CENTRAL UNIVERSITY RESEARCH ETHICS COMMITTEE (CUREC)

CUREC 3 Protocol and Application Form

Pharmacological Studies in Healthy Volunteers

SECTION A. RESEARCH DETAILS	
1. Full title of research	Effects of a 14-day combined antidepressant and behavioural intervention on emotional cognition in healthy volunteers experiencing low mood
2. Short title of research	Combined Antidepressant and Behavioural Intervention (CABIN)
3. MS IDREC reference	R74013/RE006
4. Date and version number	Version 5.0, 31st March 2022
5. Principal Investigator	Professor Catherine Harmer
6. Student (if applicable)	Ms Andreea Raslescu, DPhil candidate, University of Oxford
7. University email address	catherine.harmer@psych.ox.ac.uk andreea.raslescu@psych.ox.ac.uk
8. University telephone number	+44 (0)1865 618339
9. Medically qualified collaborator (Licensed doctor)	Dr Sandra Tamm, Department of Psychiatry, University of Oxford Medical Doctor (Karolinska Institutet, Stockholm, Sweden, 2013), Clinical internship (Karolinska University Hospital, Stockholm, Sweden, 2019), PhD in Medical Science (Karolinska Institute, 2019). Clinical residency in Psychiatry (Psykiatri Sydväst, Stockholm, Sweden, ongoing, temporary on research leave) 7 years of experience in research studies involving healthy volunteers and patients sandra.tamm@psych.ox.ac.uk
10. Funding source	This project is funded by a philanthropic gift from the Sloane Robinson Foundation. Ms Raslescu is additionally supported through a Medical Research Council (MRC) Research Training and Support Grant (RTSG) (project code BRT00030, task HQ10.01).

11. 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:		
Participants may also be recruited via advertisements targeting Oxford Brookes University, following approval from Oxford Brookes University Research Ethics Committee.		
12. Declaration of any Conflicts of Interest	None	
13. 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 (Medical Sciences IDREC), unless authorised to do so.	

SECTION B. RESEARCHERS	
1. Researcher title and name	Professor Catherine Harmer
2. Department / Institute name	Department of Psychiatry, University of Oxford
3. Role in research	Study design and data interpretation Professor of Cognitive Neuroscience DPhil, MA, DipLATHE >20 years of experience in conducting experimental medicine studies
4. Training/Experience in research ethics and/or research integrity	Online Good Clinical Practice revalidation, including: protocol and associated documents; applications, agreements and approvals; trial master files; conducting the trial; safety reporting; completed December 22nd 2020 Epigeum web-based "Research Integrity" training course; completed October 27th 2016
5. Researcher title and name	Dr Susannah Murphy
6. Department / Institute name	Department of Psychiatry, University of Oxford
7. Role in research	Study design, data analysis and data interpretation NIHR Oxford Health BRC Senior Research Fellow BA (Hons), MSc, DPhil >10 years of experience in conducting experimental medicine studies

8. Training/Experience in research ethics and/or research integrity	Online Good Clinical Practice revalidation, including: protocol and associated documents; applications, agreements and approvals; trial master files; conducting the trial; safety reporting; completed December 8th 2020 NIH web based "Protecting Human Research Participants" training course; completed August 10th 2017
9. Researcher title and name	Ms Andreea Raslescu
10. Department / Institute name	Department of Psychiatry, University of Oxford
11. Role in research	Study design, participant screening and recruitment, data collection, data analysis, results dissemination 4 years of experience in research management, including CNS clinical trials and neuroscience-focused public-private partnerships
12. Training/Experience in research ethics and/or research integrity	Epigeum web-based "Research Integrity" training course; completed October 9th 2020 WebLearn web-based "Avoiding Plagiarism" training course; completed October 9th 2020 RQA e-learning course "Introduction to Good Clinical Practice"; completed July 14th 2020
13. Researcher title and name	Ms Tereza Ruzickova
14. Department/Institute name	Department of Psychiatry, University of Oxford
15. Role in research	Study design, participant screening and recruitment, data collection 3 years of experience in research management
16. Training/Experience in research ethics and/or research integrity	Epigeum web-based "Research Integrity for Biomedical Sciences" training course; completed January 23rd 2019 WebLearn web-based "Avoiding Plagiarism" training course; completed February 8th 2019
17. Researcher title and name	Mr James Carson
18. Department/Institute name	Department of Psychiatry, University of Oxford
19. Role in research	Participant screening and recruitment, data collection, data analysis 1-year experience as a research assistant and 1-year experience as an MRes student working in psychopharmacology and cognitive neuroscience. Worked on projects involving features of clinical trial design, neuroimaging, and drug and therapy administration.

20. Training/Experience in research ethics and/or research integrity	Oxford University web-based “Good Clinical Practice” training course; completed December 13th 2019 University College London web-based “Good Clinical Practice” training course; completed October 2018

SECTION C. SYNOPSIS		
1. Please state why this research is not considered a Clinical Trial of an Investigative Medicinal Product	The present study does not fit the MHRA definition of a clinical trial, which specifies that a clinical trial of a medicinal product is designed to discover or verify/compare a drug's clinical effects, to discover or verify/compare its pharmacological effects (e.g. pharmacodynamics), to identify or verify/compare its adverse reactions, or to study its absorption, distribution, metabolism or excretion (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf). Our study will not be concerned with the clinical, pharmacological or metabolic effects of citalopram, nor with the clinical effects of combined citalopram and behavioural activation as a treatment for low mood. We seek to investigate whether the physiological and cognitive effect of citalopram is differentially modulated by different environmental conditions, as defined by the presence or absence of behavioural activation training. The period of drug administration is short (14 days) and our endpoints of interest are non-clinical, consisting of accuracy and reaction time scores derived from a series of tests of emotional cognition. Furthermore, and unlike a clinical trial, we will recruit a community sample and not a clinical sample. Therefore, we believe that the present study is an Experimental Medicine (EM) study rather than a clinical trial.	
2. List all places where research will be conducted	Department of Psychiatry Neurosciences Building, Warneford Hospital, University of Oxford	
3. Age range of participants	18-65 years (inclusive)	
4. Anticipated number of participants	135 (45 placebo group, 45 citalopram group, 45 combined citalopram and behavioural activation group)	
5. Anticipated research start date	1st March 2021	
6. Anticipated research end date	1st October 2022	
7.	**Objectives**	**Outcome Measures**
Primary	To investigate how the combined administration of citalopram and behavioural activation influences emotional cognition in participants experiencing self-reported low mood and activity levels.	Accuracy and reaction times on computer-based measures of emotional cognition (facial expression recognition task, emotional categorisation task, emotional recall task).
Secondary	To investigate how the combined administration of citalopram and behavioural activation influences	Accuracy, consistency, reaction times, monetary wins and losses, learning rate and

	reward processing in participants experiencing self-reported low mood and activity levels.	decision temperature on the Probabilistic Instrumental Learning Task.
	To investigate how the combined administration of citalopram and behavioural activation influences motor activity in participants experiencing self-reported low mood and activity levels.	Frequency of motor activity as measured by GeneActiv actigraphy watches.
	To investigate how the combined administration of citalopram and behavioural activation influences morning cortisol in participants experiencing self-reported low mood and activity levels.	Change in waking cortisol levels before and after the 2-week intervention.
8. Name of drug/substance	Citalopram	
9. Purpose of drug/substance use in this research	A body of evidence from both animal and human research suggests that antidepressant drugs may induce early changes in emotional processing that interact with environmental factors to produce a later change in mood. This experimental medicine study will examine the effect of citalopram on emotional cognition under different environmental conditions (as manipulated by the presence or absence of behavioural activation training). Participants will be administered either citalopram or placebo over the course of two weeks. Citalopram will be taken either alone or in combination with behavioural activation training.	
10. Adverse reactions and side effects posing a particular risk with this treatment	Citalopram is generally well tolerated. Previous research involving either acute or short-term citalopram administration schedules have noted few side effects, with nausea and dizziness generally being more common in participants receiving citalopram as opposed to placebo and no difference observed in terms of dry mouth, alertness, agitation or headaches (Hobbs et al., 2020). Moreover, short-term citalopram administration does not appear to alter subjective mood, anxiety, and hostility (Harmer et al., 2003, 2004; Murphy et al., 2009). During chronic SSRI treatment, these side effects have been noted: **Common (1-10%)** Anxiety; abnormal appetite; acute angle closure glaucoma; apathy; arrhythmias; arthralgia; asthenia; impaired concentration; confusion; constipation; depersonalisation; diarrhoea; dizziness; drowsiness; dry mouth; fever; flatulence; gastrointestinal discomfort; haemorrhage; headache; hyperhidrosis; hypersalivation; malaise; memory loss; menstrual cycle irregularities; migraine; myalgia; mydriasis; nausea (dose-related); palpitations; paraesthesia; QT interval prolongation; rhinitis; sexual dysfunction; skin	

	reactions; sleep disorders; altered taste; tinnitus; tremor; urinary disorders; visual impairment; vomiting; weight changes; yawning. **Uncommon (0.1 to 1%)** Alopecia; angioedema; abnormal behaviour; hallucinations; mania; movement disorders; oedema; photosensitivity reaction; postural hypotension; seizures; suicidal tendencies; syncope. **Rare or very rare (< 0.1%)** Galactorrhoea; hepatitis; hyperprolactinaemia; hyponatraemia; serotonin syndrome; severe cutaneous adverse reactions (SCARs); SIADH; thrombocytopenia.

SECTION D. ABBREVIATIONS

ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ASD	Autism Spectrum Disorders
BA	Behavioural Activation
BADS	Behavioural Activation for Depression Scale
BDI-II	Beck Depression Inventory
BIS/BAS	Behavioural Inhibition Scale/Behavioural Activation Scale
BMI	Body Mass Index
(OH) BRC	NIHR Oxford Health Biomedical Research Centre
CUREC	Central University Research Ethics Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECAT	Emotional Categorisation Task
EOS	End Of Study visit
EREC	Emotional Recognition Task
EROS	Environmental Reward Observation Scale
ETB	Emotional Test Battery
FERT	Facial Emotion Recognition Task
GDPR	General Data Protection Regulation
GP	General Practitioner
ICF	Informed Consent Form
MDD	Major Depressive Disorder
MS	Multiple Sclerosis
MS IDREC	Medical Sciences Interdivisional Research Ethics Committee

NHS	National Health Service
NICE	National Institute of Health and Care Excellence
OSF	Open Science Framework
PERL	Psychopharmacology and Emotion Research Laboratory
PHQ-9	Patient Health Questionnaire
PILT	Probabilistic Instrumental Learning Task
PIS	Participant Information Sheet
SAP	Statistical Analysis Plan
SCID-5	Structured Clinical Interview for DSM-5
SOP	Standard Operating Procedure
SSRIs	Selective Serotonin Reuptake Inhibitors
STAI	State-Trait Anxiety Inventory
VAS	Visual Analogue Scale

SECTION E. BACKGROUND AND RATIONALE

Major Depressive Disorder (MDD) is a common psychiatric condition characterised by pervasive low mood as well as changes in sleep, appetite and cognition. In the UK, it is estimated that 3 in 100 people meet criteria for MDD every week (McManus et al., 2016), costing the economy £20.2–23.8 billion every year in health service, lost earnings and lower productivity (McCrone et al., 2008).

A variety of pharmacological and psychological interventions for MDD are available. Selective serotonin reuptake inhibitors (SSRIs) are the first-choice medication for depression in the UK, as recommended by National Institute of Health and Care Excellence (NICE) guidelines. Whilst SSRIs have been demonstrated to be more effective than placebo (Cipriani et al., 2018), only about 50% of patients respond to their first-prescribed antidepressant (Trivedi et al., 2006). Understanding the mechanism through which SSRIs exert their antidepressant effect could explain why their effectiveness is not universal and allow for personalised treatments.

Experimental medicine studies conducted over the last 15-20 years have shown that SSRIs have early effects on emotional cognition, and that these precede clinically significant changes in depressive symptomatology (see Harmer et al., 2017 for a review). For example, one week of treatment with citalopram was found to decrease recognition of negative facial expressions and increase the relative recall of positive vs negative words (Harmer et al., 2004). The switch from implicit changes in cognitive bias to explicit changes in mood is thought to occur through interaction with the environment and re-learning of positive associations. Indeed, rodent studies suggest that SSRIs only induce a positive bias in memory when administered before learning (Stuart et al., 2015) and that SSRI-induced neuroplasticity only occurs in the presence of an positive/enriched environment (Branchi et al., 2013; Alboni et al., 2015).

These findings imply that an enriched environment from which patients can derive positive and meaningful reinforcement may be important for antidepressant function. This hypothesis is indirectly supported by multiple reports of a positive correlation between antidepressant treatment outcome and patients' socioeconomic status

as a proxy for environmental enrichment (Trivedi et al., 2006; Cohen et al., 2009), but to our knowledge this has not been experimentally tested in humans.

This experimental medicine study will explore whether the early cognitive effects of the SSRI citalopram are modulated by different levels of environmental enrichment. The presence/absence of environmental enrichment will be modulated through provision of two weeks of behavioural activation (BA) training to a third of our sample; BA is a psychological intervention aimed to increase levels of environmental reinforcement by monitoring and adjusting an individual's daily activities. By comparing the combined effects of citalopram and BA to those of citalopram alone and placebo alone on performance of emotional cognition tasks (Emotional Test Battery (ETB)), we will test whether the early cognitive changes induced by antidepressants are increased in the context of a more rewarding environment. We hypothesise that the participant group receiving citalopram and BA will show greater changes in emotional cognition in the expected direction (decrease in negative bias/increase in positive bias) compared to the citalopram alone and placebo alone groups after the two-week intervention.

A community sample of 135 participants experiencing self-reported low mood and low activity levels will be recruited through University/social media advertisement. Participants will be randomised into one of three groups, each undergoing two weeks of either: 1) placebo alone, 2) citalopram alone or 3) citalopram and behavioural activation training. Each participant will be asked to complete a series of computerised tasks measuring emotional cognition and reward processing before and after the two-week intervention. Additional data will be collected on participants' frequency of motor activity (using actigraphy watches) and waking cortisol levels.

Due to the nature of the intervention, the study will be single blinded only to citalopram or placebo administration. As the primary researcher will be the one administering BA, both the participants and the primary researcher will be aware of who did or did not receive the psychological intervention. However, participants will not be aware that receiving BA means they are also taking citalopram. The primary researcher, on the other hand, will be aware of this and will only be blinded to drug administration in the BA-free groups. To compensate for the lack of complete blinding, post-treatment outcome data will be collected online and not directly by the primary researcher. Moreover, before the data is analysed, participant ID numbers will be re-allocated to avoid bias in the outlier detection and data exclusion process.

Potential risks to participants involve the possibility of experiencing side effects of antidepressant drug administration. These side effects will be monitored each week, although previous studies suggest they are infrequent and usually mild. Some of our screening and questionnaire measures will also ask about difficult topics such as the presence of psychiatric symptoms and suicidal ideation, which may be distressing for some participants. Participants will be made aware of this through the Participant Information Sheet (PIS), and will be reminded that they do not have to answer any questions that they do not wish to.

Potential burdens may include limits on cycling, driving and operating heavy machinery if participants are affected by side effects such as drowsiness or sleepiness. Participants will also be recommended to limit excessive alcohol consumption during the study.

There are no direct benefits for participants to taking part in the study. Some participants may find the BA training rewarding, or the techniques discussed helpful in managing mood. Participants will be reimbursed for their time in the study.

SECTION F. PARTICIPANTS

1. Description of research participants

135 participants experiencing self-reported low mood and low activity levels, aged between 18 and 65 years (inclusive).

2. Inclusion Criteria

To be eligible for inclusion, participants must:

- Be aged between 18-65 years (inclusive)
- Be resident in the UK for the duration of the study
- Be fluent in English
- Have normal or corrected to normal vision
- Experience subjective low mood (defined as a score of 10 or above on the BDI-II)
- Experience low activity levels (self-reported)
- Be willing and able to give informed consent for participation in the research
- Have access to a computer or laptop with a functioning keyboard and reliable internet connection

3. Exclusion criteria

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

- Antidepressant treatment or medication prescribed to treat depression/low mood, currently or in the last six months
- Current psychological therapy of any kind
- Current or past probable diagnosis of psychosis, bipolar disorder, OCD, PTSD, substance abuse disorder or any eating disorder, as indicated by the SCID-5
- Current or past diagnosis of any personality disorder (e.g. borderline personality disorder) according to self-report
- Judged to be at clinical high risk of suicide
- Past suicide attempt
- Current or past hospitalisation for mental health reasons
- 1st degree relative with diagnosis of bipolar disorder
- Diagnosis of a developmental disorder (e.g. ASD, ADHD, Tourette's syndrome, severe learning disability) according to self-report; this excludes cases of mild dyslexia or dyscalculia where in the opinion of the study team such difficulties would not interfere with the performance of the tasks required in this study
- Diagnosis of a neurological disorder (e.g. epilepsy, MS) according to self-report
- Score of >30 on the BDI-II
- Current use of medication that might interact with the effects of citalopram (except for the contraceptive pill)
- Known contraindication to citalopram including: past allergic reaction to citalopram or any other medicines, diagnosis of a cardiovascular condition, glaucoma, type 1 or type 2 diabetes, diagnosis of epilepsy, undergoing electroconvulsive treatment (ECT), or current use of any other medication that is associated with prolonged QT-interval
- Any other current or past medical conditions which in the opinion of the study medic may interfere with the safety of the participant or the scientific integrity of the study
- Heavy use of cigarettes (smoke > 20 cigarettes per day)
- Heavy use of caffeine (drink > 4 250ml cups/cans of coffee/energy drinks per day)
- Severely underweight or overweight in a manner that renders them unsuitable for the study in the opinion of the study medic
- Lactose intolerance (due to the study involving administration of a lactose placebo tablet)
- Pregnancy (as determined by urine pregnancy test taken during the Part 2 screening visit), breast feeding or plans to become pregnant
- Participation in an ETB study in the past 6 months
- Participation in another drug study in the past 3 months

4. Recruitment

Participants will be recruited by word of mouth, emails to departmental and college mailing lists, posters located in University Departments, social media posts and ads (Facebook, Instagram, Twitter) as well as through websites (e.g. Daily info, Call For Participants and MQ research website). The recruitment ads and posters will state that we are looking for volunteers "low in mood and activity". They will contain brief information about the study, its inclusion and exclusion criteria and a link to an online pre-screening questionnaire (see APPENDIX A: STUDY ADVERTS).

Participants may also be recruited via advertisements targeting Oxford Brookes University, following approval from Oxford Brookes University Research Ethics Committee. Any advertisements for Oxford Brookes students and staff will contain this additional statement: "Oxford Brookes University has knowledge of this study and has permitted recruitment at the University. In the event of any questions about the study, please contact the researchers in the first instance. Should you need to contact anyone at Oxford Brookes about this further, please email: ethics@brookes.ac.uk".

We will also collaborate with Lindus Health, a small company that specialises in clinical recruitment for research studies. Lindus Health will advertise the study on Facebook separately from the research team and, upon participants clicking through, will administer a brief online screening questionnaire reflecting our inclusion/exclusion criteria as described in this protocol. Lindus Health will also collect online consent from prospective participants to pass on their contact details to the study team, and remove all participant identifiable information as soon as these details have been received by the study team.

5. Screening and eligibility assessment

All study adverts run by the research team will contain a direct hyperlink to a Qualtrics page hosting the PIS, the supplementary PIS on COVID-19 and a short pre-screening questionnaire. As such, prospective participants who are interested in the study will be able to directly access this link to find out more information; they will also be able to contact the researchers if they wish by using the contact details provided on Qualtrics and as part of the PIS. For participants recruited via Lindus Health, the study researchers will send them the hyperlink to the Qualtrics page via email upon receipt of their contact details. Participants will be given as much time as needed to decide about their participation – they can withdraw interest at any point by simply navigating away from the page. No data will be saved.

The pre-screening questionnaire will ask about their current symptoms of depression using the BDI-II (excluding sensitive questions about suicidality) and will be automatically scored. Prospective participants who wish to complete the pre-screening questionnaire will be asked to consent to the collection of these data by clicking an online box to indicate agreement to the pre-screening process. Before consenting, they will be informed of the following:

- that their preliminary eligibility will be confirmed upon completion of the questionnaire
- that, if they are eligible, their data will be stored in a pseudonymised (de-identified) format according to the information in the Participant Information Sheet
- that, if they are not eligible, they will not have to provide any personal identifiers (such as name or email) and as such the pre-screening data provided will be completely anonymous.

After submitting their answers to the pre-screening questionnaire, prospective participants who score between 10 and 30 inclusive on the BDI-II will be considered preliminarily eligible. They will be displayed a page informing them of having passed pre-screening and will be provided a unique screening ID, which will also be used to identify their pre-screening data on Qualtrics. They will also be given contact details for the research team and a link to a Calendly calendar. On Calendly, the prospective participant will input their name, email address, phone number, screening ID and preferred visit location (online via Microsoft Teams/at the Department of Psychiatry) and will select a convenient 1h timeslot for their Part 1 screening visit.

Participants whose scores fall outside the specified bounds will be displayed a “thank you” page thanking them for their interest in the study and offering a series of links to more information about citalopram, behavioural activation, and other mental health resources. No personal identifiable data will be collected. In the case of prospective participants recruited via Lindus Health, the researchers will hold participants’ names and contact details but will be unable to match these to their pre-screening data if they are not eligible to take part in the study.

Part 1 of Screening Visit

The screening visit will consist of two parts. Part 1 will be conducted either remotely (as a videoconference or telephone call) or in person at the Department of Psychiatry, Warneford Hospital. The decision about whether Part 1 will be conducted remotely or in person will depend on current COVID-19 restrictions and the participant’s preference. At the start of Part 1 of the screening visit, one of the named researchers will further explain the study

to the participant and answer any questions they have. Informed Consent will be collected prior to the administration of any screening procedures. If Part 1 of the screening visit is to be held remotely, the researcher will go through the consent form point-by-point with the participant and complete a paper version of the ICF on their behalf. The researcher will sign the ICF, scan it and send a copy to the participant for their records. The participant will then physically sign the ICF at the start of Part 2 of the screening visit, which will take place in person, and will be given another copy to keep.

During Part 1 of the screening visit, the following procedures will be performed:

- Completion of a COVID-19 Symptom Screening Form (administered before entry into the Department of Psychiatry if visit is completed in person; if the participant deems any of the COVID-19 symptoms on the form relevant for themselves or a member of their household, they will be invited to reschedule the visit; see APPENDIX B)
- Temperature check using infrared "no-touch" thermometer (in person visit only; if the participant's temperature exceeds 37.2°C they will be invited to reschedule the visit)
- The researcher will go through the PIS with the participant, and answer any questions they may have. They will then take informed consent.
- Demographic data collection (including age, gender, race, years of education, marital status, living arrangements and languages spoken)
- Taking relevant medical history (including personal and family history of psychiatric disorders; diagnoses that represent contraindications for citalopram or increase susceptibility to COVID-19; food intolerances)
- Review of concomitant medication
- Assessment for psychiatric disorders using the structured clinical interview for DSM-5 (SCID-5)
- Review of lifestyle (including daily cigarette and coffee consumption)
- Administration of the BDI-II questionnaire (a link to the questionnaire will be sent by the researcher)

Part 1 of the screening visit is expected to take approximately 1 – 1.5 hours.

Following Part 1 of the screening visit, individual participants will be discussed with the study medic to confirm eligibility before being invited for Part 2. If questions arise during screening that require input from the study medic, from either the researcher or the participant, a follow-up call with the study medic may be arranged.

Part 2 of Screening Visit

If no exclusion criteria are identified, participants will progress to Part 2 of the screening visit, which will be held in person in the Neurosciences Building of the Department of Psychiatry at the Warneford Hospital. The maximum allowed period between Part 1 and Part 2 screening is four weeks (28 days).

During Part 2 of the screening visit, the following procedures will be performed:

- Completion of a COVID-19 Symptom Screening Form (administered before entry into the Department of Psychiatry; if the participant deems any of the COVID-19 symptoms on the form relevant for themselves or a member of their household, they will be invited to reschedule the visit; see APPENDIX B)
- Temperature check using infrared "no-touch" thermometer (if the participant's temperature exceeds 37.2°C they will be invited to reschedule the visit)
- Confirmation of continued consent by the participant signing the form (if Part 1 was conducted remotely)
- Broad review of inclusion/exclusion criteria assessed at Part 1 (to check for changes in medication/therapy and diagnoses)
- Height and weight measurement (to check BMI)
- Pregnancy test (female participants only)
- Collection of payment details

Eligible participants will be immediately included into the study and randomised into one of three intervention groups using a pre-specified Randomisation List, which ensures gender balancing across intervention groups. The list will be password protected and stored on a University computer in the Department of Psychiatry. In the event of serious side effects or an adverse event it will be possible for blinding to be broken by accessing this file.

The randomisation code will be drawn up by a researcher not involved in the study, following the NIHR Oxford BRC SOP for randomisation. Participant IDs will be allocated to groups at the point of encapsulation and

participants will then be assigned Participant IDs in order. The primary study researcher will be unblinded as to whether each individual participant is meant to receive behavioural activation training.

At the end of Part 2 of the screening visit, participants will be given an actigraphy watch and asked to wear it on their non-dominant wrist at all times. They will also be given tubes for saliva collection and precise instruction on how to collect their saliva at the beginning and at the end of the intervention. In short, participants will be instructed to collect three saliva samples (using a Sarstedt Salivette system) at home immediately upon awakening and thereafter every 15 minutes until 30 minutes post-awakening. They will have to perform the procedure twice, once before and once after the intervention. During the Part 2 screening visit, the researcher will discuss with each participant the best day to take their baseline saliva samples in the week leading up to the baseline visit. This will depend on the participant's work patterns and the time the saliva samples will be due for collection at the end of the study, as the baseline and end-of-study samples will need to be collected on days of similar routine (weekday or weekend). Postage-paid packaging will be provided to all participants for the return of saliva samples and actigraphy watches.

Participants will be told they will receive the link to an online mood questionnaire daily via text, in order to check whether the intervention groups were equivalent in their subjective state report throughout the study.

All participants will receive a 2-week supply of either 20mg citalopram or placebo tablets. They will be instructed to start taking the medication after one week, to allow for baseline activity data collection for a week after participants' receipt of the actigraphy watch.

Finally, participants who are randomised to the behavioural activation group will receive a blank diary to record their activity levels over the week leading up to the Baseline visit. This will be in either paper or electronic format, whichever the participant prefers.

Part 2 of the screening visit is expected to last ~1.5 hours.

All clinical procedures in this study (including COVID-related restrictions) will be carried out with adherence to the relevant Departmental SOP's (see APPENDIX C: CLINICAL AND PSYCHOLOGY TESTING ROOMS RISK ASSESSMENT FOR RETURN TO ON-SITE WORKING IN NEUROSCIENCES BUILDING).

6. Information Provided to Participants and Informed Consent

Prospective participants will be able to access the Participant Information Sheet (PIS) and Supplementary PIS on COVID-19 (see APPENDICES D and E) by selecting the link provided on all study adverts. Written and verbal versions of both PIS's will also be presented at the start of Part 1 of the screening visit.

The PIS will detail the exact practical demands of the research, written from the participant's perspective and in simple non-technical language. It will describe when and where will they be required to attend, what procedures are involved and for how long, how data will be collected and offer brief justification of the interventions. It will also contain information about any possible risks and benefits of taking part in the research, such as side effects of the study drug. The Supplementary PIS on COVID-19 will outline the steps the researchers have taken to minimise the risk of COVID-19 infection, safety procedures for study visits and expectations from study participants with regards to their and the researchers' safety. Prospective participants will be allowed as much time as they wish to consider the information and will have the opportunity to question the Principal Investigator (PI) or other independent parties to decide whether or to participate in the research. The PIS will clearly state that the participant is free to withdraw from the research at any time, for any reason, and with no obligation to give a reason for withdrawal.

Consent for the collection of pre-screening data will be documented by asking the participant to click an online box to indicate agreement to the pre-screening process (filling in the questionnaire and being informed of their preliminary eligibility), before completion of the questionnaire. Before consenting, they will be informed of the following:

- that their preliminary eligibility will be confirmed upon completion of the questionnaire

- that, if they are eligible, their data will be stored in a pseudonymised (de-identified) format according to the information in the Participant Information Sheet
- that, if they are not eligible, they will not have to provide any personal identifiers (such as name or email) and as such the pre-screening data provided will be completely anonymous.

The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF; see APPENDIX F: INFORMED CONSENT FORM) before any study specific procedures are performed.

Written Informed Consent for study participation will require a dated signature by the participant and the researcher who presented and obtained the Informed Consent. The researcher who obtained the consent (either the primary researcher or a research assistant) will be suitably informed, qualified and experienced, and authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site. If Part 1 of the screening visit is completed remotely, the researcher will go through the consent form point-by-point with the participant and complete a paper version on their behalf, followed by the participant providing their signature at the start of Part 2 of the screening visit.

Due to the ongoing COVID-19 pandemic, study participants will be provided with guidelines for attending study visits in adherence to the latest social guidance and Departmental policy (see APPENDIX E: SUPPLEMENTARY PIS). As the situation is ongoing, participants will be updated by the researchers if the guidelines change and provided an updated supplementary PIS.

7. Participant confidentiality

The research staff will ensure that the participants' data are safeguarded. The research will comply with the Data Protection Act, which requires personal data to be anonymised as soon as it is practical to do so. Where possible, participants will be identified only by a participant ID number on documents and on any electronic database. Documents (such as consent forms) that contain identifying data and/or information allowing this to be linked to the participant ID will be stored separately under strict access controls. All documents will be stored securely and only accessible by research staff and authorised personnel.

It will be made clear to the participant that personal information shared within the course of the screening and study visits may be shared within the research team but will not be shared with anyone else. The exceptions to this are stated clearly in the Participant Information Sheet:

"Information collected about you during the course of the research will be kept confidential. Confidentiality would only be breached in the very rare circumstance that it was judged that you or someone else was at immediate risk of serious harm. In these circumstances only information necessary to ensure immediate safety would be released. The only other circumstance in which information would be released is if it was requested by an order of a court of law."

SECTION G. RESEARCH PROCEDURES

1. Baseline Assessments and Procedures

See Section F5 for full details of the assessments and procedures that will be carried out as part of the screening visit.

The baseline visit will take place remotely, approximately 7 days after Part 2 of the screening visit, and will be split into an online baseline testing session and a Microsoft Teams meeting with one of the study researchers. Thus, the baseline visit may occur over a single day or two consecutive days depending on the participant's and the researcher's availability. Each case will be discussed when the Baseline visit is booked during Part 2 of the screening visit.

Participants will receive instructions on how to access an online battery of questionnaires and tasks and will undergo ~1h of online baseline testing, including:

- BDI-II
- State Trait Anxiety Inventory (STAI) – state and trait versions
- Behavioural Activation for Depression Scale (BADS)
- Environmental Reward Observation Scale (EROS)
- Behavioural Inhibition Scale/Behavioural Activation Scale (BIS/BAS)
- Multidimensional Scale of Perceived Social Support
- Visual Analogue Scale (VAS) of antidepressant side effects (to determine baseline bodily functioning)
- Facial Expression Recognition Task (FERT)
- Emotional Categorisation Task (ECAT)
- Emotional Recall Task (EREC)
- Emotional Memory Task (EMEM)
- Probabilistic Instrumental Learning Task (PILT)

The FERT, ECAT, EMEM and EREC tasks measure emotional processing and involve the presentation of faces displaying different emotions and words with neutral, positive and negative valence. The PILT involves making choices between different shapes, some of which lead to winning money and some of which lead to losing money. Participants will be able to win up to £5 each time they complete this task 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.

After completion of baseline tests, participants will attend a 1:1 videoconference (over Microsoft Teams) with one of the named researchers during which they will receive instructions on starting their pharmacotherapy i.e., taking one capsule of either 20mg citalopram or placebo a day for the next 2 weeks. During the two weeks of citalopram/placebo administration, participants will be advised not to drink alcohol and not to carry out activities requiring full alertness, such as driving, if they are aware of any impairment, such as sleepiness. Participants will receive a text message every day reminding them to take the capsule and will be asked to respond with the time that they have taken it.

Participants randomised to the behavioural activation training group will undergo a further 1:1 behavioural activation training session lasting approximately 1.5 hours. This will involve working through the "Get active, feel good!" booklet developed at the University of Exeter (APPENDIX G). This includes psychoeducation about low mood and the principles of BA, goal setting, baseline activity monitoring and task grading according to activity type and difficulty. This booklet-based online paradigm has been successfully used in another study in the Psychopharmacology and Emotion Research Laboratory (PERL). The Baseline BA training session will be followed up by two shorter 30-minute sessions during Follow-up calls 1 and 2, for a total of three sessions.

The baseline visit is expected to last between 1.5 and 3.5 hours depending on group allocation.

In all cases, the study intervention will start on the day of the Teams meeting with the researcher, and that day will be considered day 1 of intervention.

2. Subsequent Visits

Follow-up call 1

The first follow-up call will take place 5-7 days after the Baseline visit (between days 6 and 8 of intervention). Participants will attend a 1:1 teleconference with the primary researcher (over Microsoft Teams) to ask about any side effects experienced while taking the capsule. The group receiving behavioural activation will also be asked

about progress on their behavioural activation goals and offered help with goal setting for the next few days. The follow-up call is expected to last between 15 and 45 minutes, depending on group allocation.

Follow-up call 2

The second follow-up call will take place 11-13 days after the Baseline visit (between days 12-14 of intervention). Participants will attend a 1:1 teleconference with the primary researcher (over Microsoft Teams) to ask about any side effects experienced while taking the capsule. During the teleconference, the researcher will discuss with the participant the best day to take their end-of-study saliva samples in the last 1-2 days of intervention. The window for taking end-of-study saliva samples is limited by the relatively short half-life of citalopram.

The group receiving behavioural activation will also be asked about progress on their behavioural activation goals and perform a "staying well" exercise. The follow-up call is expected to last between 15 and 45 minutes, depending on group allocation.

End Of Study (EOS) assessment

The EOS assessment will take place remotely, 12-14 days after the Baseline visit (between day 13 of intervention - day 1 post-intervention) and 1-2 days after Follow-up call 2. Participants will receive instructions on completing a slightly shorter online battery of questionnaires and tests, including:

- BDI-II
- State Trait Anxiety Inventory (STAI) – state version only
- Behavioural Activation for Depression Scale (BADS)
- Environmental Reward Observation Scale (EROS)
- Visual Analogue Scale (VAS) of antidepressant side effects
- Emotional Categorisation Task (ECAT)
- Facial Expression Recognition Task (FERT)
- Emotional Recall Task (EREC)
- Emotional Memory Task (EMEM)
- Probabilistic Instrumental Learning Task (PILT)

At the end of the EOS visit, participants will attend a 1:1 teleconference with one of the study researchers (over Microsoft Teams) during which they will be debriefed and asked to guess which treatment they received to measure the success of blinding. They will be offered to book a further telephone consultation with the study medic, who can offer further advice on the management of mood symptoms. Participants who choose to have the consultation can, if they wish, be unblinded/told by the study medic what their drug was. If requested by the participant, the study medic will write to their GP to inform them that the participant may need further advice on treatment options for their mood symptoms. At the end of the study, citalopram/placebo will be discontinued for all participants.

The EOS visit is expected to last ~1.5 hours.

Daily mood questionnaire

Throughout their participation in the study (from inclusion at the screening visit to the day of the EOS visit), participants will complete a simple online daily mood questionnaire, the link to which will be texted to their phone. Responding to the daily mood questionnaire is expected to take less than 5 minutes.

3. Sample Handling

Urine samples will be used for pregnancy tests. These will be administered during Part 2 of the screening visit by a trained member of the research team using dipstick tests. Urine samples will be destroyed immediately after the test result has been obtained.

Saliva samples will be collected by participants before and after the two-week intervention. Participants will be provided postage paid packaging and instructed to send their samples on the day of collection. Saliva samples will be processed within the OH BRC lab (Neurosciences Building, Department of Psychiatry) and rendered acellular by centrifugation within 7 days of receipt by the research team to comply with the Human Tissue Act and with the

Departmental Policy on waste disposal. The saliva will then be frozen at -20 degrees and the salivette destroyed. Prior to assay, the saliva samples will be stored in the OH BRC lab in a pseudonymised form and will not be linked to any personal identifiers. The assays will be carried out in the OH BRC lab using a commercial ELISA kit (Salimetrics Salivary Cortisol ELISA Kit, assay #1-3002). Samples will only be accessible by research staff and will be held in the custody of Professor Harmer and Dr Murphy. Any excess saliva remaining at the end of the study will be disposed of within 6 months according to HTA guidelines and the Departmental SOPs for sample disposal.

The OH BRC lab operates a COVID-secure sample handling policy, with sample handling only allowed within the Class II biohazard hood with specific risk assessments in place (see APPENDIX J: BLOOD AND SALIVA PROCESSING RISK ASSESSMENT). The CABIN study-specific SOP for saliva sample processing is provided in Appendix K.

4. 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 be required. Withdrawal from the study will result in exclusion of the data for that participant from analysis. Withdrawn participants will be replaced to make up the sample size described above (135 participants, 45 per group). The reason for participant withdrawal will be recorded.

If a participant withdraws due to an adverse reaction to the study drug or placebo tablet, the case will be consulted with the study medic to determine the best course of action. It will also be reported on the Adverse Events form and kept in the Research Master File.

5. Definition of End of Study

The end of participant involvement in the research is the date of the EOS visit of the last participant.

6. Expenses and Benefits

Participants will be paid £150 for their participation in the research, via bank transfer. Travel expenses for Part 1 and 2 of the screening visit will be reimbursed on production of receipts or mileage, up to a maximum of £50. Participants may win up to an additional £10 in the PILT (completed twice, once at baseline and once at the EOS visit).

If a participant withdraws from the study, they will be reimbursed a pro-rata amount to compensate for the amount of time they spent in the study.

SECTION H. INTERVENTIONS

Drug/Substance 1

Name of drug/substance to be used	Citalopram
Formulation and route of administration for research	20mg citalopram tablets will be encapsulated in opaque capsules
Dose and route of administration for research	20mg acute oral dose
Duration of treatment for research	Once daily for 14 days
Licence status of this drug/substance	Citalopram is a licensed drug
Usual Indication	Major Depressive Disorder
Usual Dose	20mg daily increased in steps of 20mg if required, up to a maximum of 40mg daily; dose to be increased at intervals of 3-4 weeks
Usual duration of treatment	~6 months, but can be used long-term
Where will drug/substance be sourced from?	Oxford Pharmacy Store Kennington, Oxford OX3 7JX
Where will drug/substance be stored?	Citalopram will be stored within the Neurosciences Building of the Department of Psychiatry. It will be stored at room temperature in a locked cupboard suitable for drug storage.
How will drug/substance be dispensed?	Encapsulated citalopram tablets will be dispensed from the Neurosciences Building, Department of Psychiatry, by a study medic or nurse.
How will the drug/substance be prepared by the researchers for use in this research?	Citalopram tablets will be encapsulated by trained clinical support staff using the relevant Departmental SOP (APPENDIX H: ENCAPSULATION STANDARD OPERATING PROCEDURE).

Drug/Substance 2	
Name of drug/substance to be used	Lactose placebo tablet
Formulation and route of administration for research	Placebo tablets will be encapsulated in opaque capsules
Dose and route of administration for research	One capsule a day, orally
Duration of treatment for research	Once daily for 14 days
Licence status of this drug/substance	N/A
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?	Lactose placebo will be stored within the Neurosciences Building of the Department of Psychiatry. It will be stored at room temperature in a locked cupboard suitable for drug storage.
How will drug/substance be dispensed?	Encapsulated lactose placebo tablets will be dispensed from the Neurosciences Building, Department of Psychiatry, by a study medic or nurse.
How will the drug/substance be prepared by the researchers for use in this research?	Lactose placebo tablets will be encapsulated by trained clinical support staff using the relevant Departmental SOP (APPENDIX H: ENCAPSULATION 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. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the research intervention qualify as adverse reactions.
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

A serious adverse event (SAE) occurring to a participant should be reported to the Medical Sciences IDREC where, in the opinion of the Principal Investigator, the event was '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). Reports of related and unexpected SAEs should be submitted within 15 days of the Principal Investigator becoming aware of the event. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Principal Investigator is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report.

3. SAFETY OF PARTICIPANTS

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

To ensure it is safe to administer citalopram, prospective participants will undergo a series of stringent psychiatric and physical checks. Some of these checks will rely on participant self-report, whilst some will consist of objective physical measurements.

Participants will be excluded from the study if they display severe psychiatric symptoms (including severe mood disturbances) or meet diagnostic criteria for any of the disorders outlined in the exclusion criteria. We will check this by administering the following measures:

- BDI-II
- Assessment for psychiatric disorders using the structured clinical interview for DSM-5 (SCID-5)

Participants will be excluded from the study if citalopram is counter-indicated for any of their pre-existing conditions, according to the NHS website (https://www.nhs.uk/medicines/citalopram/), are lactose-intolerant (due to the placebo tablets being lactose-based) or currently take any psychoactive medication (previous antidepressant use is permitted provided the required wash-out period has passed). We will check this by reviewing the participants':

- Relevant medical history (including personal and family history of psychiatric disorders; diagnoses that represent contraindications for citalopram or increase susceptibility to COVID-19; food intolerances)
- Concomitant medication

Participants will be excluded from the study if elements of their lifestyle and current physical condition indicate they may not be suitable for participation in a drug study. We will check this by reviewing the participants':

- Lifestyle (including daily cigarette and caffeine consumption)

- BMI (following height and weight measurement); exclusion will not occur based on BMI alone, but this will be taken into account together with the general medical background provided to inform suitability

Female participants will be excluded if they are pregnant, breastfeeding, or planning to become pregnant. We will check this by administering a urine pregnancy test during Part 2 of the screening visit. Citalopram will only be administered if the test is negative. Participants with a positive or unclear result will be withdrawn from the study.

Other eligibility criteria such as age, residency and English language proficiency will be checked using a demographics questionnaire.

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

Ineligible participants who do not fulfil the inclusion criteria at either screening visit will be sent an email with mental health resources and will be recommended to talk to their GP should their wish to get any further guidance on their mental health.

During the two weeks of citalopram/placebo administration, participants will be advised not to drink alcohol and not to carry out activities requiring full alertness, such as driving, if they are aware of any impairment. Participants will receive a text message every day reminding them to take the capsule. They will have the contact phone number of a member of the research team and be encouraged to get in contact if they have any concerns or queries during the course of the study, or if their medication or health status changes.

Formal side effects monitoring will occur three times during the study, all of them remote (at Follow-up calls 1 and 2, as well as at the EOS visit). Participants will be able to withdraw from the study at any time.

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. If breaking the code is necessary, then only the 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.

During the screening visit, we will assess participants' level of suicidal ideation using the SCID-5 interview in the first instance, with a question about suicidality also present on the BDI-II questionnaire. If participants indicate active suicidal intent, CUREC approved procedure BPG08 will be followed. The experimental session will be brought to a close and either the study medic or another suitably qualified clinician will meet with them straight away to give support and create a safety plan. At the end of the study, all participants will be sent an email with mental health resources and will be recommended to talk to their GP should their wish to get any further guidance on their mental health.

This study should not pose any significant risks to the research team, but any unforeseen issues will be resolved by communication with the Principal Investigator.

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 course of the study.

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. 14 days of low-dose citalopram administration 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?

Clinical interviews will be conducted in accordance with CUREC approved procedure AP02. The researcher carrying out clinical interviews will not suggest the presence or absence of diagnosable conditions. They will discuss any problematic symptomatology with the study medic or PI to decide whether the medic should offer a consultation to the participant, whether the participant should be encouraged to contact their GP or whether the symptoms should not be discussed with the participant. In line with GDPR, participants have the right to ask for information that is collected about them. In such rare events, participants can be shown the information without clinical interpretation. If necessary, the researcher can explain the data are not intended to lead to a clinical assessment and are only used for aggregate scores characterising the whole study sample.

Urine pregnancy test: participants will be explicitly informed that their urine samples will be tested for pregnancy and informed of their right to withdraw from the study. If they consent to providing a urine sample and the results of this test are positive, the team member completing the test 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 participant may have an undiagnosed psychiatric condition that is causing distress, CUREC approved procedure BPG08 will be followed. The researcher will seek advice from the study medic and/or 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 participant indicates that they are not currently receiving support and it is felt necessary, they will be encouraged to contact their GP.

7. Please give details of departmental SOPs (if any) that will be followed in the case of an incidental finding

N/A

4. ETHICAL CONSIDERATIONS

Some research always carries the risk of 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 vulnerable participants (e.g. children, elderly, prisoners)? **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.	Yes ☐	No ☒
2. Will taking part in the research put participants under any particular burden and/or risk? **If yes,** describe how this will be mitigated.	Yes ☒	No ☐

There is a risk that participants may have an adverse reaction to citalopram. They will be informed of all known potential side-effects prior to taking the medication. To minimise risk, participants' general health will be assessed before inclusion into the study. They will be excluded if they are currently taking any psychoactive medication or if they have any known contraindications to taking the drug (see exclusion criteria). Formal side effects monitoring

will occur three times during the study (at Follow-up calls 1 and 2, as well as at the EOS visit). During the study, participants will be able to contact the study team if they experience any bothersome side effects. Participants will be able to withdraw from the study at any time.

Participants will be advised to limit alcohol consumption during the study and not to carry out activities requiring full alertness if they are aware of any impairment, such as sleepiness. If judged necessary by the study medic, they can break the randomisation code for any individual and the participant will be immediately withdrawn from the study.

Participants may become distressed whilst discussing sensitive and/or medical topics during screening. To minimise risk, the nature of sensitive/medical information collected and how this is collected will be clearly stated in the PIS. All clinical interviews will be conducted in accordance with CUREC approved procedure AP02.

Taking part in the research may increase participants' risk of contracting COVID-19, although no more than other daily activities such as buying groceries at the supermarket. To minimise risk, the study protocol has been designed to involve as few in-person visits as possible, with data collection largely conducted online. To ensure participants' safety during the in-person screening visit, study researchers will follow Departmental protocols and provide a supplementary PIS outlining all steps taken to minimise the risk of infection and safety procedures for in-person visits.

3. 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 ☒
4. 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 ☒
5. 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 ☒

6. Please give details of any other ethical and/or safety considerations

During the global COVID-19 pandemic, human research may pose additional risks of infection with the novel Coronavirus to both participants and researchers. In devising this protocol, the research team has prioritised the safety of study participants by only requiring a single in-person visit to the Department of Psychiatry, with much of the screening and data collection happening remotely.

The research team will follow the protocol laid out in Departmental SOP "Clinical and Psychology Testing Rooms Risk Assessment for Return to On-Site Working in Neurosciences Building", a copy of which can be found in APPENDIX C. Please also refer to APPENDIX E: SUPPMELENTARY PIS and APPENDIX I: STUDY COVID-19 RISK ASSESSMENT.

SECTION J. STATISTICS AND ANALYSIS

1. Do you have a statistical plan? Yes ☒ No ☐

If no, please justify.

A statistical analysis plan (SAP) has been discussed with Professor Harmer and Dr Murphy. The SAP will be finalised and published on the Open Science Framework (OSF) after ethical approval has been granted and prior to any statistical analyses taking place.

The FERT, ECAT and EREC tasks will be analysed in accordance with recent studies published by the PERL research group such that comparisons can be easily drawn (e.g. Murphy et al., 2019).

The PILT will be analysed following the methodology described in Pessiglione et al. (2006) and adapted in Pulcu and Browning (2017).

2. Number of Participants

135

3. Have you done a sample size calculation? Yes ☒ No ☐

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

To conduct an appropriate sample size calculation, one must first identify the effect of interest and the statistical model employed to test for this effect. Our primary task of interest is the FERT, with the corresponding outcome measures of interest being percentage accuracy in identifying positive and negative facial expressions. Previous studies investigating the effect of citalopram on emotional processing in healthy volunteers have found differences in percentage accuracy for positive emotions between a citalopram-treated group and a placebo-treated group of M_{drug} = 64,62%, SE_{drug} = 3.66 vs. $M_{placebo}$ = 60.00%, $SE_{placebo}$ = 7.22, corresponding to an effect size of Cohen's d ~ 0.8 (Murphy et al., 2009).

G*Power 3.1.9.7 (Faul et al., 2007) was used to perform the sample size calculation. We performed the power calculation for the sample size needed to detect a statistically significant difference between any two groups with $p < 0.017$ (Bonferroni corrected for number of planned group comparisons), power = 0.9 and Cohen's d = 0.8. The required sample was calculated as being N= 44 per group. Therefore, our specified sample size of N= 45 study completers per group should be adequate to detect statistically significant differences in FERT accuracy scores between the different intervention groups.

4. Analysis of Outcome Measures

The analysis of outcome measures has been considered by Ms Raslescu together with her supervisors, Professor Harmer and Dr Murphy.

The following outcome measures will be computed for the core task battery employed in the study, at baseline as well as at the end of the two-week intervention:

FERT

- Accuracy (%) for each facial expression (anger, disgust, fear, happiness, sadness, surprise)
- Accuracy (%) for positive facial expressions (happiness, surprise)
- Accuracy (%) for negative facial expressions (anger, disgust, fear, sadness)
- Misclassifications for each facial expression (number of responses to each expression incorrectly classified as another expression)
- Reaction time (ms) for each facial expression (anger, disgust, fear, happiness, sadness, surprise)
- Reaction time (ms) for positive facial expressions (happiness, surprise)

- Reaction time (ms) for negative facial expressions (anger, disgust, fear, sadness)

ECAT

- Accuracy (%) to classify positive descriptor words
- Accuracy (%) to classify negative descriptor words
- Reaction time (ms) to classify positive descriptor words
- Accuracy (ms) to classify negative descriptor words

EREC

Separately for positive and negative words:

- Hits (number of words correctly recalled)
- False alarms (number of words recalled that were not on the original list presented)

EMEM

Separately for positive and negative words:

- Hits (number of familiar words identified as familiar)
- Misses (number of familiar words identified as novel)
- Correct rejections (number of novel words identified as novel)
- False alarms (number of novel words identified as familiar)

PILT

- Amount of money won
- Amount of money lost
- Net amount (amount won – amount lost)
- Reaction time to choice (ms)
- Correct response (%)
- Consistency (% choices identical to the previous one)
- Proportion of group choosing correct symbol per trial

The primary outcome measures will be percentage accuracy in identifying positive and negative facial expressions in the FERT.

Basic demographic and baseline measures will be analysed descriptively using measures of central tendency (mean) and variance (standard deviation, standard error). All other outcome measures will be analysed using repeated measures ANOVAs, or ANCOVAs adjusted for covariates of interest as defined in the SAP. ANCOVAs will also be used to assess the influence of subjective measures of behavioural activation and mood on task performance. Significant interactions will be followed up using simple main effect analyses. When the assumption of equality of variances is not fulfilled, the Greenhouse-Geisser procedure will be used to correct the degrees of freedom (Howell, 2002).

For the PILT task, we will additionally fit a standard reinforcement learning algorithm (Q learning algorithm) to each subject's sequence of choices. Constants derived from the model (learning rate, decision temperature) as well as overall model fit will be compared between groups and used to complement the non-model-based analysis.

If our experimental hypothesis is supported by the data and the group receiving citalopram and BA shows a greater change in emotional cognition than the two other groups, exploratory mediation analyses will be performed to establish whether this effect was mediated by the participants' level of activity (as measured by the actigraphy watch), behavioural activation (as measured by the BADS and/or BIS/BAS scales) or environmental reinforcement (as measured by the EROS).

Daily mood ratings will be analysed using linear mixed models for longitudinal data.

Analyses will be performed using a combination of IBM SPSS Statistics, MATLAB and R software and analysis code will be published as open access wherever possible.

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 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 information.compliance@admin.ox.ac.uk.

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

Screening documents	☒	Audio recordings	☐
Consent records including participant name (written consent forms, audio-recorded consent, assent forms (for research involving minors))	☒	Video recordings	☐
Online consent (may be anonymous)	☒	Transcript of audio/video recordings	☐
Opt-out forms	☐	Photographs	☐
Contact details for research purposes only (destroyed when no longer needed for this research)	☒	Information about the health of the participant (including mental health)	☒
Contact details kept for future studies	☐	Physiological test results / measurements	☒
Field notes	☐	MRI scans	☐
Questionnaire answers	☒	Other (please specify below)	☒
Task results (e.g. paper/online tasks, diary completion)	☒	Bank details Behavioural activation training materials	

2. For each of the types of data selected above, state how this will be transferred from where it is collected to local storage (and backed up as necessary)

Pre-screening questionnaire data will be in electronic format. They will be collected online via Qualtrics. For ineligible participants, these data will be completely anonymous and not linked to any personal or study identifiers. For eligible participants, pre-screening data will be pseudonymised by a participant screening ID. Pre-screening data downloaded from Qualtrics will be stored on a University networked drive, which will be firewall and password protected. It will also be backed up on the study OneDrive account. At the end of the study, pre-screening data from participants that have completed the study will be stored under their unique participant ID along with all other pseudonymised research data.

Participants' names and contact details (email and telephone number) will be in electronic format and not anonymised. Personal identifiable information along with the key linking this information to each participant's

unique screening number and participant ID number will be stored in a password-protected electronic spreadsheet on a University networked drive, separately from all other research data. Access to this spreadsheet will be limited to the members of the research team involved in participant screening and data collection for the purposes of planning and conducting study visits. To comply with the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, this information will be destroyed six months after the end of the study.

Consent forms will be in paper format and will include participants' names. Consent forms completed remotely by the researcher during Part 1 screening will be transported to the Department of Psychiatry on a weekly basis or at the time of the participant's Part 2 screening visit, whichever occurs first. They will only be transported using the personal car of the researcher who has taken consent and no stopovers will be made in transit. In the Psychiatry Department, consent forms will be stored securely in the Research Master File, in a locked filing cabinet in a room that is locked when unoccupied. Scans of consent forms completed by the researcher during the Part 1 screening visit will be saved on a University networked drive, which will be firewall and password protected. These scans will be deleted once the consent form is fully signed in paper format during the Part 2 screening visit and stored securely in the Research Master File.

Screening data (demographics, medical history, concomitant medication and lifestyle) will be in electronic format and pseudonymised by a participant screening ID. They will be recorded on an electronic CRF by one of the study researchers during the two-part screening visit and stored on a University networked drive, which will be firewall and password protected. It will also be backed up on the study OneDrive account. At the end of the study, screening data from participants who have completed the study will be transferred onto Excel spreadsheets and will be stored under their unique participant ID along with all other pseudonymised research data.

Payment details will be in paper format and not anonymised. Participants will fill in payment forms (containing name, address, email, national insurance number, sort code and bank account number) during the Part 2 screening visit. Completed payment forms will be held in the Research Master File, in a locked filing cabinet in a room that is locked when unoccupied, until the participant completes the study. The researchers will then pass the paper payment forms on to the Department of Psychiatry finance team, for the payment to be processed.

Questionnaire data will be pseudonymised by a participant ID number and not linked to any personal identifiers. Questionnaire data will be collected in electronic format via Gorilla Experiment Builder. Electronic questionnaire data will be downloaded from Gorilla and stored on a University networked drive, which will be firewall and password protected. It will also be backed up on the study OneDrive account after each research visit.

Computerised task data will be pseudonymised by a participant ID number and not linked to any personal identifiers. They will be collected in electronic format via Gorilla Experiment Builder. Electronic task data will be downloaded from Gorilla, stored on a University networked drive, which will be firewall and password protected. It will also be backed up on the study OneDrive account after each research visit.

Actigraphy data will be collected using GeneActiv actigraphy watches and will be extracted as soon as the participant returns the watch at the end of their involvement in the study. Actigraphy data will be pseudonymised by a participant ID number and not linked to any personal identifiers. It will be stored electronically on a University networked drive, which will be firewall and password protected. It will also be backed up on the study OneDrive account.

Saliva samples will be collected by participants and posted on the day of collection using postage-paid packaging. All parcels will be addressed to the primary researcher and received at the Department of Psychiatry. From there, the primary researcher or another member of the research team will process the samples within 7 days of receipt and render them acellular through centrifugation. Acellular samples will be stored in lab freezers in the Neurosciences Building under the participant's ID number until assayed for cortisol, and then destroyed. Following assay, data on salivary cortisol will be stored in electronic format and pseudonymised by the participant's ID number. It will be stored electronically on a University networked drive, which will be firewall and password protected. It will also be backed up on the study OneDrive account.

Data collected as part of the behavioural activation training (e.g., booklets which the researcher has completed together with the participant) will be in electronic format and pseudonymised by a participant ID number. They will be stored on a University networked drive, which will be firewall and password protected. Copies of these data will be sent via email to participants where applicable and the data will be deleted at the end of the study.

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

Paper-based consent forms will be stored in a locked filing cabinet in a room that is locked when unoccupied. Electronic data will be stored in spreadsheets (Excel/SPSS) on University networked drives and backed up on the study OneDrive account. Acellular saliva samples will be stored in lab freezers in the Neurosciences Building under the participant's ID number until assayed for cortisol, and then destroyed.

4. 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 study screening ID once they have passed pre-screening. They will also be allocated a unique participant ID number once included into the study. A key will link participants' personal details to their screening and participant IDs. This information will be stored in a password-protected electronic spreadsheet, separate from all research data. Access to this spreadsheet will be limited to the members of the research team involved in participant screening and data collection for the purposes of planning and conducting study visits. To comply with the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, this key will be destroyed six months after the end of the study.

5. Who will have access to the research data?

Researchers listed on this form will have access to participants' personal data.

The named researchers and their delegates will have access to the research data. Direct access to all data 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.

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

Researchers listed on this form will have access to participants' personal data. This will be held at the University of Oxford and will not be shared with another organisation.

If data is shared with another organisation, only anonymised data will be shared.

An anonymised dataset will be published as open access data on a secure online repository, such as Open Science Framework (https://osf.io/).

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

Once the data has been analysed and the results have been published, personal data (with the exception of consent forms) and the linking key will be destroyed by deletion (i.e. such that the content is not recoverable in any way) to comply with the General Data Protection Regulation (GDPR) and the Data Protection Act 2018. This is expected to occur within 6 months of the end of the study. Consent forms will be destroyed by shredding 10 years after the end of the study.

Screening and personal data for ineligible participants will be destroyed by deletion immediately after the screening visit.

8. Please confirm that you will store other 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 may be shared with other academic and commercial organisations in the future, including those outside of the EU. Participants will be informed of this and specific consent to this is obtained within the Informed Consent Form.

An anonymised dataset will be published as open access data on a secure online repository, such as Open Science Framework (https://osf.io/).

SECTION L. MONITORING AND OVERSIGHT

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

Ms Andreea Raslescu

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

Ms Andreea Raslescu will meet with her DPhil supervisors Professor Catherine Harmer and Dr Susannah Murphy fortnightly to discuss the progress of the study, and on an ad-hoc basis where needed. Dr Sandra Tamm will also be available for day-to-day consultation on any issues that may arise during the screening or testing process.

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 protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Medical Sciences IDREC 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.

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 0. DISSEMINATION AND FEEDBACK OF RESEARCH OUTCOMES

The results obtained from this study will form a substantial part of Ms Raslescu's DPhil thesis. Public dissemination plans include submission of at least two poster abstracts to relevant Psychiatry/Neuroscience conference committees and at least one scientific publication in a peer-reviewed journal.

Ms Raslescu, Professor Hamer and Dr Murphy will be involved in reviewing drafts of the manuscripts, abstracts, posters, press releases and any other publications arising from the study. Authors will acknowledge all funding arrangements. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be suitably acknowledged.

Participants who have indicated interest will either be sent a summary of the findings at the end of the study or will be directed to a webpage where the research team will post study-related updates if data analysis outlasts retention of participants' contact information.

SECTION P. REFERENCES

Alboni, S., van Dijk, R. M., Poggini, S., Milior, G., Perrotta, M., Drenth, T., . . . Branchi, I. (2017). Fluoxetine effects on molecular, cellular and behavioral endophenotypes of depression are driven by the living environment. *Molecular Psychiatry, 22*(4), 552-561. doi:10.1038/mp.2015.142

Branchi, I., Santarelli, S., Capoccia, S., Poggini, S., D'Andrea, I., Cirulli, F., & Alleva, E. (2013). Antidepressant Treatment Outcome Depends on the Quality of the Living Environment: A Pre-Clinical Investigation in Mice. *PLOS ONE, 8*(4), e62226. doi:10.1371/journal.pone.0062226

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., . . . Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet, 391*(10128), 1357-1366. doi:10.1016/S0140-6736(17)32802-7

Cohen, A., Gilman, S. E., Houck, P. R., Szanto, K., & Reynolds, C. F. (2008). Socioeconomic status and anxiety as predictors of antidepressant treatment response and suicidal ideation in older adults. *Social Psychiatry and Psychiatric Epidemiology, 44*(4), 272. doi:10.1007/s00127-008-0436-8

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175-191. doi:10.3758/BF03193146

Harmer, C. J., Shelley, N. C., Cowen, P. J., & Goodwin, G. M. (2004). Increased Positive Versus Negative Affective Perception and Memory in Healthy Volunteers Following Selective Serotonin and Norepinephrine Reuptake Inhibition. *American Journal of Psychiatry*, *161*(7), 1256-1263. doi:10.1176/appi.ajp.161.7.1256

Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *The Lancet Psychiatry, 4*(5), 409-418. doi:10.1016/S2215-0366(17)30015-9

Hobbs, C., Murphy, S. E., Wright, L., Carson, J., Assche, I. V., O'Brien, J., . . . Button, K. S. (2020). Effect of acute citalopram on self-referential emotional processing and social cognition in healthy volunteers. BJPsych Open, 6(6), e124. doi:10.1192/bjo.2020.107

McCrone, P., Dhanasiri, S., Patel, A., Knapp, M., & Lawton-Smith, S. (2008). *Paying the price: the cost of mental health care in England to 2026*. London: The King's Fund.

McManus S, Bebbington P, Jenkins R, Brugha T. (eds.) (2016) Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014. Leeds: NHS Digital. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/adult-psychiatric-morbidity-survey/adult-psychiatric-morbidity-survey-survey-of-mental-health-and-wellbeing-england-2014.

Murphy, S. E., Norbury, R., O'Sullivan, U., Cowen, P. J., & Harmer, C. J. (2009). Effect of a single dose of citalopram on amygdala response to emotional faces. *The British Journal of Psychiatry, 194*(6), 535-540. doi:10.1192/bjp.bp.108.056093

Murphy, S. E., Wright, L. C., Browning, M., Cowen, P. J., & Harmer, C. J. (2019). A role for 5-HT4 receptors in human learning and memory. *Psychological Medicine*, 1-9. doi:10.1017/S0033291719002836

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature, 442*(7106), 1042-1045. doi:10.1038/nature05051

Pulcu, E., & Browning, M. (2017). Affective bias as a rational response to the statistics of rewards and punishments. *eLife, 6*, e27879. doi:10.7554/eLife.27879

Stuart, S. A., Butler, P., Munafò, M. R., Nutt, D. J., & Robinson, E. S. J. (2015). Distinct Neuropsychological Mechanisms May Explain Delayed- Versus Rapid-Onset Antidepressant Efficacy. *Neuropsychopharmacology, 40*(9), 2165-2174. doi:10.1038/npp.2015.59

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., . . . Fava, M. (2006). Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. *American Journal of Psychiatry, 163*(1), 28-40. doi:10.1176/appi.ajp.163.1.28

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)	Catherine Harmer
Principal Investigator (Signature) Pasted images of signatures cannot be accepted	
Medically qualified collaborator (Name)	Sandra Tamm
Medically qualified collaborator (Signature) Pasted images of signatures cannot be accepted	
Student (Name)	Ms Andreea Raslescu
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 the research application named above.
- On the basis of the information available to me, I judge the Principal Investigator/Supervisor and student researcher (if applicable) to be aware of their ethical responsibilities in regard to this research.
- I am satisfied that the proposed project has been subject to appropriate peer review and is likely to contribute to existing knowledge and/or to the education and training of the researcher(s) and that it is in the public interest.

Head of Department (Name)	Prof. John Geddes
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 Dec 2020

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	2.0	16Jun2021	Andreea Raslescu	move administration of the BDI-II questionnaire from Part 2 of the in-person screening visit, to Part 1 of the remote screening visit
2	3.0	24Aug2021	Andreea Raslescu	Widen eligible BDI-II score interval to 10-30 inclusive
3	4.0	28Sep2021	Andreea Raslescu	Establish collaboration with Lindus Health to speed up participant recruitment

4	4.0	Jan2022	Tessa Micklethwait	Addition of undergraduate EP student (Tessa Micklethwait) to the project
5	5.0	31March2022	Andreea Raslescu	Remove BMI and COVID vulnerability related exclusion criteria; leave up to expertise of study medically qualified collaborator