CENTRAL UNIVERSITY RESEARCH ETHICS COMMITTEE (CUREC)

CUREC 3 Protocol and Application Form

Pharmacological Studies in Healthy Volunteers

ONLY FULLY SIGNED TYPE-WRITTEN APPLICATIONS WILL BE ACCEPTED, BY EMAIL

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

Should you require any assistance in completing this document, please contact CTRG in the first instance: http://researchsupport.admin.ox.ac.uk/ctrg

STUDY DETAILS	
Full Study Title	The effect of seven-day atorvastatin administration on emotional processing, reward processing, and inflammation in healthy volunteers
Internal Reference / Short title	7-day atorvastatin and emotional processing
MS IDREC Reference	R61966/RE001
Date and version number	Version 1.0, 01st January 2019
Principal Investigator	Professor Phillip J Cowen MBBS, MD, FRCPsych phil.cowen@psych.ox.ac.uk 01865 618311 Department of Psychiatry, University of Oxford
Student (if applicable)	Doctor Riccardo De Giorgi MD, MRCPsych riccardo.degiorgi@bnc.ox.ac.uk 01865 618238 Department of Psychiatry, University of Oxford Graduate reading for DPhil in Biomedical and Clinical Sciences (Wellcome Trust Doctoral Training Fellow)
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Medically qualified collaborator (Licensed Doctor)	Professor Phillip J Cowen MBBS, MD, FRCPsych phil.cowen@psych.ox.ac.uk 01865 618311 Department of Psychiatry, University of Oxford Doctor Riccardo De Giorgi MD, MRCPsych riccardo.degiorgi@bnc.ox.ac.uk 01865 618238 Department of Psychiatry, University of Oxford Graduate reading for DPhil in Biomedical and Clinical Sciences (Wellcome Trust Doctoral Training Fellow)
Sponsor	The University of Oxford
External Funding	Wellcome Trust, reference: 102176/Z/13/Z
Will you submit or have you submitted this study 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:	
Declaration of any Conflicts of Interest	None
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 Interdisciplinary Research Ethics Committee (Medical Sciences IDREC), unless authorised to do so

RESEARCH TEAM	
Investigator Title and name	Professor Catherine J Harmer
Department/Institute name	Department of Psychiatry, University of Oxford
Role in Study	Professor of Cognitive Neuroscience DPhil, MA, DipLATHE Professor Harmer will be involved in the study design and interpretation of data

	Professor Harmer has >20 years of experience of experimental medicine studies
Training/Qualification in Research Ethics	27th October 2016: Research Integrity Training (Epigeum) covering: protocols and associated documents; applications, agreements and approvals; trial master files; conducting the trial

Investigator Title and name	Mr Nicola Rizzo
Department/Institute name	Department of Psychiatry, University of Oxford
Role in Study	Medical student Mr Rizzo will be involved in the recruitment, screening, and testing of participants
Training/Qualification in Research Ethics	28th December 2018: Good Clinical Practice (Medical Research Council online)

1. TABLE OF CONTENTS

2. SYNOPSIS

Please state why this study is not considered a Clinical Trial of an Investigative Medicinal Product	This study is not a Clinical Trial of an Investigative Medicinal Product as we are not investigating the efficacy of atorvastatin but using it as a pharmacological tool to understand the role of inflammation in emotional and reward processing. This study does not fit the MHRA definition of a clinical trial as one 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).	
List all sites where study will be conducted	Neurosciences Building, Department of Psychiatry, University of Oxford, Warneford Hospital, Warneford Lane, Oxford, OX3 7JX	
Age Range of Study Participants	18-50 years old	
Planned Sample Size	50 healthy volunteers (25 per group)	
Planned Study Duration (n.b. A minimum approval period of 1 year and maximum of 5 years can be granted)	24 months	
Anticipated Start Date	1st February 2019	
Anticipated End Date	1st February 2021	
	Objectives	**Outcome Measures**
Primary	To investigate the effects of seven-day atorvastatin administration on emotional processing	Accuracy and reaction times on computer-based tasks of emotional processing (e.g. facial expression recognition, emotional categorisation and memory), comparing those receiving drug and placebo.
Secondary	To investigate the effects of seven-day atorvastatin administration on reward processing	Accuracy and reaction times on computer-based tasks of reward processing comparing those receiving drug and placebo.

	To investigate the effects of seven-day atorvastatin administration on inflammation	Changes in high sensitivity-C Reactive Protein (hs-CRP) from baseline to seven-day, comparing those receiving drug and placebo
Name of drug/substance	Atorvastatin	
Purpose of drug/substance use in this study	Work in our group has revealed that short-term (7-day) administration of antidepressants produces positive biases in the processing of emotional information in healthy volunteers. Such effect might be an important neuropsychological mechanism of antidepressant action. The current study will investigate the effect of seven-day administration of atorvastatin 20mg on emotional and reward processing tasks in healthy volunteers. There is evidence that statins may exert antidepressant effects via anti-inflammatory and anti-oxidant pathways, and it is therefore predicted that atorvastatin will have positive effects on emotional and reward processing.	
Adverse reactions and side effects posing a particular risk with this treatment	Muscle pain or weakness: usually mild and quickly responding to stopping or switching medication Elevation of liver transaminases: significant only in case of pre-existing hepatic disease Rhabdomyolysis: very rare but severe myopathy associated with elevated creatine kinase and myoglobinuria Nasopharyngitis, epistaxis, pharyngo-laryngeal pain: usually mild and quickly responding to stopping or switching medication Headache: usually mild and quickly responding to stopping or switching medication Gastrointestinal disturbances (constipation, diarrhoea, flatulence, dyspepsia, nausea): usually mild and quickly responding to stopping or switching medication New-onset diabetes mellitus: in predisposed individual with pre-existing hyperglycaemia Haemorrhagic stroke: in patients with prior haemorrhagic stroke or lacunar infarct	

3. ABBREVIATIONS

BMI	Body Mass Index
CTRG	Clinical Trials & Research Governance, University of Oxford
CUREC	Central University Research Ethics Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
ETB	Emotional Test Battery
GP	General Practitioner
hs-CRP	high sensitivity-C Reactive Protein

MS IDREC	Medical Sciences Inter-Divisional Research Ethics Committee
PIL	Probabilistic Instrumental Learning
SCID-5	Structured Clinical Interview for DSM-5
SOP	Standard Operating Procedure

4. BACKGROUND AND RATIONALE

Depression is common and associated with considerable health disability (Kassebaum-2016). Traditional antidepressants mainly work by modulating monoamine levels in the synaptic cleft (Harmer-2017); however, the evidence that depression is caused by impaired serotonin or noradrenaline activity is weak and inconsistent (Cowen-2015), and indeed current antidepressant strategies remain burdened by partial efficacy, poor side-effects profile, and a slow onset of therapeutic action (Penn-2012). Therefore, there is a pressing need to develop antidepressant medications with novel non-monoaminergic mechanisms of action (Jha-2018) – or, conversely, to identify alternative pathophysiological pathways leading to depression that can be targeted with new drugs. Intriguingly, there is growing evidence that both peripheral and central inflammation play a role in the pathophysiology of depression (Miller-2017).

Patients with depression consistently show negative biases in emotional processing, which are believed to play a key role in the aetiology and maintenance of their clinical symptoms (Roiser-2013). Overall, robust evidence suggests that early changes in emotional processing can serve as valid surrogate markers of antidepressant efficacy (Harmer-2017); for example, seven days' treatment with selective serotonin and noradrenaline reuptake inhibitors (citalopram and reboxetine respectively) compared to placebo decreases the recognition of negative facial expressions and recall of negative versus positive stimuli in healthy volunteers (Harmer-2004). Conversely, another study using the pro-inflammatory cytokine interferon-α showed that inflammatory-mediated depression can be associated with an increased recognition of negative facial expressions (Cooper-2017). Furthermore, depression associated with inflammation is characterised by significant symptoms of anhedonia (Miller-2017), which has been linked to diminished neural responses to reward anticipation (Felger-2017). Such reward-deficit is particularly refractory to conventional serotoninergic and noradrenergic antidepressants (McCabe-201), and even the antidepressant bupropion (a noradrenaline and dopamine reuptake inhibitor), whilst inducing positive changes in emotional processing, appears to worsen reward processing (Walsh-2018). However, the reversal of this deficit in reward processing is still considered as a valuable marker of target engagement for anti-inflammatory drugs in depression, as a more sensitive outcome measure than traditional rating scales designed to capture the global clinical symptomatology (Miller-2017).

The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors or statins are recommended and have been widely used since the '80s for the primary and secondary prevention of cardiovascular diseases (NICE 2014). It is now established that these medications have significant anti-inflammatory effects that are independent from their lipid-lowering properties (Jain-2005), as well as appearing early in treatment only after seven day of administration (Macin-2011). Statins are considered extremely safe drugs: their more common side-effect are muscle pain or weakness (usually mild and quickly responding to stopping or switching medication) and elevation of liver transaminases (significant only in case of pre-existing hepatic disease), whereas more serious adverse events include rhabdomyolysis (very rare but severe myopathy associated with elevated creatine kinase and myoglobinuria), new-onset diabetes mellitus (in predisposed individual with pre-existing hyperglycaemia), and haemorrhagic stroke (in patients with prior haemorrhagic stroke or lacunar infarct); however, clinical trials have ultimately concluded that such adverse events attributed to statin therapy in routine practice are not actually

caused by it (Collins-2016), especially at doses lower than 80mg/day and when used for less than 52 weeks (Li-2016). Other common (≥ 1/100, < 1/10) but usually mild side-effects include: nasopharyngitis, pharyngo-laryngeal pain, epistaxis, headache, and gastrointestinal disturbances (constipation, diarrhoea, flatulence, dyspepsia, nausea). Importantly, a potential antidepressant effect for statins has been confirmed in animals (Kilic-2012), as well as clinically in observational (Parsaik-2014) and interventional studies (Salagre-2016). Although their anti-inflammatory and anti-oxidant properties have been involved, the mechanisms underlying the antidepressant effects of statins remain unclear, therefore further translational studies have been advocated in order to elucidate this aspect (Köhler-Forsberg-2017).

In this exploratory study, we will investigate the effect of seven-day administration of atorvastatin 20mg once daily compared to placebo on emotional and reward processing tasks in 50 healthy volunteers. In view of the previous evidence that statins may exert antidepressant effects via anti-inflammatory and anti-oxidant pathways, we predict that atorvastatin will have positive effect on emotional and reward processing.

5. PARTICIPANTS

Description of Study Participants
50 healthy volunteers aged 18-50 years
Inclusion Criteria
• Male or female • Aged 18-50 years • Sufficiently fluent English to understand and complete the tasks • Body Mass Index in the range of 18-30 • Participant is willing and able to give informed consent for participation in the study • Not currently taking any regular medications (except the contraceptive pill)
Exclusion criteria
The participant may <u>not</u> enter the study if any of the following apply: • Currently any regular medications (except the contraceptive pill) • History or current significant psychiatric illness • Current alcohol or substance misuse disorder • History or current significant hepatic disease • History or current significant neurological condition (e.g. epilepsy) • Known hypersensitivity to the study drug (i.e. atorvastatin) • Pregnant, breast feeding, women of child-bearing potential not using appropriate contraceptive measures • Participation in a study that uses the same or similar computer tasks as those used in the present study • Participation in a study that involves the use of a medication within the last three months
Recruitment

Participants will be recruited by word of mouth, emails to departmental mailing lists (sent by who usually has access to those mailing lists on our behalf), and posters located in University Departments. Moreover, we will use adverts (APPENDIX A: STUDY ADVERTS) sent to Junior Common Rooms and Middle Common Rooms, displayed in Colleges and University departments and local community buildings through existing participant registries at the Department of Psychiatry and the Department of Experimental Psychology. Participants will also be recruited via advertisement through Oxford Brookes, following approval from Oxford Brookes University Research Ethics Committee. The following additional statement will be inserted into any recruitment documents for Oxford Brookes students and/or staff: "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. Adverts will also be placed on local information websites (e.g. Daily Info, Oxford University Gazette), newspapers, local magazines, on the radio, and on the lab webpage, Facebook page, and Twitter account. The adverts will contain brief information about the inclusion criteria for the study, as well as contact details for the named researchers.

After a potential volunteer has contacted the research team, they will be sent the Participant Information Sheet via email. We will also send the Participant Information Sheet via email (APPENDIX B: RECONTACT EMAIL TEMPLATE) to participants from previous studies who gave consent to be approached about possible participation in future research studies they may be suitable for. The participant will be given as much time as they need to decide whether they would like to take part and will be invited to ask any questions that they have about the study. If the participant decides that they do not want to take part in the study, they will be thanked for their interest and there will be no further contact from the research team. If the participant decides they would like to take part, they will be invited for a screening visit at the Neurosciences Building, Warneford Hospital. At the beginning of this visit, one of the named researchers will explain the study to the participant and answer any questions that they have. The researcher will then take written consent from the participant. All of the named researchers have been trained in taking informed consent.

Screening and Eligibility Assessment

Informed Consent will be obtained at the start of the screening, prior to the administration of questionnaires or the Structured Clinical Interview for DSM-5 disorders.

A maximum of four weeks will be allowed between screening and randomisation to atorvastatin or placebo. If this duration is exceeded, another screening will need to be performed to ensure eligibility.

At screening, information about demographics, medical history, concomitant medication, and psychiatric history (using Structured Clinical Interview for DSM-5) will be taken (APPENDIX C: SCREENING FORM). Female participants will also have a urine pregnancy test.

Information Provided to Participants and Informed Consent

The Participant Information Sheet (APPENDIX D: PARTICIPANT INFORMATION SHEET) will be presented to the participants, in written as well as in verbal form. Both will detail the exact practical demands of the study, written from the participant's perspective, in lay language (the nature of the study, what it will involve for the participants, the implications and constraints of the protocol, the known side-effects and any risks involved in taking part, what will happen to the data collected). It will be clearly stated that the participant is free to withdraw from the study at any time for any reason and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator, their GP, or other independent parties to decide whether they will participate in the study.

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

informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent will be suitably qualified and experienced and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent Form will be given to the participant. The original signed form will be retained at the study site.

Participant Confidentiality

The study staff will ensure that the participants' data are safeguarded. The study 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 study 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 study staff and authorised personnel.

It will be made clear to the participant that 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 be breached only 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".

6. STUDY PROCEDURES

Baseline Assessments and Procedures

Individuals who are interested in participating in the study will be invited to attend a Screening Visit (maximum 2 hours) at the Neurosciences Building, Warneford Hospital.

Demographic information will be collected:

- Age (years, months), years in full-time education

Participants' eligibility to take part will be checked by recording the following:

- Weight, height, and BMI
- Medical history (including family psychiatric history), details of current and past medication
- Current and prior use of drugs (to exclude for drug use in the three months prior to the study)
- Menstrual cycle (in order to avoid scheduling testing in the premenstrual week)
- SCID-5 interview (Structured Clinical Interview for DSM-5) to probe for current or past psychiatric illness
- Urine pregnancy test (female participants only)

The following baseline assessments will be completed (APPENDIX F: QUESTIONNAIRES):

- Beck Depression Inventory (BDI)
- Eysenck Personality Questionnaire (EPQ)

- Positive and Negative Affect Schedule (PANAS)
- Side-effects questionnaire (to determine baseline of bodily symptoms/'side-effects')
- Snaith-Hamilton Pleasure Scale (SHAPS)
- State and Trait Anxiety Inventory (STAI)
- Visual Analogue Scales (VAS) measuring subjective state

Also, phlebotomy will be undertaken to obtain a sample of:

- high sensitivity-C Reactive Protein

Participants will be asked to wait while their eligibility to take part is assessed by a medical doctor involved in the study (maximum 30 minutes). Any participant for whom additional information is required before an eligibility judgment can be made will be asked to return on a different day once this information has been obtained.

Eligible participants will be randomised to receive either 7-day atorvastatin 20mg (25 participants), or 7-day placebo (25 participants) administration. Randomisation will occur on the day of screening, or up to a maximum of 4 weeks after screening. Randomisation after the Screening Visit will occur in the event that further information is needed before determining whether participants are eligible to take part (for example, if a participant needs to follow-up with details of allergies, or previous studies they have taken part in). In this case, if more than 4 weeks have elapsed, another Screening Visit will be performed to ensure participants are still eligible. The randomisation code will be drawn up by a researcher not involved in the study using an online randomisation tool (https://www.sealedenvelope.com/simple-randomiser/v1/lists). Randomised participants will be given 7 days of the drug to take home, as well as full instructions of how and when to take them.

The atorvastatin drug and the placebo will be provided by the Oxford Pharmacy Stores and will be encapsulated at the Neurosciences Building according to previously agreed standard operating procedures (APPENDIX G: Neurosciences, SOP Number: Encapsulation Version 2: 22.10.2012). Blinding will be achieved by the identical matching of the atorvastatin and placebo treatments. Participants will not be aware of the treatment that they will be receiving; neither will the researcher, as this study is double-blind.

Allocation of treatments will be recorded on a Randomisation List, which will be updated when each new participant enters the randomised phase. The list will be held at the Neurosciences Building by a scientist uninvolved in the study.

The study medication and placebo will be stored in a secure environment at the Neurosciences Building accessible only to staff. It will be stored at room temperature and accounted for using agreed study documentation. Using the Randomisation List and the participant's unique randomisation code, staff will determine whether to dispense active or placebo tablets.

The randomisation code will be broken if a participant requires treatment for a new medical condition or experiences serious adverse reactions and either of these situations make it clinically important to know what medication they are taking. A 24/7 emergency mobile contact number will be provided on a wallet-sized card given to participants during their Research Visit. The research team member on-call will be able to contact the medical supervisor and they will make the decision to unblind. In order to unblind the participant, the medic will access the list kept in a secure cabinet at the Neurosciences Building and will disclose the allocation within a maximum of one hour. If breaking the code is necessary, 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 week of drug/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. During this week, a researcher will phone up the participant on day 2 and day 4 to check that there are no concerns. Additionally,

participants will receive a text message every day reminding them to take the study medication. They will have the 24-hour contact phone number of a member of the study team and be encouraged to get in contact if they have any concerns or queries during the study week, or if their medication or health status changes.

Subsequent Visits

The Research Visit (approximately 2 hours) will take place after day 7 of atorvastatin/placebo administration. This visit will involve administration of behavioural tasks measuring emotional and reward processing. It will take place at the Neurosciences Building, Warneford Hospital.
Participants will complete the following questionnaires before the behavioural tasks:

- Positive and Negative Affect Schedule (PANAS)
- Side-effects questionnaire
- State Anxiety Inventory (state-STAI)
- Visual Analogue Scales (VAS)

Also, phlebotomy will be repeated to obtain a sample of:

- high sensitivity-C Reactive Protein

The behavioural tasks will include the Oxford Emotional Test Battery (ETB), which has previously been found to be sensitive to the effects of antidepressants, and a reward task of Probabilistic Instrumental Learning (PIL). The ETB involves the presentation of emotion-related words and pictures of faces with different expressions. The reward task involves repeatedly choosing between two options and there is the possibility of winning up to £10 depending on the choices made (see 'Expenses and Benefits' below). All stimuli will be presented on a computer screen and participants will be required to respond via button presses on a keyboard.

Participants will be asked to report their adherence to the 7-day administration of atorvastatin/placebo.

At the end of the research visit, a member of the study team will ask participants to try to guess which treatment they received, as a measure of how successful the blinding was.

Sample Handling

Blood samples (4mL = i.e. 1 teaspoon) taken during the Screening Visit and the Research Visit for investigating hs-CRP will be handled at the Neurosciences Building's laboratory. On the same day, they will be rendered acellular by centrifugation on receipt and stored at -30^{o}C until assay. Any excess material remaining at the end of the study will be disposed of by the laboratory within 6 months according to the Human Tissue Authority guidelines. The samples will be stored in a freezer at the Neurosciences Building in an anonymised form. Access to the samples will be by the research team and the samples will be in the custody of Prof Philip Cowen who will hold the key code linking the samples to a particular individual. The samples will be analysed for once all participants have completed the study.

Female participants will be required to give a urine sample for a pregnancy test at the Screening Visit. Urine samples will be destroyed immediately after the test result has been obtained.

Discontinuation/Withdrawal of Participants from Study

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

- Pregnancy

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Informed Consent
- Loss to follow up

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

Definition of End of Study
The end of the study for participant involvement is the date of the last visit of the final participant.
Expenses and Benefits
Participants will be paid £100 upon completion of their participation in the research. In addition, they may win up to £10 depending on the choices they make in the reward task (see 'Subsequent Visits' above). If they do not complete the study, they will be given a pro-rata amount to recompense the time they did spend in the study. Reasonable travel expenses for any visits will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

7. INTERVENTION(S)

a) Drug/Substance 1

Name of drug/substance to be used	Atorvastatin
Formulation and route of administration for study	20mg atorvastatin tablets will be encapsulated in opaque capsules
Dose and route of administration for study	20mg atorvastatin once daily at night-time, oral dose
Duration of treatment for study	7 days
Licence status of this drug/substance	Atorvastatin is a licensed drug
Usual Indication	Atorvastatin is usually indicated in adult patients with primary hypercholesterolaemia, or combined (mixed) hyperlipidaemia in adult patients who have not responded adequately to diet and other appropriate measures, in adult patients with homozygous familial who have not responded adequately to diet and other appropriate measures, and in adult patients with atherosclerotic cardiovascular disease or diabetes mellitus for prevention of cardiovascular events
Usual Dose	10-80mg once daily, at night-time

Usual duration of treatment	Life-long
Where will drug/substance be sourced from?	Oxford Pharmacy Stores
Where will drug/substance be stored?	Atorvastatin will be stored within the Neurosciences Building, Warneford Hospital. It will be stored at room temperature in a locked cupboard, which is suitable for drug storage.
How will drug/substance be dispensed?	Atorvastatin will be dispensed from the Neurosciences Building, Warneford Hospital by a study medic or nurse.
How will the drug/substance be prepared by the researchers for use in this study?	Atorvastatin will be encapsulated by trained clinical trial support staff using our Standard Operating Procedure (APPENDIX G: ENCAPSULATION STANDARD OPERATING PROCEDURE).

b) Drug/Substance 2 (or placebo)

Name of drug/substance to be used	Lactose Placebo
Formulation and route of administration for study	Placebo tablets will be encapsulated in opaque capsules
Dose and route of administration for study	One capsule once daily at night-time, oral dose
Duration of treatment for study	7 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?	Placebo will be stored within the Neurosciences Building, Warneford Hospital. It will be stored at room temperature in a locked cupboard, which is suitable for drug storage.
How will drug/substance be dispensed?	Placebo will be dispensed from the Neurosciences Building, Warneford Hospital by a study medic or nurse.
How will the drug/substance be prepared by the researchers for use in this study?	Placebo will be encapsulated by trained clinical trial support staff using our Standard Operating Procedure (APPENDIX G: ENCAPSULATION STANDARD OPERATING PROCEDURE).

8. SAFETY

a) 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 study 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 study 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).

b) Reporting Procedures for Serious Adverse Events or Reactions

A serious adverse event (SAE) occurring to a participant should be reported to CTRG and 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 Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report.

c) Safety of Participants

What level of baseline screening will take place for this study?
All participants will undergo a Screening Visit to ensure only eligible participants take part. The following will be recorded at baseline screening: • Demographic information (age [years, months], years in full-time education) • Number of cigarettes smoked per day, units of alcohol consumed per week, caffeinated drinks consumed per day • Current and prior use of drugs (to exclude for drug use in the three months prior to the study) • SCID-5 interview (Structured Clinical Interview for DSM-5) to probe for current or past psychiatric illness • Beck Depression Inventory (BDI) • Eysenck Personality Questionnaire (EPQ) • State and Trait Anxiety Inventory (STAI) • Positive and Negative Affect Schedule (PANAS) • Snaith-Hamilton Pleasure Scale (SHAPS) • Side-effects questionnaire • Visual Analogue scales (VAS) To ensure it is safe to administer the drug to the participant, the following will be recorded: • Weight, height, and BMI • Medical history (including family psychiatric history) • Details of current and past medication • Urine pregnancy test (female participants only) Also, phlebotomy will be undertaken to obtain a sample of: • high sensitivity-C Reactive Protein Participation in prior studies will be recorded to exclude for individuals who have used the same/similar emotional processing tasks.
Provide details about the safety monitoring of participants and the staff/researchers carrying this out
During the week of drug/placebo administration, participants will be advised not to drink alcohol and not to carry out activities requiring full alertness if they are aware of any impairment. During the week of drug/placebo administration, a researcher will phone up the participant on day 2 and day 4 to check that there are no concerns. Participants will have the 24-hour contact phone number of a member of the study team and be encouraged to get in contact if they have any concerns or queries during the study week, or if their health status changes. The named researcher will in turn contact a qualified medical doctor if necessary.

Give details on the medical cover required and who will provide this cover
A medical doctor who is part of the research team will review the screening and make a final judgment about including participants in the study. A qualified medical doctor will be contacted if a participant expresses concern to a named researcher regarding side-effects or health status changes during the study week.
Will the participants' GP be informed about their participation in the study? If not, please justify
Participants' GPs will not be informed about their participation in the study. Seven days of atorvastatin 20mg 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, women of child-bearing potential not using appropriate contraceptive measures, or people who have any medical conditions for whom the study would not be suitable.
What is your planned procedure if an incidental finding is suspected?
Participants will be screened to exclude those with past or current psychiatric symptoms and Best Practice Guidance (BPG) 08 (Psychological distress) will be followed in order to ensure best practice in situations where participants with psychological distress are identified. The guidance in this document around confidentiality and researcher's training will also be adhered to.
If an incidental finding has clinical implications, what action will you take?
If a researcher has concerns that a volunteer may have an undiagnosed psychiatric condition that is causing distress (identified during the Screening Visit or following review of the mood-related questionnaires), CUREC guidance (BPG08) will be followed. The researcher will seek advice from the Principal Investigator who may discuss the symptoms in greater detail with the volunteer and/or offer the opportunity to speak with a senior clinical researcher. If the volunteer indicates that they are not currently receiving support and it is felt necessary, they will be encouraged to contact their GP.
Please give details of departmental SOPs (if any) that will be followed in the case of an incidental finding
As above.

d) Ethical Considerations

Will you include any vulnerable participants (e.g. children, elderly)? **If yes,** please describe how they are defined as vulnerable and detail any CUREC approved procedures or guidance that you feel apply.	Yes ☐	No ☒
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 ☐
The study will involve phlebotomy. Common risks associated with phlebotomy are pain during the procedure and bruising with associated pain afterwards. Less common risks include dizziness and the potential for fainting during the procedure. To minimise these risks, the staff undertaking the procedure will be fully trained in phlebotomy. Bruising after the event will also be reduced by promptly applying pressure on the puncture site		

after the needle is withdrawn. All participants will be fully informed about these risks in the Participant Information Sheet.

There is a theoretical risk that a participant may have an adverse reaction to the study drug. Participants will be informed of the potential side-effects prior to taking the medication. To minimise risk, the participants' general health will be assessed before being accepted into the study. They will be excluded from the study if they are currently taking any regular medications (except the contraceptive pill) or if they have any known contraindications to taking the drug (see exclusion criteria).

Statins are considered extremely safe drugs: their more common side-effect are muscle pain or weakness (usually mild and quickly responding to stopping or switching medication) and elevation of liver transaminases (significant only in case of pre-existing hepatic disease), whereas more serious adverse events include rhabdomyolysis (very rare but severe myopathy associated with elevated creatine kinase and myoglobinuria), new-onset diabetes mellitus (in predisposed individual with pre-existing hyperglycaemia), and haemorrhagic stroke (in patients with prior haemorrhagic stroke or lacunar infarct); however, clinical trials have ultimately concluded that such adverse events attributed to statin therapy in routine practice are not actually caused by it (Collins-2016), especially at doses lower than 80mg/day and when used for less than 52 weeks (Li-2016). Other common (≥ 1/100, < 1/10) but usually mild side-effects include: nasopharyngitis, pharyngo-laryngeal pain, epistaxis, headache, and gastrointestinal disturbances (constipation, diarrhoea, flatulence, dyspepsia, nausea). The potential side-effects and adverse events will be clearly stated in the Participant Information Sheet and researchers will discuss these with participants as part of the informed consent procedure.

To minimise the risk associated with side-effects, participants will be contacted on days 2 and 4 of the study week by a named researcher to check there are no concerns. All participants will have 24-hour contact details of a named researcher who they can contact during the study period. The named researcher will in turn contact a qualified medical doctor if necessary. In order to limit the risks associated with fatigue, during the week of statin/placebo administration, participants will be advised not to drink alcohol, and not to carry out activities requiring full alertness if they are aware of any impairment.

If judged necessary by the medical lead, the randomisation code will be broken for that individual by the medical supervisor and the participant will be advised to stop taking the medication and withdrawn from the study.

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 ☒
Will any procedures affect your own physical and/or psychological safety as a researcher? **If yes,** describe how this will be mitigated.	Yes ☐	No ☒
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 ☒

Please give details of any other ethical and/or safety considerations
None

9. STATISTICS AND ANALYSIS

Do you have a statistical plan? **If no,** please justify.	Yes ☒	No ☐
The IBM SPSS statistical software will be used to analyse all behavioural data. Demographic and baseline measures will be analysed using independent t-tests. Mood, anxiety, side-effects, and hs-CRP measures will be analysed using repeated measures analysis of variance (ANOVA). Behavioural task results will be analysed using between-groups analysis of variance (ANOVA). Any significant interactions will be followed up using simple main effect analyses. When assumptions of equality of variances are not fulfilled, the Greenhouse-Geisser procedure will be used to correct the degrees of freedom.		
Number of Participants		
50 healthy volunteers (25 per group)		
Have you done a sample size calculation? If yes, please give details below If no, please give details to indicate you have considered the implications the selected sample size will have on the study outcome	Yes ☒	No ☐
We will be using the Oxford Emotional Test Battery, which is a well-validated set of emotional processing tasks that are sensitive to antidepressant effects. On the facial expression recognition task, one of the main outcome variables is accuracy at recognising fearful facial expressions and a sample size of 25 per group would give 0.9 power to detect changes of the magnitude of those we have seen in a previous antidepressant healthy volunteer study [drug mean 10.64 (SD 9.77) vs placebo mean 3.36 (SD 5.96) (Harmer-2004).		
Analysis of Outcome Measures		
Data analysis will take place at the University of Oxford, Department of Psychiatry, and will be undertaken by the research team under the supervision of the Principal Investigator. All data will be analysed using a between-groups analysis of variance (ANOVA). Withdrawn participants' data will not be included in the analysis. The primary outcome measure is performance (accuracy and reaction time) in computer-based tasks of emotional processing in the comparison between drug and placebo groups. Secondary to this is performance (accuracy and reaction time) in a computer-based task of reward processing in the comparison between drug and placebo groups, and changes in high sensitivity-C Reactive Protein (hs-CRP) from baseline to seven-day in the comparison between drug and placebo groups.		

10. DATA MANAGEMENT

Management and handling of **personal data** and **special category data** of human participants, either directly or via a third party, will need to comply with the requirements of the General Data Protection Regulation (GDPR) and the new Data Protection Act, 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**. For advice on research data management and security, please consult with the University's Research Data Team (**researchdata@ox.ac.uk)** and/or your local IT department and the University's web pages on research data management.		
Will your research involve the collection of **records of consent** (e.g. written forms, audio-recorded, or other recorded consent)? **If 'yes', these will be classed as fully identifiable personal data (directly linked to an individual).**	**Yes**	No
Will your research involve the collection of **other** personal data? **If 'Yes'**, specify in what form(s) this will be stored:	**Yes**	No
• Fully identifiable (directly linked to an individual)	**Yes**	No
• Pseudonymised (potentially identifiable as data may be attributed to an individual if linkage information can be accessed elsewhere by researchers)	**Yes**	No
• Fully anonymised (i.e. cannot be linked to an individual)	Yes	No
Will any of the personal data that you collect classify as special category data? **If 'Yes'**, specify in what form(s) this will be stored:	**Yes**	No
• Fully identifiable (directly linked to an individual)	**Yes**	No
• Pseudonymised (potentially identifiable as data may be attributed to an individual if linkage information can be accessed elsewhere by researchers)	Yes	No
• Fully anonymised (i.e. cannot be linked to an individual)	Yes	No

How will any *personally identifiable data* be collected, transferred and backed up?	Screening information (name, age [years, months], contact details, medical history, psychiatric history). This information will be in paper form and non-anonymised. It will be collected by the study staff and stored securely in a locked filing cupboard in a room that is locked when unoccupied. Contact details of participants who consent to being contacted about future research will be stored on a database on University computers. Consent forms. This information will be in paper form and non-anonymised. It will be collected by the study staff and stored securely in a locked filing cupboard in a room that is locked when unoccupied.
Where, and for how long, will *personally identifiable data* be stored during and after the study?	Screening information. Screening information will be kept in a lockable filing cabinet with access only by the University researchers. For volunteers who do not wish to be contacted

	for future studies, screening information (including contact details) will be stored for up to one year of completing study analyses. Contact details may be retained after the end of the study for participants who have agreed to be contacted for future studies. Consent forms will be kept in a lockable filing cabinet with access only by the University researchers for 10 years after the end of the study.
If storing *pseudonymised data*, please confirm that identifiers will be held separately from the research data and linked through a unique study number.	Key linking codes to personal details. Key linking codes to personal details will be kept in a lockable filing cabinet with access only by the University researchers. They will be stored for up to one year of completing study analyses, and then destroyed by shredding
Who will have access to the *personally identifiable data*? If personally identifiable data is to be shared with another organisation, how will it be transferred/disclosed securely?	Only named researchers will have access to participants' personally identifiable data.
When and how will *personally identifiable data* be destroyed?	To comply with the General Data Protection Regulation (GDPR) and the new Data Protection Act, personal data will be deleted as soon as possible after it is no longer needed for the study. Screening information. For volunteers who do not wish to be contacted for future studies, screening information (including contact details) will be stored for up to one year of completing study analyses, and then destroyed by shredding. Contact details may be retained after the end of the study for participants who have agreed to be contacted for future studies. Consent forms. Consent forms will be kept for 10 years after the end of the study, and then destroyed by shredding.
Who will have access to the *research* data?	Named researchers will have access to the research data. Direct access will be granted to authorised representatives from the University of Oxford for monitoring and/or audit of the study to ensure compliance with regulations.
How will *research* data be stored?	Questionnaire data. Questionnaire data will be pseudonymised with a key linking code. Paper questionnaires will be stored securely in a locked filing cabinet in a room that is locked when unoccupied. Electronic questionnaire data will be stored on University computers in a secured building and will be firewall and password protected. Blood samples. Blood samples (4mL = 1 teaspoon) taken during the Screening Visit and the Research Visit for investigating hs-CRP will be handled at the Neurosciences Building's laboratory. On the same day, they will be rendered acellular by centrifugation on receipt and stored at -30^{o}C until assay. Any excess material remaining at the end of the study will be disposed of by the laboratory within 6 months according to the Human Tissue Authority guidelines. The

	samples will be stored in a freezer at the Neurosciences Building in a pseudonymised form with a key linking code. Access to the samples will be by the research team and the samples will be in the custody of Prof Philip Cowen who will hold the key code linking the samples to a particular individual. The samples will be analysed for once all participants have completed the study. Computer-based tasks. Computer-based tasks data will be pseudonymised with a key linking code. Electronic data will be stored on University computers in a secured building and will be firewall and password protected.
How long will *research* data be stored for?	Research data will be archived at the end of the study in the Neurosciences Building, Warneford Hospital, or in the University of Oxford's offsite archive facility. It will be archived in anonymous form and will be stored for a minimum of 10 years.
What will be done with the *research* data at the end of the storage period?	At the end of the storage period, research data will be destroyed.

11. STUDY MONITORING AND OVERSIGHT

Who will be responsible for day-to-day supervision of the study?
Professor Philip J Cowen, Doctor Riccardo De Giorgi
Give information about frequency of meetings that will be held to discuss progress/problems. Who will be present at the meetings?
The study team will meet weekly to discuss progress with the project. The Principal Investigator and named researchers will be present in these meetings.

12. ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The Investigator will ensure that this study 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, and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the Sponsor and 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.

13. INSURANCE STATEMENT

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).

14. DISSEMINATION AND FEEDBACK OF STUDY OUTCOMES

It is anticipated that the results of the study will be disseminated through the usual scientific channels at the end of the study, including peer-reviewed publication and presentation at scientific conferences. It will also form part of a DPhil dissertation and will comply with the Departmental policy on publications.

Participants will be offered the opportunity to receive a brief report summarising the findings at the end of the study.

15. REFERENCES

Collins R, et al. Lancet. 2016 Nov 19; 388(10059):2532-2561. doi: 10.1016/S0140-6736(16)31357-5

Cooper CM, et al. Psychological Medicine 2017; Page 1 of 10. doi:10.1017/S00332917170023792017

Cowen PJ & Browning M. World Psychiatry 2015 Jun; 14(2): 158–160. doi: 10.1002/wps.20229

Felger J, et al. Neuropsychopharmacology Reviews 2017; 42, 216–241. doi: 10.1038/npp.2016.143

Harmer CJ, et al. Am J Psychiatry 2004; 161:1256–1263. doi: 10.1176/appi.ajp.161.7.1256

Harmer CJ, et al. Lancet Psychiatry 2017 May; 4(5): 409–418. doi:10.1016/S2215-0366(17)30015-9

Jain MK & Ridker PM. Nat Rev Drug Discov 2005 Dec; 4(12):977-87. doi: 10.1038/nrd1901

Jha MK & Trivedi MH. Int. J. Mol. Sci. 2018; 19:233. doi:10.3390/ijms19010233

Kassebaum NJ, et al. Lancet 2016; 388(10053):1603-1658. doi: 10.1016/S0140-6736(16)31460-X

Kilic FS, et al. Neurosciences (Riyadh). 2012 Jan; 17(1):39-43

Köhler-Forsberg O, et al. CNS Drugs. 2017 May;31(5):335-343. doi: 10.1007/s40263-017-0422-3

Li H, et al. Drug Saf. 2016 May; 39(5):409-19. doi: 10.1007/s40264-016-0394-0.

Macin SM, et al. Am Heart J. 2005 Mar; 149(3):451-7. doi: 10.1016/j.ahj.2004.07.041

McCabe C, et al. Biol Psychiatry. 2010 Mar 1; 67(5): 439–445. doi: 10.1016/j.biopsych.2009.11.001

Miller AH, et al. Neuropsychopharmacology Reviews 2017;42:334–359. doi: 10.1038/npp.2016.229

NICE. NICE Clinical Guidelines 2014; 181:11. Available from: https://www.ncbi.nlm.nih.gov/books/NBK268908/

Parsaik AK, et al. J Affect Disord. 2014 May; 160:62-7. doi: 10.1016/j.jad.2013.11.026

Penn E, et al. Ther Adv Psychopharmacol 2012; 2(5):179–188. doi: 10.1177/ 2045125312445469

Roiser JP & Sahakian J. CNS Spectrums 2013; 18:139–149. doi:10.1017/S1092852913000072

Walsh AEL, et al. Front Psychiatry 2018 Oct 16; 9:482. doi: 10.3389/fpsyt.2018.00482

Salagre E, et al. J Affect Disord. 2016 Aug; 200:235-42. doi: 10.1016/j.jad.2016.04.047

16. DECLARATIONS AND SIGNATURES OF RESEARCHERS

- I/We, the researcher(s) agree:
- To start this research study only after obtaining approval from MS IDREC/CUREC;
- To carry out this research study 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 study participants;
- To notify CTRG and 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 CTRG and MS IDREC if the principal researcher on the study changes and supply the name of the successor;
- To notify CTRG and 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 study 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)	Professor Philip J Cowen
Principal Investigator (Signature)	
Medically qualified collaborator (Name)	Doctor Riccardo De Giorgi
Medically qualified collaborator (Signature)	
Student (Name)	Doctor Riccardo De Giorgi
Student (Signature)	

17. 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)	JOHN GRIGGS
Head of Department (Signature)	
Date	31st Jan 2019

18. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made