

BETTER-B: Better Treatments for Refractory Breathlessness

Submission date 11/11/2019	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 19/11/2019	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 18/08/2025	Condition category Respiratory	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

Current plain English summary as of 29/09/2020:

Background and study aims

Breathlessness which affects people with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) even when they are receiving treatment is called refractory breathlessness. It can be frightening and cause: distress, disability, anxiety and social isolation. We don't know which treatment is best for refractory breathlessness and this study aims to test whether a widely used drug called Mirtazapine can help to reduce the symptoms of refractory breathlessness when compared to a dummy drug or 'placebo'.

Caregiver part of the study

We are also finding out how refractory breathlessness affects caregivers such as close family members. Through questionnaires, we are collecting information about the caregiver's views of the refractory breathlessness that is affecting the person that they are caring for and how providing care affects the caregiver.

Who can participate?

Patients who are at least 18 years old, have COPD and/or ILD, and have severe breathlessness as assessed by your doctor

What does the study involve?

Main Study

The study team want to recruit 324 participants from 5 countries. The participants taking part are put into 1 of 2 groups at random. Neither you nor your doctor will be able to decide or know which group you are in.

One group will receive the drug mirtazapine which is being tested as a treatment and the other group will receive a dummy drug called the placebo. The drugs will be given as tablets which will be swallowed as one tablet per day for 56 days. Several study visits will take place, some will be face to face at hospital and some will be over the telephone. If your breathlessness does not get better after 14 days, you can take two tablets per day. If your breathlessness still does not get better after 28 days, you can take up to three tablets per day. During your study visits, you will also be asked to complete questionnaires about your personal experience of breathlessness and how it affects your quality of life.

Caregiver part of the study

Caregivers taking part in the caregiver part of the study will be asked to complete quality of life questionnaire booklets about their view of how breathlessness is affecting the person that they are caring for and how giving care affects themselves. This study will take place over several meetings, some will be face to face and some will be over the telephone.

What are the possible benefits and risks of participating?

We do not know the best way to treat refractory breathlessness and it is hoped that by taking part in this study you will help to find out whether Mirtazapine is an effective treatment and whether it helps to improve quality of life for those with COPD or ILD.

Taking part will involve commitment of your time to attend hospital visits or join in phone calls with the study team and to complete the forms and questionnaires. The mirtazapine treatment used as part of the study is widely used in the treatment of depression and it has fewer unwanted side effects when compared to other drugs used for the same purpose. It does still have side effects, the most common include:

reduced anxiety, increased appetite, reduced nausea, pain relief, weight gain, drowsiness, dizziness, fatigue, and dry mouth

Where is the study run from?

The study is being run by Co-Sponsors King's College London and University College Dublin in collaboration with Leeds Clinical Trials Research Unit (CTRU). The total recruitment target is 324. There are 12 sites in total with three UK partners taking part, University of Nottingham, Hull York Medical School, and King's College London, with the latter being the lead site. Internationally, we have 9 sites running in Ireland, Italy, Germany and Poland.

When is the study starting and how long is it expected to run for?

January 2019 to June 2023

Who is funding the study?

The study is funded by the EU through the Horizon 2020 programme.

Who is the main contact?

Irene Higginson (Scientific)
Principal Investigator
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Emma Batman
Clinical Trial Co-ordinator
ctru-betterb@leeds.ac.uk

Adejoke Oluyase (Public)
Trial manager
Better-b@kcl.ac.uk

Previous plain English summary as of 15/04/2020:

Background and study aims

Breathlessness which affects people with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) even when they are receiving treatment is called refractory breathlessness. It can be frightening and cause: distress, disability, anxiety and social isolation.

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When is the study starting and how long is it expected to run for?

The study will aim to begin recruitment in September 2020 for 18 months until March 2022

Who is funding the study?

The study is funded by the EU through the Horizon 2020 programme.

Who is the main contact?

Claire Dimbleby

Senior Trial Manager

ctru-betterb@leeds.ac.uk

Previous plain English summary:

Background and study aims

Breathlessness which affects people with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) even when they are receiving treatment is called refractory breathlessness. It can be frightening and cause: Distress, disability, anxiety, social isolation. We don't know which treatment is best for refractory breathlessness and this study aims to test whether a widely used drug called Mirtazapine can help to reduce the symptoms of refractory breathlessness when compared to a dummy drug or 'placebo'.

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When is the study starting and how long is it expected to run for?

The study will aim to begin recruitment in March 2020 for 24 months until March 2022

Who is funding the study?

The study is funded by the EU through the Horizon 2020 programme.

Who is the main contact?

Claire Dimbleby
Senior Trial Manager
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Study website

<https://betterbreathe.eu/>

Contact information

Type(s)

Scientific

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Additional identifiers

EudraCT/CTIS number

2019-002001-21

IRAS number

264831

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

Version 8.0; IRAS 264831

Study information

Scientific Title

An international, multicentre, randomised controlled pragmatic trial of mirtazapine to alleviate breathlessness in palliative and end of life care

Acronym

BETTER-B

Study objectives

The aim of the study is to assess the effectiveness and cost-effectiveness of mirtazapine for the reduction of patient-reported chronic or refractory breathlessness and quality of life in patients with COPD or ILD and at end of life, and on the caregiver burden and experience of their caregivers and close family members.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 13/05/2020, London Bridge Research Ethics Committee (Skipton House, 80 London Road, London, SE1 6LH, UK; londonbridge.rec@hra.nhs.uk), REC ref: 20/LO/0369

Study design

International multicentre phase III double-blind randomized placebo-controlled trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied

Refractory breathlessness in patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), including chronic fibrotic lung disease following SARS-CoV-2 infection

Interventions

Current interventions as of 15/04/2020:

Participants with refractory breathlessness and COPD/ILD will be randomised on a 1:1 basis to receive either oral Mirtazapine (starting dose 15 mg per day) or placebo (one tablet per day), using minimisation incorporating a random element. Minimisation factors used will be: disease (COPD, ILD); HADS anxiety and depression subscale scores; receipt of opioids and recruiting site.

Participants will be eligible for dose escalation to 30 mg per day at Day 14 (or two tablets of placebo) and to 45 mg per day at Day 28 (or three tablets of placebo) of the treatment period. Treatment will continue until day 56.

Participant follow-up assessments will take place at days 7, 14, 28 and 56 post start of treatment. Participants will be followed up 7 days after completing trial treatment (including dose tapering) to assess safety and toxicity of treatment.

At the end of the day 56 post start of treatment, and after dose tapering, if the participant wishes to take mirtazapine off trial, they should discuss this further with their GP.

Once the trial is open label, participants may request off trial mirtazapine from their family doctor/clinical team if they wish to do so irrespective of study arm (and maintaining blinding).

Participants will be followed-up at 180 days post start of treatment via phone to complete the final participant reported questionnaires.

Participants will be randomised using a central automated 24-hour telephone/internet service based at the Leeds CTRU.

Previous interventions:

Participants with refractory breathlessness and COPD/ILD will be randomised on a 1:1 basis to receive either oral Mirtazapine (starting dose 15 mg per day) or placebo (one tablet per day), using minimisation incorporating a random element. Minimisation factors used will be: disease (COPD, ILD); HADS anxiety and depression subscale scores; receipt of opioids and recruiting site.

Participants will be eligible for dose escalation to 30 mg per day at Day 14 (or two tablets of placebo) and to 45 mg per day at Day 28 (or three tablets of placebo) of the treatment period. Treatment will continue until day 56.

Participant follow-up assessments will take place at days 7, 14, 28 and 56 post start of treatment. Participants will be followed up 7 days after completing trial treatment (including dose tapering) to assess safety and toxicity of treatment.

At the end of the day 56 post start of treatment, and after dose tapering, the trial becomes open label.

Once the trial is open label, participants may request off trial mirtazapine from their family doctor/clinical team if they wish to do so irrespective of study arm (and maintaining blinding).

Participants will be followed-up at 180 days post start of treatment via phone to complete the final participant reported questionnaires.

Participants will be randomised using a central automated 24-hour telephone/internet service based at the Leeds CTRU.

Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Oral Mirtazapine

Primary outcome measure

Self-reported worst breathlessness over the past 24 hours measured at day 56 post start of treatment using a numerical rating scale (NRS, 0=no breathlessness to 10=worst possible breathlessness)

Secondary outcome measures

Current secondary outcome measures as of 15/04/2020:

1. Worst breathlessness over the last 24 hours as assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 7, 14, 28 and 180 post start of treatment
2. Average breathlessness over the last 24 hours assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 7, 14, 28, 56 and 180 post start of treatment
3. Number and duration of episodes of breathlessness over the last 24 hours
4. Physical and emotional aspects of breathlessness (Dyspnoea, fatigue, emotional function, mastery) as assessed by the Chronic Respiratory Questionnaire (CRQ) at days 14, 28, 56 and 180 post start of treatment
5. Physical symptoms as assessed by the Integrated Palliative care Outcome Scale (IPOS) at days 14, 28, 56 and 180 post start of treatment
6. Quality of Life (QoL) as assessed by the EQ-5D-5L and associated VAS at days 14, 28, 56, 180 post start of treatment and Australia-modified Karnofsky Performance Scale (AKPS) at days 14, 28, 56 and 180 post start of treatment
7. Anxiety and depression as assessed by the Hospital Anxiety and Depression Scale (HADS) at days 28, 56, and 180 post start of treatment
8. Perceived self-efficacy as measured by the Generalized Self-Efficacy Scale (GSES) at day 56 post start of treatment
9. The consumption of opioids as measured by opioid medication usage at days 7, 14, 28, 56 and 180 post start of treatment
10. Healthcare services received, including out of hours care, number of emergency hospital attendances and admissions within 28 and 56 days post start of treatment and in the 3 month period prior to day 180 post start of treatment as measured by the Client Services Receipt Inventory (CSRI)
11. Safety as assessed by the occurrence of:
 - 11.1. SAEs, SARs and SUSARs coded according to mild, moderate, or severe as reported at days 7, 14, 28 and 56 post start of treatment
 - 11.2. Deaths by day 56 and day 180 post start of treatment
12. Toxicity as assessed by adverse reactions (ARs) coded according to mild, moderate, or severe as reported at days 7, 14, 28 and 56 post start of treatment
13. Tolerability as assessed by the proportion of patients not withdrawing due to adverse reactions
14. Baseline demographics and characteristics will be measured to enable prognostic evaluation of those factors most associated with benefit from mirtazapine (benefit as measured by worst breathlessness over the last 24 hours at day 56 post start of treatment. Specifically assessing:
 - 14.1. Age
 - 14.2. Gender
 - 14.3. Functional status (as measured by actual functioning using AKPS, mobility using EQ-5D-5L,

and 'poor mobility' using IPOS), aetiology (COPD /ILD)

14.4. Baseline intensity of breathlessness (as measured by worst breathlessness over the last 24 hours at baseline)

14.5. Anxiety and depression (as measured by HADS)

14.6. Concomitant opioid administration

15. Formal and informal care use over the previous period as measured by the Client Services Receipt Inventory (CSRI) at days 28, 56, and 180 post start of treatment, to examine hours of care and (using country specific unit costs) costs of services

16. Acceptability of the offered treatment as assessed by the recruitment conversion rate, the number of people withdrawing from treatment, and the number of participants who request mirtazapine from their doctor/clinician after 56 days post start of treatment

17. Treatment compliance as measured by the:

17.1. Proportion and type of dropouts over 56 days post start of treatment

17.2. Proportion of tablets taken over 56 days post start of treatment

17.3. Proportion of participants who escalate dose at days 14 and 28 post start of treatment

17.4. Off trial treatment compliance to 180 days post start of treatment

18. Caregiver's perceived impact on the participant and themselves as measured by:

18.1. Worst and average rating of the participant's breathlessness over the last 24 hours as assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 28, 56, and 180 post start of treatment;

18.2. Caregiver assessment of the participant's number and duration of episodes of breathlessness over the last 24 hours;

18.3. Informal care hours as measured by the Client Services Receipt Inventory (CSRI) at days 28, 56, and 180 post start of treatment;

18.4. Caregiver self-reported burden as measured by the Zarit Burden inventory at days 28, 56, and 180 post start of treatment;

18.5. Caregiver self-reported experiences of caregiving as measured by the Positive Aspects of Caregiving Scale (PAC) at days 28, 56, and 180 post start of treatment;

18.6. Caregiver perspectives on participants' situation as measured by the Integrated Palliative care outcome scale (IPOS) at days 28, 56, and 180 post start of treatment.

18.7. Caregiver overall health and wellbeing as measured by EQ-5D-5L and associated VAS at days 28, 56, and 180 post start of treatment

Previous secondary outcome measures:

1. Worst breathlessness over the last 24 hours as assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 7, 14, 28 and 180 post start of treatment

2. Average breathlessness over the last 24 hours assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 7, 14, 28, 56 and 180 post start of treatment

3. Number and duration of episodes of breathlessness over the last 24 hours

4. Physical and emotional aspects of breathlessness (Dyspnoea, fatigue, emotional function, mastery) as assessed by the Chronic Respiratory Questionnaire (CRQ) at days 14, 28, 56 and 180 post start of treatment

5. Physical symptoms as assessed by the Integrated Palliative care Outcome Scale (IPOS) at days 14, 28, 56 and 180 post start of treatment

6. Quality of Life (QoL) as assessed by the EQ-5D-5L and associated VAS at days 14, 28, 56, 180 post start of treatment and Australia-modified Karnofsky Performance Scale (AKPS) at days 14, 28, 56 and 180 post start of treatment

7. Anxiety and depression as assessed by the Hospital Anxiety and Depression Scale (HADS) at days 28 and 56 post start of treatment

8. Perceived self-efficacy as measured by the Generalized Self-Efficacy Scale (GSES) at day 56 post start of treatment
9. The consumption of opioids as measured by opioid medication usage at days 7, 14, 28, 56 and 180 post start of treatment
10. Healthcare services received, including out of hours care, number of emergency hospital attendances and admissions within 28, 56 and 180 days post start of treatment
11. Safety as assessed by the occurrence of:
 - 11.1. SAEs, SARs and SUSARs coded according to the Common Terminology Criteria for Adverse Events (CTCAE) categorisation (v5) as reported at days 7, 14, 28 and 56 post start of treatment
 - 11.2. Deaths by day 56 and day 180 post start of treatment
12. Toxicity as assessed by adverse reactions (ARs) coded according to the Common Terminology Criteria for Adverse Events (CTCAE) categorisation (v5) as reported at days 7, 14, 28 and 56 post start of treatment
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 - 14.2. Gender
 - 14.3. Functional status (as measured by actual functioning using AKPS, mobility using EQ-5D-5L, and 'poor mobility' using IPOS), aetiology (COPD / ILD)
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 - 14.5. Anxiety and depression (as measured by HADS)
 - 14.6. Concomitant opioid administration
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16. Acceptability of the offered treatment as assessed by the recruitment conversion rate, the number of people withdrawing from treatment, and the number of participants who request mirtazapine from their doctor/clinician after 56 days post start of treatment
17. Treatment compliance as measured by the:
 - 17.1. Proportion and type of dropouts over 56 days post start of treatment
 - 17.2. Proportion of tablets taken over 56 days post start of treatment
 - 17.3. Proportion of participants who escalate dose at days 14 and 28 post start of treatment
 - 17.4. Open label treatment compliance to 180 days post start of treatment
18. Caregiver's perceived impact on the participant as measured by:
 - 18.1. Worst and average rating of the participant's breathlessness over the last 24 hours as assessed by NRS (0=no breathlessness to 10=worst possible breathlessness) at days 28, 56 and 180 post start of treatment;
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 - 18.6. Caregiver perspectives on participants' situation as measured by the Integrated Palliative care outcome scale (IPOS) at days 28, 56 and 180 post start of treatment.
 - 18.7. Caregiver overall health and wellbeing as measured by EQ-5D-5L and associated VAS at

days 28, 56 and 180 post start of treatment

Overall study start date

15/01/2019

Completion date

30/06/2023

Eligibility

Key inclusion criteria

Current inclusion criteria as of 29/09/2020:

1. Aged ≥ 18 years old
2. Diagnosed with:
 - 2.1. Chronic obstructive pulmonary disease (COPD), and/or
 - 2.2. Interstitial lung disease (ILD), including chronic fibrotic lung disease following SARS-CoV-2 infection
3. Breathlessness severity: Modified MRC breathlessness scale of:
 - 3.1. Grade 3 (I stop for breath after walking about 100 yards or after a few minutes on level ground) or
 - 3.2. Grade 4 (I am too breathless to leave the house or I am breathless when dressing or undressing)
4. On optimal treatment of the underlying condition in the opinion of the identifying clinician (see section 0 of protocol for guidance)
5. Management of the underlying condition unchanged for the previous 2 weeks
6. Reversible causes of breathlessness optimally treated in the opinion of the identifying clinician
7. If female, must be (as documented in patient notes):
 - 7.1. Postmenopausal (no menses for 12 months without an alternative medical cause), or
 - 7.2. Surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy), or
 - 7.3. Using acceptable contraception (which must be continued for 7 days after the last dose of IMP)
8. Able to complete questionnaires and trial assessments
9. Able to provide written informed consent

Previous inclusion criteria:

1. Aged ≥ 18 years old
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Participant type(s)

Mixed

Age group

Adult

Lower age limit

18 Years

Sex

Not Specified

Target number of participants

324

Key exclusion criteria

Current exclusion criteria as of 29/09/2020:

1. Existing antidepressant use, or other serotonergic active substances (e.g. linezolid, St John's wort)
2. Known contraindication to mirtazapine
3. Hypersensitivity to the active substance or to any of the components of mirtazapine or placebo (e.g. lactose intolerance)
4. Australia modified Karnofsky Performance Scale ≤ 40
5. Pregnant or breast-feeding women. For women of childbearing potential (those not post-menopausal or surgically sterile) this must be confirmed by a pregnancy test (urine) within 7 days prior to randomisation
6. Patients with acute cardiac events within 3 months prior to randomisation (e.g. myocardial infarction, unstable angina pectoris, or significant cardiac conduction disturbance) in the opinion of the identifying clinician
7. Patients with jaundice or known hepatic impairment in the opinion of the identifying clinician (e.g. bilirubin >25 micromol/L, and AST and ALT >2 times upper limit of normal)
8. Patients with known renal impairment in the opinion of the identifying clinician (e.g. creatinine >132 micromol/L and eGFR <30 mL/min/1.73m²)
9. Uncontrolled blood pressure in the opinion of the identifying clinician
10. Uncontrolled diabetes mellitus in the opinion of the identifying clinician
11. Uncontrolled seizures, epilepsy or organic brain syndrome in the opinion of the identifying clinician
12. Severe depression or suicidal thoughts in the opinion of the identifying clinician
13. History of psychotic illness (schizophrenia, or other psychotic disturbances) in the opinion of the identifying clinician
14. Bipolar disorder, or a history of mania or hypomania in the opinion of the identifying clinician

15. Currently enrolled in another interventional trial
16. Patients with known congenital QT prolongation or family history for QT prolongation
17. Use of medicines that cause QT prolongation such as macrolides and typical antipsychotics (unless required in low-dose to relieve nausea, e.g. haloperidol $\leq 5\text{mg}/24\text{h}$, levomepromazine $\leq 25\text{mg}/24\text{h}$)
18. Patients with a known history of suicide-related events

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8. Patients with known renal impairment in the opinion of the identifying clinician (e.g. creatinine $>132\text{micromol/L}$ and eGFR $<30\text{mL/min}/1.73\text{m}^2$)
9. Uncontrolled blood pressure in the opinion of the identifying clinician
10. Uncontrolled diabetes mellitus in the opinion of the identifying clinician
11. Uncontrolled seizures, epilepsy or organic brain syndrome in the opinion of the identifying clinician
12. Severe depression or suicidal thoughts in the opinion of the identifying clinician
13. History of psychotic illness (schizophrenia, or other psychotic disturbances) in the opinion of the identifying clinician
14. Bipolar disorder, or a history of mania or hypomania in the opinion of the identifying clinician
15. Currently enrolled in another interventional trial

Date of first enrolment

01/02/2021

Date of final enrolment

31/12/2022

Locations

Countries of recruitment

England

Germany

Ireland

Italy

Poland

United Kingdom

Study participating centre

Kings College Hospital

King's College Hospital NHS Foundation Trust

Denmark Hill

London

United Kingdom

SE5 9RS

Study participating centre

Castle Hill Hospital

Department of Respiratory Medicine

Castle Rd

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Hull

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HU16 5JQ

Study participating centre

Nottingham City Hospital

Nottingham University Hospitals NHS Trust

Hucknall Road

Nottingham

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NG5 1PB

Study participating centre

St. Vincent's University Hospital

Clinical Research Centre

Elm Park

Dublin

Ireland

D04 T6F4

Study participating centre

**Arcispedale Santa Maria Nuova, Presidio Ospedaliero Provinciale "Santa Maria Nuova" Azienda
Unità Sanitaria Locale-IRCCS di Reggio Emilia**
Viale Risorgimento 80
Reggio Emilia
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42123

Study participating centre
Ospedale San Sebastiano di Correggio, Presidio Ospedaliero Provinciale "Santa Maria Nuova"
Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia
Via Circondaria 29
Reggio Emilia
Italy
42015

Study participating centre
Fondazione Policlinico Universitario "A. GEMELLI" IRCCS
Largo Agostino Gemelli 8
Rome
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00168

Study participating centre
Klinikum der Universitaet zu Koeln
Kerpener Strasse 62
Koeln
Germany
50937

Study participating centre
Krankenhaus Bethanien GGMBH
Klinik für Pneumologie und Allergologie, Zentrum für Schlaf- und Beatmungsmedizin
Aufderhöher Straße 169-175
Solingen
Germany
42699

Study participating centre
Klinikum der Universität München
Georgenstraße 5
Munchen

Germany
80799

Study participating centre

Uniwersyteckie Centrum Kliniczne ul.
Smoluchowskiego 17
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Study participating centre

Mater Misericordiae University Hospital
Eccles Street
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Sponsor information

Organisation

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Sponsor type

University/education

Website

<http://www.kcl.ac.uk/index.aspx>

ROR

<https://ror.org/0220mzb33>

Organisation

University College Dublin

Sponsor details

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Dublin
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+353 1716 4593
rabia.hussain@ucd.ie

Sponsor type

University/education

Website

<http://www.ucd.ie/>

ROR

<https://ror.org/05m7pjf47>

Funder(s)

Funder type

Government

Funder Name

European Union Horizon 2020 Research and Innovation Programme (Grant No. 825319)

Results and Publications

Publication and dissemination plan

Planned publication of study protocol and main trial analysis in an open access, high-impact, peer reviewed journal approximately in 2023.

Intention to publish date

30/06/2024

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
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HRA research summary		28/06/2023	No	No
Results article	06/09/2024	16/09/2024	Yes	No
Results article	14/08/2025	18/08/2025	Yes	No