**A multi-centre, double blind, randomised, placebo-controlled, parallel group, phase II trial to determine the efficacy of intra-nodular injection of anti-TNF to control disease progression in early Dupuytren's disease, with a dose response**

**NCT Number** 03180957 **- 07 Jan 2021**

RIDD

# A multi-centre, double-blind, randomised, placebo-controlled, parallel group, phase II trial to determine the efficacy of intra-nodular injection of anti-TNF to control disease progression in early Dupuytren's disease, with a dose response (RIDD)

## Statistical Analysis Plan

Version 2.0 – 07Jan2021

Based on Protocol version 13.0 – 21Nov2019

EudraCT Number: 2015-001780-40

OCTRU Reference Number: CTU0028

| Role | Name | Title | Signature | Date |
|---|---|---|---|---|
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***Note:*** *signatures may be stored in OCTRU OF_006 Sign-off sheet as an alternative to this document*

**Oxford Clinical Trials Research Unit (OCTRU)**
**Centre for Statistics in Medicine (CSM)**

## CONTENTS

# 1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the second part of the ***multi-centre, double-blind, randomised, placebo-controlled, parallel group, phase II trial to determine the efficacy of intra-nodular injection of anti-TNF to control disease progression in early Dupuytren's disease, with a dose response run-in (RIDD) funded by Health Innovation Challenge Fund (Wellcome Trust and Department of Health) and sponsored by the University of Oxford***. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, although they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis will be carried out by an identified, appropriately qualified and experienced statistician, who will ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

## 1.1 Key personnel

*List of key people involved in the drafting and reviewing this SAP, together with their role in the trial and their contact details.*

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### 1.2 Changes from previous version of SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes will be provided. Include protocol version number and date.

| Version number<br>Issue date | Author of this issue | Protocol Version & Issue date | Significant changes from previous version together with reasons |
|---|---|---|---|
| V1.0_30Nov2015 | Bethan Copsey | Protocol_V4.0_13Aug2015 | Not applicable as this is the 1st issue |
| V1.5_21Sep2016 | Bethan Copsey | Protocol_V8.0_19Aug2016 | **Part 1 – dose choice:** The choice of dose cohorts in Part 1 will be decided by the Safety Committee following analysis. No cohorts will use systemic injections.<br>**Part 1 - secondary objectives:**<br>Expression of collagen type I and α-SMA protein in excised nodule tissue have been added.<br>Grip strength, range of motion, the Michigan Hand Outcomes Questionnaire (MHQ) and activity most restricted have been removed to reduce patient burden and encourage recruitment.<br>**Part 1 – fewer study visits:**<br>The study visit one week after injection will be replaced with a phone call. The study visits one and four weeks after surgery have been removed.<br>**Inclusion/exclusion criteria** – Updated in line with protocol.<br>**Part 2 – dose choice:** New formulation of adalimumab has been released (40mg in 0.4ml into the nodule) and therefore a new dose cohort was included. |
| V2.0_07Jan2021 | Heather O'Connor | Protocol_V13.0_21Nov2019 | Restriction of analysis plan to include only RIDD part 2.<br>Description of methods to account for readings from two durometers from some patients during the blinded analysis. |

| Version number<br>Issue date | Author of this issue | Protocol Version & Issue date | Significant changes from previous version together with reasons |
|---|---|---|---|
| | | | Inclusion of complier average causal effect analysis alongside per-protocol analysis.<br>Definition of key secondary outcomes.<br>Amendment of secondary outcome analysis to use repeated measures linear mixed effects regression in place of individual time-points ANCOVA.<br>Inclusion of sub-group analysis to account for potential differences between populations in the UK and the Netherlands, and between age groups.<br>Inclusion of new and updated dummy tables for result reporting; moved to a separate appendix.<br>Additional information on the analysis of tertiary and exploratory objectives.<br>Addition of appendix to describe the collection and analysis of data from ultrasound images. |

# 2. BACKGROUND AND OBJECTIVES

## 2.1 Background and rationale

Dupuytren's disease (DD) is extremely common, affecting 12% of people over the age of 55 years in Western countries (Lanting et al, 2014). The mean age of patients undergoing surgical treatment for the disease is 63 years (Chen, Shauver & Chung, 2011). DD has a substantial heritable component, with a twin study from Denmark estimating the overall heritability as 80% (Larsen et al, 2015). Factors such as extra-palmar disease, radial sided palmar and early onset disease have been shown to relate to the patient's Dupuytren's diathesis (Abe et al, 2004). The literature would suggest that the disease tends to be more aggressive in people with onset of DD before 50 years of age. Diagnosis is made by clinical examination of the hand.

Between 35-50% of patients with early DD manifest as nodules on the palmar aspect of the hand progress to develop finger contractures (Gudmundsson, Arngrimsson & Jonsson, 2001; Reilly, Stern & Goldfarb, 2005). The nodules are typically quiescent for a period and then become active, with progression to flexion deformities over a period of months (Bayat & McGrouther, 2006).

The mainstay of treatment is surgical excision (fasciectomy) of the diseased tissue or cords (Davis, 2013), which is recommended when patients develop flexion deformities of the digits of 30 degrees or more of the finger joints and suffer impaired hand function (Legge & McFarlane, 1980; Rayan, 2007). Over 90% of the 12,900

patients who have surgery for DD per annum in the UK undergo fasciectomy (Gerber et al., 2011). Approximately 21% of patients develop recurrence within 5 years following surgery (Rijssen et al., 2012; Rodrigues et al., 2015) and are treated with more extensive surgery that involves excision of the diseased tissue and overlying skin (dermofasciectomy). Post-operatively, patients require often 3-6 months of hand therapy and splintage (Hughes et al., 2003; Larson & Jerosch-Herold, 2008). Complications occur in approximately 20% of surgical patients (Bulstrode, Jemec & Smith, 2005; Crean et al 2011).

Alternative, less invasive techniques have been developed to disrupt the cords of diseased tissue with either a needle (Beaudreuil et al., 2012) or collagenase digestion (Hurst et al., 2009). However, recurrence rates are high, affecting 85% of patients treated with percutaneous needle fasciotomy (van Rijssen et al., 2012; Rodrigues et al., 2015) and 47% of those treated with collagenase (Peimer et al., 2013) at 5 years. The complication rate is 20% following needle fasciotomy (Crean et al., 2011) and over 70% after collagenase injection (Hurst et al., 2009), although these tend to be transient. The flexion contractures are irreversible without treatment. There is currently no approved treatment for the treatment of early DD. Numerous non-surgical treatments have been described for early stage disease, including pharmacological treatment with vitamin E or steroids, physical therapies and radiotherapy. Despite the plethora of publications, descriptions are limited to uncontrolled and unblinded studies, with no conclusive evidence for their efficacy (Ball et al 2016).

**Need for a trial**

There is a need to develop an effective therapy to prevent progression of early DD which avoids the necessity for invasive procedures and also prevents the development of recurrent disease following surgery, needle fasciotomy or collagenase injection in patients with established finger contractures.

**Investigational medical products (IMP): Adalimumab (active IMP) and placebo (saline, 0.9% NaCl)**

Adalimumab is an anti-Tumour Necrosis Factor (anti-TNF) drug, approved for use by the US Food and Drug Administration (FDA) since 2002, and European Medicines Agency (EMA) since 2003. It is used to treat rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, with 40 mg administered by subcutaneous injection once every 2 weeks. No dose adjustment is required for those aged 65 years or older. It is also prescribed for Crohn's disease and ulcerative colitis with 160 mg initially administered by subcutaneous injection, followed by 80 mg 2 weeks later and then 40 mg every 2 weeks. In clinical trials, the most common adverse reactions were injection site reactions (erythema, and/or itching, haemorrhage, pain or swelling) but most were described as mild and did not necessitate drug discontinuation. Because of its effects on the immune system, adalimumab may increase susceptibility to infections and patients are monitored for tuberculosis (TB) and Hepatitis B. In common with all anti-TNF drugs, there may be a slightly increased risk of certain types of cancer, but this link is not proven and is currently being researched. However, in our study risks should be lower as anti-TNF will be given at relatively low doses, less frequently and for a limited duration. In this trial, adalimumab is being used off-label.

This trial comprises of two parts: (1) the dose response to find an effective dose of adalimumab for downregulating the myofibroblast phenotype in the Dupuytren's nodule, and (2) the main randomised controlled trial to demonstrate the efficacy of adalimumab to treat early DD. **This SAP is for the second part of this trial.**

## 2.2 Objectives

**Primary objective**

To determine if injection with adalimumab is superior to placebo injection of normal saline in controlling disease progression in participants with early Dupuytren's disease (DD).

**Secondary objectives**

- To determine if injection with adalimumab is superior to placebo injection of normal saline in controlling disease progression in participants with early DD.
- To compare the development of Dupuytren's nodules and associated cord, flexion deformities of the fingers and impairment of hand function for participants on each treatment.
- To assess acceptability of injections to patients.
- To monitor for adverse events.

**Tertiary objectives**

- To assess if early DD injection therapy represents good value for money compared to current clinical care.
- To determine circulating levels of adalimumab and antibodies to adalimumab in the blood.

**Exploratory objective**

To investigate changes in other molecule markers relevant to the progression of DD.

## 3. STUDY METHODS

### 3.1 Trial Design/framework

The RIDD trial is designed as a ***randomised, multi-centre, double blind, placebo-controlled, parallel group, phase II trial to determine the efficacy of intra-nodular injection of anti-TNF in delaying disease progression in early DD when compared to a saline placebo***. The study will be performed across at least 3 participating centres. ***Intra-nodular injection of anti-TNF will be performed at baseline, 3, 6 and 9 months***. Primary comparison will be performed using a measure of ***change in nodule hardness from baseline***, assessed at the ***primary endpoint of 12 months,*** with secondary analysis comparisons of this measure further taking into account the ***co-endpoints of 3, 6, 9 and 18 months after first treatment***. Secondary outcome analyses will also be performed analysing observed differences on ***ultrasound imaging of nodule size, range of motion of the affected digit, grip strength, Michigan Hand Outcomes Questionnaire score, participant identified activity most restricted by DD (scored on a scale of 1-10), injection experience, progression to surgery and adverse events within the first 18 months after initial treatment between the trial treatment groups***.

| | |
|---|---|
| Grant activation: | 01Mar2015 |
| Trial Open (start of recruitment) for Part 2: | 08Jan2017 |
| First DSMC meeting (actual): | 22Mar2017 |
| End of recruitment: | 31Dec2018 (UK) |
| | 12Apr2019 (Netherlands) |
| Date expected end follow-up/start of data cleaning: | 06Dec2020 (UK) |
| | 04Jan2021 (Netherlands) |
| Expected start of final analysis: | 26Jan2021 |
| End of grant: | 30Jun2021 |

### 3.2 Randomisation and Blinding

Randomisation will be undertaken at or prior to the baseline visit prior to receiving the trial injection. Participants will be randomised 1:1 to placebo or adalimumab with stratification by age and centre. Participants will be randomised through a secure online service provided by the Oxford Clinical Trials Research Unit (OCTRU) called RRAMP. RRAMP is used to randomise participants and this will generate a Trial ID and prompt an email to Pharmacy which informs them of which IMP (drug or placebo) to dispense.

Full details of the randomisation are available in **RIDD_RBP_v9.0_18May2018**, stored in the confidential statistical section of the TMF.

The methods for blinding will be influenced by the packaging of the adalimumab being used. For part 2, pre-filled syringe is the only option for using the 40mg in 0.4ml formulation. Due to the distinctive appearance of the syringe, it is not possible to blind the healthcare professional administering the injection to treatment allocation. To protect the quality of the data, any person injecting with a pre-filled syringe will NOT be involved in administering any further trial procedures. Any healthcare professionals involved with administering any trial procedure, including outcome assessments, after the injection of IMP will be blinded to treatment.

The IMP (which will be stored in pharmacy) will be dispensed with accountability to a member of the research team who will take the IMP to a clinic room separate from the participant. Care will be taken to ensure any healthcare professionals blinded to treatment allocation are not present for the injection, and the syringe will be hidden from the participant's view.

In summary, participants and healthcare professionals involved in participant follow-up and outcome assessment will always be blinded to treatment allocation. Laboratory staff will be blinded to treatment allocation.

### 3.3 Sample Size

The sample size is based on unpublished data acquired in a pilot study 'Ultrasonographic (grey scale) characteristics of DD and their relationship to the clinical features and functional severity of the disease: a pilot study' (REC Ref. 11/SC/0447). Within the study there were 25 participants with mean nodule hardness of 53±8 for participants suffering DD and 32±3 for corresponding controls matched by age and sex.

Using the study, a minimum of 138 participants (69 per arm) would be required to detect a moderate effect size of 0.62, based on a 5 point change in nodule hardness at 12 months and assuming a standard deviation of 8 (5% significance (2-sided) and 90% power, allowing for a 20% loss to follow up).

### 3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

*Interim analysis*

There are no formal interim analyses of the outcomes planned for RIDD part 2 but these will be conducted at the request of the Data and Safety Monitoring Committee (DSMC).

*Details of the Data Safety and Monitoring Committee remit*

The role of the DSMC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor data quality and completeness. The DSMC will undertake interim review of the trial's progress including updated figures on recruitment, data quality, adherence to protocol and follow-up, and main outcomes and safety data. The DSMC will first meet before the trial starts and within

one year of recruitment commencing. Full details regarding DSMC remit are present in the RIDD DSMC Charter (**RIDD_DSMCCharter_V1.0_15Sep2017.docx**).

*Stopping guidelines*

Formal statistical methods are more generally used as "stopping" guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Reasons should be recorded for disregarding a stopping guideline. The statistical guidelines for the trial are described in outline in the protocol and in detail in the Outline Statistical Analysis Plan.

In the light of interim data, and other evidence from relevant studies (including updated overviews of the relevant randomised controlled trials), the DSMC will inform the TSC, if in their view there is proof beyond reasonable doubt that the data indicate that any part of the protocol under investigation is either clearly indicated or contra-indicated for a particular subgroup of trial participants. A decision to inform the TSC will in part be based on statistical considerations. Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard errors in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely.

### 3.5 Timing of Final Analysis

**Table 1**: Objectives, outcome measures, and time points of evaluation

| | Outcome Measures | Time point(s) of evaluation of this outcome measure | | | | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | 3 month [a] | 6 month [b] | 9 month [b] | 12 month [b, c] | 18 month [b, c] |
| **Primary objective** | | | | | | | |
| To determine if injection with adalimumab is superior to placebo injection of normal saline in controlling disease progression in participants with early Dupuytren's disease (DD) | Change in hardness of selected nodule for participants between baseline and 12 months after first treatment | | | | | * | |
| **Secondary objectives** | | | | | | | |
| To determine if injection with adalimumab is superior to placebo injection of normal saline in controlling disease progression in participants with early DD | Change in hardness of selected nodule for participants on each treatment at baseline, 3, 6, 9, 12[d] and 18 months after first treatment | * | * | * | * | * | * |
| To compare the development of DD nodules and associated cord, flexion deformities of the fingers and | Ultrasound imaging of nodule size | * | * | * | * | * | * |
| | Range of motion of the affected digit | * | * | * | * | * | * |
| | Grip strength | * | * | * | * | * | * |

| | Outcome Measures | Time point(s) of evaluation of this outcome measure | | | | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | 3 month [a] | 6 month [b] | 9 month [b] | 12 month [b, c] | 18 month [b, c] |
| impairment of hand function for participants on each treatment | Michigan Hand Outcomes Questionnaire (MHQ) | * | * | * | * | * | * |
| | Participant identified activity most restricted by DD score on a scale of 1-10 | | * | * | * | * | * |
| | Progression to surgery of the digit being assessed | | | | | | * |
| To assess acceptability of injections to patients | Injection experience | * | * | * | * | | |
| Monitor for adverse events | Adverse event monitoring comparing active and placebo groups using visual inspection of injection site | * | * | * | * | * | |
| **Tertiary objectives** | | | | | | | |
| To assess if early DD injection therapy represents good value for money compared to current clinical care [e] | Analysis of EQ-5D-5L data to estimate utilities using quality-adjusted life years (QALYs) from participants on each treatment | * | * | * | * | * | * |
| | Analysis of resource use data to estimate the cost of each treatment | | * | * | * | * | * |
| To monitor circulating levels of adalimumab and antibodies to adalimumab in the blood | Monitor circulating levels of adalimumab and antibodies to adalimumab in the blood | * | * | | | * | |
| **Exploratory objective** | | | | | | | |
| To investigate changes in other molecular markers relevant to the progression of DD [e] | Change in level of the markers | * | * | | | * | |

[a] ± 2 weeks | [b] ± 4 weeks | [c] where participants' 12- or 18-month data collection was delayed due to SARS-CoV-2 pandemic, the outcomes recorded via questionnaires should be completed within ± 4 weeks and the physical measurements should be completed within ± 3 months, where it is safe to do so, with additional questionnaires completed at the point of delayed physical outcomes measurement | [d] the nodule hardness secondary objective will account for all timepoints where this information has been collected, including the primary end-point of 12 months | [e] analysed by health economist

### 3.6 Blinded analysis

A blinded analysis of data (data analysed with no treatment information added) will be undertaken prior to the final data lock in order to clarify whether continuous variables are normally distributed and to identify participants who will be excluded from the per-protocol analysis.

Primary outcome measurements were conducted using two validated portable durometers. Following identification of potential issues with the initial study device with nodule hardness recording in patients with marked distortion of the skin close to their DD nodule, a second device which would not be affected by such distortions, was sourced and utilised. Patients in two study centres (Oxford and Edinburgh) had all subsequent measurements taken using both devices and patients in one study centre (Groningen) had all of their study measurements recorded using the newer device only. During the blinded analysis the results from the two durometers will be compared using a Bland-Altman plot. A cross-walk methodology will be used to map the results from the old tonometer to the results of the new tonometer, to allow maximum data utilisation. If this cross-walk is not effective in mapping the tonometer results, alternative measures may include favouring the results from the new device and using the results from the original device only where data for the new device are not available.

### 3.7 Statistical Analysis Outline

In the RCT (**Part 2**), all analyses will be performed on participants randomised to **Part 2** only, on an intention-to-treat basis with sensitivity analyses run on the per protocol population.

The primary outcome measure is change in nodule hardness from baseline to 12 months. There will only be one dose level used in **Part 2**, which will be 40mg of adalimumab. It is expected that all nodules will be large enough to accommodate the injection, but if not the volume of residual IMP will be recorded. The difference in the mean change of nodule hardness between the two groups will be reported with 95% confidence intervals. The comparison of change in nodule hardness between interventions will be analysed primarily using Analysis of Covariance (ANCOVA) adjusting for baseline, if it is normally distributed. As a secondary confirmatory analysis, ANCOVA adjusting for baseline nodule hardness as well as the stratification factors comprising centre (Oxford, Edinburgh or Groningen) and age (as a continuous variable) will be conducted.

If the data are not normally distributed, the data will be log-transformed in order to gain normality and geometric means with 95% confidence intervals will be reported. If data are not normally distributed after log-transformation, the non-parametric Mann Whitney test will be used with no adjustment for baseline, and the median change with 95% confidence intervals will be reported.

In order to analyse change in nodule hardness over the full time period, linear mixed effects regression will be used to compare nodule hardness between interventions utilising all time-points up to 18 months and adjusting for stratification and other important prognostic factors.

The secondary outcome measures for **Part 2** include those for **Part 1** and also grip strength, range of motion and participant reported outcomes.

For nodule size, grip strength, range of motion of the affected digit, Michigan Hand Outcomes Questionnaire, patient identified activity most restricted by DD, progression to surgery, and injection experience linear mixed effects regression models will be used. This procedure will allow for data from all follow-up time-points to be accounted for, and for adjustment for baseline measures to be made, where applicable. The time (days) between baseline injection and each follow-up time-point will be included in the models as a random effect to account for patients not all having their follow-up assessments at the same time.

As per the primary outcome, initial analyses for all secondary outcomes will be unadjusted and additional adjusted analyses will be carried out further accounting for centre (Oxford, Edinburgh or Groningen) and age (as a continuous variable) and baseline if appropriate. For all models, assessments for interaction between time since baseline treatment and baseline measurement will be carried out to assess if any effect of baseline measurement changes over time.

For all secondary outcome analyses, mean difference and associated 95% confidence intervals will be reported. If severe departures from normality are identified in secondary outcome measurements, the data will be log-transformed in order to gain normality and geometric means with 95% confidence intervals will be reported. If the data are not normally distributed – or near normally distributed – after log transformation, the non-parametric Mann-Whitney test will be used with no adjustment for baseline, and the median change with 95% confidence intervals will be reported.

# 4. STATISTICAL PRINCIPLES

## 4.1 Statistical Significance and Multiple Testing

There is no multiple testing as only a single primary objective is considered. Therefore, significance levels used will be 5%, and 95% confidence intervals will be reported. Secondary outcomes will also be analysed using a significance level of 5% and 95% confidence intervals as these are considered supportive of the primary conclusion only. Other outcomes will be considered exploratory and hypothesis generating only.

No interim analysis of primary and secondary endpoints are planned but, if requested by the DSMC, a 0.1% significance ($\alpha$=0.001) will be used.

## 4.2 Definition of Analysis Populations

Intention-to-treat (ITT): All participants analysed in their randomised groups with available outcome data.

Per-protocol (PP): The ITT population with some participants excluded. Patients will be excluded from per-protocol analysis if they did not satisfy the study eligibility criteria or did not receive the allocated treatment. The definition of the per-protocol population will be finalised during a blinded analysis of data (not separated by treatment arm) prior to the final data-lock.

Safety: All participants who started their allocated treatment, that is, those received at least one of the intervention injections they were allocated to, as defined in the protocol.

# 5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

Descriptive analysis will include a summary flow of participants through the trial and baseline stratification, demographic, and clinical characteristics of each treatment group.

## 5.1 Representativeness of Study Sample and Patient Throughput

The flow of participants through each stage of the trial, including numbers of participants assessed, randomly assigned to adalimumab or saline injection, receiving their assigned treatment, completing the study protocol, and analysed for the primary outcome will be provided in a flow diagram as suggested by CONSORT. Protocol violations/deviations and information relating to the screening data including the number of ineligible patients

randomised, participants found to be ineligible and participants who refused to participate will also be provided, with reasons where available.

**Appendix 5: Trial Recruitment, Figure 1***:* CONSORT flow diagram of participants in the trial.

### 5.2 Withdrawal from treatment and/or follow-up

The numbers (with percentages) of losses to follow-up (defaulters and withdrawals) will be reported and compared between the adalimumab and saline groups. To ensure that there are not differential losses between the groups this will be tested using absolute risk differences and associated 95% confidence intervals, and a Chi-squared test. Any deaths (and their causes) will be reported separately.

**Appendix 5: Trial recruitment, Table 1:** Patient withdrawals and reasons according to intervention groups.

**Appendix 5: Trial recruitment, Table 2:** Number of participants with data available at each time-point by intervention allocated.

### 5.3 Baseline Comparability of Randomised Groups

The patients in the two treatment arms will be described both overall and separately in terms of stratification factors (centre and age).

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

**Appendix 5: Baseline comparability of randomised groups, Table 3:** Categorical demographic baseline characteristics according to intervention allocated**.**

**Appendix 5: Baseline comparability of randomised groups, Table 4:** Continuous demographic baseline characteristics according to intervention allocated**.**

**Appendix 5: Baseline Comparability of randomised groups, Table 5:** Clinical characteristics according to intervention allocated**.**

### 5.4 Unblinding

Participants and healthcare professionals involved in participant follow-up and outcome assessment will always be blinded to treatment allocation. Laboratory staff will be blinded to treatment allocation. Due to the distinctive appearance of the pre-filled syringes, it is not possible to blind the healthcare professional administering the injection.

All cases of treatment unblinding will be listed, together with who was unblinded, reasons for unblinding and summarised (numbers and percentages).

### 5.5 Description of Compliance with Intervention

Compliance with the intervention will be summarised for both treatment arms, with compliance being reported as both participant compliance and treatment compliance.

Participant compliance

Participants will be defined as being compliant if they have received at least 75% of injections, that is, receiving three out of the four injections offered.

Treatment compliance

A summary of the treatment received, i.e. the number of injections, will be presented. If patients did not receive their intended allocation at any time-point, this will be defined as non-compliant and will be reported.

Participant compliance and treatment compliance will be examined by observing the difference in non-adherence between the two treatment arms.

Non-adherence to the protocol and reasons, such as withdrawals, will be summarised. In addition, the number of patients for which the visit does not take place within the specified window will be summarised for the two treatment arms.

**Appendix 5: Treatment compliance, Table 6:** Treatment compliance: Number of adalimumab and saline injections received according to intervention allocated.

**Appendix 5: Treatment compliance, Table 7:** Treatment deviations: Treatment received according to intervention allocated.

### 5.6 Reliability

Validation checks will be performed in order to check calculations and processes performed by a computer program by hand-checking a random sample of the largest of 5% of the available data or 20 patients. This will include if data have been imported and merged correctly. Prior to analysis, further validation checks will ensure that data are of the appropriate format, for example, within the maximum possible range of values. For example, when summary scores are calculated, these will be checked by hand calculations. Clarification will be sought by the trial office in the case of discrepancies.

## 6. ANALYSIS

### 6.1 Outcome Definitions

**Primary outcome**

Nodule hardness from baseline to 12 months: The primary outcome is hardness of nodule selected for treatment measured at 12 months post-first injection using a validated portable durometer. During the initial stages of this study researchers within the team noted that the original portable durometer being used to measure nodule hardness in the UK-based centres was potentially unable to achieve accurate measurements in patients with moderate to severe deformities of their hands due to their DD. Following this an alternative durometer with a longer probe, which would be able to overcome this issue, was sourced. To ensure patients who had nodule hardness data collected using only the original durometer were not excluded from analyses, or included with inaccurate data, all subsequent patients recruited in the UK-based centres had their nodule hardness data collected with both the original and the new portable durometer. The centre in the Netherlands only recorded data using the newer portable durometer.

The outcomes for RIDD were tested in our ultrasound study (REC Ref. 11/SC/0047) 'Ultrasonographic (grey scale) characteristics of DD and their relationship to the clinical features and functional severity of the disease: a pilot study'. Preliminary (unpublished) tonometry data from 25 patients in this trial demonstrated that the

palmar tissue of patients with untreated DD were significantly firmer than the corresponding age and sex matched controls.

Using the measurements from the portable durometers, the amount of indentation is converted to hardness reading on a scale with 100 units (internationally standardised durometer units). The time window for collecting the primary end-point nodule hardness data will allow ± 4 weeks to confer some flexibility. This will be extended to ± 3 months where physical measurements could not be safely recorded due to the SARS-CoV-2 pandemic.

**Secondary outcomes**

Nodule hardness over time: The change in hardness of the selected nodule for participants will also be assessed on each treatment at baseline, 3, 6, 9, 12, and 18 months after the first treatment.

Nodule size: Nodule size will be assessed using an ultrasound scan at baseline, 3, 6, 9, 12, and 18 months. Videos will also be obtained to ensure that the entire cross-section of the nodule has been recorded. For information on the translation of ultrasound images into measurement data for analysis please see **Appendix 4: Ultrasound images analysis.**

Grip strength: Measured using a Jamar meter (CE marked) at baseline, 3, 6, 9, 12, and 18 months. Previous studies of grip strength with patients with DD pre- and post-operatively have reported no significant change (Ball et al., 2013). It is anticipated that should a participant's nodule enlarge or become tender, then their grip strength might subsequently diminish.

Range of motion of the affected digit: Range of movement is the most frequently reported measure used to monitor DD progression and has demonstrated reliability, validity and sensitivity (Ball et al., 2013). Individual range of movement of finger joints will be measured using a goniometer at baseline, 3, 6, 9, 12, and 18 months post-first injection.

Michigan Hand Outcomes Questionnaire (MHQ): This is a patient-reported hand-specific measure that, unlike some other instruments, allows the user to separately score each hand at baseline, 3, 6, 9, 12, and 18 months. It contains six distinct scales that assess overall hand function, activities of daily living, pain, work performance, aesthetics, and patient satisfaction with hand function, with each scale being converted to a score ranging from 0 to 100 for reporting (see **Appendix 3**). The MHQ has been shown to have high test-retest reliability (Chung *et al*., 1998, Shauver & Chung, 2013) and internal consistency (Shauver & Chung, 2013), and has good construct validity depending on the condition assessed and good responsiveness (Shauver and Chung, 2013). It is a validated measure and has been shown to be sensitive to change when used to assess change in function over time in people with early DD (Broekstra, van den Heuvel, Lanting and Werker 2018) and improvement in hand function following hand surgery for established DD (Johnston et al., 2008, Herweijer et al., 2007). The MHQ was recommended following our systematic review of outcome measures for DD (Ball et al., 2013).

Patient identified activity most restricted by DD: Participants will be asked at baseline to identify the activity most restricted by DD and to rate the restriction on a scale of 1-10. At secondary co-time points (3, 6, 9, 12, and 18 months), participants will be asked to again rate the restriction of the same activity. When applied to DD, significant improvement in median scores have been reported following fasciectomy (Engstrand, Boren and Liedberg, 2009).

Progression to surgery: Only for the digit being treated at the end of follow-up (18 months post-first injection).

Injection experience: Reported by patients using an injection questionnaire which incorporates a Visual Analogue Scale of 0 (no pain) to 10 (extreme pain). Injection experience is measured after each research injection, at baseline, 3, 6 and 9 months.

Adverse events (injection site assessment): The most common adverse reaction with adalimumab is injection site reactions. The injection site will be monitored for adverse events using an 'Injection Site Response Form'; the injection responses are based on injection site reactions in the prescribing literature and in clinical trials.

**Tertiary outcomes**

Euroqol EQ-5D-5L: The EQ-5D-5L questionnaire is a preference-based instrument widely used in economic evaluation of health care technologies to assess quality of life and is the instrument preferred by the National Institute for Health and Care Excellence (NICE) to estimate utilities for the calculation of quality-adjusted life years (QALYs, National Institute for Health and Care Excellence, 2013). The responsiveness of the EQ-5D-5L instrument in early DD has not been formally evaluated, but the instrument was successfully used in a clinical trial of strengthening and stretching of the hand for people with rheumatoid arthritis (Heine et al., 2013). Moreover, recent qualitative research has shown that the main impact of DD on quality of life is on the performance of daily activities (Wilburn et al., 2013). The EQ-5D-5L includes domains on self-care and usual activities and will be able to capture improvements or deteriorations in quality of life in both treatment arms, with measurements taken at baseline, 3, 6, 9, 12, and 18 months.

Circulating levels of adalimumab and anti-adalimumab antibodies in the blood: 10 ml of serum will be collected post-injection to measure circulating levels of adalimumab and antibodies to adalimumab, with tertiary co-endpoints at 3 and 12 months post-first injection. Monitoring circulating levels of adalimumab will facilitate our understanding of the kinetics of drug absorption following intranodular injections and may provide further information regarding the optimal frequency of intranodular injection. Development of anti-adalimumab antibodies may be associated with reduction of efficacy.

**Table 2**: Outcome measures and assessment time-points

| Outcome measure | Time-point | | | | | |
|---|---|---|---|---|---|---|
| | ***Baseline*** | ***3 months*** | ***6 months*** | ***9 months*** | ***12 months*** | ***18 months*** |
| Tonometry | * | * | * | * | * | * |
| Nodule size (ultrasound) | * | * | * | * | * | * |
| Grip strength | * | * | * | * | * | * |
| Range of motion | * | * | * | * | * | * |
| Clinical assessment of the hand | * | * | * | * | * | * |
| MHQ | * | * | * | * | * | * |
| Most restricted activity score | * | * | * | * | * | * |
| Injection experience | * | * | * | * | | |
| Adverse event assessment | * | * | * | * | * | |
| Blood sample | * | * | | | * | |
| EQ-5D-5L | * | * | * | * | * | * |

| Outcome measure | Time-point | | | | | |
|---|---|---|---|---|---|---|
| | ***Baseline*** | ***3 months*** | ***6 months*** | ***9 months*** | ***12 months*** | ***18 months*** |
| Progression to surgery | | | | | | * |

### 6.2 Analysis methods: Primary outcome

The primary outcome analysis will be performed on the ITT population, comparing intervention (adalimumab) against placebo (saline, 0.9% NaCl) for all randomised participants with available nodule hardness data.

The adjusted difference in the mean change of nodule hardness between the two groups will be reported with 95% confidence intervals. The primary time point is 12 months. The primary analysis will be the comparison of change in nodule hardness between the adalimumab and saline groups using Analysis of Covariance (ANCOVA) adjusting for baseline nodule hardness, if it is normally distributed. If the data are not normally distributed, the data will be log-transformed in order to gain normality and geometric means with 95% confidence intervals reported. If data are not normally distributed after log-transformation, the non-parametric Mann-Whitney test will be used with no adjustment for baseline, and the median change with 95% confidence intervals will be reported.

As a supporting analysis, ANCOVA adjusting for baseline nodule hardness as well as the stratification factors comprising centre (Oxford, Edinburgh or Groningen) and age (as a continuous variable) will be conducted.

As a further supporting analysis, in order to analyse change in nodule hardness over the full time period, linear mixed effects regression will be used to compare nodule hardness between interventions utilising all available time-points up to 18 months and adjusting for stratification factors. Multilevel models permit all available data to be included in the analysis, thus eliminating complete case bias.

**Appendix 5: Outcome measure summaries, Table 8:** Mean (with SD) nodule hardness recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 9:** Mean (with SD) nodule hardness at 12 months by number of injections received.

**Appendix 5: Outcome measures analysis, Table 17:** Nodule hardness ANCOVA and linear mixed-effects regression results for all follow-up time-points.

#### 6.2.1 Missing data

The number and proportion of individuals in the missing category will be presented, as well as reasons for missing if known. It is anticipated that there will not be a high level of missing data for the primary outcome since the blinded assessor will measure nodule hardness at each follow-up visit attended by participants. However, data could be missing if a patient withdraws or does not attend for clinical assessment.

Missing data distributions will be explored to assess whether the assumption that data are missing at random (MAR) – a core assumption under which principal analyses will be conducted – is true. If MAR can be demonstrated, multiple imputation using chained equations (MICE) will be used to impute missing data. The use of MICE in place of more simple imputation techniques allows for variability in patients disease starting point and progression to be accounted for within the imputed dataset, across all time-points. The impact of

missing primary outcome data on modelled treatment effect will be assessed under a range of assumptions about the missing data, in which the data and missingness will be modelled jointly using a pattern-mixture model (PMM; White et al., 2018), which assesses the sensitivity of the analysis result to departures from a missing at random assumption. Sensitivity analyses, including PMM, will be run on the non-imputed ITT dataset, the non-imputed per protocol dataset and on the MICE imputed dataset to explore the missing data assumptions (see **6.2.1 – Sensitivity analysis**). Methods for handling missing data will be finalised during the blinded analysis, before the final analysis data-lock.

During the analysis, techniques other than those suggested above may be used, for instance if data are not normally distributed or in the case of new techniques being developed in the meantime. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

### 6.2.2 Sensitivity analysis

A sensitivity analysis will be carried out on a per-protocol (PP) basis to examine the robustness of the conclusions to different assumptions about departures from randomised policies. The PP population is as defined in **Section 4.2** above. Additionally, Complier Average Causal Effect (CACE) analysis will be used to assess data quality and the effect of treatment received (see **5.5 – Description of compliance with intervention** for compliance definitions). Unlike a PP analysis, CACE does not assume that those who comply with treatment are the same as those who do not. CACE analysis estimates treatment effect while accounting for whether or not participants complied with the intervention allocated to them. Further sensitivity analysis will also examine the impact of disease progression on the ability to complete follow-up assessment measures – for example, the development or presence of a new nodule in the treated finger or an adjacent finger – and the validity of multiple imputation assumptions by comparing results conducted on a dataset without any imputed values (complete case) to a dataset conducted with imputed values.

For sensitivity analyses related to Covid-19, see **Appendix 6: Response to SARS-CoV-2 Pandemic (Covid-19).**

## 6.3 Analysis methods: Secondary outcomes

The secondary analyses will be performed on the ITT population, comparing intervention (adalimumab) against placebo (saline, 0.9% NaCl) for all randomised participants with available data.

Mixed effects regression models will be used to analyse secondary outcomes data, with linear regression for continuous variables and logistic regression for binary variables. Mixed effects regression allows for data from all follow-up time-points to be accounted for, and for adjustment for stratification factors and baseline measurements to be made, where applicable. This procedure is robust and is able to deal with some missing values, either due to missed visits or patients leaving the study prematurely. The time (days) between baseline injection and each follow-up time-point will be included in the models as a random effect to account for patients not all having their follow-up assessments at the same time.

As per the primary outcome, initial analyses for all secondary outcomes will be unadjusted. These analyses will include only outcome measurement and treatment arm, with time since first injection included as a random effect and baseline outcome measurement as a fixed effect. Additional adjusted analyses will be carried out further accounting for centre (Oxford, Edinburgh or Groningen) and age (as a continuous variable). For all models, where appropriate, treatment by time interaction terms will be incorporated to account for changes in effects between treatment arms over follow-up.

For progression to surgery – a binary secondary outcome – numbers and proportions will be reported with absolute odds (odds difference) and relative odds (odds ratio), and associated 95% confidence intervals. For all continuous secondary outcomes, mean difference and associated 95% confidence intervals will be reported. For continuous measures if severe departures from normality are identified in secondary outcome measurements, the data will be log-transformed in order to gain normality and geometric means with 95% confidence intervals will be reported. If the data are not normally distributed – or near normally distributed – after log transformation, the non-parametric Mann-Whitney test will be used with no adjustment for baseline, and the median difference with 95% confidence intervals will be reported.

**Appendix 5: Outcome measure summaries, Table 10a:** Mean (with SD) nodule size, as maximal nodule feret and maximal height, recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 10b:** Mean (with SD) nodule area recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 11:** Mean (with SD) grip strength recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 12a:** Mean (with SD) affected digit range of motion active measurements recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 12b:** Mean (with SD) affected digit range of motion passive measurements recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 13a:** Mean (with SD) Michigan Hand Outcomes Questionnaire overall score recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 13b:** Mean (with SD) Michigan Hand Outcomes Questionnaire individual component scores recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 14:** Mean (with SD) score for most restricted activity recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 15:** Mean (with SD) injection experience pain score recorded at each study time-point.

**Appendix 5: Outcome measure summaries, Table 16:** Frequency and percentage of participants progressing to surgery at each study time-point

**Appendix 5: Outcome measures analysis, Table 18a:** Maximal nodule feret mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 18b:** Maximal nodule height mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 19:** Grip strength mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 20a:** Affected digit range of motion active measurements mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 20b:** Affected digit range of motion passive measurements mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 21:** Michigan Hand Outcomes Questionnaire mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 22:** Injection experience pain score mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 23a:** Absolute odds of progression to surgery, from mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 23b:** Relative odds of progression to surgery, from mixed-effects regression results for all follow-up time-points.

**Appendix 5: Outcome measures analysis, Table 24:** Most restricted activity mixed-effects regression results for all follow-up time-points

### 6.3.1 Missing data

The number and proportion of individuals in the missing category for each secondary outcome variable will be reported, as well as reasons for missing if known.

Missing data distributions will be explored to assess whether the assumption that data are missing at random (MAR) is true. For patient-reported outcomes, participants for whom full questionnaires have not been completed will be excluded from the analysis of the corresponding outcome. For partially completed patient-reported outcomes, missing values will be imputed according to scoring guidelines for the relevant PROM (see **Appendix 3**).

During the analysis, techniques other than those suggested above may be used, for instance if data are not normally distributed or in the case of new techniques being developed in the meantime. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

### 6.3.2 Sensitivity analysis

All secondary outcomes will be subject to adjusted mixed effects regression analysis with time not included within the models as a random effect to assess the robustness of the conclusions to the timing of follow-up. The key secondary outcomes, MHQ and range of motion of the treated digit, will have a sensitivity analysis carried out on a PP basis to determine the effect of changes in procedures under which the intervention was received. CACE analysis will also be used to assess data quality and the impact of compliance on these key secondary outcome measures.

For those who have progressed to surgery, an analysis excluding participants where it is not known which digit was operated on will be undertaken.

For sensitivity analyses related to Covid-19, see **Appendix 6: Response to SARS-CoV-2 Pandemic (Covid-19).**

## 6.4 Analysis methods: Tertiary and exploratory outcomes

For the analysis of circulating levels of adalimumab and antibodies to adalimumab in the blood (tertiary objective), we will report circulating levels of adalimumab by treatment arm. The mean difference between levels recorded at baseline, 3-months and 12-months in those who received at least one adalimumab injection will be explored.

For the analysis of changes in other molecular markers and biomarkers in the blood (exploratory objective), the mean difference between levels recorded in the two treatment groups at baseline, 3-months and 12-months will be reported.

If the data are normally distributed a t-test to assess for significant differences between levels at 3-months and 12-months will be applied. If the data are not normally distributed, the data will be log-transformed in order to gain normality and geometric means with 95% confidence intervals will be reported. If data is not normally distributed after log-transformation, the non-parametric Mann-Whitney test will be used with no adjustment for baseline, and the median change with 95% confidence intervals will be reported. Where significant differences are identified, correlations between the tertiary and exploratory outcomes and the primary outcome will be carried out. Further explorations of tertiary outcomes may include: (1) additional adjustments to the primary outcome model by including circulating levels as continuous covariates, and (2) further regression modelling to directly explore associations between grouped levels – using ordered categorisation – and the primary outcome.

**Safety analysis**

Adverse events are recorded as a secondary outcome in the RIDD RCT.

A Serious Adverse Event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or consists of a congenital anomaly or birth defect. All potentially related SAEs must be recorded on the trial specific SAE form and reported within 24 hours to the Study Site Team becoming aware of the event. Causality must be assessed by a medically qualified doctor. The SAE form must be sent to the Trials office. The SAE form will also be sent to an independent clinician as soon as all relevant information is available but no later than 3 calendar days from when the trial office is made aware of the event as per OCTRU SOPs for safety reporting. The independent clinician will assess the SAE for causality and expectedness and provide a response as per OCTRU safety reporting. In the event where the independent clinician disagrees with the assessment of the site PI, a discussion will be encouraged between the two to reassess the event. If either the PI or the independent clinician continue to assess the event as related, both assessments will be recorded. If the event is also serious and unexpected this will be reported as a SUSAR by the Trials Office to the MHRA, Ethics and Sponsor as per below. All related SAEs will be followed until resolved or not further information is expected. SAEs will only be considered closed when signed off by the local PI.

The safety analysis will be carried out on the safety population (see **Section 4.2**). Details for any related SAEs and SUSARs will be reported. Should sufficient numbers be reported comparison of patients experiencing related SAEs and SUSARs between the two treatment groups will be undertaken by examining 95% confidence intervals for the difference in incidence. An overall category for any SAE will also be compared.

The injection site will be monitored for adverse events using an 'Injection Site Response' Form, which is collected shortly after receiving each treatment. Frequency and percentages for types of AEs reported will be presented. Where sufficient numbers of AEs are reported, chi-squared tests will be used for comparing intervention groups at each follow-up time-point. *P*-values will be reported to 3 decimal places.

### 6.5 Pre-specified Subgroup Analysis

**Primary outcome**

Subgroup analyses to examine the role of age group, location of treating centre, known family history of DD, and alcohol intake upon the effect of the primary outcome (nodule hardness at 12-months post-first injection) will be performed. This analysis will be carried out using adjusted ANCOVA, including age and centre. For these analyses, age will be categorised into two groups of 18 to 49 years and 50 years or older, and alcohol intake will be categorised into four groups of non-drinker, up to 14 units/week, 14 to 35 units/week and more than 35 units per week. Treating centre location will also be categorised into two groups, defined as UK-based centres (Oxford and Edinburgh) and non-UK based centres (Groningen). Comparisons will be using a 2-sided significance level of 5% and 95% confidence intervals, and results will be tabulated as per the primary outcome adjusted ANCOVA and presented by strata using Forest plots.

**Secondary outcomes**

There is no pre-planned subgroup analysis for secondary outcomes.

### 6.6 Supplementary/ Additional Analyses and Outcomes

Any analyses further to the above and not specified in the analysis protocol will be exploratory in nature and it will be clearly labelled as a *post hoc* analysis and interpreted cautiously. If further analyses are carried out, a 0.01 significance levels will be used as evidence of statistical significance and 99% confidence intervals presented.

### 6.7 Harms

Adverse events are reported as a secondary outcome; see **Section 6.2 – Analysis methods (Safety analysis)** for further details.

### 6.8 Health Economics and Cost Effectiveness (where applicable)

*A summary from the protocol will be provided with reference to the relevant separate analysis plan (if applicable).*

The statistician is not undertaking this analysis.

### 6.9 Meta-analyses (if applicable)

There are no meta-analyses planned for the RIDD RCT.

## 7. VALIDATION OF THE PRIMARY ANALYSIS

To validate the primary outcome (nodule hardness) and key secondary outcomes a statistician not involved in the trial will independently repeat the analyses detailed in this SAP, by using different statistical software (if possible). The results will be compared and any discrepancies will be reported in the Statistical report (See OCTRU SOP STATS-005 Statistical Report). *If necessary, this will include derivation of the primary and key secondary outcomes from raw data.*

## 8. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using appropriate validated statistical software such as STATA, SAS, SPLUS or R. The relevant package and version number will be recorded in the Statistical report and subsequent publications.

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## 10. APPENDIX 1: GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| ANCOVA | Analysis of Covariance |
| Anti-TNF | Anti-Tumour Necrosis Factor |
| CACE | Complier Average Causal Effect |
| CI | Chief Investigator |
| DD | Dupuytren's disease |
| DSMC | Data and Safety Monitoring Committee |
| EMA | European Medicines Agency |
| FDA | US Food and Drug Administration |
| IMP | Investigational Medical Products |
| ITT | Intention-to-treat |
| MHQ | Michigan Hand Outcomes Questionnaire |
| OCTRU | Oxford Clinical Trials Research Unit |
| PP | Per-protocol |
| RCT | Randomised Controlled Trial |
| TSC | Trial Steering Committee |
| TB | Tuberculosis |
| SAP | Statistical Analysis Plan |

## 11. APPENDIX 2: RIDD PART 1; STATISTICAL ANALYSIS OUTLINE (FROM PROTOCOL)

During the dose response (**Part 1**), analysis will be carried out using data from all participants randomised to **Part 1**.

Descriptive statistics will be used to describe the demographics between the intervention groups for each dose. This difference in the mean between cases and controls will be reported with 95% confidence intervals for all continuous outcome variables. *P*-values will be reported to 3 decimal places.

The primary outcome measure for **Part 1** is expression of mRNA for α-SMA. Expression will be quantified with PCR using the standard curve method using GADPH, B2M and PGK1 as housekeeping genes to normalise the samples.

The secondary outcome measures to be analysed include expression of mRNA for COL-1A1, COL-3A1, aherin 11 and levels of α-SMA and collagen proteins, nodule size and nodule hardness.

For continuous variables, the difference in the means and the corresponding 95% confidence interval will be reported for each dose group and overall. For categorical variables, the number (and percentage) of participants in each category will be reported for each dose group and overall.

## 12. APPENDIX 3: SCORING GUIDELINES

**Michigan Hand Questionnaire**

The Michigan Hand Outcomes Questionnaire (MHQ) is made up of six subscales. The raw scale score for each of the six scales is the sum of the responses of each scale item. The raw score is converted to a score ranging from 0-100. The response categories for the pain subscale are reversed since a higher score indicates more pain. For the other five scales, higher scores indicate better hand performance.

The score for the affected hand is obtained by selecting either the right or the left hand score. The affected hand will be the hand in which the injection is received. The hand for each item is listed in the MHQ and hand dominance is also recorded. The MHQ total score will be obtained by summing the scores for all six subscales (after reversing the pain scale) and then dividing the sum score by six.

Dealing with missing data: For the full MHQ, scores are only calculated if at least three of the six scales were complete. For overall hand function, pain and aesthetics scales, respondents must have had no more than two missing values for scores to be calculated. For any missing items, the average value of the present responses is imputed as the value for the missing response.

Details are given in **Table A1** below.

**Table A1**: Scoring rules for Michigan Hand Outcomes Questionnaire

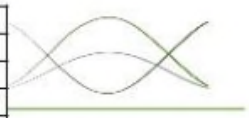
| Scale | Assessed for each hand separately? | Higher is better? | Calculated if: | Coding | Conversion formula |
|---|---|---|---|---|---|
| 1. Overall hand function | Yes | Yes | ≤ 2 missing items | Sum responses and convert to 0-100 scale | (Raw score-25)/20*100 |

| Scale | Assessed for each hand separately? | Higher is better? | Calculated if: | Coding | Conversion formula |
|---|---|---|---|---|---|
| 2. Activities of daily living (ADLs) in (i) Each hand, and (ii) Both hands | (i) Yes<br>(ii) No | (i) Yes<br>(ii) Yes | (i) ≤ 2 missing items<br>(ii) ≤ 3 missing items | Sum responses and convert to 0-100 score. Then average the scores for (i) and (ii) | (i) (Raw score-25)/20*100<br>(ii) (Raw score-35)/28*100<br>Overall:<br>(onehanded+twohanded)/2 |
| 3. Work performance | No | Yes | ≤ 2 missing items | Sum responses and convert to 0-100 score | (Raw score-5)/20*100 |
| 4. Pain | Yes | No | ≤ 2 missing items | Sum responses and convert to 0-100 score then calculate 100-raw score | If IV-A1=5 (right) or IV-B1=5 (left), pain score = 0<br>Otherwise, (Raw score-25)/20*100 |
| 5. Aesthetics | Yes | Yes | ≤ 2 missing items | Sum responses and convert to 0-100 score | (Raw score-4)/16*100 |
| 6. Patient satisfaction with hand function | Yes | Yes | ≤ 3 missing items | Sum responses and convert to 0-100 score | (Raw score-30)/24*100 |
| **Total** | **Yes** | **Yes** | **≥ 3 of the above 6 scales can be calculated** | **Average sum scores for above six scales** | |

**EQ-5D-5L**

Summary score: The percentage at each level can be reported for each of the individual items. The data can be dichotomised into 'no problems' (i.e. level 1) and 'problems' (i.e. levels 2 to 5). The values can be summarised using the UK value set defined below.

| EQ-5D-5L value set for England | | Example: the value for health state 23245 | |
|---|---|---|---|
| constant | 1.000 | Constant | =1.000 |
| Mobility = 2 | 0.057 | Minus MO level 2 | -0.057 |
| Mobility = 3 | 0.074 | | |
| Mobility = 4 | 0.207 | | |
| Mobility = 5 | 0.255 | | |
| Self care = 2 | 0.059 | | |
| Self care = 3 | 0.083 | Minus SC level 3 | -0.083 |
| Self care = 4 | 0.176 | | |
| Self care = 5 | 0.208 | | |
| Usual activities = 2 | 0.048 | Minus UA level 2 | -0.048 |
| Usual activities = 3 | 0.067 | | |
| Usual activities = 4 | 0.165 | | |
| Usual activities = 5 | 0.165 | | |
| Pain/discomfort = 2 | 0.059 | | |
| Pain/discomfort = 3 | 0.079 | | |
| Pain/discomfort = 4 | 0.244 | Minus PD level 4 | -0.244 |
| Pain/discomfort = 5 | 0.298 | | |
| Anxiety/depression = 2 | 0.072 | | |
| Anxiety/depression = 3 | 0.099 | | |
| Anxiety/depression = 4 | 0.282 | | |
| Anxiety/depression = 5 | 0.282 | Minus AD level 5 | -0.282 |
| | | State 23245 | =0.286 |



Calculating values: a worked example

Individual scores: The frequency and percentage of patients in each category for the individual items will be reported. The mean and 95% confidence interval for the VAS will be reported.

Dealing with missing data:

Although the EQ-5D is the preferred measure of HRQoL by several major health technology agencies, including the National Institute for Health and Care Excellence (NICE), the developers of the instrument have not provided recommendations or guidance on how to deal with missing EQ-5D data.

Health economic analysis will not be carried out by the statistician.

## 13. APPENDIX 4: ULTRASOUND IMAGES ANALYSIS

At each visit three ultrasound images are taken of the DD nodule being treated; these images are used to guide the treatment of the nodule. Following treatment these images are reviewed by a blinded researcher and the image with the clearest boundaries of the treated nodule is selected to be used for measurement of the nodule size. Using ImageJ the size of each nodule is estimated by calculating the maximal height and Feret of the irregular polygon drawn around the nodule by the researcher who reviewed and selected the images. The area of the nodule can also be estimated using ImageJ software. However, due to the way it is assessed, this measure has been previously identified as both more time consuming and potentially more prone to measurement error than nodule height and feret. Accordingly, nodule area, height and feret will all be summarised descriptively, and height and feret will be explored further using mixed effects regression modelling. Additional explorations of nodule area will be exploratory.

Due to the time consuming nature of the selection of images and the measurement of the nodule size, the secondary outcome analysis will focus on the difference in nodule size between baseline and 12- and 18-months only. If a patient had surgery or withdrew before a time point, then the image from the last available time point will be used.

During blinded analysis of ultrasound images, a review identified that the quality of those from The Netherlands was lower than those from the UK sites. This was due to the different machine being used. Although this allowed for safe injection into the nodule, these images were not suitable for nodule size measurements. The lower resolution of the images resulted in an inability to identify skeletal structures within the hand, which are used to map the nodule and ensure it was assessed consistently over time. Due to this issue, nodule size analysis includes only participants from the UK sites.

## 14. APPENDIX 5: FIGURES AND TABLES

All figures and tables described in this report are collated in a separate document (RIDD_SAP_Appendix5_V1.0_07Jan2021)

## 15. APPENDIX 6: RESPONSE TO SARS-COV-2 PANDEMIC (COVID-19)

Recruitment to RIDD-2 completed in the UK in December 2018 and in The Netherlands in April 2019. During the SARS-CoV-2 pandemic, all participants had completed treatment and were at the point of 12- and 18-month follow-up.

During the initial wave of the pandemic, clinic appointments were paused for all participants in both the UK and the Netherlands. Questionnaires were posted to participants to allow the collection of secondary outcomes which did not require physical assessment; MHQ, most restricted activity score, EQ-5D-5L, and progression to surgery. Physical assessments – nodule hardness, nodule size, grip strength, range of motion, clinical assessment of the hand – were only completed once it was safe to carry out clinic appointments, with these restarting up to 3 months post the due date. Participants were able to refuse to attend subsequent clinic appointments. Where participants were able to attend delayed clinic appointments, they repeated their follow-up questionnaires. Any changes to patients outcomes recorded via the questionnaires during this data collection delay will be accounted for in additional sensitivity analyses.

During the second wave of the pandemic – commencing September 2020 – clinic appointments in the Netherlands were again paused. Due to subsequent restrictions, some participants were unable to have their

18-month physical measures assessments completed. All of these participants were posted questionnaires to complete non-physical assessment and followed up by telephone to maximise data collection.

### 15.1 Impact on analyses

To understand any impact on the results for RIDD, sensitivity analyses will be carried to address the major Covid-19-related issues encountered. These will include:

(i) Excluding participants whose physical assessment measures were completed but delayed (*primary outcome only*)

(ii) Repeating subgroup analyses including only participants who experienced no Covid-19-related disruptions to follow-up (*primary and key secondary outcomes only)*

(iii) Using the second 12- or 18-month questionnaire completed by participants during delayed physical assessments, in place of their 'on-time' questionnaire (*secondary outcomes only*)

(iv) Including the second 12- and 18-month questionnaires as an additional time-point within the mixed-effects regression models (*secondary outcomes only*)

# Statistical Analysis Plan: Appendix 5 (Figures and Tables)

Based on SAP version 2.0 – 07Jan2021

| Role | Name | Title | Signature | Date |
|---|---|---|---|---|
| Author | Heather O'Connor | Author | | |
| Senior Statistician | Susan Dutton | Reviewer & Approver | | |
| Chief Investigator | Jagdeep Nanchahal | Reviewer | | |

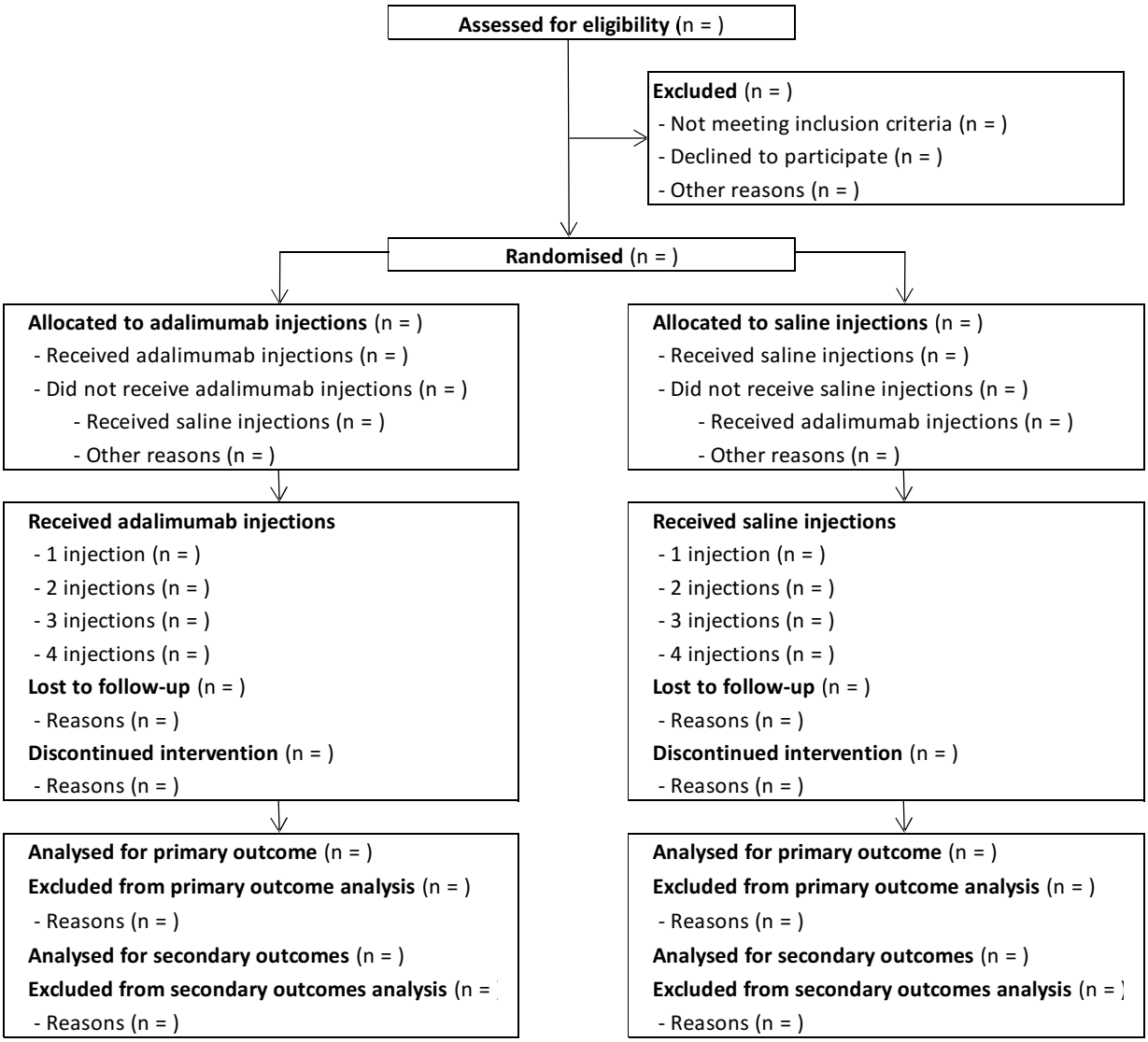
***Note:*** *signatures may be stored in OCTRU OF_006 Sign-off sheet as an alternative to this document*

**CONTENTS**

# 16. TRIAL RECRUITMENT

## 16.1 Representativeness of Study Sample and Patient Throughput

**Figure 1**: CONSORT flow diagram of participants in the trial



## 16.2 Withdrawal from treatment and/or follow-up

**Table 3**: Patient withdrawals and reasons according to intervention allocated

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Withdrawal type** | | | | | | |
| Patient withdrawal | | | | | | |
| Investigator withdrawal | | | | | | |
| Unknown | | | | | | |
| **Withdrawal time-point** | | | | | | |
| Baseline | | | | | | |
| 3 month | | | | | | |
| 6 month | | | | | | |
| 9 month | | | | | | |
| 12 month | | | | | | |
| 18 month | | | | | | |
| Missing | | | | | | |

**Table 4**: Number of participants with data available at each time-point by intervention allocated

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Baseline | | | | | | |
| 3 month | | | | | | |
| 6 month | | | | | | |
| 9 month | | | | | | |
| 12 month | | | | | | |

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| 18 month | | | | | | |
| Missing | | | | | | |

## 17. BASELINE COMPARABILITY OF RANDOMISED GROUPS

**Table 5**: Categorical demographic baseline characteristics according to intervention allocated

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Age group** [a] | | | | | | |
| 18 – 49 years | | | | | | |
| ≥ 50 years | | | | | | |
| **Centre** [a] | | | | | | |
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| **Sex** | | | | | | |
| Male | | | | | | |
| Female | | | | | | |
| Missing | | | | | | |
| **Occupation** | | | | | | |
| Manual | | | | | | |
| Non-manual | | | | | | |
| **Alcohol consumption (units/week)** | | | | | | |

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** |
| Non-drinker | | | | | | |
| Up to 14 | | | | | | |
| 14 – 35 | | | | | | |
| Over 35 | | | | | | |
| **Current smoker** | | | | | | |
| No | | | | | | |
| Yes | | | | | | |
| Missing | | | | | | |
| **Hand dominance** | | | | | | |
| Left | | | | | | |
| Right | | | | | | |
| Missing | | | | | | |

[a] *stratification variable*

**Table 6**: Continuous demographic baseline characteristics according to intervention allocated

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Age (years) [a] | | | | | | | | | |
| Age of onset of DD (years) | | | | | | | | | |
| Alcohol consumption (units/week) [b] | | | | | | | | | |
| Cigarettes smoked per week [c, d] | | | | | | | | | |

[a] *missing: adalimumab n = xx, saline n = xx |* [b] *missing: adalimumab n = xx, saline n = xx |* [c] *= only for participants reporting being a current smokers |* [d] *missing: adalimumab n = xx, saline n = xx*

**Table 7**: Clinical characteristics of all participants according to intervention groups

| | **Saline N =** | | **Adalimumab N =** | | **Total N =** | |
|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** |
| **Medical history** [a] | | | | | | |
| Epilepsy | | | | | | |
| Liver disease | | | | | | |
| Significant exposure to occupational vibration | | | | | | |
| Previous significant trauma to the affected hand | | | | | | |
| Diabetes | | | | | | |
| *Type 1* | | | | | | |
| *Type 2* | | | | | | |
| Frozen Shoulder | | | | | | |
| *Left* | | | | | | |
| *Right* | | | | | | |
| *Bilateral* | | | | | | |
| **Dupuytren's assessment** [a] | | | | | | |
| Bilateral Dupuytren's disease | | | | | | |
| Treatment for Dupuytren's disease in other hand | | | | | | |
| Plantar (Ledderhose's) disease | | | | | | |
| Peyronie's disease | | | | | | |
| Garrod's knuckle pads | | | | | | |
| Radial-sided disease | | | | | | |
| Family history | | | | | | |
| Previous treatment in hand to be injected | | | | | | |

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| *Surgery* | | | | | | |
| *Collagenase* | | | | | | |
| *Needle fasciotomy* | | | | | | |
| *Other* | | | | | | |
| **Digit to be injected** | | | | | | |
| Left: Index | | | | | | |
| Left: Middle | | | | | | |
| Left: Ring | | | | | | |
| Left: Little | | | | | | |
| Right: Index | | | | | | |
| Right: Middle | | | | | | |
| Right: Ring | | | | | | |
| Right: Little | | | | | | |

[a] *reported only for participants reporting 'Yes' response*

## 18. TREATMENT COMPLIANCE

**Table 8**: Treatment compliance: Number of adalimumab and saline injections received according to treatment allocated

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| **Injections Received** | n | % | n | % | n | % |
| **Adalimumab** | | | | | | |
| *1* | | | | | | |
| *2* | | | | | | |
| *3* | | | | | | |

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| **Injections Received** | **n** | **%** | **n** | **%** | **n** | **%** |
| *4* | | | | | | |
| **Saline** | | | | | | |
| *1* | | | | | | |
| *2* | | | | | | |
| *3* | | | | | | |
| *4* | | | | | | |

**Table 9**: Treatment deviations: Treatment received according to treatment allocated. Percentages calculated as of each time-point

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| **Injection Received** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Baseline** | | | | | | |
| *Adalimumab* | | | | | | |
| *Saline* | | | | | | |
| **3 months** | | | | | | |
| *Adalimumab* | | | | | | |
| *Saline* | | | | | | |
| **6 months** | | | | | | |
| *Adalimumab* | | | | | | |
| *Saline* | | | | | | |
| **9 months** | | | | | | |
| *Adalimumab* | | | | | | |
| *Saline* | | | | | | |

# 19. OUTCOME MEASURE SUMMARIES

## 19.1 Primary outcome

**Table 10**: Mean (with SD) nodule hardness recorded at each study time-point

| | **Saline N =** | | | **Adalimumab N =** | | | **Total N =** | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 11**: Mean (with SD) nodule hardness at 12 months by number of injections received

| | **Saline N =** | | | **Adalimumab N =** | | | **Total N =** | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| 1 | | | | | | | | | |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |

## 19.2 Secondary outcomes

**Table 12a**: Mean (with SD) nodule size, as maximal nodule feret and maximal height, recorded at each study time-point

| | **Saline N =** | | | **Adalimumab N =** | | | **Total N =** | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **Maximal nodule feret** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **Maximal nodule height** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 10b**: Mean (with SD) nodule area recorded at each study time-point

| | **Saline N =** | | | **Adalimumab N =** | | | **Total N =** | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 13**: Mean (with SD) grip strength recorded at each study time-point

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 14a**: Mean (with SD) affected digit range of motion active measurements recorded at each study time-point

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **MCP – extension** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |

| | **Saline N =** | | | **Adalimumab N =** | | | **Total N =** | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **MCP – hyperextension** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **PIP – extension** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **PIP – hyperextension** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **DIP – extension** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **DIP – hyperextension** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 12b**: Mean (with SD) affected digit range of motion passive measurements recorded at each study time-point

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **MCP – extension** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **PIP – extension** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **PIP – extension with MCP flexed** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 15a**: Mean (with SD) Michigan Hand Outcomes Questionnaire overall score recorded at each study time-point

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 13b**: Mean (with SD) Michigan Hand Outcomes Questionnaire individual component scores recorded at each study time-point

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **Overall hand function** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **Activities of daily living** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **Work performance** | | | | | | | | | |

| | **Saline N =** | | | **Adalimumab N =** | | | **Total N =** | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **Pain** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **Aesthetics** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |
| **Patient satisfaction with hand function** | | | | | | | | | |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 16**: Mean (with SD) score for most restricted activity recorded at each study time-point

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 17**: Mean (with SD) injection experience pain score recorded at each study time-point

| | Saline N = | | | Adalimumab N = | | | Total N = | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Baseline | | | | | | | | | |
| 3 month | | | | | | | | | |
| 6 month | | | | | | | | | |
| 9 month | | | | | | | | | |
| 12 month | | | | | | | | | |
| 18 month | | | | | | | | | |

**Table 18**: Frequency and percentage of participants progressing to surgery at each study time-point

| | Saline N = | | Adalimumab N = | | Total N = | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Baseline | | | | | | |
| 3 month | | | | | | |
| 6 month | | | | | | |
| 9 month | | | | | | |
| 12 month | | | | | | |
| 18 month | | | | | | |

## 20. OUTCOME MEASURES ANALYSIS

### 20.1 Primary outcome

**Table 19**: Nodule hardness ANCOVA and linear mixed-effects regression results for all follow-up time-points

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **ANCOVA** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted ANCOVA** [b] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Mixed effects regression** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] nodule hardness and treatment arm | [b] nodule hardness, treatment arm, age group and centre | [c] primary endpoint

### 20.2 Secondary outcomes

**Table 20a**: Maximal nodule feret mixed-effects regression results for all follow-up time-points

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] maximal nodule area and treatment arm | [b] maximal nodule area, treatment arm, age group and centre | [c] primary endpoint

**Table 18b**: Maximal nodule height mixed-effects regression results for all follow-up time-points

| | **Saline N =** | | | **Adalimumab N =** | | | **Treatment effect N =** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] maximal nodule height and treatment arm | [b] maximal nodule height, treatment arm, age group and centre | [c] primary endpoint

**Table 21**: Grip strength mixed-effects regression results for all follow-up time-points

| | **Saline N =** | | | **Adalimumab N =** | | | **Treatment effect N =** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] grip strength and treatment arm | [b] grip strength, treatment arm, age group and centre | [c] primary endpoint

**Table 22a**: Affected digit range of motion active measurements mixed-effects regression results for all follow-up time-points

**(i) MCP – extension**

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] active MCP extension of affected digit and treatment arm | [b] active MCP extension of affected digit, treatment arm, age group and centre | [c] primary endpoint

**(ii) MCP – hyperextension**

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] active MCP hyperextension of affected digit and treatment arm | [b] active MCP hyperextension of affected digit, treatment arm, age group and centre | [c] primary endpoint

**(iii) PIP – extension**

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] active PIP extension of affected digit and treatment arm | [b] active PIP extension of affected digit, treatment arm, age group and centre | [c] primary endpoint

**(iv) PIP – hyperextension**

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] active PIP hyperextension of affected digit and treatment arm | [b] active PIP hyperextension of affected digit, treatment arm, age group and centre | [c] primary endpoint

**(v) DIP – extension**

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] active DIP extension of affected digit and treatment arm | [b] active DIP extension of affected digit, treatment arm, age group and centre | [c] primary endpoint

**(vi) DIP – hyperextension**

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted [a]** | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted [b]** | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] active DIP hyperextension of affected digit and treatment arm | [b] active DIP hyperextension of affected digit, treatment arm, age group and centre | [c] primary endpoint

**Table 20b**: Affected digit range of motion passive measurements mixed-effects regression results for all follow-up time-points

**(i) MCP – extension**

| | **Saline N =** | | | **Adalimumab N =** | | | **Treatment effect N =** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] passive MCP extension of affected digit and treatment arm | [b] passive MCP extension of affected digit, treatment arm, age group and centre | [c] primary endpoint

**(ii) PIP – extension**

| | **Saline N =** | | | **Adalimumab N =** | | | **Treatment effect N =** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] passive PIP extension of affected digit and treatment arm | [b] passive PIP extension of affected digit, treatment arm, age group and centre | [c] primary endpoint

**(iii) PIP – extension with MCP flexed**

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] passive PIP extension with MCP flexed of affected digit and treatment arm | [b] passive PIP extension with MCP flexed of affected digit, treatment arm, age group and centre | [c] primary endpoint

**Table 23**: Michigan Hand Outcomes Questionnaire mixed-effects regression results for all follow-up time-points

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] MHQ and treatment arm | [b] MHQ, treatment arm, age group and centre | [c] primary endpoint

**Table 24**: Injection experience pain score mixed-effects regression results for all follow-up time-points

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |

[a] injection experience and treatment arm | [b] injection experience, treatment arm, age group and centre

**Table 25a**: Absolute odds of progression to surgery, from mixed-effects regression results for whole study period

| | Saline N = | | Adalimumab N = | | Total N = | | | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | Odds difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | |
| 18 months | | | | | | | | |
| **Adjusted** [b] | | | | | | | | |
| 18 months | | | | | | | | |

[a] progression to surgery and treatment arm | [b] progression to surgery, treatment arm, age group and centre

**Table 23b**: Relative odds of progression to surgery, from mixed-effects regression results for whole study period

| | Saline N = | | Adalimumab N = | | Total N = | | | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | Odds ratio | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | |
| 18 months | | | | | | | | |

| | Saline N = | | Adalimumab N = | | Total N = | | | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | Odds ratio | 95% confidence interval | | *P*-value |
| **Adjusted** [b] | | | | | | | | |
| 18 months | | | | | | | | |

[a] progression to surgery and treatment arm | [b] progression to surgery, treatment arm, age group and centre

**Table 26**: Most restricted activity mixed-effects regression results for all follow-up time-points

| | Saline N = | | | Adalimumab N = | | | Treatment effect N = | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean change | SD | n | Mean change | SD | Mean difference | 95% confidence interval | | *P*-value |
| **Unadjusted** [a] | | | | | | | | | | |
| 12 months | | | | | | | | | | |
| **Adjusted** [b] | | | | | | | | | | |
| Baseline | | | | | | | | | | |
| 3 months | | | | | | | | | | |
| 6 months | | | | | | | | | | |
| 9 months | | | | | | | | | | |
| 12 months [c] | | | | | | | | | | |
| 18 months | | | | | | | | | | |

[a] most restricted activity score and treatment arm | [b] most restricted activity score, treatment arm, age group and centre | [c] primary endpoint

# 21. SENSITIVITY ANALYSIS

## 21.1 Primary Outcome

21.1.1 Study population (Per-protocol)

21.1.2 Intervention compliance (CACE)

21.1.3 Disease progression – Progression to surgery

21.1.4 Disease progression – Development of adjacent nodules

21.1.5 Missing Data: Imputation: MICE

21.1.6 Missing Data: Pattern-mixture modelling (PMM)

21.1.7 SARS-CoV-2

## 21.2 Secondary Outcomes

21.2.1 Study population (Per-protocol): Key secondary outcomes

(a) MHQ
(b) Range of motion

21.2.2 Intervention compliance (CACE): Key secondary outcomes

(a) MHQ
(b) Range of motion

21.2.3 SARS-CoV-2: All secondary outcomes

(a) Nodule size – maximal feret
(b) Nodule size – maximal height
(c) Grip strength
(d) Range of motion – active measurements
(e) Range of motion – passive measurements
(f) MHQ
(g) Injection pain score
(h) Progression to surgery
(i) Most restricted activity