitative study. He is a currently a co-investigator, providing specialist methodological expertise, on two further NIHR funded studies and has recently published work which considers patient perspectives on treatment and participation in surgical research

The proposed research on scaphoid fractures complements our involvement in other projects investigating upper limb trauma. Our prior experience with intricacies and processes involved in running multi-centre surgical trials of upper limb fractures has prepared us to conduct this trial. We see similarities in the research infrastructure requirement, outcomes assessment and recruitment challenges between the ProFHER Trial and the scaphoid fracture SWIFFT trial. The groundwork in getting collaborating centres research ready for ProFHER and

DRAFFT will facilitate the conduct of this scaphoid fracture SWIFFT trial.

6. SERVICE USERS

Informal feedback from service users from our previous study [2] has informed the design of this study and has particularly led us to include the evaluation of patients' experiences and preferences in this trial. This aspect is addressed by the qualitative part of this trial.

We plan to have two patient representatives; Mr Nick Welch, Lay Chair of the Patient Liaison Group of the British Orthopaedic Association has agreed to be on the Trial Steering Committee. We will also approach a service user to be on the Trial Management Group and our costs cover this.

In addition service users will help develop the detailed patient information to explain the risks and benefits of this study clearly. Service users will contribute to the development of the trial materials such as the patient information documentation and consent process for trial participation and advise on how to improve compliance and reduce attrition. Patients will also be invited to comment on the Case Record Form to ensure that all aspects of care considered important by patients are captured.

Service users will help generate patient information for Shared Decision Making [98] based on findings from this trial, update the entry on Wikipedia and write the Map of Medicine [99] entry on scaphoid fracture management. In this way service users will actively participate in dissemination of the conclusions of this study in a manner that is easily accessible by patients.

7. JUSTIFICATION OF SUPPORT REQUIRED

7.1. Research costs

For York Trials Unit a key research cost is that of the Trial Manager whose employment extends the full 54 month funding period. This post is essential for all aspects of the trial management. The anticipated number and distribution of the centres and allowing for cover, such as for holidays, means that a Trial Support Officer working in liaison with the Trial Co-ordinator will also be required. This will be a full-time post during recruitment and part-time during the completion of data collection and write up of the monograph. Data management staff, economist, statistician and trial secretary are required at all time, although at variable whole time equivalents (WTEs) depending on the stage of the trial. In addition, there are some nominal small proportions of WTE for staff who are involved in the supervision of trial management, statistical and economic aspects of the trial. In addition, there are the costs of consumables incurred for aspects of data collection and management (e.g. printing of forms, scanning license, archiving, and randomisation) and travel expenses for attending regular meetings with the Trial Management Group, Trials Steering Committee, Data Monitoring Ethics Committee, and visits to participating sites. For the 5 year review, all staff costs are at a nominal small proportion of WTE. This element of the study should be set up during the trial and will mostly require careful monitoring with financial incentives and re-imbursements to encourage the trial participants to attend.

Funding is also required to facilitate the full participation of Prof Dias, the lead applicant, in every aspect of the trial and to provide clinical support and advice for the recruiting sites. This includes the part-time funding of a Research Nurse and Assistant to maximise participant recruitment and data collection at the lead site (Leicester). The lecturer will oversee the assessments of radiographic and CT scan data which will form part of work for a PhD with the Assistant. The secretary will assist in the administration and help in the transcription of interviews. Prof Rangan (Teesside) and Prof Costa (Coventry) have a small proportion of WTE to oversee the conduct of the study at the other sites contributing to the early recruitment of participants into the trial. In addition, there is funding of specialist expertise in qualitative research for the design, conduct and analyses of the interviews. The service users will also be reimbursed for travel expenses when attending meetings.

7.2. NHS Service Support costs

There are additional patient tests (i.e. CT scans) that will be included in the trial. The CT scans at baseline, 52 weeks and 5 years are not contributing to patient care and therefore the individual results of this particular activity will not be reported back to study participants or their clinicians. Hence this is a research cost which should be met by the research funder [100]. In addition, our trial costs include payment per patient recruited for the 54 month study to cover costs of a research nurses' time for tasks such as patient screening, assessing eligibility, randomising and subsequent collection of follow-up hospital data, noting complications and obtaining the initial and 52 week CT scans. There will be further per patient payments to cover similar activities during the 5 year review. Again, these activities are not contributing directly to the care of a patient. Therefore as has been

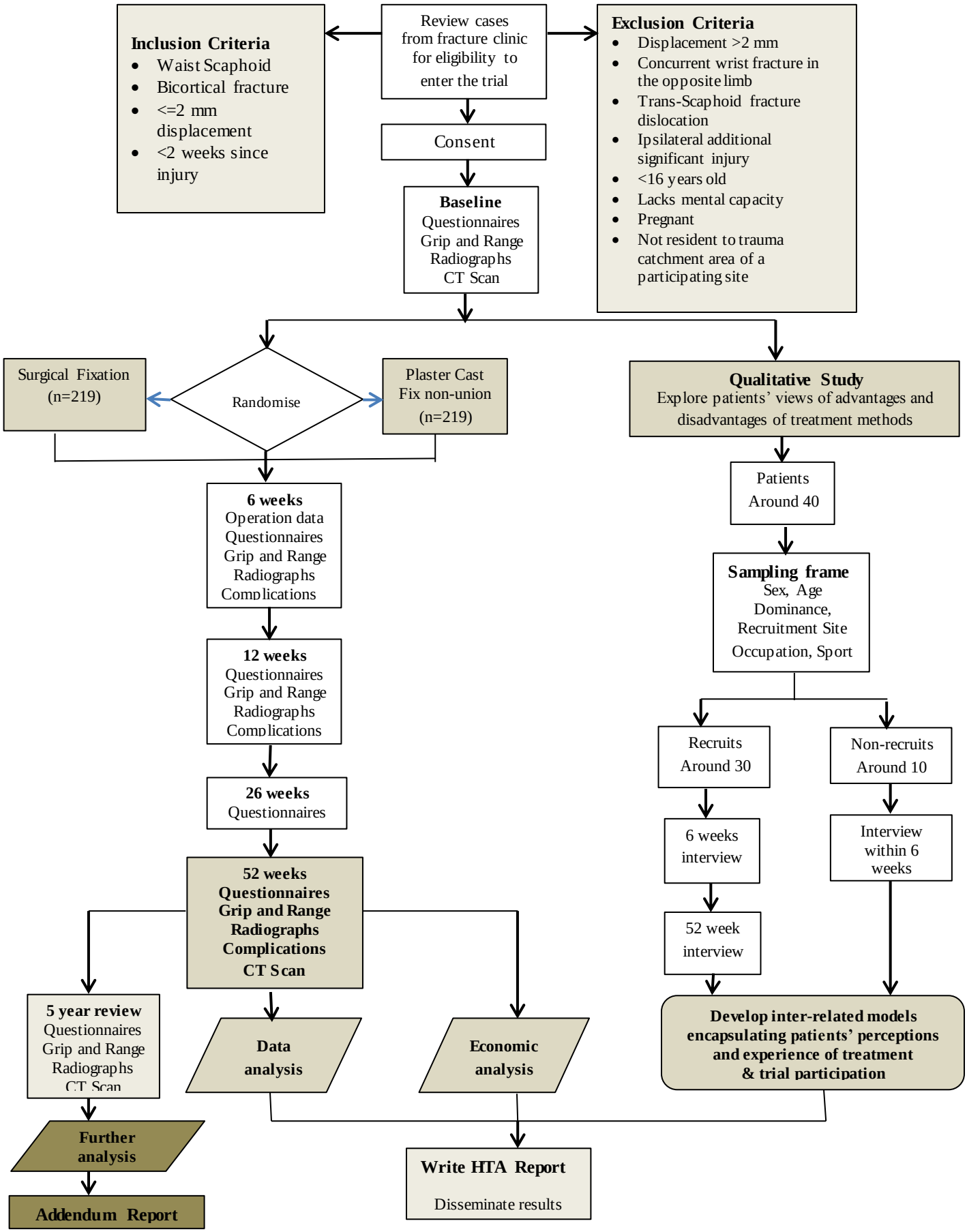
approved previously by the HTA for the ProFHER and DRAFFT trials we propose that these should be included as a research cost which has subsequently been agreed with the HTA. The cost, however, of obtaining patient consent, which is £15,330, has been agreed to be a NHS Service Support cost.

7.3. NHS Excess Treatment Costs

The excess treatment costs of the surgical intervention for this trial are estimated to be £335,946. This, however, is a pragmatic trial for which the interventions being compared are standard treatment options currently available in the NHS. We anticipate therefore that there will be no excess treatment costs overall. While this is likely to be the case in the majority of centres, this may not necessarily apply to certain hospitals, even in the context of a potentially low recruitment rate, that have a below average rate of surgery. It will be for the individual providers at the participating sites to consider the need to fund these treatment costs when deciding on approval for the trial.

The research cost of this grant application includes the costs due to the £600/patient payment for the time of the Research Nurse to perform tasks such as patient screening, assessing eligibility, randomising and subsequent collection of follow-up hospital data. Whilst this cost per patient payment may be made to the NHS to reimburse the time of a Research Nurse we are requesting this cost as a research cost because these activities are not directly contributing to patient care.

8. FLOW DIAGRAM



9. REFERENCES

1. MacDermid, J.C., *The Patient-Rated Wrist Evaluation (PRWE)© User Manual*. 2007, McMaster University: Hamilton, Ontario.
2. Dias, J.J., et al., *Should acute scaphoid fractures be fixed? A randomized controlled trial.* The Journal of bone and joint surgery.American volume, 2005. **87**(10): p. 2160-2168.
3. MacDermid, J.C., et al., *Patient rating of wrist pain and disability: a reliable and valid measurement tool.* Journal of Orthopaedic Trauma, 1998. **12**(8): p. 577-586.
4. Hove, L.M., *Epidemiology of scaphoid fractures in Bergen, Norway.* Scandinavian Journal of Plastic & Reconstructive Surgery & Hand Surgery, 1999. **33**(4): p. 423-6.
5. Clay, N.R., et al., *Need the thumb be immobilised in scaphoid fractures? A randomised prospective trial.* The Journal of bone and joint surgery.British volume, 1991. **73**(5): p. 828-832.
6. Cooney, W.P., III, J.H. Dobyns, and R.L. Linscheid, *Nonunion of the scaphoid: analysis of the results from bone grafting.* Journal of Hand Surgery - American Volume, 1980. **5**(4): p. 343-354.
7. Dias, J.J. and H.P. Singh, *Displaced fracture of the waist of the scaphoid.* Journal of Bone & Joint Surgery - British Volume, 2011. **93**(11): p. 1433-9.
8. Duppe, H., et al., *Long-term results of fracture of the scaphoid. A follow-up study of more than thirty years.* Journal of Bone & Joint Surgery - American Volume, 1994. **76**(2): p. 249-252.
9. Mack, G.R., et al., *The natural history of scaphoid non-union.* Journal of Bone & Joint Surgery - American Volume, 1984. **66**(4): p. 504-509.
10. Doornberg, J.N., et al., *Nonoperative treatment for acute scaphoid fractures: a systematic review and meta-analysis of randomized controlled trials.* Journal of Trauma-Injury Infection & Critical Care, 2011. **71**(4): p. 1073-81.
11. Symes, T.H. and J. Stothard, *A systematic review of the treatment of acute fractures of the scaphoid.* Journal of Hand Surgery: European Volume, 2011. **36**(9): p. 802-10.
12. Yin, Z.G., et al., *Treatment of acute scaphoid fractures: systematic review and meta-analysis.* Clinical Orthopaedics & Related Research, 2007. **460**: p. 142-151.
13. Modi, C.S., et al., *Operative versus nonoperative treatment of acute undisplaced and minimally displaced scaphoid waist fractures--a systematic review.* Injury, 2009. **40**(3): p. 268-273.
14. Buijze, G.A., et al., *Surgical compared with conservative treatment for acute nondisplaced or minimally displaced scaphoid fractures: a systematic review and meta-analysis of randomized controlled trials.* Journal of Bone & Joint Surgery - American Volume, 2010. **92**(6): p. 1534-1544.
15. Bond, C.D., et al., *Percutaneous screw fixation or cast immobilization for nondisplaced scaphoid fractures.* The Journal of bone and joint surgery.American volume, 2001. **83**(4): p. 483-488.
16. McQueen, M.M., et al., *Percutaneous screw fixation versus conservative treatment for fractures of the waist of the scaphoid: a prospective randomised study.* Journal of Bone & Joint Surgery - British Volume, 2008. **90**(1): p. 66-71.
17. Vinnars, B., et al., *Nonoperative compared with operative treatment of acute scaphoid fractures. A randomized clinical trial.* Journal of Bone & Joint Surgery - American Volume, 2008. **90**(6): p. 1176-1185.
18. Slade, J.F., III and T. Gillon, *Retrospective review of 234 scaphoid fractures and nonunions treated with arthroscopy for union and complications.* Scandinavian Journal of Surgery: SJS, 2008. **97**(4): p. 280-289.

19. Van Tassel, D.C., B.D. Owens, and J.M. Wolf, *Incidence estimates and demographics of scaphoid fracture in the U.S. population.* Journal of Hand Surgery - American Volume, 2010. **35**(8): p. 1242-1245.
20. *The NHS Information Centre, Hospital Episode Statistics for England. Inpatient statistics, 2005-09. Activity in English NHS Hospitals and English NHS commissioned activity in the independent sector.* 2010, The Health and Social Care Information Centre. HES Analysis: Leeds.
21. McCulloch, P., et al., *Randomised trials in surgery: problems and possible solutions.* BMJ, 2002. **324**(7351): p. 1448-51.
22. Cook, J.A., C.R. Ramsay, and J. Norrie, *Recruitment to publicly funded trials--are surgical trials really different?* Contemporary Clinical Trials, 2008. **29**(5): p. 631-4.
23. Davis, E.N., et al., *A cost/utility analysis of open reduction and internal fixation versus cast immobilization for acute nondisplaced mid-waist scaphoid fractures.* Plastic & Reconstructive Surgery, 2006. **117**(4): p. 1223-1235.
24. Singh, H.P., N. Taub, and J.J. Dias, *Management of displaced fractures of the waist of the scaphoid: meta-analyses of comparative studies.* Injury, 2012. **43**(6): p. 933-9.
25. Bhat, M., et al., *MRI and plain radiography in the assessment of displaced fractures of the waist of the carpal scaphoid.* Journal of Bone & Joint Surgery - British Volume, 2004. **86**(5): p. 705-13.
26. Ziter, F.M., Jr., *A modified view of the carpal navicular.* Radiology, 1973. **108**(3): p. 706-707.
27. Thabane, L., et al., *A tutorial on pilot studies: the what, why and how.* BMC Medical Research Methodology, 2010. **10**.
28. Watson, J.M. and D.J. Torgerson, *Increasing recruitment to randomised trials: a review of randomised controlled trials.* BMC Medical Research Methodology, 2006. **6**.
29. McDonald, A.M., et al., *What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies.* Trials [Electronic Resource], 2006. **7**.
30. Campbell, M.K., et al., *Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study.* Health Technology Assessment (Winchester, England), 2007. **11**(48): p. iii, ix-105.
31. Mason, J., *Qualitative interviewing: asking, listening, interpreting*, in *Qualitative Research in Action*, T. May, Editor. 2002, SAGE Publishers: London.
32. Strauss, A. and J. Corbin, *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*. 1990, Newbury Park, CA: Sage Publications.
33. Glaser, B.G. and A.L. Strauss, *The Discovery of Grounded Theory: Strategies for Qualitative Research*. 1967, New York: Aldine De Gruyter.
34. Grewal, R. and G. King, *Percutaneous screw fixation led to faster recovery and return to work than immobilization for fractures of the waist of the scaphoid.* Journal of Bone & Joint Surgery - American Volume, 2008. **90**(8).
35. Zlotolow, D.A., E. Knutsen, and J. Yao, *Optimization of volar percutaneous screw fixation for scaphoid waist fractures using traction, positioning, imaging, and an angiocatheter guide.* Journal of Hand Surgery - American Volume, 2011. **36**(5): p. 916-21.
36. Jeon, I.H., et al., *Percutaneous screw fixation for scaphoid fracture: a comparison between the dorsal and the volar approaches.* Journal of Hand Surgery - American Volume, 2009. **34**(2): p. 228-236.
37. Herbert, T.J., *Open volar repair of acute scaphoid fractures.* Hand Clinics, 2001. **17**(4): p. 589-99, viii.
38. Haddad, F.S. and N.J. Goddard, *Acute percutaneous scaphoid fixation A pilot study.* The Journal of bone and joint surgery.British volume, 1998. **80**(1): p. 95-99.
39. Slade, J.F., III and D. Jaskwhich, *Percutaneous fixation of scaphoid fractures.* Hand Clinics, 2001. **17**(4): p. 553-574.
40. Saeden, B., et al., *Fracture of the carpal scaphoid. A prospective, randomised 12-year*

follow-up comparing operative and conservative treatment. Journal of Bone & Joint Surgery - British Volume, 2001. **83**(2): p. 230-234.
41. Brueton, V.C., et al., *Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis.* BMJ open, 2014. **4**(2): p. e003821.
42. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**.
43. MacDermid, J.C., *Development of a scale for patient rating of wrist pain and disability.* Journal of hand therapy : official journal of the American Society ofHand Therapists, 1996. **9**(2): p. 178-183.
44. Schwartz, D. and J. Lellouch, *Explanatory and pragmatic attitudes in therapeutical trials.* Journal of Clinical Epidemiology, 2009. **62**(5): p. 499-505.
45. Ware, J., Jr., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.* Medical Care, 1996. **34**(3): p. 220-33.
46. Atroshi, I., et al., *Outcomes of endoscopic surgery compared with open surgery for carpal tunnel syndrome among employed patients: randomised controlled trial.* BMJ, 2006. **332**(7556).
47. Dias, J.J., *Definition of union after acute fracture and surgery for fracture nonunion of the scaphoid.* Journal of Hand Surgery [Br], 2001. **26**(4): p. 321-325.
48. Dias, J.J., et al., *Radiographic signs of union of scaphoid fractures An analysis of inter-observer agreement and reproducibility.* The Journal of bone and joint surgery.British volume, 1988. **70**(2): p. 299-301.
49. Ty, J.M., S. Lozano-Calderon, and D. Ring, *Computed tomography for triage of suspected scaphoid fractures.* Hand, 2008. **3**(2): p. 155-158.
50. Lozano-Calderon, S., et al., *Diagnosis of scaphoid fracture displacement with radiography and computed tomography.* Journal of Bone & Joint Surgery - American Volume, 2006. **88**(12): p. 2695-2703.
51. Amirfeyz, R., et al., *Displaced scaphoid waist fractures: the use of a week 4 CT scan to predict the likelihood of union with nonoperative treatment*. Journal of Hand Surgery: European Volume, 2011. **36**(6): p. 498-502.
52. Singh, H.P., et al., *Partial union of acute scaphoid fractures.* Journal of Hand Surgery [Br], 2005. **30**(5): p. 440-445.
53. Smith, M.L., et al., *Using computed tomography to assist with diagnosis of avascular necrosis complicating chronic scaphoid nonunion.* Journal of Hand Surgery - American Volume, 2009. **34**(6): p. 1037-1043.
54. Forward, D.P., et al., *The clinical outcome of scaphoid fracture malunion at 1 year.* Journal of Hand Surgery: European Volume, 2009. **34**(1): p. 40-6.
55. Ring, D., et al., *Both scanning plane and observer affect measurements of scaphoid deformity*. Journal of Hand Surgery - American Volume, 2005. **30**(4): p. 696-701.
56. *Terminology for Hand Surgery*, I. Leslie, Editor. 1998, International Federation of Societies for Surgery of the Hand: London.
57. Crosby, C.A., M.A. Wehbé, and B. Mawr, *Hand strength: normative values.* The Journal of hand surgery, 1994. **19**(4): p. 665-670.
58. Hanten, W.P., et al., *Maximum grip strength in normal subjects from 20 to 64 years of age.* Journal of hand therapy : official journal of the American Society ofHand Therapists, 1999. **12**(3): p. 193-200.
59. Mathiowetz, V., et al., *Grip and pinch strength: normative data for adults.* Archives of Physical Medicine and Rehabilitation, 1985. **66**(2): p. 69-74.
60. Mathiowetz, V., et al., *Reliability and validity of grip and pinch strength evaluations.* The Journal of hand surgery, 1984. **9**(2): p. 222-226.
61. Mathiowetz, V., C. Rennells, and L. Donahoe, *Effect of elbow position on grip and key pinch strength.* The Journal of hand surgery, 1985. **10**(5): p. 694-697.
62. Trampisch, U.S., et al., *Optimal Jamar Dynamometer Handle Position to Assess Maximal*

Isometric Hand Grip Strength in Epidemiological Studies. The Journal of hand surgery, 2012. **37**(11): p. 2368-2373.
63. Beighton, P., L. Solomon, and C.L. Soskolne, *Articular mobility in an African population.* Annals of the Rheumatic Diseases, 1973. **32**(5): p. 413-8.
64. NICE, *Surgical site infection-Prevention and treatment of surgical site infection: CG74*, in *NICE Clinical Guideline*. 2008, National Institute of Clinical Excellence.
65. Dias, J.J., et al., *Clinical and radiological outcome of cast immobilisation versus surgical treatment of acute scaphoid fractures at a mean follow-up of 93 months.* Journal of Bone & Joint Surgery - British Volume, 2008. **90**(7): p. 899-905.
66. *Department of Health. NHS reference costs* 2011: London.
67. Curtis, L., *Unit costs of health and social care*. 2011, PSSRU: Kent.
68. *British National Formulary*. 2011, British Medical Association and the Royal Pharmaceutical Society of Great Britain: London.
69. Adamany, D.C., E.A. Mikola, and B.J. Fraser, *Percutaneous fixation of the scaphoid through a dorsal approach: an anatomic study.* Journal of Hand Surgery - American Volume, 2008. **33**(3): p. 327-331.
70. Kind, P., *The EuroQol instrument: An index of health-related quality of life*, in *Quality of life and pharmacoeconomics in clinical trials*, B. Spilker, Editor. 1996, Lippincott-Raven Philadelphia. p. 191-201.
71. Dolan, P., *Modeling valuations for EuroQol health states.* Medical care, 1997: p. 1095-1108.
72. Kind, P., G. Hardman, and S. Macran, *UK population norms for EQ-5D.* Centre for Health Economics, University of York, 1999. **Discussion paper 172**.
73. Matthews, J., et al., *Analysis of serial measurements in medical research.* British Medical Journal, 1990. **300**(6719): p. 230-235.
74. Claxton, K.P. and M.J. Sculpher, *Using value of information analysis to prioritise health research: some lessons from recent UK experience.* Pharmacoeconomics, 2006. **24**(11): p. 1055-1068.
75. Fenwick, E., K. Claxton, and M. Sculpher, *Representing uncertainty: the role of cost - effectiveness acceptability curves.* Health Economics, 2001. **10**(8): p. 779-787.
76. Briggs, A., et al., *Missing.... presumed at random: cost-analysis of incomplete data.* Health Economics, 2003. **12**(5): p. 377-392
77. Kline, R.B., *Principles and practice of structural equation modeling*. 2010, New York: The Guilford Press.
78. Pope, C., S. Ziebland, and N. Mays, *Qualitative research in health care. Analysing qualitative data.* BMJ, 2000. **320**(7227): p. 114-6.
79. Francis, J., et al., *What is an adequate sample size? Operationalising data saturation for theory-based interview studies.* Psychology & Health, 2010. **25**(10): p. 1229-1245.
80. Altman, R.D. and G.E. Gold, *Atlas of individual radiographic features in osteoarthritis, revised.* Osteoarthritis & Cartilage, 2007. **15 Suppl A**: p. A1-56.
81. Eastley, N., et al., *Union rates after proximal scaphoid fractures; meta-analyses and review of available evidence.* Journal of Hand Surgery (European Volume), 2012.
82. Singh, H.P. and J.J. Dias, *Scaphoid Fractures and other Carpal Injuries*, in *EFORT Textbook (Hand & Wrist section)*, G. Bentley, Editor. 2011, Springer: London.
83. Singh, H.K. and J.J. Dias, *Scaphoid Fractures.* Journal of Bone & Joint Surgery - British Volume, 2011. **Focus On**: p. 1-7.
84. Ibrahim, T., et al., *Surgical versus nonsurgical treatment of acute minimally displaced and undisplaced scaphoid waist fractures: pairwise and network meta-analyses of randomized controlled trials.* Journal of Hand Surgery - American Volume, 2011. **36**(11): p. 1759-1768.e1.
85. Dias, J.J., *Scaphoid Fractures*, in *European Instructional Lectures*, G. Bentley, Editor. 2011, Springer: London. p. 107-132.
86. Dias, J., *Nonoperative treatment of Scaphoid Fractures*, in *The Scaphoid*, D.J. Slutsky and

J.F. Slade, Editors. 2011, Thieme: New York. p. 49-58.
87. Dias, J.J., *Evaluation of the results of scaphoid surgery*, in *Le Scaphoide de la Fracture a l'arthrose*, B. Lussiez, C. Rizzo, and E. Lebreton, Editors. 2004, Sauromos Medical: Montpellier. p. 317-322.
88. Dias, J.J., *Criteria for the diagnosis of healing of a scaphoid fracture or nonunion*, in *Le Scaphoide de la Fracture a l'arthrose*, B. Lussiez, C. Rizzo, and E. Lebreton, Editors. 2004, Sauromos Medical: Montpellier. p. 181-188.
89. Straw, R.G., T. Davis, and J. Dias, *Scaphoid nonunion: treatment with a pedicled vascularized bone graft based on the 1,2 intercompartmental supraretinacular branch of the radial artery. Journal of Hand Surgery (British and European Volume) 2002; 27B (5): 413–416*. Journal of Hand Surgery (British and European Volume), 2003. **28**(3): p. 282.
90. Straw, R.G., T.R.C. Davis, and J.J. Dias, *Scaphoid nonunion: treatment with a pedicled vascularized bone graft based on the 1,2 intercompartmental supraretinacular branch of the radial artery*. Journal of Hand Surgery [Br], 2002. **27**(5): p. 413-16.
91. Dias, J.J., *Scaphoid Fractures*, in *Oxford Textbook of Orthopaedics and Trauma*, C. Bulstrode, et al., Editors. 2002, Oxford University Press: Oxford. p. 1890-1908.
92. Wildin, C.J., B. Bhowal, and J.J. Dias, *The incidence of simultaneous fractures of the scaphoid and radial head*. Journal of Hand Surgery [Br], 2001. **26**(1): p. 25-27.
93. Dias, J.J., A.C. Hui, and A.C. Lamont, *Real time ultrasonography in the assessment of movement at the site of a scaphoid fracture non-union*. Journal of Hand Surgery [Br], 1994. **19**(4): p. 498-504.
94. Mody, B.S., et al., *Nonunion of fractures of the scaphoid tuberosity*. The Journal of bone and joint surgery.British volume, 1993. **75**(3): p. 423-425.
95. Dias, J.J., et al., *Suspected scaphoid fractures The value of radiographs*. The Journal of bone and joint surgery.British volume, 1990. **72**(1): p. 98-101.
96. Dias, J.J., I.J. Brenkel, and D.B. Finlay, *Patterns of union in fractures of the waist of the scaphoid*. The Journal of bone and joint surgery.British volume, 1989. **71**(2): p. 307-310.
97. Dias, J.J., et al., *Radiographic assessment of soft tissue signs in clinically suspected scaphoid fractures: the incidence of false negative and false positive results*. Journal of Orthopaedic Trauma, 1987. **1**(3): p. 205-208.
98. Coulter, A. and A. Collins, *Making Shared Decision a Reality. No decision about me, without me*. 2011, The King's Fund: London.
99. *Map of Medicine*. 2011 1/12/11 [cited 2012 22/1/2012]; Available from: http://eng.mapofmedicine.com/evidence/map/index.html.
100. *Attributing revenue costs of externally-funded non-commercial research in the NHS (ARCO)*. 2005, Department of Health: London.