Study Title: DRAFT3-CASP: Distal Radius Acute Fracture Trial 3 – Cast versus Splint; a randomised non-inferiority trial comparing clinical and cost-effectiveness of a standard care cast versus removable splint for adults with a distal radius fracture that does not require manipulation.

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The investigators declare no potential conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

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2. LAY SUMMARY

What is the problem?

There are over 100,000 fractures of the wrist (distal radius) in the UK each year; 6% of all women will have sustained such a fracture by the age of 80 and 9% by the age of 90. Following a fracture of the distal radius, if the bone fragments have remained in their normal alignment, the fracture can be treated with a support for the injured wrist, which will provide pain relief and protects from further damage as the fracture heals. Over three quarters of all distal radius fractures in adults fall into this category and outcomes are generally good.

For those patients whose fracture remains aligned, usual care is to provide the patient with a temporary 'backslab' plaster cast in the emergency department. The patient is then referred to the orthopaedic fracture clinic where the backslab is converted to a full fibre-glass cast. The patient has to return to the fracture clinic 4-6 weeks later to have their cast removed.

Recently, there has been some evidence that a removable wrist splint may provide the patient with the same support as a cast while their fracture heals. A splint can be removed by the patient themselves thereby avoiding additional visits to the hospital. This could be more convenient for patients and save money for the NHS.

What are we trying to find out?

This study will compare wrist function and pain in patients with a fracture of the distal radius treated with usual care in a cast with standard follow-up versus a removable wrist splint with discharge from the emergency department.

What will we do?

1894 adult patients with a fracture of their distal radius will be invited to take part from hospitals across the UK. Half of those that agree to take part will be treated in a cast and half in a removable splint. All of the patients will be given the same information and advice about their injury and their recovery. Which treatment a person gets will be decided by a computer to ensure a fair comparison. Everyone has an equal chance of getting either treatment. During the first two weeks, we will monitor the patients' pain and after three, six and twelve months everyone will receive a questionnaire. The questionnaires will ask about what activities they are able to do, their quality of life, any problems they might have and any costs that have been incurred because of the injury.

Who are we?

Our research team includes people who have performed large studies before, including studies about wrist injuries. Each team member brings a different skill. These include physiotherapy, emergency medicine, orthopaedic surgery, statistics, health economics and patient and public involvement.

How have patients helped develop this research?

The research question and study design has been developed by clinicians, methodologists, patients and members of the public. Following this process, two patient and public

representatives who have had wrist problems agreed to be part of the study team. This has been alongside consultation with an established patient group for existing studies in trauma care.

How will we tell people what we found out?

We will tell patients and the public the results of the study through presentations and videos. We will present the results at the annual NIHR trauma patient and public conference. We will work with health care professionals and planners to ensure the results help to shape future guidelines. We will publish the results in relevant academic journals and present at national meetings.

3. SYNOPSIS

Study Title	Distal Radius Acute Fracture Trial 3 – Cast versus Splint; a randomised non-inferiority trial comparing clinical and cost-effectiveness of a standard care cast versus removable splint for adults with a distal radius fracture that does not require manipulation		
Short title	DRAFT3-CASP		
Study registration	ISRCTN <TBC>		
Sponsor	University of Oxford Research Governance, Ethics and Assurance (RGEA) Team, Research services, University of Oxford, Joint Research Office Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7LE Email: ctrg@admin.ox.ac.uk Tel: 01865 616480		
Funder	NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton Alpha House, Enterprise Road Southampton, SO16 7NS		
Study Design	Multi-centre, Randomised, Non-inferiority trial		
Study Participants	Patients aged 16 years and older with an acute fracture of the distal radius who, in the opinion of the treating clinician, do not require a manipulation of the fracture. Patients presenting to the research team more than two weeks after they sustain their injury; those who have an open fracture; or patients who would be unable to follow trial procedures will be excluded.		
Sample Size	A minimum of 1894 participants.		
Planned Study Period	Study period from commencement of funding: 01 May 2022 - 30 April 2026. Patients will be involved for up to 12 months post-randomisation.		
Planned Recruitment period	December 2022 – November 2024 (this includes 6 months internal pilot recruitment and 20 months main trial recruitment).		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To quantify and draw inferences on observed differences in function between treatment groups	Patient Reported Wrist Evaluation (PRWE)	3 months post-randomisation
Secondary	i) observed differences in pain related to the wrist between treatment groups	Visual Analogue Scale (VAS) pain score	Baseline (post-injury), 1, 3, 5, 7, 10 and 14 days post-randomisation

To quantify and draw inferences on:	ii) observed differences in medium-term pain and function between treatment groups	PRWE PROMIS Upper Limb Physical Function Score	Baseline (retrospective pre-injury and post-injury), 7 weeks, 6 and 12 months post-randomisation Baseline (post-injury), 3, 6 and 12 months post-randomisation
	iii) observed differences in health-related quality of life between treatment groups	EQ-5D-5L	Baseline (retrospective pre-injury and post-injury), 7 days, and 3, 6 and 12 months post-randomisation
	iv) observed difference in the complication rate between treatment groups	Medical records and bespoke participant questionnaire	Up to 12 months post-randomisation
	v) healthcare and broader resource implications between treatment groups	Medical records and bespoke participant questionnaire	Up to 12 months post-randomisation
	vi) the comparative cost-effectiveness of the trial treatments	Incremental costs-effectiveness ratio expressed as incremental cost per quality-adjusted life year (QALY) gained	Up to 12 months post-randomisation. Longer term time horizon if extrapolation of cost-effectiveness is required.
	vii) To investigate the impact of injury, treatment and recovery on participants, and the outcomes that are important to them.	Interviews with participants (and relative/friend/informal carer as required).	Up to six months post randomisation.
	viii) To investigate the barriers and facilitators to trial recruitment and intervention delivery from participants and clinical/study staff perspectives.	Interviews with participants (and relative/friend/informal carer as required). Interviews and focus groups with recruitment centre staff.	Up to six months post randomisation for individual participants; Up to the end of the recruitment phase for staff.

Intervention(s)	*Removable splint with discharge from ED*
Comparator	*Cast with follow-up as per usual care at the treating centre*

4. ABBREVIATIONS

AUC	Area Under Curve
CAT	Computer Adaptive Test
CI	Chief Investigator
CRF	Case Report Form
DMP	Data Management Plan
DOB	Date Of Birth
DRAFFT	Distal Radius Acute Fracture Fixation Trial
DRAFT	Distal Radius Acute Fracture Trial
DSMC	Data and Safety Monitoring Committee
ED	Emergency Department
GCP	Good Clinical Practice
HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
ISCRTN	International Standard Randomised Control Trial Number
NHS	National Health Service
OCTRU	Oxford Clinical Trials Research Unit
PF	Physical Function
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PROMIS	Patient-Reported Outcomes Measurement Information System
PRWE	Patient Rated Wrist Evaluation
QALY	Quality Adjusted Life Year
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance
SAP	Statistical Analysis Plan

SFQ	Site Feasibility Questionnaire
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

5. BACKGROUND AND RATIONALE

5.1. What is the problem being addressed?

There are over 100,000 fractures of the wrist (distal radius) in the UK each year; 6% of all 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, an increasing burden for health and social care is expected.

Following a fracture of the distal radius, if the bone fragments are undisplaced, i.e. they remain in anatomical alignment, the fracture can be treated with a support for the injured wrist. The support provides pain relief and protects from further damage at the fracture site. Around three quarters of all distal radius fractures in adults fall into this category and outcomes are generally good; the other quarter of distal radius fractures require manipulation to re-align the bones and, in some cases, surgical fixation.[2,3]

For those patients whose fracture is undisplaced, usual care is to provide the patient with a temporary 'backslab' plaster cast (a partial cast allowing room for potential swelling) in the emergency department. The patient is then referred to the orthopaedic fracture clinic where the backslab is converted to a full (circumferential) cast. The patient has to return to the fracture clinic 4-6 weeks later to have their cast removed.

Recently, there has been some evidence that a removable wrist splint may provide the patient with the same support as a cast while their fracture heals.[4] A splint can be removed by the patient themselves thereby avoiding additional visits to the hospital. However, if the splint does not provide the same support as a cast, the patient may have inferior function in their wrist.

This study will compare functional recovery and pain in patients with an undisplaced fracture of the distal radius treated with *Cast with follow-up as per usual care at the treating centre* versus a *removable splint with discharge from ED*.

5.2. Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

If patients can be treated effectively using a removable splint, this will save patients time and inconvenience in terms of additional visits to the hospital and save the NHS money by saving over 150,000 outpatient appointments each year. As each Orthopaedic Fracture clinic visit costs £120 (NHS Reference Costs 2018/19),[5] this translates into a potential saving of £18 million per year.

However, if the removable splint cannot maintain the alignment of the fracture as well as a plaster cast, patients may have more pain, worse functional outcomes and sometimes require surgery to restore the anatomy and improve their function.[2,3,6] This is worrying and inconvenient for the patient, carries a risk of surgical complications and would incur considerable cost to the NHS.[7]

5.3. Review of existing evidence - How does the existing literature support this study?

Handoll and Madhok[8] summarised the results of a series of Cochrane Reviews of randomised controlled trials of the treatment for people with distal radius fractures and "exposed the serious deficiency in the available evidence". In the previous DRAFFT trials,[7–9] we investigated the most clinical and cost-effective treatments for patients with a displaced fracture requiring manipulation. However, these trials do not address the outcomes of patients with a distal radius fracture which does not require manipulation.

A Cochrane Review in 2003 concluded that "There remains insufficient evidence to determine which methods of conservative treatment are most appropriate for the more common types of distal radial fractures in adults".[8,10] An updated review of the literature (2003-20) regarding the optimal immobilisation technique for distal radius fracture found only one trial of 66 patients indicating that patient satisfaction was high with a removable splint compared with a plaster cast.[11]

We recently published a randomised feasibility trial involving 120 patients, which indicated that a splint (made of biodegradable material) may be a viable alternative to traditional plaster casting for distal radius fractures that did not require manipulation.[4] Subsequent surveys of Emergency Department and Orthopaedic Trauma staff showed that 39/40 centres would be willing to take part in a definitive trial of removable splint versus standard care and indeed change their practice if the results indicated that splints provided non-inferior functional outcomes and were cost-effective.

A review of trial registries did not find any registrations relevant to this research question.

6. OBJECTIVES AND OUTCOME MEASURES

The aim of this multi-centre randomised non-inferiority trial is to compare the clinical and cost-effectiveness of a standard care *cast with follow-up as per usual care at the treating centre* versus *removable splint with discharge from ED* for adults with a distal radius fracture that does not require manipulation.

6.1. Objectives

The primary objective is:

To quantify and draw inferences on observed differences in function, as measured by the Patient Rated Wrist Evaluation (PRWE), between treatment groups at three months post-randomisation.

The secondary objectives are:

i) To quantify and draw inferences on observed differences in pain related to the wrist fracture, as measured by the Visual Analogue Scale (VAS) pain score, between treatment groups in the first two weeks post-randomisation.

ii) To quantify and draw inferences on observed differences in medium-term pain and function, as measured by the PRWE and PROMIS Upper Limb Physical Function Score, between treatment groups up to 12 months post-randomisation

iii) To quantify and draw inferences on observed differences in health-related quality of life, as measured by EQ-5D-5L, between treatment groups up to 12 months post-randomisation

iv) To quantify and draw inferences on observed difference in the complication rate, including the need for subsequent manipulation or surgical fixation up to 12 months post-randomisation

v) To investigate the healthcare and broader resource implications for both treatment groups up to 12 months post-randomisation

vi) To quantify the comparative cost effectiveness of the trial treatments up to 12 months post-randomisation.

vii) To investigate the impact of injury, treatment and recovery on participants, and the outcomes that are important to them.

viii) To investigate the barriers and facilitators to trial recruitment and intervention delivery from participants and clinical/study staff perspectives.

Although most patients recover in the first three months after this injury, collecting data covering 12 months will allow us to determine the patient and economic effects of complications, most notably the need for later surgical intervention.

6.2. Outcomes measures

A schedule of data collection can be found in Table 1.

The primary outcome measure for this study is the ***Patient Rated Wrist Evaluation,*** with three months post-randomisation being the primary outcome timepoint.[12] The PRWE score is a validated questionnaire which is self-reported (filled out by the patient). It consists of 15 items specifically related to pain and the function of the wrist. The PRWE is the most sensitive outcome measure available for patients sustaining this specific injury.[12] Scoring for all of 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). In addition to the three-month primary outcome time point, PRWE will also be completed twice at baseline; a retrospective pre-injury completion and a post-injury, pre-randomisation completion, and at 7 weeks, 6 and 12 months post-randomisation.

The secondary outcome measures for this study are:

Pain score: To assess pain related to the wrist fracture in the immediate post-injury period, a visual analogue scale (VAS) on a scale of 0-100, where 0 is no pain at all and 100 is the worst pain imaginable, will be used.[12] Participants will be asked to rate their pain on the day of consent (pre-randomisation) and on day 1, 3, 5, 7, 10, and 14 post-randomisation.

PROMIS: Physical Function (PF; Upper Limb). PROMIS is a collection of patient-reported health status tools that were developed to be disease non-specific in collaboration with the US National Institute for Health.[13] For the purposes of this study, we will use the computer adaptive test "CAT" (average eight questions). PROMIS will be collected at baseline (post-injury, pre-randomisation) and 3, 6 and 12 months post-randomisation. For participants unable to complete follow-up electronically PROMIS will not be collected at the follow-up time-points.

EQ-5D: The EQ-5D-5L is a validated, general health-related quality of life questionnaire consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with five levels, the responses to which will be converted into multi-attribute utility scores using an established algorithm.[14] A second component of the EQ-5D-5L comprises a Visual Analogue Scale (VAS) measuring health from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D-5L will be collected twice at baseline; a retrospective pre-injury completion and a post-injury, pre-randomisation completion. Thereafter, the EQ-5D will be collected at day 7 and at 3, 6 and 12 months post-randomisation.

Complications: All complications up to 12 months post-randomisation will be recorded, including complications related to swelling such as pressure sores and nerve damage, as well as the need for further manipulation of the fracture or surgical intervention. Participants will be asked to report complications at day 14, week 7 and at 3, 6 and 12 months post-randomisation. If a complication is indicated by the participant, additional information will be requested from the participant's recruiting centre if required.

Health and social care resource use: Health and social care resource use will be measured in the participant questionnaires for the purposes of the economic evaluation. The cost consequences following discharge, including NHS and personal social service costs and patients' out-of-pocket expenses will be recorded via a short questionnaire 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.[15]

Table 1: Data collection schedule

Outcome Measure	Baseline	Day 1	Day 3	Day 5	Day 7	Day 10	Day 14	Wk 7	Mnth 3	Mnth 6	Mnth 12
Baseline questionnaire^	X										
Visual Analogue Scale (VAS) pain score	X	X	X	X	X	X	X				
EQ-5D-5L	X X*				X				X	X	X
PRWE	X X*							X	X	X	X
PROMIS Upper Limb Physical Function	X								X	X	X
Health and Social Care Resource Use questionnaire									X	X	X
Treatment and complications log	X						X	X	X	X	X

^ Detailed in 9.8.1

* Participants will be asked to complete the outcome measure twice - once retrospective pre-injury and once post-injury

6.3 Choice of primary outcome

Wrist function was chosen as the primary outcome because

A previous patient and healthcare professional core outcome set development exercise confirmed that patient-reported wrist pain and function were the key outcomes for patients with a fracture of the distal radius. Hence it was agreed by the study team that the Patient Reported Wrist Evaluation as the primary outcome measure is the best option from the perspective of both patients and healthcare professionals. Since both the splint and cast interventions are clearly visible to patients, there is no viable alternative to an unblinded trial in the case of these interventions.

6.4 Use of Core Outcome Sets (COS)

There is currently no established COS for distal radius fractures.

7. STUDY DESIGN

Multi-centre, two-group, randomised non-inferiority trial with parallel economic analysis and direct patient follow-up to 12 months post-randomisation. The trial will employ 1:1 treatment allocation, stratified by recruitment centre and age (<50 vs ≥50 years) with patients randomised either to *Cast with follow-up as per usual care at the treating centre* or a *removable splint with discharge from ED*. The proposed project is a two-phased study. Phase 1 (internal pilot with embedded process evaluation) will refine trial procedures and confirm the expected rate of recruitment in approximately 6 recruitment centres over a period of 6 months. Phase 2 will be the definitive trial and carried out in an additional 30 recruitment centres.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Patients aged 16 years and older with an acute fracture of the distal radius who, in the opinion of the treating clinician, do not require a manipulation of the fracture. The adoption of very broad eligibility criteria will allow a diverse and representative sample to be included.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Aged 16 years or above.
- Presenting with a fracture of the distal radius which, in the opinion of the treating clinician, does not require a manipulation of the fracture.

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Present to research team more than 2 weeks post-injury
- The fracture is open (Gustilo and Anderson >1)
- They are unable to adhere to trial procedures, e.g. patients with permanent cognitive impairment, or other concomitant severe injuries e.g. head injury.

N.B. If a patient presents with a distal radius fracture to both wrists i.e. both wrists are eligible, the patient will be included but only one wrist will be randomised – whichever, in the clinician's opinion, is the worse injury. It is expected that the other eligible injured wrist will be treated in the same way.

8.4. Co-enrolment into other studies

Participants can be co-enrolled into other studies that do not involve the wrist injury that will be part of the DRAFT3-CASP study, do not conflict with the follow-up of the study and with consideration to participant burden.

Participants that have already been involved/are currently involved in DRAFT3-CASP will only be part of the study once. If the participant returns to the Emergency Department with a different eligible injury at a later time point they will not be approached to be a part of the study again.

9. PROTOCOL PROCEDURES

9.1. Recruitment

A minimum of 1894 participants will be recruited across approximately 36 recruitment centres.
The trial will be advertised to recruitment centres and potential Principal Investigators (PIs) through professional conferences and networks, with the help of the regional Clinical Research Network and through word of mouth. The DRAFT network includes over 40 sites that have previously worked with us on multi-centre randomised distal radius trials.
Sites will be selected based on suitability. An invitation pack which includes a Site Feasibility Questionnaire (SFQ) will be provided to potential sites. The SFQ may be completed by an individual with adequate, authoritative knowledge of the site (where a site is known to the study office through previous research enterprises the SFQ may be part-completed in advance). The PI or an appropriate deputy must confirm participation and the accuracy of any SFQ submitted to the study coordinating office in Oxford.
The coordinating team will evaluate returned SFQs to ensure a site is equipped with appropriate resources to deliver the project and meet recruitment targets. Confirmation of collaboration will be provided in writing to the PI.
The predicted recruitment rate is a conservative 3.2 patients per recruitment centre per month. This rate is based on a national survey of Emergency Departments to determine the number of potentially eligible patients per month and our experience of recruitment rates achieved in previous trials of this adult population with distal radius fracture.

This study will include a six-month internal pilot and process evaluation in approximately 6 recruitment centres to confirm the projected recruitment rate can be achieved and the trial can continue into the main phase without adjustments. In the main phase, at least 30 additional recruitment centres will be enrolled. The overall recruitment is projected to take a further 20 months after the internal pilot. Participants recruited during the internal pilot will be included in the final analysis.

9.2. Screening and Eligibility Assessment

Patients will be identified in the emergency department. After radiographic confirmation of a fracture the local clinical team will confirm the eligibility (see section 8) of the individual patient to participate.

Participation will be offered regardless of the patient's gender, sexual orientation, marital status, ethnicity, religion or belief, disability or socio-economic status. Screening logs will be kept at each recruitment centre to determine the number of eligible and recruited patients, and the number who decline consent or withdraw. Screening data, as detailed in the data management plan

(DMP), will be reviewed each month by the trial management team to assess whether representative samples of patients are being approached and to ensure no selection bias occurs in any of the recruitment centres with regard to approach and inclusion/exclusion of specific groups of patients. Continued training of site staff on accurate and inclusive screening and recruitment will be done through newsletters, regular Q&As/top tips, and refresher sessions.

9.3. Informed Consent

Due to the emergency setting in which patients will be approached about this research project, there will be limited time for patients to reflect on what participation in a research project would mean. As the reduced window for consideration is a common occurrence in orthopaedic trauma research, we have allocated time and resource to optimising the process of informed consent. Through analysis of in-depth interviews with trial participants, including those who declined participation in trauma research, and with extensive input from the UK Musculoskeletal Trauma PPI group, we have identified those aspects of the informed consent process that matter most to patients. These include clear and simple patient information delivered at appropriate moments, and access to clinicians with detailed knowledge of the trial. We have responded by creating explainer videos to augment written patient information sheets (PIS) and by investing in the NIHR Associate PI scheme to ensure that in addition to senior clinicians, clinical trainees at each of the recruiting centres have a good understanding about conducting research and this trial specifically.

The information presented to potential participants and their families has been developed by the clinical members of the trial team in close collaboration with our PPI representatives, who themselves have suffered a wrist injury and can therefore give a 'lived experience' view. The development team is further enhanced by the research team's qualitative researchers who have extensive knowledge in patient experience research and optimising recruitment into clinical trials.

By using different methods to explain the reasons for research and what it would involve for the patient, including explainer videos, a wider range of patients can be fully informed prior to deciding whether they would like to take part. A dedicated member of the local research team will be available for the patients and their families to answer questions and reassure them about taking part in the study.

The Informed Consent discussion will be performed by an appropriately trained and delegated member of the research team. Participants will personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed or baseline data collected. Informed consent will be recorded electronically and PDFs of information sheets and signed consent forms being sent to the participants electronically wherever possible. Paper copies can be made available where required.

9.4. Randomisation

Randomisation to '*Cast with follow-up as per usual care at the treating centre*' or '*Removable splint with discharge from ED*' will be on a 1:1 basis using a minimisation algorithm. Randomisation will be stratified by recruitment centre, and age (<50 vs ≥50 years) via a secure, 24-hour, web-based randomisation system hosted by the UKCRC-registered Oxford Clinical Trials Research Unit. A small number of allocations will initially be performed using blocked randomisation to seed the algorithm and a random element will be included in the algorithm to prevent the predictability of treatment assignment.

Stratification by *recruitment centre* will help to ensure that any clustering effect related to the recruitment centre itself will be equally distributed in the trial groups.

Stratification on the basis of *age* (<50 vs ≥50 years) 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. The use of dual-energy X-ray absorptiometry is widely regarded as the gold standard for the assessment of bone density. However, such an investigation will not routinely be available at all recruitment centres. Therefore, we will 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. After the age of 50, bone mineral density decreased steadily in males, while in females there was an initial decline between the ages of 50 and 65, with a further decline in the age groups thereafter.[16] A study by Court-Brown et al[1] assessed over 1000 patients 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 chose an age under and over 50 years as the stratification criteria for this trial. Furthermore, the study by Court-Brown et al[1] demonstrated that in the UK, approximately 60% of patients sustaining a fracture of the distal radius were aged 50 and over, while 40% were younger.

Upon randomisation of a participant the central trial office, the main site contact and local study team will be notified. This will take place via an automated email as part of the randomisation process.

9.5. Blinding and code-breaking

The primary outcome data will be collected from participants and entered directly onto the study central database. It will not be possible to blind participants or those delivering the interventions. The local research team reviewing hospital records will also not be blind to the treatment allocation.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

This study will compare two techniques for supporting the bone fragments of the distal radius while they heal.

9.6.1. Cast with follow-up as per usual care at the treating centre

Participants will follow the standard of care 'cast' treatment pathway for their hospital. Details of the cast treatment received will be recorded but in the majority of centres this will consist of a 'backslab' – a partial plaster-of-Paris cast which is shaped to support the broken bone but allows for swelling at the site of injury. The cast is applied from below the elbow to the knuckles but does not wrap around the full circumference of the wrist. The principles of applying a backslab cast are inherent in the technique, although in this pragmatic study the details of the application technique will be left to the discretion of the treating clinician as per their usual practice. The patient should then be subsequently referred to the orthopaedic fracture clinic service (usually in the first few days after their attendance at the Emergency Department) where the cast is converted into a circumferential cast for maximum support. The patient then returns to the fracture clinic where the cast is removed, 4-6 weeks later. We will collect information about the

number and type of cast(s) participants receive and how long they wear the cast. In addition, we will record any unplanned hospital visits in relation to their index fracture.

9.6.2. Removable splint with discharge from ED

A removable splint is applied from below the elbow to the knuckles. In this pragmatic study, the type of splint will be determined by the local clinicians as per their usual practice; all NHS hospitals routinely stock removable wrist splints for use in other injuries, such as wrist sprains. As the splint can be removed by the patient without attending the fracture clinic, participants will be instructed to remove the splint themselves after a period of 4-6 weeks. We will collect information about how long the removable splint is worn by the participant. In addition, we will record any unplanned hospital visits in relation to their index fracture.

Participants in both groups will be given contact details for the hospital fracture clinic in case of any problems/concerns that arise following the fracture, as per routine clinical practice. In addition, any changes to the allocated treatment will be closely monitored.

9.7. Rehabilitation

Both groups of participants will be given the same written rehabilitation instructions on managing pain and swelling, using the injured limb and exercises to prevent stiffness. This rehabilitation booklet has been devised by a panel of therapists for the DRAFT network and includes both the period when the participant is in the cast/removable splint and when the immobilisation has been removed. Strict standardisation of rehabilitation in terms of physiotherapy or specialist hand therapy referral, volume, or protocols between the groups would be undesirable. There may be important differences in the rehabilitation needs between the interventions being evaluated. Therapy provision will therefore be as per the usual care at each centre and carefully recorded as part of resource use data collection.

9.8. Assessments

The intention is to conduct this project as a paperless trial. Participant information will be presented in electronic format and consent decisions and baseline information will be recorded on an electronic tablet in the hospital setting. Follow-up assessment questionnaires can be accessed online through personal links which will be sent to participants via text message and/or email as per their preference. It is expected that a proportion of participants (estimated <10%) will be unable to complete the follow-up assessment as per the process above, due to low IT literacy or lack of access to equipment. These participants will be offered the option of completing the questionnaires at 3, 6 and 12 months through a telephone interview, with direct data entry by the central research team member conducting the phone call. For those where telephone interview is not appropriate, the questionnaires can be sent in the post for completion.
Should queries arise from the data provided the central study office will attempt to contact the participant, the recruiting centre or the participant's GP as deemed most appropriate depending on the nature of the data query.

9.8.1. Baseline assessment

Baseline sociodemographic, injury, height, weight, smoking status and alcohol consumption data will be collected in a baseline CRF. Participants will also be asked to complete the validated

questionnaires outlined in section 6. Baseline data will be collected after the participant has provided consent but prior to randomisation.

9.8.2. Treatment assessment

After randomisation and the initial treatment have been completed, the local research team will complete a treatment CRF. This CRF will contain information on treatment received on the day of randomisation and reasons for any immediate cross-over. Information on discharge and planned appointments will be recorded.

9.8.3. Short-term assessments up to two weeks post-randomisation

Participants will receive a text/email on day 1, 3, 5, 7, 10 and 14 post-randomisation with a link to a visual analogue scale asking them to indicate their level of pain related to the wrist fracture in the previous 24 hours. On day 7 the participants will also be asked to complete the EQ-5D-5L. On day 14 participants will also be asked to indicate if they attended hospital in relation to their wrist fracture and what the nature of the visit was.

Those participants without means to complete the questions electronically, will receive a phone call on day 7 and day 14 to collect relevant outcome data. The burden on participants for daily telephone follow-up was deemed too high.

9.8.4. Remote follow-up at 7 weeks post-randomisation

Participants will be contacted 7 weeks post-randomisation to capture wrist function (PRWE) during the initial period after the immobilisation removal.

Participants in the cast group will be asked if they had any planned or unplanned hospital appointments after their initial treatment and what further treatments they received (including the replacement or removal of their cast). The treating centre will be contacted for further information if the participant indicated they received further treatment.

Participants in the splint group will be asked to indicate when they started to intermittently remove their splint, and when their immobilisation device was removed completely. They will also be asked if they had any planned or unplanned hospital appointments in relation to their fracture and what, if any, treatments they received. The treating centre will be contacted for further information if the participant indicated they received further treatment.

9.8.5. Remote follow-up at 3, 6 and 12 months

Participants will be contacted to complete questionnaires which include the PRWE, PROMIS, EQ-5D-5L, complications and resource use (see section 6).

9.8.6. Reminder schedule

A schedule of email/text reminders, follow-up phone calls and post-outs for those participants failing to complete the questionnaires will be outlined in the DMP. The schedule will detail the timeframe given to participants to complete questionnaires, which assessments will be chased and the number of reminders participants receive.

9.8.7. Process evaluation

The acceptability of the introduction of a potential treatment pathway involving immediate discharge/no planned follow-up will be explored with both participants and those involved in the clinical care of the participants with distal radius fractures that do not require manipulation.

All patients that are eligible to take part in the DRAFT3-CASP study will be provided with an information sheet inviting them to take part in the interviews – this will include patients that have declined participation in the main study. If they agree to proceed, they will complete a consent form giving their permission to be contacted about taking part in the interviews and will provide contact details. Interviews will take place up to 6 months post injury. Clinical/research staff involved in recruiting or treating participants in the DRAFT3-CASP study will also be approached by the study team to ascertain their interest in taking part.

Up to 20 interviews with participants will be conducted and up to 20 researchers/clinicians at the recruitment centres will be asked to participate in either a focus group or individual interview. To gain a breadth of experiences and views, the sample of participants will include those with a range of age, sex, both interventions, and time points since injury. For the staff, a purposive sample will be obtained reflecting a range of experience, views, roles and contexts.

Patients and clinical/research staff will be invited to take part in an interview by email or telephone and provided with a consent form to consider. If they choose to take part, a time convenient to them will be arranged.
Consent will be obtained by the researcher either electronically via email or verbally. The researcher will sign and date a form to indicate they have taken informed consent. Copies of the consent form will be sent to the participant/staff via email or post by the central study team as required. The interview may be conducted using online software, such as Microsoft Teams, or telephone depending on the circumstances. The interview will be recorded online on a University computer or via an encrypted digital recorder.

The interviews will focus on participants' experience of injury, treatment and acceptability of the splint with immediate discharge or no planned follow up (if allocated to this intervention), recovery, and participation in the study. For participants who wish to be supported during their interview e.g. due to frailty, a relative/friend/informal carer may also be interviewed. Support in this study refers to helping the participant to tell their story and fill in memory gaps. This could be reminders of their struggle with pain and sleep in early recovery or a desire to return to the hospital to talk to a doctor. The relative/friend/informal carer will be provided with a PIS and consent form to consider. If a participant requires physical support or the presence of a relative/friend/informal carer but does not require verbal support, the relative/friend/informal carer would not be considered an active participant in the interview.

For some people, talking about their experience can bring back memories and feelings. If this should happen the researcher will provide support, the participant and their relative/friend/informal carer can be offered to take a break or to continue the interview at another time. The participant and their relative/friend/informal carer can choose not to answer any questions and they can stop the interview at any point.

A range of multidisciplinary clinicians will be invited to take part in a focus group to explore their views of the study, acceptability of treatments and challenges of recovery in this group of

patients. The focus group will be facilitated by a researcher from the University of Oxford. The focus group will be conducted using online software, such as Microsoft Teams. The focus group will be recorded online on a University computer or via an encrypted digital recorder to ensure that views are recorded accurately and kept secure. This will be transferred onto a password protected University computer as soon as possible and deleted from the recorder.

Through Phenomenology,[17] we will explore participants' lived experience and what is important to them. Interviews will be semi-structured, recorded, transcribed verbatim and analysed thematically.[18] Codes, such as 'will my bones be well supported', will be collated with other similar codes to create a category, such as 'how will I know my bones have healed'. Similar categories will be drawn together under a theme such as 'knowing enough to feel positive about my recovery'. Rigour will be assured through immersion in the interviews/transcripts, reflection with the PPI representatives and team members, and an audit trail of decisions. The findings will be used to improve study information and develop support for future patients to increase their confidence to self-manage their recovery.

9.9. Early Discontinuation/Withdrawal of Participants

During the course of the study, a participant may choose to withdraw early from the study at any time, without giving reasons, and without prejudicing their clinical care.

Participants will **not** have the option to withdraw the data collected up until the point of withdrawal, as the data will be required for the intention-to-treat and safety analysis. The options for withdrawal will be explained clearly in the PIS. The type of withdrawal and reason for withdrawal, if the participant is willing to provide one, will be recorded in the withdrawal Case Report Form (CRF).

If a participant is found to have lost capacity during the period of their study participation, they will be withdrawn from the study by a member of staff upon being made aware of this. Data already collected up till this point will be retained and used in the study. No further data would be collected.

9.10. Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved.

9.11 Use of Registry/NHS Digital data

No data of this type is to be accessed for this study.

10. SAFETY REPORTING

Safety reporting for each participant will begin from randomisation and will end when the participant has reached their final main follow-up time point, at 12 months post-randomisation.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death

- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

If an SAE arises in the period between randomisation and the final follow-up visit, that is deemed related to the trial interventions, the site will complete an SAE form and record the description, date of onset, end date, severity and assessment of relatedness to trial intervention.

For the purpose of safety recording for this trial, only unforeseeable SAEs potentially related to the intervention will be reported immediately to the central trial team. When the local research team becomes aware of an SAE in a trial participant, the PI will review the SAE locally and make a decision about the causality (i.e., likelihood of the event to be related/attributed to the intervention). Further details on the grades of causality are available in the *SAE Reporting Guidelines* document in the Investigator Site File. Following the assessment of causality, the PI will assess any related events for expectedness. For any SAEs assessed as unexpected and potentially related, the details of the event will be entered on an SAE reporting form on the database, and the local research team will notify the central trial team via email or telephone within 24 hours of the PI becoming aware of the event. Once received, causality and expectedness will be confirmed by the Chief Investigator (CI) or delegate (Nominated Person). In the event that consensus is not reached between the PI and Nominated Person about assessment of causality and expectedness, this will be escalated to the CI for further discussion. However, if no consensus decision is reached about expectedness after further discussion within one working day, and the SAE is judged to be unexpected by any one of the PI, Nominated Person or CI, the event will be classified as an unexpected event.

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the CI the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the CI becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). All such events will also be reported to the Trial Management Group at their next meeting.

Adverse events (AEs) that are unrelated to the injury, intervention or treatment will not be reported.

10.3. Reporting Procedures for Foreseeable Serious Adverse Events and Adverse Events Not Defined as Serious

Foreseeable SAEs and adverse events not defined as serious that are related to the interventions will be recorded by participants (through a bespoke patient-reported complications questionnaire) or recruitment centre staff (on a site complication CRF) but will not need to be reported immediately. These events will be verified with the participant and/or by the site investigators to ensure accurate recording and avoidance of duplicate reports over the follow-up time points.

Foreseeable adverse events include:

- pressure sore (grade II or above) identified while the splint/cast is being worn
- nerve damage identified after the injury but before the splint/cast is removed
- the need for further manipulation of the fracture in the first six weeks after randomisation
- the need for surgical intervention for the fracture

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

A statistical analysis plan (SAP) and health economic analysis plan (HEAP) with full details of all analyses planned for the data of this study will be drafted early in the trial and finalised prior to any primary outcome analysis.

11.2. Description of the Statistical Methods

Standard descriptive statistics will be used to summarise the baseline characteristics by treatment group using means with standard deviations or medians with interquartile ranges as appropriate for continuous variables and numbers with percentages for binary or categorical variables. Analyses will be conducted using Stata (StataCorp LP, www.stata.com) or other well-validated statistical software.

The aim of a non-inferiority trial is to show whether the new treatment is not clinically worse (i.e., is non-inferior to) the control and therefore the interest is one-sided – it is possible that the new treatment may be better than the control, but it must not be inferior to control. In order to demonstrate this, a non-inferiority margin (ΔT), which is the maximum difference in a specified direction we are prepared to tolerate and still consider the new treatment not clinically inferior to the well-established standard treatment, is defined. Therefore, the null hypothesis is that a difference greater than ΔT exists in favour of the standard treatment (H0: $\Delta \geq \Delta T$). This will be assessed by constructing a 95% confidence interval for the difference between the two treatments which should be entirely above the non-inferiority margin for the new treatment to be declared non-inferior.

The PRWE at 3 months will be compared between the treatment groups as the dependent variable in a mixed effects linear regression model adjusting for the stratification factors. A fixed effect will be used to account for age group (<50 years or ≥50 years) and a random effect will be included to account for any heterogeneity due to recruitment centre. Additional analyses including all time-points in a multi-level linear regression model and using this to calculate the area under the curve (AUC) using a summary statistics approach will also be undertaken.[19] Similar mixed effects linear regression models will be used to analyse continuous secondary outcomes

(PROMIS, EQ5D-5L) over time. For pain VAS scores a multi-level linear regression model will be used to calculate the summary statistics AUC for each treatment group and these will be compared. The number and proportion of participants experiencing complications will be summarised by treatment group overall and by type. If sufficient complications occur these will be compared between groups using an adjusted logistic regression model analogous to the linear regression models described for continuous outcomes.

11.3. Sample Size Determination

The PRWE score is 15-item questionnaire,[20] which rates wrist function using a range of questions in two (equally weighted) sections concerning the patient's experience of pain and disability.

The DRAFFT trial[7] demonstrated that the standard deviation of the PRWE 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.[20] 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.[7]

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 questions (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).[12] The previous DRAFFT trials have used 6 points as the minimum clinically important difference. Therefore, we have chosen a non-inferiority margin of 3 points for this study.

The total number of patients required to obtain a power of 90% to detect whether a removable splint is non-inferior to a cast for the treatment of fractures of the distal radius that did not require manipulation assuming a 3 point non-inferiority margin (at 2.5% 1-sided significance) between groups for the primary outcome measure is **1514**; i.e. 757 patients with primary outcome data will be required in each treatment group. Making a conservative allowance of 20% for loss to follow-up, we plan to recruit a minimum of 1894 patients (947 per group) to ensure that a minimum of 1514 have reported primary outcome data.

11.4. Analysis populations

In a non-inferiority trial, use of the intention to treat (ITT) approach can increase the chance of falsely claiming non-inferiority. Therefore, the primary analysis will be performed on the per protocol (PP) population, that is including only those participants who received their allocated treatment and did not have a major protocol deviation. A secondary analysis will be performed on the ITT population in which all randomised participants are analysed according to their treatment allocation.

Analyses of secondary outcomes will use the ITT population.

11.5. Decision points

No interim analysis is planned. Interim analysis will only be conducted on the specific request of the DSMC. Descriptive data on screening and recruitment will be reviewed by the DSMC, and subsequently the TSC at the end of the internal pilot phase. A recommendation will be made to the funder with regards to progression to the main phase of the study.

11.6. The Level of Statistical Significance

Non-inferiority comparisons will use one-sided 2.5% significance which is equivalent to the lower bound of the 95% confidence interval being compared to the non-inferiority margin. Secondary outcome analyses will use two-sided 5% significance. 95% confidence intervals will be reported throughout.

11.7. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be summarised and patterns analysed. The main analyses will be performed on an available case basis. Sensitivity analyses using multiple imputation under a missing not at random assumption will be conducted to explore the impact of missing data on the primary outcome results.

11.8. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any proposed changes from the original SAP will be included in an updated protocol, updated SAP, and/or reported in the final report as appropriate to the timing of the changes.

11.9. Health Economic Evaluation

An economic evaluation, conducted from the recommended NHS and personal social services perspective,[21] will be embedded within the study design with cost-effectiveness expressed in terms of incremental cost per quality-adjusted life year (QALY) gained. Economic costs directly associated with the treatment options, including staff inputs and consumables in the initial emergency department and orthopaedic fracture clinic contacts, complications and follow-on management will be captured through the study case report forms. Broader resource utilisation will be captured through the participant questionnaires completed at three, six and 12 months post-randomisation. Unit cost data will be obtained from national databases such as the British National Formulary and PSSRU Unit Costs of Health and Social Care cost compendia.[22] Responses to the EQ-5D-5L at each assessment point will be converted into utility scores using nationally recommended algorithms with QALY profiles estimated using the trapezoid rule.[14] Bivariate regression of costs and QALYs, with multiple imputation of missing data, will be conducted to generate within-trial estimates of incremental cost-effectiveness associated with the removable splint. Sensitivity analyses will be undertaken to assess the impact of areas of uncertainty surrounding components of the economic evaluation. The sensitivity analyses will include re-estimation of cost-effectiveness based on cases with complete data, and re-estimation of cost-effectiveness assuming a wider societal perspective. Cost-effectiveness acceptability curves will show the probability of cost-effectiveness of the removable splint evaluated at alternative cost-effectiveness thresholds. If economic outcomes are non-convergent within the study follow-up period, then extrapolation of cost-effectiveness through decision-analytic modelling will be considered, drawing upon the best available information from the literature to supplement the study data.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the DMP.

Data collected in electronic format will be entered directly into the study database, including the collection of documentary evidence of consent. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring completeness. All data entered will be encrypted in transit between the participants/recruitment centre and server. All electronic patient-identifiable information will be held on a server located in an access-controlled server room at the University of Oxford. The data will be entered into a Good Clinical Practice (GCP) compliant data collection system and stored in a database on the secure server, accessible only to the research team based on their role within the study. The database and server are backed up to a secure location on a regular basis. For the small proportion of participants providing study data via telephone interview, this data will be entered into the study database by suitably trained central office staff.

Identifiable data of participants will be limited to contact details - including name, address including postcode, email addresses, NHS/CHI/H&C number, sex at birth, and telephone numbers, and will be accessed separately from the outcome data obtained from/about the participants and managed within the rules of the clinical database system. The baseline form will record DOB. Paper forms with identifiable data will not be collected. In all other data, participants will be identified by a study ID only. Direct access to source data/documents will be required for study-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required. Contact details and data from consent forms will be retained for 12 months after the end of the study. Electronic de-identified study data will be retained for three years after final publication of the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations. Recruitment centre staff will have access to the centrally collected patient-reported outcome data for participants that they recruit at their site on REDCap (Research Electronic Data Capture), to ensure that they can download a complete dataset for their patients at the end of the study.

12.3. Data Recording and Record Keeping

Study data will be collected and managed using REDCap electronic data capture tools hosted at OCTRU, University of Oxford.

REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Wherever possible, study data will be entered directly into the study database by site staff or participants. Data captured during phone calls to participants will be entered into the study database by suitably trained central office staff. Full details will be recorded in the DMP. The participants will be identified by a unique study specific number in any data extract. Identifiable data will only be accessible by members of the study team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g. sending follow-up reminders for online form completion or telephone follow-up).

Audio recordings of qualitative interviews will be made digitally on password-protected devices. They will be transcribed by an appropriately trained member of the central research team, and the de-identified transcriptions stored on secure servers at the University of Oxford, identified by a study ID and/or initials only, will only be accessible to the CI and those members of the Oxford research team who have been authorised to do so by the CI. The audio recordings will be retained for 12 months after transcription and then deleted. It is necessary to retain the recordings for this period as they are the source data and help us to interpret participants' responses. Access to them is required in case these are needed to refer back to these during the analysis. The recordings will form a key part of interpretation of participants' responses and will inform analysis. This is relevant to both interviews with patient participants and therapists. In the unlikely scenario that external transcription services are sought, a confidentiality agreement will be in place between the Sponsor and the transcriber, who will also be on the InfoSec third party register.

13. QUALITY ASSURANCE PROCEDURES

This study will be coordinated by the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. A rigorous programme of quality control will be implemented to ensure compliance to the current approved protocol, GCP, relevant regulations and OCTRU Standard Operating Procedures (SOPs). Quality assurance checks will be undertaken by the trial management team to ensure integrity of randomisation, study entry procedures and data collection. Inspections of the Trial Master File will be carried out by the OCTRU Quality Assurance team (at least once in the lifetime of the study, more if deemed necessary). Furthermore, the processes of consent taking, randomisation, registration, provision of information and provision of treatment will be monitored centrally.
Additionally, the study may be monitored, or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

The monitoring activities will be based on the outcome of the risk assessment. Quality control procedures will be undertaken during the recruitment and data collection phases of the study to ensure research is conducted, generated, recorded and reported in compliance with the protocol, GCP and ethics committee recommendations. The CI and the Trial manager will develop data management and monitoring plans.

13.3. Study Committees

The study will be managed and independently overseen by a number of committees.

13.3.1. Trial Management Group

The day-to-day management of the study will be the responsibility of the Trial Manager, supported by a Senior Trial Manager. This will be overseen by the Trial Management Group (TMG), who will meet monthly to assess progress. A Patient and Public Involvement (PPI) representative will be an integral member of the TMG. It will also be the responsibility of the Trial Manager to undertake training of the research staff at each of the recruitment centres. The study statistician, health economist and the information specialist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

13.3.2. Trial Steering Committee

The TSC, which includes independent members, provides overall supervision of the study on behalf of the funder. Its terms of reference will be agreed with NIHR 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 study towards its interim and overall objectives.
- review at regular intervals relevant information from other sources.
- consider the recommendations of the DSMC.
- inform the funding body on the progress of the study.

The TSC will include at least one PPI representative as an independent member.

13.3.3. Data Safety and Monitoring Committee

The DSMC is a group of independent experts external to the study who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial. The study DSMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the study. The DSMC will advise the TSC on continuation of the study at the end of the pilot phase. They will also review accruing data and 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 studies 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 study should be stopped for ethical reasons, including concerns about

participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study. Full details including names will be included in the DSMC charter.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g., consent process or administration of study intervention) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file, the TMG will decide on a case-by-case basis if a protocol deviation is considered important. All protocol deviations will be evaluated in accordance with the parameters set out by the relevant SOPs issued by OCTRU. Immediate intervention cross-overs i.e. those occurring on the day of randomisation will need to be reported as protocol deviations. Any later cross-overs will be documented but will not be required to be reported as deviations.

15. SERIOUS BREACHES.

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the study subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following sponsor approval, the protocol, informed consent form, participant information sheet and all patient-facing documents will be submitted to an appropriate Research Ethics Committee (REC), and HRA and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties. The CI will submit progress reports to the funder according to their reporting requirements.

16.5. Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database (ISRCTN registry). The study information will be kept up to date during the study, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the study declaration.

16.6. Participant Confidentiality

The study will comply with the United Kingdom General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). As per section 12, identifiable information will be kept on a separate database to the study data, with the exception of DOB which is recorded in the baseline and randomisation CRFs. Furthermore, as per section 12.3 in the protocol, audio recordings are retained for up to 12 months after the interviews have been conducted. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

Participants will not undergo any hospital visits in addition to normal care, therefore no expenses will be payable.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by the National Institute for Health and Care Research, Health Technology Assessment (NIHR134681).

17.2. Insurance

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. NHS indemnity applies in respect of the clinical treatment provided.

17.3. Contractual arrangements

A contract will be drawn up between the Department of Health and the University of Oxford. The University of Oxford will execute a collaboration agreement with the employing institutions of the grant collaborators. A model non-commercial agreement will be executed with each recruitment centre.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY (IP)

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study. The materials used for the intervention were developed at Oxford University and therefore background IP is held by the University.

19. ARCHIVING

Documents and electronic systems will be archived as per the appropriate SOPs as prepared by OCTRU.

20. REFERENCES

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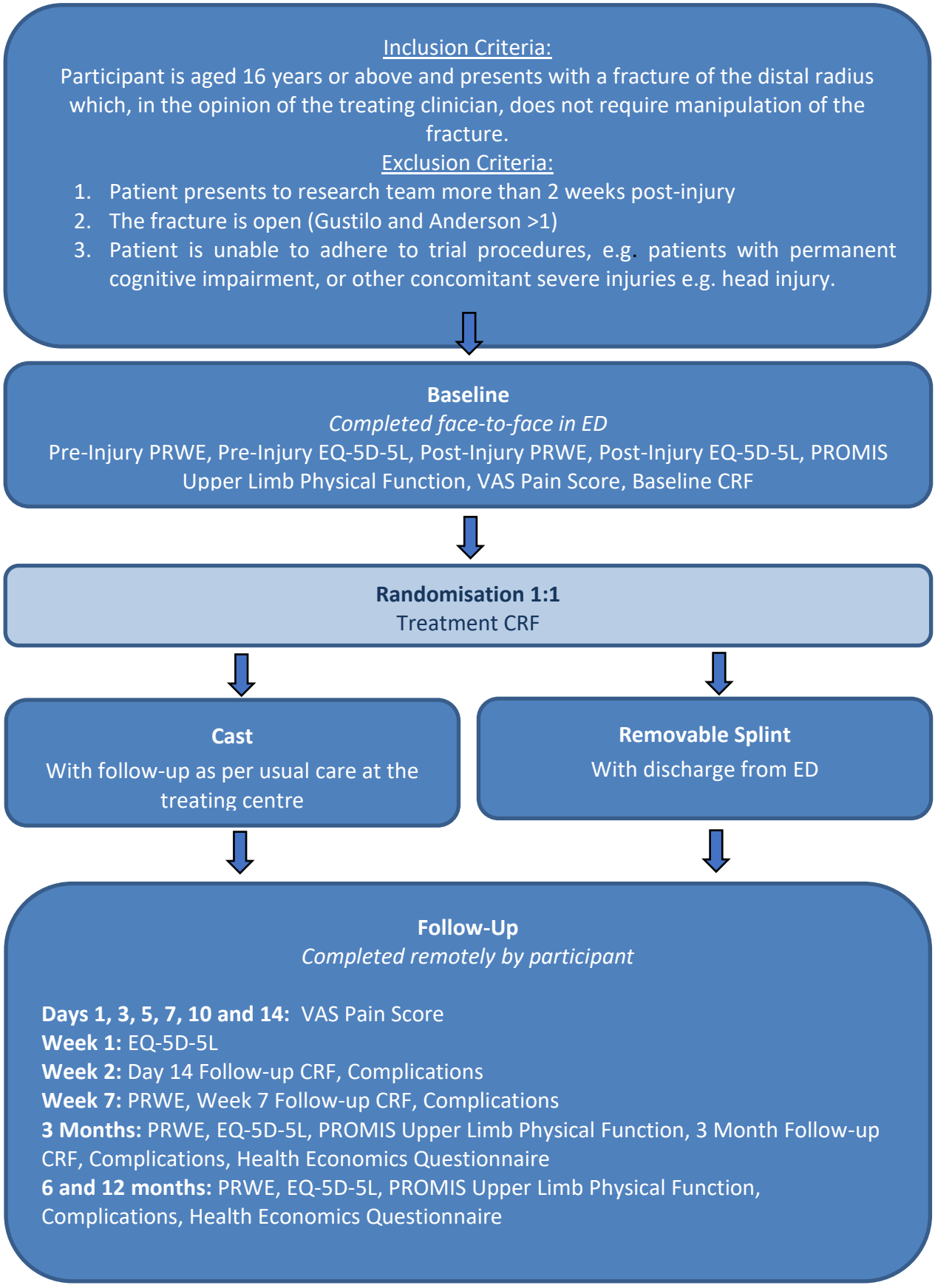
21. APPENDIX A: STUDY FLOW CHART



22. APPENDIX B: DATA COLLECTION

The data to be collected from participants on case report forms is listed below:

Screening data: (*Completed at hospital by local study team member and collected from all screened patients)*

- Date of injury
- Sex at birth
- Age on day of screening
- Ethnicity
- Index of Multiple Deprivation Score

Contact details: (*Completed at hospital by local study team member)*

- Title
- First Name
- Last Name
- In which UK Nation the participant lives
- NHS/CHI/H&C Number
- Email address
- Mobile Phone number
- Landline number
- Preferred method of contact
- Preferred time of contact
- Postal Address and Postcode

Baseline data: *(Completed at hospital by local study team member with participant)*

- Pre-Injury PRWE
- Pre-Injury EQ-5D-5L
- Post-Injury PRWE
- Post-Injury EQ-5D-5L
- PROMIS
- VAS Pain score
- Date of Birth
- Which wrist is injured
- Which is dominant hand
- Alcohol status
- Smoking status
- Height
- Weight

Randomisation form: (*Completed at hospital by local study team member)*

- Participant age (>/< 50)

- Date of consent
- Participant initials
- Date of Birth

Treatment form: *(Completed at hospital by local study team member)*

- Treatment allocation
- Date of treatment
- Type of cast treatment (Full/Backslab)
- If appointment received for routine follow-up, if not received, why not
- Was patient discharged, if not, why not

Days 1, 3, 5 and 10 post-randomisation: *(Completed remotely by participant)*

- VAS Pain Score

Day 7 post-randomisation: *(Completed remotely by participant)*

- Vas Pain Score
- EQ-5D-5L

Day 14 follow-up: *(Completed remotely by participant)*

- VAS Pain Score
- Date of any additional visits to hospital for wrist injury between initial visit to ED and day 14
- If additional visit, which department
- If the additional appointment was planned/pre-booked
- If any treatment was received
- Complications (Nerve damage/pressure sores)
- Treatment received as a result of complication
- If operation received
- Date of operation
- If participant stayed overnight for operation
- Number of nights stayed
- Type of operation

Week 7 follow-up: *(Completed remotely by participant)*

- PRWE
- If still wearing splint
- Date of splint intermittent removal
- Date of splint complete removal
- Date of additional visits to hospital between day 14 and week 7 for wrist injury
- If additional visit, which department
- If the additional appointment was planned/pre-booked

- If any treatment was received
- If participant is still wearing cast
- Date of cast removal appointment
- Date of cast removal
- Complications (Nerve damage/pressure sores)
- Treatment received as a result of complication
- If operation received
- Date of operation
- If participant stayed overnight for operation
- Number of nights stayed
- Type of operation

Month 3 follow-up questionnaire: *(Completed remotely by participant)*

- PRWE
- EQ-5D-5L
- PROMIS
- Health Economics Questionnaire
- Participant asked if still wearing splint
- Date of splint intermittent removal
- Date of splint complete removal
- If any operation received
- Date of operation
- If participant stayed overnight for operation
- Number of nights stayed
- Type of operation

Months 6 and 12 follow-up questionnaire: *(Completed remotely by participant)*

- PRWE
- EQ-5D-5L
- PROMIS
- Health Economics Questionnaire
- If any operation received
- Date of operation
- If participant stayed overnight for operation
- Number of nights stayed
- Type of operation

23. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.
Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).