CENTRAL UNIVERSITY RESEARCH ETHICS COMMITTEE (CUREC)

CUREC 3 Protocol and Application Form

Pharmacological Studies in Healthy Volunteers

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

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

All advisory text is highlighted in yellow and should be deleted before finalising the document.
Should you require any assistance in completing this document, please contact CTRG in the first instance: http://researchsupport.admin.ox.ac.uk/ctrg

STUDY DETAILS	
Full Study Title	The effect of seven day prucalopride administration on emotional processing in healthy volunteers
Internal Reference / Short title	7 day prucalopride and emotional processing
MS IDREC Reference	R57219/RE001
Date and version number	Version Three, 16th May 2019
Principal Investigator	Dr Susannah Murphy
Student (if applicable)	N/A
University email contact	Susannah.murphy@psych.ox.ac.uk
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Medically qualified collaborator (Licensed Doctor)	Professor Phillip Cowen, MD, FRCPsych, FMedSci phil.cowen@psych.ox.ac.uk 01865 618311 Department of Psychiatry, University of Oxford
Sponsor	The University of Oxford
External Funding	None
Will you submit or have you submitted this study to another ethics committee?	Yes ☐ No X
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 Harmer**
Department / Institute name	Department of Psychiatry, University of Oxford
Role in Study	Professor Harmer will be involved in the study design and interpretation of data. She is Professor of Cognitive Neuroscience, PhD Psychology, and has 20 years 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	**Professor Philip Cowen**
Department / Institute name	Department of Psychiatry, University of Oxford
Role in Study	Professor Cowen will provide academic and medical supervision of the project. He is Professor of Pharmacology, MD, FRCPsych, FMedSci
Training/Qualification in Research Ethics	'Training in Good Clinical Practice and Clinical Trial Methodology and Administration' (refresher course June 2011). Protocol and Associated Documents Course March 2013. Adverse Event Reporting (online CTRG training) 2017
Investigator Title and name	**Dr. Jessica Scaife**
Department / Institute name	Department of Psychiatry, University of Oxford
Role in Study	Recruitment, data collection, analysis
Training/Qualification in Research Ethics	Good Clinical Practise (Epigeum) training, completed 06/03/2018 Magnet Safety Training, completed 10/01/2018

Investigator Title and name	**Miss Lucy Wright**
Department / Institute name	Department of Psychiatry, University of Oxford
Role in Study	Recruitment, data collection, analysis
Training/Qualification in Research Ethics	Good Clinical Practise for Clinical Research Studies training, completed 15/11/2016 Magnet Safety Training, completed 10/01/2018
Investigator Title and name	**Miss Elizabeth Haris**
Department / Institute name	Department of Psychiatry, University of Oxford
Role in Study	Recruitment, data collection, analysis
Training/Qualification in Research Ethics	Good Clinical Practise for Clinical Research Studies training, completed 20/11/2017 Magnet Safety Training, completed on 14/02/2018
Investigator Title and name	**Ms Amy Gillespie**
Department / Institute name	Department of Psychiatry, University of Oxford
Role in Study	Recruitment, data collection, analysis
Training/Qualification in Research Ethics	Good Clinical Practise for Non-CTIMPs, Guys Hospital, completed 17/08/2016 Magnet Safety Training, completed 10/01/2018
Investigator Title and name	**Dr Angharad de Cates**
Department / Institute name	Department of Psychiatry, University of Oxford
Role in Study	Recruitment, data collection, analysis
Training/Qualification in Research Ethics	Good Clinical Practice (eGCP (Secondary Care)), completed 03/05/2017 Magnet Safety Training, completed 13/02/2019

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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 as we are not investigating the efficacy of prucalopride, but rather using it as a probe to understand the role of 5-HT4 receptors in emotional 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	Department of Psychiatry, Warneford Hospital, University of Oxford Oxford Centre for Human Brain Activity (OHBA), Warneford Hospital, University of Oxford	
Age Range of Study Participants	18-40 years	
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 March 2018	
Anticipated End Date	1st March 2020	
	Objectives	**Outcome Measures**
Primary	To investigate the effects of seven day prucalopride administration on 1. Recognition of positive and negative facial expressions 2. Performance on Auditory Verbal Learning Task	1. Accuracy (%) and reaction times on computer-based task of facial expression recognition (FERT), comparing those

	(AVLT)	receiving drug and placebo. 2. Number of words correctly recalled across blocks (and number of intrusions and repetitions)
Secondary	To investigate the effects of seven day prucalopride administration: 1. Amygdala response to emotional faces 2. Hippocampal response to novel versus repeated scenes 3. Reward sensitivity 4. Categorisation, recall and recognition of emotional words	1. BOLD fMRI signal in the amygdala during emotional faces task presentation 2. BOLD fMRI signal in hippocampus to pictures of familiar versus novel scenes. 3. Amount won, amount lost, total monetary amount earned during the task, proportion of participants choosing the correct symbol in win and loss trials of the PILT, comparing those receiving drug and placebo 4. Number of positive and negative words correctly categorised, recalled, and recognised on emotional memory task

Tertiary	To investigate the effects of seven day prucalopride administration on: 1. Vigilance to fearful and happy faces 2. Resting state networks 3. Visual short term memory 4. Cerebral blood flow using arterial spin labelling (ASL)	1. Reaction times to fearful, happy, and neutral faces in masked and unmasked conditions 2. BOLD fMRI activity during resting state 3. Accuracy and reaction time on the Oxford Memory Task (OMT) 4. Relative and global cerebral blood flow using arterial spin labelling (ASL)
Name of drug/substance	Prucalopride (Resolor)	
Purpose of drug/substance use in this study	Work in our group has revealed that short-term (7 day) administration of antidepressants that boost serotonin levels produces positive biases in the processing of emotional information in healthy volunteers. Such effects might be an important neuropsychological mechanism of antidepressant action. It is unclear whether particular serotonin receptor subtypes are particularly important in mediating these effects. The current study investigates the effect of seven-day administration of a specific agonist of the 5-HT_4 receptor subtype (Prucalopride) on emotional processing tasks. There is evidence that 5-HT_4 agonists may exert antidepressant and anxiolytic effects in animal models, and it is therefore predicted that prucalopride will have similar effects to serotonergic antidepressants on emotional processing. A previous study in our group demonstrated that a single dose of prucalopride potentiated learning and memory in healthy volunteers, but had no effect on emotional processing. This study aims to investigate whether a longer (7 day) administration of prucalopride has effects on the neural and behavioural response to emotional stimuli that are consistent with an antidepressant profile.	
Adverse reactions and side effects posing a particular risk	The side effects associated with prucalopride are headache, gastrointestinal symptoms (abdominal pain, nausea, diarrhoea), decreased appetite, vomiting, flatulence, and fatigue. There is limited information about the effects of a single dose of prucalopride in healthy volunteers, with most reported information about side effects coming from patients with	

with this treatment	constipation. Pilot work in our group demonstrated that the standard 2mg dose of prucalopride was not well tolerated in healthy volunteers, with two out of three pilot participants experiencing diarrhoea following a single 2mg dose. As a result of this pilot work, we used a 1mg dose of prucalopride in our previous study, which was well tolerated by healthy volunteers. The main side effects reported by participants in this study were fatigue, gastrointestinal sounds, and headache, but the rate of report of these side effects was not higher in the prucalopride group compared with the placebo group. We therefore plan to use the same 1mg dose in the current study.

3. ABBREVIATIONS

5-HT	Serotonin
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BMI	Body Mass Index
BOLD	Blood Oxygen Level Dependent
BPG	Best Practice Guidance
CTRG	Clinical Trials & Research Governance, University of Oxford
CUREC	Central University Research Ethics Committee
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPQ	Eysenck Personality Questionnaire
ETB	Emotional Test Battery
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
JCR	Junior Common Room
MCR	Middle Common Room
MS IDREC	Medical Sciences Inter-Divisional Research Ethics Committee
NART	National Adult Reading Test
OHBA	Oxford Centre for Human Brain Activity
PANAS	Positive and Negative Affective Schedule
PI	Principal Investigator
PIL	Probabilistic Instrumental Learning
PIS	Participant Information Sheet
SAE	Serious Adverse Event

SCID-V	Structured Clinical Interview for DSM-V
SHAPS	Snaith-Hamilton Pleasure Scale
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	Spielberger State-Trait Anxiety Inventory
VAS	Visual Analogue Scales

4. BACKGROUND AND RATIONALE

Depression is a common condition which is associated with substantial health disability (1). Selective Serotonin Reuptake Inhibitors (SSRIs) are the most commonly prescribed antidepressants. However, for many patients these drugs have limited efficacy, a poor side-effect profile, and a slow onset of therapeutic action (2). Pharmacologically, SSRIs produce an indirect activation of several serotonergic receptor subtypes. It is possible that more specifically targeting particular receptor subtypes may be a potentially useful approach to the development of antidepressant treatment that is more effective, better tolerated and faster acting.

Recent evidence from animal studies suggests that agonists of the serotonin receptor subtype 4 (5-HT_4) have rapid effects on depression- and anxiety-related behaviours. For example, administration of the 5- HT_4 agonists RS67333 and prucalopride reduces immobility in the forced swim test (3). Consistent with this, in a mouse corticosterone model of anxiety/depression, RS67333 produced rapid anxiolytic and antidepressant effects in a battery of tests, including the open field test, the elevated plus maze, the tail suspension test and the novelty suppressed feeding test (4). Importantly, these effects were seen after only three days of treatment (3,4), whereas they are usually only observed after chronic (2-3 week) treatment with conventional SSRIs. This raises the intriguing possibility that 5-HT_4 agonism might lead to more rapid and sustained activation of 5-HT neurons than SSRIs, and therefore potentially more rapid reductions in symptoms of depression when used clinically.

Work in our group has revealed that short-term treatment with conventional antidepressants such as SSRIs produces positive biases in the processing of emotional information in healthy volunteers (5). For example, seven days treatment with the SSRI citalopram decreased recognition of negative facial expressions and recall of negative vs positive stimuli (6). There is also evidence showing that antidepressants have early effects on neural activity, acting on limbic-cortical brain regions that are known to be dysregulated in depression (7). Indeed, a key study by Godlewska and colleagues from our group showed that 7-day treatment with citalopram reduced activity in the anterior cingulate, insula, amygdala and thalamus in response to fearful versus happy facial expressions. Importantly, depressed patients with the greatest reduction in neural activity across these areas went on to respond better to SSRI treatment (8).

Such effects might be important neuropsychological mechanisms in the mediation of clinical antidepressant action and may also be useful as biomarkers to screen for potential antidepressant activity of novel compounds. It is currently unknown whether activating 5-HT_4 receptors has similar effects on emotional

processing and neural activity. Such findings would be consistent with the animal studies and important further demonstration that 5-HT_4 receptor agonism might be a potentially useful avenue for antidepressant drug development. A previous study in our group revealed acute prucalopride administration (1mg) in 40 healthy volunteers potentiated learning and memory, whereby significantly more words were remembered in a test of auditory verbal learning and memory, and fewer false alarms were made in a delayed emotional recall task relative to placebo. A single dose of prucalopride did not, however, positively bias emotional processing.

This current study will therefore test the hypothesis that short-term, seven-day administration of prucalopride will have positive effects on emotional processing and neural activity. Prucalopride ("Resolor") is a 5-HT4 receptor agonist which is currently licensed for the symptomatic treatment of chronic constipation in adults. The standard dose given is 2 mg once daily with or without food, at any time of the day. Healthy volunteers will be randomised to receive seven days of prucalopride (1 mg i.e. half the standard dose) or placebo. On the seventh day of drug administration, they will complete a battery of computer-based tasks that measure emotional processing (tasks of attention, interpretation, and memory), non-emotional cognition, and undergo fMRI scanning during an emotional processing task.

5. PARTICIPANTS

Description of Study Participants
50 Healthy Volunteers aged between 18 and 40 years
Inclusion Criteria
• Participant is willing and able to give informed consent for participation in the study • Not currently taking any medications (except the contraceptive pill) • Male or female • Aged 18-40 years • Sufficiently fluent English to understand and complete the task • Right handed • Body Mass Index in the range of 18-30
Exclusion criteria
The participant may not enter the study if ANY of the following apply: • Not fluent in English • Any past or current Axis 1 DSM-V psychiatric disorder • Current usage of psychoactive medication (except the contraceptive pill, the Depo-Provera injection or the progesterone implant) • Current usage of any medication that will influence the MRI scan (the researcher will

help you decide this)

- Current or past history of drug or alcohol dependency
- Currently pregnant or breastfeeding
- Study visits due to take place during the pre-menstrual week (female participants will be asked details of their menstrual cycle to schedule the study outside this week)
- Not right handed
- Body Mass Index outside the range of 18-30
- History of cardiac, thyroid, or liver problems
- An autoimmune disorder
- Current, or a history of, gastro-intestinal disorder or irritable bowel syndrome
- Epilepsy
- Known lactate deficiency or any other problem absorbing lactose, galactose, or glucose
- Participation in a study which uses the same 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
- Smoker > 5 cigarettes per day
- Typically drinks > 6 caffeinated drinks per day
- Any contraindication to MRI scanning (e.g. metal objects in your body, pacemakers, significant claustrophobia)

Recruitment

Participants will be recruited via adverts (see APPENDIX A: STUDY ADVERTS) sent to Junior Common Rooms (JCRs) and Middle Common Rooms (MCRs), 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 may also be placed on local information websites (e.g. Daily Info, Oxford University Gazette), newspapers, local magazines, on the radio and on the lab webpage, 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 a previous study 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 Department of Psychiatry, Warneford Hospital. At the beginning of this visit, one of the named researchers will explain the study to the participant and answer any questions that he/she has. The researcher will then take written consent from the

participant. All of the named researchers have been trained in taking informed consent.

Screening and Eligibility Assessment

Informed Consent is obtained at the start of the screening, prior to administration of questionnaires or the Structured Clinical Interview for DSM-V Disorders.

A maximum of four weeks is allowed between screening and randomisation to prucalopride 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 will be taken (using Structured Clinical Interview for DSM-V). See APPENDIX C: SCREENING FORM.

An MRI screening form will be completed to ensure it is safe for participants to undergo fMRI scanning (see APPENDIX D: MRI SCREENING FORM).

Female participants will take a urine pregnancy test.

Information Provided to Participants and Informed Consent

The Participant Information Sheet (see APPENDIX E: PARTICIPANT INFORMATION SHEET) will be presented to the participants, 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 General Practitioner (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 (ICF; see APPENDIX F: 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 (PI). A copy of the signed ICF will be given to the participant. The original signed form will be retained at the study site.

Participant Confidentiality

It will 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 would 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). 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
- Number of cigarettes smoked per day, units of alcohol consumed per week, caffeinated drinks consumed per day
- 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-V interview (Structured Clinical Interview for DSM-V) to probe for current or past psychiatric illness
- Urine pregnancy test (female participants only)
- MRI screening form to ensure no contraindication to MRI scanning
- Edinburgh Handedness Inventory (see APPENDIX G: STUDY QUESTIONNAIRES)

The following baseline assessments will be completed (APPENDIX G):

- 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) - a measure of anhedonia
- National Adult Reading Test (NART) - a measure of verbal intelligence
- Side effect questionnaire (to determine baseline of bodily symptoms/'side effects')
- Visual Analogue Scales (VAS) measuring subjective state

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, using an online randomisation tool, to receive either seven-day prucalopride, or seven-day placebo administration. Randomisation will occur on the day of screening, or up to a maximum of four 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 four weeks has elapsed, another screening visit will be performed to ensure participants are still eligible.

Randomised participants will be given seven days of the drug to take home, as well as full instructions of how and when to take them. The study has a double blind design thus neither the researchers nor the participant will know whether prucalopride or placebo is given.

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

1. Research Visit One (approximately 1.5 hours) on day 6 of prucalopride/placebo administration. This visit will involve an fMRI scan taking place at the Oxford Centre for Human Brain Activity (OHBA), which is part of the Department of Psychiatry on the Warneford Hospital site.

On arrival, participants will complete the MRI screening form (APPENDIX D) once more to ensure it is still safe for them to undergo fMRI scanning.

Participants will complete the following questionnaires before and after the fMRI scan:

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

The scan itself will include:

- Structural scan
- Emotional faces task
- Memory task
- Resting state
- Arterial spin labelling
- Physiological recordings including pulse, respiration, and skin conductance – recorded using a pulse meter, respiration bellows and electrodes strapped by Velcro to fingertips.
- Eye tracking

2. Research Visit Two (approximately 2 hours) on day 7 of prucalopride/placebo administration. This visit will involve administration of behavioural tasks measuring emotional and non-emotional cognitive processing.

Participants will complete the following questionnaires before and after the behavioural tasks:

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

The behavioural tasks will include the Emotional Test Battery (ETB), which has previously been found to be sensitive to the effects of antidepressants, two tests of learning and memory, and a reward task (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 seven-day administration.

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

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 Consent
- Loss to follow up

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

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 £120 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	Prucalopride
Formulation and route of administration for study	1mg prucalopride tablets will be encapsulated in opaque capsules.
Dose and route of administration for study	1mg oral dose, daily
Duration of treatment for study	Seven days
Licence status of this drug/substance	Prucalopride is a licensed drug.
Usual Indication	Prucalopride is indicated for the symptomatic treatment of chronic constipation in adults.
Usual Dose	The usual dose given is 2 mg once daily with or without food, at any time of the day.
Usual duration of treatment	Prucalopride can be administered long- term, although the efficacy of the drug in the treatment of constipation has only been established up to 3 months.
Where will drug/substance be sourced from?	The drug will be sourced from the Oxford Pharmacy Store, Kennington in the form of 1mg film-coated tablets.
Where will drug/substance be stored?	Prucalopride will be stored within the Neurosciences Building at the Department of Psychiatry. It will be stored at room temperature in a locked cupboard, which is suitable for drug storage.
How will drug/substance be dispensed?	Prucalopride will be dispensed from the Neurosciences Building by a study medic or nurse.
How will the drug/substance be prepared by the researchers for use in this study?	Prucalopride will be encapsulated by trained clinical trial support staff using our Standard Operating Procedure (see protocol APPENDIX H: ENCAPSULATION STANDARD OPERATING PROCEDURE (SOP)).

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 taken orally, daily
Duration of treatment for study	Seven 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 tablets will be stored within the Neurosciences Building at the Department of Psychiatry. It will be stored at room temperature in a locked cupboard, which is suitable for drug storage.
How will drug/substance be dispensed?	Placebo tablets will be dispensed from the Neurosciences Building by a study medic or nurse.
How will the drug/substance be prepared by the researchers for use in this study?	Placebo tablets will be encapsulated by trained clinical trial support staff using our Standard Operating Procedure (see protocol APPENDIX H: ENCAPSULATION STANDARD OPERATING PROCEDURE (SOP)).

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-V interview (Structured Clinical Interview for DSM-V) 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)
- National Adult Reading Test (NART)
- Edinburgh Handedness Inventory
- Side effect 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)

To ensure it is safe for the participant to undergo fMRI scanning, the following will be administered

- MRI safety form to ensure no contraindication to MRI scanning

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 this week, 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? In not, please justify

Participants' GPs will not be informed about their participation in the study. Seven days of low-dose prucalopride (1mg) 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.

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

The detailed images obtained from MRI scanners, while not suitable for clinical diagnosis, may on rare occasions identify unexpected structural abnormalities. If an abnormality is noted on the structural scan of a healthy volunteer, the "WIN/OCMR/OHBA Standard Operating Procedure – Dealing with Research Neuroimaging Incidental Findings" will be strictly followed.

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 training will also be adhered to.

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

During the consent process, subjects would be informed of our standard procedure for incidental findings ("WIN/OCMR/OHBA SOP – Dealing with Research Neuroimaging Incidental Findings"). This outlines the process of involving a dedicated local hospital NHS consultant clinician in the case of a suspected abnormality, although it is stressed that a routine inspection and reporting of research scans is not carried out. In the case of a suspected abnormality, the Principal Investigator would alert our Contact Radiographer who, if appropriate (i.e. not a simple artefact) would independently inform the Contact Neurologist. They would in turn obtain the opinion of the Contact Neuroradiologist, and decide on the appropriate course of action, which might involve contact with the individual at the earliest opportunity and possible further investigation, including a hospital (NHS) diagnostic scan. This would all take place within the NHS framework and in communication with the volunteer's GP.

If a researcher has concerns that a volunteer may have an undiagnosed psychiatric condition that is causing distress (identified during the screening visit or following review of the mood-related questionnaires), CUREC guidance (BPG08) will be followed. The researcher will seek advice from the Principal Investigator who may discuss the symptoms in greater detail with the volunteer and/or offer the opportunity to speak with a senior clinical researcher. If the volunteer indicates that they are not currently receiving support and it is felt necessary, they will be encouraged to contact their General Practitioner.

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

During the consent process, participants would be informed of our standard procedure for incidental findings [APPENDIX I: WIN/OCMR/OHBA STANDARD OPERATING PROCEDURE (SOP) – DEALING WITH RESEARCH NEUROIMAGING INCIDENTAL FINDINGS].

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 X
Will taking part in the research put participants under any particular burden and/or risk? **If yes,** describe how this will be mitigated.	Yes X	No ☐

a) There is a theoretical risk that a participant may have an adverse reaction to the study drugs. 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 psychoactive medication or if they have any known contraindications to taking the drug (see exclusion criteria).

The most frequently reported adverse reactions associated with prucalopride 2mg therapy are headache (17.8%) and gastrointestinal symptoms (abdominal pain (13.7%), nausea (13.7%) and diarrhoea (12.0%)). Other side effects associated with prucalopride are decreased appetite, dizziness, vomiting, flatulence, fatigue, and gastrointestinal sounds. The terminal half-life of prucalopride is about 1 day. There is less information about the side effect profile in healthy volunteers rather than patients, or after short-term prucalopride 1mg administration, although a single 1mg dose of prucalopride was well tolerated in our previous healthy volunteer study. The potential side effects are clearly stated in the Participant Information Sheet and researchers will discuss these with participants as part of the informed consent procedure.

The drug has been tested in healthy volunteers in pharmacokinetic studies and to establish interactions with other drugs (for example, we know that prucalopride does not affect the pharmacokinetics of the oral contraceptive (9)).

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 prucalopride/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.

b) While most people do not experience discomfort in an MRI environment, the enclosed space of the scanner can potentially feel uncomfortable. Discomfort from lying still for a long period of time will be minimised with comfortable padding and positioning. Whilst in the scanner, participants will be able to use the alarm button if they wish to communicate with the operator or to interrupt scanning. People with a history of severe claustrophobia would be excluded from participation in the study. All participants will be introduced carefully to the scanner and informed that they can terminate the scan session at any stage, should they wish to do so. Once inside the scanner, participants will be able to indicate if they wish the scanning to cease by squeezing a bulb placed in their hand, or by requesting verbally. As the MRI scanner is noisy, participants will be given earplugs to minimise the noise.

MRI is a safe, non-invasive technique, which does not involve ionising radiation. Risks associated with the

magnetic field will be removed by excluding potential participants with ferromagnetic objects in their bodies (e.g., metal implants, vessel clips, shrapnel injuries) or with implanted devices, which may be damaged by the magnet (e.g., heart pacemakers). All people entering the scanning room will complete an MRI Screening safety questionnaire just before entering the scanner.		
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 X
Will any procedures affect your own physical and/or psychological safety as a researcher? **If yes,** describe how this will be mitigated.	Yes ☐	No X
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 X
Please give details of any other ethical and/or safety considerations		

9. STATISTICS AND ANALYSIS

Do you have a statistical plan? **If no,** please justify.	Yes X	No ☐
The IBM SPSS statistical software will be use to analyse all behavioural data. Demographic and baseline measures will be analysed using independent t-tests. Mood, anxiety, and side effect 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. Analysis of fMRI endpoints will be completed using the FSL software package.		
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 Emotion 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/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) from Harmer et al 2004 Am J Psych; ref 6].		
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). Analysis of fMRI endpoints will be completed using the FSL software package. Withdrawn participants' data will not be included in the analysis. The primary outcome measures are performance (accuracy and reaction time) in a computer-based task of facial expression recognition (FERT), and performance on the auditory verbal learning task AVLT, compared between drug and placebo groups. Secondary to this is the amygdala and hippocampal BOLD fMRI response to emotional faces and novel vs. repeated scenes respectively, reward sensitivity on the PILT, and number of positive and negative words correctly categorised, recalled, and recognised on emotional memory tasks. The tertiary outcome measures are reaction times to fearful vs. happy faces on the FDOT, BOLD fMRI response during resting state, performance (accuracy and reaction time) on the OMT task of visual short term memory, and relative/global cerebral blood flow using arterial spin labelling, all compared between those receiving drug and placebo.		

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
Will your research involve the collection of **other personal data**? **If 'Yes**', specify in what form(s) this will be stored:	Yes

• Fully identifiable (directly linked to an individual) • Pseudonymised (potentially identifiable as data may be attributed to an individual if linkage information can be accessed elsewhere by researchers) • Fully anonymised (i.e. cannot be linked to an individual)	Yes No No
Will your research involve the collection of **special category data**? **If 'Yes**', specify in what form(s) this will be stored: • Fully identifiable (directly linked to an individual) • Pseudonymised (potentially identifiable as data may be attributed to an individual if linkage information can be accessed elsewhere by researchers) • Fully anonymised (i.e. cannot be linked to an individual)	Yes Yes No No
How will any *personally identifiable data* be collected, transferred and backed up?	Personal data (screening information and consent forms) will be collected in paper form during the screening visit at the Neurosciences Building, Warneford Hospital. These paper documents will be transferred by the researcher to a locked filing cupboard in a neighbouring room in the Neurosciences Building for storage.
Where, and for how long, will *personally identifiable data* be stored during and after the study?	a) **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 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. b) **Consent forms.** This information will be in paper form and non-anonymised. It will be stored securely in a locked filing cupboard in a room that is locked when unoccupied. 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 will be destroyed once the data has been analysed and the results have been published, unless participants give consent to be re-contacted about studies for which they may be suitable, in which cases contact details will be retained. Consent forms will be kept 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.	Each participant will be assigned a unique study number at screening. A key will link participants' personal details to their unique study number. This document will be stored in the Research Masterfile in a lockable filing cabinet, separate from all research data. It will be destroyed along with

	consent forms – 10 years after the end of the study.
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' personal data.
When and how will *personally identifiable data* be destroyed?	Once the data has been analysed and the results have been published, screening information will be destroyed by shredding unless participants have consented for their contact details to be retained. Consent forms will be destroyed by shredding 10 years after the end of the study.
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?	a) **Questionnaire data.** Questionnaire data will be anonymised by a participant ID number and will not be linked with any personal identifiers. Completed paper questionnaires will be stored securely in a locked filing cabinet in a room that is locked when unoccupied. Anonymised electronic questionnaire data will be stored on University computers in a secured building, and will be firewall and password protected. b) **Computer-based tasks and fMRI data.** Computer-based tasks data will be anonymised by a participant ID number and will not be linked with any personal identifiers. The electronic and imaging data will be stored on University computers in a secured building, and will be firewall and password protected. c) **Personal information.** Personal information (contact details, consent forms) will be kept in a lockable filing cabinet with access only by the University researchers. Personal data may be retained after the end of the study for participants who have agreed to be contacted for future studies. For volunteers who do not wish to be contacted for future studies, personally identifiable data will be shredded as soon as possible after the completion of the study and within one year of completing study analyses. d) **Key linking codes to personal details.** This will be kept in a lockable filing cabinet with access only by the University researchers.
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?
Dr Susannah Murphy
Give information about frequency of meetings that will be held to discuss progress/problems. Who will be present at the meetings?
The study team will meet fortnightly to discuss progress with the project. The Principal Investigator and named researchers will be present in these meetings.

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 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 with a copy to CTRG.

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

15. REFERENCES

(1) Moussavi et al (2007) Lancet 370: 851-859
(2) Burbui Hotopf (2003) Br J Psychiatry 178: 129-144
(3) Lucas et al (2007) Neuron 55: 712-725
(4) Mendez-David et al (2014) Neuropsychopharmacology 39: 1366-1378
(5) Harmer et al (2009) Brit J Psychiatry 195: 102-108
(6) Harmer et al (2004) Am J Psychiatry 161 (7): 1256-63
(7) Ma (2015). Molecular Psychiatry, 1–9.
(8) Godlewska et al. (2016). Translational Psychiatry, 22-6.
(9) Van de Velde et al (2013) Drugs R D 13 (1): 43–51

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)	
Principal Investigator (Signature)	
Medically qualified collaborator (Name)	
Medically qualified collaborator (Signature)	
Student (Name)	
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.

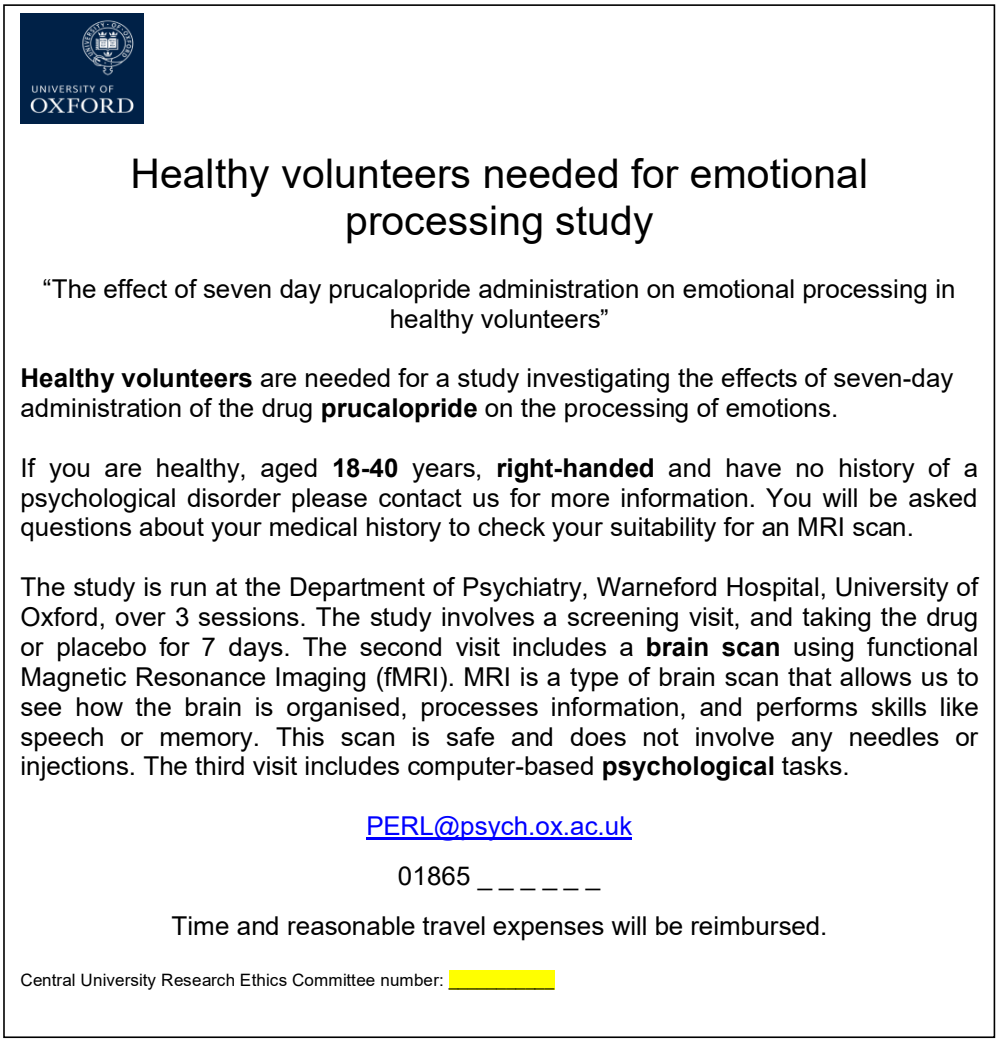
Head of Department (Name)	
Head of Department (Signature)	
Date	

18. AMENDMENT HISTORY

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

19. APPENDIX A: Study Adverts

Web advert:



UNIVERSITY OF OXFORD

Healthy volunteers needed for emotional processing study

"The effect of seven day prucalopride administration on emotional processing in healthy volunteers"

Healthy volunteers are needed for a study investigating the effects of seven-day administration of the drug **prucalopride** on the processing of emotions.

If you are healthy, aged **18-40** years, **right-handed** and have no history of a psychological disorder please contact us for more information. You will be asked questions about your medical history to check your suitability for an MRI scan.

The study is run at the Department of Psychiatry, Warneford Hospital, University of Oxford, over 3 sessions. The study involves a screening visit, and taking the drug or placebo for 7 days. The second visit includes a **brain scan** using functional Magnetic Resonance Imaging (fMRI). MRI is a type of brain scan that allows us to see how the brain is organised, processes information, and performs skills like speech or memory. This scan is safe and does not involve any needles or injections. The third visit includes computer-based **psychological** tasks.

PERL@psych.ox.ac.uk

01865 _ _ _ _ _ _

Time and reasonable travel expenses will be reimbursed.

Central University Research Ethics Committee number: _____

Version 1: 15th March 2018. CUREC Ref: _____

Poster advert:

UNIVERSITY OF OXFORD

Healthy volunteers needed for emotional processing study

"The effect of seven day prucalopride administration on emotional processing in healthy volunteers"

We are looking for **healthy volunteers** aged **18-40** years, with **no history of a psychological disorder**, who are **right-handed**, for a study investigating the effect of the drug **prucalopride** on the processing of emotions.

You would be invited to the University of Oxford **Department of Psychiatry**, Warneford Hospital, for **three sessions**.

The first session would take approximately 2 hours, involving detailed questions to see if you are eligible to take part, including questions about your medical history to check your suitability for an MRI scan. You would be given seven days of either prucalopride or placebo to take home, plus full instructions of how and when to take the study medication, as well as the 24-hour contact details of a researcher.

You would be invited to a second session (lasting approximately 1.5 hours) on the sixth day, which would involve a **brain scan** using functional **Magnetic Resonance Imaging** (fMRI). MRI is a type of brain scan that allows us to see how the brain is organised, processes information, and performs skills like speech or memory. This scan is safe and does not involve any needles or injections. On the seventh day you would be invited to a third session (lasting approximately 2 hours), which would involve **psychological tasks**.

Please contact us for more information if you are interested in participating.
Time and reasonable travel expenses will be reimbursed.

lucy.wright@psych.ox.ac.uk
01865 618319

Prucalopride Emotional Processing Study
lucy.wright@psych.ox.ac.uk

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lucy.wright@psych.ox.ac.uk
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lucy.wright@psych.ox.ac.uk
Prucalopride Emotional Processing Study
lucy.wright@psych.ox.ac.uk
Prucalopride Emotional Processing Study
lucy.wright@psych.ox.ac.uk
Prucalopride Emotional Processing Study
lucy.wright@psych.ox.ac.uk
Prucalopride Emotional Processing Study
lucy.wright@psych.ox.ac.uk

20. APPENDIX B: Re-contact Email Template

Dear _____ ,

We are emailing you because you indicated when taking part in a study at the University of Oxford Department of Psychiatry that you would be willing to be contacted about future studies that you may be suitable for. We are looking for right-handed healthy volunteers aged 18-40 years, with no history of a psychological disorder, to take part in a study entitled 'The effect of seven day prucalopride administration on emotional processing in healthy volunteers'. I have attached a Participant Information Sheet, which gives full details of what the study involves.

The purpose of the study is to investigate how short-term administration of the drug prucalopride (a licensed drug usually used to treat chronic constipation) changes how the brain deals with emotional information. Our research has previously shown that established antidepressants affect how people think about emotional information. These effects have been found to predict whether the antidepressant will help people feel better in the long term. Prucalopride, like many established antidepressants, temporarily affects the function of a brain chemical called serotonin, but does so in a different way. We are going to investigate whether or not prucalopride also has effects on the way in which the brain processes emotional information, and will measure the effects if it does.

If you would like to take part, you will be invited to the Department of Psychiatry, Warneford Hospital, for a screening visit (maximum 2 hours) where you will be asked to answer some questions about yourself, including questions about your medical history to check your suitability for an MRI scan. If you are eligible to take part, you will be given seven days of study medication to take home. On the sixth study day you will be asked to attend a research visit (approx. 1.5 hours) and have a brain scan using functional Magnetic Resonance Imaging (fMRI) to look at any effects of prucalopride on brain activity. MRI is a type of brain scan that allows us to see how the brain is organised, processes information, and performs skills like speech or memory. This scan is safe and does not involve any needles or injections. On the seventh day you will be asked to return for a second research visit (approx. 2 hours) where you will be asked to complete computerised psychological tasks measuring your reactions to emotional and non-emotional stimuli. You will be reimbursed for your time.

Please read the attached information sheet, which gives you full details of the study. If you would like to take part, or if you have any questions, please get in touch.

Best wishes,
[Named Researcher], [Qualifications], [Job title]

If you would no longer like to be contacted about studies please contact a researcher (Named Researcher: PERL@psych.ox.ac.uk, or the Principal Investigator Dr Susannah Murphy: susannah.murphy@psych.ox.ac.uk) and we will remove you from the list.

1

21. APPENDIX C: Screening Form

SCREENING FORM: THE EFFECT OF SEVEN DAY PRUCALOPRIDE ADMINISTRATION ON EMOTIONAL PROCESSING IN HEALTHY VOLUNTEERS

Participant ID: _____ Date (dd/mm/yy): _____

Confidentiality explained: ☐ Informed Consent obtained: ☐

DEMOGRAPHICS:

Participant name: _____

Gender: _____

Age (years, months): _____

Occupation: _____

Telephone number: _____

Address:_____

_____

_____

_____

Email: _____

Handedness: Right ☐ Left ☐

First Language: Fluent in English: Yes ☐ No ☐

Smoke: Yes ☐ _____ per day No ☐

Alcohol units/week: _____

Maximum units consumed on a single occasion: _____

Average caffeinated drinks per day: _____

Ethnicity: Caucasian ☐
Black ☐
Hispanic ☐
Asian ☐
Other ☐

Education Level (obtained): High School ☐
6th form college /GNVQ ☐
Undergraduate degree ☐
Post graduate degree ☐

PREVIOUS STUDIES:

Has the participant taken part in any studies at the Departments of Psychiatry or Psychology before?

☐ Yes ☐ No

Has the participant taken part in a study involving taking a drug or medicine before? (IMPORTANT: 3-month washout needed)

☐ Yes ☐ No

HEIGHT AND WEIGHT:

Height (cm): _____

Weight(kg): _____

Body Mass Index: _____

$$\text{Body Mass Index} = \frac{\text{Weight (kg)}}{(\text{Height (cm)})^2} \times 10{,}000$$

MEDICAL / SURGICAL HISTORY:

Is the participant suffering from or have they ever suffered from any significant medical or surgical condition?

☐ Yes ☐ No

Medical problem / condition	Yes	No
History of seizures / epilepsy		
History of blackouts, fainting, or dizziness while standing		

Kidney problems (hepatic / renal / urinary dysfunction)		
Liver problems (hepatitis, any chronic conditions)		
Cardiac or respiratory problems (palpitations/racing heart, asthma, dyspnoea, high blood pressure / hypotension, lung pains, persistent cough)		
Dyslexia or any other reading impairments		
Endocrine dysfunction (hormonal problems), diabetes, thyroid problems		
Autoimmune disorders		
Allergies (e.g. drugs, food intolerance like lactose intolerance)		
History of bleeding disorders (e.g. cutaneous bleeding, gynaecological bleeding)		
Skin or subcutaneous tissue disorders (e.g. rash, urticaria, purpura)		
Persistent headaches/migraines		
History of vision problems/difficulties		

If YES, list:

Diagnosis	Year of first diagnosis	Resolved	Ongoing

Is the participant currently, or have they ever suffered from:

A gastro-intestinal disorder: Yes ☐ No ☐

Irritable bowel syndrome (IBS): Yes ☐ No ☐

Is the participant lactose intolerant? Yes ☐ No ☐

Does the participant have, or have they ever had a known lactate deficiency or problem absorbing lactose / galactose / glucose?

☐ Yes ☐ No

CURRENT / PRIOR MEDICATION:

Is the participant currently taking any medication (prescribed / OTC / vitamin supplements)?

☐ Yes ☐ No

Has the participant taken any medication / drug in the month prior to the screening?

☐ Yes ☐ No

Is the participant currently taking any street drugs? (e.g. cannabis, MDMA)

☐ Yes ☐ No

Has the participant ever taken any street drugs?

☐ Yes ☐ No

If YES:

Drug name	End date	Frequency

PERSONAL AND FAMILY PSYCHIATRIC HISTORY:

Personal:

Does the participant suffer from (or have they ever suffered from) any psychological or psychiatric difficulties? (e.g. depression / anxiety / EDs)

☐ Yes ☐ No

Has the participant ever seen a psychologist / psychiatrist / counsellor in the past? (check for disorders linked to childhood e.g. ADHD, dyslexia)

☐ Yes ☐ No

Family:

Has anyone in the participant's close family seen a psychologist / psychiatrist / counsellor?

☐ Yes ☐ No

If YES, circumstances: _____

_____

PREGNANCY / BREASTFEEDING:

Is the participant currently pregnant, trying to become pregnant, or breastfeeding?

Yes ☐ No ☐ NA ☐

MENSTRUAL CYCLE:

Length of cycle: _____

Regular/irregular: _____

Date of last menstrual period: _____

Predicted date of next period: _____

STRUCTURED CLINICAL INTERVIEW FOR DSM-V AXIS 1 DISORDERS:

Has the SCID been completed: Yes ☐ No ☐

Document any "YES" responses:

Study medic: Name: _____ Signature: _____

22. APPENDIX D: MRI Screening Form

MRI SCREENING FORM
3T VOLUNTEER

OHBA FMRIB

UNIVERSITY OF OXFORD

Volunteer name _____ Gender _____

Date of birth _____ Weight _____ kg Height _____ m

Please carefully check the following. Some items can interfere with MR examinations and may be hazardous to your safety. Clearly mark your answer with a circle and add any relevant information. If you require additional space please use the back page and indicate you have done this. Your answers will be kept strictly confidential.

IF YOU HAVE ANY QUESTIONS THEN PLEASE ASK US BEFORE YOUR SCAN		
Do you have a heart pacemaker or pacing wires?	YES	NO
Have you had any heart surgery (e.g. coronary stent, PFO closure)?	YES	NO
Have you had any surgery to your head (including eyes / ears / brain), neck or spine?	YES	NO
Do you have any implanted devices (e.g. hydrocephalus shunt, nerve stimulator, cochlear implant, aneurysm clip, hernia mesh)?	YES	NO
Have you had any operations involving metallic pins / plates / screws / wires?	YES	NO
Have you had any surgical procedures or endoscopy in the last 6 weeks? (Please write below)	YES	NO
Have you **ever** had any other surgical procedures of any kind? (Please write below)	YES	NO
Have you **ever** sustained any injuries involving metal to the eyes or other part of the body (e.g. from drilling, grinding or welding)?	YES	NO
Have you ever had a serious accident (e.g. road traffic or industrial accident, explosion injury, shooting, shrapnel injury?)	YES	NO
Have you ever had a fit or blackout, or do you suffer from epilepsy or diabetes?	YES	NO
Do you have any of the following (if yes please circle): Body piercing, eye makeup, coloured contact lenses — Hearing aid, wearable medical device (e.g. drug pump, glucose monitor) — Tattoos (including cosmetic) Dentures, dental braces, dental implants — Medicated skin patch (e.g. pain, HRT, nicotine, contraceptive) — Artificial limb, prosthesis, splint, brace or support		
FOR WOMEN OF CHILDBEARING AGE: Do you have an IUD (coil)?	YES	NO
FOR WOMEN OF CHILDBEARING AGE: Could you be pregnant?	YES	NO
Are you wearing any clothing, including underwear, that contains metallic threads or has been silver impregnated (e.g. anti-microbial)?	YES	NO
Do you understand that this is a research scan and is not useful for diagnosis?	YES	NO
Have you removed your jewellery, hairgrips, hearing aids, watch, spectacles, keys and coins?	YES	NO

IMPORTANT: NO METAL OBJECTS TO BE TAKEN INTO THE MAGNET ROOM

Volunteer/Guardian signature _____ Date of study _____

Screened by (Print name) _____ Signature _____

Version: Jan 2017

23. APPENDIX E: Participant Information Sheet (PIS)

DEPARTMENT OF PSYCHIATRY
NEUROSCIENCES BUILDING
WARNEFORD HOSPITAL
OXFORD OX3 7JX, U.K.
www.psych.ox.ac.uk

TEL. (Direct) 01865 618313
Email: susannah.murphy@psych.ox.ac.uk

PARTICIPANT INFORMATION SHEET

The effect of seven day prucalopride administration on emotional processing in healthy volunteers.

University of Oxford Central University Research Ethics Committee: R57219/RE001

We would like to invite you to take part in a research project. This sheet provides some information to help you decide whether to do so. Please take time to read this carefully and discuss it with friends, family or your GP if you wish. If there is anything that you do not understand, or if you would like more information, please ask us. Please take time to consider whether you wish to take part. Thank you for reading.

What is the purpose of the study?

We are interested in how short-term administration of the drug prucalopride changes how the brain deals with emotional information. Our research has previously shown that established antidepressants affect how people think about emotional information; such as making them focus on positive facial expressions more than negative ones. These effects have been found to predict whether the antidepressant will help people feel better in the long term.

In this study, we are investigating the effect of a licensed drug called prucalopride that is usually used to treat chronic constipation. Prucalopride temporarily affects the function of a brain chemical called serotonin, but does so in a different way from established antidepressant drugs. We are going to investigate whether or not prucalopride has effects on the way in which the brain processes emotional information that are similar to those seen following antidepressant medication, which will help us to understand whether this might be a useful treatment for depression.

In order to study the effects of prucalopride, we will be using a number of computerised psychological tests designed to measure your reactions to emotional and non-emotional stimuli. We will also investigate any effects of prucalopride on brain activity by using Magnetic Resonance Imaging (MRI) brain scans, which are safe and non-invasive.

Why have I been invited?

You have been sent this information sheet because you have shown interest in hearing more about this study, either by responding to an advertisement, or because you have previously expressed an interest in hearing about studies in the department for which you may be suitable (please do let us know if this is no longer the case). You have been invited to take part because you are currently healthy, aged 18-40 years, and right-handed. We hope to include 50 healthy volunteers in the study. Unfortunately, we are not able to

include volunteers with a history of a psychological disorder such as depression or anxiety. Participants over the age of 40 years are not eligible to take part in this study. This is because many of the tasks that we use are very sensitive to reaction times, which are known to become more variable in people over 40.

Do I have to take part?

No, it is up to you to decide to join the study. We will describe the study and go through this information sheet with you to answer any questions you may have. If you agree to take part, we will ask you to sign a consent form and will give you a copy for you to keep. However, you would still be free to withdraw from the study at any time, without needing to give a reason. This would not affect legal rights you would receive. If you are a student at the University of Oxford or Oxford Brookes, there would be absolutely no academic penalty if you decide you do not want to take part in this study, or if you decide to withdraw at any point.

Exclusion Criteria

You will NOT be able to take part in the study if:

- You are not fluent in English
- You suffer from, or have ever suffered from, any kind of psychological disorder (such as depression, anxiety, or an eating disorder)
- You are on any medication that affects brain function (except the contraceptive pill, the Depo-Provera injection or the progesterone implant)
- You are on any medication that will influence the MRI scan (the researcher will help you decide this)
- You are currently, or have ever been, dependent on drugs or alcohol
- You are currently pregnant or breastfeeding
- It is your pre-menstrual week (female participants will be asked details of their menstrual cycle to schedule the study outside this week)
- You are not right handed
- You do not have a Body Mass Index in the range of 18-30
- You have a history of cardiac, thyroid, or liver problems
- You have an autoimmune disorder
- You have current, or a history of, gastro-intestinal disorder or irritable bowel syndrome
- You suffer from epilepsy
- You have lactate deficiency or any other problem absorbing lactose, galactose, or glucose
- You have previously taken part in a study which uses the same computer tasks as those used in the present study
- You have participated in a study that involves the use of a medication within the last three months
- You smoke more than 5 cigarettes per day
- You drink more than 6 caffeinated drinks per day

- You have any contradictions to MRI scanning (e.g. metal objects in your body, pacemakers, significant claustrophobia)

What will happen in the study if I decide to take part?

The study will involve three visits in total, all taking place at the Warneford Hospital, Oxford (see Figure 1: study timeline). You will be assigned by chance to receive 7 days of either prucalopride (1mg once a day; half the standard dose) or placebo. The study has a 'double blind' design meaning that neither you nor the researcher will know whether you are receiving the drug or the placebo.

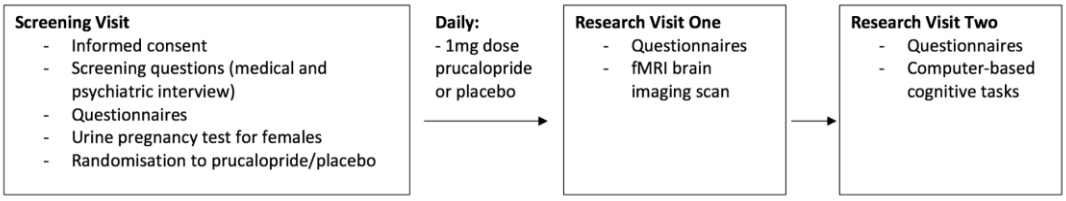

Figure 1. Study timeline

The first visit is a 'Screening visit' at the University of Oxford Department of Psychiatry, Warneford Hospital, which will last approximately 2 hours. During this visit, a researcher will meet you to go over the information sheet and explain the procedures. If you are happy to continue, they will then ask you to sign a consent form. They will ask you some detailed questions to see if you are suitable to take part, including questions about: your current and past psychological wellbeing, past traumatic experiences and abuse, your medical history (including a measurement of your height and weight), any medication that you are currently taking, and your lifestyle (alcohol/caffeine consumption, smoking, recreational drug usage). You will be asked to complete an MRI safety questionnaire including questions about your medical history to check your suitability for an MRI scan. You will also be asked to complete questionnaire measures of psychiatric symptoms/distress. If you are female we will ask you to complete a urine pregnancy test, and we will ask you about your menstrual cycle in order to avoid scheduling testing in the premenstrual week. If you feel uncomfortable at any stage of this meeting, you would, of course, be free to decline to answer any of the questions or withdraw from the study.

You will be asked to wait while a medical doctor involved in the study assesses your eligibility to take part in the study, which will take a maximum of 30 minutes. If you are suitable and are willing to proceed, we will randomly allocate you to receive either prucalopride or placebo. In the event that additional information must be provided in order to determine your eligibility, such as previous studies you may have taken part in, a maximum of four weeks may elapse between screening and allocation to prucalopride or placebo. If more than four weeks elapses, you will be asked to attend another screening visit to reassess your eligibility to take part. Once randomly allocated, you will be given seven days of the study medication to take home with you, plus full instructions of how and when to take them. During this week, we will phone you on days 2 and 4 to check that there are no concerns. You will be provided with the 24-hour contact details of a researcher who you can contact throughout the study if you have any concerns about

taking the study medication or if you're experiencing any side effects that are causing you concern. During the week of drug/placebo administration, we advise you not to drink alcohol and not to carry out activities requiring full alertness (e.g. driving) in case you notice any impairment. We will either arrange a taxi for you to come to the second and third study visits, or we will reimburse travel expenses (e.g. bus tickets).

On the sixth day of taking the study medication, you will be asked to come to 'Research Visit One', which will last approximately 1.5 hours. The visit will take place at the Oxford Centre for Human Brain Activity - also at the Warneford hospital - for an MRI brain imaging scan (see below for more details: 'What is MRI scanning?'). On arrival, one of our research team would meet you to describe what the visit will involve, and answer any questions you may have. Before the scan, you will be asked to complete an MRI safety questionnaire to review your eligibility to undergo MRI scanning. The visit will involve having a magnetic resonance scan over a period of 60-75 minutes. During the brain scan, you will be required to complete two simple tasks: one involving emotional stimuli (faces) and one involving non-emotional cues (letters/numbers). During the scan there will also be periods of time when there will be no task to complete. During these periods we will use the scanner to measure other aspects of your brain structure and blood flow, which will be helpful when we analyse the data. Additionally, we will measure your pulse, breathing rate, eye movements and skin conductance during the scan, which will also be helpful for analysing the data. This will involve wearing a thin strip of fabric around the waist and having some electrodes attached to your fingertips. Before and after the scan, you will be asked to complete questionnaires about your mood, anxiety, and side effects. You are free to decline to answer any questions on these questionnaires if you prefer not to. The research team can direct an accompanying person to an area where they can wait. Please let us know beforehand if you wear contact lenses or glasses.

On the seventh day of taking the study medication, you will be asked to come to 'Research Visit Two' at the Department of Psychiatry, Warneford Hospital, which will last approximately 2 hours. During this visit, we will ask you to complete simple computer-based tasks assessing emotional and non-emotional cognitive processing. The tasks will require you to make a response on the keyboard to pictures (for example, identify peoples' facial expressions) or to respond to positive and negative words presented on the screen. One of the tasks involves choosing between different options and there is the possibility of winning up to £10 depending on your performance in this task. This will be in addition to the reimbursement for your participation in the study (see below). We will also ask you to fill in several questionnaires about your mood and anxiety and ask you your adherence to the seven-day study medication. Possible side effects of the study medication will be monitored. At the end of this visit, we will ask you to try to guess whether you received prucalopride or placebo. We will not be able to tell you whether you received the drug or placebo at the end of the visit, though after the last participant has been tested and the randomisation code has been broken, we can send you this information if requested.

If you take part in this study, you will be paid £120 for participation on completion of the study. In addition, you may win up to £10 depending on the choices you make on one of the tasks. If you do not complete the study you will be given a pro-rata amount to recompense you for the time you did spend on the study. We will also reimburse

reasonable travel expenses.

What will happen to any samples I give?
At the screening visit, female participants will be required to give a urine sample for a pregnancy test. Urine samples will be destroyed immediately after the test result has been obtained.

What is MRI scanning?
MRI scanning works by using powerful magnetic fields to examine the tissues of the body. It is used widely in medicine to provide images inside many different parts of the body to help doctors detect diseases or to guide treatments. MRI is a routine procedure, which is safe, painless and involves no ionizing radiation. We will be using MRI scanning to obtain an image of your brain (for research purposes only). As part of this procedure, we will be using a special method called functional MRI (fMRI), which is designed to measure the activity levels in different parts of the brain. Having an MRI scan involves simply lying still inside the scanner. During this time you will be made comfortable and you will be able to contact researchers at all times. You will not feel anything, although you will hear some quite loud noises. MRI and fMRI are both extremely safe procedures and thousands of people have such scans every year. However, because of the magnetic fields involved, people who have fragments of metal or shrapnel, other metallic objects, or medical implants in their bodies are generally not suitable for MRI scanning (see 'Exclusion Criteria', above).

Are there any potential risks in taking part?
Prucalopride is usually used in the treatment of chronic constipation. When used in constipation, the following side effects have been reported as very common or common: decreased appetite, headache, dizziness, nausea, abdominal pain, vomiting, flatulence, fatigue, indigestion, diarrhoea. There is less information about side effects experienced by healthy volunteers rather than patients with constipation, but it is likely that they will be similar to when it is given to patients with constipation. There is therefore a chance that you may also experience some of the side effects listed above. The 1mg daily dose you will receive during the study is half the standard therapeutic dose. A single one-off 1mg dose of prucalopride was well tolerated by healthy volunteers in a previous study carried out in our group. Because of the risk of side effects, we will give you the 24-hour contact number of a researcher in case of concerns over the study duration. This researcher can in turn contact a qualified medical doctor if necessary. Because of the risk of fatigue, we advise you not to drink alcohol and not to carry out activities requiring full alertness, such as driving, in case you notice any impairment.

The effects of prucalopride in women who are pregnant or breastfeeding are unknown. Therefore, you must not take part in this study if you are pregnant, if you suspect that you might be pregnant, if you are trying to become pregnant, or if you are breastfeeding. If you join the study, you must use an effective form of contraception for the duration of your involvement in the study. We will also ask you to complete a pregnancy test during the screening visit. The results of this would be treated as confidential, and you are free to withdraw from the study if you do not wish to have this test or do not want the results to

be known to the research team. In the event of an unexpected positive result we would signpost you to appropriate support.

If you are intolerant to some sugars (for example lactose intolerant) it would better not to take part because the tablet contains lactose, so a reaction is possible.

MRI is safe and non-invasive and does not involve any ionizing radiation (x-rays). However, because it uses a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part. MRI scanning for research purposes would not be performed without further investigation if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body. If you think you might be claustrophobic, please discuss this in advance with the researcher, or let the radiographer or operator know before your scan. As some of the scans are noisy, we would give you earplugs to make this quieter for you. It is important that these are fitted correctly as they are designed to protect your hearing.

In preparation for your scan and for your comfort and safety we may ask you to change into pocket less and metal free "pyjama-style" top and trousers, which are available in a range of sizes. You may keep your underwear and socks on but we would ask ladies to remove underwired bras, if you have a suitable non-wired bra you may wear this instead. Please avoid any fabrics that contain metallic threads or have been silver impregnated (often marketed as anti-microbial/bacterial or anti-odour/stink). Metal jewellery including body piercing must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If you wish to wear eye makeup to your scan we can provide makeup removal wipes but you are advised to bring your own makeup to reapply. Lockers are provided to secure your personal belongings and clothing.

Participants will be introduced carefully to the scanner and allowed to leave at any stage. Whilst in the scanner participants have easy access to a call button should they wish to stop the scan or speak with the radiographer or operator.

It is important to note that we do not carry out scans for diagnostic purposes, only for research. Our scans are not routinely looked at by a doctor and are therefore not a substitute for a doctor's appointment. Occasionally, however, a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality was medically important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. You would not be informed unless the doctor considers the finding has clear implications for your current or future health. All information about you is kept confidential.

If we are concerned, based on your responses during the Screening visit or following review of your mood-related questionnaires, that you experiencing distress, you may be offered the opportunity to discuss this in greater detail with the Principal Investigator, or a senior clinical researcher. We may also encourage you to contact your GP if it is deemed appropriate.

What are the possible benefits of taking part?
There will not be any benefits to you directly in this study. You may enjoy being part of a research study, and you will be contributing to scientific knowledge and helping our longer-term goal of improving treatment for psychiatric disorders.

Will my taking part in the study be kept confidential?
Information collected about you during the course of the research would 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.

What happens to the data provided?
Research data (questionnaire, task data, and MRI scan data) will be labelled with a participant number so that no personal information will be attached to your data. This labelling will occur at the point of data collection. A linking document to match your participant ID to your personal details will be kept in a lockable filing cabinet, with access only to the University researchers should it be needed. Data will be stored on a university computer for 10 years, on a University networked drive which is backed up regularly. The computers are located in the Department of Psychiatry. Consent forms will be stored securely in paper format in a locked filing cabinet in a secure room for a minimum of 10 years.

Personal data (contact details and screening forms) will be accessible by the research team only. Personal details will not be kept electronically, but in a written record in a locked filing cabinet in a secure room. Data that will personally identify you, apart from consent forms, will be destroyed once data has been analysed and the results have been published, unless you indicate that you would like to be contacted about future studies for which you may be suitable - in which case your contact details will be stored in a database on University computers, accessible only by University researchers.

The overall results of the study may be published in scientific journals. However, all personal data will remain confidential, and no data relating to individual participants will be published.

Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that we comply with regulations. Sometimes, new methods to analyse data become available after a study has ended. Therefore we would ask for your permission to use your anonymised data in future ethically approved studies, and to share data, such as your anonymised scan data, with other researchers both inside and outside the European Union.

Data Protection
The University of Oxford is the data controller with respect to your personal data, and as such will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that

we perform in the public interest. Further information about your rights with respect to your personal data is available from
http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/

Will the research be published?
The results of this study may be published in a scientific journal and/or presented at a scientific conference. However, no information that could be used to identify any individual participant will be published or presented. If you are interested in finding out about the results of this research, please let us know, and we will make arrangements to inform you once the study is completed.

What will happen if I don't want to carry on with the study?
Even after you have signed the consent form, you are absolutely free to withdraw from the study at any time without giving any reason and without your legal rights being affected. Data can be withdrawn up to the point of study publication. If you choose to withdraw from the study, any personal data will be destroyed. Any questionnaire, task, and MRI scan data will be destroyed and not included in the study analyses.

Who has reviewed this project?
All medical research conducted in the UK must be approved by a Research Ethics Committee, who examine the ethical and scientific justifications for the study. This research has been reviewed by, and given ethics clearance by the University of Oxford Central University Research Ethics Committee.

Who do I contact if I have a concern about the study or I wish to complain?
If a participant in University-sponsored research is ever considered to have suffered harm through their participation, the University has arrangements in place to provide for compensation. If you have a concern about any aspect of this project, please speak to the Principal Investigator (Dr Susannah Murphy, susannah.murphy@psych.ox.ac.uk, 01865 618313), who will do her best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how she intends to deal with it. If you remain unhappy or wish to make a formal complaint, please contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, email ctrg@admin.ox.ac.uk, who will also inform the chair of the Research Ethics Committee at the University of Oxford.

Who is organising and funding the research?
This study is being organised by Dr Susannah Murphy at the University of Oxford, who are funding and sponsoring this research.

Contact details
If you would like any further information on this study, or if you have any concerns, please contact Dr Susannah Murphy (susannah.murphy@psych.ox.ac.uk 01865 618313).

24. APPENDIX F: Informed Consent Form (ICF)

DEPARTMENT OF PSYCHIATRY
NEUROSCIENCES BUILDING
WARNEFORD HOSPITAL
OXFORD OX3 7JX, U.K.
www.psych.ox.ac.uk

TEL. (Direct) 01865 618313
Email: susannah.murphy@psych.ox.ac.uk

INFORMED CONSENT FORM

Title of Project: The effect of seven day prucalopride administration on emotional processing in healthy volunteers

Researcher: Dr Susannah Murphy, Principal Investigator

The purpose of this study is to investigate the effects of prucalopride on emotional processing and neural activity, comparing the effects of the drug with placebo.

University of Oxford Central University Research Ethics Committee: R57219/RE001

Please initial the box next to each statement

I confirm that I have read and understood the information sheet dated _____ (Version____) for the above study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, and without any adverse consequences or academic penalty.

I have been advised about the potential risks associated with taking part in this research and have taken these into consideration before consenting to participate.

I have been advised as to what I need to do for this research (especially with regard to drug intake) and I agree to follow the instructions given to me.

I understand that research data and scan images collected during the study may be looked at by designated individuals from the University of Oxford where it is relevant to my taking part in this study. I give permission for these individuals to access my data.

I understand who will have access to personal data provided, how the data will be stored and what will happen to the data at the end of the project.

☐ I consent to answering screening questions, including questions about my physical and mental health, to confirm my eligibility to take part.

☐ I understand that this project has been reviewed, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee.

☐ I understand how this research will be written up and published.

☐ I understand how to raise a concern or make a complaint.

☐ I understand that all information will be kept strictly confidential except in the rare circumstance in which it is judged that I, or someone else, is at immediate risk of serious harm.

☐ I understand that the MRI scans in this study are for research and they are not useful for medical diagnosis, and that scans are not routinely looked at by a doctor. If a concern is raised about a possible abnormality on my scan, I will be informed if a doctor thinks this is medically important such that the finding has clear implications for my current or future health.

☐ I agree for research data collected in this study to be given to researchers, including those working outside of the EU, to be used in other research studies. I give permission for data from this study to be used in publication. I understand that any data and/or brain images of me that leave the Department will be fully anonymised so that I cannot be identified.

☐ I understand that I have been advised not to drink alcohol or carry out activities requiring full alertness (such as driving) during the week of drug/placebo administration if I am aware of any impairment.

☐ I agree to take part in this study.

☐ (Optional) I agree to being contacted about future studies for which I might be suitable, without any commitment to take part. I agree to my contact details being retained from my screening form, and entered into a database, for this purpose.

Name of participant: _____

Signature: _____ Date: _____

Name of person taking consent: _____

Signature: _____ Date: _____

One copy for participant, one for researcher

25. APPENDIX G: Study Questionnaires

Edinburgh Handedness Inventory:

Edinburgh Handedness Inventory

Surname_____Given Name_____

Date of Birth_____Sex_____

Please indicate your preferences in the use of hands in the following activities by *putting + in the appropriate column*. Where the preference is so strong that you would never try to use the other hand unless absolutely forces to, *put* ++. If any case you are really indifferent put + in both columns.

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

	Left	Right
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking Match (match)		
10. Opening box (lid)		
i. Which foot do you prefer to kick with?		
ii. Which eye do you use when using only one?		

L.Q.	Leave the spaces blank	DECLE

Beck Depression Inventory (BDI):

Participant ID: Date:

BECK INVENTORY *1996, A. T. Beck*

This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, then pick out the one statement in each group that best describes the way you have been feeling in the past two weeks including today.
Circle the number beside the statement you have picked. If several statements apply equally well, circle that which has the highest number. Be sure that you do not choose more than one statement for any group. Be sure to read all the statements in each group before making your choice.

1. 0 I do not feel sad
   1 I feel sad much of the time
   2 I am sad all of the time
   3 I am so sad or unhappy that I can't stand it

2. 0 I am not discouraged about my future
   1 I feel more discouraged about my future than I used to be
   2 I do not expect things to work out for me
   3 I feel my future is hopeless and will only get worse

3. 0 I do not feel like a failure
   1 I have failed more than I should have
   2 As I look back, I see a lot of failures
   3 I feel I am a total failure as a person

4. 0 I get as much pleasure as I ever did from the things I enjoy
   1 I don't enjoy things as much as I used to
   2 I get very little pleasure from the things I used to enjoy
   3 I can't get any pleasure from the things I used to enjoy

5. 0 I don't feel particularly guilty
   1 I feel guilt over many things I have done or should have done
   2 I feel guilty most of the time
   3 I feel guilty all of the time

6. 0 I don't feel I am being punished
   1 I feel I may be punished
   2 I expect to be punished
   3 I feel I am being punished

7. 0 I feel the same about myself as ever
   1 I have lost confidence in myself
   2 I am disappointed in myself
   3 I dislike myself

Participant ID: Date:

8.
0 I don’t critisize or blame myself more than usual
1 I am more critical of myself than I used to be
2 I critisize myself for all of my faults
3 I blame myself for everything bad that happens

9.
0 I don’t have any thoughts of killing myself
1 I have thoughts of killing myself, but I would not carry them out
2 I would like to kill myself
3 I would kill myself if I had the chance

10.
0 I don’t cry any more than I used to
1 I cry more than I used to
2 I cry over little things
3 I feel like crying, but I can't

11.
0. I am no more restless or wound up than usual
1 I feel more restless or wound up than usual
2 I am so restless or agitated that it's hard to keep still
3 I am so restless or agitated that I have to keep moving or doing things

12.
0 I have not lost interest in other people or activities
1 I am less interested in other people or things than before
2 I have lost most of my interest in other people or things
3 It's hard to get interested in anything

13.
0 I make decisions about as well as ever
1 I find it more difficult to make decisions than usual
2 I have much greater difficulty in making decisions than I used to
3 I have trouble making any decisions

14.
0 I do not feel I am worthless
1 I don't consider myself as worthwhile and useful as I used to
2 I feel more worthless compared to other people
3 I feel utterly worthless

15.
0 I have as much energy as ever
1 I have less energy than I used to have
2 I don't have enough energy to do very much
3 I don't have enough energy to do anything

Participant ID: Date:

16.
0 I have not experienced any change in my sleeping pattern
1a I sleep somewhat more than usual
1b I sleep somewhat less than usual
2a I sleep a lot more than usual
2b I sleep a lot less than usual
3a I sleep most of the day
3b I wake up 1-2 hours early and can't get back to sleep

17.
0 I am no more irritable than usual
1 I am more irritable than usual
2 I am much more irritable than usual
3 I am irritable all the time

18.
0 I have not experienced any change in my appetite
1a My appetite is somewhat less than usual
1b My appetite is somewhat greater than usual
2a My appetite is much less than usual
2b My appetite is much greater than usual
3a I have no appetite at all
3b I crave food all the time

19.
0 I can concentrate as well as ever
1 I can't concentrate as well as usual
2 It's hard to keep my mind on anything for very long
3 I find I can't concentrate on anything

20.
0 I am no more tired or fatigued than usual
1 I get more tired or fatigued more easily than usual
2 I am too tired or fatigued to do a lot of the things I used to
3 I am too tired or fatigued to do most of the things I used to

21.
0 I have not noticed any recent changes in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely

Eysenck Personality Questionnaire (EPQ):

E.P.Q. (Adult)

Name……
Occupation……..
Age……..Sex……..

INSTRUCTIONS Please answer each question by putting a circle around the "YES" or the "NO" following the question. There are no right or wrong answers, and no trick questions. Work quickly and do not think too long about the exact meaning of the questions.

PLEASE REMEMBER TO ANSWER EACH QUESTION

1. Do you have many different hobbies?	YES	NO
2. Do you stop to think things over before doing anything?	YES	NO
3. Does your mood often go up and down?	YES	NO
4. Have you ever taken the praise for something you knew someone else had really done?	YES	NO
5. Are you a talkative person?	YES	NO
6. Would you being in debt worry you?	YES	NO
7. Do you ever feel "just miserable" for no reason?	YES	NO
8. Were you ever greedy by helping yourself to more than your share of anything?	YES	NO
9. Do you lock up your house carefully at night?	YES	NO
10. Are you rather lively?	YES	NO
11. Would it upset you a lot to see a child or an animal suffer?	YES	NO
12. Do you often worry about things you should not have done or said?	YES	NO
13. If you say you will do something, do you always keep your promise no matter how inconvenient it might be?	YES	NO
14. Can you usually let yourself go and enjoy yourself at a lively party?	YES	NO
15. Are you an irritable person?	YES	NO
16. Have you ever blamed someone for doing something you knew was really your fault?	YES	NO
17. Do you enjoy meeting new people?	YES	NO
18. Do you believe insurance schemes are a good idea?	YES	NO
19. Are your feelings easily hurt?	YES	NO
20. Are *all* your habits good and desirable ones?	YES	NO
21. Do you tend to keep in the background on social occasions?	YES	NO
22. Would you take drugs which may have strange or dangerous effects?	YES	NO
23. Do you often feel "fed-up"?	YES	NO

PLEASE TURN OVER Page 1

24. Have you ever taken anything (even a pin or button) that belonged to someone else?	YES	NO
25. Do you like going out a lot?	YES	NO
26. Do you enjoy hurting people you love?	YES	NO
27. Are you often troubled about feelings of guilt?	YES	NO
28. Do you sometimes talk about things you know nothing about?	YES	NO
29. Do you prefer reading to meeting people?	YES	NO
30. Do you have enemies who want to harm you?	YES	NO
31. Would you call yourself a nervous person?	YES	NO
32. Do you have many friends?	YES	NO
33. Do you enjoy practical jokes that can sometimes really hurt people?	YES	NO
34. Are you a worrier?	YES	NO
35. As a child did you do as you were told immediately and without grumbling?	YES	NO
36. Would you call yourself happy-go-lucky?	YES	NO
37. Do good manners and cleanliness matter much to you?	YES	NO
38. Do you worry about awful things that might happen?	YES	NO
39. Have you ever broken or lost something belonging to someone else?	YES	NO
40. Do you usually take the initiative in making new friends?	YES	NO
41. Would you call yourself tense or “highly-strung”?	YES	NO
42. Are you mostly quiet when you are with other people?	YES	NO
43. Do you think marriage is old-fashioned and should be done away with?	YES	NO
44. Do you sometimes boast a little?	YES	NO
45. Can you easily get some life into a rather dull party?	YES	NO
46. Do people who drive carefully annoy you?	YES	NO
47. Do you worry about your health?	YES	NO
48. Have you ever said anything bad or nasty about anyone?	YES	NO
49. Do you like telling jokes and funny stories to your friends?	YES	NO
50. Do most things taste the same to you?	YES	NO
51. As a child were you ever cheeky to your parents?	YES	NO
52. Do you like mixing with people?	YES	NO
53. Does it worry you if you know there are mistakes in your work?	YES	NO
54. Do you suffer from sleeplessness?	YES	NO
55. Do you always wash before a meal?	YES	NO
56. Do you nearly always have a “ready answer” when people talk to you?	YES	NO
57. Do you like to arrive at appointments in plenty of time?	YES	NO
58. Have you often felt listless and tired for no reason?	YES	NO
59. Have you ever cheated at a game?	YES	NO
60. Do you like doing things in which you have to act quickly?	YES	NO
61. Is (or was) your mother a good woman?	YES	NO

62. Do you often feel life is very dull?	YES	NO
63. Have you ever taken advantage of someone?	YES	NO
64. Do you often take on more activities than you have time for?	YES	NO
65. Are there several people who keep trying to avoid you?	YES	NO
66. Do you worry a lot about your looks?	YES	NO
67. Do you think people spend too much time safeguarding their future with savings and insurances?	YES	NO
68. Have you ever wished that you were dead?	YES	NO
69. Would you dodge paying taxes if you were sure you could never be found out?	YES	NO
70. Can you get a party going?	YES	NO
71. Do you try not to be rude to people?	YES	NO
72. Do you worry too long after an embarrassing experience?	YES	NO
73. Have you ever insisted on having your own way?	YES	NO
74. When you catch a train do you often arrive at the last minute?	YES	NO
75. Do you suffer from “nerves”?	YES	NO
76. Do your friendships break up easily without it being your fault?	YES	NO
77. Do you often feel lonely?	YES	NO
78. Do you always practice what you preach?	YES	NO
79. Do you sometimes like teasing animals?	YES	NO
80. Are you easily hurt when people find fault with you or the work you do?	YES	NO
81. Have you ever been late for an appointment or work?	YES	NO
82. Do you like plenty of bustle and excitement around you?	YES	NO
83. Would you like other people to be afraid of you?	YES	NO
84. Are you sometimes bubbling over with energy and sometimes very sluggish?	YES	NO
85. Do you sometimes put off until tomorrow what you ought to do today?	YES	NO
86. Do other people think of you as being very lively?	YES	NO
87. Do people tell you a lot of lies?	YES	NO
88. Are you touchy about some things?	YES	NO
89. Are you always willing to admit it when you have made a mistake?	YES	NO
90. Would you feel very sorry for an animal caught in a trap?	YES	NO

PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED ALL THE QUESTIONS

State and Trait Anxiety Inventory (STAI):

Participant ID Date

TRAIT QUESTIONNAIRE

A number of statements that people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you GENERALLY feel. There are no right and wrong answers. Do not spend too much time on each statement but give the answer that seems to describe you best.

	Not at all	Somewhat	Moderately	Very much
1. I feel pleasant	1	2	3	4
2. I feel nervous and restless	1	2	3	4
3. I feel satisfied with myself	1	2	3	4
4. I wish I could be as happy as others seem to be	1	2	3	4
5. I feel like a failure	1	2	3	4
6. I feel rested	1	2	3	4
7. I am 'cool, calm and collected'	1	2	3	4
8. I feel that the difficulties are piling up so that I cannot overcome them	1	2	3	4
9. I worry too much over something that doesn't really matter	1	2	3	4
10. I am happy	1	2	3	4
11. I have disturbing thoughts	1	2	3	4
12. I lack self-confidence	1	2	3	4
13. I feel secure	1	2	3	4
14. I make decisions easily	1	2	3	4
15. I feel inadequate	1	2	3	4
16. I am content	1	2	3	4
17. Some unimportant thoughts run through my mind and bother me	1	2	3	4
18. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
19. I am a steady person	1	2	3	4
20. I get in a state of tension or turmoil as I think over recent concerns and interests	1	2	3	4

Participant ID Date

STATE QUESTIONNAIRE

A number of statements that people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel RIGHT NOW, that is, AT THIS MOMENT IN TIME. There are no right and wrong answers. Do not spend too much time on each statement but give the answer that seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very much
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Positive and Negative Affective Schedule (PANAS)

This scale consists of a number of words that describe different feelings and emotions. Please read each item and mark the appropriate answer in the space next to the word. Indicate to what extent you have felt this way **today.**

1. Very slightly or not at all
2. A little
3. Moderately
4. Quite a bit
5. Extremely

Interested	____	Irritable	____
Distressed	____	Alert	____
Excited	____	Ashamed	____
Upset	____	Inspired	____
Strong	____	Nervous	____
Guilty	____	Determined	____
Scared	____	Attentive	____
Hostile	____	Jittery	____
Enthusiastic	____	Active	____
Proud	____	Afraid	____

Snaith-Hamilton Pleasure Scale (SHAPS):

SHAPS Questionnaire

This questionnaire is designed to measure your ability to experience pleasure in the last few days. It is important to read each statement very carefully. Tick one of the boxes to indicate how much you agree or disagree with each statement.

I would enjoy my favourite television programme	Strongly Disagree	Disagree	Agree	Strongly Agree
I would enjoy being with my family or close friends	Definitely Agree	Agree	Disagree	Strongly Disagree
I would find pleasure in my hobbies and pastimes	Strongly Disagree	Disagree	Agree	Strongly Agree
I would be able to enjoy my favourite meal	Definitely Agree	Agree	Disagree	Strongly Disagree
I would enjoy a warm bath or refreshing shower	Definitely Agree	Agree	Disagree	Strongly Disagree
I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread	Strongly Disagree	Disagree	Agree	Strongly Agree
I would enjoy seeing other people's smiling faces	Definitely Agree	Agree	Disagree	Strongly Disagree
I would enjoy looking smart when I have made an effort with my appearance	Strongly Disagree	Disagree	Agree	Strongly Agree
I would enjoy reading a book, magazine or newspaper	Definitely Agree	Agree	Disagree	Strongly Disagree
I would enjoy a cup of tea or coffee or my favourite drink	Strongly Disagree	Disagree	Agree	Strongly Agree
I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend	Strongly Disagree	Disagree	Agree	Strongly Agree
I would be able to enjoy a beautiful landscape or view	Definitely Agree	Agree	Disagree	Strongly Disagree
I would get pleasure from helping others	Strongly Disagree	Disagree	Agree	Strongly Agree
I would feel pleasure when I receive praise from other people	Definitely Agree	Agree	Disagree	Strongly Disagree

National Adult Reading Test (NART):

NART (2nd edition)

CHORD
ACHE
DEPOT
AISLE
BOUQUET
PSALM
CAPON
DENY
NAUSEA
DEBT
COURTEOUS
RAREFY
DRACHM
AEON
PLACEBO
ABSTEMIOUS
DÉTENTE
IDYLL
PUERPERAL
AVER
HIATUS
SUBTLE
PROCREATE
GIST
GOUGE
SUPERFLUOUS
SIMILE
BANAL
QUADRUPED
CELLIST
FACADE
ZEALOT
GAUCHE
TOPIARY
LEVIATHAN
BEATIFY
PRELATE
SIDEREAL
EQUIVOCAL
NAIVE
CATACOMB
GAOLED
THYME
HEIR
RADIX
ASSIGNATE
DEMESNE
SYNCOPE
LABILE
CAMPANILE

Side Effects Questionnaire

Please indicate the level at which you are *currently* experiencing the following by placing a tick in the appropriate box.

SIDE EFFECT	ABSENT	MILD	MODERATE	SEVERE
HEADACHE				
ABDOMINAL PAIN				
NAUSEA				
DIARRHOEA				
DECREASED APPETITE				
DIZZINESS				
VOMITING				
FLATULENCE				
FATIGUE				
GASTROINTESTINAL SOUNDS				

Visual Analogue Scales (VAS):

Participant ID: _____ Date: _____

- Please indicate the extent to which you are **currently** experiencing each of the feelings below
  - The line should be regarded as the full range of each feeling
    - Mark your response with a perpendicular line: |

Not at all **Extremely**

HAPPY

_____

SAD

_____

HOSTILE

_____

ALERT

_____

ANXIOUS

_____

CALM

_____

26. APPENDIX H: Encapsulation Standard Operating Procedure (SOP)

Neurosciences	SOP Number: Encapsulation Version 1: 30.05.2012 Study Name: Ethics Number: Drug: Date:

Drug and Placebo Capsule Preparation

Purpose:	This SOP provides a standardised checklist for the preparation of drug and placebo capsules for research studies carried out in Neurosciences

Written by:	Name: Signature: Date:	Ann Sharpley

Adapted by:	Name: Signature: Date:	Clare Williams

Approved by:	Name: Signature: Date:	Philip Cowen
Approved by:	Name: Signature: Date:	Catherine Harmer
QP Approval:	Name: Signature: Date:	Michael Breese

Valid From:

Issued to: Date:

Process completed and approved Total number of pages: 16

Section 1 Documentation Preparation

Responsibilities: This SOP should always be carried out by 2 members of staff that have been trained in the following procedure and understand the principles of GMP. They will sign the delegation log for the study.

Staff Member 1:

Name:
Signature:
Initials
Date:

Staff Member 2:

Name:
Signature:
Initials:
Date:

Section 2	**Room Preparations**
Room Location:	Room G009 Research Kitchen
Clothing:	Lab coat and mop hat and latex free gloves
Room Line Cleared (tidied, cleaned with disinfectant and anti bacterial wipes and free from all other materials)	Sign: Date:

From Stock Prucalopride 2mg film-coated tablets

Capsules:	Location: Batch number: Expiry Date:
Placebo:	Location: Batch number: Expiry Date:
Drug:	Location: Batch number: Expiry Date:

Section 3 **Placebo Capsule Preparation**

Date and Time Procedure Commenced:

Number of placebo bottles to be made up today:

Number of placebo capsules to be placed in bottle:

Total number of placebo capsules to be made today:

Checklist

Procedure	**Action**	
Clothing :	Lab coat	
	Mop hat	
	Replace Latex free gloves after cleaning with new gloves	
Equipment:	Place paper dressing on cleaned work surface	
	Plastic trays x5	
	Capsule Bases	……
	Capsule Lids	……
	Placebo Tablets	……
	Plastic Bottles	……
	Labels	……

Set up

Staff member 1 Initials:

Count out required number of capsule bases
Place in 1st tray
Count out required number of placebo tablets
Place in 2nd tray

Staff member 2	Initials:	Date:

Check number of capsules bases are correct
Check number of placebo tablets are correct
Count out required number of capsule lids
Place in 3rd tray
Place 4th tray next to 3rd tray
Place 5th tray next to 4th tray
Count out required number of plastic bottles
Place plastic bottles next to 5th tray
Place label sheet next to bottles

Staff member 1	Initials:

Check number of capsules lids are correct
Check number of plastic bottles are correct
Complete first column of Section 4: reconciliation
Place all excess products (capsules, placebo tablets, spare bottles)
to one side away from assembly area

Section 4	**Assembly**

Staff member 1	Initials:

Place each tablet into body of capsule base
and pass this to Staff member 2

Staff member 2	Initials:

Check that each passed capsule base contains a tablet
Place a capsule lid firmly onto each capsule base
Check that each completed placebo capsule is securely locked
Place each placebo capsule into tray 4

Completion:

Once all completed placebo capsules have been placed onto tray 4 these can now be placed into the bottles

Staff member 2 Initials:

Count the required number of placebo capsules for the 1st bottle onto tray 5

Staff member 1 Initials:

Check the number of placebo capsules in tray 5 is correct
And then place these into a plastic bottle and securely attach the lid

Repeat this procedure for the required number of bottles

Section 5 **Labelling:**

Staff member 2: Signed: Date:

Place a sample label below:

Attach a label onto each filled bottle and a sample label onto this sheet. Sign and date across the label/page.

Section 6	**Reconciliation**	
Completed by:		
Staff member 1	Initials:	Date:
Checked by:		
Staff member 2	Initials:	Date:

	No. at start. No. used. No. rejected. No. remaining. % Reconciliation
Capsule Bases	
Placebo tablets	
Capsule Lids	
Completed placebo Capsules	
Empty Plastic Bottles:	
Completed plastic bottles:	
Labels:	
Completed Plastic Bottles with Labels	

Reconciliation limits: 100% Placebo tablets, completed capsules and labels.
100 +/-2% Capsule bases and lids, plastic bottles

Reconciliation outside of the above limits must be investigated.

Section 7	**Area Clear**	
Completed by:		
Staff member 1	Initials:	Date:
Checked by:		
Staff member 2	Initials:	Date:

Completed labelled bottles of placebo to be placed in designated locked storage

Location:

Other items to be returned
Placebo tablets
Location:

Reject and destroy excess Labels and remaining empty capsule lids and bases

Confirm the area is completely clear of materials, product and documentation before processing to the next activity

Place trays, paper sheet, mop hat and latex gloves in bin
Ensure no other study material remains
Return lab coats to hooks
Return this completed batch record to the designated file

Comments:

Date and time placebo preparation completed:

Staff member 1	Signed:	Date:	Time:
Staff member 2	Signed:	Date:	Time:

Section 8	**Room Preparation**
Room Location:	Room G009 Research Kitchen
Clothing:	Lab coat and mop hat and latex free gloves
Room Cleared (tidied, cleaned with disinfectant and anti bacterial wipes and free from all other materials)	Sign: Date:

From Stock	**Drug Capsule Preparation**
Capsules:	Location: Batch Number: Expiry Date:
Drug:	Location: Batch Number: Expiry Date:
Bottles:	Location: Batch Number: Expiry Date:
Labels:	Location: Batch Number:

Section 9 **Drug Capsule Preparation**

Date and Time Procedure Commenced:

Number of drug bottles to be made up:

Number of drug capsules to be placed in each bottle:

Total number of drug capsules to be made:

Checklist

Procedure	Action
Clothing :	Lab coat
	Mop hat
	Replace Latex free gloves after cleaning with new gloves
Equipment:	Place paper dressing on cleaned work surface
	Plastic trays x5
	Capsule Bases ……
	Capsule Lids ……
	Drug Tablets ……
	Plastic Bottles ……
	Labels ……

Set up

Staff member 1 Initials:

Count out required number of capsule bases
Place in 1st tray
Count out required number of drug tablets
Place in 2nd tray

Staff member 2	Initials:

Check number of capsules bases are correct
Check number of drug tablets are correct
Count out required number of capsule lids
Place in 3rd tray
Place 4th tray next to 3rd tray
Place 5th tray next to 4th tray
Count out required number of plastic bottles
Place plastic bottles next to 5th tray
Place label sheet next to bottles

Staff member 1	Initials:

Check number of capsules lids are correct
Check number of plastic bottles are correct
Complete first column of Section 11: reconciliation
Place all excess products (capsules, drug tablets, spare bottles) to one side away from assembly area

Section 10	**Assembly**

Staff member 1	Initials:

Place each tablet into body of capsule base
and pass this to Staff member 2

Staff member 2	Initials:

Check that each passed capsule base contains a tablet
Place a capsule lid firmly onto each capsule base
Check that each completed drug capsule is securely locked
Place each drug capsule into tray 4

Completion:

Once all completed drug capsules have been placed onto tray 4 these can now be placed into the bottles

Staff member 2 Initials:

Count the required number of drug capsules for the 1st bottle onto tray 5

Staff member 1 Initials:

Check the number of drug capsules in tray 5 is correct and then place these into a plastic bottle and securely attach the lid

Repeat this procedure for the required number of bottles

Section 11 **Labelling:**

Staff member 2: Signed: Date:

Place a sample label below:

Attach a label onto each filled bottle and a sample label onto this sheet. Sign and date across the label/page.

Section 12 **Reconciliation**

Completed by:
Staff member 1 Initials: Date:

Checked by:
Staff member 2 Initials: Date:

	No. at start.	No. used.	No. rejected.	No. remaining.	% Reconciliation
Capsule Bases					
Placebo tablets					
Capsule Lids					
Completed placebo Capsules					
Empty Plastic Bottles:					
Completed plastic bottles:					

Labels:

Completed Plastic Bottles with Labels

Reconciliation limits: 100% Placebo tablets, completed capsules and labels.
100 +/-2% Capsule bases and lids, plastic bottles

Reconciliation outside of the above limits must be investigated.

Section 13	**Area Clear**	
Completed by:		
Staff member 1	Initials:	Date:
Checked by:		
Staff member 2	Initials:	Date:

Completed labelled bottles of placebo to be placed in designated locked storage

Location:

Other items to be returned
Placebo tablets
Location:

Reject and destroy excess Labels and remaining empty capsule lids and bases

Confirm the area is completely clear of materials, product and documentation before processing to the next activity

Place trays, paper sheet, mop hat and latex gloves in bin
Ensure no other study material remains
Return lab coats to hooks
Return this completed batch record to the designated file

Comments:

Date and time Drug preparation completed: 01/02/2017

Staff member 1	Signed:	Date:	Time:
Staff member 2	Signed:	Date:	Time:

27. APPENDIX I: WIN/OCMR/OHBA Standard Operating Procedure (SOP) – 'Dealing With Research Neuroimaging Incidental Findings'

OHBA_014_V1
FMRIB_002_V1
Neuro_002_V5

OHBA, Department of Psychiatry
FMRIB, Nuffield Department of Clinical Neurosciences
OCMR, Department of Cardiovascular Medicine

SOP Number OHBA_014_V1
FMRIB_002_V5
Neuro_002_V5

SOP Title Dealing with Research Neuroimaging Incidental Findings

	NAME	TITLE	SIGNATURE	DATE
Author	Martin Turner	Primary Contact Neurologist		
Author	Pieter Pretorius	Primary Contact Neuroradiologist		
Reviewer	Stuart Clare	Associate Professor, FMRIB		
Reviewer	Clare Mackay	Professor of Imaging Neuroscience		
Authoriser	Heidi Johansen-Berg	Director, FMRIB		

1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures to be followed if, in the course of neuroimaging for research protocols, an abnormal anatomy or pathology is detected. In addition, written statements describing these procedures are provided as guidelines for inclusion in ethical applications.

2. INTRODUCTION

All volunteers giving consent to take part in neuroimaging studies are asked to indicate that they understand the scans will not be routinely formally reported by a radiologist, and that they are designed only to be used in research. Nonetheless, in the course of scanning subjects for research protocols, abnormal anatomy or pathology may be detected by a researcher or scan operator.

The vast majority of such incidental findings require no specific action other than to inform the volunteer and their GP (so it can be noted on their medical record). However, regardless of its nature, the process of informing an individual about a possible abnormality is a highly sensitive one, that can lead to significant emotional distress if handled badly.

This document summarises the FMRIB, OCMR and OHBA policies that have been agreed to address the occasional instances of abnormal anatomy or pathology (i.e., an incidental finding) being detected as part of a University of Oxford volunteer neuro research scan. The document also describes the procedures that should be followed when an abnormal neuro research scan is detected during any of the FMRIB, OCMR or OHBA magnetic resonance imaging sessions. Finally, the document also discusses the written statements that should be included with any ethics application at the time the application is made (Appendix 1).

It should be noted that dealing with abnormal scans is an extremely sensitive issue, whether or not it has any further health implications, and needs to be dealt with in a very careful and methodical way. In particular, it is of paramount importance that the relevant research participant should not be unduly alarmed by the finding, and also that information about any subsequent interaction they may have with clinicians remains confidential and fully within their control in terms of any wider disclosure. To this end, a strict procedure (described herein) should be followed in the event that an incidental finding is noted and, importantly, the investigators/scan operators present when the scan is collected **should not** attempt to discuss anything with the participant during their scanning visit. Rather, it is necessary that the designated Contact Neurologist from whom advice is sought should form an opinion of the scan before the subject is contacted in any way about their scan.

3. SCOPE

This SOP relates to all neuro scans performed at FMRIB, OCMR or OHBA.

4. DEFINITIONS

PI=Principal Investigator

5. RESPONSIBILITIES

A list of individuals currently fulfilling the following roles is maintained on the FMRIB Website.

5.1 Contact Radiographer

A senior radiographer, who coordinates the recording and referral of the incidental finding to the Contact Neurologist.

5.2 Contact Neurologist

A consultant neurologist with a local NHS contract, who, together with the Contact Neuroradiologist, determines if the incidental finding should be pursued. Discusses the finding with the participant and assumes their NHS care if necessary.

5.3 Contact Neuroradiologist

A consultant neuroradiologist with a local NHS contract, who, together with the Contact Neurologist, determines if the incidental finding should be pursued. Specifies a scan protocol for follow up scans if required.

6. SPECIFIC PROCEDURE

6.1 Procedure for dealing with an incidental finding on an MRI scan

Note that an incidental finding may be detected either at the time the scan is collected or may be identified some time later, potentially months or even years later. Regardless, as soon as any abnormality is detected the following course of action should be followed:

6.1.1 Any scan that raises cause for concern to an investigator or scan operator should, in the first instance, be shown to the Contact Radiographer as soon as practically possible after it is noticed. The investigator can then assume that the matter is dealt with, but should not expect further feedback on outcome to protect the confidentiality of the participant (whether or not the finding is significant).

6.1.2 The Contact Radiographer will make an initial decision as to whether the abnormal finding is likely to be a scan artefact, or has already been referred. If the scan finding is determined to be artefact, or has been previously referred, then no further action will be taken, and the case will be considered closed.

6.1.3 To ensure the outcome of all cases is clear and to prevent future duplicate referrals, the Contact Radiographer will track all referrals, whether or not they are passed on to the Contact Clinician, in an anonymised password-protected database that to which only they and the Contact Clinicians have access. Only the anonymised scan number, date of scanning, and findings are recorded.

6.1.4 Once an incidental finding is suspected, the Contact Radiographer will inform the Contact Neurologist as soon as practically possible. For this purpose, the scans will be provided on CD-ROM in DICOM compliant electronic format (DICOM viewer software should be included on the CD-ROM). The CD-ROM will be labelled only with the anonymized scan number. A separate piece of paper is supplied (later securely disposed) with the name and date of birth of the participant plus the scan number to allow registration for the purposes of reporting by the Neuroradiologist. These records are NOT linked to any existing NHS records that a participant may have. It should be stressed that the participant should NOT be told anything about the referral or contacted at this point, and that the number of people involved in the overall process should be minimised.

6.1.5 The Contact Neurologist will arrange for the scans to be uploaded for viewing by the Contact Neuroradiologist. The Contact Neurologist and Contact Neuroradiologist will make a joint determination as to whether the incidental finding should be pursued, with a strong aim of avoiding participant 'harm' by only including those findings clearly known to be medically important. In the event that the incidental finding does not need to be pursued (usually a normal anatomical variant that does not need to be recorded with volunteer's GP medical records) the database will be labelled as 'no action necessary', and the case will be closed.

6.1.6 'Possibly significant' findings include those without any future consequence that nonetheless need to be recorded on a volunteer's medical record so that future healthcare professionals might know when it was first observed. This GP disclosure requires the consent of the volunteer, who must then have ultimate control over who else is informed.

6.1.7 The Contact Neurologist will ask the Contact Radiographer to obtain a method of contact (ideally telephone) to discuss the scan findings. The Contact Neurologist may offer a formal consultation and physical examination at the earliest opportunity, depending on the nature of the finding. If so, then this will be done under the auspices of the NHS in a formal outpatient clinical setting. Whether or not a formal meeting is required, as a matter of standard clinical practice, the volunteer's GP will be informed of the finding and any plan for further investigation or other recommendation in a letter from the Contact Neurologist (with the prior consent of the volunteer).

6.1.8 The nature of the finding and any further action undertaken will be added to the anonymised database.

6.1.9 The Contact Neurologist will explicitly advise all volunteers who have been contacted about their scans that it would be helpful if they let the official contact mentioned in the study's Research Ethics Committee-approved Patient Information Sheet know about the finding. Additionally, they will be advised that they should NOT take part in any future neuroimaging research without disclosing the finding to the researcher beforehand. However, any decision to disclose personal health-related information (which may be highly sensitive) RESIDES WITH THE VOLUNTEER, and there must be no attempt by any researcher to ask either the subject or the Contact Radiographer to reveal the outcome of a current or previous referral.

6.1.10 Although in some cases a researcher will be informed retrospectively by the volunteer of the outcome of an incidental finding (as advised by the Contact Neurologist), the decision on whether to remove a volunteer's scan from a study lies with the PI and must be made without the expectation of automatic disclosure by the volunteer. In theory, a PI's decision to remove a volunteer from a longitudinal study because of a significant structural abnormality risks indirect disclosure when the Contact Neurologist may not have deemed it necessary to contact the volunteer. In this rare circumstance, the PI should always inform the Contact Radiographer prior to telling a volunteer that they are being removed from further study, so that it is possible for the Contact Neurologist to make contact with the volunteer to reassure them.

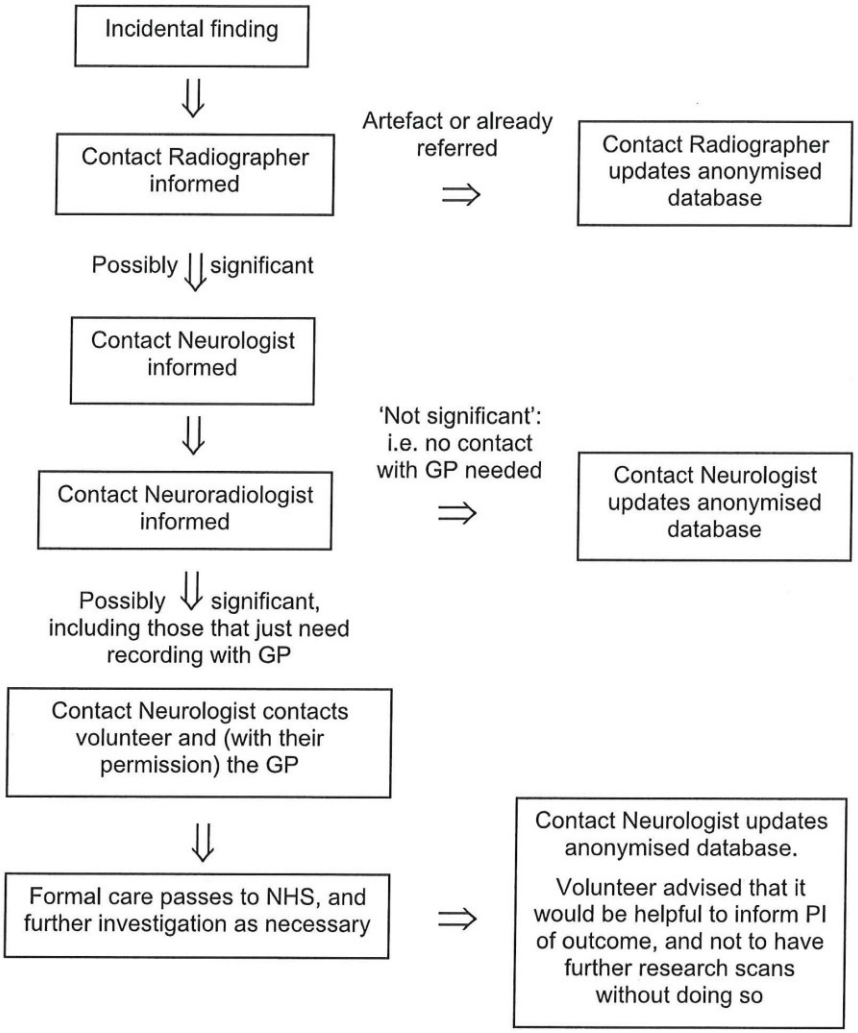

Figure1. Summary of procedures for reporting incidental findings.

7. OUTLINE OF PROCEDURES TO BE FOLLOWED BY RESEARCHERS

If you identify a possible abnormality on a scan of any subject undergoing a scan at FMRIB, OCMR or OHBA, then:

a) Inform the PI for the project, who will then inform the Contact Radiographer

b) Do NOT inform the subject of your suspicions or discuss the findings with anyone beyond the PI

c) Do NOT ask the Contact Radiographer or participant later on to reveal the outcome of any further investigation that may (or may not) have taken place

8. GUIDELINES ON VOLUNTEERS VIEWING THEIR SCANS

8.1.1 Notes on Showing Scans to Subjects

Under no circumstances should a volunteer research subject be confronted with an abnormal scan finding during their scanning visit. It is therefore recommended that subjects are not shown the images of their brains when they emerge from the scanner. Further, any promises to "show the subject their brain" should be avoided, both during volunteer recruitment and during the scan session itself. In the event that it is felt essential to show images to the volunteer, then only images that have been previewed by the scan operator should be shown.

With regard to providing subjects with images of their brain to take away, some subjects may attempt to make "diagnoses" based on their scans, and will not be able to distinguish everyday scan artefacts (signal drop out, susceptibility distortions, flow artefacts etc.) from pathology. Therefore, for many projects, it is inappropriate to provide subjects with images to take away in any form. In the cases that subjects are provided with an image of their brain then only relatively low quality laser-printer images (possibly also pseudo-colour) should ever be provided. The following text should be appended to the bottom of the images:

"These images are for illustrative purposes only. They should not be used for diagnosis."

Electronic images should **never** be provided, other than to close collaborators on the project. In the event that a volunteer requests them under the Freedom of Information Act then this request should be referred via the appropriate University channels.

8.1.2 Abnormalities Noted by Scan Operators During Volunteer Scanning

If the scan operator notes an abnormality during the scan session (i.e. when the volunteer is still in the magnet) then extreme care should be taken to avoid alarming the volunteer. The acquisition of "special" additional scans should not be attempted. Instead, the procedures referred to earlier in this document should be followed. Also, in such circumstances, it is essential that the volunteer should **not** be shown their scans.

9. GUIDELINES FOR WRITING ETHICS APPLICATIONS

When writing your ethics application, there are a number of issues that should be addressed in the documentation that relate to the potential of abnormal scan findings.

9.1.1 In the Patient Information Sheet that you write, it is recommended that the following text be included in the section titled 'Are there any risks in taking part in this study?':

It is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a doctor's appointment. Our scans are not routinely looked at by a doctor, rather our scans are intended for research purposes only. Occasionally a researcher may detect a possible abnormality. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality was medically

important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information about you is kept strictly confidential.

9.1.2 In the body of the application itself the following text is recommended:

During the consent process, subjects would be informed of our standard procedure for incidental findings ("FMRIB/OCMR/OHBA SOP – Dealing with Incidental Findings"). This outlines the process of involving a dedicated local hospital NHS consultant clinician in the case of a suspected abnormality, although it is stressed that a routine inspection and reporting of research scans is not carried out. In the case of a suspected abnormality, the Principal Investigator would alert our Contact Radiographer who, if appropriate (i.e. not a simple artefact) would independently inform the Contact Neurologist. They would in turn obtain the opinion of the Contact Neuroradiologist, and decide on the appropriate course of action, which might involve contact with the individual at the earliest opportunity and possible further investigation. This would all take place within the NHS framework and in communication with the volunteer's GP.

9.1.3 It is recommended that the following statement is included in the Consent Form itself:

"I understand that this is a research scan that is not useful for medical diagnosis, and that scans are not routinely looked at by a doctor. If a concern is raised about a possible abnormality on my scan, I will be informed if a doctor thinks it is medically important."

10. INTERNAL AND EXTERNAL REFERENCES

University of Oxford Clinical Trials and Research Governance:

http://www.admin.ox.ac.uk/researchsupport/ctrg/classification/

FMRIB Web Pages

http://www.fmrib.ox.ac.uk/support

OCMR Web Pages

http://www.ocmr.ox.ac.uk/internal/information-for-researchers/

OHBA Webpages [insert link]

11. CHANGE HISTORY

SOP no.	Effective Date	Significant Changes	Previous SOP no.
002-V1/ Neuro_002_V1 (OCMR)	1 October 2007	Formatted to new template. Slightly amended wording on giving scans to subjects. List of named contacts moved to website. Initial contact to be by clinician not researcher.	May 2006
002-V2/ Neuro_002_V2 (OCMR)	1st June 2011	Amended wording with regard to feedback and recording of outcome in scans referred.	002-V1/ Neuro_002_V1 (OCMR)
002-V3/ Neuro_002_V3 (OCMR)	1st December 2012	Amended wording for subject information sheets.	002-V2/ Neuro_002_V2 (OCMR)
002-V4/ Neuro_002_V4 (OCMR)	2nd February 2014	Amended wording with regard to feedback to the PI from the Contact Radiographer when no contact with the GP is needed Clarification of no feedback to researchers Clarified flowchart	002-V3/ Neuro_002_V3 (OCMR)
FMRIB_002_V5 Neuro_002_V5 OHBA_014_V1	15th July 2016	OHBA added to SOP. Removed reference to supplying images as TIFF since all scanners now produce DICOM.	002-V4/ Neuro_002_V4 (OCMR)