Trials

STUDY PROTOCOL

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Clinical and cost-effectiveness of flexor digitorum profundus (FDP) versus FDP and flexor digitorum superficialis (FDS) repair for complete zone 2 flexor tendon injuries (FLARE): protocol for a randomised controlled trial

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Abstract

Background Flexor tendon injuries are common and lead to over 3200 admissions for specialist surgical repair annually in England and Wales. Surgery to repair complete division of both flexor tendons in zone 2 of the hand is technically challenging. There is variation in surgical repair techniques with no high-quality evidence to support decision-making. In particular, the decision to repair both tendons or just one is contested. Surgery is followed by specialist rehabilitation, which takes at least 12 weeks. The resulting hand function can impact the patient's income, life satisfaction, well-being, self-worth, and mental health. The FLARE trial aims to determine the clinical and cost-effectiveness of repairing the flexor digitorum profundus (FDP) alone (intervention) versus the repair of both FDP and flexor digitorum superficialis (FDS) (control) for the treatment of complete zone 2, single-digit flexor tendon injuries in adults.

Methods A multi-centre, two-arm, blinded, non-inferiority, parallel group, randomised controlled trial with an internal pilot, economic evaluation, and nested qualitative study. Participants will be randomised 1:1 to receive either repair of FDP alone or repair of both FDP and FDS. A total of 310 adults will be recruited from NHS Trusts within the UK, randomised at surgery, and followed up within 7 days, 6 weeks, 3 months, and 6 months post-randomisation. The primary outcome measure is the patient evaluation measure (PEM) administered 6 months post-randomisation. Secondary outcomes include the PEM at other timepoints, Patient Related Wrist/Hand Evaluation (PRWHE), EuroQol 5 Dimensions Score (EQ-5D-5L), complications, total range of motion, grip strength, adherence to splint and therapy regimens, work outcomes, treatment and outcome satisfaction, and healthcare resource use.

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Discussion FLARE is designed with sufficient power and rigour to provide evidence on the clinical and cost-effectiveness of two surgical repair methods for single-digit, complete zone 2 flexor tendon injuries in adults. If the repair of FDP alone is as beneficial to the patient as the repair of FDP and FDS, this could save the NHS £1.8 million annually through reduced time and material costs. Furthermore, the trial findings will facilitate better shared decision-making discussions between clinicians and patients.

Trial registration ISRCTN 10918157. Prospectively registered: 12.01.2023.

Keywords Flexor tendon, Randomised controlled trial, Hand trauma, Surgery, Finger, Plastic surgery, Orthopaedic surgery, Rehabilitation, Hand therapy, Patient evaluation measure

Administrative information

Title {1}	**A randomised controlled 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 (FLARE): study protocol for a multi-centre, two-arm, blinded, non-inferiority, parallel group, randomised controlled trial with an internal pilot, economic evaluation and nested qualitative study**
Trial registration {2a and 2b}	ISRCTN 10918157 (https://www.isrctn.com/ISRCTN10918157). Prospectively registered: 12.01.2023 Enhanced Associate Principal Investigator Training Package and Additional Digital Nudge SWAT—MRC Hub for Trials Methodology Research SWAT repository #214 Registered 30.10.2023
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Role of sponsor {5c}	Study sponsor and funder have had no role in study design nor in the collection, management, analysis, or interpretation of data. They will have no role in the writing of associated publications and the decision to submit papers for publication

Introduction

Background and rationale {6a}

The zone 2 flexor region of the finger contains the flexor digitorum superficialis tendon (FDS, inserts on the middle phalanx) and the flexor digitorum profundus (FDP, inserts on the distal phalanx, see Fig. 1).

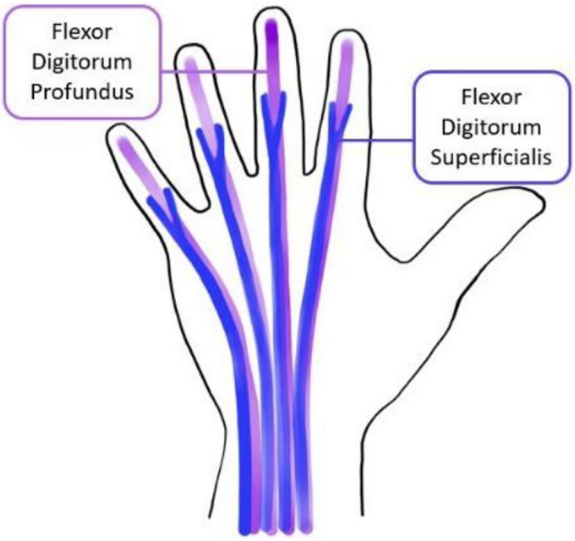

Fig. 1 Diagram showing the flexor digitorum profundus (FDP) in purple, and the flexor digitorum superficialis (FDS) in blue

Flexor tendon injuries lead to over 3200 admissions for surgery in England and Wales each year [1]. The incidence is highest in young male adults resulting in substantial socioeconomic impact [2]. Repair and rehabilitation of zone 2 flexor tendon injuries is controversial because of the unique challenges provided by the anatomy and biomechanics. Repairs in this zone are technically difficult and there is a higher risk of scar tissue forming between the tendons [3]. Rehabilitation takes at least 12 weeks and can lead to prolonged time off work and loss of income, compounded by the expense of multiple hospital trips. This has ramifications for life satisfaction, well-being, self-worth, and mental health [4]. Prolonged rehabilitation is also expensive for the health service and wider society [5].

In 2016, a national service evaluation of open flexor tendon injuries found a large majority of surgeons repaired both divided tendons in zone 2. A more recent service evaluation, during the COVID-19 pandemic, found that 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. This demonstrates that the question "Is repairing FDP alone non-inferior to repairing both tendons?" will be highly relevant to the surgical community and day-to-day surgical practice. Given this substantial variation in routine practice for this common injury, plus the lack of high-quality randomised controlled trial (RCT) evidence, there is an urgent need for a definitive RCT.

Objectives {7}

The primary objective is to 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.

Secondary objectives are to:

- Undertake an 8-month internal pilot to obtain robust estimates of recruitment and confirm trial feasibility
- Assess and compare range of motion
- Assess and compare grip strength
- Compare the complications of both types of repair
- Assess and compare patient-reported Patient Related Wrist/Hand Evaluation
- Compare costs and quality-adjusted life years of both interventions
- Undertake an embedded qualitative study

Trial design {8}

FLARE is a multi-centre, two-arm, blinded, non-inferiority, parallel group, RCT with an internal pilot, economic evaluation, and nested qualitative study. Participants will be randomised 1:1 to the repair of FDP and FDS (control) or the repair of FDP only (intervention).

During the pilot phase, mixed-methods recruitment optimisation work will be undertaken to improve the approach to recruitment during the main FLARE study. Data collection will include:

1. $n=10$ (approximately) brief qualitative interviews with key stakeholders (including co-chief investigators (co-CIs)) from FLARE and other key National Institute for Health and Care Research (NIHR)-funded hand trials; FLARE clinical co-applicants and Clinical Trial Unit (CTU) staff. These interviews will use participants' experiences of setting up the FLARE trial to identify key obstacles to recruitment.
2. Record and review Trial Management Group (TMG) meetings to keep abreast of any challenges that are occurring during the trial's set-up period.
3. Record and review study checklists and other key trial documents.

Information obtained through interviews and key trial documents will be used to identify the key issues that FLARE may face with regard to recruitment. Analysis of this information will be rapid and undertaken concurrently with data collection to allow initial troubleshooting. Where patient-related factors are raised, patient and public involvement (PPI) members will be engaged to strategise solutions.

Prior to the start of the main study, all information collected during the initial recruitment optimisation exercise will be integrated into the trial procedures and

will be under ongoing review and adapted further as appropriate.

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-randomisation. The purpose of these interviews is to ascertain vital information relating to acceptability and experience of the surgical procedure and the rehabilitation regimens.

In addition, we will conduct semi-structured interviews with hand surgeons ($n=10$) and hand therapists ($n=10$). 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 to implement the findings from the trial across the NHS.

As part of the trial, an embedded study within a trial (SWAT) will investigate the effect on recruitment rates of an Enhanced Associate Principal Investigator (API) Training Package and Additional Digital Nudge delivered by a Trial Coordinator.

Methods: participants, interventions, and outcomes

Study setting {9}

Participants will be recruited from up to 40 NHS Trusts within the UK treating flexor tendon injuries. A list of study sites is available in Supplementary Information.

Eligibility criteria {10}

Patients are required to fulfil all of the following criteria.

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

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

*One digit with both FDS/FDP tendons severed; other digits could have a superficial or partial tendon injury.

Who will take informed consent? {26a}

Informed consent will be obtained by a suitably qualified and experienced clinician or member of the research team who has been authorised to do so by the Principal Investigator. Informed consent will take place prior to any trial-related activities being undertaken. Patients will be provided with a variety of patient information materials describing the trial and will be asked to complete a consent form if willing to proceed. 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.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

There are no biological specimens collected within FLARE; therefore, additional consent for collection and use is not required.

Interventions

Explanation for the choice of comparators {6b}

Previous research showed that the majority of surgeons repaired FDP and FDS in zone 2 open flexor tendon injuries, and therefore, this was selected as the control. Both repair types are currently used in the NHS; however, there is clinical uncertainty as to which is most clinically and cost-effective.

Intervention description {11a}

As both treatment arms are routinely conducted within the NHS, the randomised treatment allocation will be delivered in accordance with standard NHS Trust procedures.

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 h 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 4-strand core repair is standard practice for 80% of surgeons in the UK (6), but will not be mandated in FLARE. The number of strands will be recorded. Similarly, an epitendinous suture (a suture around the outside edge of the tendon) will not be mandated but if used 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, including rehabilitation, 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.

Criteria for discontinuing or modifying allocated interventions {11b}

Given the nature of the study interventions, it will not be possible to discontinue either intervention once treatment has been delivered.

Strategies to improve adherence to interventions {11c}

As both surgical repairs are routinely delivered, no specific strategies have been designed to improve adherence to the intervention.

Relevant concomitant care permitted or prohibited during the trial {11d}

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 [6]. 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 restrict 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 [7]. The choice of splint will be in discussion with the patient and therapist.

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

Provisions for post-trial care {30}

Ongoing care for patients will be available through participating sites in line with standard arrangements for routine care. If there is negligent harm during the trial, when the NHS Trust owes a duty of care to the person harmed, NHS Indemnity applies.

Outcomes {12}

Primary outcome

The primary outcome measure is the patient evaluation measure (PEM) Hand Health Profile completed at baseline, six weeks, three months, and six months post-randomisation. The pre-specified primary timepoint of interest is six months post-randomisation.

The PEM is widely used in National Institute for Health and Care Research (NIHR)-funded hand trauma studies and is the main patient-reported outcome measure (PROM) used for flexor tendon injuries in the British Society for Surgery of the Hand (BSSH) United Kingdom National Hand Registry. The PEM comprises 19 items and three subscales: treatment (5 items); Hand Health Profile (11 items); and overall assessment (3 items). The 11 items which make up the Hand Health Profile subscale will be the primary outcome measure for the FLARE trial. The PEM asks questions relating to symptoms, satisfaction, and general disability, which generates a percentage, ranging from 0 to 100%, to determine a disability score, with higher scores indicating greater levels of disability [8]. The choice of outcomes was based on a recent site and condition-specific systematic review of PROM in flexor tendon injury [9].

Secondary outcomes

Secondary outcomes will be collected at six weeks, three months, and six months post-randomisation. Secondary outcomes include:

- PEM subscales.
- Patient Related Wrist/Hand Evaluation (PRWHE): is a 15-item questionnaire used to assess hand pain and disability in day-to-day activities.

- EuroQol 5 Dimensions (5L) Score (EQ-5D-5L): measures health-related quality of life in terms of 5 dimensions: mobility, ability to self-care and undertake usual activities, pain and discomfort, anxiety, and depression.
- Complications: information on all complications will be collected. Expected complications that will be recorded will include (but not be limited to) deep wound infection, rehospitalisation, nerve, and skin problems.
- Total range of motion: degree of movement at a joint.
- Grip strength (at three months): both hands will be assessed using a Jamar dynamometer.
- Adherence to splint regimen (at six weeks). Patient self-report.
- Work outcomes. Patient self-report.
- Treatment and outcome satisfaction. Net promotor score.
- Healthcare resource use: cost of each type of surgery and related complications; inpatient episodes; outpatient hospital visits and accident and emergency (A&E) admissions; primary care consultations (e.g. GP, nurse, and physiotherapy); work impact of both treatments; and return to work and return to normal activities.
- Adherence to therapy regimen. Patient self-report.

Participant timeline {13}

See the participant timeline in Fig. 2.

Sample size {14}

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 PEM represents the threshold at which treatment differences become important (based on observational data from patients with Dupuytren's contracture for the DISC trial) [10]. 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 non-inferiority within a margin of 7 points on the PEM (standard deviation = 17; upper 80% confidence limit based on the lower limit of a 95% two-sided confidence interval (CI) (equivalent to a one-sided 97.5% CI) and 20% attrition.

Recruitment {15}

Patients will be recruited from NHS Trusts within the UK treating flexor tendon injuries and with capacity to support research activity. Participants will be identified at the emergency department or hand trauma unit by the clinician and/or research nurse/practitioner. Screening and recruitment strategies will be discussed with sites at regular investigator meetings.

Assignment of interventions: allocation

Sequence generation {16a}

Eligible participants will be randomly allocated in a 1:1 ratio to the intervention or control arm using block randomisation stratified by study site with randomly varying block sizes.

Concealment mechanism {16b}

Central, secure web-based randomisation via the Research Electronic Data Capture (REDCap) interface will ensure allocation concealment and immediate unbiased allocation.

Implementation {16c}

An independent statistician at the York Trials Unit (YTU), who is not involved in the recruitment of participants, will generate the allocation schedule. The allocation schedule will be generated in STATA v17 or later and implemented via REDCap. Authorised and delegated site staff will access REDCap to randomise trial participants at the point of surgery.

Assignment of interventions: blinding

Who will be blinded {17a}

The operating surgeon, theatre staff, and delegated unblinded research staff will be informed of the randomisation allocation in order to complete the surgical repair. Participants will not be informed which repair was completed, as the surgical wound does not differ between treatments. Site clinical and delegated research team staff will be blinded to the allocation and surgical technical information during the follow-up period.

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

The primary outcome is the PEM, which is a patient-reported outcome measure, helping mitigate surgeon or outcome assessor influence. Six months after randomisation, participants will be asked which surgical treatment they think they underwent to assess the success of participant blinding. Participants will find out which treatment they received once the primary outcome has been

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

Fig. 2 FLARE trial participant timeline. [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

collected and their participation in the trial has ended. Their medical records will also be unblinded at this timepoint.

Procedure for unblinding if needed {17b}

Should unblinding be necessary, an unblinded member of the site team or member of the YTU trial coordination team can access REDCap and communicate the treatment allocation.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Baseline data will be collected after a patient has consented to participate in the trial and prior to their surgery

being completed. Outcome data will be collected within 7 days, 6 weeks, 3 months, and 6 months of randomisation using REDCap. Clinical teams will review the participant's medical notes for complications, additional surgeries, and adverse events (AEs) at the 6-month timepoint. Participants will be asked to complete questionnaires at 6 weeks, 3 months, and 6 months post-randomisation. Participant questionnaires are managed by YTU and will be sent by email or post, or administered by telephone, as preferred by the participant. To minimise attrition, we will ask participants for full contact details (including mobile phone number and email address, if available) for the purpose of data clarification and follow-up data collection.

Hospital visits can be completed in person or remotely, in accordance with NHS Trust procedures; however, the 3-month visit is encouraged to be conducted in person to enable grip strength measurements to be obtained. Guidance has been developed to support hospital teams in completing range of motion measurements in person or virtually with participants.

Plans to promote participant retention and complete follow-up {18b}

Participants have the right to withdraw without prejudice, at any time and for any reason. Should a patient no longer wish to attend hospital clinic visits, we are able to offer remote visits in accordance with their local NHS Trust policy. If a participant no longer wishes to complete trial follow-up, where possible, we will seek permission for research staff to collect data from their medical records.

Where follow-up questionnaires are not completed, we will send 2- and 4-week 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.

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

Data management {19}

Data collected by sites and completed by participants will be entered onto a secure online REDCap interface, specifically developed for this study [11, 12]. Qualitative data not captured on REDCap will be stored following YTU standard operating procedures and/or University of York policies. 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 Case Report Form (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.

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), 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 CRF with participants identified by a unique identification number. All study files will be stored in accordance with Good Clinical Practice (GCP) guidelines. 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.

Confidentiality {27}

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. 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.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

There will be no biological specimens collected within FLARE; therefore, no plans are required for the collection, laboratory evaluation, or storage of biological specimens.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Statistical analyses will be on an intention to treat (ITT) basis and statistical significance will be at the 5% level

unless otherwise stated. Statistical analyses will be conducted in the latest version of Stata (or similar statistical software) [13]. The trial will be reported according to the CONSORT guidelines for non-inferiority trials [14]. A CONSORT flow diagram will be provided to display the flow of participants through the trial. 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 compare the PEM Hand Health Profile 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 nerve injury and anaesthetic type) will be included as fixed effects. Site and participant will be included as random effects, accounting for clustering by site and repeated observations per participant. Estimates of the difference in PEM scores will be extracted for each time point (primary six months) and overall with two-sided 95% CI (equivalent to a one-sided 97.5% CI) and *p*-values. Non-inferiority will be accepted if the lower bound of the two-sided 95% CI (equivalent to a one-sided 97.5% CI) for the treatment difference at six months lies within the non-inferiority margin of seven points (greater than −7).

Continuous secondary outcome measures will be analysed using a similar covariance pattern model as used for the primary analysis. Binary secondary 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.

Interim analyses {21b}

There are no planned interim analyses for the trial.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Economic analysis

The economic evaluation takes the form of a cost utility analysis (CUA) to assess the relative cost-effectiveness of repairing FDP alone compared with repairing both FDP and FDS in patients with division of both tendons in zone 2 over 6 months post-randomisation.

The healthcare resource data will be collected at baseline, and all follow-up points using patient self-administered questionnaires and medical notes. Unit costs will be sourced from appropriate national sources [15, 16]. The trial will also assess the impact of both treatments on days of lost employment and unpaid activities.

The primary outcome for the CUA is EQ-5D-5L [17] 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 of all EQ-5D utility scores to calculate QALYs scored by the UK tariff as recommended by the National Institute for Health and Care Excellence (NICE) [18–20].

The economic evaluation will present the cost per QALY gained, to compare the cost-effectiveness of the treatments within the context of published NICE cost-effectiveness thresholds. This enables decision-maker to assess the relative value for money when allocating a health care budget. We use an NHS and personal social services (PSS) perspective following NICE guidance (19). 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 in 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 [19].

Regression methods will be used for the incremental CUA as this allows differences in prognostic variables. The cost-effectiveness acceptability curve will be constructed to demonstrate the uncertainty of the results [21]. 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.

A detailed a priori health economics analysis plan (HEAP) will be developed before the completion of recruitment to pre-specify 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.

Qualitative analysis

The data analysis for the qualitative study will follow the principles of thematic analysis, providing an interpretive exploration of the experiences, attitudes, and beliefs of different stakeholder groups [22]. The development of inductive codes and themes will be discussed as a team.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Completeness of data at follow-up will be reported by group. In non-inferiority comparisons, the intention to treat (ITT) analysis could bias towards the null, which may lead to false claims of non-inferiority; hence, we will undertake both ITT and complier average causal effect (CACE) analyses [23]. The impact of missing data on the primary analysis will be assessed using multiple imputation by chained equations.

Plans to give access to the full protocol, participant level-data, and statistical code {31c}

This document constitutes the full protocol. Datasets and statistical code used in this study will be available from the corresponding author on reasonable request following completion of the trial.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The trial coordinating centre (York Trials Unit, University of York) hosts a trial manager, trial coordinators, statisticians, a qualitative researcher, health economists, and data management team, who work alongside the Sponsor (South Tees Hospitals NHS Foundation Trust) and co-CIs (based at Frimley Health NHS Foundation Trust and South Tees Hospitals NHS Foundation Trust) to support trial delivery.

An independent trial steering committee (TSC) will meet at least annually and is composed of experienced professionals including a consultant surgeon, trial methodologist, hand specialist allied health professionals, and a medical statistician. The TSC also includes a patient and public representative.

Composition of the data monitoring committee, its role, and reporting structure {21a}

An independent data monitoring committee (DMC) will meet at least annually and is composed of experienced professionals including a consultant surgeon, health service researcher, specialist hand therapist, and a statistician. The DMC review accumulating trial data and advise the funder on the future management of the trial. The DMC will also review safety and efficacy data, and quality and compliance data, including all serious adverse events (SAEs) which are thought to be treatment-related and unexpected. Independent members of the DMC will be allowed to see unblinded data. The DMC will adopt a DAMOCLES charter [24], which will define its terms of reference and responsibilities in relation to oversight of the trial.

Adverse event reporting and harms {22}

Adverse event data will only be collected for events that are related to the original finger injury and are unexpected. Expected complications associated with flexor tendon repair surgery (see Table 1) will be captured in follow-up instruments on REDCap.

Frequency and plans for auditing trial conduct {23}

Site teams will complete an annual remote audit using a self-complete checklist issued by YTU. On site monitoring will not occur unless deemed necessary. YTU will manually check all consent and eligibility documentation on REDCap for missing, inconsistent, or invalid data, along with resolving any data queries with sites. Further details are available within the FLARE Trial Monitoring Plan.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Protocol amendments will be approved by the sponsor (South Tees Hospitals NHS Foundation Trust)

Table 1 Expected complications associated with flexor tendon repair surgery

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

and the funder (NIHR Health Technology Assessment (HTA) Programme) prior to submission to the approving Research Ethics Committee (North West—Greater Manchester Central Research Ethics Committee) and the Health Research Authority. Documentation will be provided to study sites for their local review and implementation as required.

Dissemination plans {31a}

A dissemination and publication policy has been developed with an agreement between partners including ownership and exploitation of intellectual property, and publication rights.

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 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.

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

The study findings will be published in peer-reviewed high-impact general medical, surgical, and hand therapy journals, such as Lancet, the British Medical Journal, the Journal of Hand Surgery (European), Hand Therapy, or Journal of Hand Therapy. A HTA synopsis report will be produced.

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

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.

The findings of the SWAT will be disseminated in a relevant journal read by trialists such as BioMed Central 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.

Discussion

The two types of surgical repair being compared are used for this injury; however, there is uncertainty over which is most clinical and cost-effective. The FLARE trial is a sufficiently powered and rigorously designed study to inform clinical practice for the treatment of adults with this injury.

Trial status

The current REC-approved version of the protocol is version 1.1 (dated 17 March 2023).

Recruitment into the FLARE trial commenced in August 2023 and is ongoing at the time of manuscript submission. Trial progress was reviewed by the funder in April 2024. Due to issues with progress as a result of a directly competing trial, a further pilot period of 12 months was agreed and began. Recruitment is expected to continue until at least April 2025.

Abbreviations

A&E	Accident and E-emergency
AE	adverse event
API	Associate principal investigator
BSSH	British Society for Surgery of the Hand
CACE	complier average causal effect
CI	confidence interval
Co-CIs	Co-Chief Investigators
CONSORT	Consolidated Standards of Reporting Trials statement
CRF	case report form
CTU	clinical trials unit
CUA	cost utility analysis
CVA	cerebrovascular accident
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
HEAP	health economics analysis plan
HES	Hospital Episode Statistics
HTA	Health tTchnology Assessment
IFSHT	International Federation of Societies for Hand Therapy
IFSSH	International Federation of Societies for Surgery of the Hand
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	intention to treat
MI	myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research

ONS	Office of National Statistics
PEM	patient evaluation measure
PPI	patient and public involvement
PROM	patient-reported outcome measure
PRWHE	patient-reported wrist/hand evaluation
PSS	personal social services
QALY	quality-adjusted life year
RCT	randomised controlled trial
REDCap	research electronic data capture
SAC	Speciality Advisory Committees
SAE	serious adverse event
SAP	statistical analysis plan
SWAT	study within a trial
TMG	Trial Management Group
TSC	Trial Steering Committee
UKHR	UK Hand Registry
VTE	venous thromboembolism
YTU	York Trials Unit

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-09043-x.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions {31b}
MDG and ER are co-chief investigators. JA, KGB, MDG, CH, DH, SH, LK, JCEL, LN, AR, ER, JR, RGW, and JCRW are co-applicants and grant holders and contributed to the concept and design of the trial and development of the protocol. LC is the trial manager and contributed to the development of the trial protocol and study documentation, and trial conduct, with support from EM and MW as trial co-ordinators. KB, LM, and FW are statisticians and contributed to the statistical analysis and sample size sections of the manuscript. JL and SP are health economists and contributed to the design of the economic evaluation. AH and AS are qualitative researchers and contributed to the design of the nested qualitative study. MW drafted the manuscript. All authors edited the draft and approved the final manuscript.

Authors' information
The FLARE trial is a collaborative effort between surgeons, hand therapists, and researchers.

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The study sponsor and funder have had no role in study design nor in the collection, management, analysis, or interpretation of data. They will have no role in the writing of associated publications and the decision to submit papers for publication.

Data availability {29}
The final trial dataset (fully anonymised) will be available from the corresponding author on reasonable request following the completion of planned analysis and dissemination.

Declarations

Ethics approval and consent to participate {24}
Ethical approval has been granted by the North West – Greater Manchester Central Research Ethics Committee on 7th March 2023 (REC reference: 23/NW/0004). Patients are required to provide informed consent prior to participation.

Consent for publication {32}
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. Informed consent materials are attached as supplementary materials.

Competing interests {28}
The authors declare the following competing interests:
CH is a member of the NIHR HTA Commissioning Committee (2015–2022) and Deputy Chair (2019–2022), NIHR Senior Investigator, member of the NIHR HTA General Committee (2023 to present) and Chair (2023–present), member of the NIHR CTU SAC (2020–2022), Co-Director NIHR RSS (2023–present), and member of the HTA Commissioning Sub-Board, HTA Post-Funding Committee teleconference, HTA Funding Committee Policy Group (formerly CSG), and HTA - Fast-Track Funding Committee.
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All other authors declare that they have no competing interests.

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