The University Of Sheffield.

NHS University Hospitals of Derby and Burton NHS Foundation Trust

Prospective randomised controlled trial comparing three splints for finger flexor tendon repairs

FIRST Study

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Sheffield Clinical Trials Research Unit (CTRU)

FIRST Study Protocol
Prospective randomised controlled trial comparing three splints for finger flexor tendon repairs

This document describes a clinical trial and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

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Abbreviations

Definition of terms

AE	Adverse Event
AHP	Allied Health Professional
AROM	Active Range of Movement
BAHT	British Association of Hand Therapists
BME	Black and Minority Ethnic
BSSH	British Society for Surgery of the Hand
CCC	Confirmation of Capacity and Capability
CI	Chief Investigator
CEAC	Cost Effectiveness Acceptability Curves
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DIPj	Distal Interphalangeal Joint
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
EAM	Early Active Mobilisation
EEACT	Economic Evaluation Alongside Clinical Trial
EQ-5D	EuroQol Five Dimensions Questionnaire
FDP	Flexor Digitorum Profundus
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HTA	Health Technology Assessment
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IPJs	Interphalangeal Joints
ICERs	Incremental Cost-effectiveness Ratios
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials
MICE	Multiple Imputation by Chained Equations
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
PEM	Patient Evaluation Measure
PI	Principal Investigator
PIC	Participant Identification Centre
PIPj	Proximal Interphalangeal Joint
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PROMs	Patient Reported Outcome Measures
PRWE	Patient Rated Wrist Evaluation
PRWHE	Patient Rated Wrist and Hand Evaluation
QA	Quality Assurance
QALY	Quality Adjusted Life Years
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VICTOR	Visible ImpaCT Of Research

WPAI	Work Productivity and Activity Impairment

1. General information

1.1 Investigator details

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1.4 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.5 Protocol amendments

Amendment	Summary of Changes
Substantial amendment 1	Update to the length of time required to wear the wrist element of the mini splint. Anonymised summary demographics for site staff will be requested. Addition of participant postcode collection for social deprivation. Correction to process of sharing consent forms with CTRU for monitoring purposes. Revised wording of inclusion criteria 6. REC reference and ISRCTN number added.
Non-substantial amendment 2	Update to allow for participants to receive the participant information sheet from their standard care team via email. Update to reflect staff changes in the CTRU study team.
Non-substantial amendment 3	Update to allow participants who withdraw with ongoing AEs the option to consent for routinely collected data to be used to inform safety outcomes. Addition that participants who complete questionnaires may be entered into a prize draw (subject to budget constraints) to incentivise retention.
Substantial amendment 2	Clarification to remote questionnaire completion processes. Questionnaires may be completed remotely (where required) at all time points, as per the IRAS form.
Non-substantial amendment 5	Update to project end date, following approval of extension from funder.
Substantial amendment 3	Inclusion of the FIRST impact study.

Trial Summary

Study title	Prospective randomised controlled trial comparing three splints for finger flexor tendon repairs (FIRST study)
Sponsor	University Hospitals of Derby and Burton NHS Foundation Trust
Funder	NIHR HTA 133582 (funding was also provided by the British Association of Hand Therapists (BAHT) for the iFIRST sub-study)
ISRCTN	ISRCTN10236011
Project start date	1st January 2022
Project end date	30th November 2025
Hypothesis, aims and objectives	**Hypothesis:** The trial hypothesis is that any one of the splints may be superior, in terms of mean post-randomisation scores (based on data collected at 6, 12, 26, and 52 weeks) for self-reported wrist/hand pain and functioning outcomes, to any of the others. **Aim:** To investigate the clinical and cost effectiveness of three splints in the repair of Zone I/II finger flexor tendons. **Study Objectives:** ● To determine if any splint is superior in terms of a patient-rated measure of pain and function ● To investigate how patient values and splint acceptability moderates objectively measured splint adherence, and how adherence mediates effectiveness ● To evaluate splint cost-effectiveness, from an NHS and societal perspective
Trial design	A parallel group, superiority, analyst-blind, multi-centre, individual participant-randomised controlled trial.
Internal pilot/feasibility criteria	An 8-month internal pilot will assess the feasibility of the RCT. This will include assessment of the following: ● Site set up ● Participant recruitment ● Participant allocation per protocol ● Follow-up at 6 weeks
Setting	Approximately 20 UK NHS Hospitals
Participants	Patients undergoing rehabilitation following the surgical repair of zone I/II flexor tendons will be recruited to the study. To be eligible for the study, all the following criteria must be met at the point of randomisation: 1. Participants aged 16 or over

	2. Primary repair of zone I/II finger flexor tendon 3. Surgical repairs according to BSSH guidelines To be eligible for the study, none of the following criteria should be met: 1. Associated fractures requiring fixation or additional splintage 2. Tendon lacerations involving three or more fingers 3. Revascularization surgery and/or digital nerve reconstructions requiring a nerve graft 4. Presented for treatment more than three weeks following the original injury 5. Unable to consent or comply with the rehabilitation regime, for example, due to psychological or physical disabilities 6. Currently enrolled in another hand trial
Intervention & control groups	Three intervention groups will be compared: **1: Long splint:** custom-made, thermoplastic splint, with controlled early active movement. Covers whole hand and forearm; prevents motion of the wrist, allows controlled motion of the fingers. Worn continuously for 5 weeks and, intermittently, for 1 more week, whilst not using the hand for any activities. **2: Short splint:** custom-made, thermoplastic splint. Covers fingers, but allows motion at wrist. Worn at all times for 5 weeks; intermittently, for 1 more week, can use unaffected fingers for light activities only. **3: Mini splint:** custom-made finger-based splint preventing full extension of the injured fingers but allowing the hand and fingers to be used for daily activities with a wrist support. Finger element worn at all times for 5 weeks and intermittently for 1 more week. Wrist element worn at all times for the first 3 weeks of splint wear, and intermittently for 3 more weeks.
Primary outcome(s)	The primary outcome is the mean post-randomisation total score on the Patient Rated Wrist and Hand Evaluation (PRWHE), measured at baseline 6, 12, 26 and 52 weeks post-randomisation.
Secondary outcome(s)	**Patient-reported Outcomes** 1. Patient Evaluation Measure (PEM) 2. Work productivity and activity impairment (WPAI); 3. EuroQoL EQ-5D-5L - health status questionnaire used to derive quality adjusted life years (QALYs) and used in the cost effectiveness analysis; 4. Details of any litigation/compensation for injury 5. Global rating of change question 6. Preferences for splint attributes (stated and revealed) and splint acceptability (see process evaluation) **Clinical** 1. Range of movement - using a goniometer and calculated as a Strickland score.

	2. Grip Strength 3. Adherence to the splint, assessed using a temperature sensor in the participants' splint. 4. Complications and adverse events
Duration of recruitment period and first enrolment date	Planned recruitment start: September 2022
Duration of follow-up	Participants will be followed up until 52 weeks post-randomisation.
Target sample size	429 participants
Definition of end of trial	The end of the trial is when the last recruited participant completes their 52 week follow up. Sites will be closed once data cleaning is completed and the ethics committee will be informed.

2. Introduction

2.1 Background

There is a personal and economic burden resulting from finger flexor tendon injuries.

Hand injuries in the UK have increased 57% in 15 years, accounting for 20% of emergency presentations(1). There were 7346 flexor tendon injuries in 2018-19; 75% were in working age men(2). Such injuries most frequently occur from a direct laceration to the tendon in the finger or palm of the hand. Without surgical repair and rehabilitation, divided tendons do not heal, patients cannot bend fingers, grip objects or effectively care for themselves and others. Long-term prognosis can be poor: 50% of patients report pain and functional limitations 10 years post-injury(3). Hand injuries may impact a patient's mental wellbeing and role in society, with increased dependence on others, and an inability to care for oneself or one's family(4,5). The economic impact of flexor injury is higher than for carpal tunnel release and distal radius fracture(6) with 80% indirect costs due to missed workdays. Patients with flexor tendon injuries had an average of 70 sick days(7) jeopardising financial stability(5). Our PPI group had diverse experiences ranging from 'I'm self-employed, I drive diggers and if I don't go to work, I don't earn money', to, 'I was able to take as much paid time as I wanted off'(8).

Flexor tendon repair requires optimal rehabilitation, but evidence is inadequate

A literature search 'Is the Manchester Short Splint Regime superior to the early active movement forearm-based splint regime in the rehabilitation of zone I and II flexor repairs?' was carried out of MEDLINE, EMBASE, CINAHL, EMCARE and PubMed databases. Search subject heading included "Early Ambulation" "Finger flexor Tendons", "Finger injuries" "Forearm Based Splint" "Hand Based Splint" "Manchester Short Splint" "Splinting" "Tendon Injuries" "Tendon injuries finger", Tendon Injuries, finger rehabilitation", search terms for articles within the last 10 years.

British Society of Surgery of the Hand (BSSH) guidelines recommend primary end-to-end tendon repair with multi-strand locking sutures(9). However, the outcome of flexor tendon surgery also relies on effective rehabilitation (10). Patients routinely attend weekly appointments for up to three months with full recovery taking up to one year (11). There are two components to rehabilitation: exercises to prevent hand stiffness and promote tendon glide/excursion, and custom-made splints to protect the repair. Early active mobilisation (EAM) exercise protocols are universally accepted and generally adopted in the NHS.

By comparison, there are three main custom-made splints used in the rehabilitation of zone I/II flexor repairs that aim to facilitate EAM, but also protect the newly repaired tendon:

Long - forearm and hand-based splint.

A survey of UK current practice [8] found that the long splint is the most commonly used splint following flexor tendon repairs. This has been the mainstay of clinical practice in the UK since the 1980s. This splint protects the newly repaired tendons by preventing movement at the wrist and reducing extension of the fingers. This ensures that tension on the repaired tendon is minimised. However, it does also allow controlled movement of the fingers. It provides the maximum protection to the tendon of all the splints described in this study, however it may reduce tendon excursion leading to increased adhesions and cause joint stiffness. It is also surmised that wearing a long

splint may pose cultural and diversity barriers, including not being able to wash hands before or after religious activities, cultural dress and clean hand and unclean hand practices.

Short - hand based splint.

This was developed to allow combined wrist and finger movement and is believed to reduce the risk of complications such as stiffness, fixed flexion deformities of the interphalangeal joints (IPJs) and tendon adhesions due to the increased excursion of the repaired tendons through the synergistic motion of the wrist and hand. This has been reported in a case-series comparing the short and long splint for zone I/II flexor repairs (12). Our recent survey(8) showed that the short splint has been incorporated into rehabilitation regimes for zone I/II repairs in approximately 50% of hand centres across the UK.

Mini - finger based splint.

Over the last 5 years there has been a worldwide shift in the management of extensor tendon repairs moving from using a long splint to the mini splint(13). An RCT of extensor tendon repairs(14) reported earlier recovery of function in the mini splint, as compared to the 'long'. The mini splint has therefore been widely adopted as standard practice for patients following repair of extensor tendons in hand centres across the UK and we anticipate that flexor tendon rehabilitation will replicate this pattern. For flexor tendon repairs, the mini splint is worn in combination with a wrist brace in order to limit full wrist extension.

The mini provides less protection than all the splints described, but the patient's function is thought to be improved whilst wearing the splint. This is thought to reduce joint stiffness. However, it may not allow full excursion of the flexor digitorum profundus (FDP) tendon due to a phenomenon called the 'quadriga' effect. The quadriga effect is a biomechanical phenomenon caused by interconnections between the FDP tendons to each digit, which means the tendons are unable to move independently of each other. Because of these interconnections, if the range of motion of a particular digit is limited by a splint or injury, the action of FDP to all digits is reduced and this then restricts tendon excursion. The mini splint is designed to exploit this phenomenon and consequently may not reduce tendon adhesions in the same way as the short splint.

A case series reporting outcomes of flexor tendon repairs using the mini splint demonstrated good outcomes(15). One of the recognised complications with any tendon repair is the risk of tendon rupture or gapping of the tendon. A study in 2019(16) in a series of 4 hand cadavers showed a reduction in elongation of tendon and no tendon gapping in the splinted hand compared to the non-splinted hand within zone III.

Although the mini splint has yet to be fully adopted into UK clinical practice for flexor tendon repairs, we believe it is essential to include this splint in this study in order to future proof this work.

With regard to choice of splint, two recent systematic reviews found insufficient evidence to endorse whether flexor rehabilitation should use splints with or without wrist immobilisation, and recommended an RCT (17,18). Two primary research studies compared the 'long' and 'short' splints. One, a retrospective cohort study, reported no difference in range of motion but found improved fixed flexion deformities at 12 weeks for the short splint (12). The other, a prospective pilot study, reported improved range

of motion for the short splint (19). The mini splint has not been compared formally to other splints, but a ten-patient case series reported 60% had good/excellent range of motion, with no ruptures or joint stiffness [15]. Most recently, a 2021 Cochrane review on rehabilitation following surgery for flexor tendon injuries of the hand found a “dearth of evidence”, pointing to “the urgent need for sufficiently powered RCTs”(20). Authors analysed the best ways for recovering movement in the hand after surgery to repair flexor tendons, they concluded that the studies were too small, or reported too little robust or usable information to determine which approach is best. They also reported that there was no data on the benefits and harms of rehabilitation regimes and recommended that an RCT be undertaken.

Each splint is assumed to have different associated risks and benefits, but it is unclear which, if any, offers superior outcomes. As a result of the weak evidence base, clinical practice varies between hand centres, surgeons and therapists which reflects the clinicians’ own preference, experience and beliefs.

Splint acceptability affects adherence which, in turn, affects clinical outcomes

Using the repaired hand with no splint risks rupturing the repair and complications during recovery can result in further costly surgeries and NHS care beyond a year. For example, patients who suffer a fixed flexion deformity of their digit, may find this digit hinders their function and therefore may choose to have this digit amputated. However our PPI group reported that wearing splints was ‘a pain in the backside really, getting dressed, getting undressed, sleeping’(8) and up to two thirds of patients remove their splint for daily activities (21,22). Complications during recovery can result in further costly surgeries and NHS care beyond a year. Barriers to adherence include the need to work, comfort, hygiene and knowledge of benefits (22,23). There may also be some cultural barriers to splint adherence such as the need to participate in religious activities such as hand washing and praying.

The three splints used in the NHS all differ in the amount of movement and function allowed, which probably affects initial choice, adherence and outcomes. Patients feel more protected from rupture with the Long splint, but dislike its aesthetics, discomfort and functional restriction (22), which leaves 5- 10% with scar tissue adhesions, requiring further surgery (24). The short and mini splints may be more aesthetically pleasing, offer a greater range of movement and lower risk of adhesions, but may come with an increased risk of rupture (25). Patients will hold diverse opinions on splint choice based on personal beliefs, circumstances and cultural values. Splint choice and adherence is also influenced by occupation and sick pay provision: observational studies confirm that injury compensation status impacts time off work in manual workers (26–28). Thus, what patients value and, how they make trade-offs, may moderate splint adherence which, in turn may mediate clinical effectiveness.

2.2 Rationale for current study

To summarise: (1) clinicians accept that good outcomes in flexor tendon surgery depend on effective rehabilitation (10); (2) three splints are available each with different harm-benefit profiles; (3) three systematic reviews (17,18,20) show that there is no rational basis for splint selection (20). (4) Some UK sites are already using the ‘mini’-splint with inadequate evidence (8), indicating the need to future-proof this study through its inclusion. To continue, (5) splint adherence is known to be poor (21,22); (6) a range of patient-level factors are thought to influence splint adherence (22–26). The RCT we propose is indicated because, if one splint provides superior outcomes in terms of pain and function, then patients need to know. The process evaluation we propose is indicated because knowing how patient-level factors moderate adherence, and how adherence mediates benefit and harm outcomes is critical for decision-

making. Economic evaluation is essential because, while splint costs are comparable and relatively small, the costs of treatment failure and reintervention are substantial.

The study will be conducted in accordance with the protocol and ICH GCP.

3. Aims and objectives

3.1 Hypothesis
The trial hypothesis is that any one of the splints may be superior, in terms of the mean post-randomisation scores (based on data collected at 6, 12, 26, and 52 weeks) for self-reported wrist/hand pain and functioning outcomes, to any of the others.

3.2 Aims
To investigate the clinical and cost effectiveness of three splints, and mediators of effectiveness, in the repair of zone I/II finger flexor tendons.

3.3 Objectives
- To determine if any splint is superior in terms of a patient-rated measure of pain and function
- To investigate how patient values and splint acceptability moderates objectively measured splint adherence, and how adherence mediates effectiveness
- To evaluate splint cost-effectiveness, from an NHS and societal perspective

4. Trial Design

This is a parallel group, superiority, analyst-blind, multi-centre, individual participant-randomised controlled trial.

The trial will be conducted in approximately 20 hospitals. Patients listed for, or who have recently undergone surgical repair of zone I/II flexor tendons will be identified from hand clinics/ theatre or hand therapy services and provided with study information. Participant information sheets may be provided in person, or via email where necessary, by the patients direct care team. Following surgery, eligibility will be confirmed by delegated site staff, who will explain study procedures. Participant information may also be made available via posters/business cards containing links to an online version of the participant information sheet via the study website, in hand clinics at participating sites. Participants will be given time to consider the trial following receipt of study information. Consent will be taken after all questions have been addressed. Randomisation will then ensue. Consenting participants will be randomised to receive either the Long splint, Short splint or Mini splint. Outcome data will be collected at 6, 12, 26 and 52 weeks post-randomisation.

An 8-month internal pilot will run at all sites planned to participate in the main trial, to assess the feasibility of the RCT. The progression criteria will be applied to data collected 8 months after the first site is opened. The progression criteria (site set up, participant recruitment, participant allocation per protocol and follow-up at 6 weeks) will be assessed by the Trial Steering Committee (TSC) at the end of the following month (see section 8.3).

4.1 Blinding
In view of the nature of the intervention, patients and their treating clinicians will not be blinded to the treatment allocation. To avoid the risk of bias clinical assessors at sites

measuring range of movement and grip strength will be blinded to allocation of the participant.

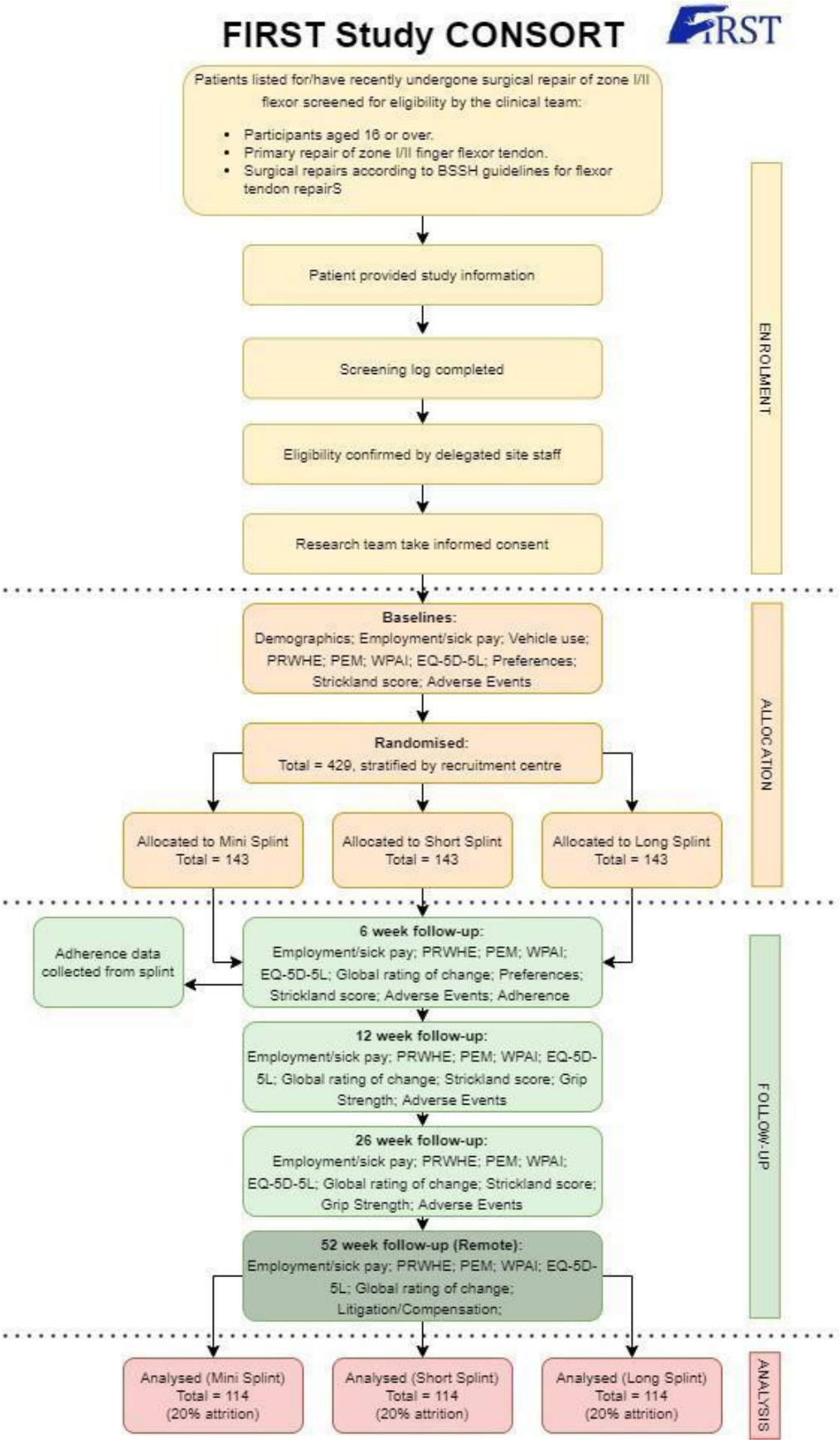
Participants will be asked to remove their splint before their clinical assessments with the blinded assessor, to ensure clinical assessors remain blind to trial allocation. Splints are not prescribed to be worn for longer than 6 weeks, so this will only be relevant to the first follow-up visit at 6 weeks. Clinical assessors will explain to participants that they are blinded to trial allocation at the beginning of the visit.

The trial statistician responsible for data analysis will remain blind until the completion of data cleaning, with the exception of data relating to treatment allocation. The quality control will be undertaken by an unblinded statistician, who will also attend DSMCs, TSCs and TMGs during the trial conduct.

4.2 Unblinding

Where clinical assessors are inadvertently unblinded, sites should complete an unblinding form and report the unblinding incident to the CTRU study manager who will maintain a log of unblinding instances. Site staff will be prompted to record and report any unblinding incidents on the clinical assessment (Strickland score and grip strength) CRFs for each visit. As participants and their treating clinicians are not blinded to treatment allocation, an emergency unblinding process is not necessary. Blinded outcome assessors should escalate any concerns which may arise to the PI or another member of staff at the site responsible for the patient's care, who are aware of treatment allocation.

5. Selection of participants



5.1 Inclusion criteria

In order to be eligible for the study, all the following criteria must be met at the point of randomisation:

1. Participants aged 16 or over.
2. Primary repair of zone I/II finger flexor tendon.
3. Surgical repairs according to BSSH guidelines for flexor tendon repairs

5.2 Exclusion criteria

Patients who meet the following criteria will not be eligible for the study.

1. Patients with associated fractures requiring fixation or additional splintage.
2. Tendon lacerations involving 3 or more fingers.
3. Revascularization surgery and/or digital nerve reconstructions requiring a nerve graft.
4. Presented for treatment more than 3 weeks following the original injury.
5. Patients unable to consent or comply with the rehabilitation regime, for example, due to cognitive, psychological or physical disabilities.
6. Currently enrolled in another hand trial.

5.3 Participant identification

Participants will be recruited from outpatient hand clinic/ therapy services.

Patients listed for a planned repair of zone I/II finger flexor tendon, or who have recently undergone surgical repair of zone I/II flexor tendons, will be identified by delegated site staff, and provided with study information.

Following surgery, all patients routinely receive a standard of care appointment with hand therapy, where decisions regarding their treatment and splint provision are made. Recruitment to the study will therefore be aligned with this appointment. Site staff will explain the study procedures and answer any questions the patient may have. Prior to consent, eligibility will be confirmed by the research team by completing an eligibility form.

All patients who are approached about the study will be recorded on an anonymised screening form with non-identifiable data. Where patients are not interested in the study, or are ineligible following surgery, this will be recorded on the screening form.

At study set up, an Equality Impact Assessment will be conducted to ensure all patients have equal opportunity to take part. The best practice guidance from The Centre for Black and Minority Ethnic (BME) Health will also be applied.

5.4 Informed consent process

The site research team will confirm patients' eligibility post-surgery by completing an eligibility form. Eligible patients will be invited to consent to the study at their first hand therapy appointment post-surgery. They will have already been provided with patient information materials and will have had time to consider their potential participation. If they are happy to proceed, written consent will be recorded at the clinic visit. Consent must be obtained for the patient to be able to take part in the trial. Instances where potential participants decline consent will be recorded on an anonymised screening form within the CRF. Where given, reasons for declining consent will be recorded.

Participant information sheets and consent forms will be translated into approximately seven different languages. Non-English-speaking participants will be given access to an interpreter if required, to answer any questions they may have.

The consent process will also include consent to the sharing of the participants' contact details with the University of Sheffield CTRU, in order to collect follow up questionnaire data.

Separate consent will be taken for the qualitative interviews. With patient consent, FIRST qualitative researchers will have access to contact details for the purposes of contact for the qualitative study. Selected participants will be sent an information sheet via email. With permission, informed consent will be recorded verbally over video call, at the time of interview by the researchers.

5.5 Co-enrolment guidelines

Concurrent participation in any other hand trials is not allowed for the duration of the study. At the point of entry into the trial, patients should not already be taking part in any other hand trial. However, co-enrolment in clinical research in other areas will be permitted.

6. Trial treatment

This study will assess the three main custom-made splints used in the rehabilitation of zone I/II flexor repairs; Long forearm and hand-based splint, Short hand based splint, and Mini finger based splint. For each type of splint, the splint will be fitted at the first hand therapy appointment post-surgery.

6.1 Patients randomised to Long splint

The forearm-based early active motion splint, or ‘Long splint’, is a custom-made, thermoplastic splint which allows controlled early active movement. It covers the dorsal aspect of the whole hand and forearm, thereby preventing motion of the wrist and allowing for controlled motion of the fingers. The Long splint will be prescribed for 5 weeks continuous wear, and intermittently for 1 more week (during the night and in vulnerable situations (e.g when in public environments or any areas the patient feels at risk of injuring their hand)). Patients are advised not to use the hand for any activities. The splint will be custom-made for the individual participant by the treating hand therapist using a thermoplastic material according to standardised study protocol.

6.2 Patients randomised to Short splint

The Manchester short splint, or ‘Short splint’, is a custom-made, thermoplastic splint which covers the dorsal aspect of the fingers but allows motion at the wrist. The Short splint will be prescribed for 5 weeks continuous wear, and intermittently for 1 more week (during the night and in vulnerable situations (e.g when in public environments or any areas the patient feels at risk of injuring their hand)). Patients are advised to only use their unaffected fingers for light activities. The splint will be custom-made for the individual participant by the treating hand therapist using a thermoplastic material according to standardised study protocol.

6.3 Patients randomised to Mini splint

The relative motion flexion splint, or ‘Mini splint’, is a custom-made finger-based splint which prevents full extension of the injured fingers but allows the hand and fingers to be used for daily activities with wrist support. The finger element will be worn continuously for 5 weeks, and intermittently for 1 more week (during the night and in vulnerable situations (e.g. when in public environments or any areas the patient feels at risk of injuring their hand)). The wrist element will be worn continuously for the first three weeks of splint wear, and intermittently for 3 more weeks (during night and in vulnerable situations e.g when in public environments or any areas the patient feels at risk of injuring their hand). The mini splint will be

custom-made for the individual participant by the treating hand therapist using a thermoplastic material according to standardised study protocol. The wrist element may be an off the shelf wrist brace.

6.4 All splints

Participants will be consented and randomised during their first hand therapy appointment post-surgery, and splints will be fabricated and fitted at the same visit by the hand therapist.

Hand Therapists will be trained in the provision of all three splints prior to commencing the study. A video of the fabrication and insertion of the sensors for each splint will be available for all treating therapists to refer to, to aid splint provision.

6.5 Adherence monitoring

Adherence will be measured using a heat sensor (orthotimer) inserted into each splint. The sensor will be removed from the splint at the six week follow-up visit and sent to Sheffield Clinical Trials Research Unit (CTRU) in order for data to be downloaded. Splint adherence will be calculated as the mean actual time divided by target wear time for the first five weeks of prescribed splint usage. Participants will be aware the monitor is there but will not have access to the adherence data.

6.6 Other Treatments

All participants will receive post-surgical rehabilitation which will be tailored to the needs of the participant. All treating therapists will be provided with best practice guidance indicating the exercise guidelines to be prescribed. This will include active and passive composite flexion exercises and active interphalangeal extension exercises for all splint groups, and wrist/ finger tenodesis exercises as appropriate for the Short and Mini splint groups only.

Any other therapy intervention deemed necessary to manage swelling, stiffness, scar adhesions and pain should be carried out as per local standard care and recorded in participants' medical notes.

Any changes to the splinting protocol will be recorded.

7. Randomisation and enrolment

Once eligibility has been confirmed, consent acquired, and baseline data taken, the participant will be randomly allocated to either the Long splint arm, the Short splint arm or the Mini splint arm on a 1:1:1 basis, using a web-based randomisation system provided by Sheffield CTRU. Patient details (ID, date of birth) and site will be entered into the randomisation system and the treatment allocation will be returned. Randomisation allocations will be based on computer-generated pseudo-random lists, stratified by site, with random permuted block sizes. Randomisation will be done by site staff during the clinic visit and participants will be informed of the outcome verbally. Their GP will also be informed of their participation in the trial, and their treatment allocation.

8. Outcomes

Anonymised sets of summary demographics for the patient population will be requested from recruiting sites, to include sex, ethnicity and employment (manual/non manual). Summary demographics will be compared to the demographics of consented participants, to evaluate equality, diversity and inclusion. Consented participants postcodes will be collected to demonstrate the demographic

spread of participants and to explore the impact of social deprivation on the study outcomes. In addition, anonymised sets of summary demographics for site staff within hand units will be requested from recruiting sites, to explore whether the diversity of recruiting staff demographics has an impact on the diversity of participants recruited to the study.

8.1 Primary outcome/endpoint

The primary outcome is the mean post-randomisation total score of the Patient Rated Wrist and Hand Evaluation (PRWHE), measured at 6, 12, 26 and 52 weeks post-randomisation. The PRWHE is a 15-item patient reported outcome for assessing wrist and hand pain/disability on a scale of 0 to 100 (0 = no pain/disability)(29). It is a modified version of the Patient Rated Wrist Evaluation (PRWE) to allow assessment of hand conditions, having the same 15-items and scoring system replacing the term “wrist” with “wrist/hand”.

8.2 Secondary outcomes/endpoints

Timepoints for secondary outcome data collection will be consistent with primary outcome data collection. Please see section 9.1.

Patient-reported Outcomes

1. Patient Evaluation Measure (PEM) - patient reported measure of care received, function, pain and wellbeing;
2. Work productivity and activity impairment (WPAI);
3. EuroQoL EQ-5D-5L - health status questionnaire used to derive quality adjusted life years (QALYs) and used in the cost effectiveness analysis;
4. Details of any litigation/compensation for injury;
5. Global rating of change question
6. Preferences for splint attributes (stated and revealed) and splint acceptability (see process evaluation)

Clinical

1. Active range of movement (AROM): The AROM of the affected digit/digits will be measured with a finger goniometer according to a standardised protocol. The Total Active Motion (TAM) will be calculated as the total active flexion of the proximal interphalangeal joint (PIPj) and distal interphalangeal joint (DIPj) motion in a composite fist position minus the extension deficit. The Strickland score will then be calculated from this measurement. Strickland $= \frac{\text{(active flexion PIPj + DIPj)- (extension deficit PIPJ +DIPj) *100}}{175}$
2. Grip Strength: This will be measured using a GripAble hand held dynamometer using a standardised protocol. Three attempts will be made on each hand the average of the 3 recorded.
3. Splint adherence: assessed using a temperature sensor in the participants' splint.
4. Complications and adverse events

All SAEs occurring from the point of consent up to the end of involvement in the trial will be reported to the CTRU within 24 hours of recognition, unless exempt (see section 10.3). Delegated site trial staff will record all adverse events and make them known to the Principal Investigator and/or Co-Principal Investigator (see section 10).

8.3 Internal pilot outcomes

Criteria are provided below to ensure the feasibility of the RCT. The progression criteria will be applied to data collected 8 months after the first site is opened. The progression criteria (site set up, participant recruitment, participant allocation per

protocol and follow-up at 6 weeks) will be assessed by the Trial Steering Committee (TSC) at the end of the following month.

Sheffield CTRU will aggregate study data to assess the feasibility of the research and intervention protocols based on the following feasibility outcomes:

Criterion	Red (% complete)	Amber (% complete)	Green (% complete)
Number of Sites opened	<15 (75%)	>=15 (75%) and <20	20 (100%)
Rate/site/month	<0.9 (<60%)	>=0.9 (60%) and <1.4	1.5 (100%)
Number of participants recruited	<144 (<60%)	>=144 (60%) and <240	240 (100%)
Allocation per protocol	<90%	>=90% and <100%	100%
% FU (% of recruited)	<50%	>=50% and <75%	75%

9. Assessments and procedures

All clinical data will be entered by research site staff onto the CTRU's in-house data management system (Prospect). Patient reported outcome measures (PROMs) data (to include the primary outcome assessment) will be completed online by the patient using a tablet in clinic at baseline, 6, 12 and 26 weeks, with paper copies available if this is not possible. PROMs may also be completed remotely via email, post or over the phone where required, if a participant is unable to attend an in person visit. At 52 weeks, all questionnaires will be completed remotely (via email/post, or over the phone). Site staff will remind participants to complete their questionnaires if they have not done so already.

Non-responders to email questionnaires may also be followed up by the CTRU research team using contact details provided by the participant, to check that outcome measures have been received and to prompt them to return the outcome measures. Contact will be attempted on contact details provided by the patient, which may include telephone contact, email or text message. Up to three contact attempts will be made. At all contact points details of how the participant can contact the research team will be included and an offer to complete the questionnaires over the telephone will be made. Complications and AEs/SAEs will be assessed at each clinic visit, and via phone call at 52 weeks by a delegated member of the research team at site. Participants will be considered lost to follow-up if they have not returned the week 52 questionnaires at the point of study closure.

Data Management (CRF design, data cleaning and validation) will be provided by the CTRU. Project-specific procedures for data management will be detailed in a data management plan.

9.1 Study assessments schedule

The study assessment schedule below details the assessments required during the course of the study. All participants will undergo these assessments, regardless of which treatment they are randomised to.

	Baseline (Clinic)	6 weeks (Clinic)	12 weeks (Clinic)	26 weeks (Clinic)	52 weeks (Remote)
Baseline and other covariates					
Pre-screening form/log (before baseline visit)	x	-	-	-	-
Eligibility form	x	-	-	-	-
Surgery details form	x	-	-	-	-
Informed consent form	x	-	-	-	-
Contact details	x	-	-	-	-
Demographics	x	-	-	-	-
Employment (including sick pay provision)	x	x	x	x	x
Vehicle use	x	-	-	-	-
Randomisation (at baseline)	x	-	-	-	-
Primary outcome					
Patient Rated Wrist and Hand Evaluation (PRWHE)	x	x	x	x	x
Patient reported measures					
Patient Evaluation Measure (PEM)	x	x	x	x	x
Work productivity and activity impairment (WPAI)	x	x	x	x	x
EuroQoL EQ-5D-5L	x	x	x	x	x
Litigation/compensation	-	-	-	-	x
Global rating of change (GRoC)	-	x	x	x	x
Preferences for splint attributes	x	x	-	-	-
Clinical outcomes					
Range of movement (Strickland score)	x	x	x	x	-
Grip strength	-	-	x	x	-
Splint adherence from heat sensor	-	x	-	-	-
Complications and AE/SAEs	x	x	x	x	x

9.2 Unscheduled visits

Participants may be seen at additional visits outside those scheduled for the study, but these visits would be part of usual care. Any adverse events or splint complications identified at additional usual care visits will be documented in the CRF. Patients will be asked at each follow up visit if they have experienced any AEs since their previous study visit.

9.3 Procedures for assessing efficacy

Efficacy is assessed by comparing the mean post-randomisation total score on the PRWHE measured at 6, 12, 26 and 52 weeks post-randomisation between the three randomised groups.

9.4 Procedure for assessing safety

Adverse events (AEs) and serious adverse events (SAEs) are discussed in Section 10. If the site research team have any concerns about a participant's wellbeing or safety during the course of the trial, this will be flagged to the patient's usual clinical team. Any complications (such as splint breakage or splint modifications) will also be recorded.

9.5 Participant withdrawals

Withdrawal from the study treatment

Participants may wish to withdraw from study treatment, or there may be a clinical need to withdraw the participant, for example, a serious adverse event which prevents the participant from wearing the splint. Participants will be encouraged to continue as participants in the study follow-up.

Withdrawal from follow-up

Participants may withdraw their consent to continue with follow-up for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/ discontinuation form and the patient notes, and no further data will be collected for this participant for the study. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent.

Participants who wish to withdraw from follow-up will be given the option to withdraw only from study visits and continue to complete follow-up remotely, where possible. Similarly, participants who DNA a research follow-up visit(s) may be given the option to complete this follow-up visit remotely. This will ensure lost data is minimised and that the primary outcome is collected in a timely manner. Sites should liaise with CTRU about any issues with study follow-up. Non-responders to email/postal questionnaires at all time points may be followed up by the CTRU research team using contact details provided by the participant, as described in section 9.

The primary outcome is collected routinely at some sites, but not at all. Where applicable, if a patient chooses to withdraw from the entire study, they will be asked if they are happy for the study team to use their routinely collected data in order to inform the primary outcome. This will be optional, but if the patient agrees, it will help to maintain the statistical power, and reduce the potential of bias introduced due to missing data when assessing trial out-comes. Participants with ongoing adverse events at the point of withdrawal will also be asked if they are happy for routinely collected data to be used to inform safety outcomes. The study team will document this discussion on a study specific form and provide the participant with a copy for their records.

Excessive participant withdrawal from follow-up has a negative impact on a study. Centres will explain the importance of remaining on study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the study. Nevertheless, if participants do not wish to remain in the study their decision must be respected. If the participant explicitly states their wish not to contribute further data to the study, this will be recorded as described above.

The impact of missing primary outcome data will be minimised to some extent by using a linear mixed model for analysis, which allows the inclusion of intermittent responders in the primary analysis. However, efforts will be made to keep participants engaged in study follow-up. Regular updates will be posted on the study website and/or communicated via email or newsletter. Vouchers will be provided, and prize draws may take place, for participants who complete follow-up questionnaires. Follow-up visits have been aligned with routine clinic visits where possible, and routine outcome data will be used wherever possible, to minimise the additional burden on participants.

9.6 Loss to follow-up

Participants will be defined as lost to follow up if they fail to return their week 52 questionnaires. If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events in clinical studies. These procedures are described in this section.

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant.
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that: ● Results in death ● Is life-threatening* ● Requires hospitalisation or prolongation of existing inpatients' hospitalisation** ● Results in persistent or significant disability or incapacity ● Is a congenital anomaly/birth defect ● Is otherwise considered medically significant by the investigator***
Related AE/SAE	An AE or SAE which is related to a research procedure
Unexpected AE/SAE	An AE or SAE which has not been pre-specified as expected.
Notable Event	An event of particular interest that does not necessarily meet the criteria for seriousness but requires expedited reporting as per the protocol.

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when,

based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Recording and reporting

Adverse events (AEs) and Serious Adverse Events (SAEs) will be recorded from the point a participant provides written informed consent for trial entry and up until participant's completion of the trial. Ongoing AE/SAEs will be followed up until the event has resolved or stabilised, or until the participant's involvement in the trial has ended.

Adverse Events (AEs)

All AEs will be assessed by site staff for relatedness and seriousness (see seriousness criteria in section 10.1).

Non-serious AEs will only be recorded where they involve the injured hand/ upper limb or are considered possibly related to the injury or its treatment. AEs will be recorded on the adverse event form within the participant CRF, and in the medical notes. Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

Serious Adverse Events (SAEs)

All AEs which meet the criteria for seriousness (see section 10.1) will be recorded in the adverse event form and in the medical notes, regardless of relatedness. SAEs will require more detailed information to be recorded. For the purposes of this study, flexor tendon rupture is considered a medically significant event, and any incidents will be recorded as SAEs.

SAEs must also be reported to the Sheffield CTRU immediately but within a maximum of 24 hours of the site becoming aware of the event, unless exempt (see section 10.3). The CTRU will coordinate ongoing monthly reporting to the Sponsor, or as soon as possible if unexpected SAE.

10.3 Study specific exemptions

The following events are expected and, should they meet the criteria for seriousness, do not require reporting to CTRU within 24 hours, but should be reported within the time frames specified below:

Within 72 hours, for ongoing safety monitoring purposes:

1. Flexor tendon rupture

Before the participants next scheduled follow-up visit:

2. Local pressure areas as a result of the splint, plaster of paris or dressings.
3. Infection leading to:
    a. Treatment with oral antibiotics.
    b. Treatment with intravenous antibiotics either as an in-patient or out-patent.
    c. Requiring surgical washout.
4. Stiffness of the affected hand requiring surgery e.g. tenolysis/arthrolysis.
5. Scar issues e.g. hypersensitivity/ hypertrophic scars.
6. Delayed wound healing requiring an extended period of dressing.
7. Complex regional pain syndrome.
8. Fixed flexion deformity of the proximal interphalangeal joint (PIPj) or distal interphalangeal joint (DIPj) requiring additional splintage.

10.4 SAE notification procedure

CTRU should be notified of all SAEs within 24 hours of the investigator becoming aware of the event, or within the timeframes specified in section 10.3, if exempt.

The SAE form must be completed by the investigator or delegated member of the research team. All SAE forms must be sent by email to ctru-saes-group@sheffield.ac.uk. Receipt of the initial report should be confirmed within one working day. The site research team should contact the study team at CTRU if confirmation of receipt is not received within one working day.

Initial SAE reports must be followed by detailed reports when further information becomes available. Participants must be followed up until the event has resolved or stabilised, or until the participants involvement in the study has ended. Follow up information will be provided on an SAE report marked as such.

10.5 CTRU responsibilities

The Sponsor usually delegates CTRU responsibility for the reporting of SAEs to the regulatory authorities and the Research Ethics Committee (REC), as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study.

10.6 SAE additional reporting

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

11. Statistics

Full details of the planned statistical analysis will be documented in a statistical analysis plan, which will be approved by the trial team and Trial Steering Committee and finalised prior to the final data lock.

11.1 Sample size

The sample size was calculated using the methodology and formula for repeated outcome measures (30). We assumed: i) 90% power; ii) 1.67% two-sided significance level (to allow for three head-to-head comparisons between the three randomised groups); iii) 1 baseline and 4 repeated assessments at 6, 12, 26 and 52 weeks post-randomisation; iv) a target difference of 6- points (31) in the post-randomisation mean PRWHE scores between any two of three groups; v) a standard deviation of 20 points for the PRWHE outcome at each post-randomisation time point (29,32); vi) an exchangeable correlation or compound symmetry of 0.50 between the repeated PRWHE assessments at 6, 12, 26 and 52 weeks post-randomisation(32,33); vii) 20% attrition. With these input parameters 114 subjects per group are required (3 x 114 =342 in total). After allowing for 20% attrition we propose to randomise 429 participants in a 1:1:1 ratio (143 Long splint: 143 Short splint: 143 Mini splint).

11.2 Statistical Analysis

Data will be reported and presented according to the CONSORT (34).

The primary effectiveness statistical analyses will be performed on an intention-to-treat (ITT) basis. There is no planned interim analysis, beyond checking the recruitment and retention rate at the end of the pilot phase. Baseline demographic, physical and clinical characteristics and health-related quality of life data will be described and summarised overall and for the three randomised groups.

The primary aims are to estimate and compare the effectiveness of 1) Long vs Short splint; 2) Long vs Mini splint; 3) Mini vs Short splint in patients undergoing zone I/II finger flexor tendon repairs.

The primary outcome will be the mean post-randomisation total score on the PRWHE measured at 6, 12, 26 and 52 weeks post-randomisation. The primary effectiveness analysis, on the ITT sample, whereby participants will be analysed in line with their randomisation allocation, regardless of compliance with the protocol, will compare the post-randomisation PRWHE scores, between the three randomised groups, using a linear mixed model incorporating all post randomisation PRWHE scores (at 6, 12, 26 and 52 weeks) as outcomes, with random effects for centre and subject (to account for the repeated observations per patient), and fixed effects for randomised group, time post-randomisation and baseline score (35). We shall assume an exchangeable correlation between the repeated measurements.

Three treatment effect contrasts will be estimated and reported from the linear mixed model: 1) Long vs Short splint; 2) Long vs Mini splint; 3) Mini vs Short splint. We will estimate 98.3% confidence intervals for the three treatment effects for simultaneous inference and to make sure that all parameters are covered with 95% confidence. This model will include all patients who provide valid PRWHE data for at least one post-randomisation follow-up time point.

Missing Data

The impact of missing PRWHE outcome data will be minimised to some extent by using the linear mixed model, which allows the inclusion of intermittent responders in the primary analysis. PRWHE scores for complete and intermittent responders will be compared descriptively. The impact of missing data will additionally be assessed using multiple imputation by chained equations (MICE). Missing outcome and covariate data will be predicted by age, rupture rate, hand dominance, available PRWHE data at other follow-up time points, and any baseline covariates found to be predictive of the outcome data. The estimates of the treatment effects and their associated confidence interval from the imputation model will be graphically displayed alongside the results for the observed data. Additional sensitivity analysis will consider scenarios whereby participants with missing data have outcomes worse than those with available data (missing not at random scenarios).

Complications, safety outcomes and adverse events

The following summaries will be presented: the number and percentages of patients reported as having Serious Adverse Events (SAEs) in each treatment arm; the number and percentages recorded as having all forms of Adverse Events (AEs) in each arm; this will be presented as overall and stratified by AE classification. Other complications (e.g damage to splint, splint modifications) will be presented and reported in a similar way to SAEs.

Secondary outcomes

The scores on the repeated continuous secondary outcomes (e.g. PEM, EQ-5D-5L, Range of movement, Grip strength, Splint adherence) will be compared between the randomised groups using a similar longitudinal mixed effects linear regression model as described for the analysis of the primary outcome. Treatment effects for each protocol stipulated follow-up points will also be presented.

Adherence to the randomised splint treatment during the first 6-weeks post-randomisation will be estimated from the heat sensor in the splint. Adherence will be summarised for each randomised group using a variety of summary measures (e.g. mean number of hours per day wearing the splint) and mean adherence compared

between the group using a linear regression model. As with the primary outcome three treatment effect contrasts, and their associated confidence intervals will be estimated and reported from the model: 1) Long vs Short splint; 2) Long vs Mini splint; 3) Mini vs Short splint.

The categorical responses from the global rating of change question at each post-randomisation time-point will be summarised by randomised group and compared between the groups using a chi-squared test.

Economic evaluation

The health economic analysis will estimate the costs and quality adjusted life years (QALYs) of each of the splints and will be conducted in two parts. First, a within-trial cost effectiveness analysis (i.e. economic evaluation alongside clinical trial (EEACT)) will be performed, and second, an analysis of the long-term cost effectiveness will be conducted using a de novo decision analytic model. The cost-effectiveness of three splints will be estimated as incremental cost-effectiveness ratios (ICERs) using full incremental analysis, accounting for any dominance. In the within trial analysis, QALYs will be estimated by calculating the area under the curve for health utility using the EQ-5D-5L and the costs will be estimated for the health service resource use up to to one year multiplied by national average costs. Long-term cost-effectiveness modelling will use the data from the trial (on proportions of patients with complications and adverse events) to estimate the lifetime QALYs and costs. Sensitivity analyses will explore the potential impact of parameters upon costs, QALYs and ICERs. Parameter uncertainty will be included in probabilistic sensitivity
analysis based on Monte Carlo simulation. Cost effectiveness acceptability curves (CEACs) will be plotted to identify the probability of each splint being cost effective for a range of threshold values for an additional QALY.

12. Ancillary sub-studies

12.1 Process Evaluation

The MRC Framework states that process evaluations should inform practice through answering three questions about how interventions work(36):

1. What is implemented?
2. How does context affect implementation and outcomes?
3. How did the effects of each intervention occur (mechanisms of impact)?

The process evaluation sub-study aims to answer the above questions via the following objectives:

1. Collect data on adherence to splint prescription
2. Collect patient reported data on (‘stated’) preferences for particular splint attributes, at baseline
3. Collect patient reported data on (‘revealed’) preferences, and splint acceptability at 6 weeks
4. Conduct qualitative interviews
5. Develop a structural equation model, to show the effect of baselines, preferences, acceptability and adherence on pain/function (PRWHE: trial primary outcome)

What is implemented?

Adherence is empirically known to be variable (22–25). The splints of all trial participants will be fitted with a temperature-monitoring device ***(a) to collect data on adherence to splint prescription.*** As adherence assessment is integrated into the

procedures for the main study, the details are included throughout the protocol (see section 6.5) and in study-specific guidance where necessary.

How does context affect implementation and outcomes?
Decisions on whether to adhere based on the importance of particular splint attributes (e.g. perceived comfort, safety, ability to conduct important activities, etc.) are seen through the prism of personal beliefs, circumstances and cultural values (e.g. the relative importance of avoiding rupture, compared to urgency of returning to work, etc.)(26–28). As such, ***(b) patient-reported data on ('stated') preferences for particular splint attributes will be collected at baseline***. However, an individual's understanding of context is usually implicit, distorted and incomplete, and requires independent reality testing (37). Therefore, ***(c) 6-week patient-reported 'revealed preferences' and acceptability data will be collected***, supplemented by ***(d) nested qualitative interviews***, to understand how context produces variation in adherence, and how that variation may be reduced(38).

Two structured survey instruments and an interview guide, informed by Sekhon's acceptability framework(39), a review of the splint adherence literature, consultation with physiotherapists and two workshops of 4 people with lived experience of wearing the different splints for flexor tendon repair (PPI work), will be used. Collection and analysis of the surveys will be integral to the trial. To understand determinants of nonadherence to the different splints and their associated harm-benefit profiles, 20 partially-nested semi-structured interviews will be conducted, sampling both within and outside of the RCT where required, based on splint type and known influential factors such as employment type and dependence on vehicle use (39–41).

Sampling outside the RCT will be pursued if the sample of consenting participants is not deemed representative of the patient population (see section 8). If a demographic is felt to be missing, sites will be asked to offer participants who decline the RCT the option to be contacted about the qualitative interviews. A separate consent to be contacted form will be available for participants who wish only to consent only to be contacted about the qualitative interviews.

Transcripts will be deductively coded to acceptability constructs(39), before a cross-case framework analysis (42). Findings will be integrated thematically with other work packages in joint display tables (43).

How did the effects of each intervention occur (mechanisms of impact)?
Informed by the interviews ***(d)***, a structural equation model will be developed ***(e)*** to show the effect of baselines (for instance, employment type or dependence on vehicle use), preferences ***(b and c)*** on adherence ***(a)*** and of adherence on pain/function (PRWHE: trial primary outcome). A secondary mediation analysis will investigate putative mediation factors (stated and revealed preferences, adherence) using direct acyclic graphs and structural equation models to test for mediation of splint on pain and function (PRWHE) through the factors. Analyses will adjust for baseline measures of the factor and possible measured confounders/moderators (e.g. age, sex). Possible mediation factors will be tested for by testing interactions between baseline factors and treatment on treatment response and safety outcomes.

12.2 Evaluation of Impact (iFIRST)

Understanding research impact can strengthen evidence-based practice, inform policy and provide insights into knowledge translation(44). The aim of the impact sub-study (iFIRST) is to evaluate the short and medium to long-term impacts of the FIRST study on allied health professionals (AHPs) and surgeons, and those directly involved in the FIRST RCT, via the following objectives:

1. Evaluate the clinical impact of the splints and guidelines used in FIRST on clinical practice
2. Evaluate the impact of FIRST on the research culture and capabilities within hand therapy teams

A structured questionnaire instrument and a semi-structured interview guide will be developed, informed by the VICTOR (Visible ImpaCT Of Research) impact tool (45) which has been specifically developed to demonstrate the impact of research in NHS organisations, with a focus on AHPs.

Online qualtrics questionnaires will be shared with all staff on the FIRST delegation logs across the 26 FIRST sites. A QR code linking to the questionnaire may be included on posters and on small business cards at hand therapy conferences and shared via email with sites, and Sheffield CTRU will also coordinate sharing the qualtrics questionnaire link directly via email to site staff. The first page of the questionnaire will specify who the investigators are, the purpose of the study, how questionnaire responses will be used, and approximate time for questionnaire completion. Readers will be asked to give their consent on the questionnaire cover page, after reading the information, and before completing the questionnaire. Demographic information will be collected from the questionnaires, such as study site, job title, role in study, age, ethnicity and length of time working in hands. As an incentive, questionnaire respondents will be entered into a prize draw to win up to £50 shopping vouchers. Email addresses will be collected at the end of the questionnaire for this purpose, though respondents may opt out from this if they wish.

To further understand the impact of FIRST, 26 1-hour interviews will be conducted by staff at University Hospitals of Derby & Burton and/or the Sheffield CTRU, to capture the 26 FIRST sites. Interviews will be conducted remotely, via video call. Potential interview participants will be site staff on the FIRST delegation log. At the end of the questionnaire, respondents will be asked if they would be happy to be contacted about participating in an interview. If yes, name and contact details will be collected via qualtrics. Potential interview participants will be sampled based on questionnaire responses and demographic details, however, depending on response rates, non-responders to the questionnaire may also be invited to interview. Interview advertisements may be shown at hand therapy conferences and shared with site staff via email, and site staff who are interested will be asked to contact the study team for further information. Potential interview participants will be provided with an interview PIS by email, and may be followed up by phone call to discuss the PIS further. If participants wish to take part, full informed consent will be recorded in an MS Teams video call and documented on a consent form by the interviewer. Participants will consent for the interview to be recorded and transcribed. Interview transcripts will be anonymised for analysis. Interview participants will be compensated for their time with a £20 shopping voucher.

Data storage
Data will be stored on the University of Sheffield’s network drive, in an access restricted location. Researchers from the University of Sheffield CTRU, University

Hospitals of Derby & Burton will work collaboratively to analyse the data. Therefore, anonymised questionnaire responses and interview transcripts will be stored in a restricted access google drive folder and coded in a shared google sheet. Interview consent forms and consent recordings will be uploaded to the google drive folder by University Hospitals of Derby & Burton researchers, to be downloaded by University of Sheffield researchers for storing in the University of Sheffield's network drive. Once downloaded, consent forms and consent recordings will be deleted from the google drive. Consent forms will be retained for the duration of the archiving period, however consent recordings will be destroyed upon completion of the FIRST study, ahead of archiving. Questionnaire responses including contact details for prize draw entry and/or consent to be contacted for interview will be exported from qualtrics and stored securely in the University of Sheffield network drive. Once prize draws and interviews are complete, the contact details will be removed from questionnaire responses. Data will be retained for seven years from the end of the FIRST study.

Analysis
Data generated from the Likert questions in the questionnaire will be analysed using descriptive frequency statistics. Data from open-ended survey questions and qualitative interview transcripts will be analysed using framework analysis. Framework analysis will be carried out using the five steps approach (46). Raw data will be systematically categorised and coded by two independent researchers. Any discrepancies will be discussed and resolved by a third researcher. Mean national scores for each domain will be reported alongside the qualitative analysis exploring researcher's experiences. Trends relating to demographics including location and department size will be reported.

Funding
The iFIRST sub-study is funded by BAHT and NIHR.

13. Trial supervision

The FIRST study will be led by the Chief Investigator and co-CI working in coordination with the co-applicants and Sheffield CTRU. The Sponsor will be University Hospitals of Derby & Burton NHS Foundation Trust. Sheffield CTRU will take responsibility for project management. There is a dedicated Study Manager who is supervised by the CI and Co-CI and senior staff in the CTRU, meeting regularly, and will liaise with the whole study team. Dan Hind will provide oversight for the delivery of all CTRU support including trial management, data management, QA, randomization, statistics, health economics, analysis reporting and dissemination. NHS REC and Health Research Authority (HRA) approval will be sought prior to commencement of the trial at participating centres. A site agreement between the Sponsor, participating site, CTRU and University of Sheffield will outline responsibilities of all parties and be signed prior to commencement of recruitment at sites. All persons responsible for recruiting patients to the trial will be required to complete Good Clinical Practice (GCP) training.

Three committees will be established to govern the conduct of this study in accordance with Sheffield CTRU Standard Operating Procedures (SOPs): a Trial Steering Committee (TSC), a Data Monitoring and Ethics Committee (DMEC) and a Trial Management Group (TMG).

13.1 Trial Steering Committee
The TSC will consist of an independent chair and other professionals with relevant clinical and academic experience and one patient representative.

The role of the TSC is to provide supervision of the protocol, and statistical analysis plan, to provide advice on and monitor the study, to review information from other sources and consider recommendations from the DMEC. The TSC will meet at regular intervals, as defined in the TSC terms of reference. The TSC can prematurely close the trial, should this be recommended by the DMEC.

13.2 Data Monitoring and Ethics Committee

The DMEC will consist of an independent statistician, and at least two independent clinicians with clinical trial expertise.

The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. The DMEC will meet at regular intervals, as defined by the DMEC charter. There will be no interim analyses (other than for the purposes of the blinded internal pilot) or definitive stopping guidelines, but the DMEC will be able to request unblinded data and recommend study termination to the TSC / funder on grounds of safety or futility.

13.3 Trial Management Group

The Trial Management Group (TMG) consists of the CI, co applicants and staff from CTRU, with site PIs and other site staff attending depending on need at each stage of the study. The CI will chair meetings to discuss the day to day running of the trial, including any implementation issues. The TMG will receive reports from the TSC and DMEC to manage trial progress.

14. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of GDPR will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties. All patients will be given a unique trial identifier (participant ID) on entry into the trial, and this will be used in all future trial correspondence outside of the direct care team and on data collection forms. Names, email addresses, phone numbers, and addresses where required (if participants prefer to receive paper questionnaires via post) will be collected on the study database, to facilitate sending and follow-up questionnaires at the week 52 remote visit, and contacting participants about the qualitative interviews, where consent to do so has been obtained. Access to personal data will be available only to those who need it.

All aspects of data management, including data protection and archiving, will be provided by the University of Sheffield CTRU in accordance with their own SOPs. The study will use the CTRU’s in-house data management system (Prospect) for the capture and storage of participant data. Project-specific procedures for data management will be detailed in a separate data management plan (DMP) in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant, in all instances where the database does not form the source data.

14.1 Archiving

Data held by the CTRU will be stored in accordance with the archiving SOP (CTRU SOP PM012). Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

15. Data access and quality assurance

FIRST will use CTRU's in house data management system (Prospect) for the capture and storage of study-specific participant data. Prospect uses industry standard techniques to provide security, including password authentication and encryption. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. The database will incorporate quality control procedures to validate the study data. Discrepancy reports will be generated to highlight missing and erroneous information.

Participant confidentiality will be respected at all times. Research data will be identified using the participants study ID number, with access to personal data only by those who need it. Directly identifiable data will not be transferred to the statisticians.

Participating investigators shall agree to allow study related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data, and documents, as required. Participants' consent for this will be obtained as part of the consent process.

Data from the temperature sensors will be held in a cloud-based system. Data will be stored and secured end-to-end encrypted on a secure server located in Germany, according to the European Data Protection Board (EDPS) guidelines. No identifiable data will be held within the cloud. Temperature sensors will be numbered and linked with participants' study IDs on a form in Prospect.

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research
- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF).

Before each site is activated, capability to conduct the trial will be assessed and documented. The CTRU will arrange a site initiation visit with each site or carry this out remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Site staff involved in splint provision will also be trained on each of the three splints. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

15.2 Risk assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU SOPs.

Central and/or on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment and will be documented in the Trial Monitoring Plan.

15.3 Reporting serious breaches and non-compliances

A “serious breach” is a breach of either: the conditions and principles of GCP in connection with the trial or; the protocol relating to the trial; which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC and within 7 days of becoming aware of a serious breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware.

15.4 On-site monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP.

A site initiation visit will be performed or carried out remotely for each participating site before each site recruits their first participant. During this visit/remote contact, the Monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and Sponsor requirements.

Regular site monitoring visits will occur throughout the study as specified in the Site Monitoring Plan and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the CRF against Investigator’s records by the Study Monitor (source document verification) (see section 13 for further details on data collection). Study Monitor will contact sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs.

Site close-out will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

15.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to share copies of consent forms with CTRU via secure NHS.net mail on an ongoing basis. This will be made clear to the participant prior to their consent to the trial.

16. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

17. Finance

FIRST is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (NIHR133582). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

All follow up visits have been timed to coincide with the timing of routine follow up visits, with the exception of the week 26 visit, for which participant travel expenses will be provided.

18. Ethics approval & regulatory compliance

Before initiation of the study at participating sites, the protocol, informed consent forms and information materials to be given to the participants will be submitted to an NHS REC. Any further amendments will be submitted and approved by the HRA and ethics committee.

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place.

Any amendments, including protocol modifications will be notified to all sites and collaborating parties to confirm ongoing Confirmation of Capacity and Capability (CCC) in light of the new information. Participants will be notified and reconsented if appropriate to the change.

19. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites.

Recruitment of study participants will not commence at a site until a letter of Confirmation of Capacity and Capability (CCC) has been issued.

20. Trial Organisation and Responsibilities

20.1 Principal Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant

staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Study Manager on logistic and administrative matters connected with the trial.

20.2 Sheffield Clinical Trials Research Unit (CTRU)
The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU Study Manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability (CCC) has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

21. Patient & Public Involvement and Engagement (PPIE)

A PPI focus group of ten patients who had recently completed their course of rehabilitation following a flexor tendon repair provided input into the design of the study, and heavily influenced the trial aims and objectives. PPI members will be invited to attend TMG and TSC meetings to input into the running of the trial.

PPI will be actively involved throughout the study, for example in reviewing patient-facing trial documentation, input into training/information videos and advising on recruitment strategy. Patient representation will aid the development and refinement of the health and social care costs instrument. Our PPI group will review and inform the qualitative interview guides and aid with the interpretation and triangulation of the qualitative data. Our PPI representatives will review our results and support dissemination through video content on professional society webinars and social media. Regular updates for study participants about recruitment and results will be guided by our PPI. At the close out and write up phase, we will seek PPI input into the final study report. To capture and evaluate the PPI impact an impact log will be completed by the PPI lead at every PPI activity.

22. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical study.

Standard NHS indemnity operates in respect of the clinical treatment that is provided.

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