DISC

Dupuytren's Interventions Surgery vs Collagenase

HEALTH ECONOMICS ANALYSIS PLAN
Version 1.0

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Contents

1. GENERAL

1.1 Document Scope

This analysis plan (HEAP) deals only with the economic analysis of the DISC trial; the statistical analysis of clinical effectiveness will be detailed in a separate plan.

1.2 Glossary

CRF	Case Report Form
CEA	Cost-effectiveness Analysis
CEAC	Cost-effectiveness Acceptability Curve
CUA	Cost-utility Analysis
CI	Confidence Interval
EQ-5D-5L	EuroQol Quality of Life Measure (5-level response version)
GP	General Practitioner
HEAP	Health Economic Analysis Plan
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-effectiveness Ratio
ITT	Intention to Treat
MAR	Missing at random
MI	Multiple Imputation
NHB	Net health benefit
NICE	National Institute for Health and Care Excellence
OT	Occupational Therapist
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALYs	Quality-adjusted life years
RCT	Randomised Controlled Trial
SOP	Standard Operating Procedure
TMF	Trial Master File
VAS	Visual Analogue Scale
YTU	York Trials Unit

1.3 Applicable Standard Operating Procedures

The YTU Health Economics SOP (SOP ID: HE01, version 1.0, 06 Feb 2015) will be followed. Data and documents relevant to the Health Economist will be kept in a Health Economics Master File on an analysis folder following the directory structure detailed in the YTU Standard Operating Procedure (SOP) entitled “Directory structure and version control” (SOP ID: DS01, version 3.0, 04 May 2016).

2. TRIAL SUMMARY

The following sections give a high-level summary of the Dupuytren's Interventions: Surgery Vs Collagenase (DISC) trial. Full details are given in the detailed trial protocol (latest version 2.1, dated 08/03/2019). The statistical analysis will be detailed in a separate Statistical Analysis Plan (latest version 1.0, dated 28/09/2021).

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the DISC trial is to determine whether collagenase injection followed by manipulation is not inferior to limited fasciectomy surgery for the correction of Dupuytren's contracture of the hand. The primary outcome used to assess non-inferiority will be patient reported scores for part two of the Patient Evaluation Measure (PEM) at 12 months post treatment.

2.1.2 Secondary Objectives

- To investigate the cost-effectiveness of collagenase compared to limited fasciectomy surgery, in adult patients with moderate Dupuytren's contracture of the hand eligible for inclusion in DISC trial[1]
- To investigate whether the correction achieved after Collagenase injection or surgical correction is maintained to 5 years (if justified by findings from the analysis at 1 year and 2 years).
- To explore patient's preferences of the different treatments (Qualitative sub study).
- To investigate if remote measurement of extension deficit using photographs is as good as goniometric measurements in clinic to determine recurrence (Photography sub study).

2.2 Design

DISC is a multi-centre, randomised controlled non-inferiority trial of collagenase injection and manipulation versus limited fasciectomy surgery for the treatment of Dupuytren's contracture. In addition to the main study, DISC contains a qualitative sub study and a photography sub study. Participants enrolled in the main study may opt to enrol in one, both or neither of the sub studies. Randomisation will be carried out using a secure randomisation service. Participants allocated to the intervention arm of the study will receive a collagenase injection, followed soon after by manipulation of the contracted cord. Participants allocated to the control arm will receive limited fasciectomy surgery. Due to the nature of the interventions under investigation, it is not possible to blind clinicians or participants to their treatment allocation. Both treatments should be delivered within 18 weeks of randomisation (as per referral to treatment time), however where possible sites should deliver treatment within 12 weeks of randomisation. The study has a total 30-month recruitment period, including an internal pilot phase of 6 months at the start followed by the main recruitment period.

[1] Patients included met all of the following criteria: (1) Male or Female and aged 18 years or over; (2) Presence of discrete palpable cord; (3) Presence of contracted joint involving the metacarpophalangeal joint and/or proximal interphalangeal joint of a finger; (4) Degree of contracture >30 degrees in either joint i.e. patient cannot put the palm of the hand flat on a table (Hueston's Table top test); (5) Able to have either surgery or collagenase injection for Dupuytren's contracture; (6) Patient is willing and able to give informed consent for participation in the study.

Following Baseline and randomisation, participants will be followed up for 24 months and will complete follow up visits at 3 months, 6 months, 12 months, and 24 months post randomisation.

2.3 Outcomes

2.3.1 Primary outcome

- ***Patient Evaluation Measure (PEM)****:* The PEM [1] is a validated 19 item patient reported outcome measure comprised of three parts.
    - Part 1 is comprised of 5 items which ask the participant about their experience of treatment and the care they received.
    - Part 2 is comprised of 11 items which ask the participant about their hand's functionality and any pain they may experience.
    - Part 3 is comprised of 3 items and provides an overall assessment of the participant's feelings about their hand condition and treatment.

  The participant assigns each item an integer score between 1 and 7, where higher scores indicate worse outcomes/experiences. The PEM was collected at baseline, immediately prior to treatment delivery and at 3, 6, 12- and 24-months post treatment. Participants are instructed to complete the PEM with respect to the hand designated as the study reference hand. The primary endpoint is the change in PEM between baseline and 12 months. PEM data will be split into three scales: (i) PEM - Hand Health Questionnaire (11 items); (ii) Hand Health and Overall Assessment Questionnaire (14 items); and (iii) Treatment Questionnaire (5 items). Full details regarding the scoring and analysis of the PEM data are given in a separate Statistical Analysis plan.

2.3.2 Secondary outcomes

2.3.2.1 Clinical outcomes

- ***URAM Unité Rhumatologique des Affections de la Main Scale****:* the URAM [2] is a validated, 9 item, disease specific disability scale assessing the difficulty experienced by the participant in performing particular tasks or movements. Each item is scored between 0 and 5 with higher scores indicating greater difficulty. Participants will complete the URAM at baseline and 3, 6, 12 and 24 months post treatment. Full details regarding the scoring and analysis of the PEM data are given in a separate Statistical Analysis plan.
- ***Michigan Hand Questionnaire (MHQ)*****:** the MHQ [3,4] is a validated, 63 question measure featuring 6 domains: overall hand function, activities of daily living, work performance, pain, aesthetics and patient satisfaction with hand function. Each item is scored between 1 and 5, with some items pertaining to a specific hand and some pertaining to both hands. Overall MHQ score calculated for the reference hand. Participants will complete the MHQ at baseline and 12- and 24-months post treatment. Full details regarding the scoring and analysis of the MHQ data are given in a separate Statistical Analysis plan.

- ***Single Assessment Numeric Evaluation (SANE):*** SANE [5] is a single patient reported numerical assessment of hand function, provided by means of a VAS. Participants are asked the following question "How would you rate your hand function today (with normal being 100%)?". Participants respond by marking a single point on a line between 0 and 100%, to indicate the extent to which they perceive their hand function as being normal. A SANE score will be collected at baseline, 2- and 6-weeks post treatment and 3, 6, 12 and 24 months post treatment.
- ***Overall hand assessment***: participants will be asked the following question "Overall, how are the problems now, with the hand in which you had treatment, compared to before?" at 3, 6, 12- and 24-months post treatment. Participants are given a choice of the following 7 responses; Cured, Much better, A little better, The same, A little worse, Much worse, Terrible. This will provide a simple global assessment of participant's subjective comparisons of their hand pre and post treatment, and how well improvement post treatment lasts over the follow up period.
- ***Joint measurements:*** various goniometric measurements will be collected and recorded by investigators in clinic. These will be used ***to assess recurrence of contracture post treatment and changes in range of motion***. The collection of this data is summarised below:

Measurement type	Baseline	Pre treatment	3 months	6 months	12 months	24 months
Active extension	x	x	x	x	x	x
Flexion	x		x	x	x	x
Passive extension	x	x	x	x	x	x

Recurrence is defined as a change in extension deficit (measured as passive extension) of the reference joint of 6° or greater between 3- and 6-months post treatment, or 20° or greater between 3- and 12-months post treatment [6]. This definition will be used to calculate and compare recurrence rates in each arm at 6- and 12-months post treatment.

Range of motion: Passive and active extension measurements and flexion measurements will be used to calculate the participant's passive and active range of motion at baseline, and 3, 6, 12 and 24 months post treatment and will be used to assess how range of motion changes over time. This will help inform the level of functionality experienced by the participant and how well this is maintained post treatment.

- ***Complications:*** Post treatment complications occurring since the previous follow up will be recorded at 3, 6, 12 and 24 months post treatment. The start and stop dates of any complications will be recorded (if not ongoing at the time of CRF completion) and other details, including relatedness to study treatment and severity, will be recorded as part of the usual trial adverse event reporting procedures. For costing purposes, outpatient visits, A&E attendances and hospital inpatient admissions related to complications will be specifically identified using an adverse event number.
- ***Further Procedures***: data on further treatments and procedures received since the previous follow up will be collected at 3, 6, 12- and 24-months post treatment. This will include the timing of the treatments, whether the treatment is related to the reference hand/finger, and details of the treatment received.

- ***Photographs in clinic***: Three photographs of participants' hands will be collected at baseline and 3, 6, 12- and 24-months post treatment. Similarly, participants consenting to the photography sub study are shown how to take the required photographs (the same images as taken in clinic) of their hand at baseline and provided with detailed instructions. Sub study participants are asked to take standardised photographs of their study reference hand at baseline (as soon after the baseline visit as possible) and 3- and 6-months post treatment. Full details regarding the scoring and analysis of the MHQ data are given in a separate Statistical Analysis plan.

2.3.2.2 Quality of life

EuroQol EQ-5D-5L

The EQ-5D-5L is a validated instrument for assessing health-related quality of life (HRQoL), comprised of 5 items, with 5 levels of response and a single general health status VAS [7]. The EQ-5D-5L measures HRQoL in terms of 5 dimensions: mobility, self-care, usual activities, pain and discomfort, anxiety and depression. For each dimension, participants rate the extent of their problem as 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'extreme problems/unable'. Participants will complete the EQ-5D-5L at baseline, 2 and 6 weeks post-treatment, and 3, 6, 12 and 24 months post-treatment. According to the responses to the EQ-5D classification system, a health status can be defined, and a single index utility assigned. The EQ-5D-5L will be used to estimate the impact of both treatments on health-related quality of life as per quality-adjusted-life years (QALYs). Details about utility estimation and the conversion of utilities into QALYs are given in section 4.3.3.

2.4 Other important information

- ***Treatment preferences:*** participants will be asked about their treatment preferences at baseline. Participants indicate whether they would prefer to receive collagenase, limited fasciectomy or have no preference. The baseline CRF is clear that their response to this question will have no impact on their chances of receiving a particular treatment. This data will be used as part of a subgroup analysis to explore the possibility that participants receiving/not receiving their preferred treatment has an effect on outcome.
- ***Demographic information (at baseline)***
    - Gender
    - Date of birth
    - Ethnicity
    - Tobacco smoking status (Never, Current, Previous)
    - Alcohol intake (Units per week)
    - Which hand is their dominant hand
- ***Condition history and diathesis indicators (at baseline)***
    - Age at which they first experienced Dupuytren's contracture
    - Details of previous treatment with surgery and/or collagenase
    - Family history of Dupuytren's contracture
    - History of Garrod's pads and details of current symptoms if applicable
    - History of Peyronie's disease if applicable
    - History of Ledderhose disease and details of current symptoms if applicable

- ***Comorbidity:*** At baseline participants will be asked to provide information about comorbid conditions they may be suffering from including how long they have had the condition, whether it is being treated at present, and whether they are satisfied with the treatment

- ***Concomitant medications****:* participants will be asked to provide the following details at baseline, to ensure they are not contraindicated to receipt of collagenase
    - whether using anticoagulants, for reasons other than a coagulation disorder
    - whether they are using anti-platelet agents
    - whether they have used tetracycline antibiotics in previous 14 days
    - to provide the following details regarding their use of concomitant medications:
        - name of medication
        - reason for use
        - dose
        - frequency
        - route of administration
        - date they started using the medication (if known)
        - date they stopped using the medication (if known and use is not ongoing)

  At the four-post treatment follow ups they will provide an update about their use of concomitant medication since the previous follow up.

- ***Condition details and clinical assessment****:* at baseline participants will undergo a brief clinical assessment which will, in addition to their goniometric measurements and patient reported assessments, provide an overall summary of the current state of their condition:
    - Hands affected
    - Number of digits currently affected
    - Joints currently affected
    - Number of joints affected on the hand being treated as part of the study
    - Joint that will be used as the designated study reference digit

- ***Adverse Events****:* an adverse event (AE) is defined as any untoward medical occurrence experienced by any DISC study participant, which may or may not have a causal relationship with the study treatment. An AE will be defined as a serious adverse event (SAE) if it fulfils one, or more, of the following criteria
    - Resulted in death
    - Was life threatening
    - Resulted in inpatient hospitalisation or prolongation of existing hospitalisation
    - Resulted in persistent or significant disability or incapacity
    - Resulted in congenital anomaly or birth defect
    - Required a surgical or medical intervention to treat/prevent any of the above

  All SAE/AEs will be reported and followed up using SAE/AE report forms. The following data will be collected:

    - Whether or not the AE/SAE was a complication associated with the study treatment
    - Specific information about the AE/SAE
    - Action taken/treatment given
    - Date of onset
    - Date of remission (if not ongoing)
    - Outcome
    - Treatment received

- Relationship to study treatment
- Expectedness
- Seriousness
- Details of death
- Follow up details

For costing purposes, outpatient visits, A&E attendances and hospital inpatient admissions related to adverse events will be specifically identified using an Adverse event number.

3. ECONOMIC DATA

3.1 Data sources

Data will be principally collected on paper CRFs, completed by both the study participants and investigators. A copy of the CRFs with the variable names from the database (known as 'specs') is kept by the Health Economist in the Health Economics folder: Y drive > DISC > Health Economics > Analysis > Rawdata > CRF specs. The CRFs saved by the Health Economist are the final versions, taken from the following area: Y drive > DISC > Analysis > Rawdata > CRF Specs. The paper CRFs approved for DISC are as follows:

FOR STUDY INVESTIGATOR COMPLETION:

- Confirmation of eligibility CRF (completed during baseline visit)
- Investigator baseline CRF
- Supplementary baseline joint measurements CRF
- Treatment delivery CRF
- Investigator month 3 CRF
- Investigator month 6 CRF
- Investigator month 12 CRF
- Investigator month 24 CRF
- Investigator month 3/6/12/24 supplementary outpatient hospital visits CRF
- Investigator month 3/6/12/24 supplementary inpatient hospital visits CRF
- Investigator month 3/6/12/24 supplementary accident and emergency visits CRF
- Supplementary concomitant medication CRF
- Adverse event initial report form
- Serious adverse event initial report form
- Adverse event follow up form

FOR STUDY PARTICIPANT COMPLETION:

- Participant baseline CRF
- Participant pre-treatment CRF (completed during treatment delivery visit)
- Participant week 2 CRF
- Participant week 6 CRF
- Participant month 3 CRF
- Participant month 6 CRF
- Participant month 12 CRF
- Participant month 24 CRF

3.2 Follow up

Patient follow up was undertaken at 3, 6, 12 and 24 months post-randomisation. Data feeding into the economic analysis were collected via the baseline, 2 and 6 weeks post-treatment, and 3, 6, 12 and 24 months CRFs and questionnaires booklets completed by participants and study investigators.

The following was performed at the Baseline assessment and was recorded in the CRF:

- Condition history (age of onset, number of digits affected, previous surgery to opposite hand)
- Joint measurements using a goniometer of the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints for each of the digits involved in both extension and flexion.
- Diathesis indicators (Age, Garrod's pads, family history, distant sides to include Peyronie's disease and Lederhosen disease).
- The Kaplan-Feinstein index (KFI) of co-morbidity including presence or absence of diabetes and epilepsy.
- Photographs of the hand.
- Clinical assessment of discreet and palpable cord(s) across or near the contracted joint(s) including pits and nodules.
- Concomitant medications.

3.3 Management of datasets and data verification

The health economics analysis will use the dataset that has been finalised by the Trial Statistician. Any external datasets will be covered in the study Data Management Plan.

3.4 Location of Data and Associated files

Data and documents relevant to the health economist will be kept electronically on the YTU analysis drive (Y:\DISC\Health Economics).

4. ANALYSIS

4.1 Methods overview

A cost-effectiveness analysis will be conducted from the perspective of the UK health system. The analysis will estimate the impact of collagenase and limited fasciectomy surgery, for adult patients with moderate Dupuytren's contracture, on the health of the patients and the costs to the NHS and personal social services (PSS), in both the short and long term.

The economic analysis will consist of the following:

- A within trial analysis with total costs and QALYs presented for both intervention groups. The time horizon of this analysis will be twelve months. This analysis will assess the short-term effect on patients' health and costs to the NHS of both treatments considered in the DISC study (see section 4.3).
- Extrapolation of mean health-related quality of life and cost estimates observed during the trial period over time if results deem appropriate. This extrapolation analysis will consider the long-term implications, in which mathematical modelling of expected future health of patients

is used to estimate lifetime costs and QALYs beyond the time frame of the study. The long-term cost-effectiveness analysis will involve the development of a new decision analytic model based on the treatments considered in the DISC trial (i.e. collagenase and limited fasciectomy). It is likely that the structure of this new model will be on the risk of recurrence, treatment for complications and need for further procedures (i.e. surgery) and its extrapolation to the longer term (see section 4.4).

- Needle fasciectomy, another type of fasciectomy, is also used as standard care in the NHS for the treatment of Dupuytren's disease. Hence, we will also conduct an additional threshold analysis to explore what the effectiveness would have to be of limited fasciectomy versus needle fasciotomy to change the cost-effectiveness threshold (see section 4.5).

The analysis will be consistent with the NICE Guide to the Methods of Technical Appraisal [8] and Decision Modelling for Health Economics Evaluation [9]. All analyses will be conducted following an intention-to-treat (ITT) basis on a locked dataset using the latest available version of Stata. The analyses will be undertaken from the perspective of the UK NHS and personal social services (PSS). Therefore, only direct costs will be included. Secondary analyses will be conducted for the societal perspective for the ITT population.

4.2 Comparators

Surgical correction of the contracture by dissecting the cords and excising them (limited fasciectomy) is the standard treatment in the UK and Europe for the management of Dupuytren's contracture of the hand [10, 11]. A recently introduced alternative treatment to correct Dupuytren's contracture is to dissolve the cord by injecting an enzyme, Collagenase, and then manually snapping the weakened cord within a few days to correct the contracture. This treatment is not however widely offered in the UK yet patients are increasingly seeking collagenase injections as an alternative treatment for Dupuytren's contracture. A benefit of this procedure is that it can be conducted within a clinic setting, however, patients do however need to attend additional clinic visits to complete the procedure. The significant side effect associated with Collagenase is the potential for tendon rupture [12], which may require surgical intervention. Initial clinical effectiveness studies of collagenase compared to a placebo [13] and recent systematic review [14] of such studies have both indicated that collagenase is found to be better than placebo, particularly for contracture affecting the metacarpophalangeal joint. There is however no robust randomised controlled trial evidence available that provides a definitive answer on the clinical effectiveness of collagenase vs surgery. Observational data in relation to recurrence of Dupuytren's contracture [14] suggests that this is higher following collagenase treatment than surgery at 3 years post treatment.

The National Institute for Health and Care Excellence (NICE) have appraised the clinical and cost effectiveness of Collagenase (NICE TA459) identifying the need to establish whether collagenase is more clinical and cost-effective compared to surgical treatment [15]. The economic evaluation conducted alongside the DISC trial will assess the cost-effectiveness of collagenase injection and manipulation versus limited fasciectomy surgery for the treatment of Dupuytren's contracture.

Patients will receive the intervention (collagenase injection) or control (limited fasciectomy) within 18 weeks of randomisation. Separate cords can be injected or operated on at the same treatment visit. However, a reference/predominant cord will be identified prior to randomisation, with follow-up assessments (e.g. recurrence, further procedures) being based on this cord.

4.2.1 Collagenase injection

Collagenase Clostridium histolyticum (Xiapex) is an enzyme activated by mixing a powder with fluid in set quantities (0.58mg) immediately prior to injection. Either 0.25ml (MCP joint) or 0.20ml (PIP joint) of reconstituted solution (0.58mg Collagenase Clostridium histolyticum) will be injected as three aliquots at set anatomical points. After an interval of one to seven days, the participant will return to clinic and, under local anaesthetic, the cord will be snapped correcting the contracture.

4.2.2 Limited fasciectomy

The diseased fascia, nodule and cord, or a part of it, are removed to correct the joint contracture [16, 17]. The intervention is undertaken under anaesthesia. Following limited fasciectomy, participants will be reviewed at a routine wound check.

4.3 Within trial analysis methods

4.3.1 Approach to analysis

The with-in trial analysis will consider the costs and health outcomes, in terms of QALYs, at a patient level based on a twelve months perspective. These data will be collected prospectively during the study. Relevant summary statistics and estimates of the quality of life and costs associated with patients will be reported both at a complete case level (i.e. dropping all cases of missing data) and after imputation (see section 4.3.4). We will estimate mean differences in total costs and QALYs between the arms, and the incremental cost-effectiveness ratio (ICER) for the collagenase to estimate the incremental cost per QALY gained. The ICERs will be calculated by dividing the mean difference in cost with the mean difference in QALYs using regression methods, which are used to take into account differences in stratification or prognostic variables, and other sources of heterogeneity. Baseline covariates will be in line with the statistical analyses. We will conduct the analysis using a bootstrap framework. The bootstrap's main advantage is dealing with skewed data, which often characterise economics data. The analysis will be conducted on an ITT basis using the latest available version of Stata.

4.3.2 Estimates of resource use and unit costs

A tailored system will be put in place to collect detailed information on the costs of collagenase and limited fasciectomy. The impact of the two interventions on subsequent morbidity costs will be assessed. During the various follow-up points, by means of administered questionnaires, we will collect the following data for the economic analyses:

- *Delivery of limited fasciectomy (collected via **Treatment delivery CRF**):*
    - Date of surgery
    - Time in theatre
    - Hospitalisation type: day case or inpatient admission (including date of discharge)
    - Unplanned admission
    - Type of anaesthetic used and anaesthetist grade

- Joints and hand treated
- Operating surgeon grade
- Assisting surgeon grade
- Antibiotics used
- Limitations identified (i.e. no cord, tight skin, pain, anxiety)
- Medications prescribed to treat limitations
- Degree of correction to reference digit
- Wound clinic appointment following limited fasciectomy: clinic duration, staff in clinic and degree of correction in the reference digit

- *Collagenase administration (collected via **Treatment delivery CRF**):*
  - Date of collagenase administration
  - Joints and hand treated
  - Volume of drug administered
  - Limitations identified (i.e. no cord, tight skin, pain, anxiety)
  - Staff in clinic during procedure
  - Unplanned admission following procedure (including AE number)
  - Joint manipulation: time, type of anaesthetic used and staff in clinic during manipulation
  - Degree of correction in the reference digit.
- *Hospital resource use after index treatment (i.e. collagenase or limited fasciectomy) – collected using **Investigator month 3-6-12-24 CRF:***
  - Outpatient visits: date of visit; clinic type; whether visit related to the reference digit/hand; whether visit related to a post-treatment complication or AE (if related AE number will be recorded); whether patient received actual treatment as opposed to reassurance/observation (i.e. physiotherapy, splint of finger, collagenase injection, limited fasciectomy, percutaneous needle fasciectomy, dermofasciectomy)
  - Accident & Emergency visits: date of visit; HRG code; whether visit related to the reference digit/hand; whether visit related to a post-treatment complication or AE (if related AE number will be recorded); whether patient received actual treatment as opposed to reassurance/observation; whether patient was admitted as an inpatients following the A&E visit
  - Inpatient admissions: date of admission; date of discharge; HRG code at discharge; whether visit related to the reference digit/hand; whether visit related to a post-treatment complication or AE (if related AE number will be recorded).
- *Hospital resource use after index treatment (i.e. collagenase or limited fasciectomy) – collected using **Participant month 3-6-12-24 CRF:***
  - Outpatient visits: number of visits to see a surgeon for follow-up assessment of hand/finger for any of the following reasons – surgical hand procedure, collagenase injection or manipulation to the finger
  - Outpatient visits to see a nurse, a physiotherapist, and occupational therapist or to the pain clinic
  - Number of visits to A&E related to the hand/finger
  - Inpatients nights in hospital related to the hand/finger

- *Primary and Community resource use after index treatment (i.e. collagenase or limited fasciectomy)* – ***collected using Participant month 3-6-12-24 CRF:***
    - Visits to GP
    - GP nurse
    - Physiotherapist
    - Occupation therapist
- *Productivity costs and private treatments* – ***collected using Participant month 3-6-12-24 CRF:***
    - Employment status (i.e. in full time, part time, not employed, not paid employment, retired)
    - Days missed of work due to the finger/hand
    - Hours lost from normal activities
    - Times seen a private hand specialist for an assessment
    - Times seen a private hand specialist for a collagenase injection
    - Times seen a private specialist for a surgical treatment

Hospital resource use will be collected using both investigator and participant forms. We anticipate that we will use investigator CRFs as the source for the primary analysis whilst patient's CRFs will be used as per sensitivity analysis if deemed appropriate. As already stated, the primary perspective of the analysis will be that of the NHS and Personal Social Services, however, given the implication of Dupuytren's disease for the patient in terms of loss of earnings and days loss of normal activities, a secondary analysis from a broader perspective will be conducted, which will include also private expenditures related to hand/finger treatment. We anticipate that costs falling on different sectors will not be added together in accordance with economic guidance [18].

The total NHS cost (e.g. base-case analysis) and total wider cost (e.g. secondary analysis) will be calculated by multiplying resource data by their unit cost. Unit costs will be sourced from published relevant sources relevant to the UK costs (e.g. BNF list prices for pharmaceuticals and PSSRU unit costs and/or NHS reference costs for healthcare resource use). The unit cost items will be summarised and presented in the report/publication. All costs will be evaluated in pounds sterling (£) for the appropriate year (e.g. 2020). In cases where costs are sourced from previously published data, costs will be inflated to the appropriate year figures. The productivity costs will be derived assuming an average workday of 7.5 hours and the average hourly wage across all UK residents as estimated from the Office for National Statistics.

Health care resource use results will be presented for both arms in terms of mean value, standard error and mean difference (with 95% confidence intervals) between the groups. Costs will be divided into two components for the analysis: costs associated with the interventions (collagenase and limited fasciectomy) and all other costs. Regression analysis will be used to relate costs to baseline characteristics.

4.3.3 Estimates of Health-Related Quality of Life

Health outcomes will be expressed in terms of the quality-adjusted life year (QALY), which captures the impact of treatment on both mortality and morbidity by 'weighting' each period of follow up time by the value corresponding to the quality of life (using the EQ-5D-5L) during that period.

The EQ-5D will be administered at baseline, 2 weeks. 6 weeks, 3-6-12 and 24 months. The raw EQ-5D-5L scores by domain will be presented to examine the movements between levels for each domain by trial arm. According to the responses to the EQ-5D classification system, a health status can be defined and a single index utility assigned. A value set for the EQ-5D-5L is now available that reflects the preference of members of the public in England for health states that are defined by the EQ-5D-5L descriptive system [19]. However, this value set is currently under revision. NICE current recommendation [20] on the use of the EQ-5D advises that utilities for the 5L are derived using the crosswalk mapping function developed by van Hout et al. (i.e. mapping of the 5L descriptive system data onto the 3L valuation set) [21]. Therefore, unless the NICE guidance is changed by the time of our analysis, the crosswalk will be used to derive utilities for the participants in the DISC trial. The overall difference in EQ-5D index scores between the arms will be examined through regression methods, consistent with the model selected in the statistical analysis. Utility scores will be converted into QALYs using area under the curve analysis [22]. The summary of QALYs at each time point and total QALYs will be presented. The difference in QALYs gained between the arms will be adjusted for baseline utility weights [23] to allow for any differences between the groups at baseline.

4.3.4 Missing data

We anticipate that there may be reasonably high levels of missing data for resource use and quality of life. We will explore the amount of missing data on costs and quality of life at each follow-up period and whether missing data is restricted to individual items of resource use or HRQoL, or is missing for all items at specific visits. We will conduct a comprehensive investigation of missing data pattern following missing data guidelines [24, 25, and 26]. The following approach will be used to impute missing data if necessary. Missing baseline covariate data will be imputed using mean imputation. Multiple imputation with chained equations will be used to impute costs and HRQoL based on patient characteristics and previous cost and HRQoL outcomes, this will be done separately for each trial arm. Multiple imputation with chained equations is the dominant method in economic evaluation [27] for dealing with incomplete data across multiple variables.

4.3.5 Impact of lost employment and unpaid activities

The DISC trial will assess the impact of both treatments on days of lost employment and unpaid activities. Hence, in addition to the base base-case analysis conducted from the perspective of the NHS and PSS, we will conduct a secondary analysis to explore the impact of productivity costs and unpaid activities on cost-effectiveness results.

4.4 Modelling methods

As already stated, the within trial economic evaluation will be based on a twelve month time horizon. However, given the time horizon, it is unlikely that all relevant costs and effects are captured in the analysis. Therefore, to estimate the long-term cost-effectiveness of CHH compared to limited fasciectomy, we will conduct additional analyses predicting the lifetime quality adjusted life expectancy and costs.

4.4.1 Literature searches

Since the start of the trial a number of literature searches have been conducted to identify publications relevant in this area. Besides, we will use the evidence identified through this review to retrieve previous cost-effectiveness models in the patient groups eligible for the DISC trial. These searches will be also useful to determine if previous mathematical models could be adapted to estimate the long-term cost-effectiveness. Similarly, the evidence retrieved from these searches will be used to populate our models if required.

4.4.2 Analytical approach

The analysis will be consistent with the NICE Guide to the Methods of Technological Appraisal [8] and Decision Modelling for Health Economic Evaluation [9]. A state-transition model will be used in this analysis (see sections 4.4.6 and 4.4.7). State-transition models use a series of health states which demark important changes to prognosis, costs, or quality of life.

The outcomes of the model will be used to determine the cost-effectiveness of collagenase injection and manipulation versus limited fasciectomy surgery in terms of lifetime cost, expected life-years and expected QALYs. These estimates will be compared across treatment options by estimating the ICER as appropriate [28]. A cost-effectiveness threshold of £20,000/QALY will be used as the base-case value to estimate the net health benefit (NMB) of each of the treatment options [29]. A threshold of £13,000/QALY will be also used as suggested by recent research [30, 31]. The NMB will be estimated as the increase in effectiveness multiplied by the amount that the decision maker is willing to pay per unit of increased effectiveness (i.e. the cost-effectiveness threshold) minus the increase in cost. The uncertainty around the model estimates will be assessed using probability sensitivity analysis (PSA) and scenario analysis. PSA explicitly incorporates the uncertainty in parameter estimates by using the range of values over which these estimates exist (characterised by an informative distribution), rather than single point estimates, as inputs into the models [32]. The choice of distribution to describe the uncertainty in individual parameters will be guided by the form of the data, the type of parameter and the estimation process for the parameter [32].

4.4.3 Analytical perspective

Consistent with the within-trial analysis, the extrapolated model will be conducted from the perspective of the UK health system. A lifetime time horizon will be used in the base-case analysis to reflect the full duration of impact of potential long term effects related to both treatments. Both costs and outcomes are discounted using a 3.5% annual discount rate consistent with current guidelines [8]. The model will be developed in Excel.

4.4.4 Decision problem

The model aims to determine the long term cost-effectiveness of collagenase injection and manipulation compared to limited fasciectomy for the treatment of Dupuytren's disease. The model will take into account the risk of recurrence, treatment for complications and need for further procedures (i.e. surgery) and its extrapolation to the longer term.

4.4.5 Population and patient heterogeneity

The population considered in the extrapolated model will be consistent with DISC. There is likely to be considerable heterogeneity in the baseline quality of life and costs, which will impact the absolute benefit and costs of treatment and subsequently influence the cost-effectiveness results. Heterogeneity will be captured by including baseline prognostic factors in regressions (costs, HRQoL)

that will inform the economic model. Selection of regression covariates will be in line with the statistical analyses.

4.4.6 Model structure

The precise structure of the model will be developed during the project in collaboration with clinical colleagues but it is likely to be based around the long-term consequences of surgical complications (i.e. recurrence).

4.4.7 Model inputs

Transition estimates

Short-term model inputs will be mainly derived directly from DISC. Similarly, we anticipate that long-term model inputs will be likely to be informed by DISC evidence. The base-case patient cohort that will be modelled will be consistent with the population observed in DISC.

Resource use and costs estimates

Consistent with the model structure, it is anticipated the costs incurred by the NHS during the first year (or two years if the data allows) will be directly sourced from DISC. Again, we anticipate that the costs associated with the long-term model will be informed using evidence from DISC.

Health-Related Quality of life inputs

As with the estimation of cost, EQ5D utility scores estimated from DISC for the first year (or two years if the data allows) will be used as model QoL inputs in the short-term model.

The systematic review of economic evidence by Brazzelli et al (2015) revealed that no preference-weighted quality-of-life values have been reported from patients with DC. Therefore, their modelling relied on pre- and post-treatment utility values estimated from the equation specified by Gu et al [15], who elicited health-state utilities for DC from the general population using a discrete choice experiment. This study sample appeared to be relatively representative of the UK population. Their utility estimates were dependent on degree of contracture, joint type and the finger in which the contracture occurred. The authors employed an anchoring method to restrict participants' preferences onto the traditional 0–1 utility scale. Hands that were unaffected by DC were assigned a perfect utility score of 1, whereas the utility value for a hand that exhibited the worst possible DC (i.e. 90° of contracture in all eight joints) was derived by asking participants what levels of the European Quality of Life-5 Dimensions (EQ-5D) 5 levels of severity (EQ-5D-5L) profile would be most likely to be affected by living with this hand. Conditional logistic logit models were employed to estimate indirect utility estimates, which were subsequently rescaled to the anchor points on the EQ-5D-5L. The utility estimates were therefore dependent on degree of contracture, joint type and the finger in which the contracture occurred.

It is likely that current evidence on the QoL relevant to the long-term analysis is still limited and diverse. Hence, evidence from DISC will be used to calculate quality of life impacts of having a recurrence and extrapolate over time using regression analysis.

4.4.8 Uncertainty and Scenario Analysis

It is widely accepted that there needs to be an assessment of how sensitive a decision based on cost-effectiveness is to uncertainty in parameter values in decision modelling. Methods for this are well

established in the literature [28, 33]. The economic model that will be developed will be probabilistic in that estimates of input parameters will be specified as full probability distributions, rather than point estimates, to represent the uncertainty surrounding their values. The choice of distribution to describe the uncertainty in individual parameters will be guided by the form of the data, the type of parameter and the estimation process for the parameter [34]. Monte Carlo simulation will be used to propagate uncertainty in input parameters through the model [32, 35] and the imprecision of the cost-effectiveness results, i.e., the decision uncertainty, will be represented using methods such as cost-effectiveness acceptability curves [35].

As is common in the conduct of models, a number of assumptions will have to be made alongside the interpretation of available evidence as necessary. The impact of the assumptions on the results will be explored by means of scenario analyses (see table 1). Specifically, we will explore the sensitivity of results to key assumptions on costs, imputation approach and time horizon for the short-term (i.e. within-trial) cost-effectiveness analysis. Besides, needle fasciotomy, another type of fasciectomy procedure, is also used as standard care in the NHS for the treatment of Dupuytren's disease. Hence, one way sensitivity analysis with respect to the needle fasciectomy will be also conducted.

4.5. Threshold analysis

Threshold analysis quantifies minimum change before the recommendation change in specific parameter value required to change the conclusions of the cost-effectiveness analysis. During the course of DISC, collagenase clostridium histolyticum (Xiapex) has been withdrawn from the European market, therefore collagenase is no longer available in the UK. This has not resulted in any change to the DISC trial protocol or analysis plans. However, if DISC results revert this decision, it would be useful to explore at what level the price of collagenase become cost-effective. Hence, we will apply threshold analysis, as an extension of our sensitivity analyses, to explore the maximum price that would result in collagenase considered cost-effective given different levels of health outcome. Finally, we will also explore what the effectiveness would have to be of limited fasciectomy versus needle fasciotomy, given the price, to change the cost-effectiveness threshold.

5. FUTURE WORK

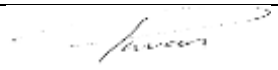
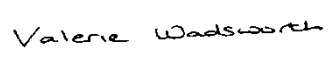
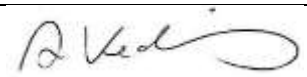
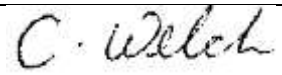
The planned follow-up in the DISC trial participants is two years. The option to investigate whether the correction achieved after collagenase injection or surgical correction is maintained to 5 years can be conducted subject to future funding.

The HAND-2 trial has also been funded by the National Institute for Health Research (NIHR) to investigate the clinical and cost effectiveness of needle fasciotomy compared to limited fasciectomy for treatment of Dupuytren's contractures. As DISC and HAND-2 trials have a common comparator arm (limited fasciectomy), there is potential for indirect comparisons. Furthermore, HAND-2 has been funded to conduct an individual patient data network meta-analysis comparison with DISC. Hence, we aim to seek early collaboration with HAND-2 to explore how best we should structure our model and analysis to make sure our DISC's model fit any posterior analysis in HAND-2.

6. INCORPORATION OF FUTURE GUIDANCE ON TAKING THE COVID-19 PANDEMIC INTO ACCOUNT IN STATISTICAL ANALYSIS

We do not anticipate any further analyses assessing the impact of the Covid-19 pandemic on the study results. However, work is currently being done in the trial's community on this topic, and should guidance relevant to the DISC trial be published, the trial team will update the HEAP with the approval of the DMEC and TSC. All updates be carried out before the end of data collection.

7.SIGNATURES OF APPROVAL

Name	**Trial Role**	**Signature**	**Date**
Prof. Joe Dias	Chief Investigator		12th October 2021
Belen Corbacho	Health Economist		12th October 2021
Dr Puvan Tharmanathan	Trial Manager		19th October 2021
Val Wadsworth	Data Manager		27th October 2021
Ada Keding	Statistician		10th December 2021
Charlie Welch	Statistician		8th December 2021

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9. APPENDICES

9.1 Planned Tables and Figures

9.1.1 Primary Analysis

9.1.2 Missing data

KEY TABLES

Table 0: Details of DISC Data Collection Schedule
Table 1: Key elements of the base-case analysis and the variation used in sensitivity analysis
Table 2: Unit costs (and sources) used to estimate total cost for each individual patient
Table 3: Hospital resource use values and medications for available cases by trial allocation, study period and resource category
Table 4: Community resource use values for available cases by trial allocation, study period and resource category
Table 5: Summary of costs accrued at 3, 6 months, 1 year and 2 years – base case (ITT)
Table 6: Participant response to EQ-5D questionnaire at each time point (absolute and relative frequency)
Table 7: Numbers and proportions of levels within the EQ-5D-5L dimensions by allocation arm at baseline and 24 months follow up (complete cases)
Table 8: EQ-5D-5L mean (SE) summary scores and quality-adjusted life year estimates
Table 9: Description of economic variables in DISC dataset
Table 10: Number and proportions of patients with complete data by treatment arm
Table 11: Logistic regression for (i) missingness of costs and QALYs on baseline variables; and (ii) for missingness between missing costs and QALYs and observed outcomes.
Table 12: Cost-effectiveness analysis summary table (base case)
Table 13: Sensitivity analysis: summary for incremental analysis (ITT), cost-effectiveness results and uncertainty under different scenarios

KEY FIGURES
Figure 1: CEA diagram: overall flow of the analysis
Figure 2: Mean EQ 5D scores at baseline and follow-up points
Figure 3: Base case cost-effectiveness acceptability curve
Figure 4: Distribution of incremental costs and QALYs
Figure 5: Pattern of missing data
Figure 6: Comparison of the distribution of imputed vs observed data

Table 0. Details of DISC Data Collection Schedule

Data will be collected using participant and investigator CRFs

Data Collected	Baseline	Treatment Delivery	2 Weeks Post Treatment	6 Weeks Post Treatment	3 Months Post Treatment	6 Months Post Treatment	12 Month Post Treatment	24 Months Post Treatment
Patient Reported Outcomes								
PEM	X	X			X	X	X	X
URAM	X				X	X	X	X
MHQ	X						X	X
EQ-5D-5L	X		X	X	X	X	X	X
SANE	X		X	X	X	X	X	X
Treatment Preference	X							
Overall Hand Assessment					X	X	X	X
Resource Use					X	X	X	X
Demographics and Medical History								
Demographics	X							
Comorbidity	X							
Concomitant Medications	X							
Condition Details and Clinical Assessment								
Condition History	X							
Diathesis Indicators	X							
Clinical Assessment	X							
Photography								
Clinician Photographs	X	X			X	X	X	X
Participant Photographs	Y				Y	Y	Y	Y
Treatment Pathway								
Randomisation	X							
Treatment Delivered		X			X			
Clinical Outcomes								
Joint Measurements	X	X			X	X	X	X
Complications		X			X	X	X	X
Further Procedures					X	X	X	X
Safety Data								
Contraindications	X	X						
Adverse Events		Y	Y	Y	Y	Y	Y	Y

Table 1: Key elements of the base-case analysis and the variation used in sensitivity analysis

Element	Base-case analysis	Variation for the sensitivity analysis
Costs	• NHS perspective following ITT • Limited fasciectomy delivered by surgeons • Micro-costing using cost data collected alongside the trial	• Societal perspective following ITT • Limited fasciectomy delivered by trainees. • HRG unit costs (i.e., LF procedure)
Missing data approach	• Data assumed to be missing at random; therefore, analysis conducted on imputed data following ITT	• Data assumed to be missing completely at random; analysis conducted on the complete case data following ITT
HRQoL missing data	• QALYs imputed at QALY level following ITT	• QALYs imputed at the index-score level following ITT
Time horizon	• Short-term cost-effectiveness up to 12 months.	• Short-term cost-effectiveness up to 24 month
Needle fasciectomy	• The comparison will be restricted to collagenase and limited fasciectomy.	• One way sensitivity analysis with respect needle fasciotomy.

Table 2: Unit costs (and sources) used to estimate total cost for each individual patient

Item	Unit cost	Source
NHS Hospital Care		
Outpatient visit		
Trauma and orthopaedics		
Pain clinic		
Hand surgery		
Occupational therapy		
Plastic surgery		
Rheumatology		
Physiotherapy		
A&E visit		
Inpatient admissions		
NHS Primary and Community Care		
GP visit at GP practice		
Nurse visit at GP practice		
Physiotherapy session in the community		
Occupational Therapy in the community		
Private care and treatments		
Private hand specialist or physiotherapist for clinical assessment		
Private hand specialist or physiotherapist for collagenase injection		
Private hand specialist or physiotherapist for surgical treatment		
Productivity cost		
Days missed of work		

Table 3: Hospital resource use values for available cases by trial allocation, study period and resource category

	Collagenase				Surgery			
Type of resource use	**N**	**Mean (SD)**	**Median (IRQ)**	**Missing (%)**	**N**	**Mean (SD)**	**Median (IRQ)**	**Missing (%)**
Outpatient visit								
3 months								
6 months								
12 months								
24 months								
A&E visit								
3 months								
6 months								
12 months								

24 months								
Inpatient admission 3 months 6 months 12 months 24 months								

Table 4: Community and private resource use values for available cases by trial allocation, study period and resource category. Days missed of work for available cases by trial allocation, study period

	Collagenase				Surgery			
Type of resource use	**N**	**Mean (SD)**	**Median (IQR)**	**Missing (%)**	**N**	**Mean (SD)**	**Median (IRQ)**	**Missing (%)**
GP visit at GP practice 3 months 6 months 12 months 24 months								
Nurse visit at GP practice 3 months 6 months 12 months 24 months								
Occupational therapist 3 months 6 months 12 months 24 months								
Physiotherapist 3 months 6 months 12 months 24 months								
Days lost of work 3 months 6 months 12 months 24 months								
Private care visits 3 months 6 months 12 months 24 months								

Table 5: Costs for cases with complete data by trial allocation and cost category (£, 20xx-xx prices)– base case (ITT)

Costs	**Collagenase Mean (SE) (£)**	**Surgery Mean (SE) (£)**
LNF surgical procedure		
Collagenase injection procedure		
Hospital Outpatient care		
Hospital Inpatient care		
Hospital A&E		
GP at surgery		
Nurse at surgery		
Occupational therapist		
Physiotherapist in the community		
Total NHS finger related costs		
Productivity costs – (a)		
Private care costs – (b)		

Costs	Collagenase Mean (SE) (£)	Surgery Mean (SE) (£)
Total broader costs (a+b)		

Table 6: Participant response to EQ-5D questionnaire at each time point (absolute and relative frequency)

Treatment group	3 weeks BT^		6 weeks BT^		Baseline		3 months		6 months		12 months		24 months	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Collagenase														
Surgery														

^ Before treatment

Table 7: Numbers and proportions of levels within the EQ-5D-5L dimensions by allocation arm at baseline,3, 6, 12 and 24 months follow up (complete cases)

		Baseline				6 months				12 months				24 months			
		Collagenase		Surgery		Collagenase		Surgery		Collagenase		Surgery		Collagenase		Surgery	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Mobility	Level 1																
	Level 2																
	Level 3																
	Level 4																
	Level 5																
Missing																	
Reporting prob.																	
Self-Care	Level 1																
	Level 2																
	Level 3																
	Level 4																
	Level 5																
Missing																	
Reporting prob.																	
Usual Act.	Level 1																
	Level 2																
	Level 3																
	Level 4																
	Level 5																
Missing																	
Reporting prob.																	
Pain/D*	Level 1																
	Level 2																
	Level 3																
	Level 4																
	Level 5																
Missing																	
Reporting prob.																	
Anxiety Deprs.**	Level 1																
	Level 2																
	Level 3																
	Level 4																
	Level 5																
Missing																	
Reporting prob.																	

Table 8: Summary of EQ-5D utility scores at each time point (all available cases) and quality-adjusted life year estimates

Utility	Collagenase (n =)		Surgery (n =)		Unadjusted mean difference (95% CI)	Adjusted mean difference* (95% CI)
Follow up	**N**	**Mean (SD)**	**N**	**Mean (SD)**		
Baseline 3 months 6 months 12 months 24 months **QALYs up to 2 years**						

** The difference at 3, 6, 12 and 24 months is adjusted for baseline utility*

Table 9: Number and proportion of individuals with complete data by treatment allocation

Complete at	Collagenase (N=)	Surgery (N=)
COMPLETE- HEALTH RELATED QUALITY OF LIFE		
Baseline		
3 months		
6 months		
12 months		
24 months		
Overall		
COMPLETE - COSTS		
3 months		
6 months		
12 months		
24 months		
Overall		
COMPLETE – BOTH HEALTH RELATED QUALITY OF LIFE AND COSTS		
3 months		
6 months		
12 months		
24 months		
Overall		

Table 10 Description of economic variables in DISC

		Missing values (%)					
		Total	**Collagenase**	**Surgery**	**Range**	**Mean**	**SD**
BASELINE VARIABLES							
OUTCOME VARIABLES FOR HEALTH RELATED QUALITY OF LIFE							
OUTCOME VARIABLES FOR COSTS							

Table 11: Logistic regression for missingness of costs and QALYs on baseline variables

	Odds ratio in logistic regression for missing data (95% CI)	
	Missing data on costs	Missing data on QALYs
Treatment allocation		
Gender		
Age		
EQ-5D at baseline Other relevant covariates as per statistical analysis		

Table 12: Cost-effectiveness analysis summary table: base case analysis

	Adjusted difference in means with SUREG~	95% confidence limits		
Difference in cots (£)				
Difference in QALYs				
	ICER~ (£ per QALY)	Probability cost-effective at £13,000/QALY	Probability cost-effective at £20,000/QALY	Probability cost-effective at £30,000/QALY

Table 13 Sensitivity analyses: Summary for incremental analysis (ITT), cost-effectiveness results and uncertainty under different scenarios

		Base-Case analysis	(Scenario 1)	(Scenario 2)
Difference in cots (£)	Mean			
	SE			
	95% CI			
Difference in QALYs	Mean			
	SE			
	95% CI			
ICER				
Probability cost-effective ^				