FLARE Trial Protocol

Full title: A randomised trial to determine the clinical and cost effectiveness of repairing flexor digitorum profundus (FDP) alone versus repair of both FDP and flexor digitorum superficialis (FDS) for treatment of complete zone 2 flexor tendon injuries: the FLexor repAir and REhabilitation (FLARE) Trial

Short title: FLexor repAir and REhabilitation (FLARE) Trial

Protocol version: 1.1 dated 17.03.2023

Trial registration:

ISRCTN number: 10918157

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Sponsor: South Tees Hospitals NHS Foundation Trust

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Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Co-Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:  Date: 12/05/2023

.....

Name: Mr David Rollins

Position: Research Governance Manager

Co-Chief Investigators:

Signature:  Date: 12/05/2023

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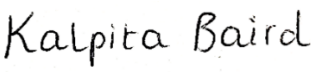
Name: Mr Matthew Gardiner

Signature:  Date: 12/05/2023

.....

Name: Ms Emma Reay

Statistician:

Signature:  Date: 12/05/2023

.....

Name: Kalpita Baird

Position: Trial Statistician

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Trial Contacts, Roles and Responsibilities

Table 1: Trial Contacts

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Trial Oversight Committees	**Trial Steering Committee:** *Chair*: David Warwick, University Hospital Southampton NHS Foundation Trust	**Data Monitoring and Ethics Committee:** *Chair*: Dr Judith Cohen, University of Hull
	Trial Management Group: *Chair*: Mr Matt Gardiner / Ms Emma Reay	

Table 2: Other Collaborators

Dr Lisa Newington Imperial College London	**Professor Amar Rangan** South Tees Hospitals NHS Foundation Trust
Professor Jeremy Rodrigues Warwick Clinical Trials Unit	**Professor Catherine Hewitt** University of York
Mr Justin Wormald University of Oxford	**Dr Lucksy Kottam** South Tees Hospitals NHS Foundation Trust
Mrs Karen Glerum-Brooks University of York	**Mr Ryckie Wade** University of Leeds
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Mr Satwinder Hira PPI Representative in England	

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Abbreviations and Glossary

AE	Adverse event
API	Associate principal investigator
APR	Annual progress report
BMC	BioMedCentral
BSSH	British Society for Surgery of the Hand
CI	Chief investigator
CONSORT	Consolidated Standards of Reporting Trials statement
CRF	Case report form
CTIMP	Clinical trial of an investigational medicinal product
CUA	Cost utility analysis
DMC	Data monitoring committee
EQ-5D-5L	EuroQol 5 dimensions (5L) score
FDP	Flexor digitorum profundus
FDS	Flexor digitorum superficialis
GCP	Good clinical practice
GDPR	General data protection regulation
GIRFT	Get it right first time
HEAP	Health economics analysis plan
HES	Hospital Episode Statistics
HRA	Health research authority
HTA	Health technology assessment
IFSHT	International Federation of Societies for Hand Therapy
IFSSH	International Federation of Societies for Surgery of the Hand
IRAS	Integrated Research Application System
ISF	Investigator site files
ISRCTN	International Standard Randomised Controlled Trial Number
MHRA	Medicines and Healthcare Regulatory Authority
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

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NIHR	National Institute for Health and Care Research
ONS	Office for National Statistics
PAG	Patient advisory group
PEM	Patient evaluation measure
PI	Principal investigator
PIS	Patient information sheet
PPI	Patient and Public Involvement
PROM	Patient reported outcome measure
PRWHE	Patient reported wrist/hand evaluation
QoL	Quality of life
RCT	Randomised controlled trial
REC	Research ethics committee
REDCap	Research electronic data capture
SAC	Speciality Advisory Committees
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedures
SWAT	Study within a trial
TMF	Trial master file
TMG	Trial Management Group
TSC	Trial steering committee
UK	United Kingdom
USA	United States of America
USD	United States Dollar
WALANT	Wide Awake Local Anaesthesia No Tourniquet
YTU	York Trials Unit

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Amendment History/Changes from Previous Version

Table 3: Amendment History

Amendment Number	**Revised Protocol Version Number and Date**	**Details of key changes made** *(including justification if required)*
NA (Change from Detailed Project Description)	1.0 dated 30/09/22	'Usual care' is replaced with 'FDP and FDS repair' throughout the protocol so that terminology is applicable across all participating organisations. **Eligibility Criteria:** Age criterion amended from ≥18 years to ≥16 years. Restriction on injury over seven days old is removed with the decision to operate made by treating surgeon. Addition of criteria on revascularisation, previous injury and contraindication to surgery. **Surgical Intervention** Requirement for 4 strand repair to be mandatory has been removed to allow for variation in practice. **Outcome measures:** Collection of baseline PROMS (pre and post injury) was not specified in the grant application. Fingertip to Distal Palmar Crease measurement removed. **Splint Sensor Activity and monitoring.** The requirement for splint sensor monitoring has been removed. The focus of the revised funding application was the surgical intervention. A pragmatic approach to rehabilitation for this trial will be taken with decision on rehabilitation pathway to be made by therapists in conjunction with patients.

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Non Substantial Amendment 2	1.1 dated 17/03/2023	**Trial Contacts** Updated to reflect key staff changes. **Method of Randomisation:** Stratification factors Digital Nerve Injury and Anaesthetic Type have been removed to reduce the predictability of the allocation schedule particularly at low recruiting sites. The randomisation schedule is now stratified by site only. **Statistical Analysis** The primary analysis model will adjust for Digital Nerve Injury and Anaesthetic Type at baseline as fixed effects. **Outcome measures:** Pre-injury collection of baseline PROMS removed for EQ-5D-5L and PRWHE. **Qualitative Study** Recruitment optimisation plan added to pilot phase. Other minor corrections to correct grammatical or typographical errors and to ensure consistency have been made throughout.

Trial Synopsis

Table 4: Trial Synopsis

Acronym	FLARE
Long Title	A randomised trial to determine the clinical and cost effectiveness of repairing flexor digitorum profundus (FDP) alone versus repair of both FDP and flexor digitorum superficialis (FDS) for treatment of complete zone 2 flexor tendon injuries: The FLexor repAir and REhabilitation (FLARE) Trial
Type of Trial	Non-CTIMP
Study Design	Multi-centre, two-arm, non-inferiority, parallel group, randomised controlled trial with an internal pilot, economic evaluation and nested qualitative study
Setting	Participating Hand Trauma Centres within the UK treating flexor tendon injuries and with facilities to support research activity
Target Population	Patients aged 16 years and over with a zone 2 flexor tendon injury, to a single digit, needing surgical repair
Intervention	Flexor Digitorum Profundus (FDP) is repaired only
Control	Repair of both Flexor Digitorum Profundus (FDP) and Flexor Digitorum Superficialis (FDS)
Primary Outcome	Patient Evaluation Measure (PEM) at 6 months post-randomisation

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Secondary Outcomes	At 6 weeks, 3 months and 6 months post-randomisation: PEM, Patient Related Wrist/Hand Evaluation (PRWHE), total range of movement, grip strength (3 month only), quality of life (EQ-5D-5L), work outcomes, treatment and outcome satisfaction, healthcare resource use, adherence to therapy regimen, splint adherence (6 weeks only), complications, adverse events and nested qualitative study.
Estimated Recruitment Period	22 months (target date of first enrolment April 2023)
Duration per Patient	6 months
Estimated Total Trial Duration	40 months (1st April 2022 to 31st July 2025)
Planned Trial Sites	Up to 40
Planned Sample Size	310 (Randomisation 1:1)
Main eligibility Criteria	**Participant Inclusion Criteria (at screening)** • Patients aged ≥ 16 years old **Participant Exclusion Criteria (at screening)** • Injuries affecting more than one digit, or the thumb • Injuries outside of Zone 2 • Injuries affecting multiple zones • Clinically infected wounds • Closed flexor tendon injury • Previous tendon, bone or joint injury in the affected digit • Patient does not have capacity to give informed consent • Patient unable to complete follow up requirements • Contraindication to surgery **Inclusion Criteria for randomisation (confirmed in surgery)** • Complete division of FDP and FDS in zone 2 of a single finger • Injury amenable to primary repair E**xclusion criteria for randomisation (confirmed in surgery)** • Injuries with loss of tendon substance or skin necessitating reconstruction • Division of both digital arteries resulting in revascularisation of injured digit • Division of both digital nerves

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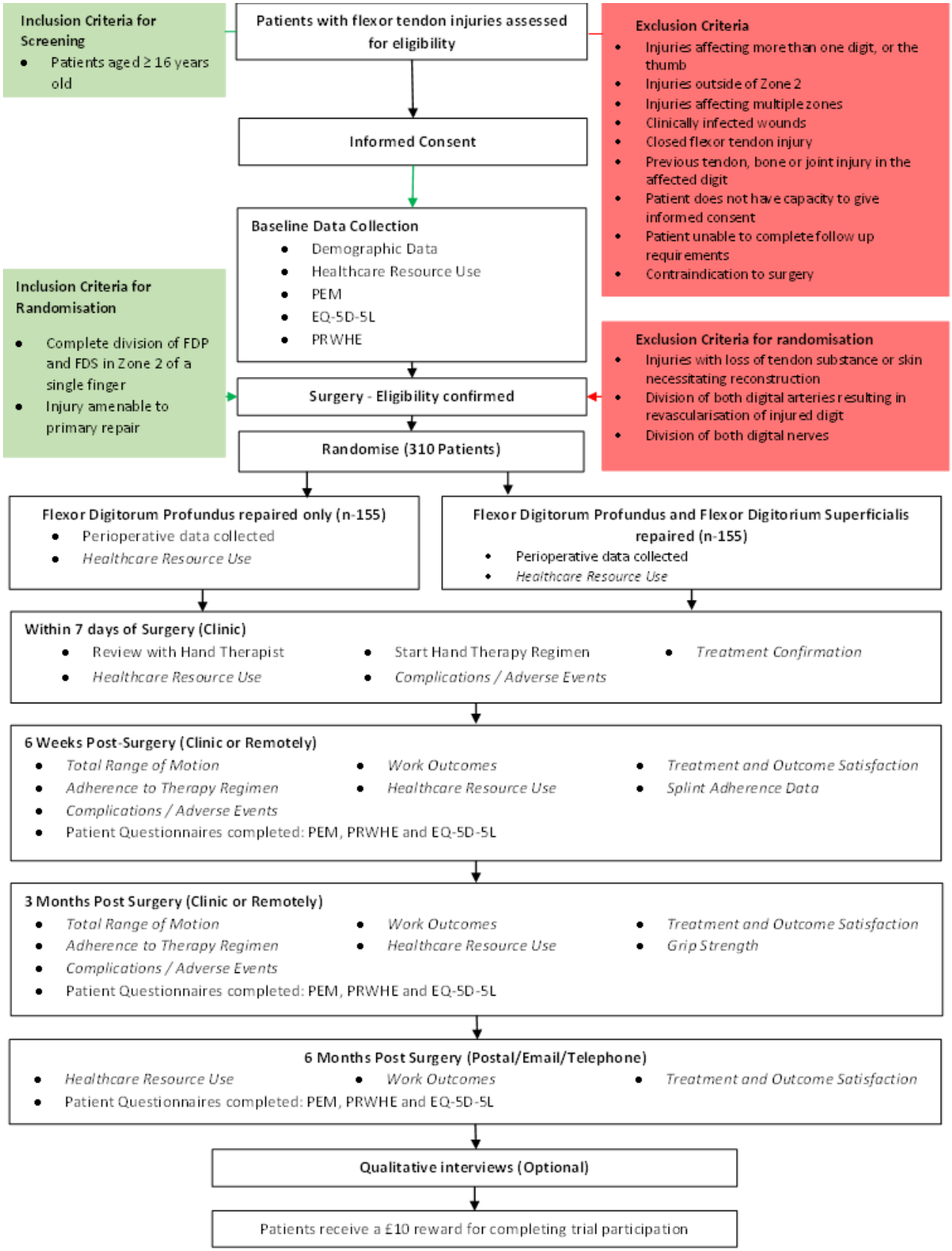
FLexor repAir and REhabilitation Trial (FLARE) Flow Chart

Figure 1: Trial Flowchart



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Study Assessment Schedule

Table 5: Study Assessment Schedule

Assessment	**Baseline**[1] *(face-to-face)*	**Randomisation / Surgery**	**Clinic Visit** *(Within 7 days of Surgical Intervention)*	**6 Week Clinic Visit**[2] *(face-to-face or remote)*	**3 Month Clinic Visit**[2] *(face-to-face or remote)*	**6 Month Remote** *(Participant Questionnaire by Email/Post/Telephone)*
Allowed variation in days				+/- 7 days	+/- 14 days	+/- 14 days
Eligibility Screen	X					
Informed Consent	X					
Demographics	X					
Randomisation		X				
Surgical Data *(including Epitendinous Suture Use)*		X				
Confirmation of Treatment			X			
Hand Therapy Review			X			
PEM	X[3]			X	X	X
PRWHE	X			X	X	X
EQ-5D-5L	X			X	X	X
Total Range of Motion				X	X	
Work Outcomes				X	X	X
Treatment and Outcome Satisfaction				X	X	X
Healthcare Resource Use	X	X	X	X	X	X
Adherence to therapy Regimen				X	X	
Splint Adherence				X		
Grip Strength					X	
Complications			X	X	X	X

[1] Baseline measures will be collected prior to randomisation

[2] This appointment may be virtual as part of routine practice

[3] Pre- and post-injury

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1. Background and rationale

1.1 General Introduction

In 1960, the renowned hand surgeon Claude E. Verdan stated, 'among the most difficult problems still to be solved in hand surgery, repair of flexor tendons in the digital sheath is not the least' [1]. He went on to say, 'most authors say it is wise not to undertake immediate tendon repair when both flexor tendons are divided in Bunnell's no man's land'. Sixty years on, repair and rehabilitation of flexor tendon injuries in zone 2 (no man's land) remains one of the most hotly debated topics in hand trauma surgery.

Repair and rehabilitation of zone 2 (Figure 2) flexor tendon injuries remain controversial because of the unique challenges provided by the anatomy and biomechanics. Unlike any other zone in the hand, there are two tendons running together in a tight flexor sheath. Repairs in this zone are technically difficult and there is a higher risk of scar tissue forming between the tendons.

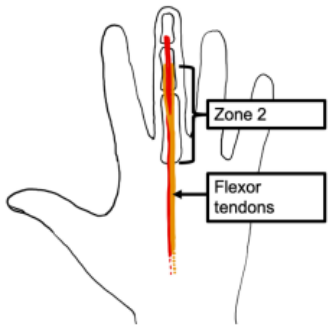

Figure 2: Schematic diagram showing the flexor zone 2 region in a left middle finger. The red tendon is flexor digitorum profundus (FDP) and the orange tendon is flexor digitorum superficialis (FDS).

Flexor tendon repair surgery

The finger flexor zone 2 contains two tendons. The flexor digitorum superficialis (FDS) tendon inserts on the middle phalanx and the flexor digitorum profundus (FDP) on the distal phalanx (see Figure 2). A national survey of open flexor tendon injuries in 2016 found a large majority of surgeons repaired both divided tendons in zone 2. More recent service evaluation, during the COVID-19 pandemic, found this proportion had fallen to half. The reduction in repairing of both tendons might be a result of the move to performing simpler surgery during the pandemic.

A systematic review of the literature for zone 2 flexor tendon repair identified three low quality studies investigating repair of FDP alone versus both FDP and FDS [2]. In 1994, Tang reported a small comparative study of 37 fingers with complete division of both tendons in zone 2C (FDS insertion) [3]. There was no difference in total active movement between the two groups at up to 12 months. Those fingers with both tendons repaired had a higher reoperation rate for rupture or adhesions. A more recent small randomised controlled trial (RCT) in a Hispanic population identified an improved range of movement with FDS repair at three months but no difference in any outcome at six months [4]. A small non-randomised comparative study of complete zone 2B (distal to A2 pulley) injuries found no statistical difference in total active or passive range of movement or power grip compared to the contralateral hand [5]. Since then, another non-randomised study of zone 2 tendon lacerations in 61 fingers found no differences in the functional outcomes when FDS (one or both slips) was repaired alongside FDP [6]. Repair of both tendons takes longer to complete and is likely to be more expensive [7-9]. Not repairing FDS might reduce the risk of scarring between the two

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tendons and allow better tendon gliding following repair [10]. These studies were likely underpowered and at high risk of bias. They do not address the existing clinical uncertainty. Surgical practice here can therefore be best informed by determining whether repairing FDP alone is not inferior to repairing both tendons.

Therefore, given the recent shift in routine surgical practice to leave FDS unrepaired and the lack of high quality RCT evidence, there is an urgent need for a definitive RCT on repair of FDP alone versus repair of both tendons to inform clinical practice.

Flexor tendon rehabilitation

Whilst the FLARE Trial no longer includes randomisation of the postoperative hand therapy regimen, it remains an essential part of the care delivered. The following section provides an overview of the rehabilitation regimens and justifies our intention to maintain a pragmatic approach to the postoperative hand therapy.

Similar levels of uncertainty surround rehabilitation of flexor tendons. A systematic review of zone 2 rehabilitation concluded there was a general acceptance that early active movement was beneficial but that further randomised trials comparing regimens were needed [11], which was confirmed by a recent Cochrane review [12].

There are three splint regimens currently used in the UK: long dorsal-blocking, short dorsal-blocking and relative motion flexion.

1.2 Rationale and Justification for the Study

Hand flexor tendon injuries are a common problem

Flexor tendon injuries lead to over 3200 hospital admissions in England and Wales each year [13]. The incidence is highest in young male adults resulting in substantial socioeconomic impact [14]. In the USA, the indirect costs of flexor tendon injury were estimated to be USD 112,888 [15].

Patients, hand therapists and surgeons have prioritised our research question

Patients and clinicians prioritised flexor tendon injuries in the James Lind Alliance Priority Setting Partnership for hand conditions. To gain further clarity, we consulted patients with experience of flexor tendon injury via focus groups from clinical practice, the NIHR 'People in Research', and 'myinjuredhand.com', a leading UK hand trauma patient information website. Their priorities were to regain full finger movement, receive a less restrictive splint and return to work quickly.

Zone 2 flexor tendon injuries cause significant morbidity in a working population

Over 70% of injuries are in healthy young men [16, 17]. Even following repair, our patient partners reported struggling to perform activities of daily living such as eating and washing. They relied heavily on friends and relatives for assistance. Rehabilitation takes at least 12 weeks and leads to prolonged time off work and loss of income, compounded by the expense of multiple hospital trips. This has ramifications for life satisfaction, wellbeing, self-worth, and mental health [18]. Prolonged rehabilitation is also expensive for the health service and wider society.

Current rehabilitation pathways cannot address national inequality

There is some evidence for inequality of service provision within musculoskeletal surgery in the UK [19]. Lane, Wormald and Rodrigues are currently leading a BSSH funded project to identify

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geographical variation in hand trauma service provision using a 20-year individual patient level data extract from the NHS Hospital Episode Statistics dataset. Personal communication with the NHS Get It Right First Time (GIRFT) initiative for hand surgery suggests there is significant variation in access to hand services, particularly in rural areas. Current guidelines remain heavily dependent on face-to-face meetings and the ability for patients to remain off work, which may contribute to this inequality. Our study will provide high quality evidence to support clinical decision making in all settings. These aspects will be explored in our nested qualitative study.

Zone 2 injury repair and rehabilitation is a priority

Complete division of tendons in zone 2 remains the most technically difficult and controversial injury to manage. Unlike other zones, restoration of tendon movement is challenging owing to the tight flexor sheath and intimate relationship between the two tendons. The aim of surgery and rehabilitation is a strong repair that allows early mobilisation and avoids the tendon re-rupturing or getting stuck (adhesion formation). There remains significant clinical variation in the surgical technique and rehabilitation for these injuries with no high-quality evidence to support decision making. Re-repair rates remain as high as 17% and 1 in 5 patients achieve only a fair or poor outcome [20].

1.3 Risks and Benefits of Flexor Tendon Repair

Both procedures will have the general surgical risks of wound infection, haematoma, bleeding, wound healing problems, damage to the adjacent structures such as nerves, blood vessels and tendons, the tendon rupturing after repair, and the repaired tendon sticking to nearby tissue.

Risks to participants from either treatment are not increased through trial participation. Measures, such as our emphasis on good practice and standardised protocols/care pathways throughout, are likely to reduce risk and could bring additional benefits.

Repairing both tendons might give more strength but there is an increased risk of a bent finger with less movement. Repairing one might give less strength but a better range of movement and is less expensive.

Within the trial, participants allocated to receive FDP repair alone may experience benefit through earlier recovery and return to work, though the purpose of the study is to provide evidence regarding this.

In the unlikely event that new information arises during the trial that may affect participant's willingness to take part, the Trial Steering Committee (TSC) will review this information to determine whether changes are required to the patient information leaflet. A revised consent form will also be produced if necessary.

1.3.1 COVID-19 Considerations

As part of capacity and capability assessments, participating sites will be asked that all interventions and follow-up can be safely delivered at site, following relevant clinical and government guidelines in place at the time. Each site will be asked to ensure that appropriate precautions are taken, and local and national guidelines are followed for all study-specific activities to limit any potential risks to participants and staff.

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Whilst patients testing positive for COVID on admission are not specifically excluded from the study, it may be that these patients will not be considered suitable for surgery. The decision will be that of the treating surgeon in line with any local restrictions in place at the time of surgery.

2. Aims and Objectives

2.1 Aim

To undertake a multi-centre, two-arm, parallel group, non-inferiority RCT to determine the clinical and cost effectiveness of whether FDP repair alone is not inferior to FDP and FDS repair, for treatment of recent complete zone 2 flexor tendon injuries in adult patients.

2.1.1 Primary Hypothesis

FDP repair alone is not inferior to FDP and FDS repair for the treatment of recent complete zone 2 flexor tendon injuries in adults based on the patient reported outcome Patient Evaluation Measure (PEM) at 6-months post-randomisation.

2.2 Objectives

Trial objectives are presented in Table 6. The primary objective is to ascertain the clinical and cost effectiveness of repairing FDP alone versus repair of both FDP and FDS for treatment of complete zone 2 flexor tendon injuries in adults.

Table 6: Trial Objectives

Objectives	Outcome measures	Timepoint(s)
Primary objective		
Determine the clinical and cost effectiveness of repairing FDP alone versus repair of both FDP and FDS for treatment of complete zone 2 flexor tendon injuries in adults	Patient Evaluation Measure	6 months
Secondary Objectives		
Undertake an 8-month internal pilot to obtain robust estimates of recruitment and confirm trial feasibility	Progression criteria (see section 3.1)	8 months
Assess and compare range of motion	ROM	6 weeks, 3 months
Assess and compare grip strength	Grip strength	3 months
Compare the complications of both types of repair	Complications and adverse event data	Up to 7 days, 6 weeks, 3 months
Assess and compare patient reported Patient Related Wrist/Hand Evaluation	PRWHE	Baseline, 6 weeks, 3 months, 6 months
Comparison of costs, quality adjusted life years and cost effectiveness of both interventions (repairing	Health resource use EuroQol EQ-5D-5L	Baseline, 6 weeks, 3 months, 6 months

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FDP alone or both FDP and FDS)		
Undertake an embedded qualitative study	Analysis of interviews with the trial participants. Analysis of interviews with hand surgeons and therapists.	6 months

3. Trial Design

The trial objectives will be addressed using a multi-centre, two-arm, parallel group, non-inferiority RCT with an internal pilot, economic evaluation and nested qualitative study. There will be an 8-month internal pilot to assess assumptions about recruitment and fidelity of implementation of the flexor tendon repair allocation. A report will be provided to the funder and, subject to approval from the funder (assuming feasibility has been established), we will proceed to the main trial.

The study has a total 22-month recruitment period, including an internal pilot phase of 8 months at the start followed by the main recruitment period. Recruitment will take place at up to 40 participating NHS Trusts. Following randomisation and treatment, all participants will be followed up for six months. This includes three clinic visits (either face-to-face or remotely) for data collection at up to one week, then six weeks and three months (visits should coincide with visits that occur as part of routine care) post-surgery and randomisation. Participants will be asked to self–report outcome data via completion of questionnaires at baseline, six weeks, three months and six months post-surgery by email, telephone or post, as per the study flow chart and schedule of assessments.

3.1 Pilot Study

We will undertake an 8-month internal pilot study to test our assumptions about recruitment and intervention fidelity to confirm whether the trial is feasible. Progression from pilot to main trial will be assessed against the following criteria: the ability to set up ten study sites, the ability to recruit trial participants at an acceptable rate and achieve a goal of at least 85% follow-up of recruited patients for the primary outcome at the six-month follow-up point. Pilot progression criteria are presented in Table 7: Progression Criteria for Internal Pilot over an 8 Month Duration.

Secondary reasons for undertaking the pilot will be to closely monitor operational aspects of the trial including participant eligibility and consent procedures, study activity and patient adherence. The target recruitment rate will be one patient per month at each recruiting site. We have taken a conservative estimate of a 50% recruitment rate but are reassured by the recent recruitment rate of 70% in the DRAAFT trial of distal radius fracture fixation [21].

In addition to addressing any recruitment issues, the pilot phase will allow revision of consenting materials and outcome collection. If needed, we will hold patient and surgeon focus groups to explore issues around trial conduct.

The internal pilot will be reviewed by the Data Monitoring Committee (DMC) who will review the pilot data and make a recommendation to the TSC and Trial Management Group (TMG) regarding any changes required and also to the funding body who will determine whether the study progresses to the full trial.

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Table 7: Progression Criteria for Internal Pilot over an 8 Month Duration

Progression Criteria	Target	Green	Amber	Red
Participant Recruitment	80	100%	75%-99%	<75%
Centres Open	10	10	7-9	<7
Randomisation rate/centre/month	1	1	0.7-1	<0.7
Primary Outcome Data Available	7	100%	85%-100%	<85%

4. Methods

4.1 Participants

Adults ≥16 years of age who have sustained an open flexor tendon injury to zone 2 of the hand only.

4.2 Study Setting

Patients will be recruited from NHS Hand Trauma Centres within the UK treating flexor tendon injuries and with capacity to support research activity. A list of all study sites will be maintained by the trial management team and held in the trial master file.

4.3 Selection of Patients

The flow of participants through the trial is illustrated in the study flow chart (Figure 1). Participants will be identified at the emergency department or hand trauma unit by the clinician and/or research nurse/practitioner, who will be responsible for recording and reporting information in the online data collection tool or case report forms (CRFs).

4.4 Ensuring equality, diversity and inclusion for study participants

It is important to offer all those who are eligible the opportunity to take part in the trial – we aim to match our trial participants to the population the research will serve. Therefore, we will ensure to include sites that serve typically underserved populations across a range of characteristics. For example, Wexham Park Hospital and The James Cook University Hospital are the lead sites and serve under-represented local populations on the basis of socio-economic position.

During site screening, we will assess the population served by each NHS Trust and alter our approach to recruitment accordingly. For example, to ensure provisions are made for the commonest languages spoken in particular areas. We are utilising web and text-based data collection in order to optimise engagement with those groups who are most likely to present with the flexor tendon injury.

We will collect anonymous data on the background of patients that are screened including age, sex, ethnicity, and socioeconomic position amongst other attributes in order to monitor the results of our inclusion strategies and identify any areas for further intervention.

We will revisit the INCLUDE roadmap [22] throughout the study period and adjust our approach to recruitment, retention and collection of primary outcome data accordingly.

We will have an ongoing dialogue with our Patient and Public Involvement (PPI) representatives in order to inform our approach to inclusive recruitment and retention.

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4.5 Eligibility Criteria

We will include all adult patients (16 years or older) with an open flexor tendon injury, who meet the eligibility criteria below.

Any questions raised about eligibility will be addressed prior to entering the participant into the study. There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study.

4.5.1 Participant Inclusion Criteria (at screening)

- Patients aged ≥ 16 years old

Inclusion Criteria for randomisation (confirmed in surgery)

- Complete division of FDP and FDS in zone 2 of a single finger
- Injury amenable to primary repair

4.5.2 Participant Exclusion Criteria (at screening)

- Injuries affecting more than one digit or the thumb
- Injuries outside of Zone 2
- Injuries affecting multiple zones
- Clinically infected wounds
- Closed flexor tendon injury
- Previous tendon, bone or joint injury in the affected digit
- Patient does not have capacity to give informed consent
- Patient unable to complete follow up requirements
- Contraindication to surgery

Exclusion criteria for randomisation (confirmed at surgery)

- Injuries with loss of tendon substance or skin necessitating reconstruction
- Division of both digital arteries resulting in revascularisation of injured digit
- Division of both digital nerves

Injuries are restricted to zone 2 as it is the most common injury and most challenging to manage owing to both tendons running in the flexor sheath.

Unilateral digital nerve injuries will be accepted on a pragmatic basis as they are often injured in addition to the flexor tendon. A recent study suggests digital nerve injury does not affect the outcome of zone 2 flexor tendon injuries [23].

Thumb injuries are excluded owing to the anatomy. There is a single thumb flexor tendon, and flexor sheath anatomy differs to the fingers. The rehabilitation regimen also differs.

4.5.3 Co-Enrolment

Co-enrolment is not permitted between patients who are taking part in the FLARE Trial and the FIRST Trial.

We will not exclude participants who are enrolled in any other study that allows co-enrolment provided that there is no direct conflict between the two studies or likely influence on the outcome of the FLARE study.

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4.6 Interventions

Eligible and consenting patients will be randomly allocated to receive tendon repair using FDP repair alone or FDP and FDS repair.

Participants will undergo treatment as per the randomisation allocation schedule under the care of one of the participating surgeons.

4.6.1 Surgical Intervention

Study treatments should be given as soon as practical following recruitment. The timing of treatment is determined by local service pressures, however standard care is to surgically explore the wound and repair the tendons within 72 hours of presentation.

Surgical exploration and washout will be undertaken for all consenting patients. Patients that are confirmed as eligible during surgery will be allocated to receive either FDP repair alone or repair of both FDP and FDS.

A minimum 4 strand core suture will not be mandated but the number of strands will be recorded. A 4-strand core repair is standard practice for 80% of surgeons in the UK. An epitendinous suture (a suture around the outside edge of the tendon) will not be mandatory but if done will be recorded. Suture choice and technique will be pragmatic. Intraoperatively, surgeons will ensure excursion of the repaired tendon(s) through a full range of movement. Tendon sheath and pulleys will be released as needed to allow unimpeded gliding. Concomitant single digital nerve injuries will be repaired.

Choice of anaesthetic will be pragmatic and based on patient and surgeon preferences and availability.

Post-operative care will be in line with routine practice at the participating site. Usually, the wounds will be dressed and a plaster of Paris dorsal blocking splint applied.

4.7 Rehabilitation and Hand Therapy

The post-operative rehabilitation will be pragmatic and follow routine practice at individual participating sites across both treatment groups.

Participants are usually seen within seven days of their surgery by a hand therapist. All rehabilitation input will be left to the discretion of the clinical care team.

During the first four to six weeks, a splint is used to provide protected finger range of movement to reduce the risk of tendon repair rupture. The participant will follow a regimen using a dorsal blocking splint or a relative motion flexion splint with wrist splint. The choice of splint will be in discussion with the patient and therapist.

To supplement standard rehabilitation advice, all trial participants will receive standardised, hand therapy information detailing the types of exercises they may perform for rehabilitation following their injury.

A record of rehabilitation input (type of input and number of additional appointments) together with any other required investigations/interventions will be self-reported by trial participants as part of the follow up questionnaires and supplemented by data recorded at clinic visits by therapists or research staff.

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Participants will be asked to complete a questionnaire to document their splint adherence.

4.8 Assessments and Follow-Up

Trial participants are expected to be enrolled in the study for up to six months for follow-up. Qualitative interviews may take place after the six-month time point so as not to interfere with patient reported measure at that point.

The study assessment schedule is provided at the beginning of the protocol (see Table 5). All participants will be followed up within seven days of their surgery and then again at six weeks, three months and six months post-surgery.

All visits up to and including the three-month visit will take place where possible as a face to face visit as most centres have a routine three-month patient follow-up in clinic.

In the event of local restrictions arising from COVID-19, or where remote visits are conducted as part of routine care, trial visits may be conducted remotely via telephone or video call.

Trial participants should also attend any routine clinical appointments that may be scheduled outside of trial visits, in line with the routine care pathway at the participating site.

4.9 Outcomes

4.9.1 Primary Outcome

The primary outcome will be the Patient Evaluation Measure (PEM) score at six months post-surgery.

PEM is widely used in NIHR funded hand trauma studies and is the main PROM used for flexor tendon injuries in the BSSH UK National Hand Registry. The questionnaire assesses the process of treatment, current state of the hand, and a general assessment. The PEM asks questions relating to symptoms, satisfaction and general disability, which generates a percentage, ranging from 0%-100%, to determine a disability score [24].

PEM will also be collected at baseline, six weeks and three months post-surgery in line with the study assessment schedule (see Table 5)

4.9.2 Secondary Outcomes

Secondary outcomes will be collected at baseline, six weeks, three months and six months post-surgery in line with the study assessment schedule (see Table 5).

These timepoints will enable identification of early complications and later re-operations and gather data to inform resource use and work impact.

- PRWHE: is a 15-item questionnaire used to assess hand pain and disability in day-to-day activities. The questions themselves evaluate level of pain and functionality; 5 questions revolve around pain levels and 10 focus on activities. A score of 100 indicates worst functional score whereas 0 represents no disability [25].
- EuroQol 5 Dimensions (5L) Score (EQ-5D-5L): measures health-related quality of life in terms of 5 dimensions: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, anxiety and depression. The EQ-5D-5L will be scored according to the User Guide [26]. EQ-5D-5L data will be collected at baseline to assess patient health related quality of life on the day (after the injury).

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- Complications: Information on all complications will be collected. Expected complications that will be recorded will include (but not be limited to) deep wound infection, (using Centres for Disease Control (CDC) and Prevention definition [27] superficial infection using CDC definition), rehospitalisation, nerve and skin problems.
- Total range of motion: Degree of movement at a joint. Measured with a goniometer.
- Grip strength: Grip Strength will be measured with a JAMAR Dynamometer. Both hands will be assessed. Three recordings will be performed on each side and the maximum of these three readings will be used. The measurement will be done with the subject seated, arm by the side, elbow bent at 90 degrees and the wrist in neutral position for rotation [28]. The second setting will usually be used for all subjects but patients with large hands may occasionally need to use the third setting. This reflects common practice and evidence-based practice in assessing grip strength [29]. Strength will be expressed as a % of opposite side to account for normal variation in strength during the day.
- Adherence to splint regimen. Patient self-report.
- Work outcomes. Patient self-report.
- Treatment and outcome satisfaction. Net promotor score
- Healthcare resource use: An accurate record of procedures at hospital level will be put in place in order to record the cost of each type of surgery and related complications via a surgical form specifically designed for this trial. Patient-reported questionnaires and hospital forms will be designed to collect information on hospital stay- (initial and subsequent inpatient episodes, outpatient hospital visits and A&E admissions); primary care consultations (e.g. GP, nurse and physiotherapy); work impact of both interventions; and return to work and return to normal activities.
- Adherence to therapy regimen

4.10 Qualitative Study

4.10.1 Recruitment Optimisation

Existing recruitment optimisation interventions are costly and resource intensive [30, 31] or take place after key design decisions have been made [32]. We therefore plan to undertake low-cost, rapid, recruitment optimisation work, making use of routinely collected trial information and rapid qualitative work to identify potential recruitment problems in our trial.

This mixed-methods recruitment optimisation work will be undertaken during the FLARE trial's set-up and internal pilot phase so that any findings can be used to improve our approach to recruitment during the main FLARE study. Data collection will include:

1. N=10 (approximately) brief qualitative interviews with key stakeholders (including chief investigators (CIs) from FLARE and other key NIHR funded hand trials; FLARE clinical co-applicants and CTU staff). These interviews will use participants' experiences of setting up the FLARE trial to identify key obstacles to recruitment. We will also conduct interviews with CIs from other high profile hand surgery trials that were closed early due to recruitment difficulties to explore any common challenges facing hand surgery trials and lessons learned.

2. Record and review Trial Management Group Meetings to keep abreast of any challenges that are occurring during the trial's set-up period.

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3. Record and review study checklists and other key trial documents (e.g. Expression of Interest forms sent to all eligible sites, Site Initiation Visit meeting minutes and correspondence; notification of study closure documents for recently closed trials) where appropriate.

Information obtained through interviews and key trial documents will be used to identify the key issues that FLARE may face with regard to recruitment, based on information from the set-up phase and internal pilot period and experience from other recent NIHR-funded hand surgery trials. This information will be combined and used to troubleshoot and develop strategies for overcoming any potential recruitment issues ahead of the main FLARE Trial.

Analysis of this information will be rapid and undertaken concurrently with data collection to allow initial troubleshooting. To facilitate this a standing agenda item on all TMG meetings, along with weekly project meetings will be held to facilitate the development of strategies for overcoming any issues identified. Where patient related factors are raised, PPI members will be engaged to strategize solutions.

At month 8, prior to the start of the main study, all information collected during the initial recruitment optimisation exercise will be integrated into the trial procedures. These research informed trial processes will be monitored over the coming months as the study progresses and will be under ongoing review and adapted further as appropriate. Feedback will be given directly to sites in this phase of the work via meetings with the trial manager/chief investigators where issues emerge.

4.10.2 Treatment Acceptability

The FLARE trial will also include a nested qualitative study. We propose to interview (n= 40) trial participants, following the primary outcome measurement at six months post-surgery. The purpose of these interviews is to ascertain vital information relating to acceptability and experience of the surgical procedure and the rehabilitation regimens.

Whilst our Patient and Public Involvement PPI work ascertained that patients would be prepared to be randomised to either single or double flexor tendon repair, there were some concerns raised relating to the potential safety of not repairing both tendons. This aspect will be explored in the qualitative work. In addition, patient views on the anaesthetic procedure used given the rapid adoption of the 'wide awake local anaesthetic no tourniquet' (WALANT) during the COVID pandemic. Our initial PPI work indicated that patients felt anaesthetic type was not important for their overall outcome but was important for patient experience and choice. We will therefore use anaesthetic type as a sampling criterion in the qualitative sampling frame and explore patient preferences and experience of anaesthetic in the interviews.

Provision of a splint and rehabilitation post-surgery is a vital part of flexor tendon repair. As three different splints are available as part of usual care following surgery, the qualitative interviews will capture the factors important to patients regarding the choice of splint and how any preferences impact on decision-making relating to the selected rehabilitation regime. As outlined in the brief, compliance to splint wearing and rehabilitation regimes is known to be problematic among this group of patients. It is important that this aspect is factored into our study design, in addition to quantitative measures of adherence we will explore this in the qualitative interviews with patients. In particular, to highlight barriers and facilitators to splint/rehabilitation compliance that can be used to inform clinical practice alongside the trial findings.

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In addition will we conduct semi-structured interviews with hand surgeons (n=10) and hand therapist (n=10), data collection will focus on their experience of delivering the intervention, challenges/facilitators associated with delivery of trial interventions and what information/training would be required in order to implement the findings from the trial across the NHS.

Semi-structured interviews will be conducted using either telephone, videoconference (e.g. Microsoft Teams or Zoom) or face-to-face, according to respondent preferences and practicalities. A topic guide will be developed in consultation with our PPI representatives. With permission, interviews will be recorded and transcribed verbatim. Anonymised transcripts will be transferred into analysis software to support management and retrieval of data. Data analysis will follow the principles of thematic analysis, providing an interpretive exploration of the experiences, attitudes and beliefs of different stakeholder groups [33]. Emerging codes and themes will be discussed as a team.

4.11 Participant Recruitment

The research team will work closely with the clinicians and research staff at each recruiting site to optimise the screening and recruitment procedures for their local circumstances.

All members of staff involved in eligibility sign-off and the informed consent process (including surgeons) will have training in Good Clinical Practice (GCP) or study specific training.

The NIHR Associate Principal Investigator (API) scheme will be utilised at participating sites to involve aspiring researchers to co-ordinate study recruitment. The APIs will be trained in study processes and will be supervised by the PI at the site. Participating sites will be encouraged to involve APIs, particularly ''out of hours'' (evenings and weekends) when research staff may not be available.

Potential participants will be provided with information about the study including a patient information sheet (PIS) at the earliest possible opportunity following presentation.

4.11.1 Recruitment Strategy

The recruitment projection for the main trial is based upon recruiting one patient per month per site based on the BSSH Flexor Tendon Audit (with an assumed consent rate of 50% of eligible patients). With staggered centre set-up and fewer recruits in the first months of site set-up, 80 patients will be recruited by month eight. The remaining 230 patients will be recruited over a further 14 months.

4.11.2 Study within a trial (SWAT)

The FLARE trial will act as a host trial for an embedded Study Within A Trial (SWAT), which aims to look at an intervention to improve recruitment.

Many interventions to improve recruitment at sites, such as site champions and incentivising clinicians with non-financial benefits are routinely used but do not have any evidence of their effectiveness. One way to provide a rigorous evaluation and evidence is to conduct a Study Within a Trial (SWAT) [34].

The objective of the SWAT is to evaluate the effect on recruitment rates using two interventions: Enhanced Associate Principal Investigator Package, and Digital Nudging.

Trainee APIs will be randomised to one of four interventions. 1) Enhanced API intervention, 2) Digital nudge email from trial coordinator, 3) both enhanced API intervention and digital nudge, 4) usual practice without enhanced API or digital nudge.

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The primary outcome will be the number of recruits at a site during the six months the API is in post. A secondary outcome will be the total number of recruits over the six months following the API being in place.

Analysis will be conducted on an intention to treat basis. A Poisson regression model, containing the two interventions (enhanced API and digital nudge) and the minimisation factors (site size, and number recruited prior to SWAT implementation included in their continuous form) will be performed. Feasibility outcomes will be reported descriptively.

The FLARE SWAT protocol will be registered on the Northern Ireland MRC Trials Hub for Methodology Research SWAT registry.

The results will be combined in a meta-analysis with those of SOFFT (ISRCTN 87904264) to increase the power of the analysis.

4.12 Screening and Recruitment Procedures

Eligible patients usually present to either an emergency department or equivalent before referral to a hand surgeon. Surgeons or research team members will identify and screen potentially eligible patients. Those with findings suggestive of flexor tendon injury on clinical assessment (straight finger with a cut and inability to bend) will be invited to participate. The patient will be provided with information about the trial and have the opportunity to ask the surgeon or research team member questions before deciding on participation.

All flexor tendon injury cases treated during the recruitment period will be recorded on the screening log or data collection tool and it will be noted whether the patient has been recruited into the trial or not. If the patient has not been recruited to the trial, the reason for this will be recorded e.g. ineligible (with reason for ineligibility), unwilling to consent.

Screening data will be collected by all participating sites to capture the number of ineligible or non-consenting patients at each site. By doing so, the trial team can identify potential areas to target to improve recruitment rates, as necessary.

Final confirmation of eligibility for the study will be completed at surgery by a delegated surgeon.

If the patient is found to be ineligible at surgical intervention, they will not proceed to be randomised, research activity for the patient will stop and the patient will be informed that they will not be continuing in the study. This will be highlighted to patients during the informed consent process. The patient will continue to receive appropriate surgical management for their tendon injury.

4.13 Informed Consent

Informed consent will take place prior to the baseline assessment being undertaken, and before surgery or randomisation.

Patients will be provided with a detailed written or online PIS, outlining the nature of the study and what it will involve for them. The information provided will clearly explain the risks and benefits of trial participation. It will be clearly stated that participants are free to withdraw from the study at any time and for any reason without prejudice to future care. Permission will be sought to inform the patient's GP of their participation in the study.

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The patient information will be made available in different formats as required (e.g., electronic or paper participant information sheets, narrated, and animation). For patients unable to read, narrated versions or voice-assisted software will be used as available through the NHS given that patients will be recruited in hospital settings. For patients unable to speak English, sites will use either a translator or telephone translation service depending on local availability.

Responsibility for recording written or electronic informed consent will be with the site PI, or staff designated by the PI, who conducted the informed consent discussion. Designated responsibility should be recorded on the site delegation log.

Potential participants will be given a contact phone number, so that they have the opportunity to ask questions of clinical staff and to discuss the trial with friends/family prior to agreement to take part. Patients will have the opportunity to ask questions to the clinical and local research team before written or electronic consent for the study is obtained. The patient will be asked at the time of approach whether they have had sufficient time to consider participation and whether they agree to consent at that time; if required, they will be given further time to reach a decision on whether to take part. Depending on local circumstances, consent will be obtained in advance of, or on the day of admission for the procedure. Appropriately delegated research staff or clinicians will obtain written or electronic informed consent.

Participants will have the right to withdraw from the study at any time. The reason for withdrawal will be recorded, where given, in the data collection tool.

Specific consent will be sought to enable the sharing of identifiable data with York Trials Unit (YTU), based at the University of York as part of the study in order to facilitate the collection of outcome data.

Consent for participation in the qualitative element of the study will be sought separately.

Consent will be sought from participants for follow-up beyond the duration of the trial using linkage to routinely collected data sources such as Hospital Episode Statistics (HES) and Office of National Statistics (ONS) data and UK Hand Registry (UKHR). This will enable the longer-term outcome following intervention to be identified from both the perspective of serious adverse events and patient reported outcomes.

In the unlikely event that new information arises during the trial that may affect the participants' willingness to take part, this will be reviewed by the Trial Steering and Data Monitoring Committee for addition to the participant information sheet. A revised consent form will also be completed if necessary.

All consent forms will be stored in accordance with local requirements. A copy of the signed consent form will be given or emailed to the participant, a further copy filed in the patient medical records and the original signed copy kept in the Investigator Site File (ISF). A copy will be sent through an agreed secure method to YTU or uploaded onto the data collection database (REDCap) for central monitoring purposes.

4.14 Randomisation and Enrolment Procedure

Participants will be randomised in theatre following final confirmation of eligibility. A member of the clinical or research team delegated to treatment allocation (randomising) will enter the relevant

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data into an online randomisation system when the patient is in theatre and inform the operating surgeon of the allocation details.

An independent statistician at YTU, who is not involved in the recruitment of participants, will generate the allocation sequence. Stratified block randomisation will be used with randomly varying block sizes. Patients will be randomly allocated 1:1 to receive either FDP repair alone or repair of both FDS and FDP tendons (refer to section 5.5.1).

Consideration will be given to communication of the allocation to the operating surgeon in order to protect the blinding if the patient is not under general anaesthetic.

Web-based randomisation will ensure allocation concealment and immediate unbiased allocation.

4.15 Blinding

The operating surgeon and theatre staff will be informed of the randomisation result in order to complete the treatment.

Participants will not be informed which treatment they have received, and the surgical wound is the same.

Site clinical and research team staff will be blinded to the allocation. A code break procedure for clinical care or safety reporting will be in place.

Outcome assessments will be performed wherever possible by assessors unaware of treatment allocation. Post-operative rehabilitation and exercises will be according to standard of care at the participating site in both groups, which means therapists can remain blinded.

The primary outcome is the Patient Evaluation Measure (PEM), which is a patient reported outcome measure, helping mitigate surgeon or outcome assessor influence.

Data on patient preferences will be collected at baseline.

Six months after randomisation, participants will be asked which surgical treatment they think they underwent to assess the success of participant blinding.

Participants will be given opportunity to find out which treatment they have received once the primary outcome has been collected and their participation in the trial has ended. At this point, the research team will send the participant a letter/email to inform them of the treatment they received where requested.

4.16 Participant Payment

The pragmatic nature means that study visits align with visits that are part of routine care so travel to hospital for the purposes of the trial alone is not anticipated.

Participants will report outcomes online. In the event of postal data collection pre-paid envelopes will be provided.

Participants will be given £10 (cash or voucher) as a goodwill gesture once their involvement in the study is completed.

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5. Data Management

5.1 Data Collection Methods

Data will be collected at baseline, within 1 week, 6 weeks, 3 months and 6 months post-surgical intervention. Baseline data will be collected at recruiting sites by a member of clinical and/or research staff. Data collected at the follow-up visits (1 week, 6 weeks and 3 months post-surgical intervention) will be collected by delegated hand therapists and/or research staff. Patient reported outcomes will be collected via questionnaire completion at 6 weeks, 3 months and 6 months via email, telephone or postal questionnaire.

YTU will manage the participant reported data collection. All reporting of data collection will be undertaken in line with the Consolidated Standards of Reporting Trials (CONSORT) statement. To minimise attrition, we will use multiple methods to keep in touch with participants. We will ask participants, for full contact details (including mobile phone number and email address if available) for the purpose of data clarification and data collection follow up.

A text message reminder will be sent on the day that participants are expected to receive their postal questionnaire or shortly after the online questionnaire is due to be completed.

We will also send 2 and 4 week email reminders where required. Where these methods fail there will be a final attempt to obtain data via telephone, prioritising the primary outcome measure. If a questionnaire is returned to YTU and the primary outcome data are incomplete or contain errors, we may telephone participants for clarification or completion of missing data.

We will also write newsletters during the trial to keep the participants informed and engaged with the trial, which can enhance response rates.

5.2 Data Entry

The data collected by sites will be entered onto a secure online Research Electronic Data Capture (REDCap) interface, specifically developed for this study [35, 36]. For data that are collected via participant report only the study data in REDCap will be the source data.

Data not captured on REDCap, will be stored and transferred following YTU standard operating procedures and/or University of York policies. The staff involved in the trial (both at the sites and YTU) will receive training on data protection. The staff will be monitored to ensure compliance with privacy standards.

Computerised data cleaning and validation checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

Data will be checked according to procedures detailed in the trial specific Data Management Plan or REDCap CRF Specification document.

An electronic audit trail system will be maintained within the data collection system to track all data changes in the database once the data has been saved initially into the system or electronically loaded.

5.3 Data Storage

All Investigators and study site staff involved with this study must comply with the requirements of the General Data Protection Regulation (GDPR) (2016/679) (2018), the Data Protection Act (2018),

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and the Caldicott Principles with regard to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the regulation(s).

Data will be collated in CRFs with participants identified by a unique identification number (i.e. the participant identification number) only. A Trial Enrolment Log at the sites will list the participant identification numbers. YTU will maintain a list of participant identification numbers for all trial participants at each site.

At the University of York, data will be held securely on the cloud-hosted REDCap server. Access to the study interface will be restricted to named authorised individuals granted user rights by a REDCap administrator at YTU.

Data not within REDCap will be hosted on University of York servers. All YTU data recorded electronically will be held in a secure environment at the University of York, with permissions for access as detailed in the delegation log.

Backups are taken daily and stored in a separate location. Snapshots are also taken at regular intervals throughout the day.

The University's backup policy can be found here: https://www.york.ac.uk/it-services/services/backups/#tab-4.

All study files will be stored in accordance with Good Clinical Practice guidelines. Study documents (paper and electronic) held at the YTU will be retained in a secure (kept locked when not in use) location for the duration of the trial. All essential documents, including source documents, will be retained for a minimum period of five years after study completion. The separate archival of electronic data will be performed at the end of the trial, to safeguard the data for the period(s) established by relevant regulatory requirements. All work will be conducted following the University of York's data protection policy which is publicly available (https://www.york.ac.uk/records-management/dp/).

5.4 Data Quality Assurance and Quality Control

South Tees NHS Foundation Trust have agreed to be the sponsor for this project and take overall responsibility for the quality of study conduct. This study will be fully compliant with the Research Governance Framework [37] and MRC Good Clinical Practice Guidance [38].

A rigorous programme of quality control will be undertaken. The day-to-day management of the trial will be the responsibility of the Trial Coordinator based at YTU. Regular meetings with the Trial Management Group will be held and will monitor adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by YTU to ensure integrity of randomisation, study entry procedures and data collection.

5.4.1 Direct Access to Source Data/Documents

The Investigator(s)/institution(s) will permit authorised representatives of the Sponsor and applicable regulatory agencies direct access to source data/documents to conduct trial-related monitoring, audits and regulatory inspection. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

Essential trial documentation (i.e. the documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced) will be kept with the Trial Master File (TMF) and Investigator Site Files (ISF). The Sponsor will ensure that this

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documentation will be retained for a minimum of five years after the conclusion of the trial to comply with standards of Good Clinical Practice.

At YTU, the CRF data will be stored for a minimum of five years after the conclusion of the trial as paper records and in electronic format in accordance with guidelines on Good Research Practice [39]. All paper records will be stored in a secure storage facility or off-site by YTU. All electronic records will be stored on a password protected server.

The PI at any participating site will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement or Organisational Information Document.

Once reporting and analysis are completed and published in all intended scientific journals, the anonymised data will be made available for other researchers if requested.

In principle, anonymised data will be made available for meta-analysis and, where requested by other authorised researchers and journals, for publication purposes. Requests for access to data will be reviewed by the co-Chief Investigators, study Sponsor and trial team.

5.4.2 Source Data List

The data collected by sites will be entered onto a secure online REDCap interface. For data that are collected via participant report only the questionnaire (completed on paper or in REDCap) will be the source data. Table 8: Source Data provides details of the data to be collected and source documents.

Table 8: Source Data

Type of Data	Source Document
Informed Consent	Informed Consent Form
Relevant Medical History and Current Medical Conditions	Patient Medical Records
Fulfilment of Eligibility Criteria	Patient Medical Records
Demographics	Patient Medical Records/Patient Self-Report
Patient Evaluation Measure (PEM)	Patient Completed Questionnaire (at baseline, 6 week, 3 months and 6 months)
Patient Rated Wrist and Hand Evaluation (PRWHE)	Patient Completed Questionnaire (at 6 week, 3 months and 6 months)
EQ-5D-5L Questionnaire	Patient Completed Questionnaire (at 6 week, 3 months and 6 months)
Health Economic Data	Patient Medical Records / Patient Completed Questionnaire
Treatment and Rehabilitation Data	Patient Medical Records and Patient Questionnaires

5.5 Statistical Considerations

5.5.1 Method of Randomisation

Eligible participants will be randomly allocated in a 1:1 ratio to either the intervention (repair of FDS only) or control (repair of both FDS and FDP) group, using block randomisation stratified by study site with randomly varying block sizes. An independent statistician at YTU, who is not involved in the recruitment of participants, will generate the allocation schedule. The allocation schedule will be generated in STATA v 17 or later.

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Randomisation will be completed in theatre and treatment will be allocated on an individual patient basis.

Randomisation will be carried out using REDCap.

5.5.2 Determination of Sample Size

There will be a 22-month recruitment period for the FLARE trial. The total target sample size will be 310 participants.

A six-point difference on the Patient Evaluation Measure (PEM) represents the threshold at which treatment differences become important (based on observational data from patients with Dupuytren's contracture for the DISC trial (HTA 15/102/04)). However, recent analysis within a flexor tendon population has found a seven-point difference on the PEM to be important and thus represents an appropriate non-inferiority margin to be used in this population. For 90% power and alpha=0.025, 310 participants are required to establish noninferiority within a margin of 7 points on the PEM (SD=17; upper 80% confidence limit (22)), based on the lower limit of a 95% two-sided confidence interval (equivalent to a one-sided 97.5% CI) and 20% attrition.

5.5.3 Pilot Phase Analysis

The recruitment rate and 95% confidence interval (CI) will be estimated from the data collected. A CONSORT diagram will be constructed to show the flow of participants through the study and the following outcomes calculated: number of patients screened, number of eligible patients; proportion of eligible patients approached for consent; proportion of eligible patients not approached and reasons why; proportion of patients approached who provide consent; proportion of patients approached who do not provide consent; proportion of patients providing consent who are randomised; proportion of patients randomised who do not receive the randomly allocated treatment; proportion of patients dropping out between randomisation and follow-up; proportion of participants for whom a primary outcome is recorded. Data will be summarised on the reasons why eligible patients were not approached, reasons for patients declining to participate in the study; reasons why randomised participants did not receive their allocated treatment and reasons for drop-out, if available. Results will be compared against the study's recruitment assumptions and progression targets using a traffic light system.

5.5.4 Statistical Analysis

For the analysis of the main trial, a CONSORT flow diagram will be provided to display the flow of participants through the study. The number of participants withdrawing from the trial will be summarised with reasons where available.

Baseline characteristics will be presented descriptively by group. All outcomes will be reported descriptively at all collected time points. Continuous data will be presented using means and standard deviations or medians and ranges as appropriate, and categorical data will be presented using frequencies and percentages.

The primary analysis will be on an intention-to-treat basis, analysing participants in the groups to which they were randomised. We will compare the Patient Evaluation Measure (PEM) scores between groups using a covariance pattern mixed-effect linear regression model, incorporating post-surgery time points (six weeks, three and six months). Treatment groups, time point, treatment-by-time interaction and baseline covariates (such as digital neve injury and anaesthetic type) will be included as fixed effects. Participant will be included as a random effect accounting for repeated

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observations per patient. Estimates of the difference in PEM scores will be extracted for each time point (primary six months) and overall with two sided 95% Cis (equivalent to a one-sided 97.5% CI) and p-values. Completeness of data at follow-up will be reported by group. In non-inferiority comparisons the ITT analysis could bias towards the null, which may lead to false claims of non-inferiority, hence we will undertake both ITT and CACE (complier average causal effect) analyses.

Total range of movement will be analysed using a similar covariance pattern model as used for the primary analysis. Differences in binary outcomes (e.g., tendon ruptures, re-operation and surgical site infection) will be analysed by logistic regression models. Differences in grip strength will be analysed by a linear regression model. Adverse events will be reported by allocation and overall, with further summaries of this data by type of event, relatedness to study treatment and expectedness. Treatment and outcome satisfaction will be analysed descriptively.

Full analyses will be detailed in the trial's statistical analysis plan (SAP), which will be reviewed and approved by the trial steering and data monitoring committees and finalised before the end of participant follow-up.

5.5.5 Health Economic Analysis

The economic evaluation consists of a within trial cost utility analysis (CUA) to assess the relative cost-effectiveness of repairing FDP alone or both FDP and FDS in patients with division of both tendons in zone 2. Costs and health outcomes associated with the interventions will be collected alongside the study.

The healthcare resource data (i.e. diagnostic procedures, surgery, anaesthetic, rehabilitation, additional surgical procedures, hospital visits and primary and community care) will be collected using patient self-administered questionnaires and hospital forms. Unit costs will be sourced from appropriate national sources. The trial will also assess the impact of both treatments on days of lost employment and unpaid activities.

The primary outcome for the economic evaluation is EQ-5D-5L collected from the trial at baseline and each follow-up and will be used to estimate quality-adjusted-life-years (QALYs) up to 6 months. We will use the area under the joining all EQ-5D utility scores to calculate QALYs scored by the UK tariff as recommended by NICE at the time of analysis.

The economic evaluation will present the cost per QALY gained, which would allow the cost-effectiveness of the strategies evaluated to be compared within the context of published National Institute for Health and Care Excellence (NICE) cost-effectiveness thresholds. This enables the decision-maker to assess the relative value for money when allocating a health care budget. We use an NHS and PSS perspective following NICE guidance. The standard perspective is adopted to ensure a level playing field when comparing the cost-effectiveness with other competing interventions. Wider social costs will be presented as a secondary analysis to explore the impact of productivity costs and unpaid activities on cost effectiveness results. This analysis provides additional supporting cost data but is not included in the base case as per NICE guidance.

Regression methods will be used for the incremental CUA analysis as this allows differences in prognostic variables. A range of sensitivity analyses will be conducted to test the robustness of the results under different scenarios, including probabilistic sensitivity analyses. The methods will follow the reference case set out by NICE.

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A detailed a priori health economics analysis plan (HEAP) will be developed at the start of recruitment and which will be followed to pre-specify the analysis and ensure an unbiased and rigorous analysis. Cost domains and outcomes are specified before the data is accessed to guarantee integrity. The document will include methods for dealing with missing data and the sensitivity analyses that will be used to assess the robustness of the cost-effectiveness ratio.

5.6 Project Management and Data Monitoring

5.6.1 Project Management

The project will be sponsored by South Tees Hospitals NHS Foundation Trust.

Each site will have a site PI who will be responsible locally for the study and where possible an Associate PI (API) who will be a trainee surgeon or another appropriate member of the research team. APIs will be encouraged to register with the NIHR API scheme.

YTU is undertaking the duties formally delegated by the trial Sponsor.

The trial manager at YTU will be responsible for all aspects of trial management. They will be supported by a trial co-ordinator(s), who will be responsible for the day-to-day support of trial sites, coordinate recruitment, data handling, and the management of the administrative trial team. The team at YTU will meet on a regular basis during the study and will work closely with the co-chief investigators (CIs), particularly at the start of the project and during the internal pilot of the study, including regular teleconferences to ensure that all aspects of preparation of study material, study site setup and the start of recruitment progress smoothly. They will keep in close contact via email and telephone throughout.

The primary responsibility for monitoring the safety of participants in clinical trials lies with the trial Sponsor. Data monitoring will be undertaken by the Trial Management Group (TMG), TSC, and a Data Monitoring Committee (DMC), on behalf of the Sponsor and Funder. The project will also be monitored by the Sponsor for whom a representative will be invited to attend the TMG and TSC meetings. The minutes/records of these meetings will be stored at YTU and will be shared with the sponsor on a routine basis.

5.6.2 Trial Management Group (TMG)

A Trial Management Group (TMG) has been established to monitor the day-to-day management (e.g. protocol and ethics approvals, set up, recruitment, data collection, data management) of the study. Chaired by the Chief Investigator, membership will include the co-applicants, coinvestigators, members of YTU (trial manager, statistician) and other research staff on the project. Throughout the project there will be regular teleconference contact supplemented by face-to-face meetings where required (at least annually). Frequency of meetings will vary depending on the stage of the trial but at least monthly during the early stages and pilot.

5.6.3 Trial Steering Committee (TSC)

Independent oversight of the study will be conducted by the Trial Steering Committee (TSC) which will provide overall supervision for FLARE on behalf of the Sponsor and Project Funder and ensure that the project is conducted to the rigorous standards set out in the UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice. The TSC will monitor the progress of the trial and provide independent advice. This committee comprises of an Independent Chair, a public contributor, and the Chief Investigator. A Sponsor representative will also be invited to attend the TSC meetings. Other study collaborators may also attend the meeting

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with the agreement of the Chair. The TSC will meet at least annually and will work to a Charter which has been agreed.

5.6.4 Data Monitoring Committee (DMC)

The study will be regularly reviewed by the independent Data Monitoring Committee (DMC) comprising of independent clinicians and health service researchers with appropriate expertise. The role of the DMC is to review accumulating trial data and advise the sponsor (directly or indirectly) on the future management of the trial.

The DMC will meet at least annually or more frequently if the committee requests, to provide project oversight to the trial. The DMC will review safety and efficacy data as well as quality and compliance data. The DMC will review all serious adverse events which are thought to be treatment related and unexpected. The independent members of the DMC committee will be allowed to see unblinded data.

The DMC will adopt a DAMOCLES charter [40]which will define its terms of reference and responsibilities in relation to oversight of the trial.

6. Safety Monitoring

6.1 Definitions

An adverse event (AE) will be defined as the following: any untoward medical occurrence in a trial participant to whom a research treatment or procedure has been administered (intervention or control) and which does not necessarily have a causal relationship with the treatment. For the purposes of FLARE, we will only collect AE data for events that are related to the original finger injury and unexpected.

Complications, which might be expected with this condition and treatments, are detailed in Table 9: Expected complications associated with flexor tendon repair surgery(section 6.2) should **not** be reported as an adverse event. These are well known complications of surgery of which the specialist clinical care teams will be experienced in managing. These complications however will be recorded in the FLARE CRFs.

Where repeated adverse events of similar type are observed, these will be discussed with the DMC and will be onward reported to Sponsor and REC should concerns be raised in relation to the type of event and/or frequency observed.

A serious adverse event (SAE) will be defined as any untoward occurrence that:

- Results in death.
- Is a life-threatening event (that is it places the participant, in the view of the Investigator, at immediate risk of death).
- Requires unplanned hospitalisation or prolongation of existing hospitalisation (unplanned refers to emergency hospitalisations resulting in an inpatient stay; prolonged hospitalisation is deemed to be where a participant's stay is longer than expected).
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions).
- Is another important medical condition.

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Important medical events that may not be immediately life-threatening, result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition of an SAE will also be considered serious.

In the context of this study, SAEs will only be reported to YTU if they appear to be related to the original injury or an aspect of taking part in the study.

Other than for fatalities, this procedure does not apply to any other SAEs which may occur during the trial which are unrelated to original injury or the trial procedures.

6.2 Collection, Recording and Reporting of Adverse Events

An appropriate member of the research team will record all directly observed AEs and all AEs reported by the trial participant up to six months following their trial treatment.

In addition, sites should follow their own local procedures for the reporting of any adverse events linked to clinical care.

All AEs requiring reporting will be recorded on an (S)AE form or REDCap data collection tool and will be reported to YTU according to the agreed timelines.

The severity and likely relationship to study treatments of any adverse events will be documented by the designated site clinician.

An event is defined as 'related' if the event was due to the administration of any research procedure. Whereas an 'unexpected event' is defined as a type of event not listed in the protocol as an expected occurrence.

All non-serious AEs whether expected or not, should be recorded in the participant's medical notes.

Related and unexpected AEs will be recorded on the study AE data collection tool by the research staff and sent to YTU within an agreed timescale (usually five days). SAEs should be notified to the Principal Investigator and to YTU within 24 hours of the research staff or clinical team becoming aware of the event.

At the time of reporting, the PI or delegated clinician will be asked to record an assessment of causality (to trial treatment) selecting an option from the list below:

- Definitely related- there is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- Probably related- there is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- Possibly related- there is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial procedures). However, the influence of other factors may have contributed to the event (i.e. the participant's clinical condition, other concomitant events).
- Unlikely to be related- there is little evidence to suggest there is a casual relationship (e.g. the event did not occur within a reasonable time after administration of the trial procedures). There is another reasonable explanation for the event (e.g. the participant's clinical condition, or other concomitant treatments).
- Unrelated- there is no evidence of any causal relationship.

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Once received, causality and expectedness will be confirmed by the Chief Investigator. SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) and Sponsor within 15 days.

All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings. All participants experiencing SAEs will be followed up as per protocol until the end of the trial.

Table 9: Expected complications associated with flexor tendon repair surgery

General surgical complications	
Deep wound infection	Superficial infection
Bleeding /haematoma	Suture abscess
Surgical site infection	Rehospitalisation
Delayed wound healing / wound dehiscence	Unexplained pain
Tourniquet related nerve injury	
Anaesthetic-related complications	
Myocardial infarction (MI)	Block related nerve lesion
Cerebrovascular accident (CVA)	
Venous thromboembolism (VTE)	Local anaesthetic toxicity
Complications specific to flexor tendon repair surgery	
Digital nerve injury / neuroma / numbness / altered sensation	Tendon adhesions
Re-rupture of tendon repair	Cold intolerance
Bow stringing	Complex regional pain syndrome
Joint stiffness	
Hand Therapy-related Complications	
Skin problems related to splint fitting	

7. Research Governance

7.1 Ethical Considerations and Approval

The study will be conducted to protect the human rights and dignity of the patient as reflected in the Declaration of Helsinki [39].

Formal NHS Research Ethics Committee (REC) approval will be sought via the Health Research Authority (HRA). Local R&D approvals (confirmation of capacity and capability or management approval) will be obtained for participating sites. Any further amendments to the trial protocol will be submitted and approved by the HRA and REC where required.

7.2 Competent Authority Approvals (Proposed action to comply with the Medicines for Human Use (Clinical Trials) Regulations 2004)

The study does not involve medicinal products and therefore does not require prior authorisation by the UK Competent Authority, the Medicines and Healthcare Regulatory Authority (MHRA).

The surgical techniques under investigation are well-recognised and accepted surgical procedures. The study does not involve the use of investigational medical devices or implants. We do not

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therefore require prior authorisation by the MHRA, under the Medical Devices Regulations (Great Britain, 2002).

7.3 Regulatory Compliance

The trial will comply with the principles of the Declaration of Helsinki [39]. It will also be conducted in compliance with the approved protocol, and the principles of GCP. An agreement will be in place between the site PI and the Sponsor, setting out respective roles and responsibilities.

All deviations from the protocol or GCP will be reported by PIs or designated site staff to YTU. The site must inform the PI as soon as they are aware of a possible serious breach of compliance, so that the sites can report this breach to the trial Sponsor (via YTU) with onward reporting to ethics and regulatory bodies as necessary. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety, physical or mental integrity of the participants in the trial, or
- The scientific value of the trial.

Processing of all trial data will comply with the General Data Protection Regulation (GDPR) (2016/679) (2018) and the Data Protection Act (2018).

7.4 Participant Confidentiality

The researchers and clinical care teams must ensure that participants' anonymity will be maintained and that their identities are protected from unauthorised parties. Participants will be assigned a unique identification number and this will be used on all data collection tools; participants will not be identified by their name. Sites will keep securely and maintain the participant Enrolment Log showing participant identification numbers and names of the participants.

All records will be kept in locked locations. All paper copies of consent forms will be secured safely in a separate compartment of a locked cabinet. Electronic copies will be stored separately to clinical information and access restricted to study personnel. Clinical information will not be released without written permission, except as necessary for monitoring by the trial monitors.

At the end of the study, data will be securely archived by participating sites and the University of York for a minimum of five years.

7.5 Trial Closure

The end of the trial will be defined as the last participant contact which will occur at approximately six months after the end of the recruitment period (end of follow-up for the last participant) and after all the data is entered and queries resolved.

An end of study declaration form will be submitted to the Research Ethics Committee (REC) and Sponsor within 90 days of trial completion and within 15 days if the trial is discontinued prematurely. A summary of the trial report and/or publication will be submitted to the REC, Sponsor and Funders within one year of the end of the trial.

7.6 Annual Progress Reports

An Annual Progress Report (APR) will be submitted to the REC which gave the favourable ethics opinion 12 months after the date on which the favourable opinion was given and thereafter until the end of the study (if applicable).

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7.7 Urgent Safety Measures

The site PI may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. These safety measures should be taken immediately and may be taken without prior authorisation from the REC.

7.8 Indemnity

This study will be sponsored by South Tees NHS Foundation Trust. If there is negligent harm during the trial, when the NHS Trust owes a duty of care to the person harmed, NHS Indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the R&D department.

NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

8. Patient and Public Involvement

We will work with patient co-applicants and a patient advisory group (PAG) with lived experience of flexor tendon injuries. The aim is to secure patient and public input to the study recruitment, retention, interpretation of results and its dissemination (refer to Table 10). Our PPI strategy is focused on flexibility and limiting the burden on contributors as our patients tend to be of working age.

We will work with a co-applicant who be invited to attend (virtual) trial management group (TMG) meetings. PPI will be a standing agenda item.

They will advise on the participants' journey and play a central role in helping to develop patient communication strategies, specifically in designing the patient information to aid study recruitment and retention. They will also comment on trial findings.

A Patient Advisory Group of six people, including the patient co-applicant, will ensure wider representation of the patient population. The PAG will meet twice during study set up, twice towards the end to plan dissemination, and once a year in between. Meetings may be scheduled outside working hours to accommodate contributors. The PPI manager will liaise with contributors individually if they cannot attend.

The PPI manager will organise the PAG meeting and determine the agenda with the TMG and patient co-applicants. The PAG will review proposed solutions for any significant issues in the participants' journey. That includes presentation and wording of information for trial participants such as a patient information sheet/video, consent form and online trial information.

The PAG will lead on production of a lay trial summary for participants and general public, and contribute to the script for animation about the trial results and a press release.

PPI TRAINING AND SUPPORT

We will organise training for patient co-applications and PAG members to brief them on the trial, help them understand their role and the value of their contributions, and signpost them to resources.

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PPI IMPACT

The PPI manager will develop keep a spreadsheet to log PPI contributions and their influence on the project. In addition, the PAG members will be asked to fill in a feedback form after each meeting to understand how contributors feel about them and how we can make them better. keep a log of PPI contributions and their influence on the project. This work will allow the TMG, patient co-applicant and the PAG to evaluate the impact of PPI. We will report the findings in the HTA monograph.

PPI LEAD

All PPI activities will be managed and coordinated by our PPI manager who will act as the primary point of contact for PPI contributors and provide ongoing mentoring and support. The manager will also provide regular updates to contributors throughout the trial.

Table 10: Patient and Public Involvement Schedule

Time Point	Meeting/Duties	Activity	PPI Members
Ethics and Trial Set Up	• Review ethics of trial processes. • Review patient information documents.	• Panel Meeting. • Email of documents for comment.	All.
Mid-way through Recruitment Stage	• Review of any recruitment issues. • Review of any other trial issues.	• Discussion with panel members on individual basis.	All.
Study Closure/Set Up of Full Trial	• Final evaluation of any recruitment or patient issues during trial. • Forward planning to improve upon full trial design.	• Panel meeting	All.
Monthly Trial Management Meetings	• Provide patient perspective on any issues or changes proposed during the course of the trial. • Feedback to other panel members at panel meetings.	• Either meeting attendance or via email update.	Public co-applicant
Note: Panel members may also be invited to review changes in patient information documents on an ad hoc basis via email, should changes be required between scheduled meetings.			

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9. Finance

This research is funded by the NIHR HTA programme (Ref: 133784).

The financial arrangements for the study will be contractually agreed between the funder (HTA), and the Sponsor (South Tees NHS Foundation Trust). Separate collaboration agreements will be put in place between the Sponsor and each of the collaborating organisations.

10. Dissemination and Publication Policy

A dissemination and publication policy will be developed with an agreement between partners including ownership and exploitation of intellectual property, and publication rights. The publication policy and the agreement will ensure that any intellectual property generated during the project is protected and that the publication process is organised in a fair, balanced and transparent manner. The TMG will be responsible for overseeing these arrangements. The creation and signature of the agreements will be the responsibility of the coordinating centre (University of York). It will be ensured that all partners have input into the document.

Targets for dissemination will include NICE, Clinical Commissioning Groups, the Department of Health and the Speciality Advisory Committees (SAC) for the curriculum for clinicians who will undertake treatment of flexor tendon repairs. The study protocol and results will be presented orally and will be made publicly available in appropriate publications and a summary of the study will be made available in plain English for patient-focused outlets.

The executive summary and copy of the trial report will be sent to NICE and other relevant bodies, including Clinical Commissioning Groups, so that the study findings can inform their deliberations and be translated into clinical practice nationally. We will also work with the relevant National Clinical Director in the Department of Health to help ensure the findings of the trial are considered when implementing policy and will work with the Speciality Advisory Committees (SAC) to incorporate the findings into the training curriculum for clinicians who will undertake treatment of flexor tendon injuries. A number of dissemination channels will be used to inform clinicians, patients and the public about the results of the study. The projected outputs are listed below.

We will seek to raise the profile of the trial via social media including a dedicated Twitter account. This will be aimed at participating site staff and focus on trial progress, trial related events, and publicising research outputs.

The study protocol will be published in a peer-reviewed, open access journal, after the study commences.

A HTA monograph will be produced.

On completion of the study, the findings of the HTA report will be presented at national and international meetings such as the International Federation of Societies for Surgery of the Hand (IFSSH) and Hand Therapy (IFSHT).

The study report will be published in peer reviewed high impact general medical, surgical and hand therapy journals; such as Lancet, the BMJ, the Journal of Hand Surgery (European), Hand Therapy or Journal of Hand Therapy.

The study results will be shared with relevant evidence synthesis teams (including within the Cochrane Collaboration) in order to ensure that results are incorporated in future systematic reviews.

A summary of the study report, written in lay language will be produced and made available to participants, members of our user group and relevant patient-focused websites. As part of the trial an information booklet on the condition, the likely recovery process and hand exercises will be produced. We will explore making this more widely available to patients following the trial.

The findings of the SWAT will be disseminated in a relevant journal read by trialists such as BMC Trials and disseminated at relevant conferences such as the International Clinical Trials Methodology Conference. Data will be made available to allow for inclusion in future meta-analyses with studies of the same intervention in other trials.

11. Department of Health and Social Care Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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13.Appendices

13.1 Appendix 1 – Study Timeline

Table 11: FLARE Planned Study Timeline

Activity	Trial Months
Set Up	Months 0-6
Internal Pilot	Months 7-14
Recruitment to Main Study	Months 15-28
6 Week Follow Up	Months 8-29
3 Month Follow Up	Months 10-31
6 Month Follow Up	Months 13-34
Recruitment to Qualitative Study	Months 13-34
Analysis and Reporting	Months 35-40

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