FLARE RCT

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

HEALTH ECONOMICS ANALYSIS PLAN

Version 1.0

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1 REVISIONS

Version	Date	Summary of changes
0.5	22 Jan. 25	Initial draft
0.7	27 Mar 25	Revised draft
1.0	14 Apr. 25	Finalised version

2 GENERAL

2.1 Document scope

The current document describes the planned analyses of economic evaluation alongside the FLARE randomised controlled trial (RCT).

This analysis plan has been checked for consistency with the FLARE RCT trial protocol v1.1 (17 Mar 2023).

2.2 Glossary

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CEAC	Cost-effectiveness acceptability curves
CUA	Cost-Utility analysis
EQ-5D-5L	EuroQol 5 dimensions with 5 levels
FDP	Flexor digitorum profundus
FDS	Flexor digitorum superficialis
GP	General Practitioner
ICER	Incremental cost-effectiveness ratio
MAR	Missing At Random

MNAR	Missing Not At Random
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PSS	Personal Social Service
QALY	Quality-adjusted Life Year
RCT	Randomised controlled trial
UK	United Kingdom
YTU	York Trials Unit

3 TRIAL SUMMARY

The following sections briefly describe the FLARE RCT. For full details please see the protocol (v1.1, 17/03/2023).

3.1 Aim and objectives

The aim of the economic evaluation is to establish the cost-effectiveness of repairing flexor digitorum profundus (FDP) alone or both FDP and flexor digitorum superficialis (FDS) in patients with division of both tendons in zone 2.

Specific objectives are:

- To estimate the costs of repairing FDP alone and repairing both FDP and FDS, and their respective related health care costs over 6 months period;
- To assess the impact of both treatments on quality of life over 6 months period;
- To conduct an incremental cost-utility analysis of repairing FDP alone compared with repairing both FDP and FDS from the perspective of National Health Service (NHS) and Personal and Social Service (PSS);
- To explore the impact of both treatments on days of lost employment and unpaid activities over 6 months period.

3.2 Design

The FLARE RCT is a multi-centre, two-arm, parallel group, blinded, non-inferiority RCT with allocation at the level of individual. The trial is being conducted in participating Hand Trauma Centres within the UK where flexor tendon injuries are treated and with facilities to support research activity. These sites are involved in the identification of study participants and are the locations for treatment delivery.

The inclusion criteria of participants: 1) are aged 16 years and over; 2) have one digit injured only, with both FDP and FDS tendons severed; 3) have multiple digits injured but only one digit with both FDP and FDS tendons severed and any other injured digits with superficial injury or a partial tendon injury; 4) injury amendable to primary repair. Criterion 1) is confirmed at screening and the rest are confirmed in surgery.

Patients are excluded if they have multiple digits injured with both FDS and FDP tendons severed, 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, contraindication to surgery, injuries with loss of tendon substance or skin necessitating reconstruction, division of both digital arteries resulting in revascularisation of injured digit, or division of both digital nerves. Patients who do not have capacity to give informed consent or unable to complete follow-up requirements are also excluded.

The sample size is set at 310. Participants are randomised to either group at 1:1 ratio, using stratified block randomisation with randomly varying block sizes. Randomisation is implemented using a web-based system by an independent statistician at York Trials Unit (YTU), who is not involved in the recruitment of participants.

Measures are collected from two sources: investigators and participants. Investigator forms will be completed at baseline, randomisation (surgery), within 7 days, 6 weeks and 3 months post-randomisation. Investigator form of additional surgery will be updated throughout the follow-up period. Participant's medical notes will be reviewed at 6 months for any complication occurring after 3 months and these will be recorded in the comments. Participant follow up questionnaires will be administered at baseline, 6 weeks, 3- and 6-months post-randomisation. The measures related to the economic evaluation are described in the following sections. For a detailed schedule of all measures please see protocol (V1.1; 17/03/2023).

4 OUTCOMES AND DATA COLLECTION

4.1 Costs

4.1.1 Interventions

4.1.1.1 Surgical interventions

Participants will undergo primary surgery as per the randomisation allocation under the care of one of the participating surgeons. The primary surgery is tendon repair of the FDP alone or FDP and FDS repair.

Following the primary surgery, secondary and/or additional surgeries might be performed as deemed necessary. These will vary depending on the condition and needs of each participant. Complications and resulting secondary surgeries will be recorded in detail in the investigator forms at within 7 days, 6 weeks and 3 months. At 6 months, a review of medical notes will record any complications and resulting secondary procedure and /or admission information occurring since 3 months review. Additional surgeries will be recorded in the additional surgery form throughout the follow-up period.

Costs of these surgical interventions and complications when no secondary surgery is required, will be estimated based on the procedure and admission information collected in investigator forms up to 6 months post-randomisation.

4.1.1.2 Hand therapy

The number and average duration of routine hand therapy sessions attended by participants will be recorded at 3 months in the investigator form. The therapist will be costed at mid-point of NHS Band 7 at the analysis year, including salary-oncosts and overheads. The costs of routine hand therapy will be estimated by multiplying therapist time costs by the total length of therapy sessions.

Additional hand therapy sessions will be collected in the investigator form at within 7 days, 6 weeks and 3 months and in the participant follow up questionnaire at 6 weeks, 3 months and 6 months. In the investigator forms, hand therapy session will be identified by clinic type within a setting (emergency care, primary care, outpatient care, inpatient care, day case) for up to three sessions. In the participant follow-up questionnaire, the number of visits to hand therapist, occupational therapist, or physiotherapist in primary care and number of appointments with hand therapist, occupational therapist or physiotherapist in hospital will be recorded. Given that these services could be overlapping but with more details in the investigator forms for up to 3 months, we will estimate the costs of additional hand therapy

sessions primarily based on the information in the investigator form up to 3 months and the costs at 6 months will be estimated solely based on the information in the participant follow up questionnaire.. These will be costed using national average unit costs based on service settings in the appropriate year at the time of analysis (1, 2).

4.1.2 Healthcare services specifically for the injured finger

As described above, healthcare services for participant's injured finger are collected from two sources up to 3 months. In investigator forms, except for hand therapy session that is accounted for in 4.1.1.2, other care related to their injured finger will also be identified by clinic type within a setting (emergency care, primary care, outpatient care, inpatient care, day case) for up to three sessions. In participant follow-up questionnaires, NHS healthcare services specifically for the injured finger are divided into two section: care received out of the hospital and care received in hospital, which are collected at 6 weeks, 3 months and 6 months. Care out of the hospital includes General Practitioner (GP), practice nurse, pharmacist, health care assistant, NHS 111, mental health services, and otherwise identified services for their finger problem. Care in the hospital includes outpatient consultation and/or procedure with a surgeon, outpatient visit with a nurse (for wound caring), outpatient visit with a hand therapist/physiotherapist/occupational therapist, outpatient visit to a pain clinic, outpatient visit to other allied healthcare professionals, and admission for further surgery to finger, admission for other treatment to finger, day case, A&E, and blood test for infection. Only number of uses of the care in and out of hospital is collected.

Outpatient visit with a hand therapist/physiotherapist/occupational therapist is accounted for in 4.1.1.2. Contacts with GP and practice nurse and care in the hospital in participant follow-up questionnaires will only be used at 6 months as these are recorded in more details in investigator forms up to 3 months. The other NHS care received out of the hospital in participant follow-up questionnaires will be costed at 6 weeks, 3 months and 6 months using a set of published national average unit costs (1, 2).

Medications taken for the finger injury will be collected by participants' follow up questionnaire. These include paracetamol, aspirin, ibuprofen, co-codamol, naproxen, oral morphine, and antibiotics. Prescribed medications will be costed using Prescription Costs Analysis of appropriate year(3) by number of prescriptions received.

4.1.3 Out-of-pocket payments related to the finger injury

Private specialist rehabilitation (physiotherapy, occupational therapy, hand therapy), surgical treatment and otherwise specified services will be collected by participant follow up questionnaires at 6 weeks, 3 months and 6 months, along with the amount of money paid by participants for them. Participants' spending on over-the-counter medications and other non-medication equipment (e.g. splint, therapeutic tape, massage equipment, etc.) will also be collected. We will further estimate participants' payment for prescription charge by collecting their exemption status.

4.1.4 Lost income and unpaid activities

Participants' change of working status, missed working days, and number of days of having unpaid carer will be collected through the participant follow up questionnaires at 6 weeks, 3 months and 6 months. The unpaid carer is defined as participant's friend or family who takes time off work to perform usual activities (e.g. household chores, shopping, etc.) that participant themselves would have performed if not for their finger injury. We will use the average earnings at the time of analysis to quantify participants' lost income and potential productivity loss due to unpaid activities.

4.2 Effectiveness measure

4.2.1 Quality-Adjusted Life Years

The EuroQoL 5 dimensions with 5 levels (EQ-5D-5L) (4) is used to assess health gain in quality-adjusted life years (QALYs). The questionnaire consists of a descriptive system and a visual analogue scale. The descriptive system consists of 5 domains, each with 5 levels (scored 1–5) that assess one's self-perceived health "today". The domains are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each domain, level 1 indicates no problems at all while level 5 indicates severe problems. Full responses under the 5 domains form a description of the person's "health state" (e.g. 11232), which can then be converted to a utility value using a mapping approach (5, 6). The EQ-5D-5L is administered at baseline, 6 weeks, 3 months and 6 months. Combining the utility values and the timepoint they are collected, QALYs will be derived using area under curve approach which assumes linear change between data collection points (7). Visual analogue scale ranges from 0 to 100 indicting participants perceived worst or best health "today".

5 ANALYSIS

5.1 Methods overview

All analyses will be carried out following an intention-to treat principle. We will present all monetary outcomes in pound sterling in the year with most up to date public sources of unit costs of service use available. Discounting is not undertaken as the costs and outcomes cover a period of 6 months only.

We will undertake analyses using the latest available version of Stata.

The descriptive statistics of the data will be presented by time point and group. The missing data pattern will be examined at this stage. Missing data will be handled primarily using multiple imputation on the assumption of missing at random (see 5.2 below). We will carry out the primary analysis in the form of a cost-utility analysis (CUA) comparing repair FDP alone to repair both FDP and FDS from the NHS and PSS perspective (5). A secondary analysis will be undertaken to explore wider societal costs from the participants' perspective.

5.2 Missing data

Missing data level will be described for all measures at all time points by groups and in total. Missing data patterns will be described accordingly.

Missing data will be handled based on the framework proposed by Faria et al (8). Missing values of baseline data are expected to be rare and unrelated to the group allocation. These missing values will be imputed by the mean of the measure of the pooled sample of both groups (9).

Missing values of data at follow-ups will be handled using multiple imputation with chained equation method, following Rubin's rule and assuming missing at random (MAR) (10). The association of missingness of each measure with group allocation and baseline covariates, and with observed values of the same measure at other follow-up points will be examined using statistical tests (univariate logistic regression for continuous and binary variables, χ^2 tests for discrete variables) with 0.05 as significant level. An imputation model will be developed, including all the measures necessary for the analysis or associated with missingness identified by the statistical tests. The number of imputation will be set as approximately the highest percentage figure of the missing data (9). The imputation will be performed by allocation groups.

All analyses will be conducted on the imputed dataset, unless otherwise specified.

5.3 Primary analysis

The primary analysis will be an incremental cost-utility analysis (CUA) of repairing FDP alone to repairing both FDP and FDS over 6 months from a NHS/PSS perspective.

Total costs from NHS/PSS perspective include costs of surgical interventions and related rehabilitation and hand therapy, and costs of healthcare services for the injured finger, including medications taken, over 6 months. The effectiveness measure is QALYs over 6 months. Both incremental costs and incremental QALYs will be estimated using linear regression, adjusting for baseline covariates that show a significant association ($p<0.05$) with dependent variables. The incremental QALYs will further adjust for baseline utility values. The appropriate models will be selected based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) information criteria. A Likelihood Ratio test will be used to indicate if random effects should be considered. The incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the incremental costs by incremental QALYs, when both are positive.

Uncertainty around the point estimate will be assessed using the non-parametric bootstrap re-sampling technique (11). Bootstrapping is an efficient method for calculating the confidence limits for variables possibly deviating from normality, as its validity does not depend upon any specific form of underlying distribution. We will use bootstrapping to generate 5,000 replicates of the sample with replacement to create a distribution for incremental costs and QALYs. The 95% CIs for incremental costs and QALYs based on the bootstrapping results will be derived using the 2.5th and 97.5th percentiles of their respective distribution. A cost-effectiveness plane will be plotted using 5,000 pairs of incremental costs and corresponding incremental QALYs with four quadrants indicating four scenarios of cost-effectiveness (more costly more effective, more costly less effective, less costly more effective, less costly less effective). Cost-effectiveness acceptability curves (CEACs) (12) will be constructed based on the bootstrap iterations to estimate the probability that FDP repair alone is cost-effective at different threshold values, compared to both FDP and FDS repair. Incremental costs per QALY gained from NHS/PSS perspective will be compared with the maximum acceptable threshold of ICER recommended by National Institute for Health and Care Excellence (NICE) (5).

5.4 Secondary analysis

We will explore wider societal costs as a secondary analysis. These include participants' out-of-pocket payments, lost income due to change of working status, and potential loss of productivity of unpaid carers. The difference between groups will be estimated using a regression model. The choice of regression model and included baseline covariates will be determined following the same approach as the primary analysis. The uncertainty surrounding the point estimate will also be examined by bootstrap technique.

5.5 Sensitivity analyses

A series of sensitivity analyses will be undertaken to assess the uncertainties of the conclusion. To assess the impact of missing data, complete case analysis will be undertaken following the same approach of the primary analysis but only on those who have complete data on costs, QALYs, and included baseline covariates.

To examine the robustness of the MAR assumption, sensitivity analyses will be carried out using pattern mixture modelling (8). This method assumes that data are missing not at random (MNAR) and sets rules for imputing to reflect this assumption. In the current analysis, we will assume that those who have missing values at follow-ups either need more health care services (higher costs) or experience worse health (lower utility values), or both at the same time. To examine how these scenarios will affect the results based on MAR assumption, the incremental costs and QALYs will be re-estimated based on data with 1) imputed costs are increased by 20%, 40% and 60%; 2) imputed QALYs are reduced by 20%, 40% and 60%; 3) the combination of 1) and 2).

6 ADDITIONAL NOTES

The full analysis will only be performed if the trial passes the pilot stage. If a trial does not meet the target sample size in pilot stage, the sample size will not be sufficiently powered for a full cost-effectiveness analysis. The results of a full cost-effectiveness analysis based on an insufficient sample are likely to be biased. We believe that presenting such results would mislead audience. Therefore, in the case of the trial stops at the pilot stage, we will present descriptive results of the healthcare resources and EQ-5D by randomised groups, as we will have done for a standalone feasibility study.

7 SIGNATURES OF APPROVAL

Trial health economist: Jinshuo Li

Signature: _  ___Date: _14 Apr. 25_____

Senior health economist: Steve Parrott

Signature: _____Date: 14/4/25

Trial manager: Liz Cook

Signature: Date: 14/04/2025

Co-Chief investigators: Matthew Gardiner & Emma Reay

Signature: Date: 28/04/2025

Signature: Date: 28/04/2025

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