TRIAL PROTOCOL

ADMINISTRATIVE INFORMATION

1. Title
A randomised controlled trial to investigate the clinical effectiveness and cost-effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) for depressed non-responders to Increasing Access to Psychological Therapies (IAPT) high-intensity therapies

1.1 Short Title/Acronym
MBCT for IAPT Non-Responders (RESPOND)

2. Trial Registration and trial reference numbers
ClinicalTrials.gov: [trial identifier, date]
ISRCTN: ISRCTN17755571 02/03/2021

IRAS number: 281532
Sponsor's number: 281532
Funder's number: NIHR200750

2.1 World Health Organisation Trial Registration Data Set

Data category	**Information**
Primary registry and trial identifying number	ClinicalTrials.gov [trial identifier, date]
Date of registration in primary registry	TBD
Secondary identifying numbers	ISRCTN ISRCTN17755571 02/03/2021
Source of monetary or material support	National Institute for Health Research (NIHR)
Sponsor	Sussex Partnership NHS Foundation Trust
Contact for public queries	dpt.respond@nhs.net
Contact for scientific queries	Thorsten Barnhofer, t.barnhofer@surrey.ac.uk
Public title	Comparing Mindfulness-Based Cognitive Therapy (MBCT) and Treatment as Usual for Patients who Are Still Suffering from Depression after the End of IAPT High-Intensity Therapy
Scientific title	A randomised controlled trial to investigate the clinical effectiveness and cost-effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) for depressed non-responders to Increasing Access to Psychological Therapies (IAPT) high-intensity therapies

Country of recruitment	England
Health condition or problem studied	Major Depressive Disorder
Interventions	Mindfulness-Based Cognitive Therapy (MBCT) versus treatment as usual (TAU)
Key inclusion and exclusion criteria	Inclusion criteria: 1) non-response to a minimal effective dose of high intensity treatment in IAPT, 2) meeting criteria for a current episode of Major Depression, 3) age 18 or older, and 4) access to a working internet connection to participate in videoconferencing assessments and interventions. Exclusion criteria: 1) eligibility for secondary care specialist services, 2) active suicidal plans, history of psychosis or psychotic symptoms, a current episode of mania, alcohol or substance abuse or dependence within the past 3 months, current post-traumatic stress disorder, obsessive-compulsive disorder or eating disorder, 3) any other significant disease or disorder that may either put the participant at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial, 4) insufficient ability to understand English
Study type	Two-arm, three site randomised controlled trial comparing MBCT and treatment as usual (TAU) with assessment of outcomes at baseline, 10-week and 34-week post-randomisation
Date of first enrolment	TBD
Target sample size	234
Recruitment status	Not yet recruiting
Primary outcome	To investigate clinical effectiveness of MBCT compared to TAU in depressed IAPT non-responders (Patient Health Questionnaire-9 at 34-week follow-up)
Key secondary outcomes	To conduct a cost-utility and cost-effectiveness analysis to provide information on whether MBCT is worthwhile economically (Adult Service Use Schedule and EQ-5D)

3. Protocol version
- Issue date: 11.11.2021
- Protocol amendment: 2.0
- Authors: TB, BD, MR, CS, BB, FR, AY, FW

3.1 Revision chronology:
- Version 00 (09.07.2020) Original

- Version 01 (14.10.2020) Changes due to adaptation of study plan:

- Primary reason for amendment: Assessments and therapy sessions to be conducted remotely via videoconferencing or telephone to adapt to demands of Covid-19 pandemic
- Additional changes (these changes in and of themselves would not justify a protocol amendment): No additional changes

- Version 01.1 (20.12.2020) Updates incorporating requests from Ethical Review
  - Primary reason for changes: Plan to contact potential participants after 14 days was not acceptable to REC and has been deleted.

- Version 01.2 (22.01.2021) Updates incorporating responses to HRA queries
  - Primary reason for changes: In order to incorporate HRA requests, data management plan has been updated to clearly state that only data without personal information will be stored over 10 years and to describe procedures for keeping contact details of patients willing to be contacted for future research. We also make explicit that audio files from qualitative interviews will be destroyed after transcription.

- Version 01.3 (11.02.2021) Minor Amendment 01
  - Primary reason for changes: Exclusion criteria now include current post-traumatic stress disorder, obsessive-compulsive disorder and eating disorder. Structured clinical interview has been changed from SCID to MINI.

- Version 01.4 (20.04.2021) Substantial Amendment 01
  - Primary reasons for changes: Offer of online mindfulness course for TAU participants has been removed. Risk procedures and definitions of adverse events are specified in additional detail in section 22. 'Harms'. Four-week limitation of time window for baseline testing has been removed. Change in section 19 'Data management' from "double" to single entry of data. Deleted reference to locked filing cabinets in sections 19. 'Data management' and 27. 'Confidentiality'. Specification of group size for MBCT groups has been changed to state range rather that single target number. Trial manager, TSC and DMEC member contacts are now included in the protocol. Tasks of the TSC and DMEC are now defined in more detail. Upper limit of age restrictions has been removed to align the study with practice of IAPT services. Added detail to exclusion criterion 'current psychological treatment' to clarify that this applies only to the time up to entry into the study. Removed redundant information from section 11.2 'Criteria for discontinuation', widened exclusion criterion 'severe medical illness' to include all conditions that may represent risk or undermine participation.

- Version 01.5 (12.05.2021) Substantial Amendment 02
  Changes: Monitoring of non-serious adverse events in section 22. 'Harms' deleted.

- Version 01.6 (05.07.2021) Substantial Amendment 03
  Changes: Reintroduced the option to recontact potential participants who had not responded to an initial email regarding participation in the trial within 14 days. Introduced split of eligibility and baseline assessment in sections 13. 'Participant timeline' and 15. 'Recruitment'. Eligibility interviews will be conducted as soon as possible after contact and baseline questionnaire assessments will be conducted within a window of four weeks before randomisation

- Versions 01.6– 2.0 (11.11.2021) Substantial Amendment 04
- Changes: Requested by TSC/IDMC and discussed at the second meeting of the committees on 07.09.2021including new members of TSC and IDMC, specified tasks of senior statistician and trial statistician, described characteristics required of PIC sites in sections 9. 'Study setting' and 15. 'Recruitment', removed exclusion criterion 2 "receiving individual psychotherapy or counselling from other sources" in section 10. 'Eligibility criteria', specified additional binarised outcomes in section 12. 'Outcomes', detailed means of contacting participants in case of non-response to initial invitation to complete follow-up assessments in section 13. 'Participant

timeline', specified assessment of treatment history with antidepressants as part of MINI interview in section 18. 'Data collection methods', included additional sensitivity analyses in section 20. 'Statistical Methods', and included monitoring of attrition in section 14. 'Sample size'. Update of section 21. 'Trial governance and data Monitoring' to include complete information on TSC/IDMC membership, update of section 22. 'Harms' to describe risk management and SAE reporting in more detail.

4. Funding

This trial is funded through the Research for Patient Benefit (RfPB) Programme of the National Institute for Health Research (NIHR), Central Commissioning Facility, Grange House, 15 Church Street, Twickenham TW1 3NL in the UK (£349,852 Research Costs; £22,930 NHS Support and Treatment Costs). The funders number for this trial is NIHR200750.

5. Roles and responsibilities

5.1 Names, affiliations, roles of protocol contributors, and other key trial contacts

Names, affiliations of protocol contributors

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Roles

TB, BD, and MR conceived of the study and TB drafted the trial application and protocol. TB, BD, MR, CS, BB, FW, and AY initiated the study design and FR helped with implementation. TB, BD, CS, BB, FR MR, FW, and AY are grant holders. FW provided statistical expertise in clinical trial design and analysis and will lead the statistical analyses. BB provided expertise in health-economic analyses and will lead on health economic analyses. Co-applicant, and PPI representative, MR, has

been involved in all stages of the development of the protocol and the grant application to the NIHR. TB drafted the amendment of the protocol (version 01) to accommodate videoconferencing delivery of therapy sessions and assessments in order to comply with restrictions due to the Covid-19 pandemic. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Other key trial contacts

Clinical Trials Unit
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Trial Steering Committee
Prof David M. Clark, University of Oxford, Oxford Centre for Anxiety Disorders and Trauma, The Old Rectory, Paradise Square, Oxford, OX1 1TW, phone: 01865 2811607, email: david.clark@psy.ox.ac.uk (Head of the Trial Steering Committee)

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Daniel Elton, danielelton@me.com (Patient Representative)

Independent Data Monitoring Committee

Prof Dean McMillan, Centre for Health and Population Sciences, University of York, phone: 01904 321359, email: dean.mcmillan@york.ac.uk (Head of the Independent Data Monitoring Committee)

Mr Nicholas Turner, Bristol Trials Centre, Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, phone: 0117 3314562, email: nicholas.turner@bristol.ac.uk (Independent Statistician)

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5.2 Name and contact information for trial sponsor
Trial Sponsor: Sussex Partnership NHS Foundation Trust
Sponsor's reference: TBD
Contact name: Ms Taffy Bakasa
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R&D Department
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5.3 Role of study sponsors and funders
The trial sponsor has ultimate authority over the management of the study.

Neither the funder nor the sponsor of the trial was involved in the design of the study and will not be involved in the collection, analysis or interpretation of data or the writing of the study report. The funder will be required to approve the final report prior to publication.

5.4 Roles and responsibilities-committees

Chief investigator and trial manager
The Chief Investigator (CI) will assume responsibility for the overall management of the trial and delivery of the work. The CI will lead the core research team (including all site leads, the trial manager, and research assistants), who will meet monthly via teleconference and receive input from the wider research group and representatives of the Patient Advisory Group at quarterly Trial Management Group meetings.

- Design and conduct of the trial
- Preparation of protocol and amendments
- Preparation of trial handbook and CRFs
- Lead core research team (including all site leads, the trial manager, and research assistants)
- Organising Trial Steering and Data Monitoring and Ethics Committee Meeting
- Managing the clinical trials office
- Writing and publication of study reports
- Participation in Patient Advisory Group Meetings
- Members of Trial Management Group

Trial Management Group
The Trial Management Group will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial.

- Study planning and monitoring
- Organisation of steering committee meetings
- Providing annual reports
- Budget administration and contractual issues with individual sites
- Liaising with CTU regarding randomisation, data verification, and trial master file

Trial Steering Committee
The group will be supplemented by half-yearly meetings of the TSC and IDMC. The TSC will be chaired by Prof David Clark (University of Oxford). The role of the TSC, which in addition to the independent chair will consist of at least two other independent members (Prof Anne Speckens, Dr Sean Ewings, Prof Steve Pilling, Dr Judy Leibowitz, Daniel Elton), including an independent patient representative, will be to provide critical scrutiny to the conduct of the proposed research and send reports to the sponsor.

- Provide overall supervision for the trial
- Monitor trial progress and conduct
- Advise on scientific credibility
- Consider and act upon the recommendations of the Independent Data Monitoring Committee (IDMC)

Independent Data Monitoring Committee

An IDMC consisting of a Chair (Prof Dean McMillan), an expert clinician (Dr Tim Sweeney) and an independent statistician (Mr Nicholas Turner) will monitor recruitment and data, to see immediately all serious adverse events thought to be treatment-related, and look at outcomes regularly in order to make recommendations to the TSC. The senior trial statistician will prepare IDMC reports and will attend IDMC meetings.

- Assess, at intervals, the progress of the trial, and the safety data
- Assess potential serious protocol infringements and recommend to the TSC whether to continue, modify, or stop the trial

Clinical Trials Unit
The clinical trials unit will be responsible for elements of the study data management including the design of case report forms (eCRFs/CRFs) and database, processing, coding and analysing study data. Data verification and cleaning will be supported by the Trial Manager, Research Assistants and statistical team.

Site leads (Principal Investigators)
The site leads will oversee recruitment, data collection and entry, and take responsibility for adherence to study protocols and the study handbook at their site. They will be part of the Trial Management Group.

- Oversee recruitment, data collection and entry at the respective site
- Take responsibility for adherence to study protocols and the study handbook
- Participation in Trial Management Group and Core Research Group meetings

Health Economists
The health economists will take responsibility for setting up assessments of service use data and health-related quality of life outcomes, data verification, and the conducting of health economic analyses and their report. They will participate in Trial Management Group Meetings.

- Setting up assessments of service use data and global health outcomes
- Data verification
- Conducting health economic analyses
- Participation in Trial Management Group Meetings

Trial Statisticians
The senior trial statistician will oversee development of the statistical analysis plan and lead the statistical analyses of the trial data. The senior trial statistician, Fiona Walker, and trial statistician, Sarah Walker, will perform data analysis.

- Develop the statistical analysis plan
- Lead the statistical analyses
- Participate in Trial Management Group Meetings

The senior trial statistician will be aware of treatment allocations and will prepare reports for the IDMC disaggregated by group. The trial statistician will be unaware of treatment allocations until after completion of analyses.

Patient Advisory Group
The Patient Advisory Group will meet quarterly during the project to advise on all aspects of the project of relevance to the experience of patients during the trial. The lead of the group has been involved in protocol development. The group will provide input on the design of relevant patient-facing documents including information leaflets and consent forms and will review risk management procedures. The patient advisory group will also contribute to the dissemination strategy.

- Advise on all aspects of the project of relevance to the experience of patients
- Contribute to protocol development
- Provide input on the design of patient-facing documents
- Review risk management procedures
- Contribute to dissemination strategy

INTRODUCTION

6. Background and rationale

Major Depression represents a pressing challenge for health care. The disorder is not only highly prevalent – 10.9% of the adult population in England suffered from an episode of depression in 2014 [1] – but also shows many characteristics of a progressive disease: if left untreated it tends to become more recurrent and chronic over time [2], with even residual levels of symptoms conferring a significantly increased risk for future relapse [3]. There is evidence for functional decline as the disorder accelerates [4], and physiological changes underlying its progression have been linked with a significantly increased risk for a broad range of physical and neurodegenerative disorders [5].

In order to address this challenge, it is imperative to provide treatments that effectively reduce symptoms in those who are affected, and thus to prevent progression into increasingly recurrent or chronic courses. Although there is still a significant unmet need, recent progress in providing access to treatment has been encouraging: while in 2000 only 23% of adults with symptoms of common mental health problems received some kind of treatment, this proportion increased to 37% in 2014 [1]. To a significant degree, this increase is due to the introduction of Improving Access to Psychological Therapies (IAPT) services, which were established with the express aim of providing patients with evidence-based psychological treatments in a timely manner. IAPT uses a stepped care approach, with those not responding to low-intensity treatment or greater complexity receiving high-intensity treatment. In 2016, IAPT services offered treatment to over 900,000 people, an access rate of 15% of the population. According to the Five Year Forward View for Mental Health published by the Mental Health Taskforce to the NHS, this number is intended to rise to at least 1.5 million adults by 2020/2021, an access rate of 25% of the population [6].

However, while the introduction of IAPT is successfully increasing access to psychological therapies, outcome reports indicate that about 50% of the depressed patients who have completed high-intensity evidence-based psychological therapies within IAPT do not reach recovery and continue to show significant levels of symptoms. Of the 203,013 patients who entered IAPT high-intensity therapy with a diagnosis of depression in 2015-16, more than 100,000 continued to show symptoms on clinical levels [7]. At the same time, progression to secondary care remains reserved for those with complex depression and high risk for suicidality. Data from the “Predicting Outcome Following Psychological Therapy in IAPT (PROMPT)” study show that of those who do not respond only 8% receive secondary care interventions [8,9], while the remainder are currently not offered any further-line treatment. Most of these patients are sent back to their GPs, who are likely to prescribe antidepressant medication. Yet, the majority of IAPT non-responders are already receiving medications [8,9]. There is a considerable gap in service provision for patients who do not respond sufficiently to high intensity evidence-based psychological therapies – a problem that is likely to come into focus even further as numbers of patients accessing IAPT are increasing.

Mindfulness-Based Cognitive Therapy (MBCT) [10], an eight-week, group-based intervention that combines intensive training in mindfulness and elements from cognitive therapy for depression, may be particularly suited for addressing this gap. While originally developed, and NICE-recommended, for the prevention of relapse in remitted patients with a history of recurrent depression, recent research has brought promising evidence that MBCT can have significant beneficial effects in patients with acute and more persistent forms of the disorder [11,12], and particularly in those who have not

responded to previous interventions [13]. In a large definitive RCT in patients who had not responded to antidepressants, Eisendrath et al. [13] found a statistically significant advantage of MBCT over a rigorous psychological control treatment on depression symptomatology, d=.32, an effect size in the small to medium range. In a smaller scale RCT, also in patients who had not responded to antidepressants, Chiesa et al. [14] reported a statistically significant benefit for MBCT relative to attention-placebo on depression symptomatology, d=.79, an effect size in the medium to large range. A further smaller scale RCT investigating the effects of MBCT in chronically depressed patients who had not responded to antidepressants has shown a statistically significant advantage on depressive symptomatology compared to treatment as usual, d=.35 [15]. However, evidence is currently not sufficient to warrant guideline endorsement for use as a further-line treatment, which is a necessary prerequisite for implementation within the evidence-based IAPT pathway.

The current trial will constitute a second definitive trial of MBCT as a further-line treatment and would thus provide an important step towards a sufficient evidence base. Furthermore, it will constitute the first trial to test MBCT following non-response to psychological therapy with results providing a direct estimate of efficacy within the IAPT pathway. If successful, the proposed research would provide the evidence necessary for adoption of MBCT for non-responders within IAPT and would thus justify the use of an easy to implement and much needed treatment option for a considerable proportion of patients who are currently not receiving sufficient support.

MBCT offers a number of advantages for addressing more persistent courses of depression. Mindfulness training is specifically aimed at helping patients become better at recognizing and disengaging from habitual and automatic maladaptive patterns of thinking. Research indicates that, through such 'decentering', the practice helps to prevent the spiralling of negative mood [16]. The training provides patients with sustainable skills that remain accessible to them after the end of the intervention, with recent evidence suggesting that 'decentering' skills further improve as patients continue using mindfulness practices following the end of the intervention [17]. MBCT might thus serve to effectively reduce symptoms [11,12] as well as keep people well for the longer term [18]. Because of its group-based format and emphasis on training skills, the intervention is particularly suited for alternative forms of delivery such as videoconferencing.

In order to provide evidence that, if positive, would be sufficient to enable a change in IAPT practice, we shall compare MBCT as delivered via videoconferencing to treatment-as-usual (TAU) in IAPT high-intensity treatment non-responders in a definitive clinical trial. TAU was chosen as comparator as it is reflective of the current state of care. We shall test the immediate effects of the intervention on depressive symptomatology as well as whether effects on symptomatology can be sustained over a period of six months, thus taking into account the high risk of relapse in early stages following treatment. In addition to testing clinical effectiveness, we shall measure service use and collect information on quality of life in order to provide information on the cost effectiveness of the intervention in IAPT high-intensity treatment non-responders. Previous research has suggested that MBCT for relapse prevention is broadly comparable to maintenance antidepressant use with an estimated cost for group attendance in person of £112 per group participant [19] with these costs likely to be lower when delivering the intervention via remote formats such as videoconferencing. However, data on the economic effects of outcome in IAPT non-responders would be needed in order to guide decisions on implementation in this particular group.

7. Objectives

Aims:

(a) To establish the clinical effectiveness in terms of reductions in depressive symptomatology and (b) cost-effectiveness of MBCT as a psychotherapeutic treatment option compared with TAU for depressed patients who have not responded sufficiently to high intensity evidence-based treatments within the IAPT care pathway.

Objectives:

(a) To undertake a definitive randomised controlled trial (RCT) of the MBCT intervention versus TAU to confirm clinical effectiveness of the treatment in depressed non-responders to high-intensity evidence-based treatments within the IAPT care pathway, and
(b) to use the data from the RCT to conduct a cost-utility and cost-effectiveness analysis to provide information on whether or not the MBCT intervention is worthwhile economically.

Hypotheses:
We hypothesise that participants who receive MBCT will
(a) show significantly stronger reductions in depressive symptomatology than participants who receive TAU both at 10 weeks post-randomisation (post-treatment; secondary outcome) and at 34 weeks post-randomisation (primary outcome) and
(b) that the MBCT intervention will be cost-effective either in terms of reductions in costs elsewhere in the health system or in improvements in outcomes at 34 weeks post-randomisation.

Qualitative analyses will investigate acceptability and implementability of MBCT taking into account the particular type of delivery format chosen.

8. Trial Design
We will randomise 234 patients who have not responded to high-intensity IAPT interventions for depression, but do not meet eligibility criteria for secondary care services, in a 2-arm trial to receive MBCT or to continue with TAU, providing a comparator that is reflective of the current state of care (and in most cases will entail continued use of antidepressant medication). We will measure outcomes at baseline, 10-week and 34-week follow-up post-randomisation. Economic analyses will investigate effects of the interventions on subsequent service use and health-related quality of life.

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

9. Study Setting
The study will be conducted at three research sites in the UK: at the Sussex Mindfulness Centre, Sussex Partnership Trust, where we will be working in collaboration with the University of Surrey, the Mood Disorders Centre at the University of Exeter and the Centre for Affective Disorders at King's College London, Institute of Psychiatry, Psychology & Neuroscience. Assessments will be conducted remotely, using videoconferencing, telephone and links to web-based questionnaires, by researchers at the three research sites. Data management will be provided by the Exeter Clinical Trials Unit at the University of Exeter. Treatments will be delivered via videoconferencing by therapists at the Centre for Affective Disorders, King's College, London, where we will be working in collaboration with the Maudsley Mindfulness Service and South London and Maudsley (SLaM) IAPT services, at Sussex Mindfulness Centre, where we will be working in collaboration with Sussex Partnership Foundation Trust and Sussex Community Trust IAPT services, and at the AccEPT Clinic, Mood Disorders Centre, University of Exeter, where will be working in collaboration with the Devon Partnership Trust IAPT service. The research sites will include further patient identification centres (PICs) where needed and helpful. Potential PICs will need to be able to recruit a considerable number of patients and in terms of their organisational features should not show outlier characteristics (for more detail see section 15. Recruitment).

10. Eligibility criteria
We will recruit depressed treatment non-responders to IAPT high intensity treatments into the study.
Inclusion criteria will be
1) non-response to a minimal effective dose of high intensity treatment for depression (primary presenting problem) in IAPT (at least 12 sessions, in line with NICE draft guideline suggestions) defined in line with the caseness threshold adopted by IAPT as a Patient Health Questionnaire-9 (PHQ-9) [20] score of 10 or higher,

2) meeting criteria for a current episode of Major Depression according to DSM-5 as assessed through the Mini International Neuropsychiatric Interview for DSM-5 (MINI 7.0.2) [21] along with a current PHQ-9 score of 10 or higher,
3) age 18 or older
4) access to a working internet connection to participate in videoconferencing assessments and interventions.

According to the IAPT database, the majority of patients who receive high intensity psychological treatment will also have received treatment with antidepressant medication, and most of these patients will therefore meet consensus criteria for treatment resistance. We will compare the sociodemographic characteristics of our sample against the characteristics of the wider group of people attending the collaborating IAPT services in order to judge representativeness of the sample.

Potential participants will be ***excluded*** if
1) based on the judgment of their IAPT therapist they are eligible for, would be seen by, and their needs would be best met by secondary care specialist services,
2) they present with a level of risk to self or others that cannot be safely managed in a primary care service context (i.e. active suicidal plans), a history of psychosis or psychotic symptoms, a current episode of mania, alcohol or substance abuse or dependence within the past 3 months, current post-traumatic stress disorder, obsessive-compulsive disorder or eating disorder,
4) they suffer from any other significant disease or disorder that may either put the participant at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial, or
5) if they have an insufficient ability to understand or read English.

Patients who are currently taking antidepressant medication will be allowed into the trial and medication use will be documented for statistical analysis. Medication use will be included as a stratification variable.

11. Interventions
Participants will be allocated to receive either MBCT or TAU in a 1:1 ratio.

11.1 Interventions for each group
MBCT combines mindfulness training with elements from cognitive therapy. We will follow the treatment manual with minor adaptations to address the fact that patients are suffering from current symptoms of depression following practice from our previous research [11,12]. The intervention will be delivered by trained MBCT therapists together with an assistant to groups with a target size of 13 patients (minimum 8 and maximum of 16) using videoconferencing on a secure online platform. This will allow participants to attend sessions through internet connection from their home or another place of their choosing. All three sites have prior experience with delivering MBCT in this format and will follow shared internal guidelines for videoconferencing delivery. All therapists will meet qualifications in line with Good Practice Guidelines and competency level 'proficient' on the MBCT Therapy Pathway. Therapists will be selected based on ratings on the MBI-TAC and receive a one-day workshop to familiarise them with the modifications of the programme necessary for use with currently depressed patients. Manual adherence and treatment fidelity will be monitored using methods established in our previous trials using the MBCT Adherence Scale [22] and MBI-TAC [23] based on the recordings of the online intervention sessions. MBCT consists of eight weekly group-based sessions and participants are asked to engage in home practice for about an hour per day using guided meditation audio recordings, with attendance and practice monitored following previously established practices. As the intervention is delivered online it will be possible for participants recruited at different sites to attend a given MBCT course. We will offer access to an online MBCT course run by therapists at a centre different from the one where the participant has been recruited, if it is deemed helpful in order to respond to demands of recruitment and time preferences by participants and provided that risk management procedures remain unaffected. In these cases,

assessments will continue to be conducted by the site where the participant has been recruited and we will require information about local emergency contacts to be in place and provided to the therapist of the group.

Participants in the TAU condition will be asked to continue with their usual care and follow the regimens suggested by their GP or mental health professional, which in most cases will consist of continuing use of antidepressant medication. Following previous practice in our trials [18], TAU participants will be invited to an interview to prevent tendencies towards 'resentful demoralisation' and highlight the importance of their contribution. As the pre-class interview for the MBCT courses, this interview will be conducted via videoconferencing.

11.2 Criteria for discontinuing or modifying allocated interventions for a given trial participant
Participants are free to withdraw their participation at any point. If a participant in either arm indicates that they wish to discontinue the trial they will not be contacted further by the research team, other than to invite them to take part in a brief written survey to ascertain their reasons for not taking part. In the MBCT arm of the trial, different levels of discontinuation are possible. A participant may discontinue therapy but remain in the trial, or they may discontinue the trial. In order to enable intention to treat analyses, we will still ask participants who opt to discontinue therapy at any point to take part in assessments, should they be willing to contribute to the research in this way.

Consideration will be given to whether it is in the participant's interests to continue or discontinue trial treatment in the event of a serious adverse reaction. If the participant, the therapist, or the research team believes that ongoing intervention or trial participation will result in, or is likely to result in, a further or ongoing serious adverse reaction, discontinuation will be recommended. Should an unexpected serious adverse reaction occur to either the therapy or the trial procedures, and if this is judged to be directly related to trial participation or to the therapy, the trial will be temporarily halted pending investigation and analysis of the extent to which future risk can be mitigated. If it is judged that this is not possible, the trial will be discontinued. This process will be led by the sponsor in collaboration with the TSC chair and chief investigator. The same process will be followed should information come to light that indicates that the therapy intervention or trial procedures are unsafe.

11.3 Strategies to improve adherence to intervention protocols
Individual interviews at the beginning of the MBCT treatment phase will serve to reinforce the rationale of the research, highlight the importance of practice and address potential barriers to engagement. Participants allocated to continue with treatment as usual will take part in an interview that will serve to reinforce their understanding of the importance of their contribution to the research and prevent tendencies towards 'resentful demoralisation'. We will offer support to help patients to familiarise themselves with the technical aspects of videoconferencing.

11.4 Relevant concomitant care and interventions that are permitted or prohibited
Patients who are currently taking antidepressant medication will be allowed into the trial and medication use will be documented for statistical analysis. All patients will be encouraged to continue treatments as usual.

12. Outcomes
Primary outcome: The primary clinical outcome will be reductions in depression symptomatology as assessed using the PHQ-9 [20]. The primary timepoint for outcome measures will be 34 weeks post-randomisation. Hence, the primary outcome will be PHQ-9 scores at 34-week follow-up (consistent with end-of-treatment monitoring in IAPT).
Secondary outcomes: Secondary outcomes include PHQ-9 measured at 10 weeks post-randomisation, and other clinical outcomes measured at 10-week and 34-week follow-up. The PHQ-9 is a widely used self-report measure of depression that represents an integral part of the management of depression in the IAPT pathway and has good psychometric properties. The authors report a test-retest reliability of .84 over a period of 48 hours [20]. Other clinical secondary outcome measures will

include the Generalized Anxiety Disorder Questionnaire (GAD-7) [25], the Phobia Scale and the Work and Social Adjustment Scale, all from the IAPT minimum data set (IAPT Toolkit, 2008/9), along with the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [26], Experiences Questionnaire (EQ) Decentering Scale [27] and Five Factor Mindfulness Questionnaire (FFMQ) [28]. A series of binarised outcomes will be derived, based on PHQ-9 and/or GAD-7. Recovery, reliable recovery, and reliable improvement will be reported using (i) PHQ-9 only to align with depression research literature; and (ii) both PHQ-9 and GAD-7, to align with IAPT practice. We will also report deterioration and reliable deterioration with regard to PHQ-9 and GAD-7 separately. We will also track symptoms weekly using the PHQ-9, GAD-7, Phobia Scale and the Work and Social Adjustment Scale.

Baseline survey: Participant characteristics assessed as part of the MINI interview will allow us to make comparisons between eligible patients who declined to participate, and those patients who participated in the trial.

Economic evaluation: The economic evaluation will take a health and social care perspective, as required for evidence presented to NICE. In addition, the cost perspective will be broadened to include the costs of time off productivity losses, since these are known to be relevant and important in those attending IAPT services [29].
Costs will be calculated by collecting service use information using the Adult Service Use Schedule (AD-SUS), a self-report measure developed by the team at King's College and used in previous trials of MBCT [19], modified for use online, to which routine unit costs will be applied [30]. We will collect data on all service use not just use related to mental health conditions, because there is evidence that successful treatment in IAPT can reduce use of all healthcare services [31]. In addition, comparison via randomised groups will ensure that any differences in cost are due to the impact of the MBCT intervention. Information on TAU will be collected via the AD-SUS, modified to ensure that all relevant services are included. Data on the use of the MBCT intervention will be collected via therapist records and costs estimated using the standard approach set out by Curtis [30], acknowledging the challenges of costing group-based interventions [32]. Outcomes for the economic evaluation will be QALYs, calculated using health utilities derived from the EQ-5D-5L [33,34]. Costs and outcomes will be combined first in a cost-utility analysis using QALYS and second in a cost-effectiveness analysis using the PHQ-9, providing information on whether or not MBCT is worthwhile in terms of costs savings elsewhere or improvements in outcomes, and information will be provided to decision makers with statistical analysis of differences in costs, cost-effectiveness planes and cost-effectiveness acceptability curves [35].

Qualitative Analyses: Qualitative analyses will be used to explore patient experience of the intervention and to understand how the treatment might best benefit patients in the IAPT pathway. Previous trials have shown considerable variation in the degree to which patients engage in mindfulness practice [13] and a major focus of the qualitative analyses will therefore be on factors influencing such engagement and its relation with dynamics of change. For this purpose, we will investigate: 1) patients' views on acceptability of MBCT and mindfulness practice, and the experience of participating in the course remotely, 2) patients' views of the changes they experience and their utilisation of mindfulness skills, and 3) patients' views of the broader impact of MBCT on their lives. A subsample of participants in the MBCT arm, estimated to be 24 (or until data saturation has been reached), will be invited to a qualitative telephone interview conducted by trained research assistants. Recruitment will be purposive, including patients across all sites, and seeking to achieve maximum variation in relation to: 1) completion/non-completion of treatment, 2) response/non-response to treatment, and 3) recruitment site (to examine contextual factors).
Written feedback provided in the protocol sheets that MBCT participants receive on a weekly basis will be used to inform subsampling and will also provide us with the opportunity to explore any unanticipated experiences and effects in more depth. In collaboration with service users, we will develop, and pilot test, a semi-structured topic guide based on the above aims. Interviews will be video-recorded, transcribed verbatim, and anonymised. Thematic analysis of interview transcripts will

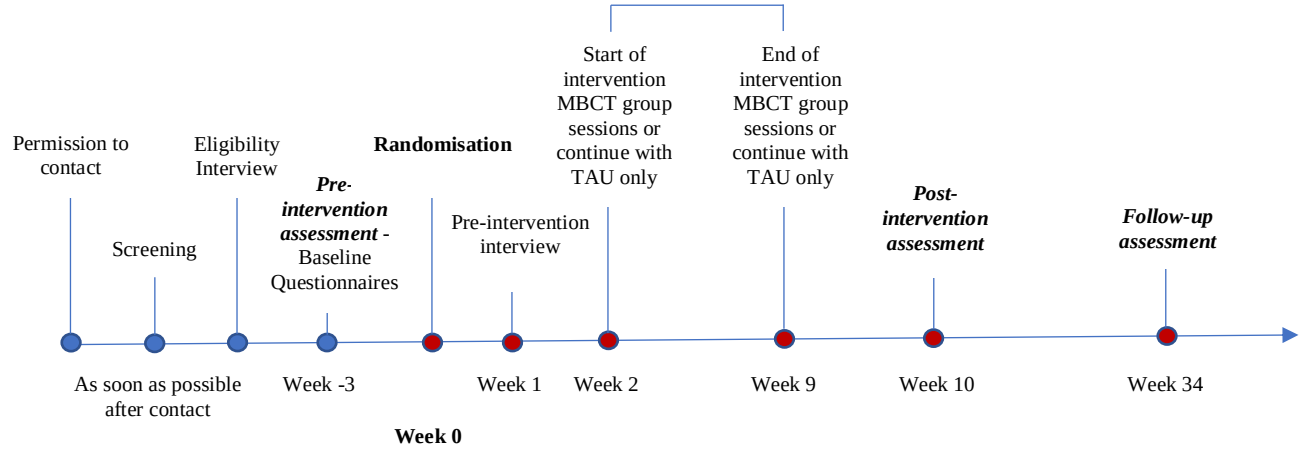
be conducted using a Framework approach [36], involving the coding and sorting of textual units according to both deductive and inductively-derived categories, and the use of matrices to review the coded data, investigate commonalities and differences and search for patterns. Coding and data management will be facilitated by NVivo software.

	STUDY PERIOD			
	Enrolment	Allocation	Post-allocation	
TIMEPOINT	*-12 to 0 weeks*	*0*	*10*	*34*
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Completion of baseline measures	X			
Allocation		X		
Follow-up assessments			X	X
Qualitative interviews			X	
INTERVENTIONS:				
MBCT		⟷	⟷	
TAU		⟷	⟷	
ASSESSMENTS:				
Clinical interview *(MINI)*	X			
Symptom measures *(PHQ-9, GAD-7, Phobia Scale, Work and Social Adjustment, WEMWBS)*	X		X	X
Process measures *(EQ Decentering, FFMQ)*	X		X	X
Health economic measures *(AD-SUS, EQ-5D)*	X		X	X
Adverse effects measure *(NEQ week 6 and 10)*			X	
Weekly tracking *(PHQ-9 weeks 2-10)*			X	

Fig. 1 Schedule of enrolment, interventions, and assessments (displayed according to Standard Protocol Items: Recommendations for Interventional Trials [SPIRIT] template).

13. Participant timeline

Interested participants will undergo screening using a brief structured telephone interview conducted by the research assistant. Potential participants will be invited for an initial assessment session to be conducted via videoconferencing to ascertain eligibility using structured clinical interviews conducted by the research assistant and assess baseline levels of symptoms (baseline assessment). Eligibility interviews will be conducted as soon as possible after the screening. Baseline questionnaire assessments will be conducted within a window of three weeks before randomisation. Participants will be randomly allocated and learn about group assignment at least a week preceding the pre-intervention interviews held with both groups. After the 9-week treatment delivery period, participants will be assessed again at 10 weeks, and 34 weeks post-randomisation. Patients will be asked to complete the follow-up assessments within a one-week window and prompted weekly using phone, text, or email for up to four weeks, if not responsive. Patients are free to receive their usual care through the NHS while they wait to start MBCT.



14. Sample Size

Following previous suggestions for defining successful treatment outcome in depression [37], the study will be powered to enable detection of a Minimal Clinically Important Difference (MCID) [24]. Using a criterion of one standard error of measurement (38), the MCID for our primary outcome measure (PHQ-9) has been estimated to range from 2.59 under best-case reliability scenarios to 4.78 under worst-case reliability scenarios [38]. In order to detect an MCID at the smaller end of this range (2.59) using a standard deviation of 5.4 (as reported for the baseline data in the clinical trial that served to estimate the above listed range of MCIDs in [39]), with 90% power at an alpha level of .05, 186 participants are required. In our previous large-scale multi-centre trial of MBCT for patients with a history of recurrent suicidal depression, 93% of participants provided follow-up data over a one-year follow-up period [18]. Considering a rate of attrition of 20%, conservatively estimated to be above that observed in our previous research, we will recruit a total sample of 234 participants (117 in each arm, 78 per site). As currently available research suggests that trials using remote delivery generally show comparable or even lower rates of attrition, we would expect this estimate to be transferable to the use of videoconferencing delivery [40]. The research team will monitor attrition at regular milestones during the trial (e.g. at the point where 50% of participants have reached their scheduled 6-month follow-up time) and consider remedial steps to increase sample size, if this is needed. We have not inflated the sample size to take account of clustering within treatment groups, as reanalyses of previous trials of MBCT have found intra-class correlations (ICCs) for primary outcomes to be negligible [41].

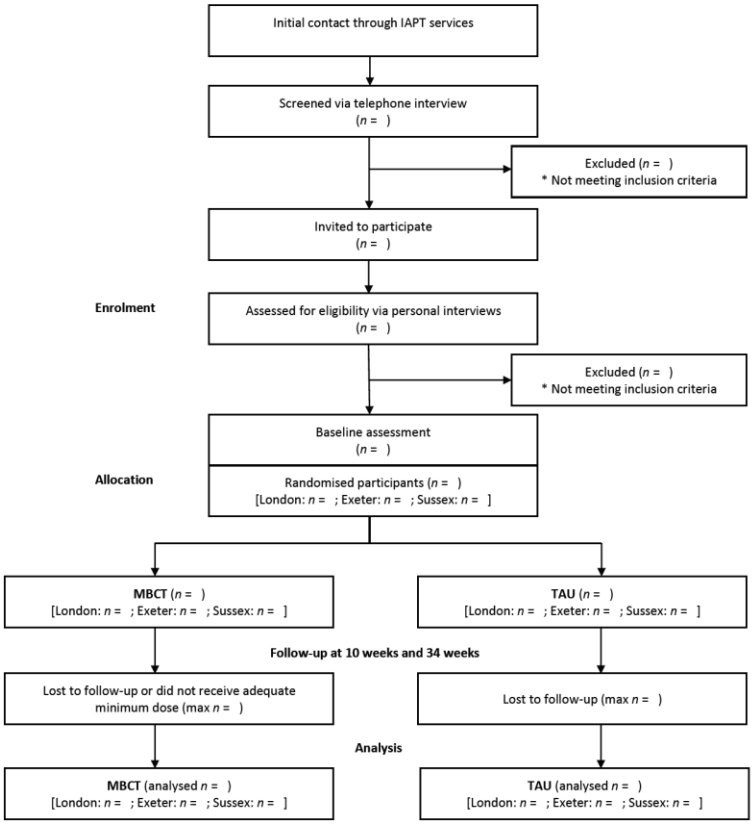


Fig. 2 CONSORT diagram describing flow of participants through the study.

15. Recruitment

Participating IAPT services will identify patients who are coming to the end of their high-intensity treatment and have not responded (PHQ-9≥10) or patients who within a 6-month window following the end of high-intensity therapy show levels of symptoms above caseness without prior remission. Data from the IAPT services originally listed as collaborators in our grant proposal indicated that we would be recruiting from a pool of more than 7500 non-responders per year. Remote delivery of the intervention will allow us to reach an even wider potential pool of participants and allow inclusion of further IAPT services given that participation in the treatment will not be restricted to people within the geographical regions of the sites. The research team will include further IAPT services as patient identification centres (PIC) to work together with the three research sites. As IAPT services can differ widely in their characteristics and organisational features of IAPT services have been shown to explain considerable variance in their outcomes (Clark et al., 2018), we will only include services that can provide a considerable number of participants and make sure that collaborating services do not show outlier characteristics. As a general rule, services included as PIC sites will have to have recovery rates above 45% and should have a percentage of IAPT therapists of more than 40%. A short participant information sheet together with a 'Permission for Researcher to Contact Form' will be sent electronically to potential participants either via email or post (in the latter case together with a stamped addressed envelope for their response). Potential participants will be invited to either contact the research team directly or send the completed 'Permission for Researcher to Contact Form' so that the researchers can contact the potential participant. If potential participants do not return the form within 14 days, they will be contacted via email, telephone or text message by service administrators, IAPT staff, or Research Network Clinical Studies Officers to check whether they have received the letter and asking them if they wish to participate in the trial. In all cases, we will follow procedures that are in line with the policy of the respective trust as covered in the GDPR statement signed by each patient and will respect any opt outs that the trust may have received via national or other routes.

Patients who are potentially interested in taking part will be contacted by the researchers for an initial screening to confirm presence of symptoms and history of high-intensity treatment for depression, and to provide further information on the research. If positive on the screen, potential participants will be invited to take part in a structured clinical interview conducted via videoconferencing to confirm eligibility and, if eligible, to complete baseline assessments by completing web-based questionnaires. Clinical interviews will be conducted as soon as possible after initial contact and screening, while baseline questionnaire assessments will take place within a window of four weeks before randomisation. The invitation for this assessment will include the patient information sheet (PIS) and informed consent will be taken before the start of the assessment by asking participants to sign and return the consent form electronically. Eligible, fully informed and consenting participants will then be entered into the study and randomisation (see Figure 2).

METHODS: ASSIGNMENT OF INTERVENTIONS

16. Allocation

We will allocate individual participants to either MBCT or TAU at a ratio of 1:1 through remote randomisation at the UKCRC-registered Exeter Clinical Trials Unit (ExeCTU), following informed consent, completion of baseline assessment and enrolment in the trial. Randomisation will use minimisation on depression severity (PHQ-9<19 versus ≥19), antidepressant use at baseline and recruitment site. Use of a validated password website will ensure concealment. Participants will be informed of their allocation by an unblinded member of the research team.

17. Blinding

As baseline assessment of participants is carried out prior to randomisation, there is no risk of disclosure of treatment allocation to the assessor at the time. Use of remote assessments, initiated through automated email, will rule out any potential effects of assessors on assessments of outcomes at 10-week and 34-week follow-ups. The statistician analysing outcome data will remain blind to treatment allocation throughout the analysis, which will be conducted with groups indicated by an anonymised code.

In the unlikely event that a participant has an adverse reaction to either treatment arm, unblinding may be necessary. We will unblind researchers only when knowledge of the treatment arm is deemed essential to the management of the patient by their GP. Any unblinding will be recorded, although we do not expect any biasing influences on follow-up assessments given that these are conducted remotely and without direct contact with the researchers.

METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

18. Data collection methods

At baseline, trained research assistants will administer clinical interviews via videoconferencing and ask participants to complete web-based self-report questionnaires via secure online portal. We will use the Mini-International Neuropsychiatric Interview (MINI) [21] to assess eligibility. Post-treatment and follow-up assessments will consist of questionnaires only and in line with procedures at baseline will be conducted remotely by asking participants to complete self-report questionnaires on a dedicated webpage via secure online portal. Self-report questionnaires will include the Patient Health Questionnaire 9 (PHQ-9, [20]) to assess severity of depressive symptoms, the Generalized Anxiety Disorder Questionnaire 7 (GAD-7, [25]) to assess severity of anxiety symptoms [25], the Phobia Scale to assess symptoms of phobia, the Work and Social Adjustment Scale to assess general levels of adjustment, the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS, [26]) to assess emotional well-being, the Experiences Questionnaire Decentering Scale [27] and the Five Factor Mindfulness Questionnaire [28] to assess candidate processes of action. Health economic analyses will use the EQ-

5D [33] as a generic measure of health status and a self-report version of the Adults Service Use Schedule (AD-SUS) to assess health service use [19].

19. Data management

Randomisation, data management, and quality assurance will be undertaken by ExeCTU under the supervision of the CI, senior trial statistician and quality assurance manager. Routine clinical notes will be stored according to standard practice within the NHS services hosting the research. Recordings of the videoconferencing therapy sessions along with the automatically produced transcripts of the sessions will be stored on a secure server at the University of Surrey where they will be accessible to the lead scientists for purposes of therapist supervision and manual adherence checks. Data from the assessments will be entered by the research team on a secure, web-based system maintained by the ExeCTU. Data from online questionnaires will be quality checked by the research team. Consent forms will be stored separately from data and data will be anonymised wherever possible.

The datasets generated during and/or analysed during the trial will be stored in a non-publicly available repository at Sussex Partnership NHS Foundation Trust upon publication of main study results. Anonymised data may be accessed and analysed by members of the project team and by researchers collaborating with members of the project team on the analysis of these data. Data sharing will be enabled using a controlled access model in line with Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials from the UK Medical Research Council [42]. Scientists seeking to access the data for use in future projects must do so via request to the CI and projects using the data must have been approved in accordance with contemporary UK ethical and regulatory processes pertaining to the release of anonymised data under these circumstances. We will follow current recommendations on anonymising and curating trial data for sharing [43].

All personal identifiable data, with the exception of the consent form and the video recordings, will be destroyed as soon as the study closes, unless participants have consented to be contacted for future research, in which case we will keep their contact details for 5 years. Audio recordings of qualitative interviews will be destroyed immediately after transcription. Research data with personal information removed and replaced through a code and original research records, including video recordings of assessment interviews and therapy sessions, will be retained for 10 years, before being destroyed. The electronic records will be kept for 10 years after the end of the study. Publications will not contain any patient-identifiable information.

20. Statistical methods

All analyses will be carried out using an a priori statistical analysis plan as agreed with the Trial Management Group, Trial Steering Committee and Data Monitoring and Ethics Committee.

Participant characteristics at baseline (including number of previous depressive episodes and IAPT service) will be set out descriptively by treatment arm. The primary analysis approach will use the intention-to-treat (ITT) principle (all participants will be included in the analysis according to their randomised allocation irrespective of the treatment actually received) including observed data only. All outcomes will be reported descriptively at baseline, and at 10 and 34 weeks' follow-up. Continuous outcomes will be analysed using linear regression models. The binary outcome variables will be analysed using logistic regression. All analyses will adjust for participant covariates used in randomisation, with adjustment for baseline scores for continuous outcomes. We will assess other participant characteristics at baseline and will consider adjusting for any covariates that are found to be substantively unbalanced, should such covariates be considered predictive of outcome. Inferential between group comparisons (MBCT vs TAU) for the primary and all secondary outcomes will be performed at 34-week follow-up. As a sensitivity analysis, we will perform a complier average causal effect (CACE) analysis for continuous outcomes only, to estimate the treatment effect while accounting for non-adherence to treatment. A participant in the intervention arm will be considered to be a 'complier', if a minimum of four treatment sessions were attended. Mixed effects regression

models with a random effect on individual participant will be performed for continuous and binary outcomes, including participants with outcome data reported for at least one follow-up time. To address the potential for clustering effects by IAPT service, we will perform sensitivity analyses using mixed effects regression models for the primary and secondary (continuous and binary) outcomes, with a random effect on IAPT service. Similarly, to address the potential for effects of clustering by therapist, Further sensitivity analyses will test for the effect of individual therapists or therapist seniority. mixed effects model with a random effect on individual therapist will also be performed. As a further sensitivity analysis, therapist seniority will be added as a fixed effect within the primary model for the primary outcome and all secondary outcomes. To explore effects under conditions of different inclusion criteria, a sensitivity analysis will be run including only those patients who failed to show reliable recovery, that is reliable change in symptoms and symptom levels below casesness. To investigate effects of missing data, a further sensitivity analysis will use multiple imputation to impute missing outcome data for continuous outcomes only. We will also perform a sensitivity analysis (primary outcome only) to include any data collected outside the 7-day window. Sensitivity analyses will be based on the ITT principle (excepting the CACE analysis). Should further sensitivity analyses be indicated, these will be described in the statistical analysis plan.

METHODS: MONITORING

21. Trial governance and data monitoring

The trial is governed by a Trial Steering Committee (TSC), which is independent from the sponsor. The role of the TSC, which includes an independent chair and four other independent members, one of whom is an independent patient representative, is to provide critical scrutiny to the conduct of the proposed research. Prof David Clark (University of Oxford) has kindly agreed to chair the TSC. We have set up an Independent Data Monitoring Committee (IDMC) comprising a chair (Prof Dean McMillan, University of York), an independent mental health statistician and a clinician. The IDMC will review serious adverse events that are thought to be trial- or treatment related and look at outcome data regularly during data collection. As the TSC, the IDMC is independent from the sponsor and has no competing interests. The TSC and IDMC will meet on a half-yearly basis.

22. Harms

Risk monitoring: In order to identify risk issues, research assistants will screen questionnaires within 72 hours of completion to check for increases in suicidality and any service use that may be indicative of a serious adverse event. A score of more than 0 on the PHQ-9 item 9 (that represents a change from the previous trial assessment) and reports of suicidal ideation, intent, plans or urges, and any risk of harm to self or others in the MINI interview or other contexts will be deemed as risk issues. Identification of a risk issue will trigger the trial team to capture more detailed information and context to assess risk in line with the trial risk protocol. Where necessary participants will be provided with support in line with the local sites risk management process.

In the MBCT arm, the site RA will routinely monitor PHQ-9 scores on a weekly basis prior to each session (or as soon after as possible in the event of participant non-completion) and immediately email the mindfulness teacher and PI if:

- a participant's score has increased by 6 points or more from baseline assessment, specifying the amount of increase, and/or
- a participant scores 1 or more on item 9 of PHQ-9, specifying what the score is and whether this score is typical or represents a change

The mindfulness teacher or appropriate clinical delegate will follow the study risk protocol to ensure appropriate contact is made with the participant to discuss their mental state, current risk and what is needed to keep themselves safe. Information from this conversation will be considered by the therapist and PI to answer the question of whether a participant should continue with treatment. All

instances in which the risk protocol has been enacted will be documented using the Risk Assessment Form and logged in the study risk management log together with contextual information and their classification.

Adverse event and serious adverse event recording and reporting: Adverse events and reactions will be defined as follows.

Adverse Event (AE): Any untoward medical occurrence in a patient treated on a study protocol, which does not necessarily have a causal relationship with a study intervention. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of study intervention, whether or not related to that study treatment.
Adverse Reaction (AR): All untoward and unintended responses related to a study intervention. A causal relationship between a study intervention and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out as there is evidence or arguments to suggest a causal relationship.
Unexpected Adverse Reaction (UAR): An adverse reaction, the nature or severity of which is not consistent with the information about the trial intervention.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Respectively any adverse event, adverse reaction or unexpected adverse reaction that:

- results in death
- is life-threatening (where the term life-threatening refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- or any other health event which in the opinion of the clinician is serious.

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

As suicidal ideation and mild self-harm are a common aspect of the clinical presentation of many mood disorders, we will only rate these as adverse events if they include suicidal behaviour or the degree of self-harm puts the individual at risk of physical injury. In particular, suicidality will be deemed as an AE or SAE, if risk is categorized as level C on our risk protocol. Routine hospitalisations and planned surgery recorded at the baseline assessment visit (pre-treatment) do not require reporting as SAEs.

Any event observed by either a researcher or therapist that could be considered as SAE will be documented on the Serious Adverse Event Form and reported to the local PI. Research Assistants will be responsible for screening the AD-SUS questionnaire within 72 hours of completion to check for potential serious adverse events. Identification of a potential SAE in the AD-SUS will trigger a telephone call to the participant to capture more detailed information and context of the event although this should not delay reporting. As reports on the AD-SUS are retrospective, the research team will assess any remaining risks and the local sites risk management process will be adhered to at any time to ensure participants receive support where necessary.

The local PI will evaluate the reported event for seriousness considering the available contextual information. All non-serious AE will be documented in the electronic patient record. If the issue is assessed as serious, the event must be reported to the CI, Trial Manager, local R&D department and Sponsor, immediately and no later than 24 hours of being made aware of the event. Initial reports of SAE can be made via email but must be promptly followed with a detailed written report using the

Serious Adverse Event Reporting Form for the Sponsor and containing sufficient detail regarding concurrent life events. The PI should ensure that follow-up information is provided when available.

The sponsor will allocate an SAE number and forward the event to the trial's Independent Clinician who is part of the Independent Data Monitoring Committee. The Independent Clinician will determine causality of the event according to the table below and also rate the event with regard to its expectedness. Independent review will be conducted within 72 hours and the outcome will be reported back to the local Research Assistant PI, CI, Trial Manager and sponsor by email using the SAE number allocated by the sponsor.

Table 1. SAE causality rating

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

SAEs classed as related and unexpected will be reported to the Research Ethics Committee by the sponsor within 7 days if it is deemed to be life-threatening or results in death and 15 days if it is non-fatal and non-life threatening.

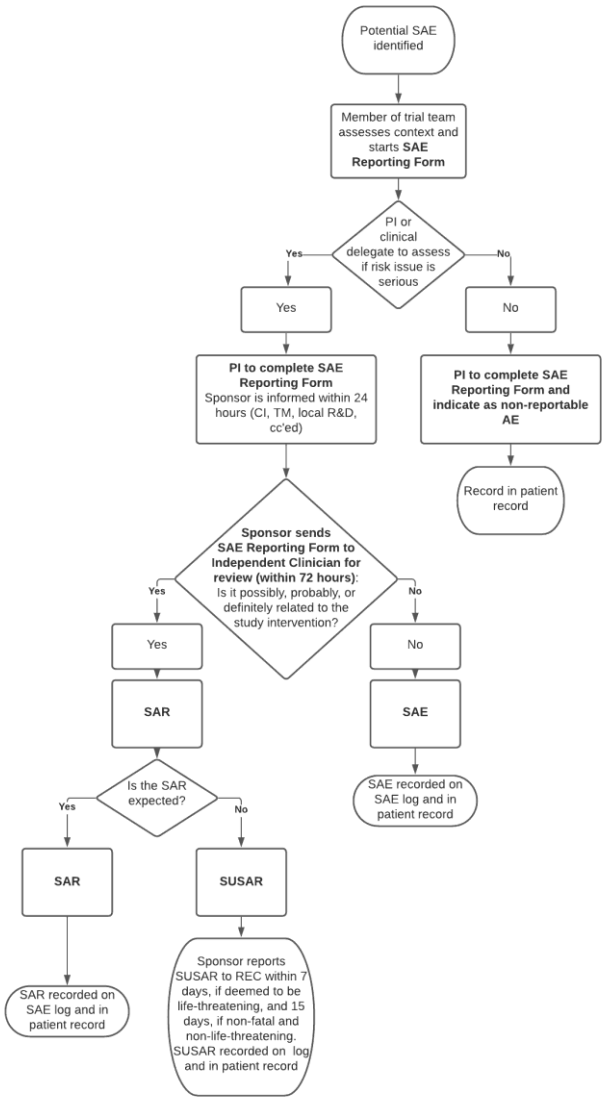


Figure 3. SAE reporting flowchart

The PIs will take responsibility for making sure that the local risk management procedures are adhered to at all times and that all risk issues are followed up until resolution.

23. Auditing

The research will be audited through established procedures at the sponsor's R&D department.

ETHICS AND DISSEMINATION

24. Research ethics approval

The project has received a favourable opinion from a sub-committee of the West of Scotland Research Ethics Service on the 18th of January 2021 (IRAS ID: 281532; REC reference: 20/WS/0177).

25. Protocol Amendments

In case amendments to the protocol are needed, we will seek to obtain sponsor approval for the amendment to be submitted. We will prepare a submission to the REC through the IRAS system

(https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool), authorised by the CI and the sponsor. The CI will communicate the outcome of the review process and any resulting changes of the protocol to the sites and inform participating organisations. Trial registrations and the published protocol will be amended accordingly.

26. Consent or assent

Informed consent will be obtained in a two-phase consent process. Participants will receive a study information sheet, produced in line with current HRA guidelines (http://www.hra-decisiontools.org.uk/consent/index.html) and informed by patient representatives, via email and first give permission for the research team to contact them for discussion of the study and screening in an initial call. Full informed consent will be taken by a study researcher via videoconferencing using electronic documents and signatures prior to the eligibility and baseline assessment. Potential participants will receive full information about the study in advance of the interview. At the point of consent, there will be further opportunity to discuss the study and for the participant to raise any questions. The opportunity to withdraw from the trial will be fully explained. Researchers will be trained in taking informed consent, including assessment of capacity to consent where appropriate, and supervised by the CI and site leads. Consent will be taken only from individuals with capacity to make an informed decision on their participation.

27. Confidentiality

Any information collected as part of the trial will be kept strictly confidential within the research team and the services involved. Both within the research team and the services confidentiality will be broken only in exceptional circumstances, if it is felt by the researcher or therapist that a patient or someone else is at immediate risk and the team will need to contact GPs or other relevant professionals.

All data will be stored and processed in line with General Data Protection Regulation (GDPR, 2018). Personal data will be link-anonymised and identified by a code known only to the research team. Names and contact details will be stored in password-protected files on secure servers and separately to link-anonymised data. In order to assess manual adherence and therapist competency, therapy sessions will be video recorded with the consent of all participants appearing in the recording. Access to these recordings and the transcripts of the sessions will be restricted to the research team and collaborating researchers. Recordings and anonymised transcripts will be stored on secure servers at the University of Surrey.

Direct quotations from qualitative interviews may be used, however it will not be possible to identify the participant from these. Clinical records will be stored on secure servers with access restricted to the trial manager and clinical team.

28. Declaration of Interests

TB is author of a book on MBCT. TB, CS, and FR regularly provide workshops on mindfulness-based interventions. CS is the research lead for the Sussex Mindfulness Centre, FR leads the Maudsley Mindfulness Service. All other investigators declare no conflicts of interests.

29. Access to data

The CI will serve as the custodian of the trial data. There are no contractual agreements in place that would limit access for the investigators.

30. Ancillary and post-trial care

Patients' GP and referring IAPT service will be informed of trial participation and the end of trial participation in writing.

31. Dissemination policy

The trial data may have the potential to inform changes in current practice within IAPT. The evaluated treatment manual of MBCT for patients with current symptoms of depression will facilitate training and dissemination of the approach within IAPT and other contexts. Insights from qualitative analyses will provide information on implementability. The findings of the research will be disseminated using the widest range possible of peer reviewed scientific journals and professional publications. We will present results at conferences and workshops, and disseminate findings through media and social media where possible. We will also disseminate findings on a local level, to participants, services and other stakeholders.

PATIENT AND PUBLIC INVOLVEMENT

The research team includes a PPI lead, MR, who will lead the Patient Advisory Group. The Patient Advisory Group will consist of the PPI lead and two other patient representatives, one from each site, as well as a carer representative. The Patient Advisory Group will meet quarterly during the project to advise on all aspects of the project of relevance to the experience of patients during the trial, with the PI in attendance. The group has been involved in protocol development in terms of recruitment, screening and data collection, the design of relevant documents for the ethics application, such as information leaflets and consent forms, and will review risk management procedures. The Patient Advisory Group will also contribute to the dissemination strategy. We will follow national good practice with regard to remuneration of PPI representatives.

TRIAL STATUS

The envisaged start date of the trial is the 1st of January 2021.

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APPENDICES

Informed consent materials:
- Letter of invitation to participants
- Permission for researchers contact form
- Patient information sheet
- Consent form