Full Study Title: A pragmatic multi-centre randomised controlled non-inferiority, cost effectiveness trial comparing injections of collagenase into the cord to surgical correction in the treatment of moderate Dupuytren's Contracture in adult patients

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**Confidentiality Statement**

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**Note: All site Principal Investigators and delegated staff must sign their relevant Protocol Read Log and be clearly identified on the site delegation log before commencing work on the DISC Trial.**

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## 1. AMENDMENT HISTORY

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| | | | | |

## 2. SYNOPSIS

| | |
|---|---|
| Study Title | Dupuytren's Interventions Surgery vs. Collagenase (DISC) |
| Internal ref. no. | Sponsor Reference No: 87230 |
| Clinical Phase | Phase IV |
| Trial Design | Multi-centre, randomised controlled, non-inferiority, pragmatic trial |
| Trial Participants | Patients with Dupuytren's contracture and meeting the following inclusion/exclusion criteria<br>Inclusion<br>• Male or Female and aged 18 years or over.<br>• Presence of discrete, palpable, contracted cord involving the metacarpophalangeal joint and/or proximal interphalangeal joint of a finger.<br>• 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).<br>• Able to identify a predominant cord for treatment, which would not require more than one Collagenase injection as treatment.<br>• Appropriate for limited fasciectomy surgery and Collagenase injection for Dupuytren's contracture (i.e. cords suitable for CCH and limited fasciectomy and not requiring skin grafting or PNF (e.g. discrete MCP cords in elderly)).<br>• Patient is willing and able to give informed consent for participation in the study. |

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| | Exclusion Criteria<br>• Severe contractures of both metacarpophalangeal joint and/or proximal interphalangeal joints (Tubiana Grade 4).<br>• History of previous intervention for Dupuytren's contracture (e.g. surgery, Collagenase injection or needle fasciectomy) on the same hand.<br>• History of any other pre-existing disorder of the hand causing significant restriction of movement and/or pain and affecting hand function e.g. post traumatic stiffness, stiffness due to other causes, infection, arthritis.<br>• Non-English speaking because of the need to complete multiple questionnaires which have not been validated in multiple languages.<br>• Resident in a location where attendance for follow up at one of the study recruiting centres will not be possible.<br>• Contraindicated for use of Collagenase including:<br>  • Hypersensitivity to: Collagenase, Sucrose, Ketorolac Trometamol, Hydrochloric acid, Calcium chloride dehydrate, Sodium chloride.<br>  • Diagnosis of a coagulation disorder<br>• Any other significant disease or disorder (including autoimmune disorders) which, in the opinion of the Investigator, may put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.<br>• Participation in another research study involving an investigational product in the past 12 weeks.<br>• Female participants who report to be pregnant or breastfeeding. |
| Planned Sample Size | 710 Participants |
| Follow-up duration | 2 years |

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|---|---|
| Planned Trial Period | 01/11/2016 – 30/04/2022 |
| Primary Objective | To investigate whether Collagenase injection is not inferior to limited fasciectomy in the correction of Dupuytren's contracture of the hand. |
| Secondary Objectives | To investigate the cost-effectiveness of Collagenase injections compared to limited fasciectomy 2 years after treatment.<br>To explore patient's experience and preference of the different treatments (Qualitative sub study) to include asking which treatment they feel is best for Dupuytren's and which treatment they would choose.<br>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).<br>To investigate if remote measurement of extension deficit using photographs is as good as goniometric measurements in clinic to determine recurrence (Photography sub study). |
| Primary Outcomes | Patient Evaluation Measure at 1 year post treatment |
| Secondary Outcomes | Unité Rhumatologique des Affections de la Main (URAM) Scale<br>Michigan Hand Questionnaire (MHQ)<br>Extension Deficit and Total Active Movement<br>Recurrence<br>Further Procedures<br>Complications<br>EQ-5D-5L<br>Resource Use<br>Time to recovery of function (using SANE via remote data collection) |
| Investigational Medicinal Products | Collagenase Clostridium histolyticum (CCH) |

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|---|---|
| Form | Injection - Powder mixed with fluid in defined quantities |
| Dose | Three aliquots are distributed via injection into an affected cord at set anatomical points through a single needle puncture.<br><br>0.25ml of reconstituted solution (0.58mg Collagenase Clostridium histolyticum) injected for a cord in a metacarpophalangeal joint.<br><br>0.20ml of reconstituted solution (0.58mg Collagenase Clostridium histolyticum) injected for a cord in a proximal interphalangeal joint.<br><br>*NB: As per the SmPC, up to two cords in the same hand can be injected at a single treatment visit, in line with the injection procedure, using separate vials for each cord. If multiple cords are injected, only the injection administered to the reference digit* (defined by the PI or treating surgeon as the worst affected digit with symptoms of Dupuytren's contracture meeting the criteria for both treatments) *will be deemed to be the trial treatment. This will make the associated hand the reference hand.* |
| Route | Injection |

## 3. ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AR | Adverse reaction |
| CACE | Complier Average Causal Effect |
| CCH | Collagenase Clostridium histolyticum |
| CI | Chief Investigator |
| CI | Confidence Interval |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| CRPS1 | Complex Regional Pain Syndrome type 1 |
| CT | Clinical Trials |
| CTA | Clinical Trials Authorisation |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| EQ-5D-5L | EuroQol Quality of Life Measure |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| HTA | Health Technology Assessment Programme |
| ICC | Intra Class Correlation Coefficient |
| ICF | Informed Consent Form |
| ICH | International Conference of Harmonisation |
| IMP | Investigational Medicinal Products |
| ISF | Investigator Site File |
| KFI | Kaplan-Feinstein Index |
| LPLV | Last Patient Last Visit |
| MCP | Metacarpophalangeal |
| MDC | Minimal Detectable Change |
| MHQ | Michigan Hand Questionnaire |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MI | Multiple Imputations |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health Research |
| NRES | National Research Ethics Service |
| PEM | Patient Evaluation Measure |
| PI | Principal Investigator |
| PIP | Proximal Interphalangeal |
| PIS | Patient Information Sheet |

| | |
|---|---|
| PNF | Percutaneous Needle Fasciotomy |
| PSS | Personal Social Services |
| QALY | Quality-Adjusted Life Year |
| R&D or R&I | NHS Trust Research & Development / Innovation Department |
| RCT | Randomised Controlled Trial |
| RDMS | Research Data Management System |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SANE | Single Assessment Numeric Evaluation |
| SAR | Serious Adverse Reaction |
| SD | Standard Deviation |
| SmPC/SPC | Summary of Products Characteristics |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TMF | Trial Master File |
| TSC | Trial Steering Committee |
| URAM | Unité Rhumatologique des Affections de la Main Scale |
| VAS | Visual Analogue Scale |
| YTU | York Trials Unit |

# 4. BACKGROUND AND RATIONALE

## 4.1 Background

### 4.1.1 The impact of Dupuyren's disease in the UK

Dupuytren's disease[1], which causes Dupuytren's contracture, is a fibro-proliferative disease, common in the male Caucasian population, and affecting over 2 million of the adult UK population.

As the contracture progresses it forms nodules and cords, drawing down the involved finger into a flexed position at either the metacarpophalangeal joint and/or proximal interphalangeal joint. The little finger is most commonly affected; the next most common is the ring finger. The disorder can be bilateral. The contracture results in an inability to straighten the finger, increasingly interferes with hand function but it is usually not painful. The disease can be graded in various ways and the commonest is the Tubiana grading based on the degree of extension deficit[2, 3]. Given the impact of Dupuytren's contracture on hand function, the longer-term trajectory of the quality of life of patients is important.

There is a genetic pre-disposition for the disease. This is particularly strong in patients younger than 40 years, when both hands are involved, when patients have Garrod's pads over the back of their proximal interphalangeal joints, when they have distant manifestations of a similar condition (e.g. Lederhose disease of plantar fibromatosis or Peyronie's disease of the penis) and when someone in their immediate family also suffers from the same disease[4].

### 4.1.2 Current treatments for Dupuytren's disease

Surgical correction of the contracture by dissecting the cords and excising them (limited fasciectomy) is the standard treatment in the UK and Europe[5, 6]. Over 17,000 of such operations are done in England each year, with little change in the rate of surgery in the preceding 5 years, incurring a cost to the NHS of more than £60 million per annum[7]. There is, however, substantial variation in the rate of surgery across England. Patients receiving surgical correction may experience complications as a result of surgery (e.g. infection, delayed healing, nerve damage, pain, stiffness, recurrence) which may delay recovery and a return to normal function. Vascular compromise and CRPS1 are serious but rare events which may arise as a result of surgical correction of Dupuytren's contracture. Patients may also require additional physiotherapy to restore movement of the joint.

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. The use of this method is widespread in the USA and was approved for use in Europe in 2011. This treatment is not however widely offered in the UK (25 units in England and 3 in Scotland offer Collagenase treatment) 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 by a variety of trained clinicians, meaning patients do not need to wait for and subsequently undergo surgery. Patients do however need to attend additional clinic visits to complete the

procedure. Many short-term side effects (e.g. swelling, pain, skin splits) resolve without any lasting effect but may delay patient recovery. The significant side effect associated with Collagenase is the potential for tendon rupture[8] which may require surgical intervention. No long term systemic effects related to Collagenase injection have been identified in previous studies in this area with patients often obtaining restored functionality and resuming routine tasks more promptly than seen in patients following surgery[8-12].

High quality evidence, comparing these two treatments is however sparse. Initial clinical effectiveness studies of Collagenase compared to a placebo[8] and recent systematic review[13] of such studies have both indicated that Collagenase is found to be better than placebo, particularly for contracture affecting the metacarpophalangeal joint[8]. 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[10] (defined as a change in extension deficit of 6 degrees between 3 and 6 months, or 20 degrees from 3 months to 1 year post treatment[10, 14]) suggest that this is higher following Collagenase treatment than surgery at 3 years after treatment. As a result further robust evidence is also required to assess the impact of recurrence, in the long and short term, on patient quality of life in relation to treatments received.

Available evidence of the cost effectiveness of Collagenase and surgical correction is based on small retrospective studies[13]. The National Institute for Health and Care Excellence (NICE) have appraised the clinical and cost effectiveness of Collagenase, recommending that a full-scale RCT should be conducted to provide a definitive answer on its effectiveness as a treatment option[13].

### 4.1.3 Rationale for DISC Trial

There is no randomised controlled trial evidence comparing clinical and cost effectiveness of the Collagenase and surgery treatments currently offered on the NHS for the treatment of Dupuytren's contracture. Evidence of patient experience and treatment preference is also limited, as is whether correction following injection is maintained as well over time as following surgery.

As a result it is not known whether contracture correction is the same after Collagenase injection as after surgery, whether this is a cost effective treatment for the NHS and which treatment patients prefer (although some data suggest that patients prefer this intervention to surgery [15]). A sufficiently powered randomised controlled trial investigating all of these important elements is therefore required to fill this evidence gap. The Dupuytren's Interventions Surgery vs. Collagenase Trial (DISC) is a pragmatic multi-centre randomised controlled non-inferiority, cost effectiveness trial comparing injections of Collagenase into the cord to surgical correction in the treatment of moderate Dupuytren's contracture in adult patients.

If Collagenase treatment is not inferior to surgery, patients will avoid surgery and potential post-operative complications by having their contracture correction carried out in an outpatient clinic. This may also reduce the time to treatment and release important resources in an already financially strained NHS. If, however, Collagenase treatment is found to be inferior to surgery then the most cost effective treatment, requiring limited further intervention due to reduction in recurrence rates, can instead be recommended.

### 4.1.4 Investigational medicinal product (IMP)

IMP for this study will be manufactured by Auxilium, marketed by Sobi, Sweden and will be provided for this study via routine hospital stocks. The SmPC provided by Auxillium for Collagenase Clostridium histolyticum injections (As approved by the European Medicines Agency authorisation 28.02.2011) will be used and will act as the reference safety material, providing detail on suspected side effects (SmPC Section 4.8) and information on interactions and cautions for use (SmPC Section 4.4). Further details in relation to side effects, interactions and cautions for use are described in Section 10 of this protocol.

All patients enrolled into the study will receive either the intervention: Collagenase injection at a single time point (three aliquots distributed via injection at set anatomical points through a single needle puncture) or the control: limited fasciectomy surgery (as described in Section 9.1).

For the purposes of the DISC Trial, the predominant, palpable cord within the reference digit ((defined as the worst cord within the worst affected digit with symptoms of Dupuytren's contracture meeting the criteria for both treatments)). This will make the associated hand the reference hand.

In line with the SmPC, up to two cords can be injected at a single treatment visit, following the injection procedure, using separate vials for each cord. If multiple cords are injected, only the reference cord injection will be deemed to be part of the trial treatment. Given the pragmatic nature of DISC, follow-up Collagenase injections will be at clinician discretion this includes the timing of manipulation and of further injections to the same cord.

At clinical discretion, participants in the control arm may have additional cords treated with limited fasciectomy at the same time as delivery of the control treatment.

## 5. OBJECTIVES

### 5.1.1 Primary Objectives

To investigate whether Collagenase injection is not inferior to limited fasciectomy in the correction of Dupuytren's contracture of the hand.

### 5.1.2 Secondary Objectives

To investigate the cost-effectiveness of Collagenase injections compared to limited fasciectomy 2 years after treatment (from the NHS and Personal Social Services perspectives).

To explore patient's experiences and preferences of the different treatments (Qualitative sub study).

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 investigate if remote measurement of extension deficit using photographs is as good as goniometric measurements in clinic to determine recurrence (Photography sub study).

# 6. STUDY DESIGN

## 6.1 Main Study

### 6.1.1 Summary of Trial Design

DISC is a multi-centre, 710 patient, randomised, non-inferiority trial of Collagenase injection and manipulation versus limited fasciectomy for the treatment of Dupuytren's contracture.

In addition to the main study, DISC contains a qualitative sub study and a photography sub study which are detailed in Sections 6.2 and 6.3. Patients 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 (three aliquots distributed via injection at set anatomical points through a single needle puncture). This will be delivered and completed at a single time point within 18 weeks following randomisation (as per referral to treatment time), however where possible sites should complete this procedure within 12 weeks post randomisation. As this is a pragmatic trial comparing surgery with injection, it is not possible to blind clinicians or participants to their treatment allocation.

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. Following Baseline, randomisation and treatment, participants will be followed up for 2 years and will complete follow up visits at 3 months, 6 months, 1 year, and 2 years post treatment. A flow diagram demonstrating the patient pathway through the study is presented in Appendix A.

The study will be managed by York Trials Unit (YTU).

### 6.1.2 Primary and Secondary Endpoints/Outcome Measures

6.1.2.1 Primary Endpoints/Outcome Measures

The primary endpoint is change in Patient Evaluation Measure (PEM)[15] between baseline and 1 year post treatment.

6.1.2.2 Secondary Endpoints/Outcome Measures

* URAM Patient Rated Outcome Measure[16]
* Michigan Hand Questionnaire[17]
* EQ-5D-5L[18]
* Resource Use including NHS resource costs, return to work, out of pocket expenses.
* Further Procedures
* Complications

- Recurrence (Primarily defined as a change in extension deficit of 6 degrees between 3 and 6 months, or 20 degrees from 3 months to 1 year post treatment[10, 14])

- Extension Deficit and Total Active Movement (for stiffness) (using goniometry and photograph data)

- Time to recovery of function (using Single Assessment Numeric Evaluation (SANE) [23] via remote data collection)

Timelines associated with collection of the above secondary outcomes are detailed in Section 8.5.

### 6.2 Qualitative Sub Study

All who consent to participate in the DISC Trial will have the option of participating in the qualitative sub study. Consent to the qualitative sub-study will not affect inclusion in the main trial.

Approximately 40 consenting participants will take part in a semi-structured interview to generate data on the benefits and difficulties that patients perceive to be associated with each treatment. Questions and topics will include: Dupuytren's symptoms and impact upon lifestyle; expectations of treatment; experience of treatment; recovery and progress in everyday activities; concerns about the future; treatment preference and recommendations for clinical guidelines. Interviewees will also be given the opportunity to raise any other issues which they consider pertinent. Interviewees will be selected purposively from those who consent to take part and initial recruitment will target 'typical cases' (where there are no complications). Subsequent recruitment may be informed by emergent issues (in the interview data or main trial conduct); we expect to recruit similar numbers from each arm of the trial.

Interviews will be timed to coincide with outcome data collection at 3 months.

### 6.3 Photography Sub Study

All participants who consent to participate in the DISC Trial will have the option of participating in the photography sub study. Consent to the sub-study will not affect inclusion in the main trial.

Participants who consent to participate in the photography sub study will be shown how to take the required photographs of their hand at baseline and will be provided with detailed instructions. Sub-study participants will be asked to take standardised photographs of their study reference hand at home at baseline, and all subsequent time points. Participants will then email, electronically transmit, or post pictures to the study team.

The aim will be to recruit sufficient participants to provide 100 valid photographs at 6 months. Participant taken photographs will be compared to goniometer readings and photographs taken by clinicians as part of the main trial during clinic visits at the same follow-up time points (listed as secondary outcome in Section 6.1.2.2) to assess whether there is good correlation between these. Angles will be measured on photographs by observers who are blind to the image source and trial treatment allocation, using anonymised digital images and a standardised measurement protocol.

Further details on the processes for this sub study can be found in the DISC Photography Sub Study Manual.

# 7. TRIAL PARTICIPANTS

## 7.1 Overall Description of Trial Participants

Patients with Dupuytren's contracture and meeting the inclusion/exclusion criteria (Section 7.2 and 7.3).

Patients will be identified from a variety of methods including clinician referral letters, surgery and GP lists and review of patients attending orthopaedic plastic surgery clinics or musculoskeletal clinics. Further details of the methods for patient approach are given in Section 8.2.

## 7.2 Inclusion Criteria

Patients to be included must meet all of the following criteria:

1. Male or Female and aged 18 years or over.
2. Presence of discrete, palpable, contracted cord involving the metacarpophalangeal joint and/or proximal interphalangeal joint of a finger.
3. 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)[19].
4. Able to identify a predominant cord for treatment which would not require more than one Collagenase injection as treatment.
5. Appropriate for limited fasciectomy surgery and Collagenase injection for Dupuytren's contracture (i.e. cords suitable for CCH and limited fasciectomy and not requiring skin grafting or PNF (e.g. discrete MCP cords in elderly)).
6. Patient is willing and able to give informed consent for participation in the study.

## 7.3 Exclusion Criteria

Patients will be excluded from study entry if any of the following apply:

1. Severe contractures of both metacarpophalangeal joint and/or proximal interphalangeal joints (Tubiana Grade 4)[3].
2. History of previous intervention for Dupuytren's contracture (e.g. surgery, Collagenase injection or needle fasciectomy) on the same hand.
3. History of any other pre-existing disorder of the hand causing significant restriction of movement and/or pain and affecting hand function e.g. post traumatic stiffness, stiffness due to other causes, infection, arthritis.
4. Non-English speaking because of the need to complete multiple questionnaires which have not been validated in multiple languages.
5. Resident in a location where attendance for follow up at one of the study recruiting centres will not be possible.
6. Contraindicated for use of Collagenase[9] including:
    - Hypersensitivity to: Collagenase, Sucrose, Ketorolac Trometamol, Hydrochloric acid, Calcium chloride dehydrate, Sodium chloride.

- Diagnosis of a coagulation disorder

7. Any other significant disease or disorder (including autoimmune disorders) which, in the opinion of the Investigator, may put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.
8. Participation in another research study involving an investigational product in the past 12 weeks.
9. Female participants who report to be pregnant or breastfeeding.

# 8. STUDY PROCEDURES

## 8.1 Informed Consent

Patients will be provided with a detailed written patient information sheet outlining the study nature, benefits, and risks. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Should new information arise during the study which may affect participant's willingness to take part, this will be reviewed for addition to the patient information sheet and a revised consent form will be completed as necessary.

The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study.

Informed consent will be obtained by a suitably qualified and experienced local research nurse or clinician who has been authorised to do so by the Chief or Principal Investigator, as detailed on the study Delegation of Authority and Signature Log for the study site. The participant must personally sign and date the latest approved version of the informed consent form before any study specific Baseline procedures are performed.

The original signed form will be retained at the study site within the Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants, retained in the participant medical notes, and provided to the study coordinating centre.

All participants who consent to participate in the main DISC trial will also be eligible to participate in the two sub-studies. Consent to the sub-studies will not affect inclusion in the main trial. Patients enrolled in the main study may opt to enrol in one, both or neither of the sub studies.

## 8.2 Patient Identification

As patients with Dupuytren's Contracture may be seen in a variety of NHS settings, various patient identification methods will be used including:

- Clinician Referral

A clinician will review the referral and if potentially suitable, a letter from the care team will be sent to the patient along with the patient information sheet. At the same time patients will be sent an outpatient clinic appointment, as per routine practice.

- Surgery Clinic and Operating Lists

The local research team will work closely with clinical colleagues to facilitate screening for the study. If potentially suitable, a letter from the care team will be sent to the patient along with the patient information sheet.

- Orthopaedic & Plastic Surgery Clinic Lists

The local research team will work closely with clinical colleagues to facilitate screening for the study. If potentially suitable, a letter from the care team will be sent to the patient along with the patient information sheet.

- Other allied clinics and centres e.g. Musculoskeletal and Physiotherapy clinics, Musculoskeletal Triage Centres

The local research team will work closely with clinical colleagues to facilitate screening for the study. If potentially suitable, a letter from the care team will be sent to the patient along with the patient information sheet.

In all instances, where screening activity is to be completed by staff in allied departments (e.g. MSK, Physiotherapy), the research team will be required to engage with each department regarding the study. The local research nurse or trial coordinator will arrange a meeting with the associated department(s) to discuss the study and will provide the department with study publicity for both patients and clinicians.

- GP Screening

The study research team will work closely with GP practices, acting as patient identification centres, to facilitate screening of patient lists and mail shots for the study. If potentially suitable, a letter from the care team will be sent to the patient along with the patient information sheet.

Following identification by one of these methods, a letter from the care team will be sent to the patient along with the patient information sheet. If the patient is interested in participating in the study, they will be asked to contact a member of the research team (by telephone, email, post or via their treating clinician) to indicate their interest.

Where patients have expressed an interest in study participation, prior to an invitation letter being sent (e.g. during a clinic visit), the research nurse may complete a telephone call to follow up for a response in relation to study participation. Where mail shots have been conducted (i.e. from GP practices) no further patient contact will be made.

Patients will then be invited to attend a clinic appointment where the clinician will assess trial suitability against study inclusion and exclusion criterion using the DISC Screening

for Eligibility Summary. A copy of the eligibility assessment will be filed in the patient notes for reference.

If suitable and the patient confirms interest in participating, the patient will then discuss the study with the local research team before consent is obtained for the study. Following informed consent, the participant will then complete the study Baseline measures as detailed in Section 8.3. During the Baseline visit the participant's reference digit will be identified (defined as the worst affected digit with symptoms caused by Dupuytren's contracture which meets criteria for both treatments). This digit will be used for delivery of the study treatment and subsequent assessments. The associated hand will be considered the reference hand.

Where patients are identified as ineligible to participate in the DISC Trial, the research site will keep an anonymised record of ineligibility reasons at an aggregate level.

## 8.3 Baseline Assessments

The following will be performed at the Baseline assessment and will be recorded in the case report form (CRF):

1) Condition history (age of onset, number of digits affected, previous surgery to opposite hand)
2) 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
3) Diathesis indicators (Age, Garrod's pads, family history, distant sides to include Peyronie's disease and Lederhose disease)[4]
4) Co-morbidity including presence or absence of diabetes and epilepsy (based on the Kaplan-Feinstein index (KFI))[20]
5) Photographs of the hand[9, 21]
6) Clinical assessment of discreet and palpable cord(s) across or near the contracted joint(s) including pits and nodules
7) Concomitant medications.

### 8.3.1 Patient Evaluation Measure (PEM)

A validated patient report questionnaire[15] of 11 items in the Hand Health and three in the Overall Assessment Questionnaire (including a transition question).

Where equal to or greater than 12 weeks elapse between baseline and treatment delivery, participants will be asked to re-complete the Patient Evaluation Measure (PEM) immediately prior to intervention delivery[15].

8.3.2 Unité Rhumatologique des Affections de la Main Scale (URAM)

A validated, nine item, six interval disease specific disability scale[16].

8.3.3 Michigan Hand Questionnaire (MHQ)

A validated, 63 question measure featuring six domains: overall hand function; activities of daily living; work performance; pain; aesthetics; patient satisfaction with hand function[17, 22]). The function and pain domains refer to patient symptoms whilst those of work and activities of daily living refer to disability and handicap. This measure assesses each hand individually.

8.3.4 EQ-5D-5L

A validated, generic health status measure asking 5 questions on mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, accompanied by a health status thermometer visual analogue scale (VAS)[18].

8.3.5 Single Assessment Numeric Evaluation (SANE)

A single, patient report, question measure assessing functionality[23].

8.3.6 Treatment Preference

A single question to assess if patients have a preference for either treatment prior to randomisation.

## 8.4 Randomisation and Codebreaking (if applicable)

The randomisation sequence will be designed by the study statistician and will be carried out via telephone or the internet using a secure, central randomisation service hosted by Sealed Envelope Ltd. This will ensure adequate allocation concealment for this study.

This service will record information to identify all potential participants and their eligibility to avoid inappropriate entry of patients into the trial. The research team at each study site will access the system to complete randomisation following participant consent and completion of Baseline assessments. Access to the system for representatives at individual sites will be coordinated and controlled by the trial project team at YTU. Both patients and clinicians will be unblinded to study treatment allocation.

The randomisation system will allocate participants 1:1 to one of the two study arms (Collagenase injection or surgery), each participant having an equal probability of allocation to either group. Block randomisation with randomly varying block sizes will be used, stratified by the reference joint type (MCP or PIP). Treatment will be allocated on an individual named participant basis, and the participant will receive their allocated treatment as soon as possible after randomisation.

## 8.5 Treatment Delivery

Joint measurements will be recompleted and participants will be asked to re-complete the Patient Evaluation Measure (PEM) immediately prior to treatment delivery[15]. Joint measurements and a photograph will be taken following treatment delivery. For the collagenase group this will be completed following joint manipulation and for the limited fasciectomy surgery group this will be completed during a wound check after surgery.

## 8.6 Subsequent Assessments

Participants will complete follow up assessments at 4 time points during the study, calculated from the date of procedure. Visits will be completed as close to due date as possible (+/- 28 days Month 3 and Month 6, +/- 3 months 1 year and 2 years). Details of these assessments are in Sections 8.5.1 to 8.5.4 and in the study procedure summary in Appendix B.

Where participants request remote follow-up (i.e. follow-up without clinic visits), the research nurse will contact the participant at each visit time point to complete a safety assessment (AE reporting). The study coordinating centre will arrange for a postal questionnaire to be sent to the participant (including a freepost envelope to facilitate return). If the questionnaire is not returned, a telephone call will be made to the participant to request completion and return.

### 8.6.1 3-month follow up visit (Clinic Visit)

The following assessments will be completed during the 3-month follow up visit:

- Patient Evaluation Measure (PEM)[15]
- Unité Rhumatologique des Affections de la Main Scale (URAM)[16]
- EQ-5D-5L[18]
- Extension Deficit and Total Active Movement [10, 11, 24, 25]
- Further Procedures and Complications
- Concomitant Medications
- Adverse Events
- Photographs[21, 26]
- Resource Use (Participants will be provided with a visit diary to record any resource use between study visits to ensure accurate recall of resources used)
- Time to recovery of function (using Single Assessment Numeric Evaluation (SANE) question [23]) and return to work.

8.6.2 6 month follow up visit (Clinic Visit)

- Patient Evaluation Measure (PEM)[15]
- Unité Rhumatologique des Affections de la Main Scale (URAM)[16]
- EQ-5D-5L[18]
- Extension Deficit and Recurrence and Total Active Movement [10, 11, 24, 25]
- Further Procedures and Complications
- Concomitant Medications
- Adverse Events
- Photographs[21, 26]
- Resource Use (Participants will be provided with a visit diary to record any resource use between study visits to ensure accurate recall of resources used)
- Time to recovery of function (using Single Assessment Numeric Evaluation (SANE) question [23]) and return to work.

8.6.3 1 year (Primary Endpoint) follow up visit (Clinic Visit)

- Patient Evaluation Measure (PEM)[15]
- Unité Rhumatologique des Affections de la Main Scale (URAM)[16]
- Michigan Hand Questionnaire[17, 22]
- EQ-5D-5L[18]
- Extension Deficit and Recurrence and Total Active Movement [10, 11, 24, 25]
- Further Procedures and Complications
- Concomitant Medications
- Adverse Events
- Photographs[21, 26]
- Resource Use (Participants will be provided with a visit diary to record any resource use between study visits to ensure accurate recall of resources used)
- Time to recovery of function (using Single Assessment Numeric Evaluation (SANE) question [23]) and return to work.

8.6.4 2 year follow up visit (Clinic Visit or Postal Follow Up (dependent on photography sub study outcome))

- Patient Evaluation Measure (PEM)[15]
- Unité Rhumatologique des Affections de la Main Scale (URAM)[16]

- Michigan Hand Questionnaire[17, 22]
- EQ-5D-5L[18]
- Extension Deficit and Recurrence and Total Active Movement [10, 11, 24, 25]
- Further Procedures and Complications
- Concomitant Medications
- Adverse Events
- Photographs[21, 26]
- Resource Use (Participants will be provided with a visit diary to record any resource use between study visits to ensure accurate recall of resources used)
- Time to recovery of function (using Single Assessment Numeric Evaluation (SANE) question [23]) and return to work.

#### 8.6.4 Remote Collection of Patient Procedure Experiences

Participants will be asked to assess experiences of the effectiveness of treatment using the following question, taken from Single Assessment Numeric Evaluation (SANE) [23]: "How would you rate your hand today as a percentage of normal (0% to 100% scale with 100% being normal)?". Participants will also be asked to complete an EQ-5D-5L assessment as part of remote data collection.

Participants will be provided with two questionnaires at their Baseline visit to collect this information at 2 weeks and 6 weeks post treatment. YTU will issue a text message prompt to participants who provide a mobile telephone number on the completion due dates.

## 8.7 Definition of End of Trial

The end of trial is the date of the last patient last visit (LPLV). This is defined as:

- Completion of 2 years follow up assessments in the study
- Withdrawal from follow up due to any reason

## 8.8 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time without prejudice. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason. The reason for withdrawal will be recorded in the CRF.

If a participant withdraws due to an adverse event, the study site will arrange follow up visits or telephone calls until the event has either resolved or stabilised.

Participants who request to fully withdraw during a study visit will be asked if they would be willing to complete the questionnaires prior to withdrawal. Where a participant fully withdraws outside of a scheduled study visit, no further follow up questionnaires will be completed.

Unless the participant specifically withdraws consent for their data to be stored, all data collected from them will continue to be stored as per the original patient consent. At a participant's request, their data collected up to the point of withdrawal can however be withdrawn from the trial and will not be used in the final analysis.

Where participants request remote follow-up (i.e. follow-up without clinic visits), the research nurse will contact the participant at each visit time point to complete a safety assessment (AE reporting). If change of status to 'follow up without clinic visits' occurs before delivery of study treatment the date of the baseline visit will be used to calculate the dates for study follow up. The trial project team will arrange for a postal questionnaire to be sent to the participant (including a freepost envelope to facilitate return). YTU will issue a text message prompt to participants who provide a mobile telephone number to remind them of the importance of completing and returning the questionnaire. If the questionnaire is not returned after 6 weeks, a telephone call will be made to the participant to request completion and return.

### 8.9 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, correspondence, completed scales and quality of life questionnaires.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study the CRF will be used as the source document as outlined in the Source Data Verification form.

Source documents that are computer-generated and stored electronically should if possible/practical be printed for review by the monitor. Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the participant's source documents. The Investigator will authorise the monitor to compare the content of the print out and the data stored in the computer to ensure all data are consistent. If electronically stored and impractical to print, each timely review of the electronically-stored data will be annotated in the patient's notes.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

# 9. TREATMENT OF TRIAL PARTICIPANTS

## 9.1 Description of Study Treatment & Pharmacy Process

### 9.1.1 Intervention - Collagenase Clostridium histolyticum injections[9]

Manufactured by Auxilium and marketed by Sobi, Sweden, Collagenase is an enzyme which works by breaking down collagen into shorter chains thereby disconnecting the cords found in Dupuytren's contracture. The enzyme is activated by mixing the powder with fluid in set quantities (0.58mg) immediately prior to injection.

Depending on the cord affected 0.25ml or 0.20ml of reconstituted solution (0.58mg Collagenase Clostridium histolyticum) is injected as three aliquots: 0.25ml for cord in a metacarpophalangeal joint, 0.20ml for cord in a proximal interphalangeal joint.

The three aliquots are distributed via injection into an affected cord at set anatomical points through a single needle puncture at a single time point. If separate cords are to be injected at the same treatment visit, this will be permited but a reference cord (i.e. predominant) must be identified. In line with the SmPC, following the injection procedure and using separate vials for each cord. If multiple cords are injected, only the reference cord injection will be deemed to be part of the trial treatment. Given the pragmatic nature of DISC, follow-up Collagenase injections will be at clinician discretion this includes the timing of manipulation and of further injections to the same cord. Collagenase injections after the procedure for the allocated treatment assignment is completed (in either trial arm) will be recorded as further procedures in the follow-up CRFs.

Patients will be scheduled for Collagenase injection within 18 weeks following randomisation (as per referral to treatment time_RTT), however where possible sites should complete this procedure within 12 weeks post randomisation. If patients have received Tetracycline antibiotics within 14 days of the injection, the procedure will be delayed (as per guidance in the reference safety material - Section 4.5). Joint measurements and Patient Evaluation Measure (PEM) will be recompleted immediately prior to treatment delivery[15]. Joint measurements and a photograph will be taken following treatment delivery. For the collagenase group this will be completed following joint manipulation.

After an interval of one to seven days, the patient then returns to clinic and, under local anaesthetic, the cord is snapped using a four-step process. Two additional visits by the patient may therefore be required for the intervention to be delivered; one for injection and one for manipulation.

### 9.1.2 Control – Limited Fasciectomy

The control treatment for the DISC trial is limited fasciectomy, a standard technique in Europe for treatment of Dupuytren's contracture [5, 6]. This procedure involves the removal, under anaesthesia and tourniquet control, of the diseased fascia, nodule and cord, or a part of it, to correct the contracture of the joint[25, 27]. As deemed clinically appropriate, the skin may then be left to heal by secondary intention, closed directly, or closed with a Z plasty or closed using a full thickness skin graft[28]. A reference digit (for study assessment purposes) will be defined prior to control treatment delivery.

Patients will be scheduled for the limited fasciectomy surgery to be completed within 18 weeks following randomisation (as per referral to treatment time-RTT), however where possible sites should complete this procedure within 12 weeks post randomisation. Joint measurements and Patient Evaluation Measure (PEM) will be recompleted immediately prior to treatment delivery[15]. Joint measurements and a photograph will be taken following treatment delivery. For limited fasciectomy surgery group this will be completed during a wound check after surgery

Additional visit(s) by the patient may therefore be required for the control treatment to be delivered.

### 9.2 Storage of Study Treatment

Collagenase will be supplied through local hospital stocks and will therefore be stored as per pre-defined processes for handling of this medication.

### 9.3 Compliance with Study Treatment

A CACE analysis will be undertaken to explore the impact of not receiving the interventions as intended. Instances where participants do not receive the allocated intervention as intended will be recorded in the CRF at 3 months.

### 9.4 Accountability of the Study Treatment

The study intervention will be supplied through routine hospital stocks at participating study sites. The Investigator will use a standard, local prescription form to request this medication from the local site Pharmacy department.

### 9.5 Concomitant Medication

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

Any medication, other than the study medication taken during the study will be recorded in the CRF.

## 10. SAFETY REPORTING

### 10.1 Definitions

10.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient, or clinical investigation participants administered a study medication or procedure (intervention or control), which does not necessarily have to have a causal relationship with the treatment (the study medication or surgery). An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease which is temporally associated with the study medication or procedure (intervention or control), whether or not considered related to the study medication or procedure (intervention or control). Adverse events, which might be expected with this condition and treatments, are detailed in the SmPC for Collagenase injections (Annex 1 – Section 4.8) and in Table 1 (Section 10.3) of the DISC study protocol for surgery. Adverse events will be reported and followed up using Adverse Event Forms. Reporting and follow up of complications associated with the intervention or control delivery will be recorded in CRFs in a structured format.

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

10.1.2 Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

10.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Where repeated serious adverse events of similar type are observed, these will be discussed with the Data Monitoring Committee (DMC) and will be onward reported should concerns be raised in relation to the type of event and/or frequency observed.

10.1.4 Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that::

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Surgical or medical intervention to prevent the above

For the purposes of this study, the following are <u>not</u> considered a SAE, but will be reported using the DISC Adverse Event Form:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the centre (e.g. stent removal after surgery)
- Hospitalization for a pre-existing condition that has not worsened
- Hospitalization for routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- Hospitalization for treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition e.g. pre-planned hip replacement operation which does not lead to further complications
- Hospitalization for treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above.

10.1.5 Expected Serious Adverse Events/Reactions

Expected Serious Adverse Events and Reactions for this trial will be taken from the reference safety material for the intervention (SPC) and Table 1 (Section 10.3) of the DISC study protocol for surgery. Such events do not require immediate reporting to the Sponsor and do not require onward reporting to the REC. Such events will be reported to the TSC, DMC and Sponsor at routine meetings.

10.1.6 Suspected Unexpected Serious Adverse Reactions

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information i.e. Collagenase Clostridium histolyticum Summary of Product Characteristics

## 10.2 Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study medication and/or procedures, will be recorded on the DISC Adverse Event Form.

The following information will be recorded: description, date of onset and end date, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

Events considered related to the study medication or procedures, as judged by a medically qualified investigator or the study sponsor will be followed until resolution or the event is considered stable. All related AEs/SAEs that result in a participant's withdrawal from the study or are present at the end of the study, will be followed up until a satisfactory resolution occurs.

The relationship of AEs to the study medication will be assessed by a medically qualified investigator.

Any pregnancy occurring during the clinical study, and the outcome of the pregnancy, should be recorded and followed up for congenital abnormality or birth defect. Thee local research nurse or clinician will question patients about their pregnancy status as per routine practice.

## 10.3 Reporting Procedures for Serious Adverse Events

All SAEs, except those expected ones defined in section 10.1.5 that do not require immediate reporting (see 10.1.5), must be reported to York Trials Unit within 24 hours of discovery or notification of the event. York Trials Unit will perform an initial check of the information and ensure that it is reviewed by the Chief Investigator (CI) or other delegated medic. Where the event is received outside of YTU operational hours the review will be completed on the next working day, with exception of the Christmas break where procedures will be implemented to ensure cover and review during this time. All SAE information must be recorded on an SAE form and sent to York Trials Unit. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form and sent to York Trials Unit.

York Trials Unit in conjunction with the Sponsor will report all SUSARs to the Competent Authorities (MHRA in the UK) and the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, York Trials Unit, in conjunction with the CI, shall submit once a year throughout the clinical trial or on request a Developmental Safety Update Report to the Competent Authority (MHRA in the UK) and Ethics Committee.

Table 1: Expected Serious and Non-Serious Adverse Events Associated with Limited Fasciectomy

| | |
|---|---|
| Amputation | Scar pain |
| Arterial injury | Scar related complications (including hypertrophy) |
| Bleeding | Stiffness |
| Complex Regional Pain Syndrome (CRPS) | Swelling |
| Delayed healing | Tendon injury |
| Infection | Edge necrosis |
| Instability | Carpal tunnel syndrome (starting within six weeks of limited fasciectomy surgery) |
| Nerve Injury | Other – Tenosynovitis (starting within six weeks of limited fasciectomy surgery) |
| Pain | Other - Trigger finger (starting within six weeks of limited fasciectomy surgery) |
| Paraesthesia (including dysaesthesia, burning and hyperaesthesia) | |

# 11. STATISTICS

Statistical analysis and health economics analysis plans will be written before any analyses are undertaken. Any subsequent amendments to the plan will be clearly documented. Analysis will be carried out on a locked dataset. All analysis will be conducted taking into consideration the reporting requirements of the Consolidated Standards of Reporting Trials (CONSORT)[29].

## 11.1 Pilot phase Analysis

The internal pilot phase analysis will test our assumptions about recruitment, specifically the ability to set up 6 study sites and subsequently recruit 48 participants. Secondary reasons for undertaking the pilot will be to closely monitor operational aspects of the trial including training, eligibility and time to consent, study activity and patient adherence. A summary of the data will be provided to the independent Data Monitoring Committee (DMC – described in Section 13.2) who will review the pilot data and make a recommendation to the Trial Steering Committee (described in 13.3) and Trial Management Group to recommend any changes required to the study team and the funding body.

To determine the success of the pilot study and the decision to continue with the study is based on the following primary feasibility objectives:

1. Set up six pilot sites to recruit with a target to recruit 48 patients from these sites.
2. To ensure that further site set up of 9 sites (inclusive of pilot sites) has been completed.

## 11.2 Description of Statistical Methods

All outcomes will be reported unadjusted descriptively at all collected time points. Continuous data will be presented using means and standard deviations, and categorical data using frequencies and percentages.

The primary analysis will be on intention-to-treat basis, analysing patients in the groups to which they were randomised. The mean difference in PEM scores between treatment groups and associated 97.5% CIs will be obtained using repeated measures regression, adjusting for PEM at baseline, contracted joints (MCP or PIP) and other relevant baseline covariates. Non-inferiority of Collagenase injections 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 1 year lies within the non-inferiority margin of 6 points.

Completeness of data at follow-up will be reported and the baseline characteristics of randomised and analysed patients compared. Compliance with randomised treatments will be presented and CACE (complier average causal effect) analysis will be performed as a sensitivity analysis. A further secondary analysis will repeat the primary model using a complete multiply imputed dataset. Treatment differences at all other follow-up time points (3 months, 6 months and 2 years) will also be reported with associated CIs.

Continuous secondary outcomes (e.g. URAM, MHQ) will be analysed using similar models to the primary analysis. Differences for binary outcomes (e.g. recurrence rates and complications) will be analysed by logistic regression models. Time to recurrence and time to restorative function will also be analysed.

### 11.3 Description of Health Economics Methods

An economic analysis will be undertaken, using individual patient data, to evaluate resource use, costs and health outcomes associated with the interventions. The analyses will be conducted from the perspective of the UK National Health Services (NHS) and Personal Social Services (PSS) perspectives.

Costs and health outcome data for the economic analysis will be collected prospectively during the study using patient-completed questionnaires at baseline, 3 months, 6 months, 1 year and 2 years.

The primary economic outcome will be the additional cost per quality-adjusted life year gained of injection treatment compared to surgical treatment. The value for money of injection treatment will be estimated in terms of cost per QALY using EQ-5D-5L data and an intention-to-treat approach as recommended by the NICE appraisal guidance[30]. Descriptive statistics of the utility scores for both trial arms at each data collection point and raw EQ-5D-5L scores according to domain will be presented. The overall difference in EQ-5D-5L index scores between the two arms will be examined through regression methods, consistent with the model selected in the statistical analysis. The EQ-5D-5L health states will be valued using a UK-based social tariff.

Costs components for health resource use (inpatient episodes, outpatient hospital visits, emergency hospital admissions and also primary care visits) (e.g. GP, nurse and physiotherapy) will be presented for both arms in terms of mean value, standard deviation and mean difference (with 95% CI) between the groups. The cost of the intervention will be estimated according to resource use related to the Collagenase injections and other resource use required for the manipulation. Costs relating to surgical procedures will be based on time in theatre, staff time, consumables and devices, and nights in hospital after the procedure. For the analysis, regression methods will be used with the base-case analysis conducted as an imputed analysis by means of multiple imputations (MI).

The assessment of cost-effectiveness will also consider patient relevant outcomes such as return to remunerative employment and recurrence. Recurrence will be assessed using the primary definition (change in extension deficit of 6 degrees between 3 and 6 months, or 20 degrees from 3 months to 1 year post treatment[10, 14]). Secondary definitions may also be used to allow comparability with other studies.

## 11.4 Description of Qualitative Methods

Data will be analysed thematically following the conventions established by Braun and Clarke[31]. Interviews will be coded independently by a dedicated qualitative researcher with a second team member ensuring consistency and validity of the coding process. Data analysis will commence before data collection is completed and coded interviews will be reviewed by the clinical lead and other team members to inform on-going data collection strategies. Key ideas and themes which help to organise the data will be identified and modelled as part of this process.

Data from each treatment arm may be considered separately with distinct models for surgery and Collagenase injection constructed along with a further model which considers Dupuytren's symptoms and impact. These models will be considered alongside the clinical and economic data to inform the study findings and to inform recommendations for future clinical practice.

## 11.5 Description of Photography Sub Study Methods

Intra Class Correlation Coefficients (ICCs) will be calculated between patient photographs and goniometer readings at 6 months for the reference digit. A Bland-Altman plot will be constructed and limits of agreement reported with 95% confidence intervals. The limits of agreement will be assessed against known standard errors of measurement and resulting minimal detectable changes (MDCs) of standard goniometric readings.

For secondary comparisons (other digits, other time points, comparison with clinician photographs), ICCs will be calculated and presented together with average ICCs over all digits by patient. Limits of agreement values and 95% confidence intervals will be reported for all secondary agreement comparisons. Potential predictors of average ICC agreement will be explored by regression analyses, including image quality characteristics and contracture severity. Intra- and inter-observer reliabilities of contracture measurements will be evaluated using repeat image assessments by the same observer and assessments from different observers for the same images.

Further details on the processes for this sub study can be found in the DISC Photography Sub Study Manual.

## 11.6 The Number of Participants

For 90% statistical power, 568 participants (284 per arm) are required to establish non-inferiority of Collagenase injections compared with surgery within a margin of 6 points on the PEM (SD=22), based on the lower limit of a 95% two-sided confidence interval (equivalent to a one-sided 97.5% confidence interval). Assuming 20% attrition at 1-year follow-up, the total target sample size is 710.

Previous survey data collected from a representative sample of 880 patients with Dupuytren's Contracture showed the standard deviation (SD) of the PEM at baseline to be 22 points. Using methods of predictive value against an anchor question for functional improvement as well as a social comparison approach for these data, we estimate that a six-point difference on the PEM at 1 year represents the threshold at which treatment differences become important, and which would represent an appropriate non-inferiority margin.

To minimise attrition, participants will be provided with an unconditional incentive of £40 at the 1 year and 2 year follow up time points. This is a proven and effective strategy for increasing follow up response rates, particularly in the context of postal questionnaires (as may be used at 2 year follow up, dependent on the results of the photography sub study) [32] and has been used previously in trials coordinated by York Trials Unit.

### 11.7 The Level of Statistical Significance

A 95% two-sided confidence interval (equivalent to a one-sided 97.5% confidence interval) will be used to assess statistical significance.

### 11.8 Criteria for the Termination of the Trial.

There will be no formal stopping rules or interim statistical analyses for this trial.

### 11.9 Procedure for Accounting for Missing, Unused, and Spurious Data.

Every effort will be made to minimise loss to follow-up, however, it is anticipated that there will be some loss to follow-up and we have accounted for this in our sample size calculation. For each outcome measure the number of non-responders will be calculated for each treatment group and response rates compared. Appropriate sensitivity analyses will be used to examine the effects of missing data on outcomes.

### 11.10 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any additions and/or amendments during development of the statistical analysis plan will be detailed, with rationale, in the document. Any deviations from the finalised statistical analysis plan will be clearly documented in the final report.

### 11.11 Inclusion in Analysis

All statistical analyses (unless otherwise stated) will follow intention to treat principles, including all participants in the groups to which they were randomised in the analysis. Sensitivity analyses accounting for missing data and compliance will be explored. A CACE analysis will be undertaken to explore the impact of not receiving the interventions as intended.

## 12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

## 13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating and trial specific procedures.

### 13.1 Monitoring

Regular monitoring will be performed according to ICH GCP and the DISC Monitoring Plan.

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating and trial specific procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

### 13.2 Independent Data Monitoring Committee

The study will be regularly reviewed by the independent Data Monitoring Committee (DMC) comprising of independent clinicians and health service researchers with appropriate expertise. Further details relating to the DMC are provided in Section 16.2.

### 13.3 Trial Steering Committee

Independent oversight of the study will be conducted by the Trial Steering Committee who will meet every 6 months during the trial. Further details relating to the TSC are provided in Section 16.1.

## 14. CODES OF PRACTICE AND REGULATIONS

### 14.1 Ethics

The DISC trial will be conducted in accordance with the Clinical Trial Regulations 2004/1031 and will be subject to approval from the Research Ethics Committee, associated competent authorities (MHRA) and the Health Research Authority prior to study activity commencing.

Risks to participants from the intervention or control treatments are not increased through trial participation. Measures, such as our emphasis on good practice and standardised protocols/care pathways throughout, are likely to reduce risk and could bring additional benefits. Consultant surgeons with experience in both techniques will deliver the study treatments and will oversee patient aftercare.

Before being enrolled in the clinical study, participants must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

An informed consent document (PIS) that includes both information about the study and the consent form will be given to the participant. This document will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. Patients will be given the opportunity to ask questions and the nature and objectives of the study will be explained. After reading the PIS, the participant must give consent in writing. The participant's consent must be confirmed at the time of consent by the personally dated signature of the participant. The written consent will then be signed off, with a personally dated signature, by the person conducting the informed consent discussions.

The original signed consent form will be retained in the Study Files. Other copies of the consent form are required:

- One copy of the informed consent form will be faxed to YTU and filed in the TMF
- One copy of the informed consent form will be kept in the patient's clinical notes where applicable. If a patient does not have clinical notes at the trial site the informed consent document will be filed in a separate folder.
- One copy will be given to the patient.

Consent is an ongoing process and will be reassessed at each study visit.

### 14.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines

### 14.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current

revision of the Declaration of Helsinki.

### 14.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice.

### 14.5 Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), Health Regulatory Authority (HRA) regulatory authorities (MHRA in the UK), and host institution(s) for approval.

Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

### 14.6 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

### 14.7 Other Ethical Considerations

Treating clinicians are permitted to exclude patients who lack mental capacity to understand the trial procedures, instructions for rehabilitation procedures and/or subsequent compliance.

## 15. DATA HANDLING AND RECORD KEEPING

### 15.1 CRF completion

The research team is responsible for prompt reporting of accurate, complete, and legible data in the CRFs and in all required reports. Any change or correction to the paper CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted.

### 15.2 Database entry and reconciliation

Study participants will be identified by a study specific participant number in the DISC database. The name and any other identifying detail will not be included in any study data electronic file.

CRFs/external electronic data will be entered/loaded in a validated electronic database using a research data management system (RDMS). Computerised data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. CRF data are entered into the research database using a rolling query-resolution system designed to identify data entry errors and protocol deviations in a timely fashion to allow accurate reconciliation.

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

### 15.3 Screening and enrolment logs

The Investigator will maintain the Participant Enrolment Log. This log remains with the Investigator, at site, and is used for unambiguous identification of each participant. The list contains the participant ID number, enrolment data, full name, date of birth, hospital number or National Health Security number (if applicable), participant address and date of study completion or withdrawal.

The participant's consent and enrolment in the study must be recorded in the participant's medical record. These data should identify the study and document the dates of the participant's participation.

The investigator will also maintain an anonymous, aggregate level screening log, documenting reasons for patient non-inclusion in this study.

## 16. STUDY GOVERNANCE

### 16.1 Trial Steering Committee (TSC)

Independent oversight of the study will be conducted by the Trial Steering Committee who will meet routinely during the trial. The TSC will monitor the progress of the trial and provide independent advice. Amongst its members will be an independent chair, a lay individual, and a clinician who is independent of the study research team. A Sponsor representative will also be invited to attend the TSC meeting.

The terms of reference for the independent data monitoring committee are provided in Appendix C for reference.

### 16.2 Data Monitoring Committee (DMC)

The study will be regularly reviewed by the independent Data Monitoring Committee (DMC) comprising of independent clinicians and health service researchers with appropriate expertise.

The DMC will meet routinely to provide project oversight to the trial. This will include monitoring the acceptability of waiting times to the study interventions which sites will have committed to being achievable when assessing their feasibility to take part. DMC will also monitor the data arising from the study and will review study documentation to ensure the protocol is accurately followed and the study is GCP compliant. The committee will recommend whether there are any ethical or safety reasons why the trial should not continue.

The minutes/records of these meetings will be stored at the YTU and will shared with the sponsor on a routine basis.

The terms of reference for the independent data monitoring committee are provided in Appendix D for reference.

## 17. FINANCING AND INSURANCE

### 17.1 Finance

The DISC Trial is funded by the Health Technology Assessment Programme (Project Number: 15/102/04)

The Schedule of Events and Statement of Activity approved by the Health Regulatory Authority (Reference: <<To be confirmed>>) contains all related costings for the DISC Trial, specifically:

- ***Research Costs*** *- the costs of the R&I itself that end when the research ends. They relate to activities that are being undertaken to answer the research questions.*
- ***NHS Treatment Costs*** *- the patient care costs, which would continue to be incurred if the patient care service in question continued to be provided after the R&I study had stopped.*
- ***NHS Support Costs*** *- the additional patient care costs associated with the research, which would end once the R&I study in question had stopped, even if the patient care involved continued to be provided.*

### 17.2 Insurance

The Clinical Negligence Scheme for Trusts is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. In certain circumstances we provide insurance cover for claims arising from non-negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

## 18. PUBLICATION POLICY

Results from this study will be written up and submitted to peer-reviewed journals. A publications policy will be generated in advance to detail authorship, acknowledgements and review processes for any publications arising from the DISC Trial.

All publications, presentations, correspondence and advertisements arising or related to the grant must acknowledge the funder using the National Institute of Health Research (NIHR) approved disclaimer.

The NIHR Programme Manager must be notified of intention to publish peer reviewed journals at least 28 days in advance of publication. Public oral or poster presentations should be notified to the NIHR Programme Manager 28 days prior to submission of an abstract. A draft copy of the proposed publication should also be provided as part of this notification.

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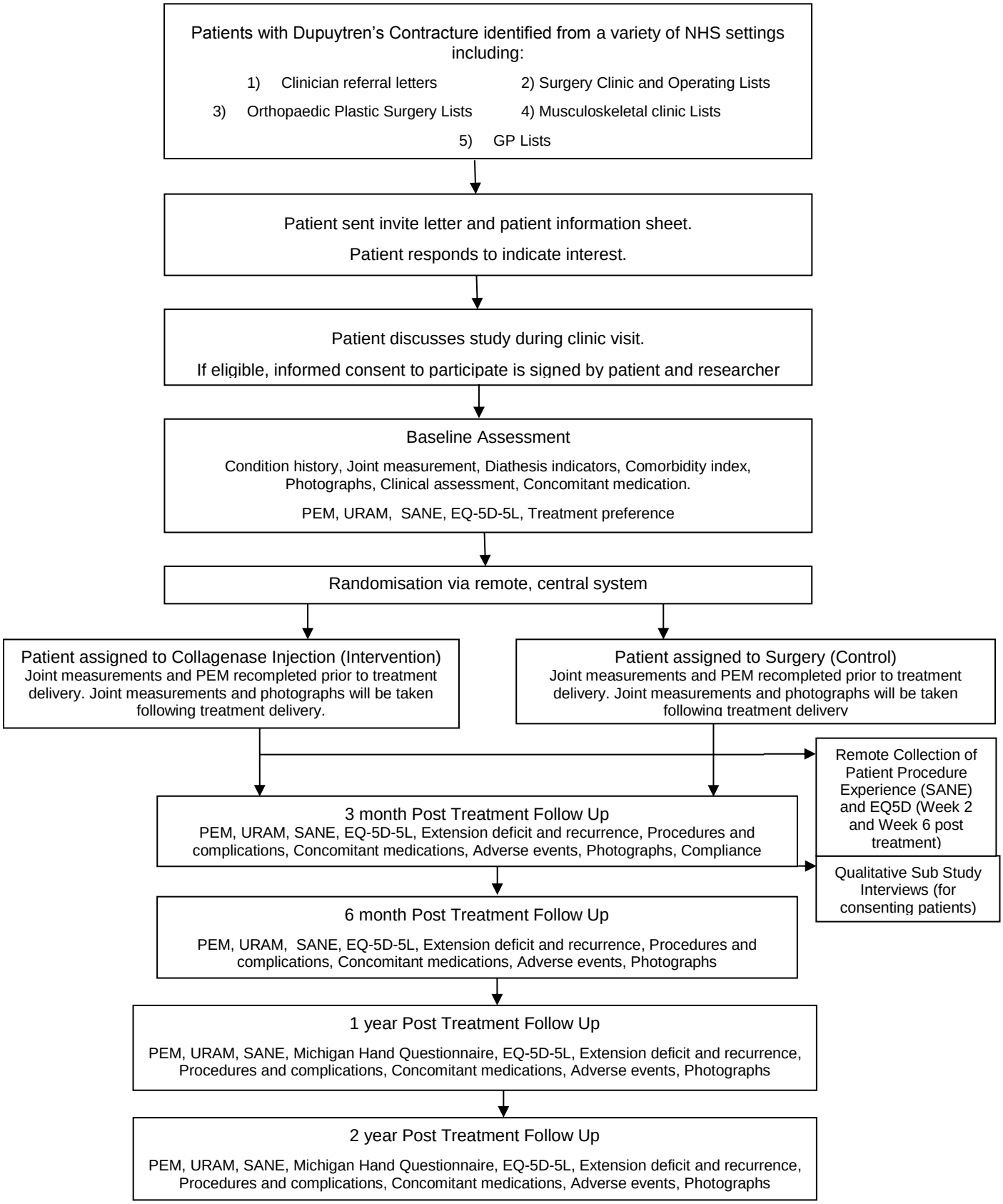
## 20. APPENDIX A: STUDY FLOWCHART



## 21. APPENDIX B: SCHEDULE OF PROCEDURES

| Procedures | Baseline | Treatment Delivery | Week 2 Post Treatment | Week 6 Post Treatment | 3 months Post Treatment | 6 months Post Treatment | 1 years Post Treatment | 2 years Post Treatment |
|---|---|---|---|---|---|---|---|---|
| Informed consent | x | | | | | | | |
| Demographics | x | | | | | | | |
| Condition History | x | | | | | | | |
| Compliance | | | | | x | | | |
| Joint measurements | x | x | | | | | | |
| Diathesis indicators | x | | | | | | | |
| Comorbidity Index | x | | | | | | | |
| Clinical assessment of cords | x | | | | | | | |
| Randomisation | x | | | | | | | |
| Intervention/Control Procedure Scheduled | x | | | | | | | |
| Concomitant medications | x | | | | x | x | x | x |
| Photographs of the hand | x | x | | | x | x | x | x |
| Patient Evaluation Measure (PEM) | x | x | | | x | x | x | x |
| Unité Rhumatologique des Affections de la Main (URAM) Scale | x | | | | x | x | x | x |
| Michigan Hand Questionnaire | x | | | | | | x | x |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| EQ-5D-5L | x | | x | x | x | x | x | x |
| Extension Deficit and Recurrence | | | | | x | x | x | x |
| Further Procedures and Complications | | | | | x | x | x | x |
| Resource Use | | | | | x | x | x | x |
| Adverse event assessments | | | | | x | x | x | x |
| Remote Collection of Patient Procedure Experience | | | x | x | | | | |

## 22. APPENDIX C: TRIAL STEERING COMMITTEE TERMS OF REFERENCE

**Terms of reference**

The Trial Steering Committee should meet once a year or more often as appropriate.

Specifically the terms of reference of the Trial Steering Committee are as follows:

- To provide overall supervision of the trial.
- To monitor and supervise the progress of the trial towards its interim and overall objectives, adherence to the protocol and patient accrual within the set time-frame.
- To review at regular intervals relevant information from other sources (e.g. other related trials), and recommend appropriate action (e.g. changes to trial protocol, stopping or extending the trial).
- To recommend appropriate action in light of points 1, 2 and 3 to ensure that the trial adheres to the Declaration of Helsinki and specifically that the rights, safety and well-being of the trial participants are the most important considerations, and prevail over the interests of science and society.
- To keep any issues discussed in the meetings or written in the minutes confidential, unless otherwise agreed.

It is also the responsibility of the Trial Steering Committee to:

- Approve any changes to the protocol during the course of the trial.
- Consider new information relevant to the trial, including reports from the DMC and the results of other studies, particularly if the results may have a direct bearing on the future conduct of the trial. On consideration of this information, the Trial Steering Committee should recommend appropriate action, such as changes to the trial protocol, additional patient information, or stopping or extending the study.
- Ensure that appropriate efforts are made to ensure that the results of the trial are adequately disseminated and that due consideration is given to the implementation of the results into clinical practice.

In addition, the Chairman should also:

- Be informed of any unexpected SAEs.
- Approve and sign the final report of the trial (for the funding body).

The main purposes of Trial Steering Committee meetings are:

- To provide the overall supervision of the trial, in particular to monitor the progress of the trial, adherence to the protocol and patient safety.
- To maximise the chances of the trial completing within the timescales set and agreed by the funding body.
- To ensure that the trial is conducted to the rigorous standards set out in the MRC Guidelines for GCP and the DoH Research Governance proposals.

It is therefore essential that, at a minimum, 2 independent members of the Trial Steering Committee attend each meeting.

## 23. APPENDIX D: DATA MONITORING COMMITTEE TERMS OF REFERENCE

### Objective

The objective of the DMC is to independently monitor the safety data and related ethics of the trial.

### Roles and Responsibilities

- Attend DMC meetings and provide advice on availability for future DMC meetings (non-attendance at three successive meetings may lead to removal from the DMC).
- To consider data monitoring plans and related ethical implications at the outset of the trial.
- Agree to any relevant statistical analysis plans (e.g. DMC plans, pilot analysis plans).
- To monitor the safety and tolerability endpoint on a continuous basis.
- To consider interim safety data at approximately four-month intervals or more frequently if any safety issues arise during the conduct of the trial. To also consider data from the formal interim analysis for the pilot phase plus any additional safety issues for the trial and relevant information from other sources (any recommendations relating to patient safety may be participant to expedited reporting to the Competent Authority).
- To review safety data to look for any emerging trends, including increases in severity or frequency of expected Serious Adverse Reaction such that they would require expedited reporting to the Competent Authority.
- In the light of the above, and ensuring the ethical considerations are of prime importance, to report (following each DMC meeting) to the TSC including Sponsor CI and YTU, to recommend on the continuation of the trial (with consideration of the stopping rules as defined in the protocol).
- To consider any requests for release of interim trial data and to recommend to the Chief Investigator on the advisability of this.
- In the event of further funding being required, to provide to the Chief Investigator appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study.

- *Monitor study progress including recruitment rate, loss to follow up and data quality*
- *Advise on protocol modifications suggested by the investigators or sponsors*
- *Monitor compliance with the protocol by participants and investigators*
- *Assess the impact and relevance of external evidence.*

*Suggest additional data analyses if relevant***Accountability & Escalation**

The DMC is accountable to the Chief Investigator and Sponsor. The DMC is responsible for escalating any issues for concern to the Chief Investigator and Sponsor.

### Confidentiality

All data and results from the trial must be kept confidential.

### Data Transfer

No publically identifiable patient data will be transferred to the DMC. Data will usually be transferred electronically to an appropriate professional email address or via standard postal routes. Where additional risk is identified, passwords or special delivery services will be used.

A Data Monitoring Committee Charter will be prepared ahead of the inaugural meeting, in line with University Hospitals Leicester SOP 1025.