DRAFFT 2 – Distal Radius Acute Fracture Fixation Trial 2

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Ethical approval
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The University of Oxford is the sponsor of this study.

Registration
The study has been registered with the current controlled trials database under reference number ISRCTN11980540

Dates
Study start date: 01/07/2016
Study end date: 31/10/2019

Abbreviations

AE – Adverse Event
CI – Chief Investigator
CRF – Clinical Reporting Form
OCTRU – Oxford Clinical Trials Unit
DMC – Data Monitoring Committee
DRAFFT 2 – Distal Radius Acute Fracture Fixation Trial
EQ-5D – EuroQol
GCP – Good Clinical Practice
HE – Health Economy/Economist
HTA- Health Technology Assessment
MRC – Medical Research Council
PACS - Picture Archiving and Communications System
PI – Principal Investigator
QA – Quality Assurance
QALY – Quality Adjusted Life Year
RCT- Randomised Controlled Trial
REC – Research Ethics Committee
RF – Research Fellow
SAE – Serious Adverse Event
SOP – Standard Operating Procedure
TMG – Trial Management Group
TSC – Trial Steering Committee
VAS – Visual Analogue Scale

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2. Synopsis

Study Title	Distal Radius Acute Fracture Fixation Trial 2	
Internal ref. no. / short title	DRAFFT 2	
Study Design	Multi-centre, multi-surgeon, parallel, two-arm, randomised controlled trial	
Study Participants	Participants of 16 years and older who have sustained an acute dorsally displaced fracture of the distal radius, who would benefit from manipulation.	
Planned Sample Size	476	
Planned Study Period	01/7/16 - 31/10/19	
	Objectives	Outcome Measures
Primary	To quantify and draw inferences on observed differences in wrist function between surgical fixation with K-wires versus plaster casting in the first year after the injury.	Patient Reported Wrist Evaluation
Secondary	1. To quantify and draw inferences on observed differences in Health-related Quality of Life between the trial treatment groups in the first year post-randomisation. 2. To determine the complication rate, including the need for further surgery, of surgical fixation with K-wires versus casting at one year post-randomisation. 3. To investigate, using appropriate statistical and economic analysis methods, the healthcare resource use, and comparative cost effectiveness at one year, of surgical fixation with K-wires versus plaster casting.	EQ-5D-5L Healthcare Resource use Complications

3. Introduction

3.1 Background

Fractures of the distal radius are extremely common injuries. In the developed World, 6% of women will have sustained such a fracture by the age of 80 and 9% by the age of 90 [1]. As the population continues to age, these figures are likely to increase further. The optimal management of fractures of the distal radius in adults remains controversial. There is a bimodal distribution in terms of age. Younger patients frequently sustain complicated, high-energy injuries involving the wrist joint. However, fractures of the distal radius are also common in older patients who are more likely to sustain low-energy fractures related to osteoporosis [2]. This study is designed to address both groups of patients, as the key management decisions pertain to all patients with a fracture of the distal radius.

In general if the bone fragments are undisplaced i.e. the bone fragments remain in anatomical alignment, fractures of the distal radius are treated non-operatively. However, if the bone fragments have displaced i.e. moved out of their normal alignment, then the treating clinician will usually recommend a 'manipulation' of the bone fragments to restore the normal anatomy. Manipulating a fracture is painful, therefore this is carried out using either local, regional or general anaesthetic.

Following the manipulation, the bone fragments can fall back out of normal alignment. Therefore the treating clinician will apply support to the bone fragments while they heal.

This trial will compare two techniques for holding the position of the bone fragments following a manipulation of a dorsally displaced fracture of the distal radius.

The first technique involves the application of a plaster cast which is shaped (moulded) over the skin to hold the bone fragments in position. This technique is simple and quick to perform, there is little risk of complications and the materials used are cheap. However, the plaster cast is not applied directly to the bone fragments and therefore it is possible for the bone fragments to re-displace under the cast, particularly when the swelling starts to settle a few days after the surgery.

The second technique involves the surgical fixation of the bone fragments using Kirschner wires (K-wires). During this procedure smooth metal wires with a sharp point are passed through the skin across the fracture site to hold the bone fragments in position while they heal. A plaster cast is applied over the top of the wires to hold the wrist joint still, but the cast does not have to be moulded into position as the wires themselves hold the bone in place. K-wire fixation therefore reduces the risk of re-displacement of the fracture. However, there are small risks from the surgery including infection and damage to the nerves or blood vessels around the wrist; K-wire fixation also takes longer than applying a plaster cast and the wires and theatre consumables cost more.

Handoll and Madhok, [3] summarised the results of a series of Cochrane Reviews of randomised controlled trials of the treatment of fractures of the distal radius and "exposed the serious deficiency in the available evidence". However, they were able to identify key areas for future research including "when and what type of surgery is indicated". In 2014, we published the results of the Distal Radius Acute Fracture Fixation Trial (DRAFFT; NIHR-HTA HTA 08/116/97). [4] In this study, we randomly assigned 461 adult patients having surgery for a dorsally displaced fracture of the distal radius to either K-wire fixation or locking-plate fixation. At the time of this study, the established literature indicated that locking plate fixation was superior to K-wire fixation, but was more expensive.

Over 90% of the patients who took part completed the study. Both groups of patients' wrist function improved in the 12 months following the fracture, but there was no difference in their wrist function at 3 months, 6 months or 12 months. Nor was there a difference in the number of complications in each group. Contrary to the existing literature, and against the increasing use of plate fixation, the DRAFFT study showed that, if a closed reduction of the fracture was possible, there is no difference between K-wires and locking-plates for patients with fractures of the distal radius. K-wire fixation is less expensive and quicker to perform.

However, there remain unanswered questions; specifically, is there any need to perform surgical fixation of the fracture following a closed reduction of the distal radius, or is a simple plaster cast as effective as the insertion of metalwork?

Therefore, we propose:

A Randomised Controlled Trial of Manipulation and surgical fixation with K-wires versus Manipulation and Casting in the Treatment of Adult Patients with a Dorsally Displaced Fracture of the Distal Radius

3.2 Good Clinical Practice

The trial will be conducted in accordance with the Medical Research Council's Good Clinical Practice (MRC GCP) principles and guidelines, the Declaration of Helsinki, Oxford Clinical Trials Research Unit SOPs, relevant UK legislation and this Protocol. GCP-trained personnel will conduct the trial.

3.3 Consort

The trial will be reported in line with the CONSORT statement.

4. Trial design

4.1 Trial summary

The proposed project is a two-phased study. Phase 1 (Internal Pilot) will confirm the expected rate of recruitment in a large-scale multi-centre randomised controlled trial. Phase 2 (Main phase) will be the proposed randomised controlled trial in a minimum of 24 trauma centres.

Internal Pilot

The pilot will take place at 5 centres over a period of 6 months. The aim of this initial phase will be to determine the number of eligible and recruited patients in the trauma centres over the course of 6 months. Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent/withdraw, will be recorded.

The trial will be stopped if the target recruitment during the internal pilot is not achieved. The Data Monitoring Committee (DMC) and Trial Steering Committee (TSC), as well as the Funder will closely monitor recruitment during the feasibility phase. If the trial is stopped, then all trial patients will be followed up per protocol. If the trial continues into the main phase, patients from the internal pilot will be included in the final analysis.

Main RCT

The main trial will be recruiting from a minimum of 24 trauma centres across the UK.

All adult patients presenting at the trial centres with an acute fracture of the distal radius are potentially eligible to take part in the trial. The broad eligibility criteria will ensure that the results of the study can readily be generalised to the wider patient population.

Prior to surgery, the research associate will collect baseline demographic data, radiographs and functional data using the Patient Rated Wrist Evaluation Score (PRWE) and health-related quality of life using the EuroQoL EQ-5D-5L. The patients will be asked to complete questionnaire to indicate both their contemporary (injured) and typical (pre-injury) status.

A randomisation sequence, stratified by centre, intra-articular extension of the fracture and age of the patient (above or below 50 years), will be produced and administered independently. Each patient will be randomly allocated to either ‘manipulation and surgical fixation with K-wires’ or ‘manipulation and plaster casting’. Both of these interventions are widely used within the NHS and all of the surgeons will be familiar with both techniques. Post-operatively each patient will be issued with standardised written rehabilitation instructions.

The research associate will perform a clinical assessment and make a record of any early complications at 6 weeks. Further routine radiographs will also be taken at 6 weeks. The functional outcome data will be collected using the PRWE and EQ-5D-5L questionnaires at 3 months, 6 months and 12 months post-randomisation. These postal questionnaires will be administered centrally by a research assistant blind to the treatment allocation. The patients will also be asked to fill out a healthcare resource use questionnaire and provide details of any late complications or interventions related to their injury.

4.2 Objectives

The primary objective is:

To quantify and draw inferences on observed differences in the Patient Rated Wrist Evaluation (a validated assessment of wrist function) between surgical fixation with K-wires versus plaster casting in the first year after the injury.

The secondary objectives are:

1. To quantify and draw inferences on observed differences in the EQ-5D-5L (a validated assessment of Health-related Quality of Life) between the trial treatment groups in the year post-randomisation.

2. To determine the complication rate, including the need for further surgery, of surgical fixation with K-wires versus casting at one year post-randomisation.

3. To investigate, using appropriate statistical and economic analysis methods, the healthcare resource use, and comparative cost effectiveness at one year, of surgical fixation with K-wires versus plaster casting.

4. To summarise descriptively the baseline characteristics and outcome for the subset of participants where adequate reduction cannot be achieved by closed manipulation of the fracture.

4.3 Outcome measures

The primary outcome measure for this study is the ***Patient Rated Wrist Evaluation*** [5]**.** The PRWE score is a validated questionnaire which is self-reported (filled out by the patient). It consists of 15 items specifically related to the function of the wrist. This data will be collected at baseline, 3, 6 and 12 months post-randomisation (see table 1). The PRWE is the most sensitive outcome measure available for patients sustaining this specific injury [6].

The secondary outcome measures in this trial are:

EQ-5D; The EQ-5D-5L is a validated, generalised, health related quality of life questionnaire consisting of 5 domains related to daily activities with a 5-level answer possibility [7 8], which will be converted into multi-attribute utility scores using established algorithm[9].

Complications; All complications will be recorded.

Radiographic evaluation; Standard posterior-anterior and lateral radiographs will be taken at baseline (pre-reduction, and post-reduction using the routine intra-operative fluoroscopic images from the operating theatre), and at the routine follow-up appointment 6-weeks after the injury. These radiographs are those used for the investigation of patients with a suspected fracture of the distal radius and for the follow-up of such patients following any intervention, so there will be no need to request any additional or special investigations. An assessment of the quality of the reduction, and the risk of subsequent loss of reduction, will be made using the criteria as described in Costa et al [10].

Healthcare resource use; *Healthcare resource use* will be monitored for the economic analysis. Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care [11]. Where these are not available the unit cost will be estimated in consultation with the Oxford University Hospitals finance department. The cost consequences following discharge, including NHS costs and patients' out-of-pocket expenses will be recorded via a short questionnaire which will be administered at 3, 6 and 12 months post-randomisation. Patient self-reported

information on service use has been shown to be accurate in terms of the intensity of use of different services [12].

TIME POINT	DATA COLLECTION
Baseline	PRWE and EQ-5D *pre-injury and contemporary*, routine radiographs of the wrist
6 weeks	Complication records, routine radiographs of the wrist, operative record
3 months	PRWE, EQ-5D, record of complications/rehabilitation or other interventions and healthcare resource use questionnaire
6 months	PRWE, EQ-5D, record of complications/rehabilitation or other interventions and healthcare resource use questionnaire
12 months	PRWE, EQ-5D, record of complications/rehabilitation or other interventions and healthcare resource use questionnaire

Table 1 Data collection time points

4.4 Sample size

The Patient Rated Wrist Evaluation (PRWE) score [5] is 15-item questionnaire, designed specifically for assessment of distal radial fractures and wrist injuries, that rates wrist function using a range of questions in two (equally weighted) sections concerning the patient's experience of pain and disability. Scoring for all the questions is via an 11-point, ordered, categorical scale ranging from 'no pain' or 'no difficulty' (0) to 'worst possible pain' or 'unable to do' (10). Five questions relate to a patient's experience of pain and ten relate to function and disability; scores for the ten function items are summed and divided by two and added to the five pain items to give a score out of 100 (best score = 0 and worst score = 100).

The DRAFFT trial [4], which included the same patient population, demonstrated that the standard deviation of the PRWE at 12 months was 16. However, other studies of patients with a fracture of the distal radius showed a standard deviation for the PRWE which was in the range 16-23 points [13]. Therefore we have chosen a conservative estimate of the standard deviation of 18 points.

The DRAFFT results also showed an approximate Normal distribution for the PRWE scores at 12 months.[4]. A 6-point mean difference between groups equates to a standardized effect size of 0.33, for an assumed standard deviation of 18 points. MacDermid et al [6], found that the PRWE is sensitive enough to detect subtle but clinically relevant changes in wrist function of this order of magnitude in patients sustaining a fracture of the distal radius. A mean difference in the PRWE of 6 points is just above the amount achieved if all the participants in one group responded they had one degree better response to any of the PRWE's constituent question (e.g. one degree less difficulty in turning a doorknob) than the other group (each degree in response contributes 5 points to the overall score). We believe the target difference (6 points) would be important to patients on both an individual and a population level, and could lead to a change in clinical practice in the UK.

The total number of patients required to obtain a power of 90% to detect a 6-point difference between groups for the primary outcome measure is 382; i.e. 191 patients will be required in each treatment group. Making a conservative allowance of just under 20% for loss to follow-up, we plan to recruit a minimum of 476 patients.

4.5 Methodology

4.5.1 Eligibility

Patients will be eligible for inclusion into the trial if:

- They have sustained a dorsally displaced fracture of the distal radius, which is defined as a fracture within 3 cm of the radio-carpal joint.
- They are over the age of 16 and able to give informed consent.
- The treating Consultant Surgeon believes that they would benefit from manipulation of the fracture.

Patients will be excluded from this trial if they have:

- The injury is more than two weeks old
- The fracture extends more than 3 cm from radio carpal joint
- The fracture is open with a Gustilo grading greater than 1 [14]
- The articular surface of the fracture (specifically the radio-carpal joint) cannot be reduced by indirect techniques. In a small number of fractures, the joint surface is so badly disrupted that the surgeon will have to open up the fracture in order to restore the anatomy
- There is evidence that the patient would be unable to adhere to trial procedures or complete questionnaires, such as cognitive impairment.

Patients who sustain injuries to areas of the body other than the lower limbs, which may affect the primary outcome measure, will still be included in the analysis. Information with regards additional injuries will be recorded at baseline, and analysis adjusted if necessary.

4.5.2 Recruitment and consenting

The DRAFFT trial [4], which included the same patient population, ran across 18 centres with an average of 2 patients recruited per centre per month. We will use the same experienced research teams and the core recruiting centres for DRAFFT 2. We anticipate achieving a conservative rate of 1.6 patients per month per centre.

During the 6 months internal pilot phase, we therefore expect that between 40-45 patients will be recruited from the 5 centres. If recruitment falls below this rate, the DMC will provide the TSC with a recommendation with regards the continuation of the study. Following the pilot phase, a minimum of 19 further sites will be enrolled over the next 6-8 months, with recruitment being completed in a 14 month period.

Informed consent will be obtained by the local research associate. A member of the clinical team will approach the patient initially about the study. If the patient is interested they will then be introduced to the research associate assigned to the study. The research associate will present the eligible patient with the Participant Information Sheet and a verbal explanation of the trial procedures. The patients will then be given the opportunity to discuss any issues related to the trial with the research associate, as well as members of their family and friends.

In general, patients who are admitted with a fracture of the distal radius will have their treatment on the following day/s, so there will be sufficient time for the patients to consider taking part in the trial.

Patients will be randomised in the operating theatre, after the surgeon has achieved an adequate closed reduction of the distal radius fracture. In cases where an adequate closed reduction of the fracture cannot be achieved, the surgeon will treat the patient according to their normal clinical practice, for example with internal fixation with a plate and screws, but the patient will not be randomised into the trial. Patients who have consented but are subsequently confirmed to be ineligible and therefore not randomised to either of the trial treatments will be followed-up as outlined in this protocol. The results of these patients will not be incorporated into the main trial analysis but summarised separately.

Any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the Trial Steering Committee; if necessary this will be communicated to all participants by the Trial Coordinator. A revised consent form will be completed if necessary.

4.5.3 Trial ID

When a patient is randomised, sufficient non-identifiable details will be logged prior to surgery, by the clinical team using a secure, encrypted, web-based system, provided by the Oxford Clinical Trials Research Unit (OCTRU). Basic information including the patient initials, age and eligibility checks will be entered. The patient will then receive a trial ID that will be used on all non-public facing trial documentation.

4.5.4 Randomisation

Those patients who consent to take part in the trial will have their treatment allocated using a secure, centralised, online randomisation service. The randomisation will occur after the manipulation of the fracture when the surgeon has determined that the fracture can be adequately reduced without the need to open the fracture to achieve reduction. All hospital treatment areas have access to online resources and so will be able to access the randomisation service in real time ensuring no delay in the treatment of the participant.

Although the great majority of these injuries are managed on planned trauma-operating lists during normal working hours, the randomisation service will be open twenty-four hours each day to facilitate the inclusion of all potentially eligible patients. Randomisation will be on a 1:1 basis, stratified by centre, intra-articular extension of the fracture and age of the patient (above or below 50 years):

Stratification by centre will help to ensure that any clustering effect related to the centre itself will be equally distributed in the trial arms. The catchment area (the local population served by the hospital) will be similar for all of the hospitals; each hospital being an orthopaedic trauma unit dealing with these fractures on a daily basis. While it is possible that the surgeons at one centre may be more expert in one or other treatment than those at another centre, all of the recruiting hospitals, and indeed all hospitals throughout the NHS, use both techniques as part of their normal practice and generally staff and surgeons will already be familiar with both forms of treatment. While this does not eliminate the *surgeon-specific (such as a learning) effect* of an individual at any one centre [15], since the manipulation of a fracture of the distal radius is a common procedure, many surgeons will be involved in the management of this group of patients; between 10 and 30 surgeons at each centre, including both Consultants and Trainees. Therefore, we anticipate that each individual surgeon will only operate on 2-3 patients enrolled in the trial, greatly reducing the risk of this surgeon-specific effect upon the outcome in any one centre. The median number of procedures per surgeon in the DRAFFT trial was 1; over 200 surgeons took part in the trial. We will collect 'operating

time' and 'complications' data, which we have previously used as surrogates for surgeon expertise/learning curves when modelling surgeon factors, [15] but experience from DRAFFT [4] indicates this is not a substantive concern for a study of this nature.

Stratification on the basis of intra-articular extension of the fracture will eliminate a major potential confounder, since disruption of this articular surface may pre-dispose to secondary osteoarthritis of the wrist [16] Recent evidence [17], suggests that other associated features of fractures of the distal radius which commonly appear in the classification systems, such as involvement of the ulna styloid process, do not actually affect the functional outcome of the injury. Therefore, we would not propose to include any other variables in the stratification of the randomisation sequence.

Stratification on the basis of age will be used in an attempt to discriminate between younger patients with normal bone quality sustaining high-energy fractures, and older patients with low-energy (fragility) fractures related to osteoporosis. Empirically, both of these groups of patients could benefit, or not, from the surgical fixation. However, the stratification may also help to identify any effect related to the quality of the patients' bone. The use of DEXA (dual energy x-ray absorptiometry) is widely regarded as the gold-standard for the assessment of bone density. However, such an investigation may be expensive and not routinely available at all centres. Therefore we propose to use age as a surrogate for bone density. In a large study in Norway involving 7600 participants, it was demonstrated that forearm bone mineral density remains stable up until the age of 50 years. After the age of 50, bone mineral density decreased steadily in males, whilst in females there was an initial decline between the ages of 50 and 65, with a further decline in the age groups thereafter [18]. A recent study by Court-Brown and Caeser [19], assessed over 1000 patient with a fracture of the distal radius. This study confirmed that there is a clear bimodal distribution for this type of fracture according to the age of the patient. The crossover of the two peaks of incidence was around 50 years of age. These studies provide strong evidence that patients over the age of 50 become increasingly vulnerable to fragility fractures of the distal radius. Therefore, we have chosen an age +/- 50 as the stratification criteria for this trial. Furthermore, the study by Court-Brown et al, [19] demonstrated that in the UK approximately 60% of patients sustaining a fracture of the distal radius are over 50 years, while 40% are younger than 50 years. The number of patients above and below this stratification age will therefore be similar, (see analysis section).

4.5.5 Pre and Post randomisation withdrawals/exclusions

Participants may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives. Once withdrawn, the patient will be advised to discuss their further care plan with their surgeon. Upon withdrawal of the patient, any data collected up until the time of withdrawal will be retained by the research team and included in the final analysis. Contact details for these patients will be destroyed.
A small proportion of patients consented to take part in the study, will be confirmed as ineligible due to inadequate reduction being achieved during manipulation. This group of patients will be followed up per protocol.

4.5.6 Blinding

The patients cannot be blind to their treatment as the wires have to be removed; usually in the outpatient clinic at the 6 weeks follow-up appointment. The treating surgeons will, of course, not be blind to the surgical/non-surgical treatment they are providing. However, the treating clinical team

will take no part in the post-operative assessment of the patients. The outcome data will be collected directly from the patient themselves.

4.6 Technologies assessed

All of the hospitals involved in this trial currently use both treatments and all of the surgeons involved will be familiar with both techniques.

All of the participants will undergo a closed (without making any incisions in the skin) manipulation of the fracture. The manipulation will be carried out using either local, regional or general anaesthetic. The choice of anaesthetic will be left to the discretion of the treating surgeon/anaesthetist as per their normal practice.

As per routine clinical practice, an image intensifier x-ray machine will allow the surgeon to judge that an adequate closed reduction has been achieved during the manipulation. The decision to accept the reduction will be left to the discretion of the treating surgeon, as per their normal practice. Only after this decision is made will the patient be randomised to one treatment of the other.

This trial will compare two techniques for holding the position of the bone fragments following a manipulation of a dorsally displaced fracture of the distal radius.

4.6.1 Plaster cast

This technique involves the application of a plaster cast which is shaped (moulded) over the skin to hold the bone fragments in position. This technique is simple and quick to perform, there is little risk of complications and the materials used are cheap. However, the plaster cast is not applied directly to the bone fragments and therefore it is possible for the bone fragments to re-displace under the cast, particularly when the swelling starts to settle a few days after the surgery. The principles of applying a moulded plaster cast are inherent in the technique, although in this pragmatic trial the type of casting material, extent of the cast and the details of the moulding technique will be left to the discretion of the treating surgeon as per their usual technique. Relevant information with regards the initial technique used and any subsequent interventions, such as cast replacement or removal, will be recorded.

4.6.2 Surgical fixation with wires

After the skin has been covered in antiseptic, the sharp wires are passed through the skin over the back of the wrist and directly into the bone in order to hold the bone fragments in the correct position. The principles of K-wire fixation are also inherent in the technique, although there are several different options for the positioning of wires. The size and number of wires, the insertion technique and the configuration of wires will be left entirely to the discretion of the surgeon as per their normal practice. A plaster cast will be applied at the end of the procedure, as per standard surgical practice, but this does not need to be specifically moulded as the wires themselves hold the bone in position. Relevant information with regards the initial technique used and any subsequent interventions, such as metal work removal, cast replacement or removal will be recorded.

4.6.3 Rehabilitation

We will ensure that all patients randomised into the two groups will receive the same standardised, written physiotherapy advice detailing the exercises they need to perform for rehabilitation following their injury. The written information was developed and tested by experienced physio/hand

therapists as part of the original DRAFFT trial. All of the patients in both groups will be advised to move their shoulder, elbow and finger joints fully within the limits of their comfort. In this pragmatic trial, any other rehabilitation input beyond the written information sheet (including a formal referral to physiotherapy) will be recorded. Patients will be asked to indicate if they had any other investigations/interventions as part of the 3 month, 6 month and 12 month follow-up datasets.

4.7 Adverse event management

4.7.1 AE and SAE 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*. Both trial interventions are used in everyday practice and their safety profile are well known. Relatedness of any AE will be considered by a medically qualified investigator at the first appropriate opportunity. Any related AE will be followed either until resolution, or the event is considered stable.

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. *Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed*.

All serious adverse events (SAE), other than those indicated as foreseeable in the protocol, will be entered onto the Serious Adverse Event reporting form and sent to the Kadoorie Trauma Unit at John Radcliffe Hospital in Oxford as soon as possible after the investigator becoming aware of them. Once received, causality and expectedness will be confirmed 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. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

Some serious adverse events are foreseeable as part of the treatment of distal radius fractures, and do not need to be reported immediately, provided they are recorded in the 'Complications' section of the Case Report Forms and/or Patient Questionnaires. These events are: complications of anaesthesia or surgery e.g. wound infection, damage to nerves, tendons or blood vessels, complex pain syndromes and thromboembolic events, and also further planned surgery for removal of symptomatic metalwork or for loss of fracture position/malunion.

All participants experiencing SAEs will be followed-up as per protocol until the event has resolved or is considered to be stable.

4.7.2 Risks and benefits

The risks associated with this study are predominantly the risks associated with the anaesthetic and manipulation of the fracture. Participants in both groups will undergo manipulation under anaesthetic and will potentially be at risk from any/all of these complications but there are no data to suggest that the risk is greater in one group or another. In the K-wire fixation group there is the additional risk of wound infection and damage to the adjacent nerves, tendons or blood vessels. In

the DRAFFT trial this risk was very low, but assessment of the number of complications in each group is a secondary objective of this trial.

4.8 End of trial

The end of the trial will be defined as the collection/receipt of the last follow-up questionnaire from the last participant.

5. Data Management

The Case Report Forms will be designed by the trial coordinator in conjunction with the trial management team. Patients will be asked to provide their contact details as well as the contact details of up to two alternative friends or family members. Collection of this additional data has proven to improve data collection substantially in other research trials. All electronic patient-identifiable information will be held on a secure, password-protected database at the University of Oxford, accessible only to the research team. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. The patient-identifiable data will be kept separately from the outcome data obtained from/about the patients. Patients will be identified by a trial ID only. Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required. All paper and electronic data will be retained for at least five years after completion of the trial.

5.1 Statistical Analysis

Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the distribution of the outcome) and graphical plots showing correlations will be presented for the primary outcome measure and all secondary outcome measures. Baseline data will be summarised to check comparability between treatment arms.

The primary outcome measure, the Patient rated Wrist Evaluation (PRWE) score at one year after injury, between the two treatment groups on an intention-to-treat basis, that according to the randomised groups irrespective of compliance with treatment allocation. A model which allows for clustering by centre will be used. In addition, early functional status will also be assessed and reported at 3 months and 6 months. Differences between treatment groups will be assessed, based on a Normal approximation for the PRWE score at 12 months post-randomisation.

The stratified randomization procedure should ensure a balance in age, intra-articular extension and the recruiting centre between test treatments. Although generally we have no reason to expect that the clustering effects will be important for this study, the data will be hierarchical in nature, with patients naturally clustered into groups by recruiting centre and surgeon though this may not lead to tangible clustering of the primary outcome [20]. Practice in DRAFFT, that has informed the design of this trial, was such that very few surgeons operated upon more than one study participant, so surgeon (random) effects were not included in the principal analysis of PWRE which will be adjusted for centre only. Although we have no reason to believe this will be different in DRAFFT 2, we will adopt an analysis plan that recognizes the potential importance of the expertise/experience of the treating surgeon on the study outcomes. Therefore a secondary analysis will use a three level model with participant within surgeon within centre. This model will formally incorporate terms that allow for possible heterogeneity in responses for patients due to the recruiting centre and the surgeon, in addition to the fixed effects of the treatment groups, patient age and intra-articular extension. As discussed earlier we anticipate that each individual surgeon will only operate on a small number of

patients enrolled in the trial, greatly reducing the likelihood of observing a surgeon-specific effect upon the outcome at any one centre.

It seems likely that some data may not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for data 'missingness' will be ascertained and reported. Although missing data is not expected to be a problem for this study, the nature and pattern of the missingness will be carefully considered — including in particular whether data can be treated as missing at random (MAR). If judged appropriate, missing data will be imputed using an appropriate approach as a sensitivity analysis. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarized.

Subgroup analyses of the two clinical stratifying variables (age and intra-articular extension) are planned. This will be undertaken for each of the stratifying variables using an extended model to formally test the interaction between each stratifying variable and the treatment factor; appropriate 95% confidence intervals will be reported for the interaction effects in addition to p-values. These analyses will be labelled as exploratory and results from this analysis will be interpreted with due caution, and reported as such; in line with recommendations for subgroup analysis made elsewhere [21]. The temporal patterns of any complications will be presented graphically and if appropriate a time-to-event analysis (Kaplan-Meier survival analysis) will be used to assess the overall risk and risk within individual classes of complications (e.g. infection).

Secondary outcome will be analysed using generalized linear model adjusting for stratification factors. All tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). Estimates of treatment effects will be presented with 95% confidence intervals. A detailed statistical analysis plan (SAP) will be agreed with the DMC at the start of the study. Any subsequent amendments to this initial SAP will be clearly stated and justified. Interim analyses will be performed only where directed by the DMC. The statistical analysis will mainly be carried out using STATA (www.stata.com).
Data from patients who were consented but subsequently not eligible to participate in the trial will be considered separately from the main trial analysis and will summarise descriptively with no formal statistical analysis.

5.2 Economic evaluation

The economic evaluation will estimate the cost effectiveness of plaster cast versus surgical K-wire in adults with a Dorsally Displaced Fracture of the Distal Radius. Primary sources (eg theatre log books) will be used to record the duration of each procedure, theatre staffing, consumables, imaging, supplementary devices, post-operative recovery time and rehabilitation inputs. Community and Social care service use will be collected at 3, 6 and 12 months post-randomization by using postal patient self-reported questionnaires. The data collected in the participant questionnaires at each time point will also record indirect costs borne by participants and carers as a result of attending hospital visits, as well as direct non-medical costs (including travel expenses), attributable to their health state. Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care [22]. As it may be not feasible to collect cost data for every item used in the operation from all 24 trauma centres across the UK participating in the trial, we plan to obtain unit costs from a sample of trauma centres for each item used for these operations and carry out a sensitivity analysis.

Health related quality of life will be estimated using the EuroQol (EQ-5D-5L) [7]. Trial participants will be asked to complete EuroQol (EQ-5D) at baseline (pre-injury and contemporary), 3, 6 and 12 months post-randomisation. Responses to the EQ-5D will be converted into multi-attribute utility scores using established algorithm [7].

A within trial evaluation will be conducted from a UK NHS and Personal Social Services perspective (PSS) (NICE, 2008) using the DRAFFT2 trial data. The outputs of the cost-effectiveness analysis will be presented in terms of expected Incremental Cost Effectiveness Ratios (ICERs), Cost Effectiveness Acceptability Curves (CEACs) generated via non-parametric boostrapping as well as Expected Net Benefit. If statistically significant differences are detected in HRQoL outcomes between the two arms of the study at 12 months, a scenario analysis will be conducted to explore the effect on cost-effectiveness of these differences persisting for 2-5 years. Further, sensitivity analyses will be conducted to consider the broader issue of the generalisability of the study results. An example would be to adopt a broader societal perspective in the economic evaluation which will include out-off pocket expenses borne by participants, informal care provided by family and friends and income loss. Regression analysis will be used to estimate the between-group differences in mean costs and Quality Adjusted Life Years (QALYs), adjusting for centre, sex, age and other baseline differences between the two trial arms. Interaction terms will be used to investigate possible treatment moderators which can be used to identify patient subgroups for whom cost-effectiveness are predictably different: e.g. age, sex, intra-articular extension of the fracture, or other relevant participant characteristics. This will also allow us to check the effect of covariates in combination, e.g. how treatment effect changes with age.

6. Trial Oversight

The day-to-day management of the trial will be the responsibility of the Trial Manager, supported by the OCTRU administrative staff. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the responsibility of the Trial Manager to undertake training of the research staff at each of the trial centres. The trial statistician and health economist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms. A TSC and a DMC will be set up.

6.1 Trial Supervision

Day-to-day management of the trial will be overseen by a Trial Management Group which is made up of the Investigators listed in Section 1 and staff working on the project within OCTRU. A TSC -with an independent Chairperson - and DMC will be set up.

The TSC, which includes independent members provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with the HTA and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least once a year during the recruitment period.

An outline of the remit of the TSC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DMC
- inform the funding body on the progress of the trial.

The DMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial.
The study DMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, review accruing data, summaries of the data presented by treatment group, and will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the Trial Steering Committee at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DMC meetings will be held at least annually during the recruitment phase of the study. Full details including names will be included in the DMC charter.

6.2 Quality control

We will institute a rigorous programme of quality control. The research manager in conjunction with the trial coordinator will be responsible for ensuring adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by the CTU to ensure integrity of randomisation, study entry procedures and data collection. The CTU has a quality assurance manager who will monitor this trial by conducting regular (at least once in the lifetime of the study, more if deemed necessary) inspections of the Trial Master File. Furthermore the processes of consent taking, randomisation, registration, provision of information and provision of treatment will be monitored. Written reports will be produced for the TSC, informing them if any corrective action is required.

6.3 Project Timetable and Milestones

We propose a 40 month study starting in July 2016. The planned trial timetable is shown below, with key milestones indicated and the responsible parties identified:

Month	By date	Activity	Milestone	Responsibility
-4-0		Ethic submission	REC approval	CI/RF
0-3	July 2016	Start Trial		
			1st TSC/DMC meeting	CI/TC
		Finalise trial protocol	Protocol final version	TMG
	Sep 2016	Complete CRF's	CRF final version	CI/Stat/TC/HE
4-10	Oct 2016	Start recruitment at pilot centres 1&2	1st trial site online	TC/CI
	Nov 2016	Start recruitment at pilot centres 3,4 &5	5 pilot sites online	TC/CI
	Feb 2017	Finish pilot recruitment	27 centre months recruitment	TC/CI
	April 2017		2nd DMC/TSC meeting	CI/TC
11-23	April 2017	Staggered launch 2-3 centres/month		TC/CI
	Oct 2017	50% total recruitment	238 pts enrolled	
	Nov 2017	Complete site initiations	All 24 sites recruiting	TC/CI
	Dec 2017	Data review first 250 pts	DMEC report	DMEC via TSC to HTA
	Jan 2018		3rd TSC meeting	CI/TC
	May 2018	End recruitment	476 pts enrolled	
24-35	May 2019	Complete follow-up all sites	476 pts completed follow-up	
36-40	July 2019	Statistical analysis		Stat
		Health economics analysis		HE
	Aug 2019	Data review all patients	DMEC report	DMEC via TSC to HTA
			Final TSC meeting	TSC
	Oct 2019	Final report HTA	HTA report	TMG

CI Chief Investigator, RF Research Fellow, TMG Trial management group, TC Trial coordinator, TSC trial steering committee, DMEC Data monitoring and Ethics Committee, Stat statistician, HE Health Economist

6.4 Funding

This study is funded by the National Institute for Health Research Health Technology Assessment (15/27/01).

6.5 Insurance and Indemnity Arrangements

The Sponsor has a specialist insurance policy in place - Newline Underwriting Management Ltd, at Lloyd's of London - which would operate in the event of any participant suffering harm as a result of their involvement in the research. Standard NHS cover for negligent harm is in place for NHS procedures. There will be no cover for non-negligent harm.

6.6 Dissemination

The study monograph will be prepared by the trial management team at the completion of the trial. No patient identifiable information will be contained in any form of dissemination of study results.

7. Protocol Amendments:

Amendment No.	Date of Amendment	Date of Approval
None to date		

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