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

[Acronym: MBCT for IAPT Non-Responders (RESPOND)]

Statistical Analysis Plan (SAP)

This Statistical Analysis Plan (SAP) was finalised on 21 April 2023; version number 1.0.

This SAP builds on the information provided in the Study Protocol v3.0 28/10/2022. The trial is registered at ISRCTN under number 17755571 02/03/2021.

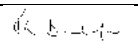
Revisions to this SAP and details of the revisions are provided below.

SAP revision number	Date of revision *(DD-MMM-YYYY)*	Timing of SAP revision in relation to analyses, eg: before interim analysis	Details of the revision	Justification for the revision
1		No revisions to date		

This SAP was produced by members of the trial team as described in the table:

Name	Affiliation(s)	Role
Dr Fiona Warren	University of Exeter Clinical Trials Unit	Senior statistician

This version of the SAP has been approved by the Trial Management Group and is signed below to confirm this.

	Author of SAP	Senior statistician	Chief Investigator
Name	Dr Fiona Warren	Dr Fiona Warren	Prof Thorsten Barnhofer
Signature			
Date (DD-MM-YYYY)	21/04/2023	21/04/2023	21/04/2023

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1. Introduction

1.1 Background and rationale

Major Depression represents a pressing challenge for health care. The disorder is not only highly prevalent – 10.9 percent 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]. It is important therefore to treat depressive episodes sufficiently. Increasing Access to Psychological Therapies (IAPT) services have been introduced as a means of providing patients with evidence-based psychological therapies in a timely manner. The services were intended to reach an access rate of 25% of the population in 2020/21. However, outcome data indicate that about 50% of the patients who receive high-intensity therapy do not recover fully.

Recent research has brought promising evidence that Mindfulness-Based Cognitive Therapy (MBCT) [6] can have significant beneficial effects in patients with acute and more persistent forms of the disorder [7, 8], and particularly in those who have not responded to previous interventions [9]. The aim of this project is to test whether MBCT could serve as an effective and cost-effective intervention for patients who have not responded to IAPT high-intensity therapy.

If successful, the proposed research would provide the evidence necessary for adoption of MBCT for non-responders within IAPT and would thus help to 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. We 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 will 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. Further information on the background to the study can be found in the Study Protocol v3.0 28/10/2022.

1.2 Objectives

Aims

To establish the

(a) 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:

(a) participants who receive MBCT will show significantly stronger reductions in depressive symptomatology measured using Patient Health Questionnaire-9 (PHQ-9) [10] 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) the MBCT intervention will be cost-effective, either in terms of reductions in costs elsewhere in the health system or in improvements in outcomes.

Estimands

Using the estimands framework [11,12], our target estimands are set out below.

Table 1 Estimands for RESPOND trial

Population	Patients aged 18 or older who have not responded to high-intensity IAPT interventions for depression (PHQ-9 score≥10 after 12 sessions), but do not meet eligibility criteria for secondary care services
Treatment conditions	Intervention: MBCT Control: TAU
Outcome variable	PHQ-9 at 34-week follow-up
Handling of intercurrent events	1. Treatment policy 2. Principal stratum (CACE analyses – see Section 1.4)
Population level summary measure	Between group mean difference

1.3 Study methods

Trial design

The study population comprises patients aged 18 or older who have not responded to high-intensity IAPT interventions for depression, but do not meet eligibility criteria for secondary care services.

Interventions

A two-arm trial, across 3 sites, will randomise 234 participants in a 1:1 ratio to receive either MBCT or to continue with TAU, 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).

MBCT intervention

The intervention will be delivered by trained MBCT therapists together with an assistant to groups of about 13 patients (minimum 8 and maximum of 16) using videoconferencing on a secure online platform. This is a change from the original intention of delivery face-to-face due to Covid-19; this amendment was documented in Protocol V01 (14.10.2020). Participants will attend sessions through internet connection from their home or another place of their choosing. 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. Manual adherence and treatment fidelity will be rated based on the recordings of the online intervention sessions using methods established in our previous trials using the MBCT Adherence Scale [13] and MBI-TAC [14].

TAU comparator arm

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 [15], TAU participants will be invited to an interview to prevent tendencies towards 'resentful demoralisation' and highlight the importance of their contribution. The pre-class interview for the MBCT courses will also be conducted via videoconferencing.

Randomisation

Participants will be allocated 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.

Sample Size

Details of the sample size calculation are provided in the study protocol. The sample size calculation is based on the primary outcome: PHQ-9 measured at 34 weeks post-randomisation. To detect an MCID of 2.59, using a standard deviation of 5.4, with 90% power at an alpha level of .05, 186 participants are required. Considering a rate of attrition of 20%, conservatively estimated to be above that observed in our previous research [15], we will aim to recruit a total sample of 234 participants (117 in each arm, 78 per site).

Framework

This trial is a fully powered definitive trial that seeks to evaluate superiority of the MBCT intervention over TAU.

Statistical interim analyses and stopping guidance

No interim analyses will be performed for efficacy or harms. As the intervention is considered to be low risk to participants, there are no formal guidelines for early termination of the trial due to potential for harm to participants. All adverse events and serious adverse events will be reported to the TSC and DMEC for their consideration; if the TSC and DMEC consider that there is sufficient cumulative evidence of harm to participants due to the intervention(s), the trial will be discontinued. Also, there are no guidelines for early termination due to futility (inability to achieve statistical significance for a treatment effect) or achieving significant results prior to full data analysis.

Timing of final analysis

We anticipate performing all analysis following final database lock, when all follow-up data (up to and including 34-week follow-up) has been entered and cleaned. Timing of each observation will be counted from the date of baseline measurement for the individual participant.

Timing of outcome assessments

We will measure outcomes at baseline, 10-week and 34-week follow-up post-randomisation. A 7-day window will be available for patients to complete the follow-up assessments and participants who do not respond within this time window will be prompted weekly to respond but no longer than until the end of a 4-week period.

1.4 Statistical Principles

Confidence intervals and p-values

All inferential analyses will be reported using 95% confidence intervals and p-values, with the threshold for statistical significance set at 0.05. No formal testing for multiple comparisons will be

performed (i.e. for multiple comparisons across the primary and secondary outcomes); the p-values for the primary analysis of the primary outcome (ITT analysis of PHQ-9 at 34-week follow-up) will be interpreted first, and the p-values for the secondary outcomes will be interpreted in the light of the overall results.

Intervention adherence and protocol deviations

Intervention adherence

To inform the Complier Average Causal Effect (CACE) analysis, a participant in the MBCT group will be considered a `complier' if a minimum of four sessions are attended; all participants in the control group will be considered as `compliers'.

Discontinuation from the study

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, a participant may discontinue therapy but remain in 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.

Analysis populations

Although the TAU condition is unlimited, it is practically highly unlikely for TAU participants to receive MBCT if this was not the participant's randomised allocation. The only possibility for a participant failing to receive the randomised intervention is if the participant did not adhere in the MBCT group. We do not expect an `as treated' analysis to be required as it is highly unlikely for a participant in the control group to receive the MBCT intervention.

1.5 Trial population

Screening data

Potential participants who believe that they may be eligible for the trial will be requested to consent to a further screening procedure and to participate in the trial if they are eligible. Data will be retained for participants who are screened but found to be ineligible. We will report data on age and sex for people who are screened, and found to be eligible, but who do not participate further in the trial.

Eligibility

The study population comprises patients aged 18 and older who have not responded to high-intensity IAPT interventions for depression, but do not meet eligibility criteria for secondary care services.

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 guideline suggestions) defined in line with the caseness threshold adopted by IAPT as a PHQ-9 score of 10 or higher [10]

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) [16] along with a current PHQ-9 score of 10 or higher

3) age 18 or older, and

4) access to a working internet connection and equipment to participate in videoconferencing assessments and interventions.

Exclusion criteria will be:

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, a current post-traumatic stress disorder, an obsessive-compulsive disorder or an eating disorder

3) 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

4) 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 in the minimisation algorithm for randomisation.

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 (Table 3).

Recruitment

Information on participant recruitment to the trial is described fully in the trial protocol.

IAPT patients who are potentially interested in taking part will be contacted by the researchers via telephone for an initial screening to assess eligibility and to provide further information on the research. Baseline assessments will then be completed. Eligible, fully informed and consenting participants will then be entered into the study and randomised (see Figure 1).

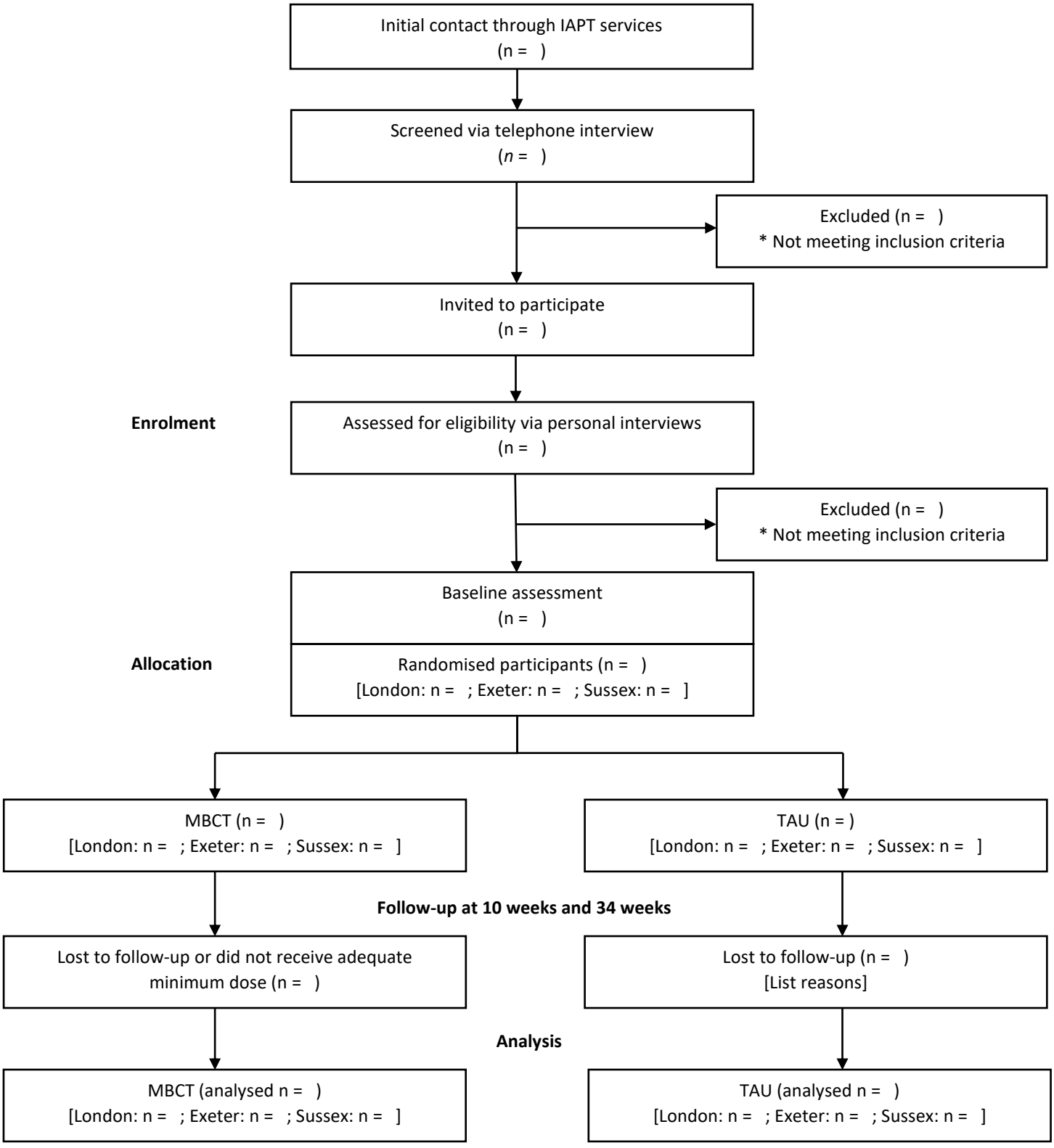

Figure. 1 CONSORT diagram describing flow of participants through the study

Withdrawal/follow-up

Participant withdrawal (from treatment in the MBCT group and follow-up for all participants) will be reported using a CONSORT flow diagram. We will report descriptively the baseline characteristics of participants who are lost to follow-up at 34 weeks, and will also explore baseline characteristics that are predictors of missing PHQ-9 data at 34 weeks, to inform the imputation modelling.

Baseline patient characteristics

Participant characteristics assessed as part of the Mini International Neuropsychiatric Interview (MINI) at baseline will allow us to make comparisons between eligible patients who declined to participate (if any), and those patients who participated in the trial (Table A1).

1.6 Statistical Analysis

Patient characteristics will be compared across the MBCT and TAU arms (Table A2).

Outcome definitions

Primary outcome

The primary clinical outcome will be reductions in depression symptomatology as assessed using the PHQ-9 [10]. 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 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.

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. Other clinical secondary outcome measures will include the Generalized Anxiety Disorder Questionnaire (GAD-7) [17], 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) [18], Experiences Questionnaire (EQ) Decentering Scale [19] and Five Factor Mindfulness Questionnaire (FFMQ) [20]. We will also track symptoms weekly during the MBCT intervention using the PHQ-9.

A series of binary outcomes will also be derived, based on PHQ-9 and/or GAD-7 at 34-week follow-up (Table 1). Definitions of these outcomes are based on conventions used by IAPT [21].

Table 2 Binary outcome measures derived from PHQ-9 and GAD-7 at 34-week follow-up

Measure #	Measure name	Underlying continuous outcome(s)	Measure definition	Notes
Outcomes based on PHQ-9 only				
1	Recovery	PHQ-9	Change from a score ≥10 at baseline to ≤9 at follow-up	Only applies to participants with a PHQ-9 score ≥10 at baseline
2	Reliable recovery	PHQ-9	Change from a score ≥10 at baseline to ≤9 at follow-up plus reduction in score by ≥6 units	Only applies to participants with a PHQ-9 score ≥10 at baseline
3	Reliable improvement	PHQ-9	Reduction in score by ≥6 units	Applies to all participants
4	Deterioration	PHQ-9	Increase in score	Applies to all participants
5	Reliable deterioration	PHQ-9	Increase in score by ≥6 units	Applies to all participants
Outcomes based on GAD-7 only				
6	Reliable improvement	GAD-7	Reduction in score by ≥4 units	Applies to all participants
7	Deterioration	GAD-7	Increase in score	Applies to all participants
8	Reliable deterioration	GAD-7	Increase in score by ≥4 units	Applies to all participants
Outcomes based on PHQ-9 and GAD-7				
9	Recovery	PHQ-9; GAD-7	Reduction from PHQ-9 ≥10 at baseline to PHQ-9 score ≤9 at follow-up AND/OR reduction from GAD-7 ≥8 at baseline to GAD-7 ≤7 at follow-up	Applies to all participants; however, those with GAD-7 ≥8 at baseline can also meet this criterion by showing recovery for GAD-7 only
10	Reliable recovery	PHQ-9; GAD-7	Change from PHQ-9 ≥10 at baseline to PHQ-9 score ≤9 at follow-up plus reduction on PHQ-9 ≥6 AND/OR reduction from GAD-7 ≥8 at baseline to GAD-7 ≤7 at follow-up plus reduction on GAD-7 ≥4	Applies to all participants; however, those with GAD-7 ≥8 at baseline can also meet this criterion by showing reliable recovery for GAD-7 only
11	Reliable improvement	PHQ-9; GAD-7	Criterion 1: Reliable improvement in PHQ-9 AND reliable improvement in GAD-7; OR Criterion 2: Reliable improvement in PHQ-9 AND no reliable change in GAD-7; OR	Applies to all participants

			Criterion 3: No reliable change in PHQ-9 AND reliable improvement in GAD-7	
12	No reliable change[1,2]	PHQ-9; GAD-7	Criterion 1: No reliable change in PHQ-9 AND no reliable change in GAD-7 OR Criterion 2: Reliable improvement in PHQ-9 AND reliable deterioration in GAD-7 OR Criterion 3: Reliable deterioration in PHQ-9 AND reliable improvement in GAD-7	Applies to all participants
13	Reliable deterioration	PHQ-9 GAD-7	Criterion 1: Reliable deterioration in PHQ-9 AND reliable deterioration in GAD-7 OR Criterion 2: Reliable deterioration in PHQ-9 AND no reliable change in GAD-7 OR Criterion 3: No reliable change in PHQ-9 AND reliable deterioration in GAD-7	Applies to all participants

[1]No reliable change in PHQ-9: change in score <6 units. [2]No reliable change in GAD-7: change in score <4 units.

Analysis methods

Primary analysis

The primary analysis approach will use the intention-to-treat 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. Descriptive data will be reported for the overall sample and for each site individually. Continuous outcomes will be analysed using linear regression models. The binary outcomes will be analysed using logistic regression. All analyses will adjust for participant covariates (depression severity (PHQ-9<19 versus ≥19), antidepressant use at baseline and recruitment site) used in randomisation, with adjustment for baseline scores for continuous outcomes. We will assess other participant characteristics at baseline (including number of previous episodes), and will consider performing a sensitivity analysis with adjustment for any covariates that are found to be substantively unbalanced for the ITT analysis using observed data only, 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.

Primary analyses will include all data collected within the overall window for each follow-up time, and will be performed by a statistician who is blinded to intervention allocation. Following presentation of the results of the primary analyses and unblinding of the trial team, the remaining additional and sensitivity analyses will be performed unblinded.

Additional analyses and sensitivity analyses

With the exception of the complier average causal effect (CACE) analysis described below, all sensitivity analyses will use the ITT approach. With the exception of the multiple imputations analysis described below, all sensitivity analyses will use observed data only.

Assessment of therapist effects

To address the potential effects of clustering by therapist, we will perform mixed effects linear regression models for the primary and secondary (continuous and binary) outcomes with a random effect on therapist. In addition, we will perform linear or logistic regression models adding therapist seniority as a predictor for the primary outcome and all secondary outcomes for the MBCT group only.

Assessment of IAPT effects

To address the potential effects of clustering by IAPT service, we will perform mixed effect regression models for the primary and secondary (continuous and binary) outcomes with a random effect on IAPT service.

Exploration of different inclusion criteria

To explore effects under conditions of different inclusion criteria, we will perform a sensitivity analysis excluding participants showed reliable improvement in PHQ-9 (i.e. a reduction by 6 points on more on PHQ-9) during IAPT treatment. This sensitivity analysis will be performed using regression modelling for the primary and secondary outcomes.

Inclusion of data collected outside the 7-day time window

We will perform a sensitivity analysis for the primary outcome only to include data collected during the 7-day data collection window only.

Complier average causal effect analysis

As a sensitivity analysis, we will perform a CACE analysis, to estimate the treatment effect while accounting for non-adherence to treatment. A participant in the intervention arm will be considered to be 'complier', if a minimum of four treatment sessions were attended. A 2-stage least squared instrumental variable regression model will be used, for the purpose of identifying those participants in the TAU group who would be `compliers' had they been allocated to MBCT, and comparing the compliers in both groups. A CACE analysis will be performed for the PHQ-9 and all continuous secondary outcomes.

Imputing missing data

A sensitivity analysis will use multiple imputation to impute missing outcome data for the primary outcome and all secondary continuous outcomes at 34 weeks. Multiple imputation using chained equations (MICE) will be used; the imputation algorithm will include baseline characteristics that are found to be predictive of missingness of the primary outcome and outcome data reported at 10-week follow-up, as well as treatment arm and minimisation variables. Logistic regression will be used to determine characteristics associated with missing primary outcome data (PHQ-9 at 34-week follow-up). Predictive mean matching will be the method for imputing individual scores; the number of imputed datasets will be determined by the percentage of participants that have missing primary outcome data. Observed and imputed data will be used to perform a sensitivity analysis of the inferential between group comparisons at 34 weeks.

Repeated measures analysis

A repeated measures analysis will be performed for the primary outcome and continuous secondary outcomes, including participants with follow-up data reported for at least one follow-up time, using observed data according to the ITT principle.

Sensitivity analysis to handle post-randomisation ineligible participants

It was noted on 22 November 2022 that an error had been made in the algorithm for detection of potentially eligible participants from one of the Sussex Partnership Foundation Trust IAPT services associated with the Sussex site. The algorithm was intended to detect all IAPT patients who had received therapy for depression and had a PHQ-9 score of 10 or more at their *final* IAPT session. However, the algorithm erroneously included all those who had scored a PHQ-9 score of 10 or higher *at any session during their therapy*, which rendered 14 participants ineligible. On further investigation, a total of 24 participants were found to be ineligible post-randomisation due to this error in coding. In addition, a participant was found to be ineligible due to not having received the recommended number of 12 therapy sessions during their initial IAPT treatment, and one participant who was already ineligible due to having a PHQ-9 at final session of less than 10, and also received fewer than 12 therapy sessions. Overall, 25 participants were randomised into the trial despite not having met required inclusion criteria. However, it was considered that these participants met all other eligibility criteria. Hence it is anticipated that these participants would be very similar to those that were eligible based on the inclusion criteria.

To address this issue, the 25 post-randomisation ineligible participants will be excluded from the primary analyses, but will be included in a sensitivity analysis for the primary outcome only.

Harms

Adverse Events (AEs) will be reported at fixed timepoints, set by frequency of DSMC meetings (to be determined). For definitions of AEs, see the protocol.

Statistical software

All analyses will be carried out using Stata v17.0 or later.

2. Related documents

#	Document Number	Document Title	Source
1	Data Management Plan		
2	Trial Master File		
3	Statistical Master File		
4	SOP_019	Deviations, Misconduct and Serious Breaches of GCP and(or) the Protocol	

3. References

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Appendix

A1 Adherence to MBCT practice

Adherence to home practice is captured with standard worksheets for MBCT. In line with common practice, we will distinguish between adherence to formal practice, i.e. meditation practices that follow recorded guidance and represent the main part of the daily homework for each week, and informal practice, i. e. smaller unguided practices that participants engage in to practice mindfulness in their daily lives. We will establish the percentage adherence to formal and informal practices in each week and derive indices of adherence to formal and informal practice by averaging over percentages across the 7 weeks of the course during which participants are asked to engage in practice. We will treat missing data as an indication that participants have not practiced and count any missing observations as 0, with the exception of cases where missing observations are clearly clustered in certain courses. The latter takes into account the fact that MBCT teachers are not always reliable in collecting home practice record sheets. If data indicate that missing values are clustered in particular courses, i.e. below 10% of data, we will exclude data from this course and treat them as missing rather than an indication that participants have not practiced.

A2 Example tables

Table A1 Comparison of characteristics between patients who agreed to participate in the trial and eligible participants who declined to participate

Patient characteristic	**Trial participants**	**Eligible participants who declined to participate**	**Total**
Age (years)	Mean (SD)	Mean (SD)	Mean (SD)
Gender			
Male	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)

Table A2 Characteristics of participants in the trial by intervention arm: eligible participants only

Patient characteristic	**MBCT (n=)**	**TAU (n=)**	**Total**
Age (years)	Mean (SD); median [min, max]	Mean (SD); median [min, max]	Mean (SD); median [min, max]
Gender			
Male	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)
Site			
Devon	n (%)	n (%)	n (%)
Sussex	n (%)	n (%)	n (%)
London	n (%)	n (%)	n (%)
IAPT service			
Categories tbc	n (%)	n (%)	n (%)
Marital status			
Single	n (%)	n (%)	n (%)
Married / Civil partnership	n (%)	n (%)	n (%)
Cohabiting	n (%)	n (%)	n (%)
Separated / divorced	n (%)	n (%)	n (%)
Widowed	n (%)	n (%)	n (%)
In a long-term relationship	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)
Ethnicity			
White	n (%)	n (%)	n (%)
Asian or Asian British	n (%)	n (%)	n (%)
Black, African, Caribbean or Black British	n (%)	n (%)	n (%)
Mixed or multiple ethnic groups	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)
Highest educational attainment			
None	n (%)	n (%)	n (%)
GCSE or equivalent	n (%)	n (%)	n (%)
A-Level or equivalent	n (%)	n (%)	n (%)
Undergraduate or equivalent	n (%)	n (%)	n (%)
Postgraduate or equivalent	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)
Annual household income			
£0-10,000	n (%)	n (%)	n (%)
£10,001-£20,000	n (%)	n (%)	n (%)

£20,001-£30,000	n (%)	n (%)	n (%)
£30,001-£40,000	n (%)	n (%)	n (%)
£40,001-£50,000	n (%)	n (%)	n (%)
£50,001-£60,000	n (%)	n (%)	n (%)
£60,001-£70,000	n (%)	n (%)	n (%)
£70,001-£80,000	n (%)	n (%)	n (%)
£80,001-£90,000	n (%)	n (%)	n (%)
£90,001-£100,000	n (%)	n (%)	n (%)
£100,001-£150,000	n (%)	n (%)	n (%)
£150,001-£200,000	n (%)	n (%)	n (%)
£200,001+	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)
Number of previous episodes of depression	Mean (SD); median [min, max]	Mean (SD); median [min, max]	Mean (SD); median [min, max]
Age of onset of depression	Mean (SD); median [min, max]	Mean (SD); median [min, max]	Mean (SD); median [min, max]

Table A3 Characteristics of participants in the trial by intervention arm: all randomised participants

Patient characteristic	**MBCT (n=)**	**TAU (n=)**	**Total**
Age (years)	Mean (SD); median [min, max]	Mean (SD); median [min, max]	Mean (SD); median [min, max]
Gender			
Male	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)
Site			
Devon	n (%)	n (%)	n (%)
Sussex	n (%)	n (%)	n (%)
London	n (%)	n (%)	n (%)
IAPT service			
Categories tbc	n (%)	n (%)	n (%)
Marital status			
Single	n (%)	n (%)	n (%)
Married / Civil partnership	n (%)	n (%)	n (%)
Cohabiting	n (%)	n (%)	n (%)
Separated / divorced	n (%)	n (%)	n (%)
Widowed	n (%)	n (%)	n (%)
In a long-term relationship	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)
Ethnicity			
White	n (%)	n (%)	n (%)
Asian or Asian British	n (%)	n (%)	n (%)
Black, African, Caribbean or Black British	n (%)	n (%)	n (%)
Mixed or multiple ethnic groups	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)
Highest educational attainment			
None	n (%)	n (%)	n (%)
GCSE or equivalent	n (%)	n (%)	n (%)
A-Level or equivalent	n (%)	n (%)	n (%)
Undergraduate or equivalent	n (%)	n (%)	n (%)
Postgraduate or equivalent	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)
Annual household income			
£0-10,000	n (%)	n (%)	n (%)
£10,001-£20,000	n (%)	n (%)	n (%)

£20,001-£30,000	n (%)	n (%)	n (%)
£30,001-£40,000	n (%)	n (%)	n (%)
£40,001-£50,000	n (%)	n (%)	n (%)
£50,001-£60,000	n (%)	n (%)	n (%)
£60,001-£70,000	n (%)	n (%)	n (%)
£70,001-£80,000	n (%)	n (%)	n (%)
£80,001-£90,000	n (%)	n (%)	n (%)
£90,001-£100,000	n (%)	n (%)	n (%)
£100,001-£150,000	n (%)	n (%)	n (%)
£150,001-£200,000	n (%)	n (%)	n (%)
£200,001+	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)
Number of previous episodes of depression	Mean (SD); median [min, max]	Mean (SD); median [min, max]	Mean (SD); median [min, max]
Age of onset of depression	Mean (SD); median [min, max]	Mean (SD); median [min, max]	Mean (SD); median [min, max]

Table A4 Characteristics of patients participating in the study compared with users of IAPT

Patient characteristic	**Trial participants**	**IAPT patients**	**Total**
Age (years)	Mean (SD); median [min, max]	Mean (SD); median [min, max]	Mean (SD); median [min, max]
Gender			
Male	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)
Prefer not to say	n (%)	n (%)	n (%)

Table A5 PHQ-9 outcome at baseline, 10- and 34-week follow up: all eligible participants

Descriptive statistics						
	Baseline		**10-weeks follow-up**		**34-weeks follow-up**	
	MBCT (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)
PHQ-9: mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n
Inferential analyses: between group[1] mean difference (95% confidence interval)						
	10-week follow-up			**34-week follow-up**		
PHQ-9	**Mean difference**	**95% CI**	**p-value**	**Mean difference**	**95% CI**	**p-value**
ITT, observed data only						
CACE, observed data only						
ITT, observed data only, random effect on therapist						
ITT, observed data only, random effect on IAPT service						
ITT, observed data only, excluding participants who showed reliable improvement in IAPT						
ITT, observed data only, including participants with data reported outside 7-day window						
ITT, observed data only, including participants randomised in error						
ITT, observed and imputed data						
Repeated measures analyses (interaction between intervention arm (TAU as reference) and timepoint (10-week follow-up as reference))					**34-week follow-up x MBCT**	
Interaction coefficient (95% confidence interval), p-value						
	Baseline		**10-week follow-up**		**34-week follow-up**	
	MBCT (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)
ITT, observed data only						

MBCT: Mindfulness based cognitive therapy. TAU: treatment as usual. [1]For all inferential analyses, the reference group is TAU. All analyses adjusted for recruitment site, antidepressant medication use and depression severity (PHQ-9<19 versus ≥19).

Table A6 Secondary continuous outcomes at baseline, 10- and 34-week follow-up: all eligible participants

Descriptive statistics: mean (SD), n						
	Baseline		**10-weeks follow-up**		**34-weeks follow-up**	
	MBCT (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)
Generalized Anxiety Disorder Questionnaire (GAD-7)						
Phobia Scale						
Work and Social Adjustment Scale (WSAS)						
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)						
Experiences Questionnaire (EQ) Decentering Scale						
Five Factor Mindfulness Questionnaire (FFMQ)						
Inferential analyses: between group[1] mean difference (95% confidence interval)						
	10-week follow-up			**34-week follow-up**		
	Mean difference	**95% CI**	**p-value**	**Mean difference**	**95% CI**	**p-value**
ITT, observed data only						
Generalized Anxiety Disorder Questionnaire (GAD-7)						
Phobia Scale						
Work and Social Adjustment Scale (WSAS)						
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)						
Experiences Questionnaire (EQ) Decentering Scale						
Five Factor Mindfulness Questionnaire (FFMQ)						
CACE, observed data only						
Generalized Anxiety Disorder Questionnaire (GAD-7)						

Phobia Scale						
Work and Social Adjustment Scale (WSAS)						
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)						
Experiences Questionnaire (EQ) Decentering Scale						
Five Factor Mindfulness Questionnaire (FFMQ)						
ITT, observed data only, random effect on therapist						
Generalized Anxiety Disorder Questionnaire (GAD-7)						
Phobia Scale						
Work and Social Adjustment Scale (WSAS)						
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)						
Experiences Questionnaire (EQ) Decentering Scale						
Five Factor Mindfulness Questionnaire (FFMQ)						
ITT, observed data only, random effect on IAPT service						
Generalized Anxiety Disorder Questionnaire (GAD-7)						
Phobia Scale						
Work and Social Adjustment Scale (WSAS)						
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)						
Experiences Questionnaire (EQ) Decentering Scale						
Five Factor Mindfulness Questionnaire (FFMQ)						
ITT, observed data only, excluding participants who showed reliable improvement in IAPT						
Generalized Anxiety Disorder Questionnaire (GAD-7)						
Phobia Scale						
Work and Social Adjustment Scale (WSAS)						
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)						
Experiences Questionnaire (EQ) Decentering Scale						
Five Factor Mindfulness Questionnaire (FFMQ)						
ITT, observed and imputed data						
Generalized Anxiety Disorder Questionnaire (GAD-7)						
Phobia Scale						
Work and Social Adjustment Scale (WSAS)						
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)						

Experiences Questionnaire (EQ) Decentering Scale						
Five Factor Mindfulness Questionnaire (FFMQ)						
Repeated measures analyses (interaction between intervention arm (usual care as reference) and timepoint (10-week follow-up as reference))					**34 weeks follow-up x MBCT**	
Interaction coefficient (95% confidence interval), p-value						
Generalized Anxiety Disorder Questionnaire (GAD-7)						
Phobia Scale						
Work and Social Adjustment Scale (WSAS)						
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)						
Experiences Questionnaire (EQ) Decentering Scale						
Five Factor Mindfulness Questionnaire (FFMQ)						

MBCT: Mindfulness based cognitive therapy. TAU: treatment as usual. [1]For all inferential analyses, the reference group is TAU. All analyses adjusted for recruitment site, antidepressant medication use and depression severity (PHQ-9<19 versus ≥19).

Table A7 Binary outcomes based on PHQ-9 and/or GAD-7 at 34-week follow-up: eligible participants only

Outcome[1]	**MBCT n/N (%)**	**TAU n/N (%)**	**MBCT vs TAU OR[2] (95% CI), p-value**
Logistic regression model[3]			
Recovery: PHQ-9			
Reliable recovery: PHQ-9			
Reliable improvement: PHQ-9			
Deterioration: PHQ-9			
Reliable deterioration: PHQ-9			
Deterioration: GAD-7			
Reliable deterioration: GAD-7			
Recovery: PHQ-9, GAD-7			
Reliable recovery: PHQ-9, GAD-7			
Reliable improvement: PHQ-9, GAD-7			
Improvement: PHQ-9, GAD-7			
No change: PHQ-9, GAD-7			
Deterioration: PHQ-9, GAD-7			
Mixed effects logistic regression model[3]: random effect on therapist			
Recovery: PHQ-9			
Reliable recovery: PHQ-9			
Reliable improvement: PHQ-9			
Deterioration: PHQ-9			
Reliable deterioration: PHQ-9			
Deterioration: GAD-7			
Reliable deterioration: GAD-7			
Recovery: PHQ-9, GAD-7			
Reliable recovery: PHQ-9, GAD-7			
Reliable improvement: PHQ-9, GAD-7			
Improvement: PHQ-9, GAD-7			
No change: PHQ-9, GAD-7			

Mixed effects logistic regression[3]: random effect on IAPT service			
Recovery: PHQ-9			
Reliable recovery: PHQ-9			
Reliable improvement: PHQ-9			
Deterioration: PHQ-9			
Reliable deterioration: PHQ-9			
Deterioration: GAD-7			
Reliable deterioration: GAD-7			
Recovery: PHQ-9, GAD-7			
Reliable recovery: PHQ-9, GAD-7			
Reliable improvement: PHQ-9, GAD-7			
Improvement: PHQ-9, GAD-7			
No change: PHQ-9, GAD-7			
Deterioration: PHQ-9, GAD-7			
Logistic regression model[3]: excluding participants who showed reliable improvement during IAPT treatment			
Recovery: PHQ-9			
Reliable recovery: PHQ-9			
Reliable improvement: PHQ-9			
Deterioration: PHQ-9			
Reliable deterioration: PHQ-9			
Deterioration: GAD-7			
Reliable deterioration: GAD-7			
Recovery: PHQ-9, GAD-7			
Reliable recovery: PHQ-9, GAD-7			
Reliable improvement: PHQ-9, GAD-7			
Improvement: PHQ-9, GAD-7			
No change: PHQ-9, GAD-7			
Deterioration: PHQ-9, GAD-7			

MBCT: Mindfulness based cognitive therapy; OR: Odds ratio; TAU: Treatment as usual. [1]All analyses used the ITT principle with observed data only. See Table 1 for full definitions of binary outcomes. [2]OR derived from logistic regression. [3]Adjustment for recruitment site, antidepressant medication use and depression severity (PHQ-9<19 versus ≥19).

Table A8 PHQ-9 outcome at baseline, 10- and 34-week follow up: all eligible participants by site, descriptive data only

	Baseline		**10-weeks follow-up**		**34-weeks follow-up**	
	MBCT (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)
Devon						
PHQ-9: mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n
Sussex						
PHQ-9: mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n
London						
PHQ-9: mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n

MBCT: Mindfulness based cognitive therapy. TAU: treatment as usual.

Table A9 PHQ-9 outcome at baseline, 10- and 34-week follow up: all randomised participants

Descriptive statistics						
	Baseline		**10-weeks follow-up**		**34-weeks follow-up**	
	MBCT (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)	**MBCT** (N=X)	**TAU** (N=X)
PHQ-9: mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n	mean (SD), n
Inferential analyses: between group[1] mean difference (95% confidence interval)						
	10-week follow-up			**34-week follow-up**		
PHQ-9	**Mean difference**	**95% CI**	**p-value**	**Mean difference**	**95% CI**	**p-value**
ITT, observed data only						

MBCT: Mindfulness based cognitive therapy. TAU: treatment as usual. [1]For all inferential analyses, the reference group is TAU. All analyses adjusted for recruitment site, antidepressant medication use and depression severity (PHQ-9<19 versus ≥19).

Table A10 PHQ-9 outcome at 34-week follow up: adjustment for therapist seniority, MBCT group only, eligible participants only

Outcome	34-week follow-up		
	Mean difference[1]	**95% CI**	**p-value**
PHQ-9			
GAD-7			
Phobia Scale			
WSAS			
WEMWBS			
Experiences Questionnaire Decentering Scale			
FFMQ			
	Odds ratio[1]	**95% CI**	**p-value**
Recovery: PHQ-9			
Reliable recovery: PHQ-9			
Reliable improvement: PHQ-9			
Deterioration: PHQ-9			
Reliable deterioration: PHQ-9			
Deterioration: GAD-7			
Reliable deterioration: GAD-7			
Recovery: PHQ-9, GAD-7			
Reliable recovery: PHQ-9, GAD-7			
Reliable improvement: PHQ-9, GAD-7			
Improvement: PHQ-9, GAD-7			
No change: PHQ-9, GAD-7			
Deterioration: PHQ-9, GAD-7			

[1]Analyses adjust for randomisation variables

Table A11 Predictors of PHQ-9 missingness at 34 weeks: eligible participants only

	Odds ratio (95% CI)	**p-value[1]**
Treatment (MBCT)		
PHQ-9 (baseline)		
Depression severity (baseline)		
Antidepressant use (baseline)		
Recruitment site		
Age (years)		
Sex		
Male		
Female		
Other		
Prefer not to say		
Marital status		
Single		
Married / Civil partnership		
Cohabiting		
Separated / divorced		
Widowed		
In a long-term relationship		
Prefer not to say		
Ethnicity		
White		
Asian or Asian British		
Black, African, Caribbean or Black British		
Mixed or multiple ethnic groups		
Other		
Highest educational attainment		
None		
GCSE or equivalent		
A-Level or equivalent		
Undergraduate or equivalent		
Postgraduate or equivalent		
Prefer not to say		
Annual household income		
£0-10,000		
£10,001-£20,000		
£20,001-£30,000		
£30,001-£40,000		
£40,001-£50,000		
£50,001-£60,000		

£60,001-£70,000		
£70,001-£80,000		
£80,001-£90,000		
£90,001-£100,000		
£100,001-£150,000		
£150,001-£200,000		
£200,001+		
Prefer not to say		
Number of previous episodes		
Age at first onset		

MBCT: Mindfulness based cognitive therapy. [1]Global p-value to be used for categorical variables with more than two levels.

Table A12 Number of sessions attended by participants allocated to MBCT: eligible participants only

Number of sessions	Mean (SD), n; median [min, max]
4 or more	n (%)
0-3	n (%)
0	n (%)
6-8	n (%)

Table A13 Number of sessions attended by participants allocated to MBCT: all randomised participants

Number of sessions	Mean (SD), n; median [min, max]
4 or more	n (%)
0-3	n (%)
0	n (%)
6-8	n (%)