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Repurposing anti-TNF for treating Dupuytren's disease

Submission date	Recruitment status	[_] Prospectively registered
15/10/2015	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/11/2015	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
03/01/2024	Skin and Connective Tissue Diseases	

Plain English summary of protocol

Background and study aims
Dupuytren's disease (DD) is a common condition which causes the fingers to gradually curl into the palm so that they can no longer be straightened. It is caused by a thickening of the thin layer of tissue which lies under the skin of the palm (connective tissue). This thickening often starts in a small area, causing a small, hard lump (nodule) to form under the skin. Although these nodules are effectively harmless, over time they grow into cords of shortened (contracted) tissue which pull the fingers towards the palm. There is large variation in how quickly the disease progresses, and there are currently no effective treatments for early stage disease to slow or prevent progression. Once the disease is advanced, the main way of treating the hand deformity is by surgically removing the contracted tissue. This operation can take a long time to recover from and patients often require a long period of physiotherapy. New theories are emerging that DD may be caused by a protein called tumour necrosis factor (TNF), which causes inflammation . Adalimumab is a drug which blocks the action of TNF and is normally used to treat arthritis. The current study consists of two parts. In part one, the study aims to find out the effectiveness of treatment with adalimumab at different doses in patients with advanced DD. In part two, the study aims of find out whether injections of adalimumab can help treat patients with early stage DD.

Who can participate?
Adults with late stage Dupuytren's disease (part one) who are having surgery to remove the Dupuytren's tissue, and adults with early stage Dupuytren's disease (part two) which is getting worse.

What does the study involve?
Before starting either part of the study, all potential participants are seen by a doctor to check they are able to take part. Other visits include physical tests to see how well the hand functions, questionnaires about health and hand function, blood tests, and ultrasound imaging and digital photographs of the hand. In part one, participants are asked to attend a clinic at the hospital to receive an injection of either adalimumab or a placebo (dummy injection) two weeks before their surgery. Some participants receive bigger doses than others so that the best dose can be found. They are also asked to donate their surgically removed Dupuytren's tissue so it can be examined in the laboratory. They are also seen by researchers over three months when they attend the

clinic as part of their usual surgery care. In part two, participants are asked to attend a clinic seven times over eighteen months. On four of these visits, participants are given injections of either adalimumab or a placebo. Participants are equally likely to receive adalimumab as the dummy. In both parts of the study, none of the researchers working with the participants, and none of the participants, know who receives which.

What are the possible benefits and risks of participating?
In part one, there are no direct benefits to participants, as they will be receiving the surgery whether they take part or not. In part two, participants may benefit from the possibility of adalimumab slowing the development of the disease, but there will be no direct medical benefit to participants who receive the dummy injection. For all participants there is a risk of experiencing unwanted side effects from the adalimumab, such as redness, swelling or pain at the injection site, or sore throat or sinus infections.

Where is the study run from?
1. Oxford University Hospital (UK) (Part 1 and 2)
2. Western General Hospital – Edinburgh (UK) (Part 2)
3. University Medical Centre Groningen (Netherlands) (Part2)
4. St Johns Hospital – Livingston (UK) (Part 1)

When is the study starting and how long is it expected to run for?
October 2015 to June 2021

Who is funding the study?
1. Wellcome Trust (UK) Grant Code: 102538 (HICF)
2. Department of Health (UK)
3. 180 Therapeutics (UK)

Who is the main contact?
1. Mrs Nicola Kenealy (Public)
ridd@kennedy.ox.ac.uk
2. Professor Jagdeep Nanchahal (Scientific)

Contact information

Type(s)
Public

Contact name
Mrs Nicola Kenealy

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Type(s)
Scientific

Contact name
Prof Jagdeep Nanchahal

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-001780-40

ClinicalTrials.gov (NCT)
NCT03180957

Protocol serial number
10.0

Study information

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

Acronym
RIDD

Study objectives
Part 1: To establish an effective dose of the research drug for treating Dupuytren's disease by analysing patient’s tissue in the laboratory.

Part 2: To determine whether dose of the research drug controls disease progression better than the placebo in patients with early Dupuytren's disease.

Ethics approval required

Old ethics approval format

Ethics approval(s)
NRES Committee South Central - Oxford B, 23/06/2015, ref: 15/SC/0259

Study design
Multi-centre double-blind randomised placebo-controlled phase II trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Dupuytren's disease of the hand

Interventions
Interventions as of 09/11/2016:
Part 1: Dose response. Participants will have advanced Dupuytren's and will be scheduled for surgery to treat the contracture. Up to 40 participants will be recruited and the ratio of participants receiving adalimumab to saline placebo will be 3:1. All participants will be injected on one occasion, two weeks before their planned surgery, into their Dupuytren’s nodule. The maximum dose that may be used is 80 mg adalimumab.

Part 2: Randomised controlled trial. Participants with early stage Dupuytren's will be randomised 1:1 to receive injections of either adalimumab or saline (placebo control). The dose will be 40 mg adalimumab or the equivalent volume of saline. Participants will receive 4 treatments, 3 months apart over a year.

Original interventions:
Part 1: Dose response run-in. Participants will have advanced Dupuytren's and will be scheduled for surgery to treat the contracture. There will be 5 dose cohorts with progression to the next, higher, dose group only if no more than 1 patient from the cohort of 8 has an unplanned admission to hospital or unplanned surgery related to the surgery for Dupuytren’s disease of the affected finger. Within each dose cohort, 6 participants will be injected on one occasion with adalimumab, and 2 participants will be injected on one occasion with the same volume of saline (placebo control).
The doses will be:
1. 0.3 ml into the Dupuytren's nodule (15 mg adalimumab)
2. 0.5 ml into the Dupuytren's nodule (25 mg adalimumab)
3. 0.7 ml into the Dupuytren's nodule (35 mg adalimumab)
4. 0.7 ml into the Dupuytren's nodule (35 mg adalimumab) AND 0.8 ml subcutaneously into the abdomen (40 mg adalimumab)
5. 0.7 ml into the Dupuytren's nodule (35 mg adalimumab) AND 2 x 0.8 ml subcutaneously into the abdomen (80 mg adalimumab)

Part 2: Randomised controlled trial. Participants with early stage Dupuytren's will be randomised 1:1 to receive injections of either adalimumab or saline (placebo control). The dose will have been determined from the results of Part 1. Participants will receive 4 treatments, 3 months apart over a year.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Adalimumab (humira)

Primary outcome(s)
Current primary outcome measures (as of 14/02/2018):
Part 1:
Expression of mRNA for α-SMA in the nodule tissue removed as part of planned surgery 12-18 days after treatment.

Part 2:
The hardness of the hand overlying the treated nodule measured using tonometry before, and at 12 months after treatment.

Previous primary outcome measures:
Part 1:
Expression of mRNA for α-SMA in the nodule tissue removed as part of planned surgery 12-18 days after treatment.

Part 2:
The hardness of the hand overlying the treated nodule measured using tonometry before, and at 3, 6, 9, 12 and 18 months after treatment.

Key secondary outcome(s))
Current secondary outcome measures (as of 14/02/2018):
Part 1:
1. Expression of mRNA for COL-1A1, COL-3A1 and cadherin 11 in the nodule tissue removed as part of planned surgery 12-18 days after treatment
2. Levels of α-SMA protein and collagen protein in the removed nodule tissue
3. The hardness of the hand overlying the treated nodule measured using tonometry at baseline and 2 weeks after treatment
4. Nodule size and vascularity measured with ultrasound imaging at baseline and 2 weeks after treatment
5. Assessment of the injection site for adverse events by observation at each research visit
6. Visual assessment of surgical wounds using hand photographs

Part 2:
1. Nodule size measured with ultrasound imaging at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
2. Grip strength measured with a dynamometer at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
3. Range of motion of the affected digit measured with a goniometer at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
4. Patient reported outcomes are measured using the Michigan Hand Outcomes Questionnaire (MHQ) and the rating of the activity most restricted by Dupuytren’s disease at baseline and at 3, 6, 9, 12 and 18 months after first treatment

5. The experience of the injection rated by the participant immediately after each treatment
6. Progression to surgery of the finger being assessed during the 18 month follow-up
7. Assessment of the injection site for adverse events by observation at each research visit
8. The hardness of the hand overlying the treated nodule measured using tonometry before, and at 3, 6, 9 and 18 months after treatment.

Previous secondary outcome measures as of 08/11/2016:
Part 1:
1. Expression of mRNA for COL-1A1 and COL-3A1 in the nodule tissue removed as part of planned surgery 12-18 days after treatment
2. Levels of α-SMA protein in the removed nodule tissue
3. The hardness of the hand overlying the treated nodule measured using tonometry at baseline and 2 weeks after treatment
4. Nodule size and vascularity measured with ultrasound imaging at baseline and 2 weeks after treatment
5. The experience of the injection rated by the participant immediately after treatment
6. Assessment of the injection site for adverse events by observation at each research visit

Part 2:
1. Nodule size measured with ultrasound imaging at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
2. Grip strength measured with a dynamometer at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
3. Range of motion of the affected digit measured with a goniometer at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
4. Patient reported outcomes are measured using the Michigan Hand Outcomes Questionnaire (MHQ) and the rating of the activity most restricted by Dupuytren's disease at baseline and at 3, 6, 9, 12 and 18 months after first treatment
5. Clinical assessment of the hand at baseline and at 3, 6, 9, 12 and 18 months after first treatment
6. The experience of the injection rated by the participant immediately after each treatment
7. Progression to surgery of the finger being assessed during the 18 month follow-up
8. Assessment of the injection site for adverse events by observation at each research visit

Secondary outcome measures (part 1) as of 07/03/2016:
1. Expression of mRNA for COL-1A1 and COL-3A1 in the nodule tissue removed as part of planned surgery 12-18 days after treatment
2. The hardness of the hand overlying the treated nodule measured using tonometry at baseline and 2 weeks after treatment
3. Nodule size and vascularity measured with ultrasound imaging at baseline and 2 weeks after treatment
4. Assessment of the injection site for adverse events by observation at each research visit

Original secondary outcome measures:
Part 1:
1. Expression of mRNA for COL-1 in the nodule tissue removed as part of planned surgery 12-18 days after treatment
2. The hardness of the hand overlying the treated nodule measured using tonometry at baseline, 2 weeks after treatment
3. Nodule size and vascularity measured with ultrasound imaging at baseline, 1 and 2 weeks after treatment
4. Grip strength measured with a dynamometer bat baseline, 2 weeks after treatment and at 12

weeks after surgery
5. Range of motion of the affected digit measured with a goniometer at baseline, 2 weeks after treatment and at 12 weeks after surgery
6. Patient reported outcomes are measured using the Michigan Hand Outcomes Questionnaire (MHQ) and the rating of the activity most restricted by Dupuytren's disease at baseline, 2 weeks after treatment and at 12 weeks after surgery
7. The experience of the injection rated by the participant immediately after treatment
8. Assessment of the injection site for adverse events by observation at each research visit

Part 2:
1. Nodule size and vascularity and cord extent measured with ultrasound imaging at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
2. Grip strength measured with a dynamometer at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
3. Range of motion of the affected digit measured with a goniometer at baseline, and at 3, 6, 9, 12 and 18 months after first treatment
4. Patient reported outcomes are measured using the Michigan Hand Outcomes Questionnaire (MHQ) and the rating of the activity most restricted by Dupuytren's disease at baseline and at 3, 6, 9, 12 and 18 months after first treatment
5. Clinical assessment of the hand at baseline and at 3, 6, 9, 12 and 18 months after first treatment
6. The experience of the injection rated by the participant immediately after each treatment
7. Progression to surgery of the finger being assessed during the 18 month follow-up
8. Assessment of the injection site for adverse events by observation at each research visit

Completion date
30/06/2021

Eligibility

Key inclusion criteria
Current participant inclusion criteria (as of 14/02/2018):
Part 1:
1. Aged 18 years or above
2. Participant is willing and able to give informed consent for participation in the study
3. Diagnosed with Dupuytren's disease affecting the fingers resulting in flexion deformities of greater than 30° at the metacarpophalangeal joint and or the proximal interphalangeal joint with impaired hand function and awaiting surgery
4. The Dupuytren's disease nodule to be treated must be distinct and identifiable
5. Female participants of child bearing potential, and male participants whose partner is of child bearing potential, must be willing to ensure that they or their partner use effective contraception throughout the treatment period and for 5 months following the last research injection. Acceptable methods of contraception include: a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods), injectables, the combined oral contraceptive pill (at a stable dose for at least 3 months before entering the study), an intrauterine device, vasectomised partner, or true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant).
6. Participant results from safety screening tests within normal ranges within 8 weeks of enrolment, with the exception that an earlier clear CXR result may be used where this is in accordance with the time frames of local standard procedures for anti-TNF screening.
7. Able (in the Investigators opinion) and willing to comply with all study requirement

8. Willing to allow his or her general practitioner to be notified of participation in the study
9. Sufficient language fluency to ensure informed consent is obtained and to complete the questionnaires pertaining to hand function

Part 2:
1. Aged 18 years or above
2. Participant is willing and able to give informed consent for participation in the study
3. Patients with early Dupuytren's disease nodules who also show progression of the disease in the previous 6 months with flexion deformities of their fingers of less than 30° at the metacarpophalangeal and/or at the proximal interphalangeal joint, i.e. total flexion deformity of up to 60°
4. The Dupuytren's disease nodule to be treated must be distinct and identifiable.
5. Female participants of child bearing potential, and male participants whose partner is of child bearing potential, must be willing to ensure that they or their partner use effective contraception throughout the treatment period and for 5 months following the last research injection. Acceptable methods of contraception include: a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods), injectables, the combined oral contraceptive pill (at a stable dose for at least 3 months before entering the study), an intrauterine device, vasectomised partner, or true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant).
6. Participant results from safety screening tests within normal ranges within 12 weeks of enrolment, with the exception that an earlier clear CXR result may be used where this is in accordance with the time frames of local standard procedures for anti-TNF screening.
7. Able (in the Investigators opinion) and willing to comply with all study requirement
8. Willing to allow his or her general practitioner to be notified of participation in the study
9. Sufficient language fluency to ensure informed consent is obtained and to complete the questionnaires pertaining to hand function

Previous participant Inclusion Criteria:
Part 1:
1. Aged 18 years or above
2. Participant is willing and able to give informed consent for participation in the study
3. Diagnosed with Dupuytren's disease affecting the fingers resulting in flexion deformities of greater than 30° at the metacarpophalangeal joint and or the proximal interphalangeal joint with impaired hand function and awaiting surgery
4. The Dupuytren's disease nodule to be treated must be distinct and identifiable
5. Female participants of child bearing potential, and male participants whose partner is of child bearing potential, must be willing to ensure that they or their partner use effective contraception throughout the treatment period and for 5 months following the last research injection. Acceptable methods of contraception include: a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods), injectables, the combined oral contraceptive pill (at a stable dose for at least 3 months before entering the study), an intrauterine device, vasectomised partner, or true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant).
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6. Participant results from safety screening tests within normal ranges within 8 weeks of enrolment, with the exception that an earlier clear CXR result may be used where this is in accordance with the time frames of local standard procedures for anti-TNF screening.
7. Able (in the Investigators opinion) and willing to comply with all study requirement
8. Willing to allow his or her general practitioner to be notified of participation in the study
9. Sufficient language fluency to ensure informed consent is obtained and to complete the questionnaires pertaining to hand function

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
181

Key exclusion criteria
Current participant exclusion criteria (as of 03/08/2018):
Part 1:
1. Participant has previously had fasciectomy, dermofasciectomy, needle fasciotomy, collagenase injection, steroid injection or radiotherapy to treat Dupuytren's disease in the digit concerned
2. Female participant who is pregnant, lactating or planning pregnancy during the course of the study and for 5 months following last injection
3. Male participant who is planning a pregnancy during the course of the study and for 5 months following last injection

4. Significant renal or hepatic impairment
6. Scheduled elective surgery or other procedures requiring general anaesthesia during the study other than the scheduled Dupuytren's surgery
7. Participant who has ever been diagnosed with cancer, is terminally ill or is inappropriate for placebo medication
8. Systemic inflammatory disorder such as rheumatoid arthritis or inflammatory bowel disease
9. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study
10. Participated in another research study involving an investigational medicinal product in the past 12 weeks
11. Known allergy to any anti-TNF agent
12. Have HIV or hepatitis B or C
13. Known to have an infection or history of repeated infections
14. History of Tuberculosis (TB)
15. Have Multiple Sclerosis (MS) or other demyelinating disease
16. History of local injection site reactions
17. Needle phobia
18. Have moderate or severe heart failure
19. Being treated with coumarin anticoagulants, such as warfarin
20. Have known lung fibrosis (thickening of lung tissue)
21. Being treated with concomitant biologic DMARDS
22. Have received a live vaccine within the previous 4 weeks. Participants may receive concurrent vaccinations but must avoid the use of live vaccines for 12 weeks after their last injection.
23. Have received parenteral steroid within the previous 6 weeks
24. Participants with epilepsy or a known allergy to tetracaine may take part in the study but will not receive Ametop gel as a local anaesthetic. Participants with a known allergy to lidocaine or prilocaine will not receive lidocaine/prilocaine cream/EMLA cream as a local anaesthetic.

Part 2:
1. Participant has previously had fasciectomy, dermofasciectomy, needle fasciotomy, collagenase injection to the digit to be treated or steroid injection to treat Dupuytren's disease in the hand concerned
2. Female participant who is pregnant, lactating or planning pregnancy during the course of the study and for 5 months following last injection
3. Male participant who is planning a pregnancy during the course of the study and for 5 months following last injection
4. Significant renal or hepatic impairment
5. Scheduled elective surgery or other procedures requiring general anaesthesia during the study
6. Participant who has ever been diagnosed with cancer, is terminally ill or is inappropriate for placebo medication
7. Systemic inflammatory disorder such as RA or inflammatory bowel disease
8. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study
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20. Being treated with concomitant biologic DMARDS
21.Have received a live vaccine within the previous 4 weeks. Patients Participants may receive concurrent vaccinations but must avoid the use of live vaccines for 12 weeks after their last injection
22. Patients at risk of Hepatitis B infection

Previous participant exclusion criteria:
Part 1:
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3. Male participant who is planning a pregnancy during the course of the study and for 5 months following last injection
4. Significant renal or hepatic impairment
6. Scheduled elective surgery or other procedures requiring general anaesthesia during the study other than the scheduled Dupuytren's surgery
7. Participant who has ever been diagnosed with cancer, is terminally ill or is inappropriate for placebo medication
8. Systemic inflammatory disorder such as rheumatoid arthritis or inflammatory bowel disease
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12. Have HIV or hepatitis B or C
13. Known to have an infection or history of repeated infections
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15. Have Multiple Sclerosis (MS) or other demyelinating disease
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19. Being treated with coumarin anticoagulants, such as warfarin
20. Have known lung fibrosis (thickening of lung tissue)
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22. Have received a live vaccine within the previous 4 weeks. Participants may receive concurrent vaccinations but must avoid the use of live vaccines for 12 weeks after their last injection.
23. Have received parenteral steroid within the previous 6 weeks
24. Participants with epilepsy or a known allergy to tetracaine may take part in the study but will not receive Ametop gel as a local anaesthetic. Participants with a known allergy to lidocaine or prilocaine will not receive lidocaine/prilocaine cream/EMLA cream as a local anaesthetic.

Part 2:
1. Participant has previously had fasciectomy, dermofasciectomy, needle fasciotomy, collagenase injection or steroid injection to treat Dupuytren's disease in the hand concerned
2. Female participant who is pregnant, lactating or planning pregnancy during the course of the

study and for 5 months following last injection
3. Male participant who is planning a pregnancy during the course of the study and for 5 months following last injection
4. Significant renal or hepatic impairment
5. Scheduled elective surgery or other procedures requiring general anaesthesia during the study
6. Participant who has ever been diagnosed with cancer, is terminally ill or is inappropriate for placebo medication
7. Systemic inflammatory disorder such as RA or inflammatory bowel disease
8. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study
9. Participated in another research study involving an investigational medicinal product in the past 12 weeks
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23. Patients at risk of Hepatitis B infection
24. Have received parenteral steroid within the previous 6 weeks

Date of first enrolment
20/10/2015

Date of final enrolment
31/12/2018

Locations

Countries of recruitment
United Kingdom

England

Scotland

Netherlands

Study participating centre
St John's Hospital
Howden Road West
Howden
Livingston
United Kingdom
EH54 6PP

Study participating centre
Nuffield Orthopaedic Centre
Oxford University Hospitals NHS Foundation Trust
Windmill Road
Headington
Oxford
United Kingdom
OX3 7HE

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
United Kingdom
EH4 2XU

Study participating centre
University Medical Center Groningen
Hanzeplein 1
9713 GZ Groningen
PO Box 30.001
Groningen
Netherlands
9700 RB

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Not defined

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Department of Health (United Kingdom)

Funder Name
180 Therapeutics

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Jagdeep Nanchahal (jagdeep.nanchahal@kennedy.ox.ac.uk).
Type of data: participant study data
When the data will become available and for how long: June 2020
By what access criteria data will be shared, including with whom: All requests for sharing anonymised patient-level data will be considered by the chief investigator in conjunction with the management group as appropriate and in accordance with the data sharing policies of the sponsor and the funders.
For what types of analyses and by what mechanism: It is not possible to list the types of analyses. Each request will be considered on its own merit
Whether consent from participants was obtained: Yes
Comments on data anonymization: All data was anonymised during the trial with participants being given a trial ID number.
Any ethical or legal restrictions: none

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	part one results	01/07/2018		Yes	No
Results article	Cost-effectiveness	29/04/2022	03/05/2022	Yes	No
Results article		15/11/2022	03/01/2024	Yes	No
Protocol article		16/11/2017	11/08/2022	Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes