Bone & Joint Open

Supplementary Material

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Additional methods of within-trial analysis

Supplementary Table i. Unit cost table for the within-trial economic evaluation.

Trial interventions	Unit cost	Data source
Cost of injection	£352.14 per injection	The drug used in this trial was Humira 40 mg/0.4 ml solution for injection pre-filled syringes (AbbVie, UK) – NHS indicative price £704.28, Drug Tariff price £704.28 for two pre-filled syringes. Hence, the cost for one trial injection is £352.14. Information obtained from https://bnf.nice.org.uk/medicinal-forms/adalimumab.html on 28Jan2021. The price that NHS hospitals pay may vary from this list price, but discounts are confidential. Partially used syringes are discarded, i.e. the full drug cost is used for each participant. (Note: at the time of the analysis, Celltrion (South Korea) produced Yuflyma 40 mg/0.4 ml solution for injection pre-filled syringes at the same drug tariff as described for AbbVie above.) More diluted preparations cannot be used for this trial, as demonstrated in the previous phase 2a trial.[1] Recently, Celltrion Healthcare UK Ltd (UK) also started marketing the same dilution, at the same drug tariff cost. Other providers only manufacture the drug in different formulations, and therefore are unsuitable for the sensitivity analysis. No costs were applied for the saline injections. In sensitivity analyses, we investigated the effect of a range of lower adalimumab costs.
Administration of injection	£122	As per the health-economics analysis plan[2] we assumed that the injection would be administered by a clinically qualitied clinician at consultant level in the outpatient setting: Weighted average of all first and follow-up plastic surgery and trauma & orthopaedics non-admitted face-to-face attendances, CL (Consultant Led) tab This cost is included for the adalimumab arm only, as the usual care is no treatment.
Anaesthetic cream	£1.08	Ametop 4% gel: an entire tube (1,500 mg) is used. NHS indicative price: £1.08 for one tube of 1.5 g. This cost was applied where indicated in the patient records.
Hepatitis B test	£4.38	Required screening before adalimumab treatment. This cost was applied to participants in the Adalimumab arm only. Cost based on CCG prices.
ELiSpot TB screening	£67.61	Required screening before adalimumab treatment. This cost was applied to participants in the Adalimumab arm only. Cost based on CCG prices.
Hospital attendances		All costs related to hospital attendances are based on the National Schedule of Reference costs – Year 2018-2019. The ICD-10 code M72.0 – Palmar fascial fibromatosis (Dupuytren) was used.

Trial interventions	Unit cost	Data source
Surgeries		Surgery costs are based on the DC (Day Cases) tab. The costs represent the weighted average costs for the procedures listed under the relevant HRG codes.
Needle fasciotomy	£1,094	Procedure code: T54.1 – Division of palmar fascia HRG code HN45A - Minor Hand Procedures for Non-Trauma, 19 years and over
Fasciectomy	£1,810	Procedure code: T25.2 - Digital fasciectomy HRG: HN44A/ HN44B - Intermediate Hand Procedures for Non-Trauma, 19 years and over
Dermofasciectomy	£2,475	Procedure code: T56.1 - Dermofasciectomy HRG: HN34A/ HN34B - Major Hand Procedures for Non-Trauma, 19 years and over
Splint costs	£37.50	Participants receive custom-made splints following each surgery (excluding radiotherapy). Costs of materials were estimated as £11.50 Time for preparation of the customized splint was estimated to be 20 minutes. An average cost per hour for hospital based scientific and professional staff across band 5 to 9 was estimated as £77, based on Personal Social Services Research Unit (PSSRU), online unit cost database of health and social care professionals 2017/2018. Total costs associated with the splint are hence estimated as the sum of the material cost (£11.50) and staff costs for 20 minutes (£26.00) in line with the OTTER trial.[3] This cost is applied to each participant who underwent surgery.
Outpatient care		
Hand surgery: Surgeon consultation	£122	Weighted average of all first and follow-up plastic surgery and trauma & orthopaedics non-admitted face-to-face attendances, CL (Consultant Led) tab
Hand surgery: Radiotherapy	£191	Procedure code: X65.4 – Delivery of a fraction of external beam radiotherapy NEC HRG code: SC97Z - Same Day Radiotherapy Admission or Attendance (excluding Brachytherapy), OPROC (Outpatient Procedure) Tab; weighted average of plastic surgery and trauma & orthopaedics
Hand surgery: Steroid/collagenase injection	£136	Procedure code: S52.1 – Insertion of steroid into subcutaneous tissue HRG code: JC43A – Minor skin procedures, 19 years and over, OPROC (Outpatient Procedure) Tab; weighted average of plastic surgery and trauma & orthopaedics Note: only one participant fell into this category. Based on their other trial information and a notes review, they were classed as having received a steroid injection, rather than collagenase.
Hand surgery: Dressing change	£101	Weighted average of all follow-up plastic surgery and trauma & orthopaedics non-admitted face-to-face attendances, NCL (Non Consultant Led) tab
Radiology: Ultrasound scan	£57	Weighted average costs of ultrasound scans with and without contrast in an outpatient setting (currency codes RD40Z, RD41Z, RD42Z, RD43Z)
Physio or hand therapy	£58	Weighted average of all physio- or hand therapy non-admitted face-to-face attendances, NCL (Non Consultant Led) tab
Preoperative assessment	£118	Some participants specified a pre-operative assessment in their questionnaires (free text). In the NHS, these may be appointments with a consultant or a nurse, telephone or email assessments. Therefore, the appointments are costed as the weighted average

Trial interventions	Unit cost	Data source
		of all consultant and non-consultant-led non-admitted face-to-face and non-face-to-face first and follow-up attendances related to plastic surgery and trauma & orthopaedics. CL (Consultant Led) and NCL (Non Consultant Led) tabs.
X-ray	£22	Cost for imaging in an outpatient setting, plain film, IMAG (diagnostic imaging tab).
Primary and community care		
GP – appointment at the GP surgery	£39	Cost per patient contact lasting, on average, 9.22 minutes: PSSRU 2019-20 (Chapter 10, page 126).
GP – phone call with GP	£15	Cost per intervention including other costs: PSSRU 2019-20 (chapter 10, page 129). Average consultation length of 4 minutes.
Practice nurse – appointment at GP surgery	£11	Personal Social Services Research Unit (PSSRU) unit costs of health and social care 2020, table 10.2. £42/hr including qualifications. Average consultation lasting 15.5 mins – referenced in PSSRU 2015 (based on the 2006/07 UK general practice survey).
Physiotherapist	£63	NHS Reference Cost schedule 2018-19, tab CHS, service code A08A1
Medication costs		
	Cost per tablet	Costs are based on the British National Formulary published by the National Institute for Health and Care Excellence (https://bnf.nice.org.uk/ , accessed on 28 January 2021)
Codeine	£0.04 per tablet	Codeine phosphate 15 mg, NHS indicative price £1.06 for 28 tablets.
Diclofenac	£0.14 per tablet	Diclofenac potassium 25mg tablets, NHS indicative price 3.86 for 28 tablets.
Flucloxacillin	£0.06 per tablet	Flucloxacillin 250mg capsules, NHS indicative price £1.80 for 28 tables.
Ibuprofen	£0.02 per tablet	Ibuprofen 200mg caplets, NHS indicative price £0.25 for 16 tablets.
Naproxen 500 mg	£0.10 per tablet	Naproxen 500mg tablets, NHS indicative price £2.86 for 28 tablets.
Paracetamol	£0.02 per tablets	Paracetamol 500mg tablets, NHS indicative price: £0.68 for 32 tablets.
Paracetamol - codeine	£0.02 per tablets	Co-codamol 8mg/500mg caplets, NHS indicative price: £0.70 for 32 tablets.

eMethods 1. Detailed methods on the within-trial economic evaluation

Full details of the planned analyses have been described in the economic evaluation plan.[2]

Note that the RIDD trial collected data from two sites in the UK (Oxford and Edinburgh), as well as from one site in the Netherlands (Groeningen). In line with the statistical analysis of this trial, only the UK participants are included in this within-trial analysis.

Data collection

Quality of life

Generic HRQoL was measured using the Euroqol-5 Dimensions-5 Levels questionnaire (EQ-5D-5L). Participants were asked to describe their health over the past 4 weeks in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and rate any problems with regards to these health states (none, slight, moderate, severe and unable/extreme). Participants also completed a 100-point visual analogue scale (VAS; 0=worst health you can imagine to 100=best health you can imagine). The EQ-5D is a standardized measure of health providing a simple generic measure of health for clinical and economic appraisal.

The EQ-5D-5L was completed at baseline, three, six, nine, 12 and 18 months post randomization.

Responses to EQ-5D-5L questionnaires were converted into utility scores using the cross-walk to the 3-level version,[4] using the UK time trade-off tariff. QALYs were calculated using the area under the curve approach,

which involves estimating the average EQ-5D utility between each follow-up time, and weighting by survival time. Partially completed EQ-5D-5L questionnaires are considered missing.

Resource use

Resource use was collected from patients and trial sites.

The main analyses, a health system perspective i.e. National Health Service (NHS) and personal social services (PSS)) was adopted. The following costs were included in the related costing:

Participants were asked to report on healthcare use for Dupuytren's disease (DD) in their injected finger. Specifically, participants were asked to report their outpatient hospital use, community healthcare use (GP/ nurse appointments, occupational therapists, physiotherapists, and calls to NHS 111 [NHS Direct], medication use, and personal social services (meals on wheels, laundry services, social worker contact, and care worker contact). Data were collected at three, six, nine, 12 and 18 months post randomization, and covered the period since the last protocol stipulated trial visit. In addition, sites recorded incidence of surgeries in the hand treated in the trial. The type of surgery (Needle fasciotomy, Fasciectomy, Dermofasciectomy, Collagenase) was collected. In line with the patient reported health resource use, surgeries were reported if they occurred in the injected digit.

Additional data were collected on the effect of participants' DD from a societal perspective. Data were collected on the effect on paid work, and financial costs incurred to the participants, their partners, relatives or friends due to their DD in their injected finger.

Participants were also asked about any hospital admissions due to their DD in their injected finger during the trial follow-up. All of these could be matched up to surgeries reported by the trial sites, and were hence not reported separately.

Methods for assigning UK-based cost estimates

Cost data were sourced from NHS Reference Costs, the British National Formulary (BNF), Unit Costs of Health and Social Care[5] or as self-reported by the participants. Details of unit costs used are presented in Supplementary Table i. All unit costs were inflated, where necessary, to 2018-19 prices using the healthcare and community health services inflation index and NHS cost inflation index (NHSCII).[6]

The adalimumab injections were costed at £352.12 per injection (Humira 40mg/0.4ml solution, BNF information accessed in January 2021, confirmed accurate in February 2021), plus staff cost at consultant level to facilitate the injection (£122), plus £1.08 for anaesthetic cream (where used). Screening for Hepatitis B and Tuberculosis were also applied for each participants at a cost of £4.38 and £67.61, respectively.

No costs were applied to the saline injections. Costs for injections were applied based on the randomization allocation, i.e. participants allocated to adalimumab who received saline by accident (one participant) were costed as if they had received adalimumab, and vice versa.

Missing data

We followed best practice methods for addressing missing data in cost-effectiveness studies.[7] Missing baseline data were imputed using unconditional mean imputation. Data on receipt of allocated interventions were considered to be complete, i.e. no imputation were performed. For components of resource use where participants provided responses to any questions in the resource diary, we imputed missing values as zero. For example, if a participant indicated that they attended some outpatient services, but left the section on primary and ambulatory care unanswered (i.e. missing), we assumed that no primary and ambulatory services were used. Healthcare resource use was classed as missing if the entire resource use questionnaire was missing, or if the participant did not complete the relevant follow-up.

We used multiple imputation by chained equations to impute missing data on EQ-5D-5L utility scores, and cost components (except costs related to the allocated intervention), at each follow-up time point.[8] Each missing value was imputed as a function of age, recruitment site, and baseline and follow-up EQ-5D-5L score, total NHS costs, injection costs, binary indicator of surgeries performed, change from baseline in nodule area, nodule ferret and flexion deformity in the relevant follow-up tie periods, and whether participants were reported as awaiting surgery at the end of the study. The imputation model was run separately by randomized treatment. We used predictive mean matching to create a total of 50 imputed datasets. We imputed costs and EQ-5D-5L utility score in each period. No deaths were observed, and no corresponding adjustments had to be made to the imputed data. Due to low numbers of surgeries observed especially in the earlier follow-up periods, we imputed data on whether any surgery occurred (rather than if a specific surgery had occurred) for participants who had withdrawn before or during the relevant follow-up time period and therefore data on surgery was missing. The

mean cost of all observed surgeries were applied to participants for whom surgeries were imputed. Note: 50 imputations were performed in line with the statistical analysis of the trial, and are not reflective of the amount of missing data observed in this study.

Within-trial analysis

Following multiple imputation, we estimated total costs and QALYs for all participants from the date of study recruitment to 12 months (follow-up period of primary interest), from 12 to 18 months and for the full follow-up period.

We reported descriptive statistics (means, SD as a minimum) for resource use, costs, and EQ-5D-5L utilities at each follow-up time point using only complete data. Differences between arms for the EQ-5D-5L utilities were estimated using multi-level mixed effects linear regression models, to allow for multiple follow-ups clustered within participant. The model was adjusted for treatment allocation, an interaction between follow-up time and treatment allocation, age at randomization and recruitment site, and baseline utility score. QALYs were analysed using linear regression models adjusted for baseline utilities, age at randomization and recruitment site. Combined costs were analysed using linear regression models adjusted for age at randomization and recruitment site, and other outcomes were analysed by unadjusted regression models. Analyses were performed on the imputed datasets, using Rubin's rule to estimate the adjusted mean difference and standard error for each outcome.

Our analysis followed intent-to-treat principles wherein healthcare resource use, costs and EQ-5D scores were analysed according to treatment allocation, regardless of the treatment actually received. We did not discount total costs and QALYs as the time horizon of the analysis of primary interest was 12 months.

We estimated the incremental cost-effectiveness ratio (ICER) by dividing the mean cost difference between adalimumab and standard care by the mean QALY difference.

We estimated the joint uncertainty around incremental total costs and QALYs (i.e. the difference between adalimumab and standard care), and in the cost-effectiveness, by bootstrapping at 1,000 times from each of the 50 imputed datasets (creating at least 50,000 bootstraps), running the estimation model on each bootstrapped dataset and extracting the estimated treatment effects. From these bootstrapped results, we calculated the probability that adalimumab injections were cost-effective compared with standard care at different threshold values per QALY gained and plotted the results on a cost-effectiveness acceptability curve.[9] These were calculated by estimating the proportion of bootstrap replicates with a net monetary benefit (NMB) above 0 for each threshold value, where the NMB was given by the product of the mean difference in QALYs and the threshold value minus the mean difference in costs.

Sensitivity analyses

The following sensitivity analyses were performed:

- analysis on the per-protocol (PP) population only, including participants who received at least three injections (unless injections were not delivered due to nodule regression), received no surgery during the follow-up, and only received their randomized treatment (i.e. excluding cross-overs)
- investigating the effect of lower adalimumab costs, and presenting the ICER for each of these
- including only the subset of surgeries that were deemed to be due to progression of the study nodules, and not due to disease in other nodules
- including costs for surgeries for participants who were reported to be awaiting surgery at the 18-month study visits (i.e. investigating the impact of potentially delayed surgeries due to Covid-19 or long waiting times)

As a sensitivity analyses, we performed a complete case analysis, including only individuals who provided complete data over the 12 months trial duration.

Summaries for societal costs reported during the trial, including days of work missed, travel costs incurred, help with household tasks, childcare for participants, their partners or friends/relatives, are summarized in the Supplementary Table x. We did not do a sensitivity analysis from a wider perspective since non-NHS costs reported by trial participants were negligible. Subgroup analyses and analyses exploring heterogeneity were not conducted due to the size of the trial.

Additional tables and figures from the within-trial analysis

Supplementary Table ii. Data availability over time.

Timepoint	EQ-5D-5L utility score			Health Resource questionnaire		
	Adalimumab (N = 70)	**Saline (N = 70)**	**Total (N= 140)**	**Adalimumab (N = 70)**	**Saline (N = 70)**	**Total (N= 140)**
Baseline	69 (99%)	69 (99%)	138 (99%)	n/a	n/a	n/a
3 months	67 (96%)	65 (93%)	132 (94%)	68 (97%)	66 (94%)	134 (96%)
6 months	64 (91%)	65 (93%)	129 (92%)	65 (93%)	64 (91%)	129 (92%)
9 months	64 (91%)	65 (93%)	129 (92%)	64 (91%)	65 (93%)	129 (92%)
12 months	63 (90%)	65 (93%)	128 (91%)	64 (91%)	66 (94%)	130 (93%)
18 months	65 (93%)	63 (90%)	128 (91%)	65 (93%)	64 (91%)	129 (92%)

n/a, not applicable.

Supplementary Table iii. EQ-5D-5L utilities and QALYs by treatment arm (imputed data for 140 UK participants).

Outcome measure	Adalimumab	Saline	Treatment effect	
	Mean (SE)	Mean (SE)	Mean difference (95% CI)	p-value
EQ-5D-5L utility score*				
Baseline	0.877 (0.014)	0.850 (0.012)		
3 months	0.875 (0.013)	0.854 (0.013)	0.006 (-0.028 to 0.040)	0.732
6 months	0.866 (0.016)	0.858 (0.015)	-0.007 (-0.043 to 0.029)	0.715
9 months	0.884 (0.015)	0.857 (0.016)	0.012 (-0.023 to 0.048)	0.493
12 months	0.874 (0.017)	0.848 (0.015)	0.011 (-0.026 to 0.048)	0.559
18 months	0.864 (0.013)	0.857 (0.015)	-0.008 (-0.044 to 0.029)	0.680
QALYs†				
0 to 12 months	0.875 (0.012)	0.855 (0.012)	0.004 (-0.019 to 0.027)	0.733
12 to 18 months	0.433 (0.007)	0.425 (0.007)	0.001 (-0.015 to 0.017)	0.876
0 to 18 months	1.308 (0.017)	1.280 (0.017)	0.005 (-0.031 to 0.042)	0.774

*Differences and p-values derived from mixed effects model adjusted for baseline utility, age, and site, using a treatment and time interaction.
†Differences and p-values derived from linear regression model adjusted for baseline utility, age, and site.

CI, confidence interval; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; QALY, quality-adjusted life-year; SE, standard error.

Supplementary Table iv. EQ-5D-5L utilities and QALYs by treatment arm (available data).

Outcome measure	Adalimumab				Saline				Treatment effect	
	N	Mean (SD)	Median (IQR)	Range	N	Mean (SD)	Median (IQR)	Range	Mean difference (95% CI)*	p-value
EQ-5D-5L utility score†										
Baseline	69	0.877 (0.118)	0.837 (0.806 to 1.000)	0.397 to 1.000	69	0.849 (0.102)	0.837 (0.795 to 0.906)	0.604 to 1.000		
3 months	67	0.876 (0.108)	0.837 (0.795 to 1.000)	0.659 to 1.000	65	0.855 (0.104)	0.837 (0.795 to 1.000)	0.497 to 1.000	0.002 (-0.031 to 0.036)	0.891
6 months	64	0.873 (0.126)	0.837 (0.782 to 1.000)	0.548 to 1.000	65	0.857 (0.124)	0.837 (0.767 to 1.000)	0.555 to 1.000	0.002 (-0.032 to 0.036)	0.897
9 months	64	0.886 (0.117)	0.863 (0.837 to 1.000)	0.548 to 1.000	65	0.859 (0.127)	0.837 (0.768 to 1.000)	0.550 to 1.000	0.011 (-0.023 to 0.045)	0.530
12 months	63	0.875 (0.124)	0.837 (0.795 to 1.000)	0.555 to 1.000	65	0.847 (0.118)	0.837 (0.768 to 1.000)	0.567 to 1.000	0.011 (-0.023 to 0.045)	0.525
18 months	65	0.868 (0.102)	0.837 (0.795 to 1.000)	0.642 to 1.000	63	0.858 (0.120)	0.837 (0.767 to 1.000)	0.587 to 1.000	-0.004 (-0.038 to 0.030)	0.809
EQ-5D VAS†										
Baseline	70	87.3 (9.8)	90 (85 to 95)	55 to 100	69	88.9 (8.1)	90 (85 to 95)	70 to 100		
3 months	67	89.0 (8.1)	90 (85 to 95)	65 to 100	66	88.0 (9.4)	90 (80 to 95)	60 to 100	2.3 (-0.4 to 4.9)	0.100
6 months	64	87.5 (11.3)	90 (80 to 95)	45 to 100	65	86.8 (11.6)	90 (80 to 95)	40 to 100	2.0 (-0.7 to 4.7)	0.145
9 months	64	89.3 (9.8)	91 (85 to 95)	60 to 100	66	90.1 (7.5)	91 (85 to 95)	65 to 100	0.5 (-2.2 to 3.2)	0.702
12 months	64	87.3 (10.9)	90 (80 to 95)	60 to 100	66	89.0 (10.8)	92 (85 to 96)	50 to 100	-0.3 (-3.0 to 2.4)	0.810
18 months	64	88.0 (10.9)	90 (83 to 95)	50 to 100	63	88.8 (9.7)	90 (84 to 95)	60 to 100	0.7 (-2.1 to 3.4)	0.635
QALYs‡§										
0 to 12 months	58	0.883 (0.097)	0.896 (0.824 to 0.959)	0.635 to 1.000	62	0.854 (0.097)	0.862 (0.788 to 0.925)	0.559 to 1.000	0.007 (-0.016 to 0.031)	0.536
12 to 18 months	63	0.434 (0.052)	0.417 (0.396 to 0.499)	0.318 to 0.499	62	0.425 (0.054)	0.417 (0.396 to 0.458)	0.297 to 0.499	0.001 (-0.015 to 0.017)	0.871
0 to 18 months	58	1.322 (0.143)	1.302 (1.239 to 1.458)	0.953 to 1.499	60	1.280 (0.147)	1.282 (1.187 to 1.386)	0.879 to 1.499	0.012 (-0.026 to 0.050)	0.526

*Mean-imputed baseline data were used in the statistical model. Observed data are displayed in the summary statistics.

†Differences and p-values derived from mixed effects model adjusted for baseline utility, age, and site, using a treatment and time interaction.

‡QALYs were calculated only where EQ-5D-5L utility scores were available for all timepoints within the relevant follow-up period.

§Differences and p-values derived from linear regression model adjusted for baseline utility, age, and site.

CI, confidence interval; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; IQR, interquartile range; QALY, quality-adjusted life-year; SD, standard deviation; VAS, visual analogue scale.

Supplementary Table v. Resource use by treatment arm (available data).

Outcome measure	Adalimumab (n = 70)	Saline (n = 70)	Total (n = 70)
Number of injections per participant			
no injections received	0 (0%)	0 (0%)	0 (0%)
at least 1 injection received	70 (100%)	70 (100%)	140 (100%)
at least 2 injections received	69 (99%)	64 (91%)	133 (95%)
at least 3 injections received	64 (91%)	64 (91%)	128 (91%)
at least 4 injections received	57 (81%)	60 (86%)	117 (84%)
Participants who received injections at each follow-up time point			
baseline	70 (100%)	70 (100%)	140 (100%)
3 months	68 (97%)	64 (91%)	132 (94%)
6 months	63 (90%)	63 (90%)	126 (90%)
9 months	59 (84%)	61 (87%)	120 (86%)
Number of injections received			
1	1 (1%)	6 (9%)	7 (5%)
2	5 (7%)	0 (0%)	5 (4%)
3	7 (10%)	4 (6%)	11 (8%)
4	57 (81%)	60 (86%)	117 (84%)
Surgeries received during follow-up			
baseline to 3 months			
none	69 (99%)	69 (99%)	138 (99%)
data unavailable*	1 (1%)	1 (1%)	2 (1%)
n3 to 6 months			
none	68 (97%)	65 (93%)	133 (95%)
data unavailable*	2 (3%)	5 (7%)	7 (5%)
6 to 9 months			
none	65 (93%)	64 (91%)	129 (92%)
fasciectomy	1 (1%)	0 (0%)	1 (1%)
data unavailable*	4 (6%)	6 (9%)	10 (7%)
9 to 12 months			
none	65 (93%)	62 (89%)	127 (91%)
needle fasciotomy	0 (0%)	1 (1%)	1 (1%)
data unavailable*	5 (7%)	7 (10%)	12 (9%)
12 to 18 months			
none	63 (90%)	57 (81%)	120 (86%)
needle fasciotomy	1 (1%)	0 (0%)	1 (1%)
fasciectomy	1 (1%)	5 (7%)	6 (4%)
dermofasciectomy	0 (0%)	1 (1%)	1 (1%)
Type of surgery unknown**	0 (0%)	1 (1%)	1 (1%)
data unavailable*	5 (7%)	6 (9%)	11 (8%)
Surgeries performed throughout the trial			
needle fasciotomy	1 (1%)	1 (1%)	2 (1%)
fasciectomy	2 (3%)	5 (7%)	7 (5%)

Outcome measure	Adalimumab (n = 70)	Saline (n = 70)	Total (n = 70)
dermofasciectomy	0 (0%)	1 (1%)	1 (1%)
Type of surgery unknown**	0 (0%)	1 (1%)	1 (1%)
Community healthcare			
GP - appointment at GP surgery			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	1/64 (2%)	2/65 (3%)	3/129 (2%)
12 months	2/64 (3%)	1/66 (2%)	3/130 (2%)
18 months	0/65 (0%)	1/64 (2%)	1/129 (1%)
GP - phone call			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	1/64 (2%)	1/129 (1%)
GP - home visit			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Practice nurse - appointment at GP surgery			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	1/64 (2%)	1/129 (1%)
Occupational therapist			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Physio- or hand therapy			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	2/65 (3%)	2/64 (3%)	4/129 (3%)
Call to NHS direct			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)

Outcome measure	Adalimumab (n = 70)	Saline (n = 70)	Total (n = 70)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Personal social services			
Meals on wheels			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Laundry services			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Social worker			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Care worker			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Outpatient hospital use			
Surgeon consultation: NHS			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	1/65 (2%)	0/64 (0%)	1/129 (1%)
9 months	1/64 (2%)	1/65 (2%)	2/129 (2%)
12 months	1/64 (2%)	4/66 (6%)	5/130 (4%)
18 months	3/65 (5%)	5/64 (8%)	8/129 (6%)
Surgeon consultation: private			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Radiotherapy: NHS			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)

Outcome measure	Adalimumab (n = 70)	Saline (n = 70)	Total (n = 70)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	1/64 (2%)	1/129 (1%)
Radiotherapy: private			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Steroid/collagenase injection:			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	1/66 (2%)	1/130 (1%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Steroid/collagenase injection:			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Dressing change: NHS			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	1/64 (2%)	0/65 (0%)	1/129 (1%)
12 months	0/64 (0%)	1/66 (2%)	1/130 (1%)
18 months	1/65 (2%)	3/64 (5%)	4/129 (3%)
Dressing change: private			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Ultrasound scan: NHS			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	1/64 (2%)	1/129 (1%)
Ultrasound scan: private			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)

Outcome measure	Adalimumab (n = 70)	Saline (n = 70)	Total (n = 70)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Physio- or hand therapy: NHS			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	2/65 (3%)	3/64 (5%)	5/129 (4%)
Physio- or hand therapy: private			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Emergency department: NHS			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Emergency department: private			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)

Supplementary Table vi. Health service costs over the 18-month trial period (in £) (imputed data).

Outcome measure	Adalimumab	Saline	Treatment effect	p-value*
	Mean (SE)	**Mean (SE)**	**Difference (95%CI)***	
Total cost of injections	2030 (43)	0 (0)	2028 (1944 to 2112)	< 0.001
Ambulatory care costs 0-12 months†	14 (10)	21 (12)	-6 (-37 to 25)	0.694
Surgery costs 0-12 months	26 (26)	16 (16)	14 (-46 to 74)	0.657
Total NHS & PSS cost 0-12 months	2070 (53)	37 (27)	2035 (1919 to 2152)	< 0.001
Ambulatory care costs 12-18 months†	14 (9)	73 (33)	-58 (-126 to 9)	0.091
Surgery costs 12-18 months	43 (31)	195 (71)	-154 (-307 to -2)	0.047
Total NHS & PSS cost 12-18 months	57 (39)	268 (95)	-213 (-417 to -9)	0.041
Total NHS & PSS cost 0-18 months	2127 (69)	305 (102)	1822 (1577 to 2068)	< 0.001

*Differences and p-values derived from linear regression model adjusted for age and site. The means (SE) for each group are unadjusted; the difference between the unadjusted group means will therefore not equal the adjusted treatment effect.
†Ambulatory costs include primary care visits, outpatient visits, and medication costs.
CI, confidence interval; PSS, personal and social services; SE, standard error.

Supplementary Table vii. Health service costs over the 18-month trial period (in £) (available data).

Outcome measure	Adalimumab				Saline				Treatment effect	
	n	Mean (SD)	Median (IQR)	Range	n	Mean (SD)	Median (IQR)		Difference (95% CI)*	p-value
Total cost of injections	70	2030 (362)	2185 (2185 to 2187)	546 to 2189	70	0 (0)	0 (0 to 0)	0 to 0	2028 (1943 to 2113)	< 0.001
Ambulatory care costs 0-12 months†	62	15 (93)	0 (0 to 0)	0 to 713	63	24 (103)	0 (0 to 0)	0 to 683	-7 (-42 to 28)	0.688
Surgery costs 0-12 months	65	28 (229)	0 (0 to 0)	0 to 1848	68	17 (137)	0 (0 to 0)	0 to 1132	16 (-48 to 80)	0.625
Total NHS cost & PSS 0-12 months	62	2187 (294)	2186 (2185 to 2188)	1638 to 4201	63	42 (235)	0 (0 to 0)	0 to 1815	2148 (2054 to 2243)	< 0.001
Ambulatory care costs 12-18 months†	65	15 (75)	0 (0 to 0)	0 to 461	64	78 (281)	0 (0 to 0)	0 to 1357	-62 (-134 to 10)	0.092
Surgery costs 12-18 months	65	46 (267)	0 (0 to 0)	0 to 1848	67	202 (600)	0 (0 to 0)	0 to 2513	-152 (-313 to 9)	0.064
Total NHS & PSS cost 12-18 months	65	61 (340)	0 (0 to 0)	0 to 2309	64	232 (775)	0 (0 to 0)	0 to 3870	-174 (-384 to 35)	0.102
Total NHS & PSS cost 0-18 months	62	2251 (471)	2186 (2185 to 2189)	1638 to 4658	61	287 (864)	0 (0 to 0)	0 to 4149	1965 (1714 to 2215)	< 0.001

*Differences and p-values derived from linear regression model adjusted for age and site. The means (SE) for each group are unadjusted; the difference between the unadjusted group means will therefore not equal the adjusted treatment effect.

†Ambulatory costs include primary care visits, outpatient visits, and medication costs.

CI, confidence interval; PSS, personal and social services; SE, standard error.

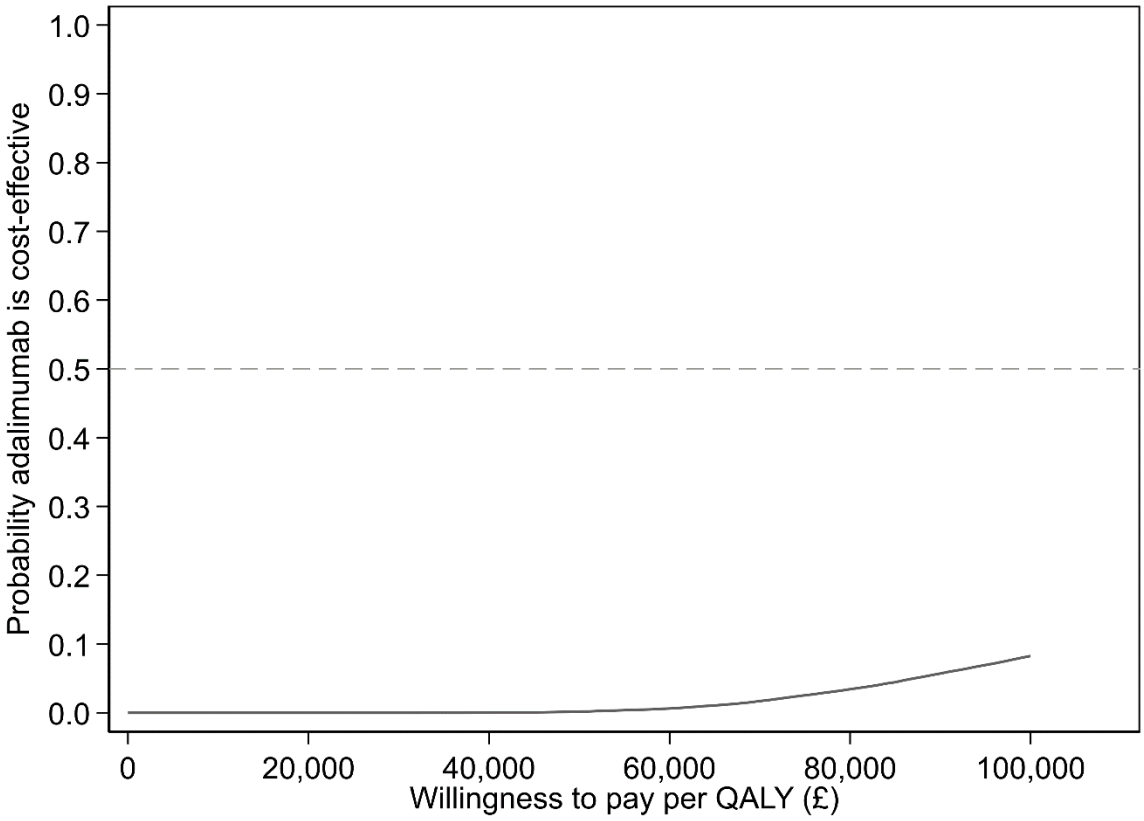

Fig a. Cost-effectiveness acceptability curve (12-month follow-up). QALY, quality adjusted life year.

Supplementary Table viii. Sensitivity analyses.

Outcome measure	**Mean adalimumab (SE)**	**Mean saline (SE)**	**Mean difference (adalimumab vs saline) (95% CI)**
ITT population (0 to 18 months)			
N	70	70	-
QALYs[$]	1.308 (0.017)	1.280 (0.017)	0.005 (-0.031 to 0.042)
Total NHS & PSS costs baseline to 18 months (including intervention)*	2127 (69)	305 (102)	1822 (1577 to 2068)
Adalimumab injection costs*	2030 (43)	0 (0)	2028 (1944 to 2112)
Incremental cost-effectiveness ratio (ICER): cost per QALY gained			
	-	-	-£342,873[+]
Probability of cost-effectiveness at willingness to pay threshold of £20,000 per QALY (NHS & PSS perspective)	-	-	0%
Per-protocol population (0 to 12 months)			
N	60	58	-

Outcome measure	Mean adalimumab (SE)	Mean saline (SE)	Mean difference (adalimumab vs saline) (95% CI)
QALYs[$]	0.884 (0.012)	0.863 (0.012)	-0.004 (-0.028 to 0.019)
Total NHS & PSS costs baseline to 12 months (including intervention)*	2132 (21)	0 (0)	2131 (2088 to 2174)
Adalimumab injection costs*	2131 (21)	0 (0)	2130 (2088 to 2172)
Incremental cost-effectiveness ratio (ICER): cost per QALY gained			
	-	-	-£476,045
Probability of cost-effectiveness at willingness to pay threshold of £20,000 per QALY (NHS & PSS perspective)	-	-	0%
Assuming total injection costs of £50 (per injection, including drug and administration), baseline to 12 months			
N	70	70	
QALYs[$]	0.875 (0.012)	0.855 (0.012)	0.004 (-0.019 to 0.027)
Total NHS & PSS costs baseline to 12 months (including intervention)*	226 (36)	38 (27)	193 (104 to 281)
Adalimumab injection costs*	186 (4)	0 (0)	186 (178 to 193)
Incremental cost-effectiveness ratio (ICER): cost per QALY gained			
	-	-	£47,721
Probability of cost-effectiveness at willingness to pay threshold of £20,000 per QALY (NHS & PSS perspective)	-	-	31%
including only surgery costs where surgery prompted by study nodule, baseline to 12 months			
N	70	70	
QALYs[$]	0.875 (0.012)	0.855 (0.012)	0.004 (-0.019 to 0.027)
Total NHS & PSS costs baseline to 12 months (including intervention)*	2044 (43)	38 (27)	2007 (1907 to 2107)
Adalimumab injection costs*	2030 (43)	0 (0)	2028 (1944 to 2112)

Outcome measure	Mean adalimumab (SE)	Mean saline (SE)	Mean difference (adalimumab vs saline) (95% CI)
Incremental cost-effectiveness ratio (ICER): cost per QALY gained			
	-	-	£496,390
Probability of cost-effectiveness at willingness to pay threshold of £20,000 per QALY (NHS & PSS perspective)	-	-	0%
costing surgery for those awaiting surgery at the end of their follow-up			
N	70	70	
QALYs[$]	0.875 (0.012)	0.855 (0.012)	0.004 (-0.019 to 0.027)
Total NHS & PSS costs baseline to 12 months (including intervention)*	2070 (53)	37 (27)	2035 (1919 to 2152)
Adalimumab injection costs*	2030 (43)	0 (0)	2028 (1944 to 2112)
Incremental cost-effectiveness ratio (ICER): cost per QALY gained			
	-	-	£503,410
Probability of cost-effectiveness at willingness to pay threshold of £20,000 per QALY (NHS & PSS perspective)	-	-	0%

[$]Differences derived from linear regression model adjusted for age, site, and baseline utility score.
*Differences derived from linear regression model adjusted for age and site.
The means for each group are unadjusted; the difference between the unadjusted group means will therefore not equal the adjusted treatment effect.
[+]Adalimumab injections provide a small QALY benefit, but are more costly than standard care.
CI, confidence interval; PSS, personal and social services; QALY, quality adjusted life year; SE, standard error.
Note: the ICER was generated from un-rounded figures, meaning that the figure cannot be replicated exactly from the rounded figures shown in the table.

Supplementary Table ix. Considering the impact of different injections costs on the total NHS & PSS costs, baseline to 12 months.

Cost per injection (£)	Adalimumab Total cost (£)		Saline Total cost (£)		Cost difference (£)*				QALY mean	ICER (£)
	Mean	SE	Mean	SE	Mean	Lower 95% CI limit	Upper 95% CI limit	p-value		
0	40	37	37	27	7	-81	96	0.869	0.004	1,833
10	77	37	37	27	45	-44	133	0.323	0.004	11,011
20	115	36	37	27	82	-7	170	0.071	0.004	20,188
30	152	36	37	27	119	30	207	0.009	0.004	29,366
40	189	36	37	27	156	67	244	0.001	0.004	38,543
50	226	36	37	27	193	104	281	< 0.001	0.004	47,721
60	263	36	37	27	230	142	318	< 0.001	0.004	56,898
70	300	36	37	27	267	179	356	< 0.001	0.004	66,076
80	337	36	37	27	304	216	393	< 0.001	0.004	75,253
90	375	36	37	27	341	253	430	< 0.001	0.004	84,431
100	412	36	37	27	378	290	467	< 0.001	0.004	93,609
110	449	37	37	27	416	327	504	< 0.001	0.004	102,786
120	486	37	37	27	453	364	542	< 0.001	0.004	111,964
130	523	37	37	27	490	401	579	< 0.001	0.004	121,141
140	560	37	37	27	527	437	616	< 0.001	0.004	130,319
150	597	37	37	27	564	474	654	< 0.001	0.004	139,496
160	635	37	37	27	601	511	691	< 0.001	0.004	148,674
170	672	37	37	27	638	548	728	< 0.001	0.004	157,851
180	709	38	37	27	675	585	766	< 0.001	0.004	167,029
190	746	38	37	27	712	622	803	< 0.001	0.004	176,206
200	783	38	37	27	749	658	841	< 0.001	0.004	185,384
210	820	38	37	27	787	695	878	< 0.001	0.004	194,561
220	857	38	37	27	824	732	916	< 0.001	0.004	203,739

Cost per injection (£)	Adalimumab Total cost (£)		Saline Total cost (£)		Cost difference (£)*				QALY mean	ICER (£)
	Mean	SE	Mean	SE	Mean	Lower 95% CI limit	Upper 95% CI limit	p-value		
230	895	39	37	27	861	768	953	< 0.001	0.004	212,916
240	932	39	37	27	898	805	991	< 0.001	0.004	222,094
250	969	39	37	27	935	842	1,028	< 0.001	0.004	231,272
260	1,006	40	37	27	972	878	1,066	< 0.001	0.004	240,449
270	1,043	40	37	27	1,009	915	1,104	< 0.001	0.004	249,627
280	1,080	40	37	27	1,046	951	1,141	< 0.001	0.004	258,804
290	1,117	41	37	27	1,083	988	1,179	< 0.001	0.004	267,982
300	1,155	41	37	27	1,121	1,024	1,217	< 0.001	0.004	277,159
310	1,192	41	37	27	1,158	1,061	1,254	< 0.001	0.004	286,337
320	1,229	42	37	27	1,195	1,097	1,292	< 0.001	0.004	295,514
330	1,266	42	37	27	1,232	1,134	1,330	< 0.001	0.004	304,692
340	1,303	43	37	27	1,269	1,170	1,368	< 0.001	0.004	313,869
350	1,340	43	37	27	1,306	1,207	1,405	< 0.001	0.004	323,047

*Differences and p-values derived from linear regression model, adjusted for age and site.

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Supplementary Table x. Exploration of non-NHS costs – percentage of participants who reported any of the relevant costs.

Outcome measure	Adalimumab	Placebo	Total
Missed work - participant			
3 months	0/68 (0%)	1/66 (2%)	1/134 (1%)
6 months	1/65 (2%)	0/64 (0%)	1/129 (1%)
9 months	1/64 (2%)	0/65 (0%)	1/129 (1%)
12 months	0/64 (0%)	1/66 (2%)	1/130 (1%)
18 months	2/65 (3%)	1/64 (2%)	3/129 (2%)
Missed work - partner			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Missed work - relative/partner			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Travel cost - participant			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	2/64 (3%)	2/129 (2%)
Travel cost - partner			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	1/65 (2%)	0/64 (0%)	1/129 (1%)
Travel cost - relative/partner			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	1/64 (2%)	1/129 (1%)
Childcare - participant			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)

Outcome measure	Adalimumab	Placebo	Total
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Childcare - partner			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Childcare - relative/ partner			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Home work - participant			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Home work - partner			
3 months	0/68 (0%)	0/66 (0%)	0/134 (0%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
Home work - relative/ partner			
3 months	1/68 (1%)	0/66 (0%)	1/134 (1%)
6 months	0/65 (0%)	0/64 (0%)	0/129 (0%)
9 months	0/64 (0%)	0/65 (0%)	0/129 (0%)
12 months	0/64 (0%)	0/66 (0%)	0/130 (0%)
18 months	0/65 (0%)	0/64 (0%)	0/129 (0%)

Additional methods of model-based extrapolation

eMethods 2. Additional assumptions and methods of the model-based extrapolation

More detailed description of the model

Definitions:

- Quiescence was defined as having all three of the following:
    - nodule area stayed the same or decreased between baseline and 18 months AND
    - hardness measured by the standard durometer stayed the same or decreased between baseline and 18 months, AND
    - ≤ 5° increase in active flexion deformity in the joint closest to the study nodule between baseline and 18 months (hyperextension is given a negative flexion deformity value). Including flexion deformity in the definition of quiescence ensures that patients who do have disease progression during the trial are not incorrectly counted as being quiescent. The rationale for using active flexion deformity in this analysis is that: 1) inclusion criteria were based on active flexion deformity; and 2) active flexion deformity more accurately reflects what the patient can do with their hand.
- Late-stage DD was defined as active flexion deformity > 30° in the joint closest to the study nodule. In calculating the proportion of patients with late-stage DD by 18 months within the trial population, patients who had had had needle fasciotomy, fasciectomy or dermofasciectomy (DF) or surgery of an unknown type during the trial were also counted as having late-stage DD at 18 months.
- Ectopic disease is defined as the presence of one or more out of plantar, Peyronie's disease, or Garrod's knuckle pads. Patients with ectopic disease have previously been shown to have greater propensity for disease progression, so we tested whether ectopic disease had an impact on the model parameters estimated on the RIDD data.
- Treatment success in late-stage DD was defined as a reduction in flexion deformity to ≤ 5°, while treatment failure was defined as any other outcome from surgery (following Brazzelli et al[10]).
- Recurrence in late-stage DD was defined as a return to flexion deformity ≥ 20°, after surgery has reduced flexion deformity to ≤ 5°, following Brazzelli et al.[10] There is debate in the literature about which cut-off should be used to define recurrence, although we follow the methods of Brazzelli et al[10] as specified in the health economics analysis plan.[2]

The base case analysis compared three strategies for managing early-stage DD (sensitivity analyses comparing against steroids and radiotherapy are described in the last section of eMethods 2):

- No disease-modifying treatment for early-stage DD. No use of adalimumab at any stage in the disease pathway.
- Four initial adalimumab injections at the start of the trial period, with no subsequent use of adalimumab or any treatments for early-stage DD in the model period
- Four initial adalimumab injections at the start of the trial period, followed by a further course of four adalimumab injections in quiescent patients as soon as the patient feels that their condition has reactivated and the nodule is starting to get bigger again. No retreatment with adalimumab in patients who were not quiescent following initial treatment. The duration of this quiescence will be a random parameter in the model. No limit was set on the maximum number of treatment courses that patients could have.

The model focuses on the impact of treating (or retreating) one nodule and does not capture the impact of other nodules. Many RIDD participants had more than one nodule, so patients' baseline utility may have been reduced by DD in other joints. Adalimumab would normally need to be administered separately to each nodule, so the cost of treating multiple nodules would be additive, although there is no evidence on the impact that treating multiple nodules would have on quality of life. In clinical practice, the severity of DD in multiple nodules may be taken into account when deciding whether or not to operate in late-stage DD and if surgery is done, all nodules in the same hand would normally be operated on.

A cohort of individual patients with active early-stage DD (based on the placebo arm of the RIDD trial) are followed over time through a sequence of treatments. Treatment for early-stage DD may lead to quiescence (which may be maintained by retreatment). During periods of quiescence, the patient will not experience changes in flexion deformity. By contrast, during periods when the patients are not quiescent, patients will

experience progressive changes in flexion deformity that reflect the average change in flexion deformity during the RIDD trial for placebo-treated patients with and without ectopic disease, and the variability between patients in that sample.

As described in the main paper and Figure 1, once patients' flexion deformity which is 30°, they are assumed to have late-stage DD and move between the health states for late-stage DD used by Brazzelli et al.[10] Patients initially enter the untreated state and have a chance of undergoing surgical treatment each cycle. If they have surgery, they will move into either the treatment success state (i.e. surgery reduced flexion deformity to ≤ 5°) or the treatment failure the following cycle. From the failure state, they have a chance of moving on to the next line of treatment each cycle. From the success state, patients have a chance of recurrence each cycle, at which point they will have the same type of surgery again until the reach the maximum number of tries at that type of surgery, at which point they will move onto the next line of treatment.

The model begins at the end of the 18-month trial (after the initial course of adalimumab). Costs and quality-adjusted life-years (QALYs) accrued during the 18-month trial period were added to those estimated during the model to give lifetime outcomes; this was done by adding the mean costs during the 18-month trial period (with multiple imputation, averaged over 50,000 bootstraps) to the point estimate from the model.

The model used six-month cycles. The time horizon for the analysis was 55 years from randomization, since this was the general population life expectancy of the youngest UK patient randomized to placebo.[11] The costs and QALYs of each trial participant were estimated until the individual died, or until 55 years from randomization (whichever happened sooner).

In the base case analysis, we assumed, based on common treatment pathways[12] that:

- the first line of surgical treatment for late-stage DD is percutaneous needle fasciotomy (PNF) and that patients will have up to 3 PNFs if each is successful;
- the second line of surgical treatment for late-stage DD is limited fasciectomy (LF), which may only happen once;
- the third line of surgical treatment for late-stage DD is DF, which may only happen once;
- following failure or recurrence of DF, patients will receive "best supportive care" and have no further surgery and remain in the recurrence or failure state indefinitely. This was assumed to not include joint fusion or amputation.

Patients will only have the maximum number of operations of each type if the earlier ones were successful (i.e. reduced flexion deformity to ≤ 5°) and they recurred to flexion deformity ≥ 20°: any failure (i.e. post-surgery flexion deformity > 5°) means that patients move up to the next treatment (i.e. if the 2nd fails, then move on to LF). A sensitivity analysis explored the impact of assuming that the treatment pathway for late-stage DD ends after 3 PNFs, since this was the most cost-effective treatment sequence in the analysis by Yoon et al.[13]

Other treatments for early-stage DD (e.g. vitamin A, physiotherapy) were not evaluated in the study because there is insufficient evidence on their efficacy,[14] and as these interventions are very rarely used in clinical practice. Collagenase was not included in the model pathway because it has previously been shown to be more costly and no more effective than PNF.[10] Amputation and joint fusion were not included in the model pathways because they occur relatively rarely and we are not aware of any data on the outcomes of treatment or utilities after surgery. Omitting these from the pathway is unlikely to change the conclusions about whether adalimumab is cost-effective because these interventions occur in a very small proportion of patients long after adalimumab treatment has finished.

Costs for each intervention used in the model were based on drug prices,[15] NHS tariffs[6,16] and published studies[13] (Supplementary Table xi). In early-stage DD, the only NHS costs applied during the model period was for adalimumab injections, since non-treatment costs within the trial period were negligible. In late-stage DD, we included the cost of the procedure itself, outpatient visits, physiotherapy and dressing changes, plus managing hand-related adverse events (Supplementary Table xi and *Assumptions* section below).

Pre-randomization utilities for each trial participant were assumed to change over the trial period depending on their age, whether they were quiescent and (once they progressed too late-stage DD) which late-stage DD

disease state they were in. EQ-5D utilities were assumed to be 0.0197 (95% confidence interval (CI) 0.0040 to 0.0352) higher during any cycle in which patients were quiescent, based on a regression conducted on RIDD participants (see *Methods for the analysis of within-trial data used as inputs for the model* section below). Each disease state for late-stage DD was associated with a utility decrement, which was based on the values used by Brazelli et al:[10] since Brazelli et al assumed that treatment success had a utility of 1 (which did not reflect utilities in our sample), we estimated disutilities for recurrence and failure that equalled 1 minus the utilities used by Brazelli et al. Each cycle spent in the failure state was associated with a 0.224 utility decrement (compared with the utility patients would have had if they still had early-stage DD). Each cycle spent in the recurrence state (or the untreated late-stage DD that patients enter when they first develop late-stage DD but have not yet undergone surgery) was associated with a 0.035 utility decrement (compared with the utility patients would have had if they still had early-stage DD). In all cases, utility was assumed to decrease with age based on the equations estimated by Ara and Brazier[17] (see *Assumptions* section).

A half cycle correction was used to adjust QALYs in the year when patients died, but was not applied to costs, since all treatments were assumed to be given at the beginning of the cycle (see *Assumptions* section below).

Costs and QALYs after the end of the 18 month trial were discounted at 3.5% per annum, following National Institute for Health and Care Excellence (NICE)'s reference case.[18] Life expectancy was not discounted. Costs and QALYs accrued during the 18-month trial were not discounted in line with the base case within trial economic evaluation.

Differences between the conceptual model of the HEAP and the final model

The model structure was developed based on a systematic review of previous economic evaluations in DD[19] and extensive discussions with clinicians specialising in the management of DD.

The model differs from that outlined in the health economics analysis plan (HEAP)[2] in the following respects:

- The model used individual patient simulation in order to more naturally model the transition from early-stage to late-stage DD and differs slightly from a Markov structure in the way that transitions to late-stage DD occur. The model simulated a cohort of RIDD participants and allowed their individual utilities and flexion deformity to change over time. Flexion deformity changed by different amounts each cycle and when the individual's flexion deformity reaches 30°, they are considered to have late-stage DD. This means that the probability of developing late-stage DD increases with the duration of active early-stage DD and is higher for patients who enter the model with high flexion deformity. By contrast, the HEAP stated that a Markov structure would be used, whereby the probability of progressing to late-stage DD would be either constant over time or vary with time since randomization. Other than the transition from early-stage to late-stage DD, the model structure mirrors a Markov model with individual patient simulation. Using individual patient simulation also facilitates a great deal of flexibility in treatment sequences, retreatment criteria and allowing for heterogeneity.
- "Treatment success" was defined as "quiescence". No distinction is made between treatment failure and recurrence in early-stage DD, other than the fact that patients with "treatment failure" who do not reach quiescence for initial treatment have three more years with progression of flexion deformity than patients who achieve quiescence lasting three years. Within the final model, quiescence is assumed to last three years for all patients, rather than applying a probability of recurrence each cycle.
- Since a 2020 study showing that mortality among 42,000 people with DD was 50% higher than among people without DD,[20] we allowed for the excess mortality of DD within the model.

Additional assumptions for the model-based extrapolation

Assumptions around disease progression and treatment in early-stage DD:

- We used RIDD data to calculate the probability of patients achieving quiescence and the probability of developing late-stage DD during the 18-month trial period (see 'Methods for the analysis of within-trial data used as inputs for the model' for details).
- Quiescent patients were assumed to have 0% chance of progressing to late-stage DD for X years. In the absence of external data on the duration of quiescence, the base case analysis assumed that quiescence lasts for double the duration of the trial (3 years) regardless of whether quiescence was

achieved with adalimumab treatment or without treatment. This was varied in sensitivity analysis between the trial duration (1.5 years) and 5 years (~3 time the trial duration). The lower limit (1.5 years) represents a very conservative estimate, since the trial results show that nodule area and hardness were still decreasing 1.5 years after starting treatment.[21]

- Patients who did not reach quiescence with initial treatment were assumed to not receive subsequent courses of treatment.
- Patients with late-stage DD at end of trial enter the model in the late-stage DD state (with a history of surgery where appropriate). Regardless of whether they have already had surgery, they will therefore spend at least six months in the untreated DD state, before potentially having the first surgical procedure applicable to that treatment arm. The RIDD sample is too small to reliably estimate impact of surgery and only one patient had 18-month flexion deformity after surgery. The cost of surgery during the trial period will be captured in the within-trial costs for each study arm.
- Data for all patients randomized to placebo in RIDD were used to estimate the rate of change in flexion deformity in patients who were not quiescent but had progressive early-stage DD (see 'Methods for the analysis of within-trial data used as inputs for the model' for details).
- within the model, patients who are quiescent at the end of the trial are assumed to have end of trial flexion deformity equal to their flexion deformity at randomization, since only patients with a < 5° change in flexion deformity are counted as quiescent.
- End of trial flexion deformity for patients who have progressive early-stage DD at the end of the trial was estimated based on the regression predicting change in flexion deformity as a function of ectopic disease.
- Within the model, no costs were associated with early-stage DD in the absence of treatment because the costs are negligible within the trial. Costs relating to late-stage DD or surgery for late-stage DD are captured separately within the model and costs accrued in each arm during the trial were added to the costs estimated in the model.
- We assumed that the effect of subsequent courses of adalimumab on flexion deformity is the same as was observed for patients' first course during the trial.
- No costs or disutilities were applied for treatments for early-stage DD. Within the trial, no treatment-related adverse events were observed other than minor site reactions (itching, redness, bruising, haematoma), which arose more commonly in the saline group.[21] Steroid injections are associated with complications (including diabetes) and radiotherapy carries a risk of malignancy although there are no data on the magnitude of this risk.[22,23]

Assumptions regarding patient pathway in late-stage DD:

- Patients are considered to move from early-stage to late-stage to DD when their flexion deformity first reaches ≥ 30°.
- The switch from early to late-stage DD is assumed to be irreversible for that digit (even if flexion deformity is reduced through surgery, patients cannot go back to the early-stage DD part of the model and/or have early-stage DD treatments)
- When patients first move from early-stage DD to late-stage DD, they move into an initial state of "untreated late-stage DD" and have a certain probability of having treatment each year. In the base case analysis, we based the probability of treatment for untreated late-stage DD on Brazzelli's estimate of the proportion of patients having retreatment with PNF.[10]
- After patients' flexion deformity reaches 30°, all patients will have at least six months' delay before undergoing the first surgical treatment for late-stage DD
- Patients will be retreated with the same intervention for late-stage DD if they have recurrence after initial success (up to the maximum number of repeats for that treatment), but will move to the next treatment if they have any failure. For example, in the base case analysis, where we modelled a treatment pathway where patients had up to three PNF operations, followed by up to one LF operation, followed by DF, the following treatment pathways would be possible (where patients move between states every six months):
    - PNF, success, recurrence, PNF, success, recurrence, PNF, success, recurrence, LF, recurrence, DF
    - PNF, success, recurrence, PNF, failure, LF, success, recurrence, DF
    - However, these pathways were not permitted because once patients fail one type of surgery they will not receive it again and as patients cannot move back to earlier treatments:

        - PNF, failure, PNF
        - PNF, failure, LF, failure, PNF
- We assumed that no patients with late-stage DD would have steroids, radiotherapy or adalimumab. However, we did include the cost of physiotherapy, outpatient visits and dressing changes around the time of surgery.
- Late-stage DD patients will always have at least a year's gap between any 2 operations if they fail treatment (the same as the Brazzelli[10] model).
- Late-stage DD patients will always have at least six months' gap between recurrence and subsequent retreatment (this is the same as the Brazzelli[10] model)
- When patients are in the recurrence, failure or untreated late-stage DD states, there is a probability of them undergoing surgery each cycle. The probability of undergoing treatment is assumed to vary depending on what treatment they are going to happen next, but is assumed to be independent of what treatment may have had previously. (The model has separate parameters for the probability of having the first surgery of type X from the failure/untreated state and for the probability of having retreatment with X from the recurrence state, but in the base case analysis these are set to the same).
- Treatment is assumed to be the first thing that happens in each cycle. Retreatment criteria are applied based on the flexion deformity at the end of the last cycle.
- We assumed that the probability of success (i.e. correction of flexion deformity) with DF is the same as for LF, since Bainbridge et al[24] found that the mean number of Tubiana stages that patients improved was very similar for LF and DF. We assumed that treatment for early-stage DD has no impact on the outcomes of late-stage DD treatment (except to potentially delay progression to late-stage DD).
- A proportion of patients undergoing surgery for late-stage DD were assumed to have physiotherapy, outpatient visits and/or dressing changes. Since the Brazzelli et al used expert opinion to elicit the number of these consultations,[10] we used the mean number of such consultations among the RIDD participants undergoing surgery; although these are based on very small numbers of patients, they represent the only available UK data that we are aware of.
- Each operation for late-stage DD has a probability of intraoperative adverse events.[25] The analysis considered only hand-related complications from late-stage DD surgery that lead to hospital intervention and specifically excluded the impact on cardiovascular events associated with late-stage DD surgery,[25] loss of hand function.[26] Following Brazzelli et al, intraoperative adverse events lead to additional costs and a temporary decrease in quality of life.[10]
- We assumed that the procedure cost and the probability of failure/recurrence/complications is unaffected by previous surgery (as assumed previously). This assumption is supported by the Mendelar study,[27] which found no difference in extension deficit or Michigan hand score between first and subsequent operations.

Assumptions around mortality in late-stage and early-stage DD:

- Mortality rates during the modelled period were based on all-cause mortality rates for the general population,[11] multiplied by published hazard ratios showing mortality for patients with DD, compared with those with no DD.[20]
- Data on all-cause mortality for the general population in 2017 to 2019 were obtained from the Office of National Statistics.[11] The mortality rates (m_x) from the United Kingdom life table 2017 to 2019 for each individual year of age were applied to each trial participant based on their age and gender: for example, a man randomized at age 30 were subjected to the mortality rate for 35-year-old men during the fifth year after randomization, whereas a woman randomized at age 50 was subjected to the mortality rate for 55-year-old woman during the fifth year after randomization.
- Mortality rates for patients aged between 101 and 119 were assumed to equal mortality at age 100.
- All patients who reached 120 years of age were assumed to die that year to ensure that the model did not project implausible life expectancies.
- The hazard ratio for DD vs no DD from a UK database linkage study[20] was used to adjust annual mortality data[11] for each patient using the life table methods of Pharoah and Hollingworth.[28] The excess mortality for DD was assumed to apply to both early-stage DD and late-stage DD. For simplicity, we assumed that the hazard ratio for mortality with DD versus no DD was constant over time and with age and that the prevalence of DD was constant; although there is evidence that

people with DD actually have lower mortality during the first 12 years after diagnosis and higher mortality after that this,[20] the impact on treatment on mortality is not known and could not be captured in the model. We used the unadjusted hazard ratio from Kuo (1.48; 99% CI, 1.29 to 1.70) because the available life tables are not adjusted for risk factors. These simplifications are unlikely to have any significant effect on the results because the hazard ratio is simply used to estimate the length of time that each patient spends in the model. In addition to there being no evidence on how or whether mortality differs between early-stage and late-stage DD, it was important to assume no difference in mortality to avoid assuming that treatments that reduce flexion deformity in early-stage DD would have a mortality benefit, which cannot be concluded from the evidence at present. By contrast, assuming a constant hazard ratio for all patients means that the excess mortality for DD simply reduces the amount of time that patients on all treatments accrue costs and quality-of-life.

- We added the QALYs accrued in the trial to those projected by the model; since no patients died during the trial period, the lifetime projections incorporate no mortality during the first 18 months after randomization.
- In principle, there could be interactions between DD treatments and interventions for other conditions that affect life expectancy or that have non-additive effects on quality of life, although these are beyond the scope of this analysis since such interactions are likely to affect only a minority of patients. For simplicity, we assumed that life expectancy, quality of life impact of other conditions, and the excess mortality for DD will remain constant in the future and that interventions that may affect life expectancy or the quality of life impact from other conditions are adopted based on standard decision rules.
- UK life tables were based on pre-COVID data (2017 to 2019)[11] and no adjustment was made to estimate the impact that Covid may have on mortality rates in the future, since the long-term impact of the virus is not yet known.
- Surgery for late-stage DD and injections for early-stage DD were assumed to always occur at the beginning of the six-month cycle, other than adalimumab, which was assumed to be given at the beginning of the cycle and exactly half way through the cycle. No half cycle correction was therefore applied for treatment costs. All other costs captured in the model (e.g. outpatient visits, physiotherapy, dressing changes and time off work) are likely to arise around the time of surgery, so were also applied in full if the patient died within six months of surgery. For quarterly injections (such as adalimumab), we applied the cost of 1.5 injections in the cycle in which the patient died, based on the assumption that all patients dying within cycle c will have the first injection and half of them will have the second.
- A half-cycle correction was applied for QALYs: in the cycle when patients died, they were assumed to accrue half of the QALYs and half of the non-NHS costs that they would otherwise have accrued.

Assumptions around utilities and QALYs:

- While they have early-stage DD, patients' quality-of-life will be based on that individual's pre-randomization EQ-5D utility, minus any age-related decline in quality-of-life and plus improvement in QoL due to quiescence. Utilities in late-stage DD were based on the values used by Brazzelli et al.[10] The QALYs accrued during the trial were added to model outcomes to give lifetime QALYs.
- An improvement in quality of life compared with baseline was applied to all cycles spent in the quiescent state; this was based on a regression predicting QALYs accrued between month 6 and month 18 in RIDD, with multiple imputation of missing post-baseline data (see *Methods for the analysis of within-trial data used as inputs for the model* section). Quality-of-life at the end of each cycle was based on whether the patient was quiescent on the last day of that cycle. In the cycle during which quiescence ends, patients' quality-of-life was assumed to linearly revert to their pre-randomization quality-of-life (minus any age modifier). For example, if the duration of quiescence is between 3.0 and 3.49 years, the full QoL benefit of quiescence will be applied during cycles 1-3; during cycle 4, patients will get half of the QoL benefit of quiescence. If patients are retreated as soon as quiescence ends, they are assumed to continue to experience the quality-of-life benefit of quiescence for life.
- Once patients progress to late-stage disease, their quality-of-life will drop to the same value as recurrence, but may be increased again through successful surgery (or decreased by unsuccessful surgery) based on published utilities. The disutility for recurrence (0.035) was used for untreated late-stage DD as this is likely to reflect the utility of RIDD participants who have only just developed late-

stage DD and may be Tubiana stage 2 or the top of stage 1. This was thought to be more appropriate for the RIDD sample than assuming that patients' utility goes down to the disutility of failure (0.224, based on Tubiana stage 3) as soon as they developed late-stage DD. There were insufficient patients in the RIDD trial with flexion deformity > 30 to estimate utilities for late-stage DD from the trial data.
    - in all other cases, the disutilities associated with each late-stage DD state were based on those used by Brazzelli et al.[10] We converted Brazzelli's utilities to disutilities and subtract those disutilities from each patient's baseline utility to ensure that patients' utility did not increase when they developed late-stage DD, which would not be clinically plausible.
        - Success = Tubiana Stage 0 utility 1, disutility 0
        - Recurrence = Tubiana Stage 1 utility 0.965, disutility 0.035
        - treatment failure = Tubiana Stage 3 utility 0.776, disutility 0.224
    - During the six-month period in which surgery occurs, patients' utility was assumed to remain at the value for the failure state; after the six-month period, patients' utility will change to the value of success or failure depending on the outcome of treatment. For simplicity, we assumed that all patients will there is no difference in the time interval between surgery and improvement in quality of life between operations in between first-line and second-line. While this is unlikely to be the case in practice,[24] this simplifying assumption in late-stage DD is unlikely to have a substantial effect on the conclusions for early-stage DD.
- We applied the age-related decline from Ara and Roberts Model 1[17] to decrease utility year-on-year as patients age. The effect of aging was applied additively, with patients' utility in cycle c ($utility_{c,i}$) being equal to their pre-randomization utility ($utility_{BL,i}$), plus any modifiers capturing the effect of quiescence, late-stage DD or treatment failure, recurrence or success, plus the age effect. Following Dakin et al 2020,[29] we used the age ($\beta 1$) and age-squared ($\beta 1$) coefficients from Model 1 to estimate the impact of ageing on quality-of-life as a function of the number of years since randomization:
$$utility_{c,i} = utility_{BL,i} + [modifier] + (\beta 1 \cdot age_c + \beta 2 \cdot age_c^2) - (\beta 1 \cdot age_{BL} + \beta 2 \cdot age_{BL}^2)$$
- QALYs were based on the area under the curve. Utility was estimated at the end of each cycle based on whether the patient was quiescent, had progressive early-stage DD or which late-stage DD state they were in. If the patient was alive for the whole cycle, QALYs during the six-month cycle were equal to the average of the utility at the beginning and utility at the end of the cycle, divided by two.
- Successful surgery for late-stage DD was assumed to return patients to their pre-randomization utility (minus any age-related decline in QoL). The difference between success and baseline utility was varied over a normal distribution with mean 0 and a standard error equal to that for the utilities for recurrence and failure in order to parameterize the uncertainty around this assumption.
- Patients who are about to undergo their 2nd or subsequent surgery for late-stage DD were assumed to have the same utility as the "failure" state, regardless of whether they have failed treatment or recurred after successful treatment. This assumption matches that of Brazzelli et al.[10]
- For simplicity, we assumed that there was no difference in the time interval between surgery and improvement in quality of life between operations in between first-line and second-line. In practice, there is evidence that this delay is longer for more invasive surgery,[24] although this simplifying assumption in late-stage DD is unlikely to have a substantial effect on the conclusions for early-stage DD.
- A form of half-circle correction was applied for QALYs, in that if a patient died during that cycle, we assumed that patients died three months through the cycle and assumed a linear interpolation in utility between start of cycle and what would have been end of cycle. QALYs in the cycle in which a patient dies therefore equalled (1.5*start of cycle utility + 0.5 * end of cycle utility)/8.
- Following Brazzelli et al,[10] we applied a disutility for six weeks and a cost for patients who had complications relating to the hand that led to hospital intervention after late-stage DD surgery. These costs were applied in full regardless of whether the patient died in that cycle since treatment was given at the beginning of the cycle. Although Alser et al[25] found that primary DD surgery increases the risk of acute kidney injury, cardiovascular events, and respiratory/urinary infections, we excluded these events from the model because costs unrelated to DD were excluded from the within-trial analysis and as including these outcomes could lead to double counting the excess mortality for DD, would greatly complicate the model and would have minimal impact on the results on interventions for early-stage DD. Complications and long-term adverse effects from surgery that did not lead to hospital intervention were excluded, following Brazzelli.[10]

Supplementary Table xi. Data inputs for the model-based extrapolation. Min and max represent the minimum and maximum values using one-way sensitivity analysis to generate the tornado diagram.

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
u_Quiesence	Difference in utility between quiescent and non-quiescent patients (quiescence coefficient in the equation predicting the QALYs between 6 months and 18 months).	0.0395			bootstrap	0.0159	0.0079	0.0704	Regression on RIDD. Utilities were based on EQ-5D-5L cross-walked to EQ-5D-3L UK TTO tariff.
f_18m_ectopic	Coefficient for ectopic disease in the equation for change in active flexion deformity between baseline and 18 months. This is 3 times the change per cycle	8.5189			bootstrap	3.2853	2.1683	15.3596	Regression on RIDD
f_placebo_cons	Constant coefficient in the equation for change in active flexion deformity between baseline and 18 months. This is 3 times the change per cycle	0.8631			bootstrap	1.5382	-2.0005	4.1074	Regression on RIDD
p_late_NT	Proportion of patients in the placebo group who have late-stage DD at the end of the trial	0.2149			bootstrap	0.0487	0.1286	0.3143	Regression on RIDD
p_late_A	Proportion of patients in the placebo group who are quiescent at the end of the trial	0.1800			bootstrap	0.0494	0.1000	0.2857	Regression on RIDD
p_quiescent_NT	Proportion of patients in the A group who have late-stage DD at the end of the trial	0.2209			bootstrap	0.0556	0.1286	0.3429	Regression on RIDD
p_quiescent_A	Proportion of patients in the A group who are quiescent at the end of the trial	0.3696			bootstrap	0.0614	0.2571	0.4857	Regression on RIDD
f_SA_Quies_A	Mlogit output - used to estimate % quiesence in sensitivity analsyis controlling for flexion	0.8023			bootstrap	0.4491	-0.0404	1.7329	Regression on RIDD

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
f_SA_Quies_flex	Mlogit output - used to estimate % quiesence in sensitivity analsyis controlling for flexion	-0.0062			bootstrap	0.0187	-0.0464	0.0279	Regression on RIDD
f_SA_Quies_cons	Mlogit output - used to estimate % quiesence in sensitivity analysis controlling for flexion	-1.1033			bootstrap	0.3999	-1.9189	-0.3942	Regression on RIDD
f_SA_Late_A	Mlogit output - used to estimate % late in sensitivity analysis controlling for flexion	0.6484			bootstrap	0.7954	-0.8610	2.3087	Regression on RIDD
f_SA_Late_flex	Mlogit output - used to estimate % late in sensitivity analysis controlling for flexion	0.1313			bootstrap	0.0308	0.0824	0.2019	Regression on RIDD
f_SA_Late_cons	Mlogit output - used to estimate % late in sensitivity analysis controlling for flexion	-1.8266			bootstrap	0.6713	-3.4881	-0.7387	Regression on RIDD
p_suc_PNF	Probability of correction in contracture to within 0–5° of full extension: PNF	0.41	68	99	beta	0.038	0.335	0.485	Brazelli[10] (van Rijssen et al 2012[30])
p_recurrence_PNF	6-monthly probability of recurrence (i.e. return in contracture of at least 20°): PNF	0.0248	1.6	56	beta	0.019	-0.013	0.063	Brazelli[10] (van Rijssen et al 2012[30])
p_TreatRecurrence_PNF	6-month probability of further treatment if treatment fails/during recurrence: PNF	0.73	33	12	beta	0.066	0.601	0.859	van Rijssen et al 2012[30], following Brazelli[10]
p_IntraOpAE_allsurgery	Probability of serious local complications requiring further hospital intervention within 90 days (excluding amputation): PNF, LF & DF combined	0.60%	903	149930	beta	0.000	0.006	0.006	Alser et al[25] (Table 1): incidence of serious local complications requiring hospitalisation within 90 days of all DD surgery (all local complications, minus numbers of amputations)
c_Procedure_A	Cost of adalimumab and administration per 2 injections	£950			fixed		713.86	£950	Cost of Humira 40mg/0.4ml solution for injection, 2 pre-filled syringes £704.28, plus 2 outpatient consultations (£122, weighted average of consultant-led plastic surgery and trauma & orthopaedics non-admitted face-to-face

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
									attendances), plus 2 tubes of Ametop 4% anaesthetic gel (£1.08).[15] Lower limit based on Yuflyma 40 mg/0.4 ml solution (£633.70 for 2 syringes) delivered by a GP (£39[6]). Alternative value based on the assumption that the cheapest plausible price for a concentrated adalimumab formulation is the lowest price charged for a different anti-TNF (Erelzi 50 mg/1 ml solution of etanercept (£643.50 for 4 syringes) delivered by a GP (£39[6])).
c_Procedure_PNF	Procedure cost: PNF	£1,132			fixed		£566	£1,697	Procedure code: T54.1 – Division of palmar fascia. HRG code HN45A - Minor Hand Procedures for Non-Trauma, 19 years and over,[16] plus cost of splint (£37.50). Varied +-50% to generate tornado diagram.
c_Physio	Cost per physiotherapy session	£58			fixed		£29	£87	Weighted average of all physiotherapy non-admitted face-to-face attendances, NCL (Non Consultant Led) tab.[16] Varied +-50% to generate tornado diagram.
c_OutpatientFU	Cost per outpatient consultation	£122			fixed		£61	£183	Weighted average of all first and follow-up plastic surgery and trauma & orthopaedics non-admitted face-to-face attendances, CL (Consultant Led) tab.[16] Varied +-50% to generate tornado diagram.
c_Dressingchange	Cost per dressing change	£101			fixed		£0	£152	Weighted average of all follow-up plastic surgery and trauma & orthopaedics non-admitted face-to-face attendances, NCL (Non Consultant Led) tab.[16] Minimum value of 0 assumes dressing changes occurred during

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
									outpatient visits rather than requiring a separate visit. Upper limit +50% of mean.
n_Physio_PNF	Number of physiotherapy appointments in the 6 month-period that includes surgery	0.375	2.032258	0.184524	gamma	0.263	0.000	0.891	8 patients having PNF in RIDD providing data on resource use
n_dressingchange_PNF	Number of dressing changes in the 6 month-period that includes surgery	0.375	1	0.375	gamma	0.375	0.000	1.110	8 patients having PNF in RIDD providing data on resource use
n_OutpatientFU_PNF	Number of OutpatientFU appointments in the 6 month-period that includes surgery	0.375	0.828947	0.452381	gamma	0.412	0.000	1.182	8 patients having PNF in RIDD providing data on resource use
c_Complications	Cost per complication requiring treatment	£2,017			fixed		£1,009	£3,026	Based on Brazelli table 19.[10] Varied +-50% to generate tornado diagram.
HR_DD	Hazard ratio for mortality with DD compared with no DD	1.48			lognormal	0.054	1.000	1.700	Kuo et al.[20] Unadjusted hazard ratio for DD vs no DD in UK. 1.48; 99% CI, 1.29 to 1.70. Minimum for tornado diagram set to 1 to test the impact of assuming no excess mortality
u_AE	Lost QALYs from AEs: disutility of -0.0615 for 6 weeks	0.0071	0.057705	8.074168	beta	0.029	0.000	0.115	Brazelli et al[10] "this is half a decrement on the European Quality of Life-5 Dimensions-3 levels (of severity) instrument (EQ-5D-3L) of a move from no pain or discomfort to some pain or discomfort" on the UK time trade-off tariff. The QALY loss was varied between 0 and that for loss of 6 quality-adjusted weeks in tornado diagram and this range was treated as 95% CI when estimating alpha and beta.
u_S	Disutility for the success state: i.e. how much lower utility is for patients in the success state compared with trial baseline	0	0	0	normal	0.020	-0.039	0.039	Successful treatment was assumed to return patients to their baseline utility. The difference between success and baseline utility was varied over a normal distribution with a standard error equal

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
									to that for the utilities for recurrence and failure in order to parameterize the uncertainty around this assumption
u_R	Disutility for the recurrence state and untreated late DD: i.e. how much lower utility is for patients in the recurrence state compared with trial baseline.	0.035	2.915699	80.39	beta	0.020	-0.004	0.101	We subtracted the utility for this state used by Brazelli[10] from 1 to give a disutility; Brazelli's values were based on those from Gu study: a discrete choice experiment conducted on a UK general population sample.[31] Estimated SE from alpha given in monograph. Maximum value is based on utility for Tubiana stage 2
u_F	Disutility for the failure, treatment and untreated late DD states: i.e. how much lower utility is for patients in these states compared with trial baseline	0.224	97.06763	336.27	beta	0.020	0.101	0.263	We subtracted the utility for this state used by Brazelli[10] from 1 to give a disutility; Brazelli's values were based on those from Gu study: a discrete choice experiment conducted on a UK general population sample.[31] Estimated SE from alpha given in monograph. Minimum value is based on Tubiana stage 2
u_age	Change in utility for each additional year of age	-0.0002587			normal	0.000	-0.00099	0.00047	Ara & Brazier 2010, Model 1.[17] Correlated with age squared, using a variance-covariance matrix supplied by the authors. This was estimated on a random sample of adults in England (the Health Survey for England) using the EQ-5D-3L UK time trade-off tariff.
u_agesquared	Change in utility for each additional unit of age-squared	-0.0000332			normal	0.000	-0.00004	-0.00003	
Duration_quiescence	Number of years that quiescent nodules will stay quiescent for, before starting to progress	3			lognormal	0.233752	1.500	5.000	Assumption: point estimate assumes that quiescence will assumed twice as long as the trial duration as hardness and area are still decreasing at 18 months. Lower limit assumes quiescence ends at the end of the trial

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
									and the upper limit assumes it lasts just over 3 times the duration of the trial.
discountrate	Discount rate for costs and QALYs	0.035			fixed		0.000	0.050	NICE[32] & HM Treasury. Varied between no discounting and 5% discount rate.
p_suc_LF	Probability of correction in contracture to within 0–5° of full extension: LF	0.71	89	36	beta	0.041	0.631	0.789	Brazelli[10] (van Rijssen et al 2012[30])
p_recurrence_LF	6-monthly probability of recurrence (i.e. return in contracture of at least 20°): LF	0.0054	0.5	56	beta	0.008	-0.010	0.020	Brazelli[10] (van Rijssen et al 2012[30])
p_TreatRecurrence_LF	6-month probability of further treatment if treatment fails/during recurrence: LF	0.4	4	6	beta	0.155	0.096	0.704	van Rijssen et al 2012,[30] following Brazelli[10]
c_Procedure_LF	Procedure cost: LF	£1,848			fixed		£924	£2,771	Procedure code: T25.2 - Digital fasciectomy. HRG: HN44A/ HN44B - Intermediate Hand Procedures for Non-Trauma, 19 years and over,[16] plus cost of splint (£37.50). Varied +-50% to generate tornado diagram.
n_Physio_LF	Number of physiotherapy appointments in the 6 month-period that includes surgery	2.2	19.36	0.11	gamma	0.500	1.220	3.180	5 patients having LF in RIDD
n_dressingchange_LF	Number of dressing changes in the 6 month-period that includes surgery	2.8	6.88	0.41	gamma	1.068	0.707	4.893	5 patients having LF in RIDD
n_OutpatientFU_LF	Number of Outpatient FU appointments in the 6 month-period that includes surgery	2	20	0.1	gamma	0.447	1.123	2.877	5 patients having LF in RIDD
LRR_TreatRecurrence_DFvLF	Estimate of the natural log of the ratio between the probability of a patient who failed their last treatment going on to have DF, compared with a patient whose next treatment is LF	-0.693			normal	0.354	-1.387	0.001	Expert opinion JN. SE was set such that the upper 95% confidence interval indicates no difference in retreatment probability between LF and DF
rate_recurrence_DF	6-monthly probability of recurrence (i.e. return in contracture of at least 20°): DF	0.000603	0.5	56	beta	0.000	0.001	0.001	Armstrong: defining recurrence as cords that have "progressed to recontracture"

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
c_Procedure_DF	Procedure cost: DF	£2,513			fixed		£1,256	£3,769	Procedure code: T56.1 – Dermofasciectomy. HRG: HN34A/ HN34B - Major Hand Procedures for Non-Trauma, 19 years and over,[16] plus cost of splint (£37.50). Varied +-50% to generate tornado diagram.
n_Physio_DF	Number of physiotherapy appointments in the 6 month-period that includes surgery	8	1	8	gamma	8.000	0.000	23.680	1 patient having DF in RIDD. SE set to same as mean
n_dressingchange_DF	Number of dressing changes in the 6 month-period that includes surgery	4	1	4	gamma	4.000	0.000	11.840	1 patient having DF in RIDD. SE set to same as mean
n_OutpatientFU_DF	Number of OutpatientFU appointments in the 6 month-period that includes surgery	4	1	4	gamma	4.000	0.000	11.840	1 patient having DF in RIDD. SE set to same as mean
Parameters used in sensitivity analyse but not in the base case analysis									
c_Procedure_RT	Cost of procedures for 6 months: Radiotherapy	£1,910			fixed		£1,337	£13,890	Base case analysis assumes 10 doses as this is most common. Lower limit on cost represents cost for 7 doses. Point estimate and lower limit: Procedure code: X65.4 – Delivery of a fraction of external beam radiotherapy NEC; HRG code: SC97Z - Same Day Radiotherapy Admission or Attendance (excluding Brachytherapy), OPROC (Outpatient Procedure) Tab; weighted average of plastic surgery and trauma & orthopaedics.[16] Upper limit based on: Procedure code: X65.4 – Delivery of a fraction of external beam radiotherapy NEC; HRG code: SC97Z - Same Day Radiotherapy Admission or Attendance (excluding Brachytherapy).[16]
c_Procedure_Steroid	Cost of procedures for 6 months: steroid injections	£341			normal	£12	£318	£364	Number of injections based on Ketchum et al, counting all patients having > 3

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
									injections as though they had 3 injections, in order to get an estimate of the likely number of injections that were administered in the first course. Cost/dose estimated as: Hand surgery: Steroid/collagenase injection. Procedure code: S52.1 – Insertion of steroid into subcutaneous tissue HRG code: JC43A – Minor skin procedures, 19 years and over, OPROC (Outpatient Procedure) Tab; weighted average of plastic surgery and trauma & orthopaedics.[16]
p_quiescent_Steroid	Proportion of patients having steroids who are quiescent at the end of the 18-month period	0.97	73.00	2.00	beta	0.019	0.129	1.000	Scenario 1: Point estimate is based on the proportion of hands showing "regression of disease (i.e. notable softening and flattening of the focus of disease)".[33] Min assumes the probability of quiescence is the same as the lower 95% CI for placebo. Max based on upper 95% CI for % quiescent. The minimum and point estimate are highly optimistic because nodules were not measured objectively, data were analysed retrospectively and (unlike RIDD) did not exclude patients who did not have a history of disease progression. The study by Ketchum was used as it was the largest study on steroids identified in a systematic review.[14] Scenario 2 assumes that the probability of quiescence with steroid is the same as for adalimumab (with the two varying together in PSA)

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
Duration_quiescence_Steroid	Duration of quiescence with steroids	0.50	0.614633	0.813493	gamma	0.638	0.500	3.000	Assumption: In Ketchum, patients could have another course of steroids every six months. The duration of quiescence was varied between 6 months (minimum possible in the model) and three years (same as with placebo and adalimumab). Standard error was estimated assuming that the minimum and maximum represented a 95% CI
c_NonNHS_A	Non-NHS cost associated with the operation (assumed to be incurred straight after the procedure)	£0			fixed		£0	£0	
c_NonNHS_Steroid	Non-NHS cost associated with the operation (assumed to be incurred straight after the procedure)	£0			fixed		£0	£0	
c_NonNHS_RT	Non-NHS cost associated with the operation (assumed to be incurred straight after the procedure)	£0			fixed		£0	£0	
c_NonNHS_PNF	Non-NHS cost associated with the operation (assumed to be incurred straight after the procedure)	£96	£1	£96	gamma	£96	£0	£1,344	Yoon: 1 day off work,[13] valued based on weekly wage of £585/week.[34] SE was assumed to equal the mean
c_NonNHS_LF	Non-NHS cost associated with the operation (assumed to be incurred straight after the procedure)	£3,552	£1	£3,552	gamma	£3,552	£1,638	£5,760	Yoon: 37 days off work,[13] valued based on weekly wage of £585/week.[34] SE was assumed to equal the mean
p_suc_DF	Probability of correction in contracture to within 0–5° of full extension: DF	0.71	89	36	Linked	0.041	0.631	0.789	Assume that the probability of success with DF is the same as for LF, since Bainbridge et al. found that the mean number of Tubiana stages that patients improved was very similar for LF and DF [24]
p_recurrence_DF									Converting rate to probability
p_Treat_PNF	Proportion of patients who will have surgery in each cycle (of those who have failed their last treatment and								Assumed to be the same as for retreatment with PNF

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
	have never received PNF): If PNF is next treatment								
p_Treat_LF	Proportion of patients who will have surgery in each cycle (of those who have failed their last treatment and have never received LF): If LF is next treatment								Assumed to be the same as for retreatment with LF
p_Treat_DF	Proportion of patients who will have surgery in each cycle (of those who have failed their last treatment and have never received DF): If DF is next treatment								Assumed to be the same as for retreatment with DF
p_TreatRecurrence_DF	6-month probability of further treatment if treatment fails/during recurrence: DF								Equals probability for LF multiplied by RR for DF vs LF
p_IntraOpAE_DF	Probability of serious local complications requiring further hospital intervention (excluding amputation): DF								Assumed to be the same for all late-stage DD surgery[25]
p_IntraOpAE_LF	Probability of serious local complications requiring further hospital intervention (excluding amputation): LF								Assumed to be the same for all late-stage DD surgery[25]
p_IntraOpAE_PNF	Probability of serious local complications requiring further hospital intervention (excluding amputation): PNF								Assumed to be the same for all late-stage DD surgery[25]
p_late_Steroid	probability of late-stage DD 18 months after steroid treatment								Steroid scenario 1: no chance of late-stage DD within 18 months based on Ketchum. Scenario 2: Assumed to be same as for adalimumab (with the two varying together)
Duration_quiescence_RT	Duration of quiescence with radiotherapy (years)								Assumed to be the same as for adalimumab and placebo

Parameter	Definition	Mean	Alpha	Beta	distribution	SE	Min	Max	Source
p_quiescent_RT	probability of quiescence 18 months after RT treatment								Assumed to be same as for adalimumab
p_late_RT	probability of late-stage DD 18 months after RT treatment								Assumed to be same as for adalimumab
c_NonNHS_DF	Non-NHS cost associated with the operation (assumed to be incurred straight after the procedure)								Assumed to be the same as for LF
Additional fixed parameters used in base case analysis									
prevalanceDD	Prevalence of DD. Used to estimate DD-specific mortality	0.166667	N/A	N/A	Fixed	N/A	N/A	N/A	Kuo 2020[20]
f_rMSE_changeflex	Root-mean squared error of the change in flexion deformity between baseline and 18 months. Used to introduce random variation between loops in the changing flexion deformity, mirroring a distribution of individual patients	12.60787	N/A	N/A	Fixed	N/A	N/A	N/A	Bootstrapped from RIDD: Mean change in flexion deformity between baseline and 18 months in the placebo group (see below)
	Annual mortality rates by age and sex								Office of National Statistics National Life Tables 2017-19[11]

DD, Dupuytren's disease; DF, dermofasciectomy; EQ-5D-3L, EuroQol five-dimension three-level questionnaire; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; LF, limited fasciectomy; PNF, percutaneous needle fasciotomy; TTO, time trade-off.

Methods for the analysis of within-trial data used as inputs for the model

The multiply imputed dataset used for the within trial analysis was analysed to estimate three parameters:

- Proportion of patients in each arm defined as having quiescence or late-stage DD at 18 months. Multinomial logistic regression with manual backwards stepwise regression was used to assess whether four variables that had previously been shown to influence disease progression affected the probability of being quiescent or the probability of having late-stage DD rather than continuing with progressive early-stage disease: baseline active flexion deformity; family history in a first-degree relative; ectopic disease; and age of onset in years. Quiescence and late-stage DD are defined above. We began with a model containing all variables plus treatment allocation and dropped the variable with the highest p-value for quiescence each time until the model contained only statistically significant variables ($p < 0.05$). All models controlled for randomized treatment allocation and this was retained in the model regardless of statistical significance because this is the key driver of treatment effect. No variables had a statistically significant effect on quiescence at the 0.05 level, so the final analysis was based on the crude proportion of patients with quiescence and late-stage DD in each arm to avoid any parametric assumptions. Flexion deformity had no significant effect on quiescence ($p = 0.837$), but significantly increased the chance of late-stage DD ($p < 0.001$); this variable was dropped from the final model used in the base case analysis, although an mlogit model controlling for flexion deformity was used in a sensitivity analysis.
- Mean change in flexion deformity between baseline and 18 months in the placebo group. This analysis was estimated on the placebo group since it is applied to patients who are not receiving active treatment and those who do not achieve quiescence. All placebo participants were included in this analysis (including those who achieve quiescence and those who progressed to late-stage DD) in order that the model can predict the rate at which untreated patients will progress to late-stage DD and allow for any subsequent periods of quiescence that may naturally occur in untreated patients. Ordinary least squares regression with manual backwards stepwise regression was used to predict the mean change in flexion deformity as a function of the same four variables: baseline active flexion deformity; family history in a first-degree relative; ectopic disease; and age of onset in years. The variable with the highest p-value was sequentially dropped until the model contained only statistically significant variables ($p < 0.05$). In this analysis, ectopic disease was found to increase the change in flexion deformity by 8.5° (95% CI 2.5 to 14.6) over 18 months ($p = 0.006$), while baseline flexion deformity, family history and age of onset had no significant effect. Model parameters were therefore based on ordinary least squares regression predicting flexion deformity change as a function of ectopic disease. The change in flexion deformity between baseline and 18 months was divided by 3 to obtain the mean change over each six-month period. It should be noted that changes in flexion deformity are not normally distributed.
- Mean QALYs between six months and 18 months. Since no patients died during the trial, this was used as a measure of the impact that quiescence and/or treatment had on mean EQ-5D utility between six months and 18 months. QALYs accrued in the first six months of the trial were excluded, since patients had not yet received three injections. Ordinary least squares regression was used to predict QALYs as a function of baseline EQ-5D utility, treatment allocation, quiescence at 18 months and the interaction between treatment allocation and quiescence. As for other analyses, the variable with the highest p-value was sequentially dropped until the model contained only statistically significant variables ($p < 0.05$); the interaction was dropped at the same time as either main effect. Adalimumab had no significant effect on QALYs after controlling for baseline EQ-5D and quiescence ($p = 0.31$). Quiescence was found to increase EQ-5D utility by 0.039 (95% CI 0.008 to 0.070; $p = 0.014$) and baseline EQ-5D was also highly significant ($p < 0.001$). The final model therefore comprised ordinary least squares regression, controlling for quiescence at 18 months and baseline EQ-5D utility.

Given the sample size of 140 patients, it was not feasible to explore the impact of other covariates within these models. Each analysis combined results of 50 imputed datasets using Rubin's rule and was conducted in Stata version 17 (StataCorp, USA).

The models selected by the processes above were bootstrapped to obtain a set of correlated coefficients for use in PSA. Twenty bootstraps were independently drawn for each of the 50 imputed datasets and parameters for all of the three above analyses were estimated for each of the 1,000 bootstraps. Each PSA replicate used one of the 1000 sets of coefficients. This ensured that correlations within equations and between equations were propagated into the analysis. The root mean squared error from the model predicting the mean change

in flexion deformity in the placebo group was also estimated for each bootstrap; the mean of this value was used within the model as a measure of the between-patient variance.

The population of individual patient data used to run the model was based on 69 of the 70 UK patients randomized to placebo (excluding one patient who had missing data on baseline EQ-5D).

Technical details of the simulation

Parameter values for use in probabilistic sensitivity analysis (PSA) were drawn from the relevant distributional using Microsoft Excel 2016. A CSV file containing the parameter values for the point estimate, minima and maxima for the tornado diagram and alternative values for many of the sensitivity analysis and probabilistic parameter values was stored and used for the simulation within Stata.

The model was built and run in Stata version 17.

Random numbers for transitions within each loop were generated in Stata. To make sure that patients are either categorized as quiescent or late-stage or neither but never both, the random number used to assign patients to late-stage disease was set to be equal to 1 minus the random number used to assign patients to quiescence. Furthermore, any patient who has already been categorized as having quiescent disease in that loop will not be classed as having late-stage disease; this condition will only apply in extreme PSA replicates in which the probability of late-stage disease and the probability of quiescence sum to > 1.

To minimize Monte Carlo error for differences between arms, patient p has the same random number for mortality in all arms of the model within cycle c of loop n; likewise for late-stage DD transitions, AE from late-stage DD interventions and flexion deformity changes. The random number will differ between patients and between loops, but not between arms. This makes sure that patients will always live for the same length of time regardless of treatment allocation and reduces the number of loops that are needed for the model to converge. However, random numbers determining whether patients are quiescent or not and whether they have late-stage DD or not will vary between arms, because the probability against which they are compared differs between arms.

For each patient who has progressive early-stage DD at the start of cycle c, flexion deformity at the end of cycle c equals their flexion deformity at the end of cycle c-1 ($flexion_{c-1,i,b,p,t}$), plus a value for their change in flexion deformity this cycle that is randomly sampled. The randomly sampled change in flexion deformity equals the linear prediction from the model predicting change in flexion deformity between baseline and 18 months (which depends on whether the patient has ectopic disease), plus an error term ($error_{c,i,p}$, sampled from a normal distribution with mean of zero and a standard deviation of 12 [the root-MSE from the regression]). The error term for flexion deformity was common to all treatment groups to minimize unnecessary random differences between treatment groups, but was sampled independently in each cycle (*c*) in each loop (*i*) and for each patient (*p*) and each PSA replicate (*b*)).

$$flexion_{c,i,b,p,t} = flexion_{c-1,i,b,p,t} + (\beta 0_b - ectopic_p \cdot \beta ectopic_b + error_{c,i,p,b})/3$$

Because the change in flexion deformity varies randomly and some patients have high flexion deformity at baseline, some patients who do not have late-stage DD at the end of the trial will have a simulated end of trial flexion deformity > 30. Within the structure of the model, these patients were assigned the utilities and costs of progressive early-stage DD during the first cycle of the model and their flexion for deformity may go up or down during cycle 1; if their flexion deformity is > 30 at the end of cycle 1, they will spend cycle 2 in the untreated late-stage DD state and may undergo surgery in cycle 3. By contrast, patients who have late-stage DD at the end of the trial will have untreated late-stage DD during cycle one and may have surgery in cycle 2.

Flexion deformity is updated in early-stage disease, transitions in late-stage disease and age at the end of the cycle: treatment decisions that occur in this cycle are based on the flexion deformity at the beginning of the cycle.

Within each PSA replicate in the model, the duration of quiescence was rounded to the nearest six months. For example, if the duration of quiescence within PSA replicate 1 was 3.2 years, patients would be retreated every 6 cycles in the adalimumab with retreatment arm and within the arms without retreatment (e.g. in cycle 4,

cycle 10 & cycle 16), the quality-of-life benefits for quiescence were applied for the first 18 months of the model and flexion deformity begins to change in cycle 7.

Monte Carlo error (MCE) was estimated as the square root of the variance[35] around the mean costs and QALYs in each treatment group and the incremental costs and QALYs across 100 repeated runs of the model, using the mean values for all parameters. This measure indicates the imprecision around the estimates that is introduced by simulating individual patients through random numbers and it is important to run sufficient numbers of loops of the model to estimate mean outcomes accurately and avoid over estimating standard errors. MCE was calculated based on repeated runs of the model with point estimates because the way that the model is set up (with identical patients in each treatment group and using the same random numbers for all treatment groups within any given loop) make it difficult to reliably estimate MCE analytically.

One hundred loops were run for each of the 1000 parameter sets for each of the 69 patients in each of the treatment groups (a total of 6.9 million loops). One thousand parameter sets were used for PSA: the number needed to give SEs to ±10% accuracy.[36] By plotting the MCE against $1/\sqrt{Number\ of\ loops}$,[35] we found that 128 loops were sufficient to ensure that the MCE around the difference in modelled QALYs between adalimumab retreatment and standard care was < 10% of the standard error around this measure, while 23 loops were sufficient for the MCE around the difference in cost between adalimumab once and no treatment was < 10% of its SE. Since the standard error around the difference in QALYs between adalimumab once and placebo was much smaller, 334 loops would have been needed per parameter set to achieve MCE < 10% of the SE, which was not feasible (estimated simulation time: 78 days) and was not deemed necessary since adalimumab once dominated no treatment. MCE was larger around total costs and total QALYs than incremental costs and QALYs because the same random numbers were used for all treatment groups (other than the transition to quiescence or late-stage DD at the end of the trial), although these outcomes are not presented for one-way sensitivity analyses or PSA.

Mean costs, QALYs and life expectancy and mean differences between groups shown in tables are based on the mean across all 1000 probabilistic parameter sets (a total of 6.9 million loops per treatment group). With 6.9 million loops, the MCE around the mean difference in modelled QALYs between adalimumab retreatment and standard care was only 0.000048. Using the mean across PSA replicates ensures that point estimates capture any nonlinearity between input parameters and outcomes. The 1000 runs of 100 loops took 23.3 computer-days to simulate using multi-user simulation servers.

It was not possible to use the formula developed by O'Hagan et al.[36] to eliminate bias from standard errors because the analysis has a three-level structure with loops nested in patients within each PSA replicate,[37] although since MCE ~10% of SEs, the degree of bias should be minimal.

However, since it was not feasible to replicate PSA for each one-way sensitivity analysis, tornado diagrams and sensitivity analyses are based on runs of the model using the mean value for each parameter shown in Supplementary Table xi, with the exception of the values changed in that sensitivity analysis. Within tornado diagrams, the base case value is based on point estimates for all parameters. Each sensitivity analysis used for the tornado diagram or scenario analysis (and the mean against which the sensitivity analyses are compared) was based on 200 loops to minimize chance differences between analyses. Chance differences between sensitivity analyses were also minimized by using the same seed for all sensitivity analyses and the mean against which the sensitivity analyses are compared. One hundred parameter sets each with 200 loops took 5 days to simulate on a multi-user server.

The model was validated by careful examination of the code, assessing the face validity of outcomes, examining the variables generated for each patient in each cycle and by running the model using a number of extreme data inputs to check that these changes had the expected result. The extreme data inputs included assuming that everyone had quiescence at the end of the trial, assuming everyone had late-stage DD at the end of the trial, applying no cost for adalimumab, applying no cost for interventions for late-stage DD, etc. Since there are very few other datasets on early DD, it was not possible to externally validate the model.

Expected value of perfect information

The expected value of perfect information (EVPI) and the expected value of perfect parameter information (EVPPI) were estimated from the 1000 probabilistic replicates using the Sheffield Accelerated Value of Information software on release version 2.2.0 (2021-06-04) of SAVI - Sheffield Accelerated Value of Information.[38] Results were reported at a £20,000/QALY ceiling ratio. Unless otherwise stated, EVPI and EVPPI are reported from an analysis comparing standard care, one course of adalimumab and repeated adalimumab. The seven parameters bootstrapped from the RIDD trial, plus the duration of quiescence were evaluated as a group, since all these parameters could be estimated from a new trial with longer follow-up.

The value of perfect information for the UK population over the next 10 years was based on an estimate of the number of prevalent cases of progressive early-stage DD that meet the RIDD inclusion criteria. There are very limited data on the prevalence of early-stage DD, so this figure should be treated as an estimate. The number of patients receiving treatment was not adjusted for time preference.

We applied estimates of the prevalence of different trends in Western populations at age 55, 65 and 75 from a systematic review and meta-analysis[39] to UK population estimates[40] (Supplementary Table xii). We assumed that the prevalence at age 55 applied to everyone in the UK population aged 50-59, that the prevalence at age 65 applied to 60-69-year-olds and that the prevalence at age 75 applied to everyone aged 70 years and over. We also conservatively assumed that there were no cases of different trends in people aged under 50 years, although it is known that this is not the case.[39]

Supplementary Table xii. Number of people with Dupuytren's disease in the UK.

Age group	Prevalence of Dupuyten's[39]	UK population in each age band[40]	No. cases DD
55 years (assumed to apply to 50 to 59 years)	12%	9,126,868	1,095,224
65 years (assumed to apply to 60 to 69 years)	21%	7,211,199	1,514,352
75 years (assumed to apply to 70+ years)	29%	9,153,257	2,654,445
Total			5,264,020

DD, Dupuytren's disease.

In the absence of UK data on the proportion of DD patients who have early-stage disease, we used data from a study in the Netherlands, which recruited a sample of patients from the general population. Of the 169 patients with DD, 81% (137) had palmar nodules without contracture (Iselin degree I) in a population-based study in the Netherlands[41]; on that basis, we assumed that 4.27 million people in the UK have early-stage DD (81% of 5,264,020). Since 39% (112/284) patients screened for RIDD did not meet inclusion criteria,[21] we assumed that 61% of patients with early-stage DD meet RIDD criteria. On that basis, we estimated that 2,584,411 people in the UK currently have progressive early-stage DD meeting RIDD criteria. In the absence of reliable data on incidence, we used this prevalent population as the estimate of the number of people affected by the decision over the next 10 years. There is substantial uncertainty around this figure: in particular, the proportion of people with early-stage DD may be lower in the UK than in the Netherlands and the prevalence is likely to be non-zero in under 50s and higher than 29% in over 75's, but, conversely, many patients with progressive early-stage DD may not seek treatment or be unwilling to have injections.

Sensitivity analyses

The following sensitivity analyses were run to assess the uncertainty around model results:

- The following analyses were done using alternative input values and results are based on 100 loops per patient:
    - No excess mortality for DD. As well as testing the impact of assuming that DD does not affect patients' mortality, this tests whether conclusions are likely to be sensitive to interactions with other treatments affecting length of life.
    - No discounting
    - No direct utility benefit from quiescence

- No age-related decline in utility
- Adalimumab price based on Yuflyma 40mg/0.4ml solution (£633.70 for 2 syringes[15]) delivered by a GP (£39[6]) plus a tube of Ametop 4% anaesthetic gel per injection (£1.08): £715.86 per 6 months or £1428 per course
- Retreatment with 3 doses of adalimumab rather than four: £712.83 per 6 months or £1426/course (including administration in an outpatient consultation and local anaesthetic)
- Adalimumab price £625 per 6 months or £1250/course, including administration and local anaesthetic (arbitrary value)
- Adalimumab price based on 3 doses of Yuflyma[15] (including administration in an GP consultation and local anaesthetic): £535.40 per 6 months or £1071 per year
- Adalimumab price £470 per 6 months or £940 per course, including administration and local anaesthetic (arbitrary value)
- Adalimumab price based on the cheapest etanercept formulation (Erelzi 50mg/1ml solution of etanercept (£643.50 for 4 syringes[15]) delivered by a GP (£39[6]) with Ametop 4% anaesthetic gel (£1.08/injection): £401.91 per 6 months or £804 per course
-
- Using Tubiana stage 2 utilities for failure, recurrence and untreated states (utility 0.101 lower than early-stage DD[10])

- The following analyses were done using additional runs of the model, each with 100 loops:
  - Controlling for flexion deformity when estimating probability of quiescence or late-stage DD. The base case analysis used the crude proportion of patients who were quiescent or had late-stage DD at the end of the trial as data inputs. This sensitivity analysis instead used an mlogit predicting quiescence or late-stage DD as a function of baseline flexion deformity as well as treatment allocation; this was run within the same set of bootstraps on the trial data as the base case inputs; the parameters are shown in Supplementary Table i.
  - Assuming that the sequence of late-stage DD treatments is up to three PNF procedures followed by BSC (the most cost-effective strategy evaluated by Yoon et al, which considered sequences of up to three operations), as opposed to the base case sequence (three PNF then one LF then one DF)

The following assumptions were applied in a sensitivity analysis to conduct early modelling comparing the cost-effectiveness of first-line adalimumab with first-line radiotherapy or steroids:

- Radiotherapy:
  - QALYs in the first 18 months with radiotherapy were assumed to be equal to the QALYs accrued in the adalimumab arm of the trial.
  - The cost of radiotherapy was based on 10 doses. It was assumed that there was no difference in other costs between radiotherapy and no radiotherapy.
  - This was run alongside the base case analysis and scenario 1 for steroids and is therefore based on the mean across 1000 parameter sets, each run using 100 loops.
- Two scenarios were modelled for steroids:
  - scenario 1 (best case):
    - 97% of patients were assumed to achieve quiescence, based on the proportion of early-stage DD patients who had “softening and flattening” in the study by Ketchum et al.[33]
    - 0% of patients were assumed to progress to late-stage DD within 18 months.
    - This was run alongside the base case analysis for 480 of the probabilistic parameter sets, each run using 100 loops.
  - Scenario 2:
    - probability of quiescence and probability of late-stage DD are the same as for adalimumab.
    - This was run alongside the base case analysis for 587 of the probabilistic scenarios, each run using 100 loops.
  - In both cases:
    - QALYs in the first 18 months with steroids were assumed to be equal to the QALYs accrued in the adalimumab arm of the trial.
    - quiescent patients have three injections required every six months to maintain quiescence.

We did not do a sensitivity analysis from a societal perspective since the within-trial analysis showed that non-NHS costs in early DD were negligible.

Subgroup analyses and analyses exploring heterogeneity were not conducted due to the size of the trial.

Additional figures and tables from the model-based extrapolation

Additional results of base case analysis

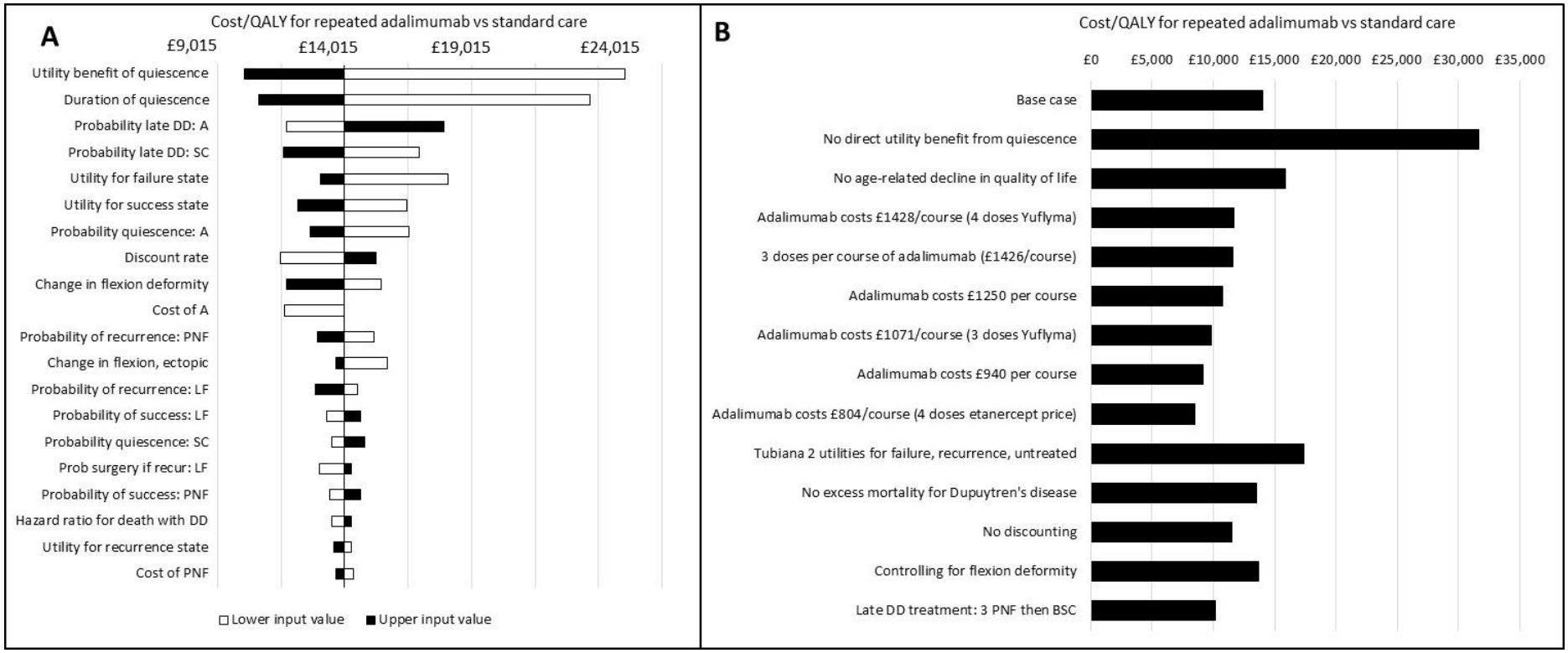

Fig b. Tornado diagram showing the results of (A) one-way sensitivity analyses and (B) scenario analyses on the cost per quality-adjusted life-year (QALY) for repeated courses of adalimumab compared with standard care. In panel (A) the 20 parameters that had the greatest effect on the results are shown in descending order; the black bars represent the cost/QALY using the maximum value for each parameter, while the white bars represent the cost/QALY using the minimum value. All other parameters were held at their point estimates; since the model is non-linear, base case results therefore differ slightly from the average across probabilistic runs shown in Table 4 of the main manuscript. The ranges over which each variable was varied in one-way sensitivity analyses are given in Supplementary Table xi. The cost of adalimumab courses in panel B comprises the cost for the entire course of injections, including administration and local anaesthetic; details of all sensitivity analyses are given in the 'Sensitivity analyses' section above.

A, adalimumab; DD, Dupuytren's disease; LF, limited fasciectomy; QALY, quality-adjusted life-year; PNF, percutaneous needle fasciotomy; SC, standard care.

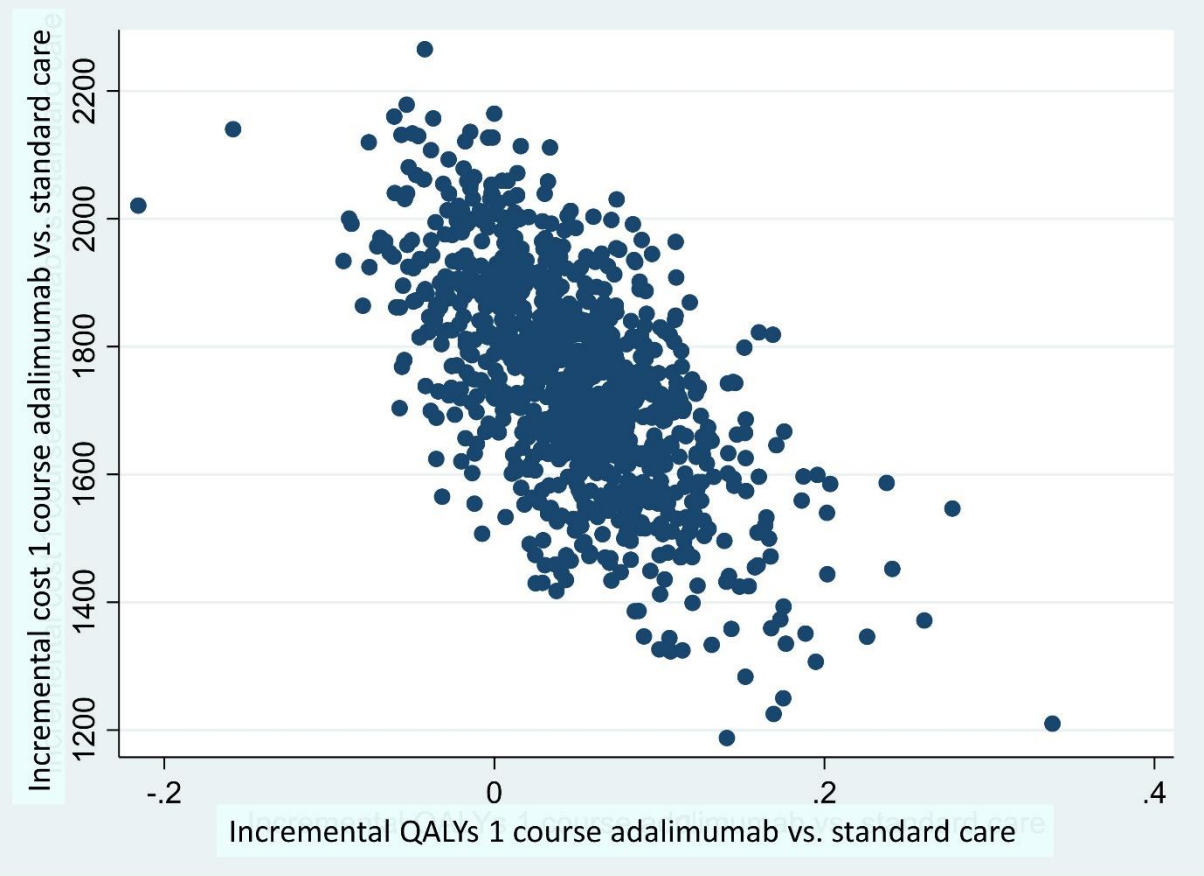

Fig c. Scatter graph on cost-effectiveness plane: 1 course adalimumab versus standard care. QALY, quality-adjusted life-year.

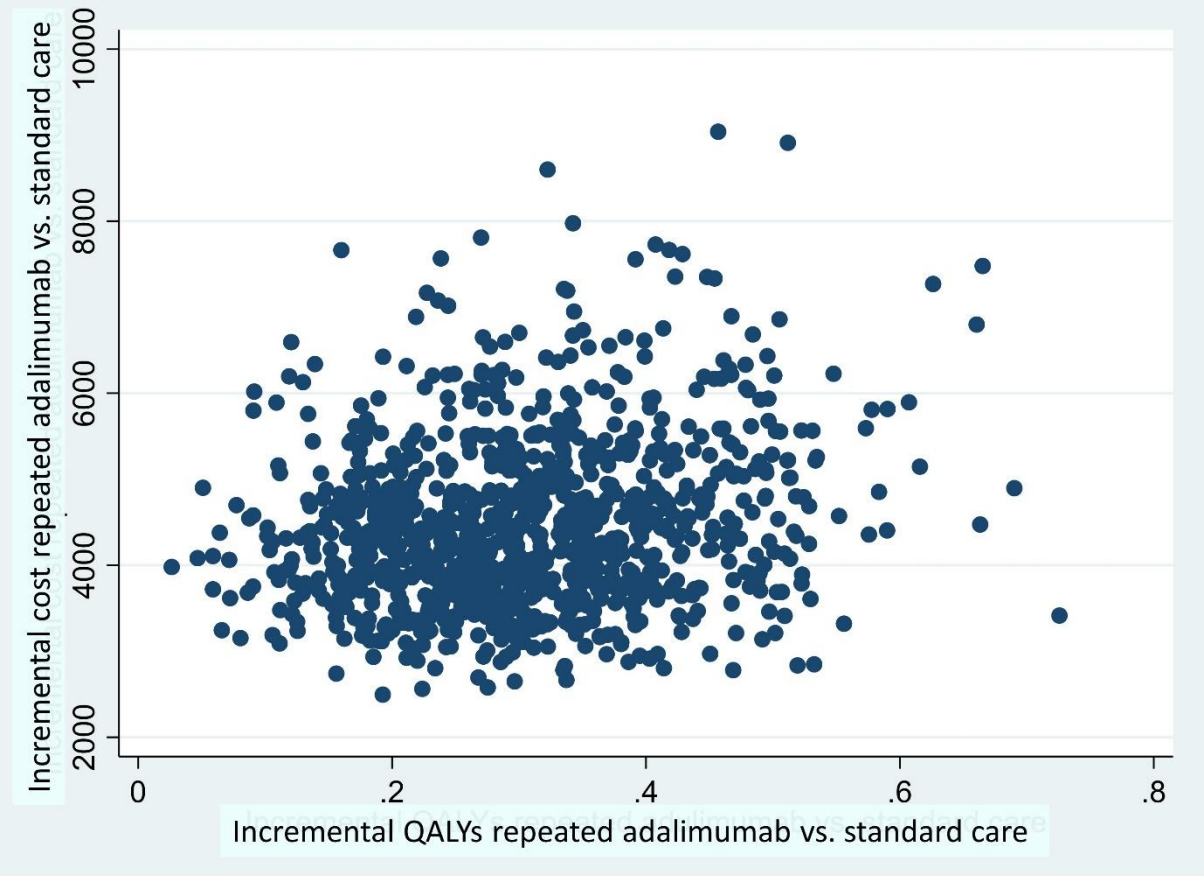

Fig d. Scatter graph on cost-effectiveness plane: repeated adalimumab versus standard care. QALY, quality-adjusted life-year.

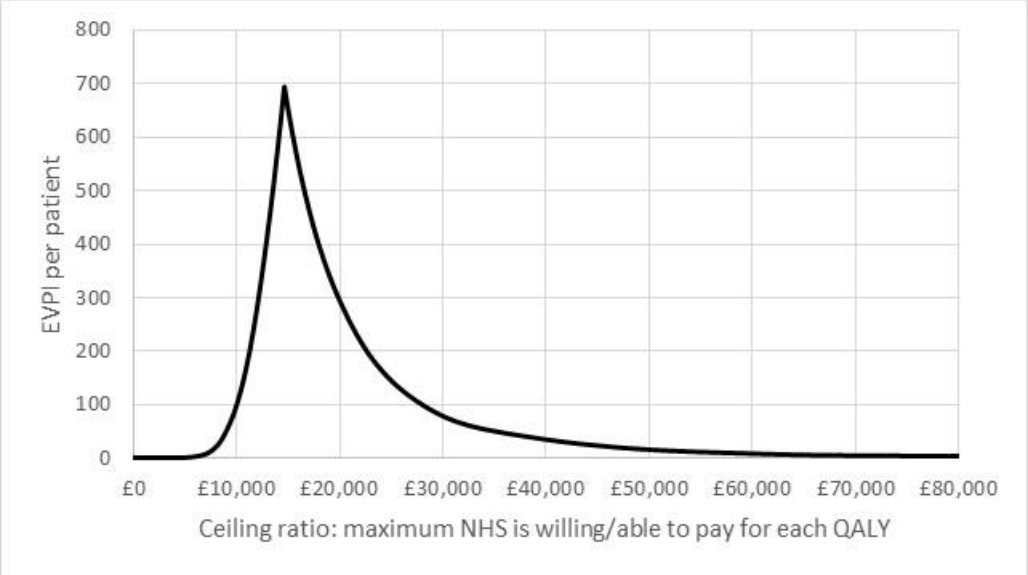

Fig e. Expected value of perfect information (EVPI) per patient. QALY, quality-adjusted life-year.

Using the Sheffield Accelerated Value of Information,[38] most influential individual parameter was the utility of quiescence, followed by the probability that adalimumab-treated patients have late-stage DD at 18 months. The EVPI for the group of parameters estimated from the RIDD sample was £97.96 per patient (£272 million for the population); this could be viewed as the maximum benefit from a confirmatory phase III trial similar to RIDD. Collecting additional data, or extended follow-up, in order to also get data on the duration of quiescence increased the maximum value of such a trial by £7.48 per patient (£19 million for the population) to £105. Eliminating all uncertainty around the parameters relating to the costs, utilities, success rates, recurrence rates and uptake of interventions for late-stage DD would be valued at £79 per patient (£205 million for the population) for the decision about adalimumab treatment alone, excluding the benefits that such information would have for informing decisions about the best course of treatment once patients develop late-stage DD.

Scenario analysis: additional comparators

Adding radiotherapy as a fourth treatment option within the base case analysis increased EVPI by only £21 to £293 per patient at a £20,000/QALY ceiling ratio. The probability of radiotherapy being the best value for money out of the treatments considered never exceeded 0.5% (figures not shown because they are indistinguishable from the base case).

Adding steroids as a fourth option within the base case analysis using the steroid scenario B decreased the EVPI to £80 per patient at a £20,000/QALY ceiling ratio (Figures f and g).

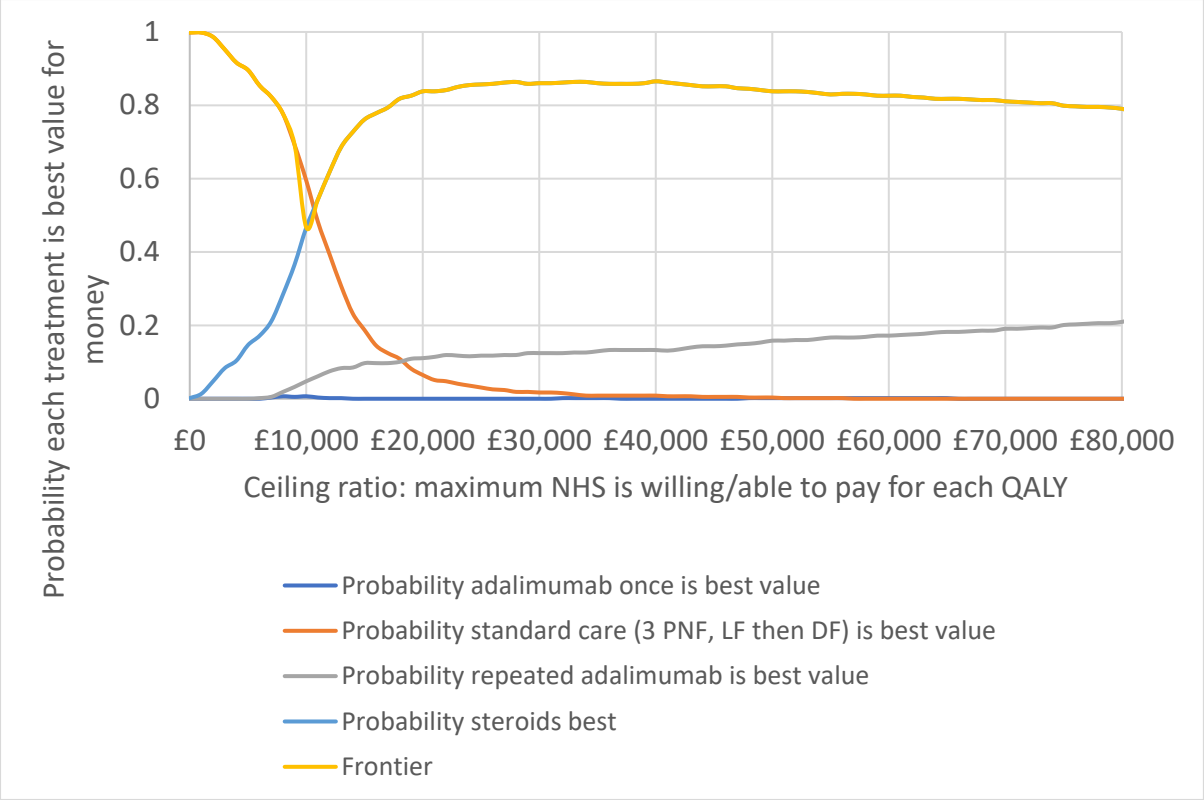

Fig f. Cost-effectiveness acceptability curve for steroid scenario B, adding steroids as a fourth treatment option. DF, dermofasciectomy; LF, limited fasciectomy; PNF, percutaneous needle fasciotomy; QALY, quality-adjusted life-year.

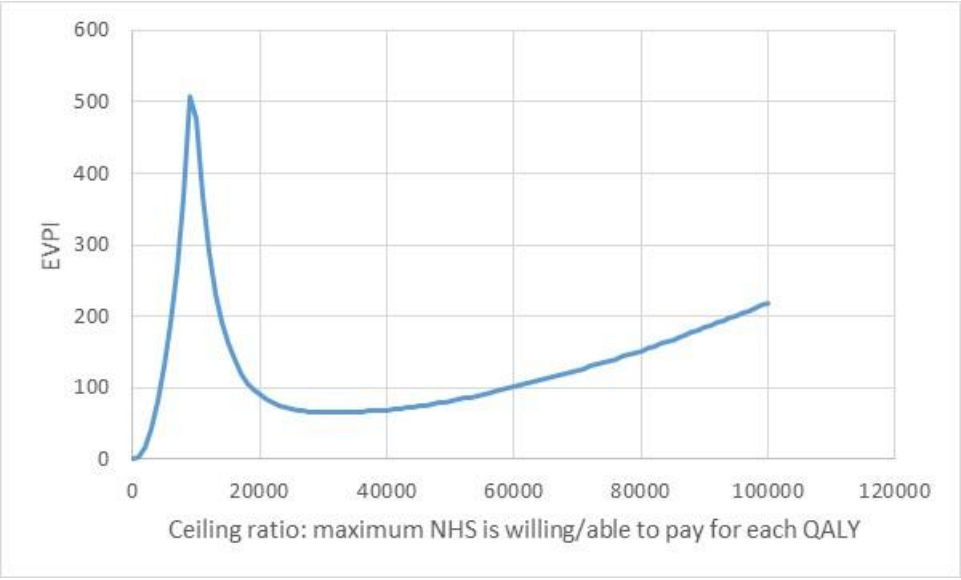

Fig g. Expected value of perfect information (EVPI) for steroid scenario B, adding steroids as a fourth treatment option. QALY, quality-adjusted life-year.

Supplementary Table xiii. Results of scenario analyses of the model-based economic evaluation with additional comparators. Values in brackets represent 95% confidence intervals.

Outcome	Time period	Standard care: up to 3 PNF	Standard care: up to 3 PNF, then LF then DF	1 course adalimumab	Repeated courses adalimumab	Steroids: Scenario 1†	Steroids: Scenario 2‡	Radiotherapy
QALYs*	Trial	1.279 (1.247 to 1.313)	1.279 (1.247 to 1.313)	1.286 (1.248 to 1.320)	1.286 (1.248 to 1.320)	1.286 (1.248 to 1.322)	1.286 (1.248 to 1.322)	1.286 (1.248 to 1.320)
	Model	9.67 (9.23 to 10.04)	10.15 (9.80 to 10.49)	10.19 (9.86 to 10.51)	10.45 (10.10 to 10.79)	11.01 (10.59 to 11.46)	10.46 (10.14 to 10.81)	10.19 (9.86 to 10.51)
	Lifetime	10.95 (10.49 to 11.33)	11.43 (11.08 to 11.78)	11.48 (11.14 to 11.80)	11.74 (11.40 to 12.08)	12.30 (11.87 to 12.75)	11.75 (11.42 to 12.10)	11.48 (11.14 to 11.80)
NHS costs*, £	Trial	2,136 (1,998 to 2,277)	307 (134 to 514)	2,136 (1,998 to 2,277)	2,697 (2,439 to 2,888)	2,697 (2,439 to 2,888)	4,046 (3,908 to 4,187)	2,697 (2,439 to 2,888)
	Model	725 (543 to 970)	1,416 (1,056 to 1,887)	1,333 (993 to 1,780)	7,774 (1,898 to 9,627)	3,884 (1,613 to 5,329)	1,333 (996 to 1,803)	7,774 (1,898 to 9,627)
	Lifetime	2,861 (2,628 to 3,130)	3,552 (3,165 to 4,036)	5,298 (4,782 to 5,820)	10,840 (4,645 to 12,778)	6,581 (4,068 to 8,138)	5,379 (5,018 to 5,845)	10,840 (4,645 to 12,778)
Life expectancy, yrs		22.6 (22.0 to 23.2)	22.6 (22.0 to 23.2)	22.6 (22.0 to 23.2)	22.6 (22.0 to 23.2)	22.6 (22.0 to 23.2)	22.6 (22.0 to 23.3)	22.6 (22.0 to 23.2)
Years with early-stage DD during modelled period		9.71 (6.39 to 12.08)	9.71 (6.38 to 12.05)	10.39 (7.23 to 12.72)	13.25 (10.52 to 15.61)	21.10 (20.39 to 21.77)	13.21 (10.52 to 15.65)	10.38 (7.28 to 12.77)
Number of courses of treatment for early-stage DD		0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	1.0 (1.0 to 1.0)	3.65 (2.35 to 5.74)	38.90 (11.48 to 46.16)	16.47 (5.73 to 23.75)	1.0 (1.0 to 1.0)
Number of operations for late-stage DD		0.77 (0.56 to 1.05)	1.36 (1.0 to 1.88)	1.30 (0.94 to 1.79)	0.93 (0.63 to 1.32)	0.03 (0.0 to 0.09)	0.93 (0.63 to 1.32)	1.30 (0.94 to 1.80)

*Discounted at 3.5% per annum.

†Based on a run of probabilistic sensitivity analysis with 480 parameter sets, each with 100 loops that overlap with the base case analysis but not scenario 2. Overall 97% of patients were assumed to achieve quiescence, based on the proportion of early-stage Dupuytren's disease (DD) patients who had "softening and flattening" in the study by Ketchum et al.[33] Also, 0% of patients were assumed to progress to late-stage DD within 18 months.
‡Based on a run of probabilistic sensitivity analysis with 480 parameter sets, each with 100 loops that overlap with the base case analysis but not scenario 1. Probability of quiescence and probability of late-stage DD was the same as for adalimumab.
DD, Dupuytren's disease; PNF, percutaneous needle fasciotomy; QALY, quality-adjusted life-year.

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