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Developing and testing a new treatment for Posttraumatic Stress Disorder (PTSD): Retrieval dependent Nitrous Oxide Therapy (R-NOT)

Submission date
27/08/2025

Recruitment status
Recruiting

Registration date
01/12/2025

Overall study status
Ongoing

Last Edited
21/01/2026

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Posttraumatic stress disorder (PTSD) is a condition that can develop after experiencing or witnessing a traumatic event. Symptoms include distressing memories, avoidance of event reminders, and increased tension. While several effective treatments exist, they can take weeks to show results and may not work for everyone.

This study tests a new treatment targeting one of PTSDs most troubling symptoms: intrusive memories (IM) — unwanted, distressing recollections of traumatic events. The treatment being tested is called Retrieval-dependent Nitrous Oxide Therapy (R-NOT). It involves recalling an intrusive memory followed by inhaling a 50/50 mix of nitrous oxide and oxygen (also known as “gas and air”) for an hour. Is it thought that this gas can help weaken the emotional power of traumatic memories.

Who can participate?
Patients with PTSD who are referred from a collaborating NHS Talking Therapies Services (NHS-TTSs)

What does the study involve?
This study tests the effects of one treatment session of R-NOT. Participants will be recruited only from the NHS NHS-TTSs in London. The study aims to find out if R-NOT can be developed in a way that is easy to administer by trained professionals. The study also aims to test whether people with PTSD find R-NOT an acceptable and helpful treatment.

After a screening interview, participants will take part for approximately 14 days, during which they will be asked to complete some questionnaires and interviews about the treatment. There are two Research Sites that all participants will attend during their participation:

• Clinical Psychopharmacology Unit (CPU) at University College London (UCL)
• Clinical Research Facility (CRF) at University College London Hospital (UCLH)

Participants will first complete a screening call with the R-NOT study team to see if it is appropriate and safe for them to take part. They will then complete a Baseline visit at the CPU at UCL with a trained R-NOT research team member and then attend their Treatment visit at UCLH. The treatment session will be carried out by a trained health care professional. After that, there will be a Follow-up call with a trained R-NOT research team member. To test how the treatment affects your memories of the traumatic event, participants will be asked to make a note of any unpleasant memories about the event using an online diary and smartwatch for a week before and after the Treatment visit.

The results from the study will be used to conduct bigger studies with more people. If those studies are successful, R-NOT could provide an extra treatment option to patients in the NHS that may produce beneficial effects more quickly than existing treatments for PTSD.

What are the possible benefits and risks of participating?
Although the intervention will not guarantee an improvement in your PTSD symptoms, if R-NOT works as expected, participants might find that their PTSD symptoms improve. However, it is possible that they will not experience any benefits.

As with all research studies, there are also risks of taking part. However, because gas and air (50% nitrous oxide) is a very safe drug, the side effects mentioned here are generally mild and get better after you stop breathing the gas. The memory retrieval procedure used is also brief, and should not be more risky than ordinary everyday occurrences in your life. However, zero risk to participants cannot guaranteed.

Mild and short-lived side effects include unusual feelings of ‘floating’ or being outside of your body, or having unusual thoughts and feelings, dizziness and sleepiness. Some people also feel sick and may vomit while inhaling gas and air (50% nitrous oxide), so participants will be asked to avoid food and drink (except water) before the treatment visit. Research team members are trained to help participants with any short-lived distress while you are inhaling the gas. Serious side effects of gas and air (50% nitrous oxide) are extremely unlikely in the current study, because participants are only receiving a small amount of the gas.

Where is the study run from?
University College London (UCL), UK.

When is the study starting and how long is it expected to run for?
The study is starting in early 2026 and is going to run for approximately three months.

Who is funding the study?
Medical Research Council, UK.

Who is the main contact?
The R-NOT study team, r-not@ucl.ac.uk

Contact information

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Public

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Additional identifiers

Integrated Research Application System (IRAS)
1008993

Protocol serial number
178733

Central Portfolio Management System (CPMS)
58899

Study information

Scientific Title
Developing and testing a novel memory-therapeutic treatment for PostTraumatic Stress Disorder (PTSD): Retrieval-dependent Nitrous Oxide Therapy (R-NOT)

Acronym
R-NOT for PTSD

Study objectives
This is an initial external pilot/prototyping study in which we will design and iteratively refine a prototype of the 'unit-of-treatment' of a novel therapy for posttraumatic stress disorder (PTSD). The objective, therefore, is to develop a replicable treatment session (the unit-of-treatment) of Retrieval-dependent Nitrous Oxide Therapy (R-NOT) that is optimised for feasibility, tolerability and acceptability. Through an assessment of side effects, we will determine whether aspects of the session need to be modified to increase tolerability (e.g. by using prophylactic or rescue anti-emetics) and/or reduce participant burden (e.g. to reduce or eliminate the use of a wrist-worn monitor; frequency of assessments). Essential elements of a treatment manual will be developed as part of this study. A mixed methods approach will be used to assess response to treatment and acceptability; analyses will be descriptive. Although primary and secondary 'outcome measures' will be used, these are not intended to assess efficacy. Rather, their inclusion is to preliminarily determine their acceptability and likely sensitivity to change in the subsequent studies of R-NOT.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 12/11/2025, London – Central (3rd Floor, 3 Piccadilly Place, London Road, Manchester, M1 3BN, United Kingdom; +44 (0)207 104 8000; londoncentral.rec@hra.nhs.uk), ref: 25/LO/0693

Primary study design
Interventional

Allocation
N/A: single arm study

Masking
Open (masking not used)

Control
Uncontrolled

Assignment
Single

Purpose
Treatment

Study type(s)

Health condition(s) or problem(s) studied
Posttraumatic stress disorder (PTSD)

Interventions
The single-session R-NOT intervention is comprised of two interactive components: a standardised intrusive memory (IM) retrieval procedure followed by inhalation of a premixture of 50% nitrous oxide + 50% oxygen (for up to 60 minutes).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
50% nitrous oxide premixed with 50% oxygen

Primary outcome(s)
1. Change in PTSD symptom severity measured using the PTSD checklist for DSM-5 (PCL 5-weekly version) at Baseline to Follow-up (day 15)

Key secondary outcome(s))
1. Rapid change in PTSD and depressive symptoms measured using the PCL-5-daily and the Quick Inventory of Depressive Symptomatology (QIDS)-daily at the day before to the day after the treatment visit

2. Changes in intrusive memory (IM) occurrences and characteristics; changes in real-time physiological response to IMs measured using number of IM occurrences vividness, distress, dissociation, nowness (retrospective daily online IMs diary) and real-time occurrences and heart rate and skin conductance response to occurrences (Empatica EmbracePlus Smartwatch) at from 7 days before to 7 days after the Treatment visit

3. Mental health and adaptive functioning measured using QIDS (weekly version), Patient Health Questionnaire-9 (PHQ-9), Generalised Anxiety Disorder-7 scale (GAD-7), WHO Disability Assessment Schedule (WHODAS 2.0), Brief Pittsburgh Sleep Quality Index (B-PSQI) and Posttraumatic Cognitions Inventory (PCI) at baseline to follwo up (day 15)

4. PTSD and depressive symptoms measured using Clinician-Administered PTSD Scale (CAPS-5) and Montgomery-Asberg Depression Rating Scale (MADRS) at screening to follow up (day 15)

Completion date
01/04/2026

Eligibility

Key inclusion criteria
1. Aged 18–65 years
2.Ability to provide informed consent
3. Meeting DSM-5 criteria for PTSD as determined by the CAPS-5
4. Experiencing ≥1 distressing intrusive memories per week

5. Sufficient level of English understanding and expression to allow independent completion of assessment instruments and provide written descriptions of memories
6. Access to the internet and a smartphone or similar device on a daily basis
7. Awaiting psychological treatment for PTSD
8. Female participants of childbearing potential (i.e. are not surgically sterilised or postmenopausal) must be willing to use an effective method of contraception (hormonal or barrier method of birth control) or be abstinent from consent to 48 hours after treatment discontinuation

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Currently engaged in a psychological therapy for PTSD
2. Change in psychotropic medication in last four weeks or planned change during the course of the study
3. Concomitant treatment with ketamine or memantine
4. Recreational use of nitrous oxide more than once in the past 6 months
5. Current alcohol or substance dependence (other than nicotine and caffeine) as suggested by the AUDIT and SDS, and judgement of the team after discussions
6. The diagnostic instrument used to assess depression severity (MADRS) alongside judgement of the team after discussions suggests that depression is the primary diagnosis
7. Current psychosis
8. Active suicide risk
9. Currently participating in another research study or clinical trial related to PTSD, or research that involves a medication
10. Pregnancy or actively attempting to conceive (female participants)
11. Medical contraindications including, but not limited to (at the discretion of the CI/treating clinician):
11.1. Pneumothorax (current or recent)
11.2. Middle ear disease, infection or recent surgery
11.3. Recent cranial surgery or head trauma
11.4. Respiratory disease (COPD, severe asthma, interstitial lung disease)

11.5. Diagnosed chronic vitamin B12 or folate deficiency
11.6. Risk factors associated with chronic vitamin B12 or folate deficiency without vitamin supplementation (coeliac or inflammatory bowel disease; vegan diet)
11.7. Use of medications known to impair B12 absorption (e.g. metformin, H2-receptor antagonists and proton-pump inhibitors)
11.8. Recent (less than 2 weeks) dental work: extractions, implants, sinus lifts
11.9. Neurological conditions (stroke, encephalopathy, Parkinson's, brain tumour, multiple sclerosis, poorly controlled epilepsy, dementia or diagnosed cognitive impairment)

Date of first enrolment
15/01/2026

Date of final enrolment
01/04/2026

Locations

Countries of recruitment
United Kingdom

England

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Study participating centre
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Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Study data will be shared with others in accordance with the local policies, ethical requirements and data protection and sharing regulations. Anonymised study data will be shared with others via the dissemination of publications and presentation of results at relevant conferences. Anonymised study data may also be uploaded and stored in suitable and secure repositories, in line with funder requirements.

IPD sharing plan summary
Stored in non-publicly available repository