STUDY PROTOCOL

Economic evaluation plan of a randomised controlled trial of intra-nodular injection of anti-TNF and placebo among patients with early Dupuytren’s disease: Repurposing Anti-TNF for Treating Dupuytren’s Disease (RIDD) [version 1; referees: 2 approved]

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Abstract
Dupuytren’s disease (DD) is a common fibroproliferative condition of the palmar and digital fascia of the hand; however, there is currently no approved treatment for early stage DD. The objective of this paper is to describe the methods applied to assess the cost-effectiveness of adalimumab injections compared to placebo for controlling the progression of early stage DD in the Repurposing Anti-TNF for Treating Dupuytren’s Disease (RIDD) trial. Measure of effectiveness and resource use will be obtained from a randomised clinical trial, carried out in three healthcare centres, and recruiting a minimum of 138 patients aged 18 years and above with a diagnosis of early stage DD. Resource use and utility measures (quality-adjusted life years) will be collected at 3, 6, 9, 12 (primary outcome endpoint) and 18 months post-randomisation. A within-trial cost-utility analysis (CUA) will be conducted at 12 months and if the intervention is effective, a decision analytic model will be applied to estimate the lifetime effectiveness and costs. The analysis will be performed from a health system (National Health Service and personal social services) perspective. Sensitivity analysis will be conducted to assess the robustness of the results.

RIDD is the first randomised controlled trial with an economic evaluation conducted among patients with early stage DD. The protocol described here records our intent to conduct both a within-trial CUA alongside the RIDD study and a lifetime CUA using decision-analytic modelling.

Keywords
dupuytren, anti-TNF, adalimumab, economic, cost-effectiveness
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Competing interests: JN is the co-founder of 180 Therapeutics LP, which has exclusively licensed intellectual property pertaining to the treatment of Dupuytren’s disease and is funding the purchase of the investigational medicinal product to be used in this trial. The funder has no role in the trial design or collection, management and analysis or interpretation of data and dissemination of results.

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Introduction

Dupuytren’s disease (DD) is a common and progressive fibroproliferative disorder of the palmar and digital fascia of the hand that affects 0.6% of the general population aged 18 years and 12% among those aged 55 years in Western countries1. Current treatment for DD, which includes fasciectomy, needle fasciotomy and collagenase fasciectomy, aims to correct the flexion deformities and restore hand function and is recommended when the digital flexion contractures limit hand function and/or the proximal interphalangeal joint is flexed to 30 degrees or more. Ideally, treatment of DD would be directed towards patients with early stage disease, defined as flexion deformities of 30 degrees or less at the metacarpophalangeal and/or at the proximal interphalangeal joint (with a maximum total flexion deformity of 60 degrees), in order to prevent progression of cords development and flexion contractures of the digits. However, there is currently no approved therapy for the treatment of early stage DD and a recent systematic review suggested a lack of robust evidence for treatments, including radiotherapy and intra-nodular steroid injection, proposed for this group of patients1.

No previous study reporting economic evaluations of interventions for patients with early stage DD has been identified1. However, there were four studies, all of which included evidence from various sources, rather than a single randomised controlled trial, that reported the cost-effectiveness of collagenase clostridium histolyticum injection, percutaneous needle fasciectomy and limited fasciectomy among patients with late stage DD.

Here, we present a summary of a health economics analysis plan being undertaken to the second part of the Repurposing anti-TNF for treating Dupuytren’s disease (RIDD) trial, which targets patients with early stage DD. A detailed description of the study design is available in the published protocol which contains details on the methodology (e.g. recruitment, interventions, approval/consent, etc.)5. This trial has been registered with the European Clinical Trials Database (EudraCT: 2015-001780-40) and its Ethics Reference is 15/SC/0259. In brief, a minimum of 138 participants aged 18 years old and above, with early stage DD will be recruited from two UK centres and one centre from the Netherlands. Participants will be randomised to receive either anti-TNF (adalimumab) or placebo (normal saline) injection in a 1:1 ratio. The optimal dose and formulation of adalimumab was found to be 40 mg in 0.4 ml in our dose-ranging phase 2a clinical trial1. The primary objective of the second part of the trial is to determine if optimal dose of anti-TNF injection is superior to placebo injection in controlling disease progression among patients with early stage DD by assessment of nodule hardness at 12 months after the first treatment. Secondary objectives include comparing the development of Dupuytren’s nodules and its associated cord, flexion deformities of the fingers and impairment of hand function for participants between each treatment arms and monitoring for adverse events6.

Methods

The objectives of the economic evaluation conducted in this study are to assess the cost-effectiveness of anti-TNF compared to placebo among patients with early stage DD via a within-trial cost-utility analysis (CUA), and to model lifetime cost-utility if anti-TNF is shown to be effective in controlling disease progression at 12 months follow-up (primary outcome end point).

Study design

The first proposed economic evaluation involves conducting a CUA of anti-TNF compared with placebo using quality-adjusted life years (QALYs) gained as the main health outcome measure alongside the clinical trial at 12 months. The second proposed economic evaluation consists of using decision-analytic modelling to perform a lifetime CUA based on RIDD trial results and additional data from published literature for predicted lifetime QALYs and healthcare costs.

For both analyses, a health system (National Health Service (NHS) and personal social services (PSS)) perspective will be adopted for the base case analysis, where the economic evaluation is conducted with the most likely or preferred set of assumptions and values, as recommended by the National Institute of Health and Clinical Excellence (NICE)7, while the societal perspective will be examined as part of the sensitivity analysis.

Estimation of costs

Direct medical costs related to trial (drug administration). As we assume that there are no significant differences in direct medical cost between trial arms other than the drug being administered, direct medical cost related to the trial, e.g. manpower is excluded from the cost estimation. The type of injection (adalimumab or saline), the estimated volume administered in case of partial administration as well as any optional application of local anaesthetic cream will be recorded in the trial case report forms (CRFs). In the case of anaesthetic cream application, a dosage of 1500 mg will be assumed7. Potential adverse events at the injection site (local itching, redness, blister, nerve injury, local bruising, and haematoma) will be captured in the CRF. Unit cost of the injection will be obtained from the latest version of the British National Formulary (BNF)8 (Table 1).

Other direct medical costs. Utilisation of health and social care services that are not related to the trial will be collected through a patient-completed questionnaire at 3, 6, 9, 12 and 18 months after the baseline injection. The questionnaires will capture the frequency of use of community-based health and social care services, number and duration of admissions to inpatient wards, number of diagnostic tests (ultrasound scan), use of outpatient services (physiotherapy, emergency department, surgeon consultation, radiotherapy, dressing change) and medication use for the past three months at each follow-up time points. Unit costs for each resource item will be sourced from the latest available national sources, e.g. NHS Reference cost and personal social care service research unit (PSSRU)9,10. The defined daily dose (DDD) of each trial-related medication will be obtained from the World Health Organisation (WHO) website using the relevant anatomical
**Table 1. Resource items utilised in RIDD trial.**

| Resource item                                                                 | Unit | Source           | Reference to source |
|------------------------------------------------------------------------------|------|------------------|---------------------|
| **Direct medical costs related to trial (drug administration)**              |      |                  |                     |
| Success of injection (fully)                                                  | ml   | BNF              | [8]                 |
| Success of injection (partial)                                                | ml   | BNF              | [8]                 |
| Anaesthetic cream                                                            | mg   | BNF              | [8]                 |
| **Other direct medical costs**                                               |      |                  |                     |
| Inpatient care                                                               | visit| NHS Reference cost | [9]               |
| **Outpatient care**                                                          |      |                  |                     |
| Hand surgery: Surgeon consultation                                            | visit| NHS Reference cost | [9]               |
| Hand surgery: Radiotherapy                                                   | visit| NHS Reference cost | [9]               |
| Hand surgery: Steroid/collagenase injection                                  | visit| NHS Reference cost | [9]               |
| Hand surgery: Dressing change                                                | visit| NHS Reference cost | [9]               |
| Radiology: Ultrasound scan                                                   | visit| NHS Reference cost | [9]               |
| Physio- or hand therapy                                                      | visit| NHS Reference cost | [9]               |
| Emergency department                                                         | visit| NHS Reference cost | [9]               |
| **Primary and community care**                                               |      |                  |                     |
| General Practitioner                                                         | visit| PSSRU            | [10]                |
| General Practitioner home visit                                              |      | PSSRU            | [10]                |
| General Practitioner phone call                                              | phone call | PSSRU   | [10]                |
| Practice nurse                                                               | hour | PSSRU            | [10]                |
| Physiotherapist                                                             | hour | PSSRU            | [10]                |
| Occupational therapist                                                       | hour | PSSRU            | [10]                |
| Calls to NHS 111                                                             | hour | PSSRU            | [10]                |
| Medication                                                                   |      | BNF              | [8]                 |
| **Direct nonmedical cost**                                                   |      |                  |                     |
| Personal social services                                                      |      |                  |                     |
| Meals on wheels                                                              | day  | PSSRU            | [10]                |
| Laundry services                                                             | load | North Yorkshire County Council | [11] |
| Social worker                                                                | visit| PSSRU            | [10]                |
| Care worker/help at home                                                      | visit| PSSRU            | [10]                |
| Misssed work                                                                 |      | RIDD trial       |                     |
| Travel                                                                       |      | RIDD trial       |                     |
| Child care                                                                   |      | RIDD trial       |                     |
| Help with housework                                                           |      | RIDD trial       |                     |
| **Indirect cost**                                                            |      |                  |                     |
| Income lost                                                                  |      | RIDD trial       |                     |

BNF, British National Formulary; NHS, National Health Service; PSSRU, Personal Social Service Research Unit.

therapeutic chemical (ATC) classification code. Unit costs of these medication will be obtained from the BNF (Table 1).

**Direct nonmedical cost and indirect cost.** Data collected in the participant questionnaires at each time point will also capture the direct non-medical (personal social services, travel expenses, cost of childcare and help with housework) and indirect costs (income loss) borne by participants and carers as a result of their health state. Unit costs will be obtained from national sources or patients (Table 1).
Estimation of health utilities
Impact on participants’ health-related quality of life in each arm will be assessed using data from the EQ-5D-5L (five-level version) instrument collected at baseline, 3, 6, 9, 12 and 18 months from baseline\textsuperscript{13}. As per the NICE position statement, responses to the EQ-5D-5L will be converted into multi-attribute utility scores using an approved “cross-walk” to the three-level instrument and its established utility algorithm for the UK, using the mapping function developed by van Hout \textit{et al.}\textsuperscript{14}.

The responsiveness of the EQ-5D-5L instrument in early stage DD has not been evaluated and hence the quality of life impact according to number and severity of affected fingers will also be assessed based on utilities from a recent discrete choice experiment using responses from the UK general adult population\textsuperscript{15}.

Decision-analytic modelling
The second proposed economic evaluation will comprise a lifetime Markov cohort model with a 6-month cycle length which will be constructed if anti-TNF is shown to be effective in controlling the disease progression at 12 months follow-up. A Markov model approach was chosen as the events occur repeatedly over time.

The preliminary model (Figure 1) will consist of the following health states: treatment success and failure of early stage DD, recurrence of early stage DD, development of late stage DD, treatment success and failure of late stage DD, recurrence of late stage DD and death. Late stage DD will be defined as flexion deformities of 30 degrees or greater at the metacarpophalangeal or at the proximal interphalangeal joint with a limitation of hand function. Recurrence for early stage DD will be defined as an increase in nodule hardness or size on ultrasound scan or increase of flexion deformity following successful treatment. Recurrence for late stage DD will be defined as the recurrence of contracture of 30 degrees or more in a joint of the digit that was successfully treated to achieve correction to within 5 degrees of neutral\textsuperscript{16}. Treatment success for both early stage DD and late stage DD would be defined as no change or an improvement in nodule hardness or size, or flexion deformity. Treatment failure for both early- and late stage DD will be defined as...
progression of the disease such that the patient seeks further intervention, usually as a result of deteriorating hand function and/or flexion deformity at the interphalangeal joints of more than 30 degrees. Age and sex-specific all-cause mortality data will be incorporated in the model based on interim UK life tables, which are available from the Office of National Statistics, if there are no published evidence which indicates a difference in mortality between patients with DD and equivalent controls.

Model parameters such as the costs, health utilities and transition probabilities for early stage DD in the first 12 months will be informed using data from the second part of the RIDD trial while those for late stage DD will be obtained from 18 months data of the RIDD trial and published literature, including Brazelli et al.17 and Gu et al.18.

Adverse events from the treatment of early stage DD, if any, will be modelled using data from the RIDD trial while adverse events/complications for treatment of late stage DD will be modelled using published literature, for example the publication by Chen et al.19.

Data analysis

Inflation and discounting. Due to the small trial sample size (n=35) to be recruited from the Netherlands and to simplify the analysis, the same unit costs (in UK Sterling pounds) for resource utilisation in the Netherlands will be assumed as we do not foresee significant differences in the health resource utilisation between UK and the Netherlands. However, if there is a significant difference in relevant cost items such as length of stay, we will adjust them to the average value in the country of interest for the base case analysis (UK). This is in line with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guideline which recommends doing multivariable cost regressions to adjust for country effects as one of its recommendations for estimating country-specific costs for multinational studies15. All costs will be revalued for analysis when appropriate and reported to latest UK prices using the NHS hospital & community health services (HCHS) index for health service resources. For lifetime estimates, the costs and QALYs will be discounted at 3.5% according to UK Treasury guidelines20.

Statistical analysis. Analysis will be performed on an intention-to-treat basis. Mean and associated measures of uncertainty of costs for each cost category, as well as for estimated QALYs, will be calculated at each time point within each trial arm. Differences between these means will be calculated and tested for statistically significant differences from zero using parametric t-tests.

Cost-utility analysis. Data collected will be used to calculate the cost and QALY per trial participant over the 18 month time horizon of the trial; the baseline to 12 months trial data will be used in the within-trial CUA, while the 18 months trial data will be used in the long term decision analytic model. In the base case analysis, costs examined from the health system perspective would consist of the direct medical costs and direct nonmedical costs. Using these data, the mean difference in costs and the mean difference in QALYs between the control group (placebo) and the intervention group (anti-TNF) will be estimated to give an incremental cost effectiveness ratio (ICER) and an estimate of incremental net benefit (INB). A cost-effectiveness threshold of £20,000 per additional QALY as recommended by NICE will be used to estimate the cost-effectiveness of the intervention21. An intervention with an ICER below the £20,000 per QALY threshold will generally be considered cost-effective.

Missing data. The nature and pattern of the ‘missing-ness’ will be carefully considered; reasons for missing data will be ascertained and reported if possible and, if necessary, multiple imputation methods will be applied to address the missing data.

Sensitivity analysis. Several deterministic (one-way sensitivity analysis) and a probabilistic sensitivity analysis to explore uncertainties surrounding key parameters in the within-trial economic evaluation (e.g. including societal perspective) and decision-analytic modelling (e.g. transition probabilities) will be undertaken. In order to explore the missing data assumptions, sensitivity analysis will be run on the per-protocol population and multiple imputation method. Cost assumptions in the analysis will also be modified if relevant.

Results from the deterministic sensitivity analysis will be presented in Tornado diagrams in order to compare the relative importance of the parameters. Results from the probabilistic sensitivity analysis will be presented using cost-effectiveness acceptability curve (CEAC) which shows the probability that anti-TNF is cost-effective relative to placebo across a range of cost-effectiveness thresholds. The CEAC will be generated based on the proportion of bootstrap replicates with positive incremental net benefits22,23. The probability that anti-TNF is less costly or more effective than placebo will be based on the proportion of bootstrap replicates that have negative incremental costs or positive incremental health benefits, respectively.

Discussion

RIDD is the first randomised controlled trial with an economic evaluation conducted among patients with early stage DD; previous studies had utilised decision analytic models (two using expected value decision analytic models and two using Markov models) to estimate the cost-effectiveness in the management of late stage DD17.

Key strengths of the economic evaluation conducted alongside the trial include a comprehensive assessment of health and social care services resource usage and a reliable method for estimating unit costs from published national sources24. Economic evaluation conducted alongside the trial also allows reliable estimates of cost effectiveness to be produced at low marginal cost and a wide range of statistical and econometric tests can be utilised since data will be at an individual level25.

Key limitations of the economic evaluation include response bias and non-response bias due to the nature of the data collection (via patient-reported questionnaires)26. Response bias occurs when there is a systematic difference in the way participants answered such that their answers do not accurately represent...
their experience, while non-response bias occurs when there is a systematic difference in characteristics between the respondents and non-responders\(^2\). Furthermore, we are not considering the health system perspective of the Netherlands due to the relatively small number of patients being recruited although we would be adjusting for any country effects in our analysis.

In our view, presenting this methodology paper, which serves as a standard operating procedure, before the end of the trial helps safeguard the transparency and consistency of the steps that should be followed as part of the evaluation\(^3\). This in turn will improve the robustness of our evaluation of the health economic data from the RIDD trial.

### Data availability

No data are associated with this article.

### Grant information

The RIDD Trial is funded by the Health Innovation Challenge Fund (HICF), a parallel funding partnership between the Wellcome Trust and the Department of Health UK. MEP, MD, SL, AG, JN are funded by the Wellcome Trust HICF grant [102538, assigned to J Nanchahal]. Costs for the IMP are covered by I80 Therapeutics LP.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Version 1

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The aim of this study is to describe the methods for assessing the cost-effectiveness of adalimumab injections compared to placebo for the management of dupuytren’s disease. The authors propose a within-trial economic evaluation over 12 months and a model-based economic evaluation over a lifetime horizon if the intervention is found to be effective.

This protocol is very well written and the methods adequately described. Resource use, cost and health outcome data collection for the economic evaluation have been adequately described.

A potential limitation of the within-trial economic evaluation is the placebo comparator. Normally, you would want to compare treatments with usual care/practice.

The paper states on page 3 that “For both analyses, a health system (National Health Service (NHS) and personal social services (PSS)) perspective will be adopted for the base case analysis” A health system can be broader than this depending on how you choose to define it.

With respect to the costing, even though assume the same unit costs for the UK and Netherlands has been justified in this case, it may be worth exploring other options (e.g. the effect of multicountry costing) in sensitivity analysis.

The model could also be better described. E.g. the description provided in the paper just mentions treatments for early and late stage DD but does not give an indication of what these treatments are.

The authors state that a DAM will be conducted if the intervention is found to be effective at 12 months. A better justification should be provided for this.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes
Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Health Economics

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 14 January 2019

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I have no concern about economics methods as they seem robust and according to current best practice for such analyses. The research team has extensive experience in their field of health economics and clinical trials. Therefore the authors place the team in a great position to undertake and informs a timely research question.

The authors have appropriately justified the need for this study. The economic evaluation plan provides a thorough overview of the cost-effectiveness analysis that will be conducted in the RIDD trial. Nevertheless I have some comments/questions the authors might want to address:

- In addition to the main within-trial economic evaluation (cost per QALY approach in accordance with NICE guidance), the co-applicants also plan to conduct modelling work if deemed appropriate. The authors say that they will only do the model if the treatment is effective. I advise the authors to explain this further (e.g effective on primary outcome statistical significance / primary outcome not statistical significance / effective on secondary outcomes / effective on QoL).

- I would suggest including a section to summarize the review of existing literature. The authors are planning to use a number of economic evaluations, however they give no detail about databases searched, number of relevant evaluations identified, model structure in relevant papers, categories of resource use included in the models etc. They could include a table as Annex to give further details on this.

- The authors should provide the reader with a justification for the need of the long term model. A key point is to clarify what is the treatment expecting to capture, which I would advise to explain further in the text. Is the treatment expected to delay progression to late DD? If this is the case: (i) how quickly this is expected (e.g is the follow-up of the trial enough to capture this?); and (ii) how is this captured? If this is captured in the RIDD trial this should be listed (i.e percentage of patients that become late DD). If this is not captured in the trial, is there any relevant study that relates the
primary or secondary outcome to late DD? I think this is a critical point, because if treatment is not expected to delay progression then it’s all about symptomatic management, and if this is the case there might be no need for such a sophisticated model.

- Similarly, I would suggest to provide more detail on the statistical analysis which will inform the model: how it is planned to estimate transition probabilities, utilities of health states and costs. My main concern is how the authors are planning to implement the model, given that the trial has 138 patients to inform transitions. It might be helpful to justify the numbers in the analysis plan; and consider the possibility of simplifying the model structure according to these numbers.

- Regarding utilities, I would like to see further details about how they are getting the utilities from the trial. For example, details about the statistical model that will be used to define eq5d given the health state. Similarly, more detail should be given to how costs related to health stated will be estimated (e.g sources).

- In relation to direct costs, I am not sure I understand the decision of excluding man power. In clinical practice it won’t be about the new drug vs placebo but the new drug vs current treatment. Therefore, I don’t think excluding man power is correct, as cost-effectiveness is about clinical practice, and in clinical practice there will be staff costs related to the treatment, even if outpatient visit is only £80, this should also be considered.

**Is the rationale for, and objectives of, the study clearly described?**
Yes

**Is the study design appropriate for the research question?**
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Partly

**Are the datasets clearly presented in a useable and accessible format?**
Not applicable

*Competing Interests:* No competing interests were disclosed.

*Referee Expertise:* Health economist

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.