MILESTONE

fMRI investigation of the neural mechanisms of Emotional Cognitive Bias Modification as an adjunct therapy to SSRIs in depression

PROTOCOL

Short title: Emotional cognitive bias modification in depression (MILESTONE RCT)

This protocol has regard for the HRA guidance

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GENERAL INFORMATION

RESEARCH REFERENCE NUMBERS

IRAS ID number	282861
Trial registry number and date	37448835; 12/11/2020
Protocol version number and date	Version 2.0, 10/11/2023
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Sponsor	University of Bristol
REC number	20/LO/1118
CPMS ID number	47029
Funder reference number	MR/S035648/1

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: *signed by e-mail adam.taylor@bristol.ac.uk* Date: 08/09/2020.

Name (please print): Adam Taylor

Position: Head of Research Governance

Chief Investigator:

Date: 08/09/2020

Signature: 

Name: Professor Ian Penton-Voak.

i. KEY TRIAL CONTACTS

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Funder(s)	MRC Experimental Medicine Challenge Grant

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CBM	Cognitive Bias Modification
CI	Chief Investigator
CRF	Case Report Form
CUBRIC	Cardiff University Brain Research Imaging Centre
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trials Number
MRI	Magnetic Resonance Imaging
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
OSF	Open Science Framework
PIC	Participant Identification Centre
PIL	Participant Information Leaflet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	fMRI investigation of the neural mechanisms of Emotional Cognitive Bias Modification as an adjunct therapy to SSRIs in depression.
Internal ref. no. (or short title)	Emotional Cognitive Bias Modification in Depression (MILESTONE).
Trial Design	Mechanistic study. Two group randomised controlled trial (RCT) with allocation at the level of the individual. Participants randomised to treatment with SSRIs plus Emotional Cognitive Bias Modification therapy (CBM) or SSRI plus Sham Cognitive Bias Modification therapy.
Trial Participants	Primary care patients with depression who have sought treatment for depression and who have received a prescription of SSRIs.
Planned Sample Size	84 participants.
Treatment duration	1-2 weeks.
Follow up duration	6 weeks.
Planned Trial Period	January 2020 to December 2023, extended to July 2024.
Purpose of trial	We will investigate whether a remotely delivered psychological therapy (CBM) has the potential to be an adjunct therapy to SSRIs in depression.
Primary outcome	Our primary outcome is group differences (CBM v Sham CBM) in brain activation in the amygdala in response to happy faces in comparison to rest in the amygdala (assessed with fMRI derived blood oxygen level dependent responses) during the post therapy scanning session 1-2 weeks later.
Secondary outcomes	Secondary outcomes will be group differences (CBM v Sham CBM) in: Happy v. Sad comparisons in the amygdala, Happy v. Sad and Happy v Rest in the medial and dorsolateral pre-frontal cortex and occipital cortex. Mood assessments, both functional (e.g. quality of life assessments) and depressive and anxious symptoms.
Intervention	Emotional Cognitive Bias Modification (CBM) therapy. This aims to change the way participants interpret emotional expressions.
Comparator	A Sham CBM therapy. This modified version of the CBM therapy does not aim to change participants perception of expressions.

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
MRC Experimental Medicine Challenge Grant	This study has been fully funded by an MRC Experimental Medicine Challenge Grant.
NIHR Bristol Biomedical Research Centre	This study was also supported by the NIHR Biomedical Research Centre (BRC) at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol.
NIHR Clinical Research Network	Provision of service support costs for practices and local research support staff (Clinical Studies Officers).
Primary Care Research Wales	Provision of service support costs for practices.
Cardiff University Brain Research Imaging Centre	Provision of MRI scanning environment, technical support, data management.

v. ROLE OF SPONSOR AND FUNDER

This report is independent research funded by an MRC Experimental Medicine Challenge Grant (Funder reference number MR/S035648/1), with support from the Bristol NIHR BRC. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research Bristol Biomedical Research Centre, the Department of Health, or the Sponsor. The Sponsor and Funder have no role in the study design, data collection, data analysis, interpretation of data, or manuscript writing. Dissemination of results will include the publication of a detailed report, written by the MILESTONE study team.

vi. ROLES AND RESPONSIBILITIES

Trial Management Group (TMG)

The Trial Management Group (TMG) will comprise all investigators involved in the trial, the trial manager, administrative staff. Members of the TMG contribute to the trial in the following ways: trial design, trial recruitment and trial conduct, trial management, trial logistics and cost management, trial methods, statistical data analysis, and publication. The TMG will meet approximately monthly to oversee the day-to-day management of the trial. The TMG will be provided with detailed information regarding trial progress. Most meetings will be face to face.

Trial Steering Committee (TSC)

The TSC is an independent, multidisciplinary group chaired by Professor Michael Browning, Alexandra Wright-Hughes, the Statistician and 2 PPI representatives (TBC). Their role is to provide independent oversight, progress monitoring, and expert advice during the conduct of the trial. The TSC also includes members of the MILESTONE team – Ian Penton-Voak (Chief Investigator), Nicola Wiles (Co-Investigator) and Alison Burns (Trial Manager). Meetings will take place every 6 months.

Data Monitoring and Ethics Committee (DMEC) (a separate DMEC is dependent on what is agreed with the TSC once formed)

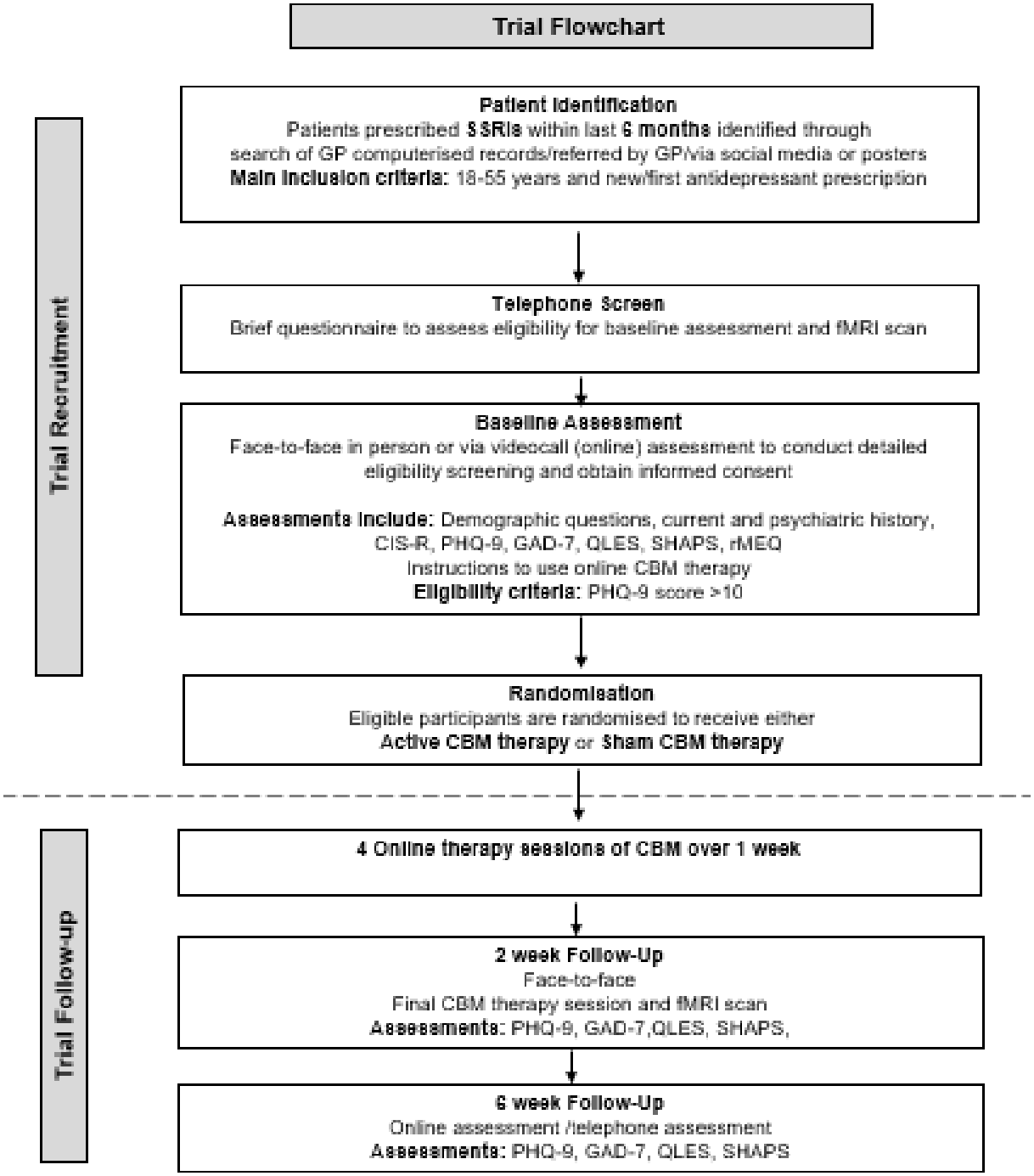
The DMEC is an independent, multidisciplinary DMEC group which we will combine with the TSC. Their role will be to safeguard the interests of trial participants, monitor the safety and efficacy of the therapy, and monitor the overall conduct of the study. The DMEC will advise the TSC on whether there are any ethical or safety reasons why the trial should not continue.

vii. PROTOCOL CONTRIBUTORS

The Chief Investigator and all the Co-investigators, Trial Manager have all contributed to the Protocol.

viii. KEY WORDS:	Depression; randomised controlled trial; emotional cognitive bias modification; functional magnetic resonance imaging (fMRI).

ix. TRIAL FLOW CHART



1 BACKGROUND

Processing of emotional information is critical to social functioning but is disrupted in many psychiatric disorders, including Major Depressive Disorder (MDD). Negative processing biases are present in depression and predict relapse in remitted patients, suggesting that biases play a causal role in the onset and maintenance of depression. A recent large trial (STAR*D) indicates that pharmacotherapy is ineffective in one-third to a half of patients[1]. Furthermore, mounting evidence suggests that pharmacotherapies alone (e.g., selective serotonin reuptake inhibitors, SSRIs) do not sufficiently improve positive affect in patients[2], and that they work best in combination with psychological therapies[3]. While recent advances in psychological therapy for depression focus on promoting positive biases, there are still difficulties in treating anhedonia, which is associated with poorer outcomes[4]. There is little work that examines what the minimum effective psychological therapy may be in addition to drug treatment, and a similar lack of studies examining mechanisms of action of such adjunct therapies. We will investigate whether a remotely delivered psychological therapy has the potential to act as an adjunctive therapy to SSRI antidepressants. We will assess whether this therapy can aid the recognition of positive emotional cues, and hence provide context to improve the therapeutic effectiveness of SSRI, as indexed by neural responses to emotional faces. Secondary outcomes will include mood and anxiety measures, to inform future studies of efficacy.

fMRI studies have provided good evidence that SSRIs reduce neural responses to negative emotional faces, particularly in the amygdala. Both behavioural and neural changes in response to emotional stimuli are associated with later improvement in mood. More direct causal evidence that changes in amygdala activity influence mood come from fMRI-neurofeedback studies[5]. Our brief, automated Emotional Cognitive Bias Modification (CBM) technique leads to robust and generalizable changes in emotional expression perception, with fMRI results in adults with low mood demonstrating it also increases amygdala activity in response to expressions of happiness[6]. Notably, CBM has less effect on responses to negative emotions, in contrast to SSRI administration which reliably impacts the processing of negative emotions, but has less robust effects on the processing of positive emotions[7]. Meta-analysis indicates that effective antidepressant action relies on both increasing brain activity to positive stimuli, and decreasing activity to negative stimuli in the amygdala[8]. This suggests that the combination of CBM and SSRI treatment might be particularly effective, but mechanistic studies of the effects of combining behavioural and pharmacotherapy are rare.

The neural mechanisms underlying emotion processing in mood disorders have received considerable attention. Structural differences between patients and healthy controls, and impairments in cortico-limbic system function, are well described. Treatment-related changes in these neural correlates have also been studied, and some studies indicate a causal role for specific patterns of activation in mood disorders. As such, neural responses to emotional stimuli may represent potential therapeutic targets. Neuroimaging studies also provide insights into treatment mechanisms. Antidepressants cause rapid changes in neural responses to emotional stimuli in limbic areas (reviewed below). Furthermore, serotonergic transmission modulates cortico-limbic connectivity[9]. Mechanistically, this may reflect increased inhibitory control over areas involved in emotional processing[10].

In addition to causing rapid changes in the limbic system, SSRIs increase neural plasticity. Hippocampal neurogenesis is considered to play an important role in therapeutic effects[11], although the mechanisms underlying these effects remain debated[12]. The context of treatment is important, with positive expectations, physical activity and a positive social environment interacting with SSRI-induced brain plasticity to deliver positive treatment outcomes – while plasticity presents the opportunity for relearning emotional processing, it will be most successful if there are positive emotional contexts in the environment from which to learn[3]. Although pharmacological antidepressant treatment appears most effective when combined with other, non-pharmacological rehabilitation techniques that allow neural plasticity to generate network structures that represent positive environments[12], there are few mechanistic studies of adjunctive therapies. Our rationale

is that by combining a CBM technique with SSRI pharmacotherapy in patients, we may harness synergistic effects of both when SSRI-induced neural plasticity is high. By modifying emotion perception directly through training – a known cognitive deficit in depression that has well-studied neural correlates, and simultaneously through pharmacotherapy, our approach allows us to examine the neural mechanisms that predict treatment success. We will investigate, then, whether our emotional learning task may provide a context to increase the therapeutic effects of SSRI. Supporting evidence for our approach comes from a series of SSRI challenge studies in both healthy and depressed samples. These studies show that anti-depressants cause a reduction in negative biases in behavioural emotion perception tasks and decreased neural activity, particularly in the amygdala, in response to negative emotional stimuli[7]. Neurocognitive models suggest that antidepressant medication has early effects on emotional processing biases that result in therapeutic benefit only after sufficient time has elapsed to allow interaction with others, where alteration in these biases gives rise to more positive social interactions, placing negatively biased emotion perception on the causal pathway for depression. A key finding in support of this argument is that early changes in both behavioural tasks and neural activity predict later treatment response.

Our own CBM task has strong effects on emotion perception that generalise well to other emotion expression tasks[13]. In effect, our CBM technique aims to provide a controlled, paired down social experience that will change participants' processing of ambiguous emotions, shifting their appraisals away from negative and towards positive. Evidence for a therapeutic effect of CBM training alone on mood is equivocal, however. Although some trials in healthy and analogue samples have delivered positive effects in mood[14],[15], others have yielded null outcomes[16]. One recent study suggests that while CBM did not improve the primary outcome measure of social anxiety in adolescents, there was evidence of lower self-reported depression symptoms after training, with further reduction at 2-week follow up[17]. A further study in healthy adults[18] showed no evidence of change on the majority of cognitive and mood measures, although there was some evidence of training improving a self-report measure of stress impact and a cognitive measure of anhedonia. There was also some evidence that CBM outcomes may be influenced by the severity of trait anxiety[19]. A clear limitation of research using our CBM technique to date, and indeed of most CBM work, is the lack of research in clinical samples to date.

We have conducted an fMRI study of our emotional CBM therapy in a sample of young people with low mood (Beck Depression Inventory-ii scores >14).[20] This study indicates that training increases neural activation to happy faces compared to sad faces, with this effect driven by greater neural activity for happy faces. We see this increase in activation for this contrast at both the whole brain level and among our a priori Regions Of Interest (ROIs), specifically the medial prefrontal cortex and bilateral amygdala[16].

The supporting evidence above suggests that SSRI plus CBM therapy may deliver a greater increase in neural responses to positive emotional stimuli, particularly in the amygdala, than SSRI alone. As amygdala responses have been implicated in recovery from depression, this is an important step towards improving our understanding of causal mechanisms in depression and may also provide initial evidence for a treatment strategy based on a potential neural treatment target.

2 TRIAL OBJECTIVES

We propose to conduct an RCT to establish whether there are any differences in the neural correlates of emotional processing (based on fMRI scans) following treatment with SSRI plus emotional CBM compared with SSRI plus sham CBM in patients with depression, recruited through primary care or from the general population.

3 TRIAL DESIGN

This study is a two-parallel group RCT with allocation at the level of the individual. Participants, researchers, and those undertaking statistical analysis will be blind to treatment allocation.

4 TRIAL SETTING

The study will be based at the University of Bristol. Patients will be recruited from primary care (GP practices) set in the surrounding areas of Bristol, North Somerset, South Gloucestershire, BANES, Gloucestershire and Somerset, in and around the Cardiff area. GP practices will act as Participant Identification Centres (PICs). The study will also be advertised outside of the NHS and individuals will be able to self-refer to the study.

5 PARTICIPANT ELIGIBILITY CRITERIA

5.1 Inclusion criteria

- Aged 18-55 years.
- Have a NEW or FIRST episode of depression (defined as not prescribed an antidepressant in the previous 6 months).
- Prescribed a course of antidepressant medication.
- Score > 10 on PHQ-9.

SSRI antidepressant medication includes; sertraline, citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, zimelidine and vortioxetine.

5.2 Exclusion criteria

- Prescribed an antidepressant in the previous 6 months.
- Alcohol or substance dependency.
- Bipolar disorder.
- Schizophrenia/Psychosis.
- Dementia.
- Currently under psychiatric care (including those referred but not yet seen) for depression
- Unable to access online CBM sessions (via PC, laptop, smartphone, tablet).
- Cannot complete questionnaires unaided or would require an interpreter.
- Are taking part in another trial involving a psychological/drug therapy.
- Have been receiving a course of high intensity psychological therapy for depression or anxiety in the last 6 months.
- Have a contra indication for fMRI scanning/imaging
    - Significant hearing impairment (aids cannot be worn in the scanner).
    - Significant visual impairment that is not corrected by glasses/contact lenses. e.g., double vision or loss of vision in one eye, severe cataracts.
    - Metal objects in or around the body which cannot be removed (braces, pacemaker, metal fragments, hearing devices, accidents involving metal fragments).
    - History of established central nervous system disease or injury (e.g., cerebro-vascular disease, multiple sclerosis, Parkinson’s disease, traumatic brain injury).

- Epilepsy, type 1 diabetes (insulin pump or electronic device attached), or thermoregulatory problems, including Raynaud's disease.
- Location sensitive tattoos to the head, neck, or genital area; (patients exceeding; tattoos covering >5% of the body; longest dimension>20cm; or multiple tattoos <20cm apart will be discussed with the radiographer).
- Body Mass Index >35 kg/m^2.
- Too physically unwell to tolerate a 30-minute fMRI scan, including musculo-skeletal disorders which make lying supine and still difficult.
- Claustrophobia.
- Pregnant or trying-to-become pregnant.
- We will ask participants not to take recreational drugs for 72 hours prior to each test session and not to drink alcohol for 24 hours prior to each test session.

COVID-related

- *The study will adhere to the latest COVID-19 CUBRIC and government guidelines.*

6 TRIAL PROCEDURES

6.1 Recruitment

The trial aims to recruit participants with depression from primary care and the general population. We plan to recruit 84 patients over 31 months, with a target of approximately 6 patients randomised per month. We will use three methods of recruitment: in-consultation and record search recruitment, and advertisements outside the NHS.

6.1.1 Participant identification

Method 1: in-consultation

GPs (Participant Identification Centres) can identify patients during face-to-face in person consultations or via videocall or telephone consultations who are starting or have very recently started (within the last 6 months) on an SSRI antidepressant that they think might be suitable for the trial. They will introduce the trial and ask the patient for their permission to be contacted by the research team. Verbal permission to be contacted can be taken during telephone and videocall consultations.

Method 2: record search

GP practices (Participant Identification Centres) will conduct a search of their computerised records for potentially eligible patients (defined as those who are aged 18-55 years old, who have been recently prescribed an SSRI antidepressant – within 6 months). Practices will be asked to exclude those who would be unsuitable due to the exclusion criteria listed in section 5.2. The record search will be conducted using a combination of primary care diagnostic codes, and manual screening of resulting lists by practice staff including a practice GP.

Potentially eligible patients will then be either texted/ called by the GP or mailed an invitation to participate by the GP practice, asking for their permission to be contacted by the research team. Patients who have not responded after one weeks will be sent one reminder letter/text or a follow up call by the practice.

Patients will be able to respond anonymously if they wish to decline participation and will be able to provide a reason for declining. We will also ask practices to provide anonymised data for all patients identified by the record search (age, gender, reason for exclusion by practice). This data will be used to report the generalisability of results.

Method 3: Advertisements outside the NHS

The study will also be advertised via social media (e.g., twitter, websites and Lindus Health, a commercial recruitment agency), posters or equivalent materials. This will provide information about how an individual can obtain further information/ take part, including relevant contact details. Interested individuals will be directed to complete an expression of interest form online using 'Jisc Online surveys' an online survey tool designed for academic research (https://www.onlinesurveys.ac.uk) or via paper equivalent if required/preferred. The data is secure and strict information security standards are followed and the data is processed in compliance with GDPR. This will include patient contact details, details of their GP and brief questions to ascertain eligibility. As part of this EOI, the potential participant would be asked to confirm their agreement that the research team can inform their GP about study participation and that their GP can be contacted if the team has any concerns around issues relating to safety (in line with the study's policy for managing risk – section 8.3). In response to their EOI the research team will text/email suitable individuals a PIS sheet to read before the researcher calls. Those identified via Lindus Health's social media strategy will be directed to complete a pre-screener questionnaire on their website, this will identify potentially suitable participants. This is similar to the EOI mentioned above. With their consent suitable participants' contact details will be emailed to the research team.

Potential participants who agree to contact via any of the three recruitment methods (in-consultation/ letter/ advertising) will be telephoned by the local research team and screened for suitability for a baseline appointment (See section 6.1.2).

6.1.2 Telephone Screening

Primary care patients with depression who have been referred to the study or completed the expression of interest form will be telephoned by a researcher. The researcher will briefly explain the study, check that a patient information sheet has been received and answer any questions the participant may have. With verbal consent, the researcher will then proceed with a brief telephone screening questionnaire. This will include questions about: the participant's age; gender; adherence to medication; whether they are receiving care from psychiatric services for their depression; whether they could complete questionnaires unaided; whether they are taking part in a research study involving a psychological/drug therapy, or had any high intensity psychological therapy.

The researcher would also check they would be willing and suitable to have an fMRI scan (e.g., Do you have a surgical implant; are you pregnant or trying to become pregnant?; do you have a pacemaker or hearing aid). In addition, we will ask participants for permission to contact their GP, if necessary, in the rare event that there is some uncertainty about whether MRI would be safe. The screening call is likely to take 10-15 minutes.

Those meeting the telephone screening criteria would then be invited to have a baseline appointment with a researcher to explain the trial, perform the baseline assessment, establish eligibility, and obtain written informed consent (see 6.1.3).

A full list of study questionnaires is presented in Appendix 1.

6.1.3 Baseline assessment

This appointment will take place face-to-face in person at the patient's home, GP surgery, University of Bristol premises, or another mutually convenient location, where it is safe to do so and will take approximately 60 minutes. Alternatively, the appointment will take place remotely, with the patient completing online questionnaires on their own smartphone, tablet or computer, and the researcher providing support via telephone or videocall. The researcher will explain the study in more detail, answer questions the participant may have, and obtain written informed consent. The researcher will check whether the participant's circumstances have changed since they completed the screening questionnaire (for example if they have stopped taking their medication, still able to have an fMRI scan) in order to check they are still eligible for a baseline assessment.

Potentially eligible participants will then be asked to complete the following questionnaires. These will include the:

- Revised Clinical Interview Schedule (CIS-R)[21]: a detailed psychiatric instrument that will give an ICD10 diagnosis.
- Sociodemographic questions will include age, gender, employment status, educational qualifications, ethnicity, housing, and marital status.
- Patient Health Questionnaire (PHQ-9)[22] a brief measure of depressive symptoms.
- General Anxiety Disorder questionnaire (GAD-7)[23] a brief measure of anxiety.
- Quality of Life Enjoyment and Satisfaction Questionnaire (QLES)[24] a brief measure of life enjoyment and satisfaction.
- Snaith-Hamilton Pleasure Scale (SHAPS)[25] a measure of anhedonia.
- Reduced Morningness-Eveningness questionnaire (rMEQ)[26].

Patients who conduct baselines face-to-face in person will complete paper questionnaires, those conducted remotely will complete them online using 'Jisc Online surveys' – an online survey tool designed for academic research (https://www.onlinesurveys.ac.uk). The data is secure and strict information security standards are followed and the data is processed in compliance with GDPR.

Participants who score 11 or more on the PHQ-9 will be told they are eligible to enter the trial.

Eligible participants will also be familiarized with accessing and using the CBM package online. Each session of CBM will be administered on the Gorilla.sc online experimental platform. No identifying information will be stored on the Gorilla platform, which is ISO/IEC 27001:2005 and GDPR compliant (https://gorilla.sc/support/info/faq#dataprotectionandsecurity). Arrangements for their fMRI appointment will also be made for them to come to CUBRIC (Cardiff University Brain Research Imaging Centre) within 1 week of completing the CBM therapy sessions.

6.2 Informed consent for trial participation

Prior to commencing the baseline assessment, the researcher will obtain written informed consent from the patient relating to their participation in the trial.

Informed consent will be obtained either via an online consent form completed on Jisc Online surveys (if the baseline assessment is being conducted remotely) or via a paper-based informed consent if the researcher is meeting with the patient face-to-face in person. Patients attending a face-to-face appointment will be given a copy of their written consent form to keep, if completed online on Jisc Online surveys, patients will be able to save and print a copy or email a copy to themselves. A copy will also be sent to the patient's GP if they are eligible to take part in the study.

Participants will be reminded that they are free to withdraw from the trial at any time without giving reasons and without prejudicing his/her further treatment. We will seek consent to use data collected up to the point of withdrawal, and this will be explained in the information sheet. In addition, in line with open access data requirements, information may also be used to support other research in the future and may be shared anonymously with other researchers. The information sheet will also explain that if there are concerns about their welfare or the welfare of others, we would need to break confidentiality and inform their GP.

6.2.1 Additional consent provisions for collection and use of participant data in ancillary studies

As part of the baseline consent procedure, patients who give informed consent for trial participation will be asked to indicate whether they would be willing to be contacted about future related research.

6.3 Randomisation

Randomisation will be minimised on gender, age (<35 years; ≥35 years), and depression severity (PHQ-9 score <17 vs. ≥17). The minimisation variables are important prognostic indicators and will ensure a balance between the two groups.

6.3.1 Method of implementing the randomisation/allocation sequence

Once eligibility has been confirmed at the baseline assessment and informed consent obtained, participants will be randomly assigned to one of two groups: (1) active CBM therapy or (2) sham CBM therapy. Randomisation will be by means of a computer-generated code, implemented by an individual not involved in the recruitment process. Participants will be sent an email that includes the link to the online website for CBM therapy by this third-party within 48 hours of the baseline appointment.

6.4 Blinding

We will use a triple blind experimental design, with participants, researchers and analysts all blinded to allocation until data analysis is complete. At the end of the study participants will be unblinded to provide them with their group allocation.

6.5 Planned Allocations

Participants will be randomised to either receive active CBM or Sham CBM (see section 7 for detail).

6.6 Follow-up assessments

Trial follow-up assessments will be conducted at 2 and 6 weeks after randomisation. Participants will be followed up by a face-to-face assessment at 2 weeks then a telephone/online or via videocall assessment at 6 weeks.

2 week post-randomisation

During the first week, participants are required to complete four computerised online therapy sessions within 7 days of randomisation. Each therapy session takes about 8-12 minutes. Researchers will monitor online completion of the CBM therapy daily and prompt participants if necessary. Participants will only be able to complete one session per day and will not be able to complete more than the required number of sessions.

2 weeks post-randomisation

The day before the scanning appointment a researcher will complete a pre-visit screening and contact the participant (via telephone/ text) to confirm their appointment and informally inquiry about any COVID symptoms. Where a participant self-reports symptoms associated with the COVID-19 virus, the researcher will rearrange the visit. Participants will be reminded about ongoing COVID safety at CUBRIC, including the use of mask wearing, (where safe and appropriate), hygiene (cleaning all surfaces and equipment the participant comes into contact with) and maintaining social distances where possible.

The researcher will meet the participant face-to-face in person at Cardiff University Brain Research Imaging Centre (CUBRIC) (see 6.7 for CUBRIC Protocol) and participants will be asked to complete the final session of the therapy before having a scan. During fMRI scanning, participants will complete 3 tasks – a learning task (this will involve participants trying to determine which of two stimuli leads to reward (points gain) or loss (points deduction), a memory task (participants have to respond according to whether the currently presented letter on the screen matches or doesn't match the letter that was presented, *n*-items) and a facial emotion processing task (a simple blocked design face perception task involving the presentation of sad, happy or fearful facial expressions), as used for our pilot work and other studies antidepressant drug action (See section 6.7 for more detail of the tasks).

Participants will also complete a paper or online questionnaire at this appointment - including all the mood assessments (PHQ-9, GAD-7, QLES, SHAPS). Appointments will take approximately 2 hours.

6 weeks post-randomisation

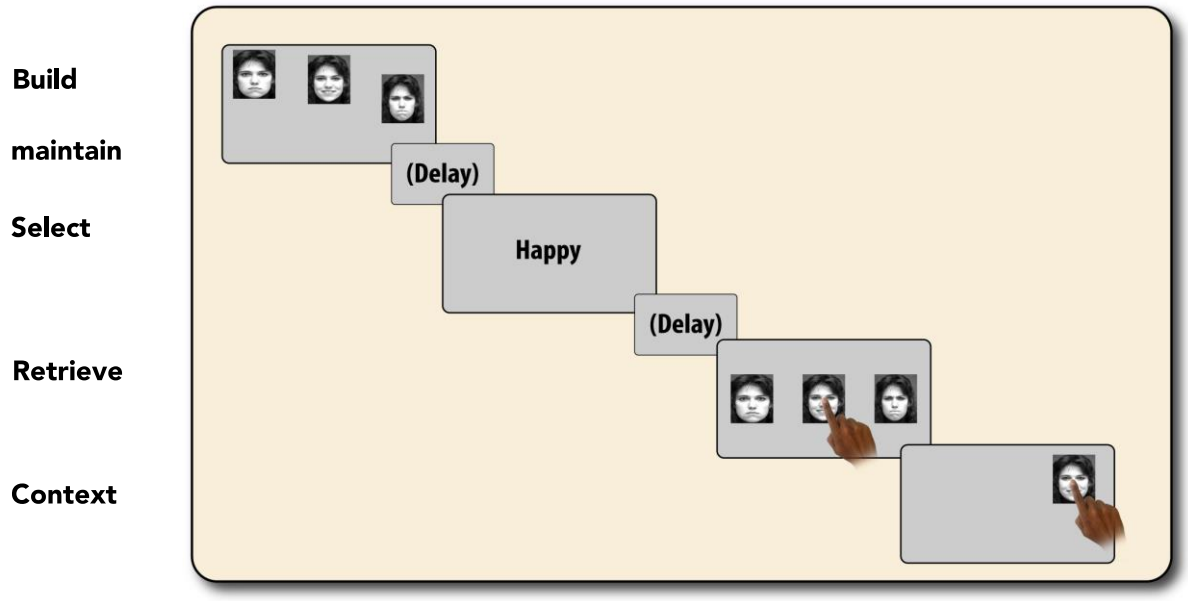
The 6 weeks follow-up questionnaires will be completed online. Participants who are unable to complete online will be contacted and asked to complete the questionnaires by telephone or by videocall. This will include all the mood assessments collected at baseline and the 2 week follow-up appointment.

Participants will also be asked to complete a short task, an emotional episode formation task.

Emotional Episode Formation task

Participants are presented with three facial expressions (the same person in a happy, neutral or angry state) at different locations on the screen. They will need to remember the facial expression of the faces and their location on the screen. Participants will then be informed that they only need to attend to one of those faces, i.e., after short delay, they need to identify the happy faces and move it to the location where it was presented.

Figure 1. Schematic of the Emotional Episode Formation Task



A full schedule of questionnaires is attached as Appendix 1.

Retention strategy

Due to the ongoing Covid-19 situation it is possible that baseline and the 6 week follow-up appointments may be conducted via videocall, and that this may be a preferred option for some people even when face-to-face appointments can begin again.

6.7 Protocol at CUBRIC

Participants will visit CUBRIC for an fMRI scan. CUBRIC is part of Cardiff University's Science and Innovation Campus and based in Cardiff, Wales. Travel will be arranged by the research team for participants. The study will comply with the current local COVID-19 guidelines set out by CUBRIC.

Upon arriving at CUBRIC participants will be briefed about the study and given an opportunity to ask questions before performing an MRI safety check. A safety screen will be conducted to make sure it is safe to go near the magnetic field and then an additional safety check once the participant is in the controlled area. They will be asked to change into MRI safe clothing (e.g., scrubs) in a designated area. Participants will then complete the final therapy session run on the gorilla platform, (8 min), complete the follow-up questionnaire, be asked to undertake short practice versions of the all the tasks on a computer, and then undergo an MRI scan lasting about 50 minutes.

MRI protocol

- Resting state fMRI scan (5 min)
- Face processing task (15 mins)
- Probabilistic reversal learning task (20 mins)
- A full anatomical MRI scan (7 min)
- n-back working memory task (5 mins)

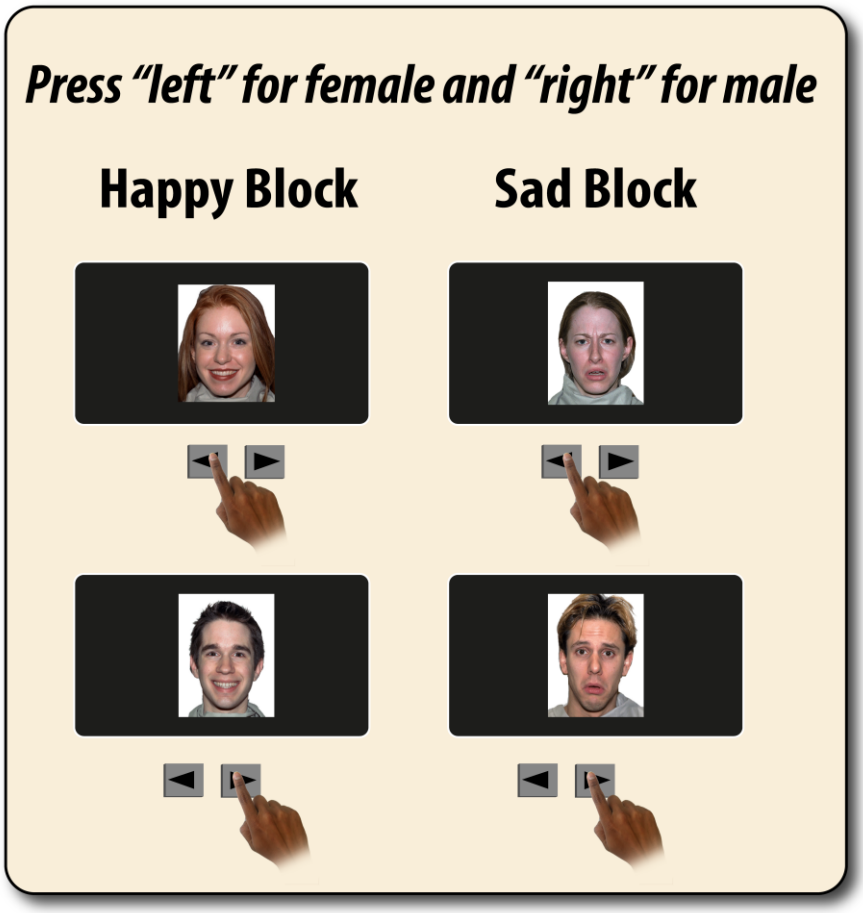
Resting State fMRI Scan

Here the participant does not have to explicitly perform any task. They will be asked to just sit back and close their eyes while the scan is performed. This will allow us to establish baseline functional connectivity (communication between brain regions) and see whether the connectivity pattern changes with the intervention.

Face Processing Task

Participants will be presented with blocks of faces, for example, either happy, sad or fearful faces. Participants respond by identifying the gender of the face by using the MRI-compatible button box. This will enable us to identify the neural correlates of viewing happy, sad or fearful faces (see Figure 2).

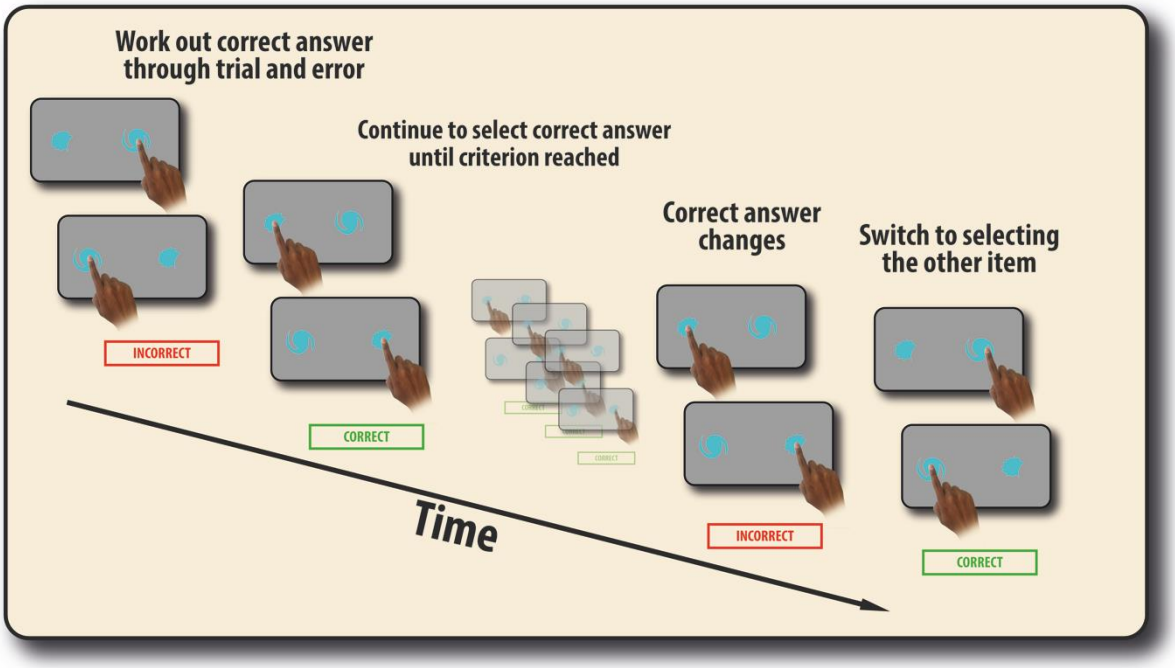
Figure 2: Face Processing Task This task involves the participant viewing faces with different emotional expressions. Participants are asked to judge the gender of the face (male or female).



Probabilistic Reversal Learning Task

Altered neural activity when receiving positive and negative feedback is widely seen in depression. The task will involve participants trying to determine which of two stimuli leads to reward (points gain) or loss (points deduction). This will enable us to identify the neural correlates of responding to positive and negative feedback (see Figure 3).

Figure 3: Reward and Punishment Reversal Learning Task. This task measures a participant's ability to fixate or change their behaviour in response to reward and punishment, respectively. Participants are able to choose between two items. They are told that their goal is to find out, via trial and error, which items the computer has chosen as the correct answer. After selecting an item twice, they are presented with correct or incorrect feedback that informs them whether they have, respectively, chosen the right or wrong shape. They need to continue to select the correct item until the answer changes (signalled by receiving 'incorrect' feedback) and switch responding to the other item.



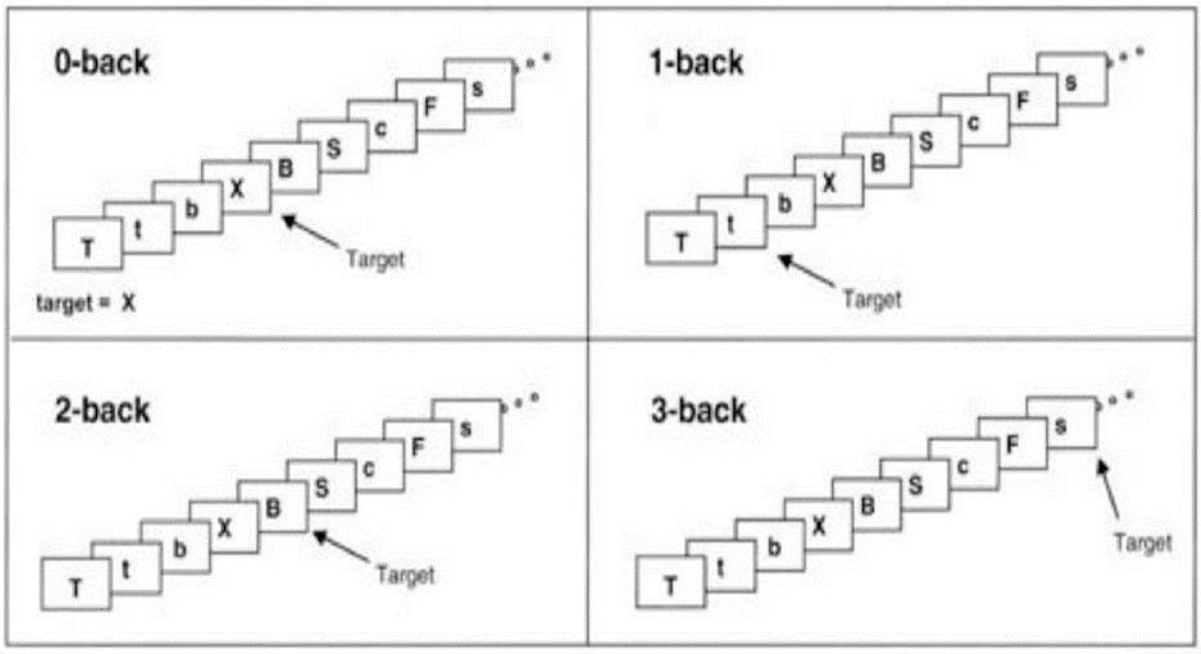
Anatomical MRI Scan

An anatomical scan will be acquired for its utility in providing detailed images of brain anatomy. This is essential information required to analyse brain imaging data.

n-back working memory task

Participants will be presented with a series of letters at the centre of the screen. Participants have to respond according to whether the currently presented letter on the screen matches or doesn't match the letter that was presented *n*-items. Here, there will be two blocks: 1-back and 3-back (see Figure 4).

Figure 4. Illustration of the n-back task.



6.8 Withdrawal of trial participants

Participants have the right to withdraw from the trial at any time for any reason, without their medical care being affected. Where possible, data already collected will continue to be used in the trial. If a participant withdraws from the study completely, no further data will be collected. If a participant withdraws, the reason for and type of withdrawal will be documented.

6.9 End of trial

For the purposes of reporting, we define the end of this trial as the collection of the last data item for trial participants. This will be the online questionnaire completed at the 6 weeks follow-up.

7 TRIAL THERAPY AND COMPARATOR

7.1 Trial therapy

The active CBM therapy consists of five computerised online therapy sessions in which participants are presented with brief psycho-educational information about the role of cognitive biases in depression, and then perform an intervention in which they judge the emotion displayed on screen in a simple, two alternative forced choice procedure.

Each therapy session takes about 8-12 minutes to complete, and participants are required to complete four sessions within 7 days of starting the study, and then complete the final therapy session at their appointment at CUBRIC before scanning at 2 weeks post-randomisation.

The intervention targets the recognition of facial expression of emotions by initially assessing the threshold for detecting one emotion over another in a set of images with ambiguous expression (a 15-face continuum in which faces morph from happiness to sadness, see Figure 5). Training uses feedback to shift the participant's threshold, leading to an increased tendency to make positive attributions to

ambiguous emotional stimuli (i.e. the cognitive bias that leads to negative interpretation of emotional faces is attenuated).

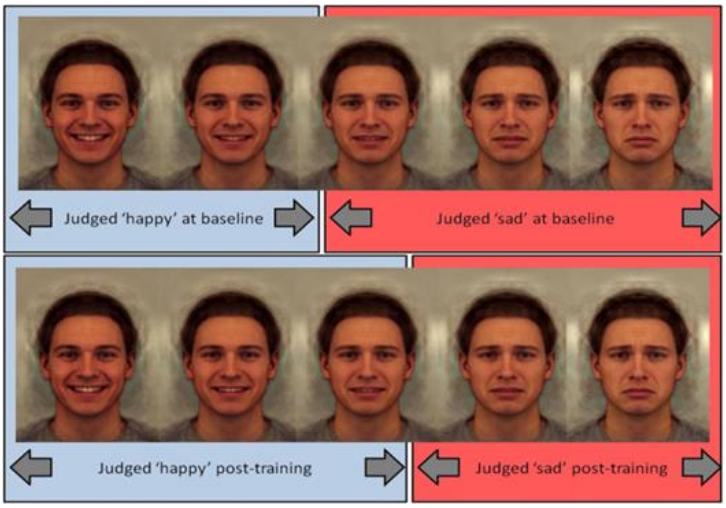


Figure 5. Training consists of feedback to shift the participant's balance point, estimated by presenting exemplar faces from a 15-frame morphed face image continuum using a two-alternative forced choice procedure. In the training condition, the 'correct' classification is shifted towards 'happy'; the two images nearest the balance point that the participant would have previously classified as 'sad' at baseline are considered 'happy' in terms of feedback. Feedback in the control condition is based directly on baseline performance and has no effect on responses. Sessions last 8 minutes and are fully automated.

The baseline phase of each session consists of 45 trials (with each face of the continuum presented three times). The task requires the participant to make a forced choice judgement as to whether the presented face is displaying a 'sad' or 'happy' expression. Images are presented one at a time, in random order, for 150 ms. Stimuli are preceded by a fixation cross, which is presented for a random period ranging from 1500 to 2500 ms. Subsequent to presentation, and to prevent processing of afterimages, a backward mask of noise is presented for 250 ms, followed by a prompt asking the participant to respond. This remains on screen until the participant makes a response (i.e., a judgement of 'sad' or 'happy'). This baseline block allows us to determine where in the continuum the participant switches from making primarily 'happy' judgements to primarily 'sad' judgements.

Following the baseline block, two training blocks are presented to participants. In the CBM therapy group, the feedback is tailored such that the "correct" categorisation of the two faces towards the full sad face from the balance point is changed from 'sad' to 'happy' to shift individual balance point through feedback learning. For two of the faces closest to the balance point that was initially categorised as sad by the participant, they are given feedback that this is incorrect, and it should be categorised as 'happy' (see fig 4). In the training blocks, there are 31 trials, in which images 1-2 (unambiguously happy) and 14-15 (unambiguously sad) are presented once, images 3-5 and 11-13 presented twice, and images 6-10 are presented three times. Different faces are presented on each day of training.

7.2 Trial comparator – usual care

Our comparator is a sham CBM therapy. This mimics the active CBM therapy but with one key difference. In sham training blocks, the feedback given is based directly on the participant's baseline threshold – so, the feedback does not attempt to change bias, as it reflects the participants response baseline. Our earlier work shows that this procedure is perceptually hard to distinguish from the active therapy, and that it has no effects on emotion perception[14-18].

8 PARTICIPANT SAFETY

8.1 Risk policy for researchers

Should a trial researcher become concerned for the safety of a patient participant (for example, if the participant expresses suicidal ideation or recent self-harm at any point during participation, including during the screening call) or be concerned about the safety of others, the researcher will follow the study's detailed Patient Safety Protocol SOP (see Appendix 3) for researchers, and seek advice from the Co-Investigator with clinical responsibility (Clinical CI). If suicidal ideation is expressed, the researcher would speak to the patient about this, encourage the patient to speak to their own GP, and seek permission from the patient to pass the clinical information to the GP. Should the patient refuse permission, the Clinical CI would assess the risk information and call the patient if necessary. The Clinical CI would break confidentiality and pass information to the patient's GP without the patient's consent if this was deemed necessary to protect the safety of the patient and only if the patient continued to decline to give permission for their GP to be contacted. This policy would be explained in the patient information sheet.

CUBRIC safety procedures will minimise the risk to the researchers. Researchers will follow the current CUBRIC Covid guidelines. Researchers can wear face masks (where safe and appropriate), maintain hygiene (cleaning surfaces and equipment they come into contact with) and social distancing, wherever possible. A fully trained radiographer or suitably qualified MR Operator will also be present at the time of the scanning and hence no lone working will take place. If CUBRIC policies are followed, there should be no additional risk to the participant or researcher.

8.2 Risk and burden for participant

We will ensure that fMRI safety protocols are rigorously applied to ensure that patients with contraindications for fMRI do not enter the study. The safety and suitability of patients for research fMRI scans will be regularly assessed at appropriate intervals over the course of the study. Participants will be initially screened over the telephone prior to making an appointment, telephoned/texted 24 hours before their scan to confirm appointment and they have no symptoms suggestive of COVID-19, then screened after entering the MR control room to ensure that they have emptied their pockets of all objects (particularly objects unsafe in an MRI environment such as coins). The patient's GP may also be contacted if there is any ambiguity regarding their suitability and safety to have an MRI scan.

Participants may misunderstand the information and think that they have had a clinical (diagnostic) brain scan. In order to reduce the risk of this misunderstanding, we have clearly explained in the Patient Information Sheet (PIS) that we will not be able to make any clinical diagnoses from the scan. Participants understanding of this will be checked by the CUBRIC research team prior to scanning.

In the event of a clinical abnormality being identified, the Incidental Findings Policy will be followed (see section 8.3)

This study could be burdensome for participants as they will be asked to travel to CUBRIC in Cardiff, Wales**;** this may be more challenging for people when they have depression. However, we will arrange transportation (e.g. a free taxi service, or pay travel expenses if participants want to make their own way there) and provide clear advice on how to find the centre and any further information that might be required to facilitate their visit. A researcher will meet the research participant at CUBRIC reception when they arrive. In recognition of the time taken to participate in the study, participants will be offered £100 (voucher) for attending their scanning appointment then a further £10 (voucher) on completion of the 6 week follow up assessment, and all travel expenses will be paid.

The total time in CUBRIC is likely to be approx. 2 hours and as participants will be actively completing tasks, this will require some concentration. Patients may have difficulty with concentration and memory as these can be symptoms of depression. The research team will be aware of this and will be supportive and encouraging during the scanning session.

The MRI Scanner is noisy, and participants may feel claustrophobic. We have explained this in the PIS, and patients with claustrophobia will be advised not to take part in the scan. Earplugs or headphones will be provided to reduce the noise experienced. If patients become uncomfortable in the scanner, they will be able to alert the staff by activating an alarm, and they will be able to leave the scanner.

The highest standards of safety will be followed in order to mitigate the ongoing effects of COVID-19. Patients will called/texted the day before their scanning appointment to confirm they have no symptoms suggestive of COVID-19. The study team and participant can wear face masks (where safe and appropriate), maintain hygiene (cleaning all surfaces and equipment the participant comes into contact with) and maintain social distances wherever possible. In order to reduce any ongoing COVID-related risks of travelling to and from the imaging centre by public transport, a free door-to-door taxi service will be offered.

8.3 Study Incidental Findings Policy and Procedure

In line with standard CUBRIC procedures, in the event that a scan reveals a suspected abnormality that was unknown to the MR authorised person in charge of the scan and which they suspect might require investigation, the following procedure must be adopted:

1) So as to avoid distress to participants arising from false alarms, staff must not disclose their concerns to the study participant.
2) The MR-authorised person involved must, without delay, report his/her concerns to the Chief investigator (CI) of the study.
3) The study Chief Investigator will as a matter of urgency, contact a medical professional for their informal assessment of the MRI scan to see if it warrants contacting the participant's General Practitioner (GP).
4) If the informal assessment by the medical professional is that a clinical MRI examination is required, then the study CI should contact the participant's GP by telephone and follow up with a written letter. The letter should state that a medical professional has reviewed the research scan and is of the opinion that a clinical MRI examination is warranted. It should also state that the participant concerned has not been informed.
5) The decision as to whether the participant should be informed, and the task of informing and referring the participant for a clinical MRI examination is the responsibility of the GP.

In the interests of participant confidentiality, the MR authorised person will only share this information with the study Chief Investigator.

8.4 Recording and Reporting Adverse Events

We will employ the following standard definitions of adverse events.

Adverse Event

Any untoward medical occurrence in a study participant to whom an intervention has been administered, including occurrences which are caused by or related to that intervention. An adverse event can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the intervention or research procedures whether or not considered to be related to the intervention/research procedures.

Adverse events that might be expected to occur at a higher rate in this group of participants include episodes of self-harm not requiring hospital admission and worsening of depression sufficient to require referral to a clinician. Although these AEs are expected, they will still be reported in this study. Variations in mood, including worsening of depression that does not lead to self-harm or hospitalisation, are commonly seen during therapy and would not be reported as individual adverse events.

Serious Adverse Event (SAE)

An adverse event is considered **serious** if it:

- results in death.
- is life-threatening (refers to an event during which the participant was at risk of death at the time of the event, it does not refer to an event which might have caused death had it been more severe in nature).
- requires hospitalisation, or prolongation of existing hospitalisation.
- results in persistent or significant disability or incapacity.
- is otherwise considered medically significant by the investigator.

Expected SAEs that are a more common occurrence in this study population regardless of the study are listed below. Although these SAEs are expected, they will still be reported in this study.

- Self-harm leading to hospitalisation.
- Suicidal attempts leading to hospitalisation.
- Worsening of depression leading to hospitalisation.

Admission to hospital for pre-planned surgery for pre-existing conditions will not be reported as an SAE.

Suspected Serious Adverse Reaction (SSAR)

Any serious adverse event that is suspected (possibly or probably or definitely) to be related to the intervention.

Non-IMP Suspected Unexpected Serious Adverse Reaction (non-imp SUSAR)

An SAE that occurs in a non-IMP trial and is:

“Related” – that has, possibly, probably, or definitely resulted from administration of any of the research procedures, **and**

“Unexpected” – that is, the type of event is not listed in the protocol (or above) as an expected occurrence.

8.4.1 Adverse Events/ Serious Adverse Event Procedures

1. The participants in this study, people with depression, are slightly more likely than the general population to experience typically defined '**adverse events**' and '**serious adverse events**' such as self-harm, suicidal attempts, and worsening of depression.
2. Participating GPs and MILESTONE researchers will be asked to report adverse events/serious adverse events to the Clinical Lead, (David Kessler). Details of the participant's study ID, what the adverse event was and the date on which it occurred will be required as well as other information (see Appendix 4).
    a. Suspected serious adverse events should be reported to the study team as soon as possible and within 24 hours. A telephone call between the research team and the patient/GP will occur to enable the appropriate SAE notification forms to be completed promptly by the study team.
    b. Non-serious adverse events should be reported to the study team within 5 days.
3. All reported adverse events will be then reviewed promptly by the clinical lead or their nominated deputy clinician.
4. The Sponsor is University of Bristol (UoB) and the University has a Service Level Agreement with UH Bristol (UHB) to ensure that all SAE reporting is managed by UH Bristol on behalf of the University. For that reason, all relevant SAEs must be recorded and reported to UH Bristol, in accordance with UH Bristol Research Safety Reporting Standard Operating Procedure.

8.4.2 Responsibilities

We will ask participants to inform the research team of any adverse events that occur during their time in the study.

GPs will be asked to notify the researcher team of any suspected serious adverse events within 24 hours, and any spontaneously reported non-serious adverse events which may be related to the study, within 5 days.

The research team should also be alerted to any AEs reported by patients as part of follow-up assessment.

The research team will then complete AE/SAE forms and pass these to the clinical lead for review. The researchers will inform the Chief Investigator (CI) Ian Penton-Voak, Trial Steering Committee/ Data Monitoring Committee.

The UoB research team are responsible for reporting SUSARs to the REC.

8.4.3 Procedure for Recording and Reporting Adverse Event/Serious Adverse Events

1. On notification of an **adverse event/serious adverse event** the researcher will complete a **MILESTONE RCT Adverse Event Form** (Appendix 4).
2. In line with University of Bristol procedures (http://www.bristol.ac.uk/red/research-governance/registration-sponsorship/specific-advice/adverseevent.html) an adverse event record form will be completed by the researcher paying specific attention to information regarding the nature and timescale of events i.e. when the event started, the details of the

AE/SAE, any potential study relation, action taken and resolution / closure of the AE/SAE. Further information should be requested from the participant as necessary for SAEs.

3. All AEs will be recorded and reported from the point of consent (baseline assessment) until the 6 week follow-up assessment or point of withdrawal from the study.

4. **All Suspected SAEs/ SUSARs should be reported to UHBristol within 24 hours.**

5. The clinical lead (or their nominated deputy) will review the SAE form and assess the seriousness, relatedness and expectedness as follows:

   Confirmation of seriousness (whether the event is an adverse event or serious adverse event)
   Causality – i.e. relatedness of the event to the study intervention, according the following definitions:

   - *Unrelated – where an event is not considered to be related to the study intervention*
   - *Unlikely to be related* – where an event is considered unlikely to be related to the study intervention
   - *Possibly* – although a relationship to the study intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
   - *Probably* – the temporal relationship and absence of a more likely explanation suggest the event could be related to the study intervention
   - *Definitely* – known effects of the study intervention, suggest that study intervention is the most likely cause.

   Expectedness of the event. Is the event an anticipated event even if the research had not been taking place?

6. All completed **adverse event reporting forms** should then be passed to the CI, Prof. Ian Penton-Voak, so that he can maintain an overview of all study AEs.

7. All **adverse event reporting forms** should then be returned to the Trial Manager, who will record the AE/SAE in the MILESTONE project file, ensuring it is noted when the event occurred, the details of the AE/SAE, any potential study relation, action taken and resolution / closure of the AE/SAE.

8. The numbers and details of AE/SAE will be reported to the Trial Management Group at regular meetings. The Trial Steering Committee/ Data Monitoring Committee will be informed of AE/SAEs at the next scheduled meeting.

9. Details of AE/SAE will be provided as required in the REC Annual Report Form for non-CTIMP trials. Further details can be found at http://www.hra.nhs.uk/research-community/during-your-research-project/safety-reporting/

8.4.4 Procedure for Reporting Serious Adverse Events

1. If an adverse event is deemed to be **serious**, the researcher should also:

(i) Complete the *__UH Bristol SAE initial report form, and SAE follow up report form__ (see Appendix 5) (if the event is unresolved at the time of the initial report form) and report the event to the clinical lead or their nominated deputies as soon as possible after notification of the event.

The completed UH Bristol Initial Report form must be sent to UH Bristol by email: research@uhbristol.nhs.uk **within 24 hours**. If any initial report forms are submitted to the sponsor with missing information, they must be re-submitted and signed within at least 72 hours of the initial report.

Any requested follow-up information will be submitted as soon as possible. Identifiable information must **not** be sent to UH Bristol.

*The Sponsor is University of Bristol and the University has a Service Level Agreement with UH Bristol to ensure that all SAE reporting is managed by UH Bristol on behalf of the University. For that reason, all relevant SAEs must be recorded and reported to UH Bristol, in accordance with UH Bristol Research Safety Reporting Standard Operating Procedure from: http://www.uhbristol.nhs.uk/research-innovation/for-researchers/templates-and-sops/templates-and-guidance/

(ii) The UoB research team will inform the Trial Management Group, Trial Steering Committee/Data Monitoring Committee at the next scheduled meeting.

2. Non-IMP SUSARs

(i) Where the **serious adverse event** is both **related and unexpected (a non-IMP SUSAR),** the study team must **also** notify the Research Ethics Committee **within 15 days** of the team becoming aware of the event.

(ii) Details of non-IMP SUSARs must be also provided as part of the Annual Progress Report to the REC. Further details can be found at http://www.hra.nhs.uk/research-community/during-your-research-project/safety-reporting/

(iii) Unexpected Serious Adverse Events which, after review are thought to be intervention/study-related (non-IMP SUSARs) will be brought to the Chair of the TMS/DMC's attention within 7 days of notification. The Trial Management Group should be informed at the next scheduled meeting.

8.5 MRI safety

Screening will be conducted by a study researcher, but in the rare event of any uncertainty regarding their suitability for a fMRI scan, we may contact the GP to request clarification regarding their medical history (with patient consent). The fMRI scan will **not** be examined for abnormalities as it is not a diagnostic scan. However, should an unexpected potential abnormality be discovered, we may contact the GP.

8.6 Responsibilities

Chief Investigator:

- Maintain oversight of the safety of participants in the trial, including an ongoing review of the risk/benefit. The clinical Lead will provide clinical advice to the CI in this regard.

Clinical Lead:

- Will check individual reports of AEs and use medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated.
- Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Sponsor:

University Hospitals Bristol NHS Foundation Trust (UH Bristol) will monitor safety information on behalf of the Sponsor. UH Bristol will review the trial AE reporting SOP prior to the start of the trial.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, the group will periodically review safety data.

Data Monitoring and Ethics Committee (DMEC):

In accordance with the Trial Terms of Reference for the DMEC, group will periodically review overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

The combined TSC and DMEC will advise the trial team on the frequency of review of individual and cumulative SAEs.

8.7 Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the intervention, or an unrelated event.

8.8 Reporting urgent safety measures

If any urgent safety measures (USM) are taken, the CI will notify the REC immediately where possible, and no later than 3 days from the date the measures are taken, and the circumstances giving rise to those measures. The Sponsor will then follow-up with written notification within 3 days of the action being taken, i.e. in the form of an amendment, describing the event, the measures taken and justification for the measures taken. NHS R&D offices will be notified in accordance with local policies/procedures. The DMEC will be asked to review information relating to USM and report recommendations to relevant parties.

9 STATISTICAL CONSIDERATIONS

9.1 Outcome measures

9.1.1 Primary Outcome

The primary outcome will be brain activation in the amygdala in response to happy faces in comparison to rest in the amygdala (assessed with fMRI derived blood oxygen level dependent responses) during the post therapy scanning session.

9.1.2 Secondary Outcomes

Secondary outcomes will be happy versus sad comparisons in the amygdala, happy versus sad and happy versus rest in the medial and dorsolateral pre-frontal cortex and occipital cortex. Additional secondary outcomes will include mood assessments, both functional (e.g., quality of life assessments) and depressive and anxious symptoms.

9.2 Justification of sample size

Our prior fMRI evidence (N=36) indicates that our intervention, relative to control, leads to increased amygdala activation in the happy > sad contrast in the left amygdala (effect size of d = 0.69, $p<0.05$). A sample size of 72 will give >80% power to detect a similar effect in a replication sample at a 5% alpha level. We will recruit 84 participants (42 in each condition), allowing for ~20% attrition during the intervention period. Mood outcomes will be underpowered and therefore will be presented descriptively (i.e., without corresponding inferential statistics). but will provide estimates of likely effect size that may inform future trials of efficacy.

9.3 Statistical analysis

fMRI Data will be pre-processed in the standard way using Statistical parametric Mapping version 12[27] realigned to correct for movement, slice-time corrected for the staggered acquisition time, co-registration of functional and structural (anatomical) images, normalization of functional images to standard template). Finally, the imaged will be smooth with an 8mm full width half maximum.

A general linear model will be constructed that will contain the main regressors, e.g., the appearance of ‘happy’, ‘sad’ and ‘fearful’ faces. Each of these regressors will be convolved with a hemodynamic response function and nuisance regressors of no-interest (e.g., movement).

We will then make contrasts to address our primary and secondary outcomes using a summary statistics approach, where contrasts are generated at the individual subject level and then passed to a second, group level to enable statistical inference. For our main outcome (neural response to happy faces) we will generate contrasts (happy minus implicit baseline) for each individual subject (across both sham and active groups). These contrasts will be then subjected to an independent t-test that examines the main hypothesis that the amygdala response to happy faces is higher in the intervention compared to the control group. To enhance our ability to detect an effect we will restrict our analysis to the amygdala (defined structurally). To correct for multiple comparisons within the search volume we will use a voxelwise familywise error correction threshold generated using random field theory. Similar procedures will be carried out for our secondary outcomes.

All mood assessments, both functional (e.g., quality of life assessments) and depressive and anxious symptoms will be analysed using linear regression, with adjustment for baseline values and demographic variables, which may be possible due to a small sample size.

10 DATA MANAGEMENT

10.1 Data collection tools and source document identification

Data will be collected in a variety of formats. Baseline consent will be documented using online or paper consent forms. Screening, baseline, and follow-up data will be collated using validated and bespoke electronic and paper questionnaires, or directly online using Jisc Online surveys. Much of the baseline data (CISR) will be entered directly into the computer by the participant. The remaining baseline and follow-up trial questionnaires will be completed on paper by the participant (with assistance from researchers if required or directly online using Jisc Online surveys with the assistance from the researchers via videocall or telephone. The 6 week questionnaire will be completed online and directly entered by the participant, again using Jisc Online surveys. As this trial data will be entered directly onto the questionnaires, the questionnaires are considered the primary source documents in this trial. Similarly, where patients or researchers have entered data directly onto electronic questionnaires, these will be source data. Participants will be sent a link to log directly onto Jisc Online surveys.

Imaging data collected from 3T fMRI scans, conducted on site at CUBRIC, will also be a source of data. fMRI data will be collected in FSL format, a freely available and comprehensive library of analysis tools for fMRI. Data will be shared between the University of Bristol and Cardiff University. In general, no personally identifiable imaging data will be shared with external researchers. Groups summaries, and processed images, will be shared on a public database consistent with the principles of open science.

The University of Bristol will store the consent forms and paper questionnaires until the end of the study, at which time they will be archived. Formal SOPs will be developed for each aspect of trial data management and entry.

The Sponsor is the University of Bristol and the University has a Service Level Agreement with Cardiff University, CUBRIC for the provision of support services by CUBRIC.

10.2 Data handling and record keeping

All data will be backed up immediately after generation onto the University of Bristol Research Data Storage Facility (RDSF). The RDSF provides secure, long-term storage for research data. This provides nightly backup of all data, with further resilience provided by three geographically distinct storage locations. A tape library is used for backup purposes and also for long-term, offline data storage. Only authorised users can access data stored within the RDSF. The RDSF is managed by Bristol's Advanced Computing Research Centre (ACRC) which has a dedicated steering group and a rigorous data storage policy (https://www.acrc.bris.ac.uk/acrc/RDSF_policy.pdf).

The RDSF upholds and reinforces Bristol's wider Information Security Policy (http://www.bris.ac.uk/medialibrary/sites/infosec/documents/isp-01.pdf).

Data will be stored in the RDSF for at least 20 years. Data on data.bris will also be stored for a minimum of 20 years.

Personal data (e.g., mood questionnaire responses, MRI scans, behavioural data collected online) will be collected during this study. Participant level data on the RDSF will be based on unique numbers assigned to each participant. These numbers will be used to link data collected online to other data sources. No sensitive or identifiable information will be kept on the RDSF. Linkage between identifying information and data (fMRI, questionnaire, online collected) will instead be stored on the secure University of Bristol. Participant consent forms will include reference to the fact that participants can withdraw their data up to ten months post study completion (in order to allow time to amalgamate data before the data is made available online) and will include details regarding the long-term plans of how the data will be stored and shared. Participant contact details and a link to participant data will therefore be kept for ten months post study completion. This metadata will be stored separately, on the secure

University of Bristol Experimental Psychology server, which is encrypted, and password protected. Importantly these data will be stored on a separate server to the participant data stored on the RDSF. After one year, these electronic files containing contact details will be destroyed and all data deposited on data.bris under a level of restriction that is considered appropriate, and will be anonymised.

Trial SOPs will detail the data handling procedure.

10.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections - in line with participant consent.

10.4 Archiving

An archiving plan will be developed. At the conclusion of the trial and the final report submitted, all identifiable essential data will be archived for 20 years in accordance with the Sponsor and NIHR guidance. This will be in a secure location and available on request for audit and inspection by regulatory bodies. Anonymised electronic data will be stored indefinitely. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

11 MONITORING, AUDIT AND INSPECTION

Trial monitoring is undertaken by UH Bristol on behalf of the Sponsor, in line with a Service Level Agreement. A detailed Quality Assurance and Monitoring plan will be developed in consultation with the Sponsor and UH Bristol and will be detailed separately. The plan will be shared with the Trial Management Group (TMG) and Trial Steering Committee (TSC).

The CI and those collecting data will be responsible for data quality. After approximately 10% of data collection has been completed, the study will undergo a quality assessment by an independent researcher.

During this monitoring process all CRFs and study documents will be assessed as well as participant engagement and the investigator's laboratory management. Improvements will be made as necessary. The majority of data will be collected electronically, ensuring a high level of data quality. Post-study checks will be conducted on hardcopy data entry by an independent researcher.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 NHS Research Ethics Committee (REC) review and reports

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013), the principles of Good Clinical Practice and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted to a Research Ethics Committee for review.

The trial will not commence until all relevant regulatory approvals are in place. Any subsequent amendments will be submitted to the REC, on the agreement of the Sponsor, and will not be implemented

until the REC has granted favourable opinion. All REC correspondence will be retained in the Trial Master File.

Annual progress reports will be submitted to the REC/HRA within 30 days of the anniversary date on which favourable opinion was given and annually until the trial is declared ended. Progress reports will also be submitted to the funder in line with MRC reporting requirements (on the ResearchFish platform). Copies of these reports will be sent to the Sponsor prior to submission. Copies of all relevant reports will be made available to the DMEC and TSC as appropriate.

An end of study report will be submitted to the REC within 90 days of the end of the trial. A final report will be submitted to the MRC, Sponsor and REC within one year of the end of the trial.

12.2 Peer review

The protocol and ongoing trial will be reviewed by the independent joint Trial Steering Committee/Data Monitoring Committee, and by the funder as part of the annual progress review.

12.3 Public and Patient Involvement

Given patient engagement plays an important part in treatment response, we presented our intervention (in the form of a digital app) to patients recruited through the NIHR Bristol Biomedical Research Centre. Feedback indicated that the relevance of the CBM task to mood was unclear. Once the role of cognitive bias in depression was explained to the group, they felt the intervention was appropriate. To provide a supportive environment for the current study, we will include psychoeducational training information alongside our active CBM / Sham CBM therapy, and our PPI work will help shape this aspect of the study. Further PPI work will be conducted through the NIHR BRC to shape this brief psychoeducational component.

PPI members of these groups have also provided feedback on patient information for trial participants.

We will send a summary of the results of this trial to participants who indicate they wish to receive this, and to the GP practices involved in recruitment activities. We also plan to disseminate findings in the community e.g. via the CRN PPI group, and relevant community organisations.

12.4 Regulatory Compliance

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) and all applicable regulatory requirements including the Research Governance Framework. The Chief Investigator or designee will ensure that all appropriate approvals (e.g., Research Ethics Committee and NHS R&D) are in place prior to patients being enrolled in the study.

Any subsequent amendments to the study protocol or related documents will be submitted to the appropriate regulatory bodies for approval.

Progress and end-of-study reports will be sent to regulatory bodies in line with the relevant requirements.

12.5 Data protection and patient confidentiality

All investigators and trial staff must comply with the requirements of the Data Protection Act 2018 and General Data Protection Regulations with regards to the collection, storage, procession, and disclosure of personal information and will uphold these data protection principles.

Personal information will be stored securely. Participants will be identified only by a trial ID number on the questionnaires, and any questionnaire data will be stored separately to identifiable participant data. fMRI data will be stored securely. Access to data will be restricted to the minimum number of individuals necessary for quality control, audit, and analysis. Identifiable data will be stored for 20 years, and anonymised digital data will be stored indefinitely. The Chief Investigator is the data custodian.

The study team will make data transparency information available to participants in line with the HRA guidance on the General Data Protection Regulations (GDPR).

12.6 Insurance and indemnity

This study will be sponsored by the University of Bristol. The University has Public Liability Insurance to cover the liability of the University to research participants. In the event that something goes wrong, and a participant is harmed during the research study there are no special compensation arrangements. If a participant is harmed and this is due to someone's negligence then they may have grounds for a legal action for compensation against Bristol University or the NHS Trust or one of the other parties to the research, but they may have to pay their own legal costs.

Dr David Kessler has medical indemnity for clinical activities with the Medical Defence Union.

12.7 Access to the final trial dataset

A data sharing plan will be developed at the outset of the trial. This will describe who will have access to the dataset, and the process of requesting access to the dataset. The study data will be posted to data.bris under a level of restriction that is considered appropriate.

13 DISSEMINATION POLICY

Dissemination will be in accordance with the MILESTONE Study dissemination policy.

The trial will be reported in line with CONSORT guidelines. On completion of the trial, we plan to prepare peer-reviewed papers outlining the main results, and a detailed final report which will be submitted to the funder, MRC. We aim to send a summary of the trial results to those trial participants who have indicated they would like to receive this following publication of the study findings.

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15 APPENDICES

15.1 Appendix 1 – Schedule of Questionnaires

Questionnaire	Pre-baseline screening call	Baseline	Pre-2 week appointment	2 week appointment	6 week follow-up
Phone screen: Age, gender, ability to complete questionnaires unaided, participation in other research, on antidepressant medication, low mood/depression, eligible for fMRI scan	Y				
Baseline informed consent form		Y			
Consent to pass summary scores to GP		Y			
Consent to be sent results of study		Y			
Biographic and demographic data (e.g. employment status, qualifications, ethnicity, housing status, marital status, history of depression		Y			
CIS-R		Y			
Antidepressant adherence		Y		Y	Y
PHQ-9		Y		Y	Y
GAD-7		Y		Y	Y
QLES		Y		Y	Y
SHAPS		Y		Y	Y
rMEQ		Y			
CBM tasks				Y	
Emotional Episode formation task					Y

15.2 Appendix 2 – Amendment History

Amendment No.	Previous version	New version	Date implemented	Author(s) of changes	Details of changes made

15.3 Appendix 3 – Suicide Ideation SOP

Standard Operating Procedure for Suicidal Ideation

1. PURPOSE

This Standard Operating Procedure (SOP) has been written to describe the procedure for suicidal ideation that may be expressed by MILESTONE RCT participants during participation in the trial.

2. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/20/EC (in the UK, these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments and where applicable incorporates elements of ICH GCP tripartite guidelines (E6).

People with depression can experience suicidal thoughts and ideas (suicidal ideation), therefore this SOP is in place to ensure that when this is identified in MILESTONE RCT participants it is recorded and reported. This SOP sets out instructions to achieve uniform performance and includes specific instructions for recording suicidal ideation and sets out procedure, documentation, timescale and reporting lines.

3. SCOPE OF THIS SOP

This SOP applies to all MILESTONE participant contact, both pre and post consent.

4. RESPONSIBLE PERSONNEL

Researchers/CSO's –reporting instances of suicidal ideation to study Clinical Lead and participant GP's. Documenting such instances on paper and completing entries onto study database.

Co-investigators – for reviewing reports of suicidal ideation, advising Researchers/CSO's. To monitor adherence to procedure. Training in procedure. Study Manager – for management over site.

5. PROCEDURE

5.1 Definition of suicidal Ideation

In the MILESTONE trial each participant is administered the PHQ9 questionnaire at screening/baseline and their follow-up appointments and the CIS-R via computer at baseline. On completion of each assessment the MILESTONE Researcher will ensure that any suicidal ideation is identified and dealt with following the below procedure.

A person may indicate suicidal ideation either by responding to specific questions on the PHQ-9 or within the CIS-R (baseline), which identify suicidal ideation, or they may disclose information during the interview.

The question used to identify suicidal ideation within the PHQ9 questionnaire is Q9 and asks about the frequency of 'Thoughts that you would be better off dead or of hurting yourself in some way'.

Over the last 2 weeks, how often have you been bothered by the following problem:

Q9

0. Not at all
1. Several days
2. More than half the days
3. Nearly every day

A response of '3' (Nearly every day) to Q9 of the PHQ9 would indicate the participant is experiencing suicidal ideation.

The question used to identify suicidal ideation within the CIS-R (at baseline) is as follows:

DEPTH Q9. In the PAST SEVEN DAYS, have you thought of killing yourself?

1. No
2. Yes, but I would never commit suicide
3. Yes, I have had thoughts about it in the past week

A response of '2' (yes, but I would never commit suicide) or '3' (yes, I have had thoughts about it in the past week) to question 'DEPTH9' indicates the participant is experiencing suicidal ideation. This will automatically generate an alert on the CIS-R output report. The Researcher will check the CIS-R output for this alert at baseline.

Please note, the CISR output may display 'suicide intent: patient feels life isn't worth living'. This statement does not refer to the above suicide ideation questions, and is not a statement that the patient wants to end their life, so this is not included as criteria to trigger the suicide ideation SOP procedure.

Patients who disclose information during an interview (face-to-face, online or telephone) to the Researcher indicating that they have attempted suicide or that they have been thinking of ways to commit suicide will be considered to have suicide ideation.

5.2 Implementation of procedure

GPs are responsible for the on-going clinical care of participants. Therefore, researchers, have a duty of care to ensure that the GP is aware of suicide ideation expressed by participants.

Researchers must initiate the suicide ideation SOP each time a participant expresses thoughts of suicide or self-harm. This may be as a result of responses to questionnaire items or the participant may disclose information during an interview that leads the researcher to believe that there is a significant suicide risk. In both instances, the researcher, with the participant's permission, should inform the participant's GP and notify the Clinical Lead (or nominated deputy).

Whenever a Researcher becomes aware that a patient is at risk, the Researcher should first of all ascertain whether or not the patient has talked to his/her doctor. The Researcher should reinforce the importance of maintaining a dialogue with the GP and ask for permission to pass the information to the GP (see

Appendix A4 - **suggested scripts**). Researchers are not clinically trained and should not attempt to assess the seriousness of the disclosure but should adhere to the policy.

If the participant agrees for this information to be disclosed to their GP, the Researcher should contact the participant's GP within **48 hours**** to pass on the information obtained. In cases where the **participant scores '3 (nearly every day)' for Q9 on the PHQ9, the Researchers must telephone the GP.** Where a participant's CISR output shows they have had suicidal thoughts in the past, Researchers should ascertain when these thoughts occurred. Researchers should then take this information to the Clinical Lead to assess the level of risk and whether Researchers should report this information by telephone or by letter.

If the participant's GP is not available, then the Researcher should ask to speak to the duty doctor. The Researcher should make it clear to the GP that no risk assessment has been performed and that clinical responsibility for the study participants remains with the GP. A letter (**Form A1 – GP Letter**) should be sent to the GP confirming this notification.

**If the Researcher believes the participant is in immediate danger, the Researcher must immediately contact the GP, who will take appropriate action, or call an ambulance.

If the participant refuses permission for the researcher to inform the GP then the researcher should immediately consult the Clinical Lead or his/her nominated deputy who will then examine the patient's data and if necessary, will assess the patient. If it is concluded that there is a significant risk, the patient's GP will be notified **with or without** the patient's consent. However, the Clinical Lead or deputy would contact the GP without first assessing the patient if serious risk was already identified, again with or without the patient's consent. In these cases, the decision should be explained to the patient as soon as possible.

The confidentiality clause in the Patient Information Sheet also covers disclosure of risk to others. If such a disclosure occurs regarding self-harm or risk to others, Researchers should complete a the disclosure Form (**Form A2 Disclosure form**) and pass this to the Clinical Lead as soon as possible who will assess the risk and break confidentiality if appropriate.

The correct sequence of action is laid out in the flow chart **Figure 1**.

Participants who disclose suicidal ideation will continue with MILESTONE until trial conclusion or a decision to withdraw is made by the participant.

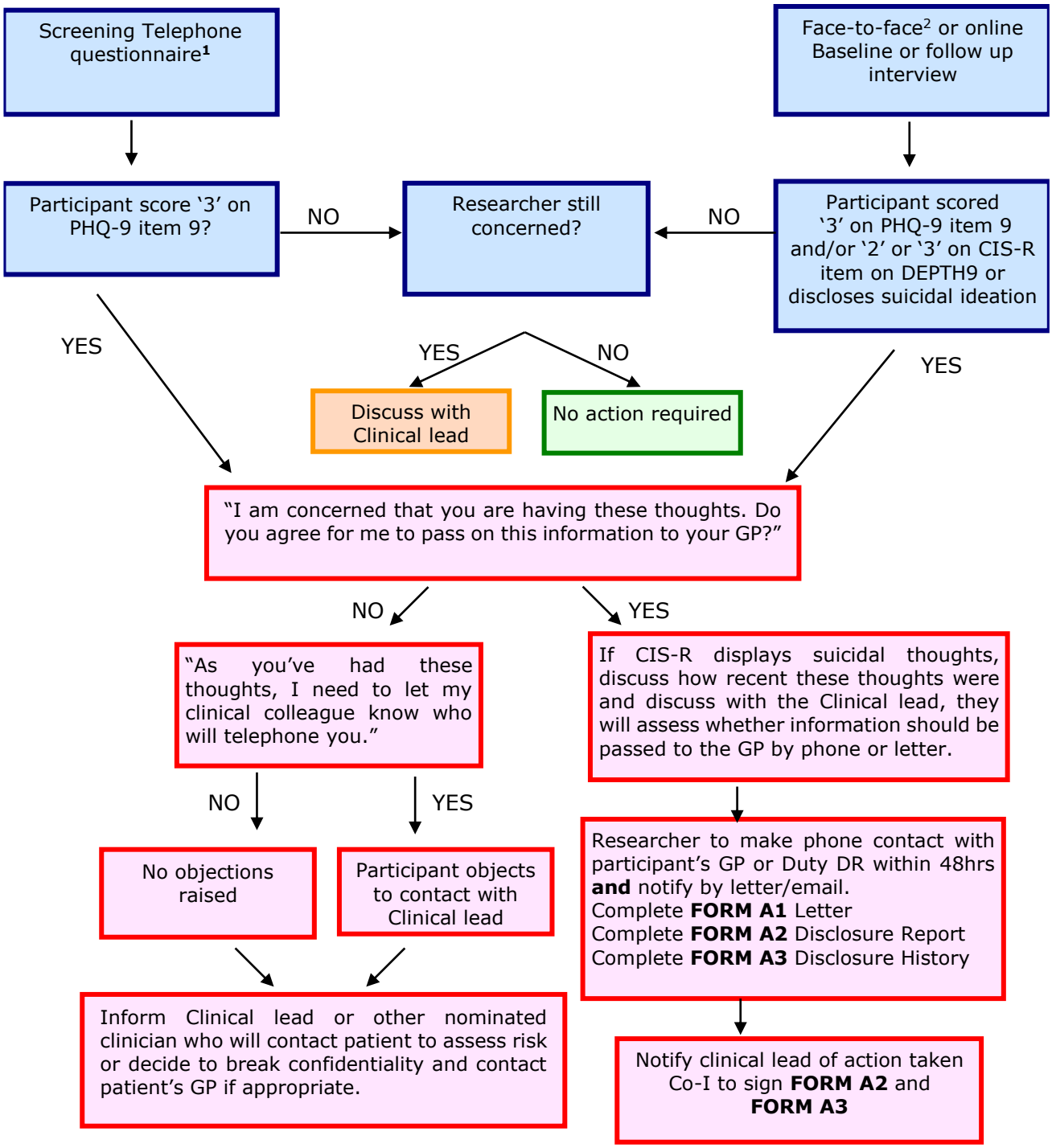
Figure 1 – Suicide ideation proforma

The following action must be taken and recorded by researchers (qualitative or quantitative) whenever a participant discloses suicidal ideation to the researcher or identifies the following responses on the below items

- **a participant scores '3' on item 9 of the PHQ-9**
- **'2' or '3' on the item 'DEPTH9' on the CIS-R**

[1] If situation arises on initial screening questionnaire and participant is eligible to continue, complete the telephone screen before initiating the pro forma

[2] If situation arises on baseline questionnaire, researcher should complete pre-assessment questionnaire before initiating the pro forma



Nominated Clinicians: David Kessler Tel: 0117 331 4031 Mobile: 07976475261.

6. REFERENCES

None.

7. APPENDICES

Appendix A4 – Suggested scripts for participant conversations

8. TEMPLATES/ LOGS ASSOCIATED TO THIS SOP

A1 Form – Letter to GP V1

A2 Form – Disclosure Report Form V1

A3 Form – Disclosure History Record V1

9. SOP DISSEMINATION AND TRAINING

SOPs will be distributed to the concerned staff. Staff concerned by the SOP will sign the SOP training log.

In some instances, the SOP or the changes to the SOP will be basic. The training will constitute of the person reading the SOP and being provided with the opportunity to ask specific questions to the author of the SOP. In some instances, the staff member being trained will carry out the procedure under supervision of the author of the SOP or under supervision of a staff member who has been trained and is using the SOP.

10. SIGNATURE PAGE

Author and Job Title:	Alison Burns (Trial Manager)
Signature:	
Date:	
Authorised by: **Name and Job Title**	
Signature:	
Date:	

Form A1 - GP Letter V1

Dear Doctor

Notification of possible thoughts of self-harm

Patient Name:……..... **DOB: ……/……/…….**

I am writing to notify you that the above patient, who is participating in/was screened for participation the MILESTONE trial, reported thoughts of self-harm on [**date**] and agreed to this information being passed to you. Although the patient is participating in/was screened for the trial responsibility for clinical management remains with the practice.

Possible thoughts of self-harm were identified by the following (please tick as appropriate)**:**

The patient indicated on the PHQ9 questionnaire that over the past two weeks they have had "thoughts that they would be better off dead or of harming themselves", / **nearly every day** ☐

The patient indicated on the CIS-R questionnaire that they have had "thoughts about killing themselves" in the past **seven days** ☐

The patient further disclosed the following information:

……..…

……..……

……

…….

Furthermore, the patient informed us that they:

Have notified you of these thoughts ☐

Have not notified you of these thoughts ☐

This letter is for information and to aid with clinical care. The responsibility for clinical care remains with the practice throughout the trial. MILESTONE outcome assessments do not include a risk assessment. Clinicians may therefore wish to discuss this further with the patient before making a record on the patient's notes that may have wider implications.

Yours sincerely,

Name: Contact phone No.:

STRICTLY CONFIDENTIAL

Form A2 – Disclosure Report Form V1

PATIENT DETAILS			
Date of Incident:	**Patient ID:**	**Name:**	**Sex:**

Details of disclosure (continue onto separate sheet if necessary)

Outcome:

Please indicate type (tick all that apply):

Self harm:	☐	**Criminal offence:**	☐
Irrational behaviour:	☐	**Child protection issue:**	☐
Death:	☐		

ADDITIONAL RELEVANT INFORMATION

DETAILS OF PATIENT'S GP

Practice:

Address:

Post code:

Tel No:

Name of Researcher	**Date**	**Signature**
Name of PI	**Date**	**Signature**

Form A3 – Disclosure History Record v1

PARTICIPANT ID:_____ NAME:_____ DOB: _____ GP PRACTICE: _____

Time point	Date	Risk Identified	Researcher	GP Informed	Name of GP	Date GP Informed	Disclosure	Signature of clinician
Screening		Yes/No		Yes/No				
Baseline		Yes/No		Yes/No				
2 weeks		Yes/No		Yes/No				
6 weeks		Yes/No		Yes/No				

Nominated Clinicians:

Name:	Position	Location	Phone	Mobile
Prof. David Kessler	Professor of Primary Care	UoB	(0117) 33 14031	07976475261

Appendix A4

Suggested Scripts V1:

Disclosure via questionnaire

Thank you very much for answering these questions to us. We really appreciate your taking part in the study; the information you give us is invaluable and may help others who suffer from depression or low mood. However, I notice from the questionnaire you completed that you have been feeling quite down recently and have had thoughts of harming yourself. Have you spoken to your doctor about these thoughts? These thoughts are very common in depression and it is really important to talk (keep talking) to your doctor about them. We'd like to tell your GP about these thoughts and hope this is ok with you.

Disclosure during interview (face-to-face or telephone)

I am concerned about some of the things you have told me. Have you spoken to your doctor about them? It is important that your doctor knows about the way you feel, as they will be able to make sure that you have the necessary support in place.

If patient is hesitant or refuses

Many people find it hard to bring these things up during a consultation, but your doctor can offer you help with these feelings. If he/she knows how you are feeling, he/she will be able to talk to you about it and together you can decide on the best way to treat you. The doctors in charge of this study strongly recommend we tell your GP.

If patient continues to refuse

That fine, but as I am not a medical doctor, I do have let my colleague know about the way you are feeling. He may phone you in the next day or so to have a talk to you about the way you are feeling.

15.4 Appendix 4 – Adverse Event Form

1	MILESTONE study ID number	
2	Date Event Started	
3	Date Event Stopped	
4	Please describe the event, any treatment given and the outcome	
5	Outcome	❑$_1$ Resolved ❑$_2$ Resolved with sequelae ❑$_3$ Ongoing ❑$_4$ Patient died ❑$_5$ Unknown
6	Intensity:	❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe
7	Causality: Relationship to study intervention/procedures	❑$_1$ Not related ❑$_2$ Unlikely to be related ❑$_3$ Possibly related ❑$_4$ Probably related ❑$_5$ Definitely related
8	Expectedness	❑$_1$ Expected ❑$_2$ Unexpected
9	Please indicate why you consider this event to be serious (tick all that apply)	❑$_1$ Not serious ❑$_2$ Results in death* ❑$_3$ Life threatening* ❑$_4$ Results in hospitalisation or prolongation of existing hospitalisation* ❑$_5$ Resulted in persistent or significant disability/ incapacity* ❑$_6$ Congenital anomaly or birth defect* ❑$_7$ Other (please specify)* _____
10	Type of adverse event	❑$_1$ AE ❑$_2$ Unrelated **or** expected SAE* ❑$_3$ Related **and** unexpected SAE (SUSAR)*
11	Date research team notified	
12	How notified (i.e. participant/researcher/ /GP at interview/telephone call/ /withdrawal)	
13	Name of person recording AE	
14	Reviewer (clinical lead) signature	
15	Reviewer (clinical lead) name	
16	Clinical lead review date	
17	Action recommended	

* Event is considered serious– report to UH Bristol within 24 hours. If event is serious, unexpected **and** related (SUSAR), it will also need to be reported to the REC within 15 days using a Safety Report Form.

15.5 Appendix 5 – UH Bristol SAE initial report form, and SAE follow up report form

TMPL_025 SAE/SUSAR INITIAL REPORT FORM

R&I use only	Date received:

To be completed by the person filling in the SAE form			
UH Bristol/UoB study reference number		R&I case reference number (R&I use only)	
Subject ID/Initials		Study site:	
		Onset date of SAE	

IRAS number			
1. Study Title (use short title where available):			
2. Details of subject affected by SAE/SUSAR			
Subject study ID: Initials:			
3. Details of SAE/SUSAR (further space available in section 10)			
Main diagnosis (or main symptom if diagnosis not known) (to be used as quick reference of event):			
Onset Date **(**when event became serious)	**Date investigator/research team became aware of event**	**End date and time (if applicable)**	**OR Duration**
Full description of event/reaction, including body site, reported signs and symptoms:			

Event is defined as serious because it (tick as many as apply): ☐ resulted in death ☐ is/was life-threatening ☐ resulted in persistent or significant disability/incapacity ☐ required hospitalisation ☐ prolonged an ongoing hospitalisation ☐ resulted in a congenital anomaly or birth defect ☐ other – please specify* **Please give further details in Section 5 'Outcome'**		*Specify:	
Maximum intensity if not life threatening or results in death (up until time of initial report)	Mild ☐	Moderate ☐	Severe ☐

To be completed by person filling in the SAE form			
UH Bristol/UoB study reference number		R&I case reference number (R&I use only)	
Subject ID/Initials		Study site:	
		Onset date of SAE	

SAE/SUSAR INITIAL REPORT FORM

Sheet number: _____of _____

Complete Table 4 - if applicable

4. Details of IMP/device/intervention(s) if applicable									
Brand name:	Indication	Batch no.	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	Suspected cause of SAE /SUSAR? (Y/N)
For blinded studies, was the randomisation code broken?		☐	*Yes	☐	No	☐ N/A			
*If yes, give details:									

Continue on new sheet if necessary; please identify how many sheets have been used.

To be completed by person filling in the SAE form			
UH Bristol/UoB study reference number		R&I case reference number (R&I use only)	
Subject ID/Initials		Study site:	
		Onset date of SAE	

SAE/SUSAR INITIAL REPORT FORM

5. Outcome (*further space available in section 10)*				
☐Resolved*	☐ Resolved with sequelae*	☐ Ongoing*	☐ Died* (give cause and post-mortem details if available)	☐ Unknown
*Give details:				
Was the patient withdrawn from the study?		Yes ☐		No ☐
6. Location of (onset of) SAE *(further space available in section 10)*				
Setting (e.g. hospital*, home, GP, nursing home):				
*If SAE occurred on UH Bristol precinct give exact location:				
7. Action taken and further information *(further space available in section 10)*				
Please describe action taken (including details of IMP where applicable e.g. drug withdrawn, clinical investigations, treatment received etc…):				

Other information relevant to assessment of case e.g. medical history, family history, test results, concomitant medication.

8. Causality and Expectedness (to be completed by delegated appropriately qualified individual*)		
Is the SAE related to the drug/device/intervention? ☐ Not related ☐ Unlikely to be related		***In addition to this form, and within 5 days:*** [1]**For unexpected SAEs, if event ongoing, please complete and return all sections of the follow up report form.** [2]**For expected SAEs, if event ongoing, please complete and return sections 1, 2 and 3 of the follow up report form.**
☐ Possibly related* ☐ Probably related* ☐ Definitely related*	***If possibly, probably or definitely related, was the SAE unexpected? ☐ Yes[1] ☐ No[2] (Unexpected means not described in the Reference Safety Information	

9. Sponsor notification (only complete where sponsor is not UH Bristol)	
Has the Sponsor been notified of the SAE/SUSAR?	☐ Yes, give date: ☐ No[+]
[+]***Please note, you must inform the Sponsor within 24 hours of becoming aware of the event.***	

10. Additional information (refer to section number)	
Section no.	Further information

11. Chief/Principal Investigator or delegated appropriately qualified individual* (at this site)		
Name: (please print)		
Job title/role in study:		
Contact address:		
Email address:		
Telephone No:		
Signature:		Date:
I confirm that the contents of this form (pages 1, 2, 3, 4) are accurate and complete		

*** This must be a medically qualified individual if a CTIMP or interventional surgical study**

To be completed by person filling in the SAE form			
UH Bristol/UoB study reference number		R&I case reference number (R&I use only)	
Subject ID/Initials		Study site:	
		Onset date of SAE	

12. Details of person completing this report (if different to CI/PI/delegated other above)		
Name (please print)		
Job title/role in study:		
Contact details		
Signature		**Date:**
I confirm that the contents of this form (pages 1, 2, 3, 4) **are accurate and complete**		

Please tick this box if additional pages have been used: ☐

Number of additional pages used (if applicable): ☐

TMPL_026 SAE/SUSAR <u>FOLLOW UP</u> REPORT FORM

To be completed by person filling in the SAE form			
UH Bristol/UoB study reference number		R&I case reference number (R&I use only)	
Subject ID/Initials		Study site:	
		Onset date of SAE	

1. Further details of SAE/SUSAR				
Event name/ summary (to be used as quick reference of event):				
Further details of event/reaction, including body site, reported signs and symptoms and diagnosis where possible:				
Maximum intensity (up until time of follow up report)	Mild ☐	Moderate ☐	Severe ☐	
2. Outcome				
☐ Resolved*	☐ Resolved with sequelae*	☐ Ongoing*	☐ Patient Died (give cause and post-mortem details if available)	☐ Unknown
*Give details:				
End date and time (where applicable)		OR Duration		

Was the patient withdrawn from the study?	Yes ☐	No ☐

To be completed by person filling in the SAE form			
UH Bristol/UoB study reference number		R&I case reference number (R&I use only)	
Subject ID/Initials		Study site	
		Onset date	

3. Additional action taken and further information since initial report
Please describe further action taken:
Further information or missing data relevant to assessment of case e.g. medical history, family history, test results.

4. Chief/Principal Investigator or delegated appropriately qualified individual* (at this site)		
Name (please print)		
Job title/role in study:		
Contact details		
Signature		**Date:**
I confirm that the contents of this form (pages 1, 2 ± 3) **are accurate and complete**		

*** This must be a medically qualified individual if a CTIMP or interventional surgical study**

5. Details of person completing this report (if different to CI/PI/delegated other above)		
Name (please print)		
Job title/role in study:		
Contact details		
Signature		**Date:**
I confirm that the contents of this form (pages 1, 2 ± 3) **are accurate and complete**		

Continue on new sheet if necessary; please identify how many sheets have been used. ☐

UH Bristol/UoB study reference number		Subject ID/Initials	
Onset date of SAE		Study site:	

SAE/SUSAR FOLLOW UP REPORT FORM

Sheet number: _____of _____

6. STUDY IMP – details of administration. **NB complete for IMP studies only**									
Brand name:	Indication	Batch no.	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	*Or* duration of treatment

For blinded studies, was the randomisation code broken?	☐*Yes	☐No	☐ N/A
*If yes, give details:			

Continue on new sheet if necessary; please identify how many sheets have been used.