Central University Research Ethics Committee (CUREC)

CUREC 3 Protocol and Application Form

Pharmacological Studies in Healthy Volunteers

Only fully signed type-written applications will be accepted, by email

Please complete this Protocol and application form if your study involves the administration of a licensed drug, herbal remedy, or food supplement to healthy volunteers AND is not a clinical trial.

All advisory text is highlighted in yellow and should be deleted before finalising the document.
Should you require any assistance in completing this document, please contact the MS IDREC Secretariat - ethics@medsci.ox.ac.uk.

Section A. Research details

1. Full title of research	An fMRI investigation of the effects of selective histamine-3 receptor antagonism on cognitive and emotional processing in healthy individuals	
2. Short title of research	Pitolisant effects on affect and cognition exploratory study (PEACE Study)	
3. MS IDREC reference	R83940/RE001	
4. Date and version number	Version 1.1, 31st January 2023	
5. Principal Investigator (PI)	Dr Susannah Murphy	
6. PI's training in research ethics and/or research integrity Research integrity training within the past 3 years is compulsory for all University research staff and students. Please enter date of relevant course completion (one of 1a, 1b or 1c must be completed).	**Course Title**	**Date completed**
	1a. Research Integrity Core Course (New researchers & students)	
	1b. Research Integrity Refresher Course (Experienced researchers)	08/12/2021
	1c. Other (please specify title)	
	2. Supplementary Module – Research involving human participants	
	3. Information Security Training	06/07/2022
7. Student name and degree programme (if applicable)	Michael James Colwell, DPhil in Psychiatry	
8. Department/Institute name	Department of Psychiatry	
9. University email address	Susannah.murphy@psych.ox.ac.uk	

10. University telephone number	+44 (0)1865 618313
11. Medically qualified collaborator (Licensed doctor)	Professor Philip Cowen
12. Funding source	The study is funded by a Medical Research Council funding (grant code: HQR01610)
13. Will you submit or have you submitted this research to another ethics committee?	Yes ☐ No ☒
If other relevant approvals for this research are required (e.g. from other universities' ethics committees) please attach them and give more details below:	
14. State any conflicts of interest and explain how these will be addressed	None
15. Confidentiality Statement	This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Oxford, the Investigator Team and members of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC), unless authorised to do so.

Section B. Researchers

1. Researcher title and name	Prof Catherine Harmer	
2. Department / Institute name	Department of Psychiatry, University of Oxford	
3. Role in research	Professor of Cognitive Neuroscience; Research Group Lead (PERL)	
4. Training in research ethics and/or research integrity Research integrity training within the past 3 years is compulsory for all University research staff and students. Please enter date of relevant course completion (one of 1a, 1b or 1c must be completed).	**Course Title**	**Date completed**
	1a. Research Integrity Core Course (New researchers & students)	
	1b. Research Integrity Refresher Course (Experienced researchers)	
	1c. Other (e.g. GCP - please specify title) GCP	December 2020
	2. Supplementary Module – Research involving human participants	
	3. Information Security Training	

1. Researcher title and name	Michael James Colwell	
2. Department / Institute name	Department of Psychiatry	
3. Role in research	DPhil Student	
4. Training in research ethics and/or research integrity Research integrity training within the past 3 years is compulsory for all University research staff and students. Please enter date of relevant course completion (one of 1a, 1b or 1c must be completed).	**Course Title**	**Date completed**
	1a. Research Integrity Core Course (New researchers & students)	28/05/2022
	1b. Research Integrity Refresher Course (Experienced researchers)	N/A
	1c. Other (e.g. GCP - please specify title)	Good Research Practice (MRC) - 07/12/2021 Research, GDPR and confidentiality (MRC) - 28/07/2019 Human Tissue Act training (MRC) - 23/05/2022
	2. Supplementary Module – Research involving human participants	07/12/2020
	3. Information Security Training	23/05/2022
1. Researcher title and name	Dr. Marieke Martens	
2. Department / Institute name	Department of Psychiatry	
3. Role in research	Post-doctoral researcher, neuroimaging support	
4. Training in research ethics and/or research integrity Research integrity training within the past 3 years is compulsory for all University research staff and students. Please enter date of relevant course completion (one of 1a, 1b or 1c must be completed).	**Course Title**	**Date completed**
	1a. Research Integrity Core Course (New researchers & students)	N/A
	1b. Research Integrity Refresher Course (Experienced researchers)	March 2022
	1c. Other (e.g. GCP - please specify title)	Human Tissue Act training - 02/02/2022 Human Tissue Act training (MRC) - 23/05/2022
	2. Supplementary Module – Research involving human participants	

	3. Information Security Training	15/07/2022

Section C. synopsis

1. Please state why this research is not considered a Clinical Trial of an Investigative Medicinal Product	Pitolisant is being used to assess the effect of manipulation of brain histaminergic pathways on affect and cognition in healthy volunteers. Pitolisant is already licensed in the UK for the treatment of narcolepsy on healthy volunteers. No specified clinical end points (safety or efficacy) will be measured.	
2. List all places where research will be conducted	1. Neurosciences Building, Department of Psychiatry, Oxford 2. Oxford Centre for Human Brain Activity (OHBA), Department of Psychiatry, Oxford 3. Oxford Centre for Functional MRI of the Brain (FMRIB), John Radcliffe Hospital, Headington, Oxford OX3 9DU (contingency location if OHBA capacity is low)	
3. Age range of participants	18-45	
4. Anticipated number of participants	56 (28 per group)	
5. Anticipated research start date	November 20th 2022	
6. Anticipated research end date	November 28th 2023	
7.	**Objectives**	**Outcome Measures**
Primary **Secondary**	**Primary outcomes:** To investigate the effect of histamine-3 receptor antagonism via a single-dose of pitolisant on behavioural performance and fMRI BOLD signal during tasks of learning and memory (memory encoding task) and complex verbal working memory tasks (verbal *n*-back task). **Secondary objectives:** 1) To investigate the effect single-dose of pitolisant on fMRI resting state BOLD signal across regions of interest (frontoparietal,	**Primary outcome measures:** 1. Brain activation (fMRI BOLD signal) and performance (accuracy/response time) during the fMRI memory encoding task in the hippocampus and related networks. 2. Brain activation (fMRI BOLD signal) and performance (choice behaviour) during the verbal *n*-back task in task-dependent areas including the prefrontal and temporal cortices. **Secondary Outcome measures:** 1. Changes in resting state functional connectivity across frontalparietal,

	cortico-striatal, and hippocampal areas). 2) To investigate the effects of single-dose pitolisant on behavioural cognitive performance in tasks of verbal and visual working memory (Instrumental n-back, Change Detection Task), social cue processing (Facial Emotional Recognition Task), sensitivity to reward and loss (Probabilistic Instrumental Learning Task) and emotional/non-emotional response inhibition (Emotional Go/No-Go Task) 3) To investigate the effect of single-dose pitolisant on subjective cognition (PDQ).	cortico-striatal and hippocampal regions (fMRI BOLD signal) 2. Change in performance (accuracy/response time) on emotional go/no-go task 3. Change in performance during the Probabilistic Instrumental Learning Task 4. Change in performance (accuracy/response time) during Instrumental *n*-back task 5. Change in performance in the Change Detection Task 6. Change in performance (accuracy/response time) during Facial Emotional Recognition Task 7. Changes in measures of subjective cognition (Perceived Deficits Questionnaire [PDQ]
8. Name of drug/substance	Pitolisant (Brand name: Wakix)	
9. Purpose of drug/substance use in this research	Cognitive and affective processing are underpinned by monoaminergic neurotransmission and neurosteroid systems, yet there are many aspects of these systems that remain unknown in humans. In particular, monoaminergic histamine 3 (H_3) receptors are abundant in CNS regions underpinning cognitive processing (prefrontal cortex, hippocampus, and striatum), yet their role in humans remains unclear. Evidence from animal models suggests H_3R antagonism improves cognitive functioning, however these specific effects are yet to be examined in humans. Similarly, the function of sigma-1 (σ-1) receptors in the brain is not well understood in humans despite strong evidence of pro-cognitive effects in animal models. We will investigate the effect of pitolisant, a dual H_3R antagonist and σ-1R agonist, on cognitive and affective processing, in addition to changes in functional connectivity. We will measure these effects through a battery of neuropsychological tasks (*e.g.,* Affective Go/No-Go Task; Instrumental dual *n*-back task), self-rated measures of cognitive function (PDQ), and resting state fMRI and fMRI data acquisition during the verbal n-back and memory encoding tasks.	
10. Adverse reactions and side effects posing a particular risk with this drug/substance	Pitolisant is approved for use and licensed in the US (FDA – 2019 [1]), EU and UK (EMA – 2016 [2]) for treatment of narcolepsy. Safety and tolerability data from clinical studies of pitolisant in narcolepsy of up to 8 weeks administration reveal its most common adverse effects are nausea (6%), insomnia (6%), and anxiety	

	(5%) [1]. Most relevant to this protocol is its tolerability profile in a single dose (40mg) in healthy volunteers, where 1 in 6 participants experienced increased sleep duration, dystonia and dizziness [3]. A recent study in healthy volunteers showed no cardiac safety signals in individuals taking up to the maximum dose of pitolisant (36mg/day) [5]. In this study, we will use a single dose of 36mg pitolisant within its recommended dose range (4.5–36 mg/day) [1,2]. Study participants will be screened to exclude those presenting with QT prolongation via ECG assessment as cautioned by the FDA [1], in addition to cautions contraindications for those with gastrointestinal disorders, epilepsy, mental health difficulties, clinical eating disorders and severe obesity by NICE [4].

Section D. Abbreviations

Define all unusual or 'technical' terms related to the research. Add or delete rows as appropriate. Maintain alphabetical order for ease of reference.

BMI	Body Mass Index
BOLD	Blood-Oxygen Level Dependent
BRC	Biomedical Research Centre
CNS	Central Nervous System
CUREC	Central University Research Ethics Committee
DHEA	Dehydroepiandrosterone
DSM-V	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
EGNG	Emotional Go/No-Go Task
EMA	European Medicines Agency
FDA	Food and Drug Administration
FERT	Facial Emotional Recognition Task
fMRI	Functional Magnetic Resonance Imaging
FMRIB	Oxford Centre for Functional MRI of the Brain
GAD-7	Generalised Anxiety Disorder Assessment
GCP	Good Clinical Practice
GP	General Practitioner
H_3R	Histamine-3 receptor
ICF	Informed Consent Form
ICF	Informed Consent Form

MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MS IDREC	Medical Sciences Interdivisional Research Ethics Committee
NICE	National Institute for Health and Care Excellence
OHBA	Oxford Centre for Human Brain Activity
PANAS	Positive and Negative Affect Schedule
PDQ	Perceived Deficits Questionnaire
PEACE	Pitolisant effects on affect and cognition exploratory (study)
PFC	Prefrontal Cortex
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PILT	Probabilistic Instrumental Learning Task
PIS	Participant Information Sheet
PPI	Personal Protective Equipment
SCID	Structured Clinical Interview for DSM-5
SCID	Structured Clinical Interview for DSM-5
SOP	Standard Operating Procedure
VAS	Visual Analogue Scale
WIN	Wellcome Centre for Integrative Neuroimaging

Section E. Background and rationale

While strides have been made in characterising the neurochemical basis of human neurocognitive processes through pharmacological investigation of glutamatergic, dopaminergic and serotoninergic agents, animal models suggest other neurotransmitter systems play an equally important role in higher cognitive processes and mood regulation [6,7]. Among these, the monoaminergic histamine-3 receptor (H_3R) system, which is expressed only within the human CNS [8], has demonstrated potential pro-cognitive and mood enhancing effects via antagonist ligands in rodents [9-11]. These beneficial effects are thought to be mediated by modulation of growth factor expression and hypothalamus-pituitary axis function, respectively [12].

H_3R is highly expressed within fronto-limbic regions including the prefrontal cortex (PFC), hippocampus and striatum. Higher H_3R density is associated with lower activity in the dorsolateral PFC during tasks of working memory, in addition to an association with decreased performance [13] . Further, the hippocampus has a high binding affinity for H_3R antagonist ligands, where H_3R antagonism leads to increased theta oscillatory activity in the region [14] – hippocampal theta oscillations are considered vital for learning and memory processing [15]. Further, the H_3R system is considered essential for modulating basal ganglia (including striatal regions) circuitry which is considered vital for modulating response inhibition, decision-making and reward processing [16]. Finally, given the high expression of H_3R density in limbic regions, predominantly the hypothalamus [17], it is suggested that the H_3R may play a role in systems which regulate the interface between cognitive and emotional processing.

Recent clinical approval of selective histamine 3 antagonist pitolisant, considered a first-in-class medication by the FDA [1], has allowed a novel opportunity to explore its direct effects on human cognition and relevant changes in functional connectivity within fronto-limbic regions of high H_3R density. Recent positron emission tomography investigation of a single-dose of pitolisant (36mg) in humans demonstrated that it produces high occupancy of H_3R throughout key brain regions involved in cognitive and emotional processing [17].

In this study, we will use a single dose of pitolisant (36mg) to assess its acute effects on cognitive domains of memory (*n*-back tasks, memory encoding fMRI tasks), decision-making (PILT), resting state functional connectivity (resting state fMRI), emotional/non-emotional executive functioning (Go/No-Go task), and emotional social cues processing (FERT). After screening for inclusion eligibility, healthy volunteers will be randomised to receive either a single dose of pitolisant or placebo in a double-blind, randomised design.

Pitolisant (sold as Wakix®) is currently approved and marketed across the US (FDA) and EU (EMA) for the treatment of narcolepsy with or without cataplexy in adults. For this clinical indication, it is recommended that a dose of 4.5mg – 36mg per day is used [1,2]. Clinical safety data from clinical studies reveals pitolisant to be safe and well-tolerated when used within this dose range in both patients with narcolepsy and healthy volunteers [18]. The most common adverse events reported in trial were nausea (6%), insomnia (6%), and anxiety (5%); many of these side effects are from long-term administration of the drug, and are therefore less likely to present healthy individuals during a single-dose study design.

Section F. Participants

1. Description of research participants

56 healthy volunteers aged 18-45

2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the research
- Not currently taking any medications which may interfere with pitolisant, including psychoactive medications
- Not currently using antihistaminergic medication
- Aged 18-45 years
- Male or female
- Sufficiently fluent English to understand and complete cognitive tasks and questionnaires
- Body Mass Index above or below 18-30
- Right handed

3. Exclusion criteria

The participant may not enter the study if ANY of the following apply:

- Current pregnancy (as determined by urine pregnancy test taken during screening visit), planning to become pregnant or breast feeding
- Any past or current history of severe and/or serious psychiatric disorder, including but not limited to schizophrenia, psychosis, bipolar affective disorder, major depressive disorder, obsessive compulsive disorder

- Clinically significant abnormal values for urine drug screen, blood pressure measurement (in accordance with AP20 'non-invasive blood pressure') and ECG. A participant with a clinical abnormality or parameters outside the reference range for the population being studied may be included only if the Investigator considers that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures
- History of, or current medical conditions which, in the opinion of the investigator, may interfere with the safety of the participant or the scientific integrity of the study, including epilepsy/seizures, brain injury, hepatic or renal disease, acid-related gastro-intestinal problems, Central Nervous System (CNS) tumours, neurological conditions
- Current or past history of drug or alcohol dependency
- Severe lactose intolerance
- Use of recreational drugs (e.g. cannabis, cocaine, amphetamines) within past 3 months
- Participation in a study which uses the same computer tasks as those in the present study (determined by asking participants about previous studies participated in during screening) within past 3 months
- Participation in a study that involves the use of a medication within the last three months
- Smoking > 5 cigarettes per day
- Consumption of a high amount of caffeine per day (> 400ml caffeine) (*e.g.,* 5 or more cups of coffee)
- Participant is unlikely to comply with the clinical study protocol or is unsuitable for any other reason, in the opinion of the Investigator
- Any contraindication to MRI scanning (e.g. metal objects in your body, pacemakers, significant claustrophobia)
- Not right handed

4. Recruitment

Participants will be recruited from the general population by using posters (with rip-off tabs) and advertisements in the local press and on the internet (see APPENDIX A - STUDY ADVERT; APPENDIX N - STUDY ADVERT TOKENS (TO TAKE FROM POSTER)). Adverts will be sent to Junior Common Rooms and Middle Common Rooms, displayed in colleges and university departments and local community buildings. Adverts may also be placed on local information websites (e.g. Daily Info, Oxford University Gazette), newspapers, local magazines, on the radio and on the lab webpage, and online advertisements via Call for Participants (https://www.callforparticipants.com/) and Meta adverting (Facebook and Instagram) – with text and imagery adapted from only the information provided in 'APPENDIX A - STUDY ADVERT'. The adverts will contain brief information about the inclusion criteria for the study, as well as contact details for the named researchers.

After a potential volunteer has contacted the research team to indicate potential interest, they will be sent the Participant Information Sheet via email. The participant will be given as much time as they need to decide within reasonable limits whether they would like to take part, and will be invited to ask any questions that they have about the study. If the participant decides that they do not want to take part in the study, they will be thanked for their interest and there will be no further contact from the research team. If the participant decides they would like to take part, they will be invited for a screening visit at the Department of Psychiatry, Warneford Hospital. At the beginning of this visit, one of the named researchers will explain the study to the participant and answer any questions that he/she has. The researcher will then take written consent from the participant. All of the named researchers have been trained in taking informed consent.

5. Eligibility assessment

Screening eligibility for study participation occurs at two time-points:

Online screening:
Consent to participate in the online screening will be sought initially, where participants will be provided with a copy of the Participant Information Sheet (see APPENDIX F: PARTICIPANT INFORMATION SHEET)

and required to give informed consent in accordance with the statements on Informed Consent Form (APPENDIX G: INFORMED CONSENT FORM). Consent will be collected on the Qualtrics system via digital signature entry. Participants will be informed that further written consent will need to be obtained at a later date at the first in person visit (screening visit). After consent is obtained, an automated online screening (via Qualtrics) will occur which will ask participants to provide the following details;

- History of medical and psychiatric difficulties (incl. family history where appropriate).
- Age
- Current and past medication use (incl. use of recreational drugs).
- Handedness
- Basic MRI screening form for contraindications check (*e.g.* surgically implanted metal objects or pacemakers)
- Prior participation in research studies in the Department of Psychiatry and/or Department of Experimental Psychiatry

In instances where a participant selects an option that could suggest ineligibility on the Qualtrics questionnaire, Qualtrics would then route them to a free-text box to provide further information. Qualtrics reports will be parsed and then checked if participants are eligible to proceed to the next screening visit. Please find the Qualtrics questionnaire details in 'APPENDIX B - ONLINE CONSENT FORM (QUALTRICS PRINT)' and 'APPENDIX D - ONLINE SCREENING FORM (QUALTRICS PRINT)'.

Screening visit:
Participants who met the eligibility criteria during the online screening then would be invited to book themselves into an in-person screening visit occurring at the Neurosciences Building, Warneford Hospital Site. The visit will take approximately 60-90 minutes to complete. A physical copy of informed consent will be taken at the start of visit as the consent obtained during the online screening would have been done remotely. The screening visit involves the following procedures (APPENDIX J - SECONDARY SCREENING FORM):

- Personal contact details collection (paper)
- MRI Screening Form (APPENDIX H - 3T VOLUNTEER SCREENING FORM)
- Further demographic data including gender and years in education
- Weight, height measurement
- Vital signs assessment (blood pressure and ECG to check for heart electrical abnormalities)
- 12 lead ECG
- Urine drug screening
- Urine pregnancy test
- Working memory task (to assess baseline cognitive ability for randomisation procedure)
- SCID-V Interview (Structured clinical Interview for DSM-V, a set of standard clinical questions asking about current and past psychiatric illness)

All physical health assessments will be overseen by the study medical officer (Prof Phil Cowen) or other delegated medical professional. For the ECG assessment, a chaperone will be offered to participants according to the risk assessment. All clinical procedures in this study will be carried out following a study-specific and WIN-specific risk assessments, particularly pertaining to COVID-19 risk (APPENDIX C - NEUROSCIENCES BLDG RISK ASSESSMENT; APPENDIX L – WIN RISK ASSESSMENT FOR RTOSW) If participants fit the study criteria they will then be invited for the second visit: 'Study visit'. A maximum of six weeks is allowed between the Screening Visit and the Study Visit. If this duration is exceeded, another screening will be performed to ensure eligibility.

6. Information Provided to Participants and Informed Consent

The Participant Information Sheet (see APPENDIX F: PARTICIPANT INFORMATION SHEET) will be presented to the participants, and verbally communicated to participants (in-person screening). Both will detail the exact practical demands of the study, written from the participant's perspective, in lay language (the nature of the study, what it will involve for the participants, the implications and constraints of the protocol, the known side effects and any risks involved in taking part, what will happen to the data collected). It will be clearly stated that the participant is free to withdraw from the study at any time for any reason and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish to consider the information, and the opportunity to ask question the Investigator, their General Practitioner (GP) or other independent parties to decide whether they will participate in the study.

A physical copy of the latest approved version of the Informed Consent Form (ICF; see APPENDIX G: INFORMED CONSENT FORM) that participants consented to at the online screening (via digital signature on Qualtrics) must be signed by participants during the screening visit. This will be done before any study-specific procedures are performed.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent will be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator (PI). A copy of the signed ICF will be given to the participant. The original signed form will be retained at the study site. During the online Screening Visit, an electronic version of the ICF will be completed and then a paper version will be completed at the start of the in-person screening Visit (see Section F5).

Due to the ongoing COVID-19 pandemic, study participants will be provided with guidelines for how to adhere to the latest social guidance policy (see APPENDIX K: COVID-19 GUIDELINES FOR RESEARCH PARTICIPANTS). As the situation is ongoing, participants will be updated by the researchers if the guidelines change and provided an updated guidelines document.

Section G. Research Procedures

1. Baseline Assessments and Procedures

Baseline assessments and procedures will take place at the online screening and screening visit. They will consist of the following:

Online screening:

Consent to participate in the online screening will be sought initially, where participants will be provided with a copy of the Participant Information Sheet (see APPENDIX F: PARTICIPANT INFORMATION SHEET) and required to give informed consent in accordance with the statements on Informed Consent Form (APPENDIX G: INFORMED CONSENT FORM). Consent will be collected on the Qualtrics system via digital signature entry (APPENDIX B - ONLINE CONSENT FORM (QUALTRICS PRINT)). Participants will be informed that further written consent will need to be obtained at a later date at the first in person visit (screening visit). After consent is obtained, an automated online screening (via Qualtrics) will occur which will ask participants to provide the following details;

- History of medical and psychiatric difficulties (incl. family history where appropriate).
- Age and other demographic information including gender
- Estimation of weight and height
- Current and past medication use (incl. use of recreational drugs).
- Handedness
- Basic MRI screening form for contraindications check (*e.g.* surgically implanted metal objects or pacemakers)
- Prior participation in research studies in the Department of Psychiatry and/or Department of Experimental Psychiatry

In instances where a participant selects an option that could suggest ineligibility on the Qualtrics questionnaire, Qualtrics would then route them to a free-text box to provide further information. Qualtrics reports will parsed

and then checked if participants are eligible to proceed to the next screening visit. Please find the Qualtrics questionnaire details in 'APPENDIX D - ONLINE SCREENING FORM (QUALTRICS PRINT)'.

Screening visit:

Participants who met the eligibility criteria during the online screening then would be invited to book themselves into a screening visit occurring at the Neurosciences Building, Warneford Hospital Site. The visit will take approximately 60-90 minutes to complete. A physical copy of informed consent will be taken at the start of visit as the consent obtained during the online screening would have been done remotely. The screening visit involves the following procedures:

- Personal contact details collection (paper)
- Weight, height measurement
- Vital signs assessment (blood pressure and ECG to check for heart electrical abnormalities)
- 12 lead ECG
- Urine drug screening
- Urine pregnancy test
- Digital Span Task – Forward/Backwards (to assess baseline cognitive ability for randomisation procedure); this task will require participants to repeat a sequence of numbers in a particular order (forwards or backgrounds) orally to the researcher.
- SCID-V Interview (Structured clinical Interview for DSM-V, a set of standard clinical questions asking about current and past psychiatric illness)
- MRI screening form

All physical health assessments will be overseen by the medical officer attached to this study (Prof Phil Cowen) or other delegated medical professional. For the ECG assessment, a chaperone will be offered to participants according to the risk assessment. All clinical procedures in this study (including COVID-related restrictions) will be carried out following a study-specific risk assessment and in adherence to the standard operating procedure of Neurosciences Building risk assessment (see APPENDIX C - NEUROSCIENCES BLDG RISK ASSESSMENT). If participants fit the study criteria they will then be invited for the second visit: 'Study visit'. A maximum of four weeks is allowed between the Screening Visit and the Study Visit. If this duration is exceeded, another screening will be performed to ensure eligibility.

2. Subsequent Visits

Study Visit

Participants who are medically approved to take part in the study after the screening visit are invited to take part in the study visit. Prior to the study visit, and after the screening visit, participants will be randomised using the variance minimisation algorithm described above to ensure a balance of covariates of interest across treatment and placebo groups. The randomisation code will be drawn up by a researcher not involved in the study using an randomisation procedure known as variance minimisation, following a procedure outlined by Sella, Raz & Cohen Kadosh (2021) [19]. Participants will be allocated to placebo or treatment groups based on gender, level of education, and their digit span score (as an index of general intelligence). Allocation of treatments will be recorded on a Randomisation List which will be updated when each new participant enters the randomised phase. The Randomisation List will be held securely within the Neurosciences Building by the study medic (Prof Cowen). Pitolisant and placebo agents will be kept securely within a locked medicines cabinet also within the Neurosciences building.

During the visit, participants will receive either a single dose of pitolisant (36mg single dose) or placebo. They will receive the dose at the Neurosciences Building, Warneford Hospital site. The study has a double-blind design thus neither the researchers nor the participant will know whether pitolisant or placebo is given. On arrival, participants will briefly be reviewed to ensure the inclusion criteria are still satisfied. Prior to drug or placebo administration, the following procedures will be undertaken:

- Inclusion/exclusion criteria review

- Completion of the MRI screening form (APPENDIX H - 3T VOLUNTEER SCREENING FORM) once more to ensure it is still safe for them to undergo fMRI scanning.
- Clinical screening, mood and side effects questionnaires (to establish baseline) on qualtrics – PHQ-9, GAD-7, PANAS, PDQ and Need for Cognition Scale

Providing eligibility still holds following review, participants will then take the single dose of pitolisant or placebo. There will then be a two-hour monitoring period to allow for the drug (where appropriate) to metabolise and activate within the system. Participants will then be escorted to OHBA where they will undertake an MRI scan (or, FMRIB if nil capacity at OHBA). First participants will be asked to change into MRI safe scrubs and screened for MRI safety by the scan operator / radiographer. MRI scans will be undertaken in accordance to the CUREC approved MRI scanning procedure (APPENDIX M - CUREC APPROVED MRI INVESTIGATIONS PROCEDURE). The scan itself will include:

- Structural scan (T1 and T2-weighted imaging)
- Probabilistic Learning Task (fMRI) – this task requires participants to choose one of two pairs of symbol every trial. One of these pairs will be associated with a win probability and the other not, with each pair corresponding to reciprocal probabilities. Participants are asked to make choices based on what symbol will maximise their win-loss ratio and increase monetary outcome. Participants will be instructed that they will be reimbursed at the end of the study based on their performance during this task (participants can win up to £20 total depending on performance).
- Memory task (fMRI) – This task requires participants to learn presented emotionally neutral stimuli (images) prior to the scan, then during the scan they will be asked to recall if the stimuli presented during the scan were previously seen using a two-button press.
- Verbal *n*-back task (fMRI) – it will require participants to concentrate on a series of letters (upper case and lower case)stimuli displayed centre-screen and pressing a button according to a rule provided before each block (*e.g.* press spacebar if you see an image you previously saw three images ago).
- Resting State fMRI – this will not require participants to perform any tasks and will take approximately 7 minutes to complete
- Arterial spin labelling
- Physiological recordings including pulse, respiration, and skin conductance –recorded using a pulse meter, respiration bellows and electrodes strapped by Velcro to fingertips.
- Eye tracking

Once the scanning has completed (approximately 1.5 hours), participants will be escorted back to the Neurosciences Building, Warneford Hospital site. Here, participants will complete the remaining:

- Affect, Mood, Subjective Cognition and Side Effects questionnaires (for end-point):
    - PHQ-9
    - GAD-7
    - Visual Analogue Scale
    - Perceived Deficits Questionnaire
    - Side Effects Questionnaire
    - PANAS
    - Need for Cognition Scale
- Instrumental *n*-back task – this widely used task will be done after scanning is complete; it will require participants to complete a version of the n-back task in the scanner, but this time participants are rewarded or punished for performance. Participants will start with £1.00 and can earn up to £10 based on performance (similar to the PILT), but cannot lose less than £0.00. This task will involve more complex levels of working memory processing (including 4-back, 5-back).
- A change detection task – a short task of visual working memory which requires participants to view an array of 'items' (e.g. coloured blocks) for a short period of time, and after a short period they are shown the same array once again with one subtle change (e.g., one colour has been changed). Participants must identify the change.

- Emotional Go/No-Go task (EGNG) -- this task follows a 'go/no-go' format where participants will be presented stimuli on-screen which they are instructed to either press a button for 'go' trials or inhibit their response. Emotional and non-emotional distractors will be used to check the effect of emotional distraction on response inhibition.
- Facial Emotional Recognition Task (FERT) – the widely-used task will ask participants to recognise the emotion of faces displayed on the screen in sequence; emotions include: sad, surprised, angry, disgusted, happy, neutral).

Once participants had completed these procedures then the study visit will end. Before leaving, participants will be given a wallet-sized card with key details about the study and contact information of a member of the study team to contact if they have any questions. The card will also include the phone number of the out-of-hours BRC on-call medic service in case they need medical advice related to the study out of standard office hours. At the end of this visit, participants will be advised not to drive, cycle or operate machinery, in case they experience any side effects from the drug. To ensure participants get home safely after the visit, the researcher will either arrange a taxi or travel expenses (e.g. bus tickets) for the journey will be reimbursed.

Participants will be followed-up the day following the study visit with a mood/side effects questionnaire in addition to debriefing and reimbursement details processing. This follow-up should between 30-45 minutes to complete.

The cognitive tasks include measures of executive functioning, decision making and memory. Memory ability is measured through the fMRI memory and instrumental n-back tasks, both of which require participants to recall presented stimuli at a later date. The EGNG will measure response inhibition (executive functioning), requiring participants to continuously press a keyboard input while occasionally being prompted to inhibit their response; this task will rely on affective prompts (*e.g.* a face with a particular emotional expression) or non-affective prompts (*e.g.* a phrase such as "do not press spacebar"). The FERT measures emotional processing, and involves the presentation of faces displaying different emotions. In another task of instrumental learning (PILT), participants will be asked to choose between shapes, some of which lead to winning money and some of which lead to losing money – participants will be able to win up to £10 which will be added to the reimbursement they receive at the end of the study. All stimuli will be presented on a computer screen and participants will be required to respond via button presses on a keyboard.

Mood questionnaires are short self-report inventories, including PHQ-9, GAD-7, Need for Cognition Scale, and Positive and Negative Affect Scale.

3. Biological Sample Handling

Urine samples will be used for drug screening and pregnancy tests. These will be administered at the Screening VisitStudy visit. The urine tests will be administered by a trained staff member using dipstick tests. After the results are obtained the sample will be disposed of. All urine testing will adhere to approved procedure AP24 'taking urine samples'.

4. Will the research include any audio, video or photographic recordings?

No.

5. Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the research at any time. In addition, the Investigator may discontinue a participant from the research at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the research or retrospectively having been overlooked at screening)

- Significant protocol deviation
- Significant non-compliance with treatment regimen or research requirements
- Withdrawal of consent
- Loss to follow up

If a participant is withdrawn, no further procedures or observations will continue to be required. Withdrawal from the study will result in exclusion of the data for that participant from analysis. Withdrawn participants will be replaced. The reason for withdrawal if given will be recorded in the Participant Log of the Research Master File.

6. Definition of End of Study

The end of the study for participant involvement is the date of the last visit of the final participant.

7. Please detail all expenses or gifts that will be offered to participants.

Guidance is available in Best Practice Guidance: 05 Payments and incentives in research.

Participants will be paid £140 upon completion of their participation in the research. In addition, they may win up to £20 depending on the choices they make in some tasks. If they do not complete the study, they will be given a pro-rata amount to recompense the time they did spend in the study.

Reasonable travel expenses (up to £20 per visit) for any visits will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

Section H. Interventions

Drug/Substance 1

Name of drug/substance to be used	Pitolisant (Wakix)
Formulation, dose and route of administration for research	Two film-coated tablets (18mg x 2 [36mg]) for oral administration will be encapsulated in opaque capsules
Duration of treatment for research	Single dose
Licence status of this drug/substance	Active license from EMA and FDA for the treatment of narcolepsy with or without cataplexy in adults
Usual Indication	Adults with Narcolepsy with or without cataplexy
Usual Dose	4.5mg – 36mg per day
Usual duration of treatment	Continuous use
Where will drug/substance be sourced from?	Pharmacological Wholesaler via Oxford Health NHS FT
Where will drug/substance be stored at site?	Pitolisant will be stored within the Neurosciences Building at the Department of Psychiatry. It will be stored at room temperature in a locked cupboard, which is suitable for drug storage.
How will drug/substance be dispensed?	Pitolisant will be dispensed from the Neurosciences Building by a study medic or nurse.

How will the drug/substance be prepared by the researchers for use in this research?	Pitolisant will be encapsulated by trained clinical trial support staff using our Standard Operating Procedure.

Drug/Substance 2	
Name of drug/substance to be used	Lactose placebo
Formulation, dose and route of administration for research	Two placebo tablets will be encapsulated in opaque capsules.
Duration of treatment for research	One capsule; single dose
Licence status of this drug/substance	Single dose
Usual Indication	N/A
Usual Dose	N/A
Usual duration of treatment	N/A
Where will drug/substance be sourced from?	Placebo tablets will be sourced from HSC (www.hsconline.co.uk).
Where will drug/substance be stored at site?	Placebo tablets will be stored within the Neurosciences Building at the Department of Psychiatry. They will be stored at room temperature in a locked cupboard, which is suitable for drug storage.
How will drug/substance be dispensed?	Placebo tablets will be dispensed from the Neurosciences Building by a study medic or nurse.
How will the drug/substance be prepared by the researchers for use in this research?	Placebo tablets will be encapsulated by trained clinical trial support staff using our Standard Operating Procedure.

Section I. Safety	
1. Definitions	
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a substance has been administered, including occurrences which are not necessarily caused by or related to that substance.
Adverse Reaction (AR)	An untoward and unintended response in a participant to a substance, which is related to any dose administered to that participant. A causal relationship between the administered substance and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that:

	• results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the research treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product set out in its summary of product characteristics (SmPC).

2. Reporting procedures for serious adverse events or reactions

Any adverse event (AE) occurring to a participant will be reported to the MS IDREC. Reports of related (resulted from administration of any of the research procedures) and unexpected (the type of event is not listed in the protocol as an expected occurrence) adverse events will be reported as soon as possible once the Principal Investigator becomes aware of the event. Unrelated/expected adverse events will be reported within 10 working days of the Principal Investigator becoming aware of the event.

All SUSARs will be reported to the MHRA in addition to the MS IDREC. For fatal and life-threatening SUSARs, this will be reported as soon as possible, but no later than 7 calendar days after the PI is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. Non-fatal or non-life-threatening SUSARs will also be reported as soon as possible, and no later than 15 days after the PI is first aware of the reaction.

All reports to the MHRA will be via the Yellow Card Scheme.

3. Safety of participants

1. What level of baseline safety screening will take place for this research?

All participants will undergo a two screening visits (one online; one in-person in the Department of Psychiatry) to ensure only eligible participants take part. The following will be recorded at baseline screening:
• Demographic data, including age (years and months), years in full time education, gender
• Medical history review, details of current and past medication
•SCID-V Interviews (Structured clinical Interview for DSM-V, a set of standard clinical questions asking about current and past psychiatric illness)
• Weight, height measurement
• Vital signs assessment (blood pressure, heart rate)

• 12 lead ECG (to check for heart electrical abnormalities)
• Urine drug screening
• Urine pregnancy test (females only)
• MRI Safety questionnaire

2. Provide details about the safety monitoring of participants and the staff/researchers carrying this out

On the study visit, where the participant will either take a single dose of pitolisant or placebo, participants will be advised to have not consumed alcohol within the past 24 hours. Participants will be asked to arrive via walking or public transport or taxi, and will be asked to continue to avoid driving, operating heavy machinery or using a bicycle for at least the following 12 hours (maximum half-life of pitolisant). All participants will receive a phone number for calling an out-of-hours BRC on-call medic service in case they need medical advice related to the study after the study visit has taken place.

The randomisation code will be broken if a participant requires treatment for a new medical condition/experiences serious adverse reactions and either of these situations make it clinically important to know what medication they are taking. In order to unblind the participant, the study medic/delegated medic will have access to the randomisation code and can unblind if necessary within a maximum of 1 hour. If breaking the code is necessary then only that individual's code will be broken. Data from unblinded participants will not be admitted to analysis. If unblinding occurs, the researcher will record the reason and result of the unblinding, as well as the date and time of the event.

3. Give details on the medical cover required and who will provide this cover

A medical doctor who is part of the research team will review the screening and make a final judgment about including participants in the study. A qualified medical doctor will be contacted if a participant expresses concern to a named researcher regarding side effects or health status changes during the study week.

4. Will the participants' GP be informed about their participation in the research? In not, please justify

Participants' GPs will not be informed about their participation in the study. A single dose of pitolisant is not regarded as a clinically significant intervention and is not expected to have any impact on participants' health or wellbeing. We are excluding participants who are pregnant, breastfeeding or who have any medical conditions for whom the study would not be suitable.

5. What is your planned procedure if an incidental finding is suspected?

Participants will be screened to exclude those with past or current serious psychiatric illness and Best Practice Guidance (BPG) 08 (Psychological distress) will be followed in order to ensure best practice in situations where participants with psychological distress are identified. The guidance in this document around confidentiality and researcher training will also be adhered to.

Incidental findings from MRI investigations at WIN facilities will be treated in accordance with the Incidental Findings SOP (APPENDIX I - INCIDENTAL FINDINGS FOR NEUROIMAGING RESEARCH SOP).

Urine pregnancy and drug screens: participants will be explicitly informed that their urine samples will be tested for pregnancy and recreational drug use, both in the pre-screening telephone call and during the Screening Visit, and informed of their right to withdraw from the study. They will also be told in advance that if the drug screen returns positive results, they will be excluded from the study. If participants consent to providing a urine sample for the pregnancy test and the test result is positive, the researcher will act in accordance with the pregnancy urine test SOP (APPENDIX O - URINE PREGNACY TEST SOP), wherein they will feed the result back to the medic covering the visit or a member of the research team, before communicating the result to the participant and providing any relevant advice. Results of the screening will remain confidential within the study team and participants will be informed of this.

6. If an incidental finding has clinical implications, what action will you take?

If a researcher has concerns that a volunteer may have an undiagnosed psychiatric condition that is causing distress (identified during the screening visit or following review of the mood-related questionnaires), CUREC

guidance (BPG08) will be followed. The researcher will seek advice from the Principal Investigator who may discuss the symptoms in greater detail with the volunteer and/or offer the opportunity to speak with a senior clinical researcher. If the volunteer indicates that they are not currently receiving support and it is felt necessary, they will be encouraged to contact their General Practitioner.

4. Ethical considerations

Research usually carries the risk of some ethical challenge. If this is the case you need to demonstrate your awareness of the problem and your response to mitigate ethical objections.

For guidance on ethical issues, please see http://researchsupport.admin.ox.ac.uk/governance/ethics/resources, however the following areas are often a cause for concern:

1. Will the research involve any participants considered vulnerable in the context of the research (e.g. children, elderly, prisoners, adults at risk)? **If yes,** please describe how they are defined as vulnerable and detail any CUREC Approved Procedures or guidance that will be applied to the research (for current documents and templates see https://researchsupport.admin.ox.ac.uk/governance/ethics/resources).	Yes ☐	No ☒
2. Will the research involve deliberate deception of participants? **If yes**, justify why deception is used, describe deception and debriefing process, and include debriefing documents in the application	Yes ☐	No ☒
3. Could the proposed research affect your own physical and/or psychological safety as a researcher? **If yes,** describe how this will be mitigated.	Yes ☐	No ☒
4. Does your research raise issues relevant to the Counter-Terrorism and Security Act (the Prevent Duty), which seeks to prevent people from being drawn into terrorism? **If yes,** please say how you plan to address any related risks. Please see advice on this on our Best Practice Guidance Web Page.	Yes ☐	No ☒

5. Please list any stakeholder or community engagement that has been, or will be, undertaken in relation to the research

Prior to this research study, we engaged in a public and patient involvement project to learn more about the experiences of cognitive impairment in persons with lived experience of depression. This projected highlighted the many consequences of cognitive impairment to clinical engagement and quality of life, as well as the desire for therapeutics to be developed which may address these issues. Full details of this project will be published in an article (Colwell *et al.,* in review), or can be accessed upon request.

6. Please give details of any other research-specific ethical and/or safety considerations, not related to drug/substance administration

During the MRI procedure, there is a small risk that participants feel some degree of discomfort given the enclosed space of the scanner. Discomfort from lying still for a long period of time will be minimised with comfortable padding and positioning. Whilst in the scanner, participants will be able to use the alarm if they wish to communicate with the operator or to interrupt scanning. People with a history of severe claustrophobia would be excluded from participation in the study. All participants will be introduced carefully to the scanner and informed that they can terminate the scan session at any stage, should they wish to do so. Once inside the scanner, participants will be able to indicate if they wish the scanning to cease by squeezing a bulb placed in their hand, or by requesting verbally. As the MRI scanner is noisy, participants will be given earplugs to minimise the noise.
MRI is a safe, non-invasive technique, which does not involve ionising radiation. Risks associated with the magnetic field will be removed by excluding potential participants with ferromagnetic objects in their bodies (e.g., metal implants, vessel clips, shrapnel injuries) or with implanted devices, which may be damaged by the magnet (e.g., heart pacemakers). All people entering the scanning room are screened for such objects. All people will complete an MRI Screening safety questionnaire before taking part in the study. In the instance of incidental findings emerging from neuroimaging data, study researchers will follow the relevant incidental findings SOP (APPENDIX I - INCIDENTAL FINDINGS FOR NEUROIMAGING RESEARCH SOP). Researchers helping during the MRI scanning process will undertake complete magnet safety training and an in-person building induction at WIN facilities to ensure maximal awareness and safety around the scanner and for each research volunteer.

7. Will any data or information from this study be provided to individual participants?

N/A

Section J. Statistics and analysis

1. Do you have a statistical plan? **If no,** please justify.	Yes ☒	No ☐

N/A

2. Number of Participants

56 healthy volunteers (28 per group)

3. Have you done a sample size calculation? If yes, please give details below If no, please give details to indicate you have considered the implications the selected sample size will have on the research outcome	Yes ☒	No ☐

The selected sample size was informed by a priori statistical power analysis (APPENDIX P – POWER CALCULATION READ-OUT) for a one-way fixed effects ANOVA approach within a healthy volunteer population via G*Power Software (Statistical power: 80%; Estimated effect size: 0.4; Alpha level: 0.05), which requires a total sample size of 52 to power (an additional 4 persons will be recruited in case of data quality issues and/or drop-out). The sample size calculation is conservative and informed by a previous placebo-controlled cross-over study of cognitive function in healthy volunteers (*N*=16) following a short course of an histamine-1 agonist/histamine-3 antagonist (betahistine) [20]. The study demonstrated large between-group differences in n-back accuracy ($\eta_p^2 = 0.74$) and BOLD activation within the Inferior frontal gyrus and medial temporal gyrus during the n-back task ($\eta_p^2 = 0.78$ and $\eta_p^2 = 0.79$, respectively).

4. Analysis of Outcome Measures

R Software will be used to analyse all psychometric, cognitive and neuroimaging data. Sample characteristic data (*e.g.* age, gender, and years in education) will be analysed using an appropriate analysis of variance (e.g. t-test or Mann-Whitney U), depending on model assumptions being satisfied. Cognitive and neuroimaging data will be analysed using a between-groups ANOVA approach, with appropriate normality transformations and Greenhouse–Geisser correct where the distribution and/or degrees of freedom does not meet model assumptions. Post-hoc analyses will be corrected using Bonferroni (or Bonferroni-Holm) correction. Analysis of fMRI endpoints will be completed using the FSL software package.

Section K. Data management and handling

All information provided by participants is considered **research data** for the purpose of this form. Any research data from which participants can be identified is known as **personal data**; any personal data which is sensitive is considered **special category data**.

Management of personal data, either directly or via a third party, must comply with the requirements of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018, as set out in the University's Guidance on Data Protection and Research. In answering the questions below, please also consider the points raised in the Data Protection Checklist and whether, for higher-risk data processing, a separate Data Protection Impact Assessment may also be required for the research. Advice on research data management and security is available from Research Data Oxford and your local IT department. Advice on data protection is available from the Information Compliance team.

1. Please mark 'X' against the data you will collect for your research

Screening documents	☒	Audio recordings	☐
Consent records including participant name or other identifiers (e.g. written consent forms, audio-recorded consent, assent forms)	☒	Video recordings	☐
Consent obtained anonymously (e.g. via online survey)	☐	Transcript of audio/video recordings	☐
Opt-out forms	☐	Photographs	☐
Contact details for the purpose of this research only	☒	Information about the health of the participant (including mental health)	☒
Contact details for future use (guidance)	☐	Physiological test results / measurements	☒
Task results (e.g. questionnaires, diary completion)	☒	Scans (e.g. MRI, Ultrasound)	☒
Data already in the public domain. Specify the source of the data:	☐	IP addresses (refer to Best Practice Guidance 09: Data collection, protection and management for guidance)	☐
Previously collected (secondary) data	☐	Other (please specify below)	☐
Bank (or other) details required for reimbursement	☒		

2. How and where will each type of data be stored whilst the research is ongoing (until the end of all participant involvement)?

List each type of data selected above, and explain how each will be physically transferred (including movement/sharing of audio files, paper records, electronic downloads etc.) from where it is collected to a suitable storage site (e.g. Nexus365 OneDrive for Business, SharePoint, University servers). State the storage location for each.

Refer to Best Practice Guidance on data collection, protection and management (BPG09).

Screening information which contains personal/sensitive information (*i.e.,* date of birth, name, address, contact number) will be stored on a separately to non-identifiable screening information (e.g., age, gender, educational level *etc*). The former will be stored on a physical form which will be included in the trial master file and will be destroyed at the end of the study, while the latter information will be digitally as an encrypted (password protected) dataset on a secure university network drive. These data will be linked to personal identifiers via a linkage code. For any physical data which needs to be transported from one building to another (i.e. OHBA/FMRIB to the Neurosciences Building, and vice versa) this will be undertaken by a member of the research team, and physical files will be secured within a locked briefcase during this transfer. The secure network drive can be accessed in both the OHBA/FMRIB and Neurosciences building using a computer with access to the university network. All research data storage will adhere to best practice guidance BPG09 'data security'.

Consent forms will be in paper form and will include participants' names. These will be stored securely in a locked filing cabinet in a room in the Neurosciences Building (Department of Psychiatry).

Psychometric, cognitive task and MRI data will be de-identified and linked via linkage codes to personal identifiers. These data are digital and will be kept on a secure university network drive throughout the duration of the study. Some data will be collected electronically using Qualtrics software and this data will be downloaded from Qualtrics and stored on a University networked drive.

Personal contact details will not be kept electronically, but in a written record in a locked filing cabinet in a room (General Office 2) in the Neurosciences Building (Department of Psychiatry) which requires key card access to enter.

The radiographer's copy of the MRI screening form will stay at OHBA/FMRIB where it will be kept for up to 5 years in a secure location.

Participant bank details will be shared with colleagues from the finance team via electronic format.

3. Will you use a unique participant number on research data instead of participant name?

If yes, state whether or not you will retain a list of participant names against numbers (pseudonymisation via a linkage list).

Where will the list be stored, and when will it be destroyed?

Each participant will be assigned a unique study number at screening. A key will link participants' personal details to their unique study number. This document will be stored in the Research Masterfile in a lockable filing cabinet, separate from all research data. Both participants' personal details and linkage information will be destroyed when the study has concluded, and the results have been written up and published. Participants' consent forms will be kept for a minimum of 10 years after the completion of the study after which they will be destroyed.

Imaging data is automatically coded at source with a scan identifier that cannot be directly linked to the participant by anyone outside of the centre where the data was acquired. Imaging data is accessible by researchers working on this research and authorised centre staff. The scan identifier and imaging data will be stored on a secure database at that centre, with participant name encrypted. The data will be stored indefinitely.

4. Who will have access to the research data?

Named researchers will have access to participants' personal data and research data. Direct access will be granted to authorised representatives from the University of Oxford for monitoring and/or audit of the study to ensure compliance with regulations.

Data which has been fully de-identified may be shared with other academic and commercial organisations in the future, including those outside of the UK and the EU. Participants will be informed of this and specific consent to this is obtained within the Informed Consent Form.

Identifiable (without defacing) Imaging data is accessible by researchers working on this research project and authorised WIN Centre staff.

5. If research data is to be shared with another organisation, how will it be transferred / disclosed securely?

If data is shared with any other organisation, only data without personal information will be shared.

In line with data reproducibility initiatives, we plan to share de-identified and de-faced MRI Brain Imaging Data Structure compliant data (t1,t2-weighted and fMRI images) via OpenNeuro (https://openneuro.org/faq; further information on defacing and GDPR protocol: https://open-brain-consent.readthedocs.io/en/stable/gdpr/), in addition to de-identified participant and behavioural data and analysis scripts via OSF (https://osf.io/).

6. When and how will identifiable data be destroyed or deleted?

N.B. If any identifiable data will be retained beyond the end of the study and/or indefinitely, please state what data this is, and the reasons for retention (e.g. contact details for future studies; photos used in publication). This must be clearly stated on participant information, and specific consent obtained.

Once the data has been analysed and the results have been published, personal data forms and the linking key will be destroyed by shredding. Consent forms will be destroyed by shredding 10 years after the end of the study. De-identified questionnaire and task data will be archived at the end of the study and will be stored for a minimum of 10 years. The name and any identifying detail will not be included in any study data electronic file.

7. Please confirm that you will store other (non-identifiable) research data safely for at least 3 years after final publication or public release and adhere to any additional research funder policies. For more information about the University policies, please see the University's web pages on research data management. **If 'Yes'**, please give details of who will store the data and on storage format, location and security. **If 'No'**, please provide further details.	Yes ☒	No ☐

Data which has been fully de-identified will be stored in either filing cabinets or password-protected spreadsheets. Participant consent forms will be stored within the trial master file which will be held within a locked filing cabinet.

Filing cabinets are locked and secure, located in a room which is locked when not in use (room located in the Neurosciences Building, Department of Psychiatry). Password-protected spreadsheets will be stored on University networked drives.

Section L. Monitoring and oversight

1. Who will be responsible for day-to-day supervision of the research?

Dr Susannah Murphy

2. Give information about frequency of meetings that will be held to discuss progress/problems. Who will be present at the meetings?

The study team will meet fortnightly to discuss progress with the project. The Principal Investigator and named researchers will be present in these meetings.

Section M. Ethical and regulatory considerations

Declaration of Helsinki

The Investigator will ensure that this research is conducted in accordance with the principles of the Declaration of Helsinki.

Approvals

The application form/protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Medical Sciences IDREC, and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all amendments to the original approved documents.

Annual Progress Report

The CI shall submit an Annual Progress Report to the Medical Sciences IDREC within one month of the anniversary of approval.

Section N. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

Section O. Dissemination and feedback of research outcomes			
1. Will you preregister this research?		Yes ☒	No ☐
2. If yes, please state the platform where it will be preregistered	We will pre-register this research on a clinical trials registry (clinicaltrials.gov).		
3. How will you disseminate project outcomes at the end of the research?	The study will be published in a peer-reviewed journal and may be presented at academic conferences. The study will be written up as a chapter of a doctoral (DPhil) thesis. A brief summary of the study findings will be provided to participants, upon request.		

Section P. References

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Section Q. Declarations and signatures of researchers

In providing signatures, the MS IDREC Secretariat will accept either:

Option 1: Email confirmations sent from a University of Oxford email address. Separate emails should be sent by each of the relevant signatories as outlined below, indicating acceptance of their responsibilities.

Option 2: That the form be fully-signed with handwritten (wet-ink) signatures. Please scan these and the rest of the form pages to create a single PDF document and email to us.

I/We, the researcher(s) agree:

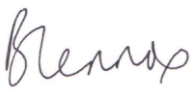
- To start this research only after obtaining approval from MS IDREC/CUREC;
- To carry out this research only if funding is adequate to enable it to be carried out according to good research practice and in an ethical manner;
- That it is the responsibility of the Principal Investigator to ensure that all researchers working on this project are qualified and either experienced, or have received appropriate ethical training, to conduct the research described;
- To provide additional information as requested by MS IDREC/CUREC before approval is secured and as research progresses;
- To maintain the confidentiality of all data collected from or about participants;
- To notify the MS IDREC in writing immediately of any proposed change which would increase the risks that any participant is exposed to and await approval before proceeding with the proposed change;
- To notify the MS IDREC if the Principal Investigator on the research changes and supply the name of the successor;
- To notify the MS IDREC in writing within seven days if any serious *adverse event* occurs in the course of research;
- To use data collected only for the research for which approval has been given;
- To grant access to data only to authorised persons; and
- To maintain security procedures for the protection of personal data, including (but not restricted to): removal of identifying information from data collection forms and computer files, storage of linkage codes in a locked cabinet and password control for access to identified data on computer files.

Principal Investigator (Name)	Dr Susannah Murphy
Principal Investigator (Signature) Pasted images of signatures cannot be accepted	
Medically qualified collaborator (Name)	Professor Philip Cowen
Medically qualified collaborator (Signature) Pasted images of signatures cannot be accepted	
Student (Name)	Michael J Colwell
Student (Signature) Pasted images of signatures cannot be accepted	

Section R. Acceptance by Head of Department/Faculty*

*or other senior member of the department if the Principal Investigator is the Head of Department. Example nominees include Deputy Head of Department, or, for student projects, Director of Graduate Studies.

- I have read this application, and am aware of the research proposed.
- To the best of my knowledge, the proposed design and scientific methodology do not raise concerns.
- I support this research in principle, subject to ethical and other necessary reviews.

Head of Department (Name)	Prof Belinda Lennox
Head of Department (Signature) Wet-ink signature (not pasted electronic image) *or* The Head of Department/nominee can send an email (including PI name and study title) to ethics@medsci.ox.ac.uk confirming the above	
Date	18th Oct 2022

Section S. Amendment history

List details of all protocol amendments here whenever a new version of the protocol is produced.

This is not necessary prior to initial ethics submission.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.0	31/01/2023	Michael Colwell	Change from adaptive n-back task to instrumental n-back task. Addition of Change Detection Task Increase dose of pitolisant from 18mg to 36mg. Change reimbursement from £150 to £140; change travel cap to £20.