HEALTH TECHNOLOGY ASSESSMENT

VOLUME 19 ISSUE 73 SEPTEMBER 2015
ISSN 1366-5278

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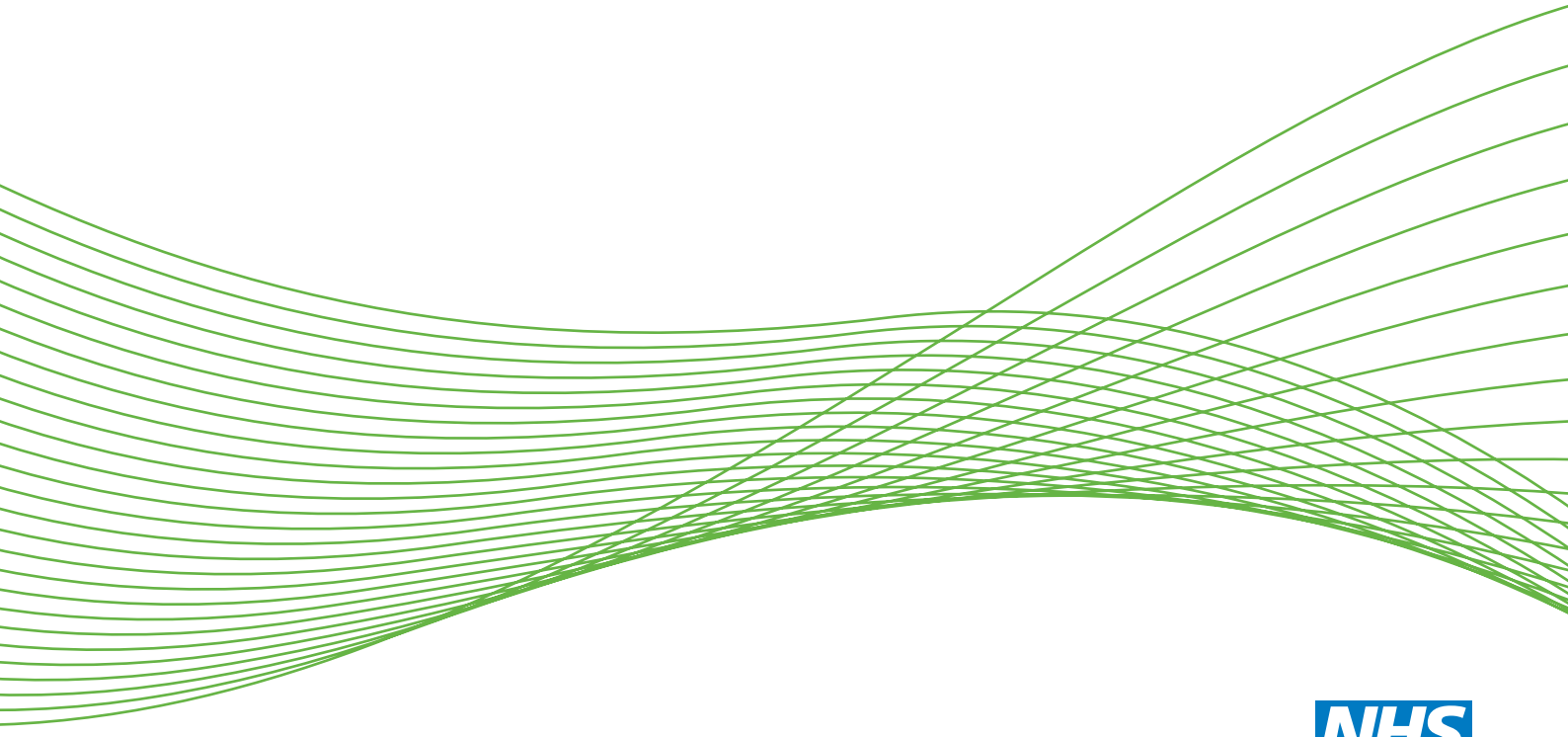

NHS
National Institute for Health Research

DOI 10.3310/hta19730

The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: results of a randomised controlled trial (the PREVENT study)

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Declared competing interests of authors: Willem Kuyken declares that he is a codirector of the Mindfulness Network Community Interest Company.

Published September 2015
DOI: 10.3310/hta19730

This report should be referenced as follows:

Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, *et al*. The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: results of a randomised controlled trial (the PREVENT study). *Health Technol Assess* 2015;**19**(73).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 08/56/01. The contractual start date was in January 2010. The draft report began editorial review in October 2014 and was accepted for publication in February 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

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Abstract

The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: results of a randomised controlled trial (the PREVENT study)

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Background: Individuals with a history of recurrent depression have a high risk of repeated depressive relapse/recurrence. Maintenance antidepressant medication (m-ADM) for at least 2 years is the current recommended treatment, but many individuals are interested in alternatives to m-ADM. Mindfulness-based cognitive therapy (MBCT) has been shown to reduce the risk of relapse/recurrence compared with usual care but has not yet been compared with m-ADM in a definitive trial.

Objectives: To establish whether MBCT with support to taper and/or discontinue antidepressant medication (MBCT-TS) is superior to and more cost-effective than an approach of m-ADM in a primary care setting for patients with a history of recurrent depression followed up over a 2-year period in terms of preventing depressive relapse/recurrence. Secondary aims examined MBCT's acceptability and mechanism of action.

Design: Single-blind, parallel, individual randomised controlled trial.

Setting: UK general practices.

Participants: Adult patients with a diagnosis of recurrent depression and who were taking m-ADM.

Interventions: Participants were randomised to MBCT-TS or m-ADM with stratification by centre and symptomatic status. Outcome data were collected blind to treatment allocation and the primary analysis was based on the principle of intention to treat. Process studies using quantitative and qualitative methods examined MBCT's acceptability and mechanism of action.

Main outcomes measures: The primary outcome measure was time to relapse/recurrence of depression. At each follow-up the following secondary outcomes were recorded: number of depression-free days, residual depressive symptoms, quality of life, health-related quality of life and psychiatric and medical comorbidities.

Results: In total, 212 patients were randomised to MBCT-TS and 212 to m-ADM. The primary analysis did not find any evidence that MBCT-TS was superior to m-ADM in terms of the primary outcome of time to depressive relapse/recurrence over 24 months [hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.67 to 1.18] or for any of the secondary outcomes. Cost-effectiveness analysis did not support the hypothesis that MBCT-TS is more cost-effective than m-ADM in terms of either relapse/recurrence or quality-adjusted life-years. In planned subgroup analyses, a significant interaction was found between treatment group and reported childhood abuse (HR 1.89, 95% CI 1.06 to 3.38), with delayed time to relapse/recurrence for MBCT-TS participants with a more abusive childhood compared with those with a less abusive history. Although changes in mindfulness were specific to MBCT (and not m-ADM), they did not predict outcome in terms of relapse/recurrence at 24 months. In terms of acceptability, the qualitative analyses suggest that many people have views about (dis)/continuing their ADM, which can serve as a facilitator or a barrier to taking part in a trial that requires either continuation for 2 years or discontinuation.

Conclusions: There is no support for the hypothesis that MBCT-TS is superior to m-ADM in preventing depressive relapse/recurrence among individuals at risk for depressive relapse/recurrence. Both treatments appear to confer protection against relapse/recurrence. There is an indication that MBCT may be most indicated for individuals at greatest risk of relapse/recurrence. It is important to characterise those most at risk and carefully establish if and why MBCT may be most indicated for this group.

Trial registration: Current Controlled Trials ISRCTN26666654.

Funding: This project was funded by the NIHR Health Technology Assessment programme and the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care South West Peninsula and will be published in full in *Health Technology Assessment*; Vol. 19, No. 73. See the NIHR Journals Library website for further project information.

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List of abbreviations

AD-SUS	Adult Service Use Schedule
ADM	antidepressant medication
BDI-II	Beck Depression Inventory, second edition
BNF	*British National Formulary*
CBT	cognitive–behavioural therapy
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions three-level version
FFMQ	Five Factor Mindfulness Questionnaire
GP	general practitioner
GRID-HAMD	GRID-Hamilton Depression Rating Scale
HR	hazard ratio
HRSD	Hamilton Rating Scale for Depression
ICC	intraclass correlation coefficient
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
LEG	Lived Experience Group
LIFE	Longitudinal Interval Follow-up Evaluation
m-ADM	maintenance antidepressant medication
MBCT	mindfulness-based cognitive therapy
MBCT-TS	mindfulness-based cognitive therapy with support to taper/ discontinue antidepressant medication
MBI-TAC	Mindfulness-Based Interventions – Teacher Assessment Criteria
MBSR	mindfulness-based stress reduction
MHRA	Medicines and Healthcare products Regulatory Agency
MOPS	Measure of Parenting Scale
MRC	Medical Research Council
MSCL	Medical Symptom Checklist
NICE	National Institute for Health and Care Excellence
PSS	Personal Social Services
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SCID	Structured Clinical Interview for DSM-IV
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
SWAD	Staying Well After Depression
TSC	Trial Steering Committee
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life-BREF

Plain English summary

Research has shown that people who have had three or more episodes of depression have a high risk of becoming depressed again; however, this risk can be reduced if antidepressants are taken for 2 years after recovery or if patients attend a course of mindfulness-based cognitive therapy (MBCT).

The PREVENT trial was designed to find out if over 24 months MBCT with support to taper/stop antidepressants (MBCT-TS) reduced the number of relapses/recurrences compared with continuing antidepressants for patients who had experienced three or more previous episodes of depression. In total, 424 people took part and half were randomly allocated to attend an MBCT-TS course and stop taking antidepressants and half were allocated to stay on their antidepressants.

Our results suggest that MBCT-TS is not better than antidepressants at preventing depression recurring; at the end of the 24-month period the number of people who had become depressed again was very similar in both groups (MBCT-TS 44%, antidepressants 47%). It would seem that both treatments were relatively effective at keeping people well. We did not find a difference between the two treatments in terms of cost. However, we did find that for people who are at a higher risk of relapse/recurrence MBCT-TS may in fact be more effective than antidepressants and we recommend that further research is carried out to explore this relationship in more depth.

Scientific summary

Background

Depression typically runs a relapsing and recurrent course. Without ongoing treatment, individuals with recurrent depression have a high risk of repeated depressive relapses/recurrences throughout their life, with rates of relapse/recurrence typically in the range of 50–80%. Major inroads into the substantial health burden attributable to depression could be made through interventions that prevent depressive relapse/recurrence among people at highest risk. If the factors that make people vulnerable to depressive relapse/recurrence can be attenuated, the recurrent course of depression could potentially be broken.

Currently, most depression is treated in primary care and maintenance antidepressant medication (m-ADM) is the mainstay approach to preventing relapse/recurrence. The UK's National Institute for Health and Care Excellence (NICE) recommends that, to stay well, people with a history of recurrent depression should continue on m-ADM for at least 2 years. However, adherence rates tend to be poor, m-ADM is protective only for as long as it is taken and is contraindicated for some groups, patients at higher risk receive less protection from m-ADM and many patients express a preference for psychosocial interventions that provide long-term protection against relapse/recurrence.

Mindfulness-based cognitive therapy (MBCT) was developed as a psychosocial intervention to teach people with recurrent depression the skills to stay well in the long term. A systematic review and meta-analysis of six randomised controlled trials ($n = 593$) suggests that MBCT significantly reduces the rates of depressive relapse/recurrence compared with usual care or placebo, corresponding to a relative risk reduction of 34% [risk ratio 0.66, 95% confidence interval (CI) 0.53 to 0.82]. A key remaining uncertainty is whether MBCT provides an alternative for people wishing to discontinue m-ADM. There is accumulating evidence that MBCT may confer most benefit to patients at greatest risk.

Objectives

The overarching policy aim and research question of the PREVENT trial was to establish whether MBCT with support to taper and/or discontinue antidepressant medication (MBCT-TS) is superior to and more cost-effective than an approach of m-ADM in a primary care setting for patients with a history of recurrent depression followed up over a 2-year period in terms of a primary outcome of preventing depressive relapse/recurrence. Secondary outcomes were depression-free days, residual depressive symptoms, psychiatric and medical comorbidity, quality of life and cost-effectiveness over 24 months. The trial also sought to address whether an increase in mindfulness skills is the key mechanism of change of MBCT and explore barriers to participation in MBCT-TS within the PREVENT study.

Methods

The PREVENT study was a two-arm, multicentre, single-blind superiority trial randomly allocating patients in a 1 : 1 ratio to receive either MBCT-TS or m-ADM. The m-ADM was constant over the 2 years of the study and the psychosocial intervention was a front-loaded, 8-week relapse/recurrence prevention programme. Patients in the MBCT-TS arm received support to taper their antidepressant medication (ADM). The trial included a parallel economic evaluation to examine the cost-effectiveness of MBCT-TS compared with m-ADM. It included a mixed-methods process evaluation to examine the acceptability and mechanism of action of MBCT.

Participants were considered for inclusion if they:

- had had three or more previous major depressive episodes in which depression was the primary disorder and which were not secondary to substance abuse, bereavement or a general medical condition
- were aged ≥ 18 years
- were on a therapeutic dose of ADM in line with *British National Formulary* (BNF) and NICE guidance
- were open either to continue taking antidepressants for 2 years or to take part in a MBCT class and stop their ADM.

Participants were considered unsuitable for inclusion if they:

- were currently depressed
- had a comorbid diagnosis of current substance abuse
- had organic brain damage
- had current/past psychosis, including bipolar disorder
- displayed persistent antisocial behaviour
- engaged in persistent self-injury that required clinical management/therapy
- were undergoing formal concurrent psychotherapy.

Searches were carried out of computerised general practice databases to identify patients who were currently being prescribed a therapeutic dose of ADM in line with BNF and NICE guidance. Subsequent to each participant giving written informed consent, participants were randomly allocated to receive either m-ADM or an 8-week MBCT class that included support to taper/discontinue their m-ADM (MBCT-TS) using computer-generated random permuted blocks and stratified by recruitment locality (four sites) and participants' symptomatic status (asymptomatic vs. partially symptomatic).

- *MBCT-TS*. MBCT is a manualised, group-based skills training programme designed to enable patients to learn skills that prevent the recurrence of depression.
- *m-ADM*. Patients in the m-ADM arm received support from their general practitioner (GP) to maintain a therapeutic level of ADM in line with BNF and NICE guidelines.

Data collection

Participants were assessed at six time points: baseline (prior to randomisation), 1 month after the end of the 8-week MBCT-TS programme, which varied between 12 and 24 weeks post randomisation (or the equivalent time in the m-ADM arm) and 9, 12, 18 and 24 months post randomisation.

The primary outcome measure was time to relapse/recurrence of depression. Relapse/recurrence was defined as an episode meeting *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition (DSM-IV) criteria for a major depressive episode. At each follow-up we recorded the secondary outcomes: number of depression-free days, residual depressive symptoms, quality of life, health-related quality of life and psychiatric and medical comorbidities.

The economic perspective included all hospital and community health and social services plus productivity losses, known to be a substantial cost in depression.

Mechanisms were examined through an embedded process study in which the hypothesised mechanism (change in mindfulness) was assessed before and after MBCT and outcome was assessed at 24 months' follow-up. Acceptability was examined through an embedded qualitative study that enabled participants to provide their views and experiences of the acceptability of MBCT through interviews and feedback booklets.

Statistical analysis

Statistical analyses were conducted in accord with International Conference on Harmonisation (ICH-9) statistical guidelines for clinical trials and updated Consolidated Standards of Reporting Trials (CONSORT) guidelines for trials. All statistical analyses were undertaken in Stata version 13 (StataCorp LP, College Station, TX, USA) following a predefined analysis plan agreed with the Trial Steering Committee (TSC).

The study was powered to detect a hazard ratio (HR) of 0.63 between the two treatments at 24 months for the primary outcome, with 90% power and a two-sided 5% alpha level, assuming a small clustering effect [intraclass correlation coefficient (ICC) = 0.01] and allowing for 20% loss to follow-up, producing a target sample size of 420 (210 per arm).

The primary analysis was a between-group comparison of time to relapse/recurrence at 24 months using a Cox regression proportional hazards model adjusted for stratification variables.

Secondary outcomes were compared across all time points using repeated-measures mixed-regression models. Missing data were assumed missing at random and sensitivity analysis examined the effect of missing data using multiple imputations. Between-group inference for secondary outcome analyses was based on the complete case and imputed data sets are reported.

Interaction terms were used to undertake predefined exploratory subgroup analyses on the primary outcome, across the stratification variables (recruitment centre and baseline depression severity) and reported levels of childhood abuse. Participants with a more abusive childhood reported experiencing childhood physical or sexual abuse and/or scored above the median score for the Measure of Parenting Scale (MOPS) abuse subscale. Participants completed the MOPS at baseline as part of an embedded process–outcome study. The abuse subscale asks participants to indicate how true they felt certain statements about their parents' behaviour were, for example 'parent was physically violent or abusive to me', 'parent made me feel unsafe'. Participants were categorised as either in the lower abusive childhood group (i.e. scored below the median score for the MOPS abuse subscale and did not report childhood physical or sexual abuse) or in the higher abusive childhood group (i.e. scored above the median score for the MOPS abuse subscale or did report childhood physical or sexual abuse).

Differences in mean costs were analysed using standard parametric *t*-tests with the validity of results confirmed using bias-corrected, non-parametric bootstrapping (repeat resampling). The primary economic analysis compared MBCT-TS and m-ADM from the health and social care perspective preferred by NICE; secondary analyses included productivity losses.

Results

Between 23 March 2010 and 21 October 2011 we recruited 424 patients, of whom 212 were allocated to receive MBCT-TS and 212 were allocated to receive m-ADM. Primary outcome data were collected for 90% (383/424) of the participants. The remaining participants' data were censored at their last follow-up. We retained 86% (366/424) of participants over the 24-month follow-up period, with 5% (20/424) lost to contact and 8% (34/424) withdrawing consent for further follow-up; in addition, 1% (4/424) died during the trial. The pattern of primary outcome missing data was identical across trial arms (14% in each arm).

With respect to the primary outcome, primary intention-to-treat analysis showed no evidence of a reduction in the hazard of relapse/recurrence with MBCT-TS compared with m-ADM (HR 0.89, 95% CI 0.67 to 1.18; $p = 0.43$), with 44% (94/212) of the MBCT-TS patients relapsing compared with 47% (100/212) of the m-ADM patients [log-rank χ^2 (1) = 0.67; $p = 0.41$].

There was no difference in treatment effect on the primary outcome across either stratification variable subgroup of severity of depression at baseline or recruitment centre. However, there was evidence of a significant interaction between severity of reported childhood abuse and treatment group (HR 0.53, 95% CI 0.29 to 0.95; $p = 0.03$). Specifically, compared with m-ADM, MBCT-TS reduced the risk of relapse/recurrence for participants with a higher severity of reported childhood abuse (47% vs. 59%) whereas there was a slightly higher risk of relapse/recurrence with MBCT-TS compared with m-ADM in the lower severity of childhood abuse subgroup (42% vs. 35%). Given their non-randomised nature, these secondary analyses are prone to selection bias and confounding.

With respect to the secondary outcomes, there was no evidence of MBCT-TS's superiority over m-ADM.

Over 24 months' follow-up, group attendance in the MBCT-TS arm was estimated to cost £112 per participant and the average cost of antidepressants was £40.10 in the MBCT-TS group and £69.79 in the m-ADM group. Use of other health and social care services differed little between groups and hence there was no significant difference in the total health and social care cost per participant between the MBCT-TS group (£2484.52) and the m-ADM group (£2360.41; mean difference £124, 95% CI £–749.98 to £972.57; $p = 0.80$). The results including patient costs (productivity losses and out-of-pocket expenditure) were also non-significant (mean difference £449, 95% CI –£842.18 to £1286.26; $p = 0.68$). There were no significant differences in quality-adjusted life-years (QALYs) over follow-up and the cost–utility and cost-effectiveness analysis did not support the hypothesis that MBCT-TS is cost-effective compared with m-ADM.

To examine MBCT's mechanism of action, meditational analyses were conducted, which showed that, although changes in mindfulness were specific to MBCT (and not m-ADM), they did not predict outcome in terms of relapse/recurrence at 24 months.

In terms of acceptability, the qualitative analyses suggest that many people have views about (dis)continuing their ADM, which can serve as a facilitator or a barrier to taking part in a trial that requires either continuation for 2 years or discontinuation. The most commonly cited reasons for non-participation in the PREVENT trial were related to the treatment interventions provided. Together these accounted for 40% of all reasons given. Within this, the largest category related to use of ADM (19% of all responses). Most commonly, people reported that they did not want to stop taking ADM (49% of ADM reasons). Other reasons were that people were no longer taking ADM (24%), were currently coming off ADM (9%) and were happy with their current ADM use (11%).

Discussion

There was no evidence for the superiority of MBCT-TS over m-ADM for patients with recurrent depression in terms of the primary outcome of time to depressive relapse/recurrence over 24 months or any of the secondary outcomes. Cost-effectiveness analysis does not support the hypothesis that MBCT-TS is more cost-effective than m-ADM in terms of either relapse/recurrence or QALYs.

Relapse/recurrence rates in people with three or more previous episodes can be as high as 80% over 2 years. Moreover, meta-analyses consistently suggest that m-ADM reduces the odds of relapse/recurrence by two-thirds compared with placebo, a halving of the absolute risk. Therefore, it is likely that MBCT would provide benefits over and above either no treatment or pill placebo.

Across both treatment arms, outcomes were comparatively good over the 2 years of follow-up in terms of relapse/recurrence (MBCT-TS 44%, m-ADM 47%), residual symptoms and quality of life.

MBCT is hypothesised to work through teaching mindfulness, a skill that enables people to recognise and respond resiliently in the face of early warning signs of depressive relapse/recurrence. Using a meditational design and a self-report measure of mindfulness we found that, although changes in mindfulness are specific to MBCT, they do not predict relapse/recurrence at 24 months. However, we used a self-report measure and it is possible that alternative approaches to establishing mechanisms of action are needed.

The main barrier to participation in the PREVENT trial at the point of recruitment appears to be expectations surrounding m-ADM use. This applied to both arms of the trial. For most people, their concerns centre on being randomised to MBCT-TS, as they do not consider themselves to be in a position to taper their m-ADM. For a smaller group of people, reluctance to participate relates to being randomised to the m-ADM arm, as this carries an expectation of continuing on m-ADM for 2 years, a prospect that may not be acceptable.

Consistent with an emergent pattern of findings, MBCT may confer most benefit to patients at greatest risk of relapse/recurrence. A reported history of abuse and adversity is associated with worse outcomes among those who suffer from depression. Perhaps MBCT confers resilience in this group at highest risk because patients learn skills that address some of the underlying mechanisms of relapse/recurrence, a question that we will explore in a subsequent publication from this trial. Studies are needed that have the primary aim of establishing the effectiveness and mechanism of action of MBCT for those at differing levels of risk of relapse/recurrence, with robust measures of risk.

Implications for practice and directions for future research

1. MBCT-TS is not superior to m-ADM over 2 years of follow-up for patients with recurrent depression.
2. Benchmarked against epidemiological data, both treatments were associated with enduring positive outcomes in terms of relapse/recurrence, residual depressive symptoms and quality of life.
3. This study provides important evidence that MBCT-TS may confer ongoing protection for patients who would like an alternative to m-ADM.
4. For patients at low risk, m-ADM, which requires less patient commitment and is less costly, may be indicated, whereas, for patients at highest risk, more intensive treatments such as MBCT may be indicated. However, studies have tended to operationalise risk in somewhat different ways (e.g. early adversity, unstable remission, a higher number of previous episodes, early age of onset) and, although these risk factors overlap, future research should examine how and through what mechanism risk is conferred and resilience learned.

Trial registration

This trial is registered as ISRCTN26666654.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research and the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care South West Peninsula.

Chapter 1 Introduction

Background

Depression is a major public health problem that, like other chronic conditions, tends to run a relapsing and recurrent course,[1] producing substantial decrements in health and well-being.[2] The World Health Organization (WHO) predicts that by 2020 depression will be the second leading cause of disability in the world.[3] The cost of mood disorders in the UK has been calculated at 7% of national income with a direct cost to health services of £3B.[4] More than 50% of patients experience at least two episodes of depression.[5] Moreover, without ongoing treatment, people suffering recurrent depression suffer relapse/recurrence at rates as high as 80%, even after successful acute treatment.[5,6] Thus, most of the prevalence, burden and cost of depression is a consequence of relapse/recurrence and the majority of the burden attributable to depression could be offset through interventions aimed at preventing depressive relapse/recurrence.[7]

Current treatments for depression in primary care

Currently, the majority of depression is treated in primary care and treatment with maintenance antidepressant medication (m-ADM) is the mainstay approach to preventing relapse/recurrence.[8–11] To stay well the National Institute for Health and Care Excellence (NICE) recommends that people with a history of recurrent depression continue m-ADM for at least 2 years.[8] However, many patients experience unpleasant side effects, rates of m-ADM adherence tend to be low and patients often express a preference for psychosocial interventions.[12–14] Service user organisations, such as Depression Alliance, therefore advocate greater availability of psychosocial therapies. Government advisors Layard and Clark[4] recommend that there should be parity of esteem for mental and physical health. That is, today, evidence-based treatment should be as available for mental illness as for physical illness. They provide a compelling narrative that this would be a cost-effective approach to enhancing the mental health of the nation. In line with this, significant government initiatives, such as Improving Access to Psychological Therapies, aim to offer accessible, acceptable and cost-effective psychosocial models of care and the last 10 years has seen significant progress in the accessibility of evidence-based mental health services in the UK.[4,15,16]

Psychosocial approaches to prevent depressive relapse/recurrence

There is a strong evidence base for psychosocial treatments for recurrent depression, most notably cognitive–behavioural therapy (CBT) and interpersonal therapy, and promising evidence for several other therapies.[8,17] Policy initiatives, user groups and professional consensus recommend as priorities for future research the development of psychosocial interventions to prevent depressive relapse/recurrence and the use of non-traditional delivery systems, such as group interventions, to maximise accessibility and cost-effectiveness.[18,19] Mindfulness-based cognitive therapy (MBCT) is a psychosocial group-based relapse prevention programme. It was developed from translational research into mechanisms of depressive relapse/recurrence.[20] It is recommended by NICE as a psychological approach to relapse prevention for people who are currently well but who have experienced three or more previous episodes of depression.[8] There is much clinical enthusiasm for MBCT, as evidenced by the high rates of patient engagement, the development of MBCT therapist training programmes in the UK at the Universities of Bangor, Exeter and Oxford and more recently the development of an All Party Parliamentary Group on Mindfulness.[21] Implementation of MBCT throughout the NHS is patchy and variable but becoming more widespread.[22,23] In summary, MBCT shows the potential to contribute significantly to reducing the prevalence of depression in UK primary care settings.

Review of the evidence for mindfulness-based cognitive therapy up to the trial start date

Efficacy and effectiveness

The first two MBCT randomised controlled trials (RCTs) of patients with a history of recurrent depression, currently in remission and not receiving any active treatment, reported in 2000[24] and 2004.[25] Both found that MBCT plus usual care halved the rate of relapse/recurrence compared with usual care alone over 60 weeks of follow-up [hazard ratio (HR) 0.47, 95% confidence interval (CI) 0.27 to 0.84;[25] HR 0.28, 95% CI 0.13 to 0.60[24]]. In both trials patients were able to seek help as they normally would over the course of the study and rates of treatment update were comparable across both arms of the trial. However, to provide a robust test of the potential effectiveness of MBCT over usual care, both trials included only people not currently receiving antidepressant medication (ADM) at the time of study entry. Moreover, as a first test of MBCT, the comparison was usual care rather than another active treatment.

A systematic review published in 2007 that included these first two trials and two further replications in Europe showed a significant additive effect of MBCT over usual care for patients with recurrent depression, but only for patients who have experienced three or more previous episodes.[26] This is the same evidence that led to NICE's guidance that MBCT be offered as a relapse prevention approach to patients with three or more episodes of depression.

Exploratory pilot trial

Through a Medical Research Council (MRC)-funded pilot trial[27–29] we sought to address the gaps in the evidence base outlined in the previous section by comparing MBCT with the current mainstay approach to relapse prevention, m-ADM. In this pilot trial 123 patients who were currently taking m-ADM to manage recurrent depression were randomised to either continue m-ADM or take part in a MBCT course and then taper and discontinue their m-ADM. The findings suggested that MBCT may not only provide an alternative to m-ADM (relapse/recurrences at 15 months: MBCT 47%, m-ADM 60%), but also, in an adequately powered definitive trial, produce superior outcomes (*Figure 1*).[28] Finally, the study suggested that MBCT may also be superior to m-ADM in terms of improved quality of life, reduced residual depressive symptoms and reduced psychiatric comorbidity. The study's stated aims and outcomes were:

i. *Examine feasibility*. The achievement of all study milestones within budget and on time demonstrated feasibility.
ii. *Establish recruitment methods*. An acceptable and effective recruitment methodology was developed as evidenced by our over-recruitment by 54%.
iii. *Establish a training model for MBCT therapists*. We developed a model of training with input from John Teasdale, one of the developers of MBCT.
iv. *Cost MBCT*. The MBCT intervention was estimated to cost circa £200 per participant,[28] which compares favourably with an estimated cost of £750 for individual CBT.[16]
v. *Elicit service user feedback*. At the end of the pilot trial all participants were interviewed and asked about their experience of MBCT as a relapse prevention programme.[30] These studies informed the PREVENT study to maximise MBCT's acceptability and application to supporting patients taper and discontinue their m-ADM.

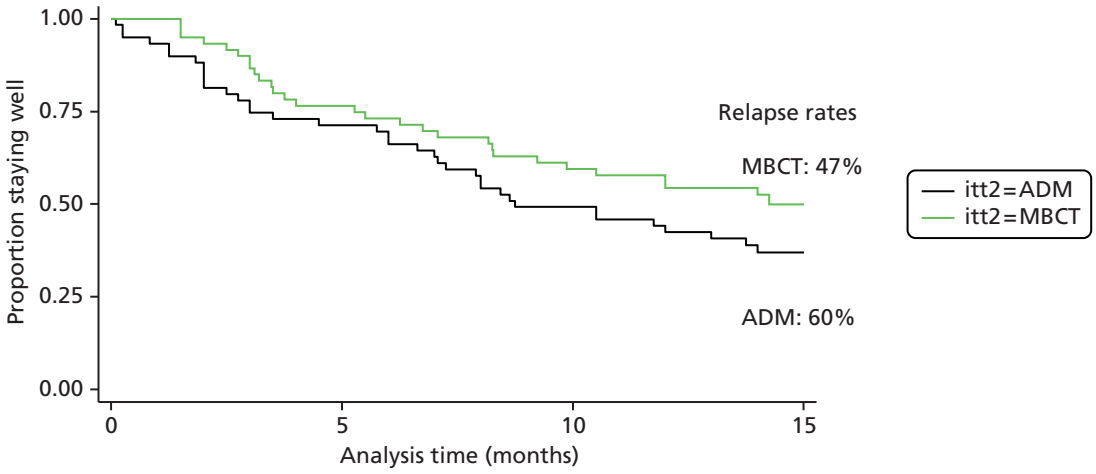

FIGURE 1 Kaplan–Meier survival curve in the exploratory trial. Survival estimates by intention to treat.

Costs and cost-effectiveness

To inform commissioning of care for people with recurrent depression we must establish MBCT's cost-effectiveness over an adequate follow-up period. In our pilot trial[28] we found that the per-person cost for the MBCT group was £274 more than that for the m-ADM group but this difference was not significant. Cost-effectiveness analyses suggested that the additional cost of MBCT may be justified in terms of improvement in the proportion of patients who undergo relapse/recurrence, but only if willingness to pay for such improvements is ≥ £600. In terms of depression-free days, the incremental cost-effectiveness ratio (ICER) of MBCT is comparable with that in similar studies, with a ratio of £30 per depression-free day for total costs and £14 per depression-free day for health service costs. (Please note that these costs were reported in reference 28 in international dollars using a conversion rate of 0.6.) Recent ICERs for collaborative care programmes include £20 in terms of total outpatient costs[31] and £12 in terms of total inpatient and outpatient costs.[32] Estimates of £8–14 have been reported for a depression relapse prevention programme.[33] Exploration of costs over time suggested that differences in cost converge and MBCT becomes cheaper than m-ADM over the final 3-month period of the study. If this trend were to continue, the relative cost-effectiveness of MBCT may increase over time. Future studies should consider longer follow-up periods to test this hypothesis.

Process studies to examine acceptability and mechanism of change

As with the cost-effectiveness of MBCT, the evidence for the mechanism of change in outcomes with MBCT therapy is limited. Coelho *et al.*[26] found no evidence of the 'specific effectiveness of MBCT, despite this being the logical progression from the current research' (p. 1004). In other words, no trials had shown whether MBCT works through its specific hypothesised mechanisms and/or through non-specific cognitive–behavioural, psychoeducation and group/therapist support components. They therefore recommended 'the need for randomised controlled trials to compare MBCT with other non-pharmacological approaches' (p. 1005) and the inclusion of tests of the specific and non-specific mechanisms of change.

Proposed mechanisms of action

Mindfulness-based cognitive therapy's theoretical premise is that depressive relapse/recurrence is associated with the reinstatement of negative modes of thinking and feeling that contribute to depressive relapse and recurrence.[34] This 'reactivated' network of negative thoughts and feelings can perpetuate into a depressive episode. Laboratory studies support this model by showing that recovered depressed patients revert to a depressive information processing style following a sad mood induction (for a review see Segal *et al.*[35]). Following successful treatment for depression, those patients showing greater reactivation of dysfunctional thinking styles in response to a sad mood provocation are at the highest risk of relapse/recurrence over an 18-month period.[35] Moreover, patients who recovered with CBT showed significantly less cognitive reactivation than those who recovered with ADM. Attenuating the reactivation of dysfunctional thinking styles may therefore represent one mechanism by which CBT helps prevent depressive relapse/recurrence. Mindfulness skills are taught as a means to note distressing thoughts and feelings, hold such experiences in awareness and cultivate acceptance and self-compassion to break up associative networks and offset the risk of relapse/recurrence.[34] This dimension of mindfulness, which involves meeting distressing thoughts and feelings with kindness, empathy, equanimity and patience, is woven into mindfulness-based applications and is thought to be crucial to the change process.[36] Intentional attention is learned in the first three MBCT sessions using a range of core mindfulness practices (the body scan, mindful movement and mindfulness of the breath). As well as developing attention, these early sessions highlight habitual patterns of reactivity that arise during meditation (e.g. intrusive negative thoughts) and the associated aversion and judgements (e.g. 'I am no good at this, I am just more aware of how badly I feel'). As the person learns mindfulness skills, he or she learns to give less authority to self-judgement and blame – the fuel for depressive thinking – and to respond to these states with compassion, in short to step out of habitual unhelpful patterns of thinking.[36] Elucidating these putative mechanisms of action of MBCT will improve theoretical understanding of how this relatively new treatment works and provide the opportunity to enhance efficacy through emphasis of these mechanisms.

Our previous mechanisms study, which was embedded in the pilot trial, demonstrated that, consistent with MBCT's theoretical premise, increases in mindfulness and self-compassion across treatment mediated the effect of MBCT on depressive symptoms at 15 months' follow-up.[37] Furthermore, MBCT changed the relationship between post-treatment cognitive reactivity and depressive outcome. In patients receiving m-ADM, greater reactivity predicted poorer outcome, replicating previous findings.[35] However, following MBCT there was no support for this toxic relationship between reactivity and outcome, with an indication that enhancement of self-compassion had nullified this relationship. These findings were consistent with an evidence synthesis arguing that MBCT works through a 'retraining of awareness and non-reactivity, allowing the individual to more consciously choose those thoughts, emotions, and sensations, rather than habitually reacting to them' (p. 569).[38] The results are also in line with data using a self-report measure of cognitive reactivity showing that MBCT attenuates reactivity and its impact on depression.[39] This is reflected in distinct neural responses to sad mood in people who had undergone MBCT, suggesting a neural basis for these findings.[40] The findings suggest that, whereas negative mood may reactivate dysfunctional thinking patterns in people who have participated in a MBCT class, it is their response to these dysfunctional thoughts that is altering their impact at follow-up.

Rationale for the research

In summary, the evidence for MBCT indicates that it is more effective than usual care in preventing depressive relapse/recurrence in people with a history of three or more episodes. Moreover, there is preliminary evidence from our pilot trial to indicate that it may be cost-effective and that it works through its hypothesised mechanism. An editorial published in 2012 in the *British Medical Journal*[41] concluded that key remaining uncertainties include (1) whether or not MBCT provides an alternative for people wishing to discontinue m-ADM, (2) how acceptable MBCT is and (3) what mechanism MBCT works through.

Aims and objectives

The overarching policy aim and research question of the PREVENT trial was to establish whether MBCT with support to taper and/or discontinue antidepressant medication (MBCT-TS) is superior to and more cost-effective than an approach of m-ADM in a primary care setting for patients with a history of recurrent depression followed up over a 2-year period.

The specific objectives of the PREVENT trial were to compare MBCT-TS and m-ADM for patients with recurrent depression in terms of:

- time to depressive relapse/recurrence over 2 years (primary outcome)
- depression-free days, residual depressive symptoms and health-related quality of life at 1 month post treatment and 9, 12, 18 and 24 months post randomisation and psychiatric and medical comorbidity at 12 and 24 months post randomisation (secondary outcomes)
- costs and cost-effectiveness as assessed by incremental cost per relapse/recurrence prevented and incremental cost per quality-adjusted life-year (QALY) at 1 month post treatment and 9, 12, 18 and 24 months post randomisation.

In addition, we asked whether or not an increase in mindfulness skills is the key mechanism of change of MBCT.

To address these policy and explanatory questions patients were recruited through primary care and treated in accessible primary care or community settings. This was a single-blind, parallel RCT examining MBCT-TS compared with m-ADM. The m-ADM was constant over the 2 years of the study and the psychosocial intervention was a front-loaded, 8-week relapse/recurrence prevention programme. Patients in the MBCT-TS arm received support to taper their ADM. The process studies employed mixed methods.

Chapter 2 Mindfulness-based cognitive therapy with support to taper and/or discontinue antidepressant medication

Mindfulness-based cognitive therapy

Mindfulness-based cognitive therapy is an 8-week, group-based programme (12–15 participants per group) designed to teach skills that prevent the recurrence of depression.[20] It is derived from both mindfulness-based stress reduction (MBSR), a programme with demonstrated efficacy in ameliorating distress in people suffering chronic disease,[42] and CBT for acute depression,[43] a programme with demonstrated efficacy in preventing depressive relapse/recurrence.[44] MBCT is based on theoretical and empirical work showing that depressive relapse/recurrence is associated with the reinstatement of automatic modes of thinking, feeling and behaving that are counterproductive in contributing to and maintaining depressive relapse and recurrence (e.g. self-critical thinking and behavioural avoidance).[45]

Participants learn to recognise these 'automatic pilot' modes and respond to them in more functional ways by employing complementary cognitive–behavioural and mindfulness practices. This involves recognising early warning signs of depressive relapse/recurrence, being able to 'turn towards' them with kindly interest and decentring in ways that 'nip them in the bud'. The cognitive–behavioural component involves responding to negative thinking and behavioural activation. In the latter stages of the course participants develop a 'response/action plan' that sets out strategies for responding when they become aware of early warning signs of relapse/recurrence. The mindfulness component involves extensive practice of mindfulness skills (e.g. meditation practices) designed to improve participants' attentional control, ability to decentre from negative thinking and emotion regulation and increase self-compassion. There is a movement towards meeting difficulty with curiosity, a quality of allowing and self-compassion before deciding on skilful ways of responding. Participants are encouraged to bring these skills in to all aspects of their lives.

Adaptations made to the mindfulness-based cognitive therapy programme for the PREVENT trial

In the PREVENT trial delivery of MBCT followed the manual as described by Segal, Williams and Teasdale[34] with a few adaptations based on (1) the need for therapists to support MBCT participants in tapering their ADM and (2) experience from the pilot trial.[28] Participants attended a one-to-one orientation session with the therapist followed by group sessions lasting 2.25 hours over 8 consecutive weeks. Session content included guided mindfulness practices (i.e. body scan, sitting meditation, movement); inquiry into participants' experience of these practices; weekly review of home practice (i.e. 40 minutes of mindfulness practice per day with the guidance of a CD, bringing mindfulness into everyday life); and teaching of/dialogue around cognitive–behavioural skills. MBCT-TS patients also received an additional four group reunion sessions during the first year of follow-up to provide ongoing support and rehearse the key components of the interventions. The first of these booster sessions occurred within 3–5 weeks after the end of the 8-week MBCT-TS programme as this was the time when patients would be tapering their ADM and may be in most need of support. Such booster sessions significantly enhance relapse/recurrence prevention[46] and were a match for general practitioner (GP) attention, which was part of ongoing clinical management in the m-ADM group. A list of the individual adaptations and when they were made is provided in *Table 1*.

TABLE 1 Adaptations to the MBCT programme

Rationale for adaptation	Adaptation	When it came into effect
Preparation for tapering of medication at session 6 by increasing understanding of relapse/recurrence and ways of taking action/responding at an earlier stage	• Inviting participants to complete a short questionnaire prior to the orientation session around relapse/recurrence signatures and ways of taking action • Broadening relapse/recurrence signature to include responding (to link with what is learned on the 8-week course) as well as action • Basing the learning about participants' depression at orientation around their relapse/recurrence signature	• In the 1-hour one-to-one orientation session with the therapist prior to the group starting
	• Having the relapse/recurrence signature and ways of responding/acting as work in progress throughout the course – holding it in mind and actively adding to it	• Referring to the relapse/recurrence signature at appropriate moments in inquiry throughout the course • Actively inviting dialogue as part of the home practice review from session 3 onwards
Involving GPs in the participants' response plan	• Inviting participants to provide a copy of their plan for us to send to their GP on completion of the group with the discharge letter	• Relapse/recurrence signature/action plan introduced at the orientation session • Plan collected at first follow-up
Supporting participants around the early stages of tapering	• The first follow-up session was planned shortly after the group ended (3–5 weeks) • The content was around maintaining practice, turning towards the difficult and adding to relapse/recurrence signatures. This session was with the original group but subsequent follow-up sessions involved merged groups from all trial groups	• 3–5 weeks after session 8 – this date was included with the initial dates and so in many ways felt like session 9
Teaching about depression at an experiential level, allowing participants to track their process with awareness, to illustrate the potential for relapse/recurrence around a drop in mood and how mindfulness may offer the possibility of somewhere else to stand rather than being dragged down the spiral	• A sequence of introducing the automatic thoughts questionnaire as a practice, brief inquiry, breathing space, brief inquiry, watching slides from *The Black Dog* illustrated book, brief inquiry, walking practice, brief inquiry, 'Healing from Within' DVD, summary of session	• Session 4
Allowing more space for working with difficulty	• Simplifying the sitting practice to include breath, body and working with difficulty. Following this up with an optional CD 'Exploring the Difficult' for home practice	• Session 5

Chapter 3 Trial design and methods

Study design

The PREVENT trial was a two-arm, multicentre, single-blind superiority trial randomly allocating patients in a 1 : 1 ratio to receive either MBCT-TS or m-ADM. The trial included a parallel economic evaluation to examine the cost-effectiveness of MBCT-TS compared with m-ADM and a mixed-methods process evaluation that used qualitative methods to assess the acceptability of MBCT-TS from the perspectives of patients and included a quantitative analysis of potential mediators.

Setting, participants and recruitment

We recruited participants from 95 general practices in urban and rural settings in four UK centres: Bristol, Exeter and East Devon, North and Mid Devon and South Devon. Inclusion and exclusion criteria for patient participation were refined through the pilot trial[28] to maximise real-world applicability to the population of people in primary care with recurrent depression who are treated with ADM and who are interested in considering a psychological approach to relapse/recurrence prevention. They are also based on our experience of running a Devon NHS Primary Care Trust-commissioned depression service (see www.centres.ex.ac.uk/mood/).

Inclusion criteria

Participants were considered for inclusion if they:

- had a diagnosis of recurrent major depressive disorder in full or partial remission according to the *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition (DSM-IV)[47]
- had had three or more previous major depressive episodes in which depression was the primary disorder and it was not secondary to substance abuse, bereavement or a general medical condition
- were aged ≥ 18 years
- were on a therapeutic dose of ADM in line with the *British National Formulary* (BNF)[48] and NICE guidance[8]
- were open either to continue taking antidepressants for 2 years or to take part in a MBCT class and consider stopping their ADM.

Exclusion criteria

Participants were considered unsuitable for inclusion if they:

- were currently depressed, as assessed using the Structured Clinical Interview for DSM-IV (SCID)[47]
- had a comorbid diagnosis of current substance abuse (patients with previous substance abuse were eligible for inclusion as long as they were in sustained full remission)
- had organic brain damage
- had current/past psychosis, including bipolar disorder
- displayed persistent antisocial behaviour
- engaged in persistent self-injury that required clinical management/therapy
- were undergoing formal concurrent psychotherapy.

Recruitment procedure

The recruitment strategy for the PREVENT trial built on the protocol used in the pilot trial, which proved acceptable and effective.[29] This is summarised in the following pathway:

1. General practice searches identified patients who had been prescribed ADM at a therapeutic dose in the last 3 months.
2. GPs were then asked to screen this list to exclude any patients who they knew met the exclusion criteria.
3. Letters were sent to the remaining patients enclosing an information pamphlet and reply form.
4. Interested patients were telephoned to discuss the study and a short eligibility screening interview was conducted over the telephone. Information about the study and MBCT was available to help people to begin to make an informed decision about participation. This included the timings and locations of the MBCT groups. The vast majority of exclusions were identified at this stage.
5. Patients who met the telephone screening criteria were invited to attend a face-to-face baseline interview.
6. Consenting patients who met the PREVENT inclusion criteria joined the trial during the baseline assessment.
7. Within a month of the start of the next MBCT-TS group a current GRID-Hamilton Depression Rating Scale (GRID-HAMD)[49] score was obtained for each participant so that randomisation could occur.

Although the majority of referrals were through GP surgeries, interested patients were also able to self-refer into the study. We employed a number of different strategies to advertise the trial including placing posters in carefully targeted sites, developing a website, regional media coverage and leaflet dropping in local chemists.

Patients were recruited in cohorts during recruitment 'time slices' that corresponded to the 6–8 weeks before the next MBCT-TS group was due to start. Baseline assessments were conducted as close as possible to the start of the MBCT-TS group as residual depressive symptoms are a powerful predictor of relapse/recurrence.[50] On average, each researcher recruited six patients per month (*Figure 2*).

Randomisation and concealment

Patients were randomised in a 1 : 1 ratio to either MBCT-TS or m-ADM using computer-generated random permuted blocks and stratified by recruitment locality (four sites) and symptomatic status (asymptomatic: GRID-HAMD score < 8 vs. partially symptomatic: GRID-HAMD score ≥ 8). Stratification by locality enabled a proportionate workload for research staff and therapists. Residual depressive symptoms are a powerful predictor of relapse/recurrence.[50] Moreover, the pilot trial suggested the importance of this stratification variable in predicting outcome.[27] To ensure concealment randomisation was conducted using a password-protected trial website that was maintained by the Peninsula Clinical Trials Unit (CTU), a UK Clinical Research Collaboration (UKCRC)-accredited CTU. Participants were informed of the outcome of randomisation in a letter sent from the trial administrator. Research assessors were blind to treatment allocation; in cases in which blindness was broken participants were assigned to another research assessor. The fidelity of this masking was moderate, with assessors correctly guessing allocation for 56% of assessments. Given the nature of the interventions, patients and clinicians were aware of treatment allocation.

Patients were randomised in the month before the next MBCT-TS group began. If a participant's baseline assessment occurred more than a month before the next MBCT-TS group began he or she received a brief 'randomisation assessment' before being randomised. During this assessment the patient was asked to give a verbal reaffirmation of his or her wish to take part in the trial and researchers ensured that the patient's situation had not changed significantly and also obtained a current GRID-HAMD score.

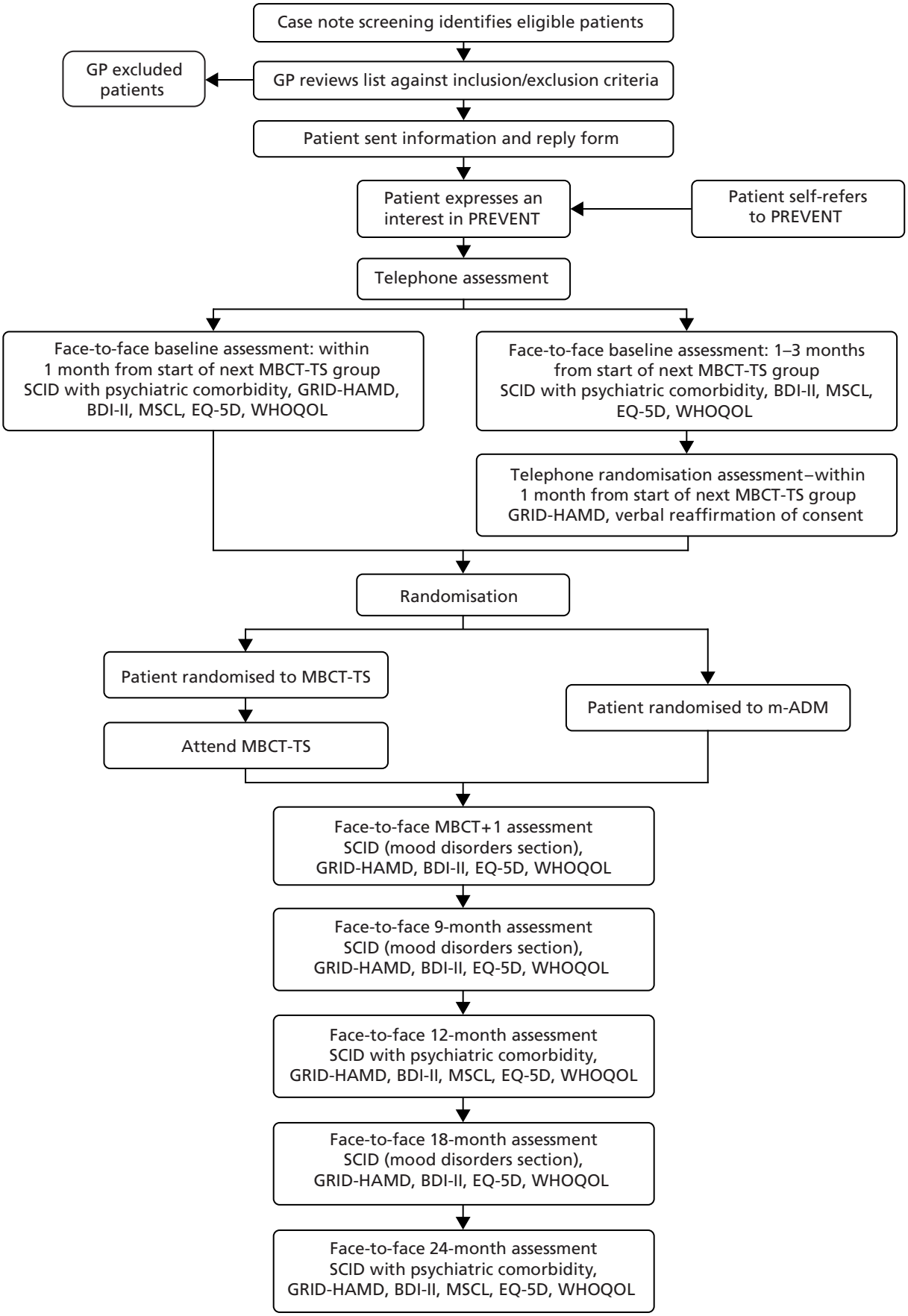

FIGURE 2 Summary of the PREVENT recruitment process and follow-up assessments. BDI-II, Beck Depression Inventory, second edition; EQ-5D, European Quality of Life-5 Dimensions; MSCL, Medical Symptom Checklist; WHOQOL, WHO Quality of Life.

Health technologies assessed

Maintenance antidepressants

The m-ADM relapse/recurrence prevention intervention consisted of maintenance of the ADM treatment that was an inclusion criterion for the trial. Participants were monitored and treated by their physician in a primary care setting. During the maintenance phase, physicians were asked to manage m-ADM in line with standard clinical practice and the BNF. Primary care physicians were asked to meet with patients regularly to review their medication. Changes in medication sometimes occurred during the maintenance treatment stage but physicians and participants were asked to ensure that the dose remained within therapeutic limits. The trial GPs (Dr Richard Byng and Dr David Kessler) and trial psychiatrist (Professor Glyn Lewis) provided materials for all participants and participating GPs on m-ADM and ongoing support as required.

We encouraged participants to adhere to medication for the full length of the trial by sending them letters signed by the chief investigator and their GP after each follow-up, reminding them that the trial was seeking to compare staying on antidepressants for 2 years with taking part in mindfulness classes and stopping ADM. If difficulties with continuation of medication were identified, the trial manager first contacted the participant to understand the difficulty and then whenever appropriate encouraged the participant together with his or her GP to consider maintaining m-ADM in line with standard clinical practice and the BNF. Patients in the m-ADM arm who did not maintain m-ADM in line with BNF and NICE guidelines still remained in the trial and follow-up data were collected as per those who did maintain m-ADM in line with guidelines.

Mindfulness-based cognitive therapy with support to taper and/or discontinue antidepressant medication

A total of 21 MBCT-TS groups were delivered by four therapists in a variety of settings including university campuses, hospital sites and other community-based rooms. Two of the therapists ran seven groups, one ran five and one ran two groups. Two of the groups ran in the evening and the rest were held during the day from Monday to Friday. There were between 4 and 14 participants in each group with an average of 10 per group [standard deviation (SD) 2.6 per group]. The treatment programme involved eight 2.25-hour group sessions, normally over consecutive weeks, with up to four refresher sessions offered in the year following the end of the 8-week programme. In line with previous MBCT trials,[24,28,51] an adequate dose of MBCT-TS was defined as participation in at least four of the eight MBCT-TS group sessions. If participants did not receive an adequate dose of MBCT-TS they were not asked to taper/discontinue their m-ADM; however, outcome data were still collected as per those who did receive an adequate dose.

The four MBCT therapists were all mental health professionals (two clinical psychologists and two occupational therapists). They had post-qualification experience ranging from 9 to 30 years, with an average of 19 years (SD 8.9 years). All had extensive training and experience in leading MBCT groups (minimum 4 years) and a long-standing ongoing personal mindfulness practice (minimum 7 years). An independent check on therapist competency was established before therapists progressed to running trial groups. An experienced MBCT therapist independent of the trial rated at least two videotapes of MBCT-TS therapy sessions and, using the Mindfulness-Based Interventions – Teacher Assessment Criteria (MBI-TAC),[52] made an overall judgement about whether the therapists were competent. During the trial, all four therapists received supervision every 2 weeks for 3 hours; this was attended once per month by the chief investigator.

All trial groups were videotaped with a digital camera for therapist supervision and checks on therapist competence and adherence. Randomly selected samples of two sessions for each 8-week course (42 sessions in total) were assessed by a MBCT expert independent of the trial team. As for the initial competency checks the MBI-TAC was used and these checks indicated that the MBCT teaching was at and above required levels (*Table 2*). The mean total adherence score in the trial (23.6, SD 4.30) was at least comparable with those reported in the psychometric evaluation of this scale[53] and indicate acceptable adherence to protocol. There were no significant differences between therapists' total adherence scores as determined by one-way analysis of variance (ANOVA) ($F_{3,37} = 0.64$; $p = 0.59$).

TABLE 2 Profile of MBCT session teacher competency scores across the 42 sampled sessions

MBI-TAC domains	Count (and percentage) for each rating across 42 tapes					
	Incompetent	Beginner	Advanced beginner	Competent	Proficient	Advanced
Coverage, pacing and organisation of the session curriculum	0 (0)	0 (0)	1 (2.4)	5 (11.9)	14 (33.3)	22 (52.4)
Relational skills	0 (0)	0 (0)	1 (2.4)	8 (19.0)	10 (23.8)	23 (54.8)
Embodiment[a]	0 (0)	0 (0)	1 (2.4)	8 (19.5)	13 (31.7)	19 (46.3)
Guiding mindfulness practices	0 (0)	0 (0)	3 (7.1)	1 (2.4)	15 (35.7)	23 (54.8)
Conveying course themes through interactive inquiry and didactic teaching	0 (0)	0 (0)	2 (4.8)	7 (16.7)	15 (35.7)	18 (42.9)
Facilitation of the group learning environment	0 (0)	0 (0)	2 (4.8)	12 (28.6)	11 (26.2)	17 (40.5)

a Under the domain of embodiment there was one occasion when the external assessor felt unable to rate.

Participants in the MBCT-TS arm were encouraged to taper and discontinue their m-ADM and the study team provided guideline information to physicians and participants about typical tapering/discontinuation regimes and possible withdrawal effects; however, the actual timeline and regime used were determined by physicians and participants. The original MBCT manual[34] was adapted to include more work on developing a relapse/recurrence signature and response plan that explicitly included participants considering reduction/discontinuation of m-ADM. Participants in the MBCT-TS arm who experienced a significant deterioration following tapering were encouraged to use the skills developed as part of the treatment. Letters signed by the chief investigator and trial GP were sent to each participant's GP, copied to the participant, prompting the GP to have a discussion with the participant about a suitable tapering/discontinuation regime after 4–5 weeks of the MBCT-TS group. At the end of the MBCT-TS group another letter was sent reminding the GP to ensure that a tapering/discontinuation regime was in place. We also encouraged participants to taper/discontinue their medication by writing to them and their GP after each follow-up reminding them that the trial was seeking to compare staying on antidepressants with taking part in mindfulness classes and stopping ADM.

If at any time the study team became aware of difficulties with medication tapering/discontinuation, the trial manager first contacted the participant to understand the difficulty and then whenever appropriate encouraged the participant together with his or her GP to once more consider tapering/discontinuing m-ADM. Participants in the MBCT-TS arm who did not taper or discontinue their m-ADM still remained in the trial and follow-up data were collected as per those who did discontinue.

If participants experienced a relapse/recurrence during the course of the trial we encouraged them to discuss the most appropriate treatment with their GP and made no further requests that they consider tapering/discontinuing their medication. However, participants who had relapsed still remained in the trial and further secondary outcome data were collected on the same schedule as per participants who had not relapsed.

Data collection

Baseline assessments did not occur more than 3 months from the start of the next MBCT-TS group, with the start defined as the first orientation session. Following randomisation, participants were assessed at five time points: 1 month after the end of the 8-week MBCT-TS programme (or the equivalent time in the m-ADM arm), which varied between 12 and 24 weeks post randomisation, and 9, 12, 18 and 24 months post randomisation.

Outcomes

Primary outcome

The occurrence of any depressive relapse/recurrence, and time from randomisation to relapse/recurrence, were assessed using the Longitudinal Interval Follow-up Evaluation (LIFE),[54] a form of the SCID[47] designed for longitudinal studies of depression. A participant was judged to have had a relapse/recurrence if he or she was diagnosed as having a major depressive episode (a score of 5 for 2 consecutive weeks) at any time during the 24-month follow-up period. In conducting the SCID-LIFE interviews, researchers took care to establish the onset of the relapse/recurrence as closely as possible. If the day could not be established they tried to establish the closest week and take the mid-point of that week; if the week could not be established then the closest month or season was established and the mid-point taken.

An experienced clinical psychologist with formal training in the use of the SCID supervised the training of the research staff. To examine inter-rater reliability, we followed the method described in the first MBCT RCT,[24] which had the added benefit of guaranteeing that all assessments were carried out blind to treatment condition. For every first actual, borderline or probable relapse/recurrence, a blinded and experienced rater second rated an audio recording of the SCID interview. In total, 198 recordings were second rated, with agreement being recorded on 89.9% of the recordings. The kappa coefficient for agreement between the study interviewer and the blinded rater was 0.62, suggesting good agreement. When there were disagreements between the first and second rater, consensus was reached through discussion. If a relapse/recurrence was considered marginal, a conservative position of no relapse was recorded. Once a judgement about relapse/recurrence was made, the onset of relapse/recurrence was dated from randomisation to the point at which criteria were met.

A subset of 112 SCID diagnoses were also second rated by an experienced rater who was independent of the trial and agreement was recorded on 95.5% of these diagnosis. The kappa coefficient for these ratings was 0.89, suggesting excellent agreement.

Secondary outcomes

Depression-free days were calculated using the SCID interview and residual depressive symptoms were assessed with the observer-rated interviewer-administered 17-item GRID-HAMD[49] and a well-established self-report measure, the Beck Depression Inventory, second edition (BDI-II).[55] Psychiatric comorbidity was assessed with the full SCID,[47] medical comorbidities were assessed at baseline, 12 and 24 months using the MSCL[56] and health-related quality of life status was assessed using the European Quality of Life-5 Dimensions three-level version (EQ-5D-3L)[57,58] and the WHO Quality of Life-BREF (WHOQOL-BREF).[59,60]

Depression-free days

Depression-free days were calculated from the SCID by first establishing the duration in days of any episodes of depression throughout the follow-up period using the method described earlier. Care was taken to establish the last day of a relapse/recurrence or recurrence of clinically significant symptoms. As before, if the day could not be established then the mid-point of the shortest time period that could be established was used. Each new reported recurrence of depression required that there was a period of 2 months in which remission from the previous episode had been achieved. If there was no remission between two recorded episodes the second episode was regarded as a continuation of the first.

Residual depressive symptoms

The GRID-HAMD is a 17-item modified version of the popular depression rating scale developed by Hamilton in 1960.[61] This scale is an interviewer-administered measure of depressive symptoms with an emphasis on somatic symptoms. Scores range from 0 to 88, with higher scores representing higher levels of depression. The GRID-HAMD was designed to permit the rater to consider the dimensions of intensity and frequency independently for each relevant item in the scale. Symptom intensity is considered on the 'vertical axis' and symptom frequency on the 'horizontal axis'. Symptom intensity, which includes degree of symptom magnitude as well as subjective distress and functional impairment, is rated as absent, mild, moderate, severe or very severe. Symptom frequency is rated as absent, occasional, much of the time or almost all of the time. The GRID-HAMD was administered at every assessment during the 24-month follow-up period.

The vast majority of depression trials fail to measure or report the reliability of their employed instruments, especially secondary outcome measures such as the GRID-HAMD. In the rare circumstances in which reliability is measured, it is carried out in an arbitrary and atheoretical manner. As such, and for the purposes of this trial, we compared the inter-rater reliability of the GRID-HAMD using a subsample of 20 assessments. This sample size was selected in accordance with the method of Walter *et al.*[62] for calculating the sample size for inter-rater reliability analyses. Walter *et al.*[62] estimated that a sample size of about 18–20 observations made between two raters is sufficient to obtain an expected intraclass correlation coefficient (ICC) of 0.9, with a minimum acceptable ICC of 0.7. Further, there is evidence which suggests that the reliability of the GRID-HAMD ratings is dependent on the assessor's experience.[63] Thus, 10 of the 20 observations were randomly selected from assessments completed by an experienced assessor and 10 were selected from assessments completed by a more novice assessor. All 20 assessments from both researchers were obtained from the 18-month follow-up period. The overall ICC for the 20 observations was 0.98, suggesting excellent agreement. The ICC for the 10 assessments completed by the experienced assessor was 0.99, while the ICC for the remaining 10 assessments completed by the novice assessor was 0.86, both suggesting excellent agreement.

The BDI-II[55] is a 21-item self-report instrument developed to measure the severity of depression with an emphasis on affective and cognitive symptoms. Higher scores represent greater depression severity (range 0–63) and minimal (0–13), mild (14–19), moderate (20–28) and severe (29–63) symptom severity ranges have been specified. The BDI-II was administered at every assessment during the 24-month follow-up period.

Medical and psychiatric comorbidities

We used the MSCL and the SCID relevant modules at baseline and 12 and 24 months' follow-up. The MSCL is a list of 115 common medical symptoms and respondents are asked to indicate those that they have experienced as bothersome in the past month.[56] The score is the total number of symptoms checked. Although the reliability and validity of the MSCL have not been evaluated, several studies of MBSR have shown significant reductions in the MSCL score associated with participation in the programme.[64–67]

Health-related quality of life

Health-related quality of life status was assessed using the EQ-5D-3L,[57,58] a non-disease-specific measure for describing and valuing health-related quality of life. It has particular value as a measure because it is capable of generating a generic preference-based measure of outcome (the QALY) that allows for outcomes and cost-effectiveness to be compared across disease areas.[68,69] The measure includes a rating of own health in several domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a rating of own health by means of a 'thermometer' (score 0–100). It has been used extensively and thus has large comparative data sets and its psychometric properties are adequate.[57] The EQ-5D-3L was administered at every assessment during the 24-month follow-up period.

Quality of life was assessed using the WHOQOL-BREF,[59,60] a generic 26-item measure covering the domains of physical health, psychological health, social relationships and environment. It differs from the EQ-5D-3L in providing a more subjective and holistic assessment of quality of life, rather than a self-report measure of health status. The WHOQOL-BREF is based on a longer version of the original instrument, the WHOQOL-100.[70,71] The WHOQOL-BREF was administered at every assessment during the 24-month follow-up period.

Adverse events

We followed the guidelines laid down by the Medicines and Healthcare products Regulatory Agency (MHRA) for identifying, acting on and reporting adverse events, which were defined as any event that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity or consisted of a congenital anomaly or birth defect.

As soon as a researcher became aware of an adverse event they reported this to the trial manager, who then completed a serious adverse event form (see *Appendix 1*). Copies of these forms were sent to the Data Monitoring Committee (DMC), the main NHS Research Ethics Committee and the trial sponsor. No adverse reactions were judged by these committees to be suspected unexpected serious adverse reactions or SUSARs.

Sample size

Different relapse prevention interventions with different populations produce different absolute rates of depressive relapse/recurrence. Therefore, we based our sample size on estimated HRs for MBCT-TS compared with m-ADM rather than estimated absolute relapse/recurrence rates. We canvassed service users and clinicians who concurred that a relative reduction in relapse/recurrence of 10% would be clinically important. We used the systematic review of MBCT compared with usual care for patients with recurrent depression that reported HRs of 0.28–0.47 for relapse/recurrence.[26] We applied several conservative assumptions (first row of *Table 3*). First, even though the pilot trial data suggest that the HR was improving in favour of MBCT as the length of follow-up increased,[28] we assumed a HR of 0.63 at 15 months to power the trial at 24-months' follow-up. Second, even though attrition from MBCT trials to date is consistently < 15%, we assumed an attrition rate of 20% over the 24 months of follow-up. Finally, in spite of evidence to the contrary, we assumed that there may be a small clustering effect (ICC = 0.01). The resultant sample size calculation assumptions and outputs are shown in *Table 3*, based on 90% power and significance set at 0.05. This led to a total sample size of 420 across the two groups.

For the secondary outcomes, meta-analyses of generic mindfulness approaches suggest medium effect sizes in terms of changes in depressive symptoms[72,73] and our pilot trial suggested medium effect sizes for the secondary outcomes of residual depressive symptoms, psychiatric comorbidity and quality of life.[28] The sample size estimate for our policy question enabled us to detect a medium between-groups effect size (standardised mean difference or Cohen's $d = 0.40$) for the main secondary outcomes.

TABLE 3 Sample calculation scenarios

Study	Comparison	Mean HR	ICC	Design factor	Attrition rate	Sample size per group[a]
Conservative scenario	MBCT vs. m-ADM	0.63	0.01	1.11	20%	210
Kuyken *et al.*[28]	MBCT vs. m-ADM	0.63	–0.02	1.0	7%[b]	160
Ma and Teasdale[25]	MBCT vs. usual care	0.28	–0.008	1.0	3%[c]	14[d]
Teasdale *et al.*[24]	MBCT vs. usual care	0.47	–0.04	1.0	5%[c]	41[d]

a Sample size necessary for 90% power at 5% significance at 24 months.
b At 15 months.
c At 60 weeks.
d Assuming exponential survival function.

Statistical analysis

Statistical analyses were conducted in accordance with International Conference on Harmonisation (ICH-9) statistical guidelines for clinical trials[74] and updated Consolidated Standards of Reporting Trials (CONSORT) guidelines for trials.[75,76] All statistical analyses were undertaken in Stata version 13 (StataCorp LP, College Station, TX, USA) following a predefined analysis plan agreed with the Trial Steering Committee (TSC).

Baseline equivalence was assessed descriptively by comparing the summary baseline characteristics and outcome values in both groups (MBCT-TS and m-ADM). Although there was a difference in gender between groups (see *Table 8*), as we know of no strong evidence that gender moderates MBCT treatment outcomes[28] it was decided not to include and adjust for this variable in statistical models.

The primary analysis model for all primary and secondary outcomes was conducted on an intention-to-treat (ITT) basis, that is, between-group comparison based on the random allocation of patients and using complete data sets. All models adjusted for the stratification variables (centre and severity of depression). For the primary outcome the primary analysis included all patients and censored for missing data at 24 months' follow-up. To examine the sensitivity of the results to missing data, secondary outcomes models were also run following multiple imputation (using the 'ICE' and 'MIM' Stata commands and 10 imputation cycles) and based on the assumption that data were missing at random.

The primary outcome (time to relapse/recurrence) was analysed using a Cox regression proportional hazards model including treatment condition (MBCT-TS/m-ADM). We assessed the proportionality of hazards over time by plotting −ln[−ln(survival)] against ln(analysis time) and tested this using Schoenfeld residuals.[23,24] We found no major violations of the proportional hazards assumption. Secondary outcomes were compared using hierarchical repeated measures regression models adjusting for outcome at baseline.

To explore potential treatment moderator effects, interaction terms were included in the Cox regression model for the primary outcome at 24 months for three predefined subgroups: the two stratification variables (centre and severity of depression) and participants in two groups characterised by how abusive their childhood had been. Participants with a more abusive childhood reported experiencing childhood physical or sexual abuse and/or scored above the median score for the Measure of Parenting Scale (MOPS)[77] abuse subscale. Participants completed the MOPS at baseline as part of an embedded process–outcome study.[78] The abuse subscale asks participants to indicate how true they felt certain statements about their parents' behaviour was, for example 'parent was physically violent or abusive to me', 'parent made me feel unsafe'. Participants were categorised either in the lower abusive childhood group (i.e. scored below the median score for the MOPS abuse subscale and did not report childhood physical or sexual abuse) or in the higher abusive childhood group (i.e. scored above the median score for the MOPS abuse subscale or did report childhood physical or sexual abuse).

Given the variable levels of patient adherence to the stated treatment protocol in both the ADM-m and the MBCT-TC groups, we sought to undertake predefined secondary (per-protocol) analyses to examine the potential impact on the primary outcome at 24 months. We first described adherence in the PREVENT trial according to the principles set out by Dodd *et al.*[79] in their systematic review exploring adherence reporting in RCTs by reporting the rates of adherence in the format displayed in *Box 1*.

We then undertook two secondary analyses of the primary outcome comparing groups according to whether participants had (1) received an adequate dose of treatment and (2) adhered to treatment as invited. Definitions of these groups are displayed in *Table 4*.

BOX 1 Categories of adherence to treatment in each trial arm

For the m-ADM arm

- The number of participants who remained on a BNF therapeutically stable dose for the duration of the trial.
- The number of participants who did not remain on a BNF therapeutically stable dose for the duration of the trial.

For the MBCT-TS arm

- The number of participants who did not initiate MBCT-TS treatment.
- The number of participants who initiated MBCT-TS treatment.
- The mean, mode and SD of number of MBCT-TS sessions (0–8) and follow-up sessions attended (0–4).
- The number of participants who completed MBCT-TS treatment.

For those who attended four or more MBCT-TS sessions

- The number of participants who made no reduction to their ADM dose.
- The number of participants who reduced their ADM dose.
- The number of participants who discontinued their ADM.

TABLE 4 Definitions of adherence for each reported secondary sensitivity analysis

Group	Adequate dose of treatment	Adhering to treatment as invited
m-ADM	BNF therapeutic dose of ADM throughout follow-up period	BNF therapeutic dose of ADM throughout follow-up period
MBCT-TS	Attended four or more classes	Discontinued or reduced ADM *and* attended four or more classes

Data management

Missingness within an outcome measure

Data entry and cleaning were overseen by the trial manager and research staff checked each outcome measure for missing data during every assessment and when possible collected missing items at this point. In cases in which ambiguous data were not clarified with the participant we operated a 'score down policy', meaning that if two items were checked the item with the lower rating was entered. When $< 10\%$ of the total or subtotal items for one outcome were missing, the mean as an integer of the missing items subscale was imputed in place of the missing value. If $> 10\%$ of the total was missing then the whole questionnaire was recorded as missing and, if $> 10\%$ of any one subtotal was missing, the whole of that subtotal was marked as missing.

Missing assessments

When substantive missing values arose, analyses was undertaken to assess their impact on the findings of the trial. Missing data were assumed to be 'missing at random',[80] regression-based models were used to assess the relationship between covariates and outcome measure in completers and missing cases were substituted with a predicted outcome value.[81] A sensitivity analysis (with and without imputed data) was undertaken to assess the potential impact of imputation on the trial findings.

Ethical approval and research governance

Multicentre ethical approval for the study was given by the South West Research Ethics Committee (reference number 09/H0206/43) and local research governance approval was obtained for all sites (NHS Devon covering Exeter and Mid and North Devon – PCT0739; NHS Bristol, covering the Bristol site – 2010–004; NHS Plymouth and NHS Torbay, covering the South Devon site – PLY-TOR001). The trial was registered with the International Standard Randomised Controlled Trial Register with the reference number ISRCTN26666654. This trial was classed as a Clinical Trial of an Investigational Medicinal Product (CTIMP) as the MBCT-TS arm randomised patients to alter their standard ADM and as such approval to commence the trial was received from the MHRA (EudraCT number 2009–012428–10). A summary of the changes made to the original protocol is given in *Table 5*.

The University of Exeter sponsored the trial, which was hosted in the Mood Disorders Centre [see www.centres.ex.ac.uk/mood/ (accessed 16 March 2015)], a clinical research setting specialising in translational research hosting current MRC-, Wellcome Trust-, National Institute of Mental Health- and National Institute for Health Research Health Technology Assessment (HTA) programme-funded trials. The trial was overseen by the independent TSC (Chris Leach – Chairperson, Richard Moore and Glenys Parry) and the DMC (Paul Ewings – Chairperson, Andy Field and Joanne MacKenzie).

TABLE 5 Summary of changes to the original PREVENT protocol approved by the South West Research Ethics Committee

Change to protocol	Date
Case note screening not undertaken by research staff and subsequent changes to the patient information sheet	December 2009
Replacement of the follow-up measure SHAP with the DPES	December 2009
Pilot of 3-month follow-up measures on formally depressed individuals who will not be taking part in the main trial	December 2009
Ask pharmacists to insert a short flyer about the trial when dispensing ADM	December 2009
Reimburse reasonable costs incurred when attending MBCT-TS groups for participants who would otherwise be unable to join the trial	July 2010
Pilot qualitative feedback booklets with former NHS patients who have taken part in a previous MBCT group	July 2010
Addition of the FFMQ, SCS, DPES, CERQ and DSC at the 24 months' follow-up	April 2012
Addition of two follow-ups at 36 and 48 months following an invitation from the National Institute for Health Research HTA programme to submit a bid; however, we were unsuccessful in obtaining the funding and therefore these additional follow-ups did not take place	April 2012
Collaboration with the Mental Health Research Network (MHRN) to give all participants an exit questionnaire at their final follow-up exploring the reasons why they chose to take part in the research	June 2012
Change of principal investigator at the Bristol site because of a move to University College London (Dr David Kessler replaced Professor Glyn Lewis)	June 2012
Permission to ask for consent to conduct further analysis on participants' previously provided DNA sample	August 2013

CERQ, Cognitive Emotion Regulation Questionnaire; DPES, Dispositional Positive Emotions Scale; DSC, Depressed States Checklist; FFMQ, Five Factor Mindfulness Questionnaire; SCS, Self-Compassion Scale; SHAP, Snaith–Hamilton Pleasure Scale.

Informed consent

Our recruitment process gave patients several points at which they could learn about the project, either from reading the patient summary pamphlet and information sheet or through discussion with their GP, research staff or others. Consent was finally given through an interview with a researcher following an opportunity for questions. Research staff were trained and all interviews were recorded and supervised.

Participant welfare

Patients' GPs approved their participation in the trial and were informed about the outcome of randomisation. The trial psychiatrist (Glyn Lewis) and GPs (Richard Byng and David Kessler) were on hand to offer participants' GPs further information about the trial and to support GPs in their management of participants' ADM. At the end of the MBCT-TS group, trial staff wrote to GPs to remind them that ADM tapering should normally have started and to ask them to be mindful of the possibility of relapse/recurrence. Over the follow-up period the MBCT-TS patients were invited to attend reunion sessions every 3 months and the therapists remained available by telephone throughout this period. If symptom exacerbation occurred without a full relapse/recurrence, initial management was encouraged to be within the appropriate treatment arm; however, if either patient preference and/or clinical judgement indicated other interventions, these were pursued.

Confidentiality

All of the information collected was kept strictly confidential and held in accordance with the principles of the Data Protection Act 1998.[82] Each participant was assigned a research number and all data were stored without subject identification. Data were held on a secure database on a password-protected computer at the University of Exeter. Access to data was and continues to be restricted to the research team. To enable follow-up contacts it was necessary to identify patients, but access to contact details (e.g. name and address) was restricted to the key members of the research team who arranged appointments. Any information about patients obtained (with their consent) from their medical records was recorded against their research number. Interviews audiotaped as part of the qualitative study (using a digital voice recorder) were transcribed verbatim and stored securely. Recordings of MBCT-TS sessions were stored securely (indexed by research number only) on a password-protected computer at the University of Exeter.

Disclosure of suicidal thoughts protocol

As the participants in this study have depression, it was appropriate to have a policy in place should any participant disclose suicidal thoughts to a research officer. Research officers assessed participants' depression status at the study's intake assessment and at each follow-up, which included questions about suicidal thoughts and plans. If a participant disclosed any suicidal thoughts the research officer followed the TSC-approved suicidal thoughts protocol and completed a suicidal thoughts report (see *Appendix 1*), which was countersigned by the site clinical lead. The information in this report was forwarded to the participant's GP to better inform his or her clinical management. The patient information sheet informed the participant that if we were very concerned about his or her safety, or someone else's safety, we would need to break confidentiality.

Unexpected serious adverse events

We followed the guidelines laid down by the MHRA for identifying, acting on and reporting adverse events [see www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm (accessed 16 March 2015)]. We adopted its definitions of adverse events and serious adverse reactions, reporting a total of 10 serious adverse events, none of which were classified as SUSARs by the TSC or the DMC.

Patient and public involvement

The PREVENT trial has benefited from the expertise of many people with lived experience of mental health difficulties including members of a locally organised voluntary group called the Lived Experience Group (LEG). The LEG has assisted the PREVENT trial at every stage of its development and the following sections detail a few examples of the ways in which the PREVENT trial has been shaped by patient and public involvement.

Protocol development

Patient and public involvement was sought in the development of the initial study protocol when developing the proposal and in the finalisation of the protocol prior to starting the trial through co-authorship (Rev. Paul Lanham).

Risk training

We sought the advice of the LEG both on the processes contained in the disclosure of suicidal thoughts protocol and in training and supporting our research team to activate this protocol. This training was particularly valuable as many of our team were anxious about discussing suicidal thoughts and did not feel confident in their ability to explore such thoughts with participants and GPs. The training gave researchers the chance to role-play these discussions, with advice and reassurance from the LEG.

Seeking consent

A member of the LEG provided specific training to our research staff to ensure that the consenting process was coherent and transparent.

Patient information

Given the variability of people's experiences and the importance of the patient information sheet, we asked a number of different members of the LEG to review the early drafts and combined the suggestions into our final version.

Management and governance of the trial

Sitting on both our Trial Management Group and our TSC is the previous Chairperson of the Board of Trustees for the charity Depression Alliance, the Rev. Paul Lanham. Rev. Lanham has a lifetime history of living with mental health difficulties and his involvement has been key in helping to ensure that the trial is asking questions that are relevant and valid.

Qualitative interviews and feedback

A large component of our trial was asking the research participants about their experiences of the therapies offered (see *Chapter 7*). We did this predominantly by asking all participants to complete an eight-page feedback booklet and also by conducting in-depth interviews with a subset of participants. Both the feedback booklet and the interview questions were reviewed and then trialled by several members of the LEG, who suggested a number of fundamental changes. The benefit of these changes became apparent as we began the process of analysis and could see the richness of the data that were emerging.

Dissemination of results

It was very important to us that we disseminate the results of our trial to the participants who took part and that this was carried out in the most sensitive and accessible way possible. We organised three separate events across the recruitment sites to disseminate the results of our trial to participants and consulted with a PREVENT trial participant who had since joined the LEG about the format and content of these events. This participant co-organised and chaired the largest of the events.

Chapter 4 Trial results

Participant flow

During the 19 months of recruitment, between 23 March 2010 and 21 October 2011, we identified 28,597 patients from GP practice searches. GPs excluded 8989 patients as unsuitable and invitation letters were sent to the remaining 19,608 patients. Although we asked all GPs to provide reasons for excluding patients, in 56% of cases this information was missing. For the remaining exclusions the most common reasons given were dementia (2%), psychosis (2%) and substance abuse (1%). In total, 3060 patients responded positively to our invitation and a further 89 patients self-referred. Full telephone screens were completed for 2188 patients, which resulted in 498 patients attending for a baseline assessment, of whom 424 patients were randomised. The most common reasons why patients were not eligible for the PREVENT trial were that they had recently stopped taking ADMs or wanted to reduce them (30%), they had not had three previous episodes of depression (19%) or they were currently depressed (17%). The reasons given for not wishing to take part in the PREVENT trial are explored in *Chapter 7*. Primary outcome data were collected for 90.3% (383/424) of participants and the remaining participants' data were censored at their last assessment. We retained 86.3% (366/424) of participants over the 24-month follow-up period, with 4.7% (20/424) lost to contact, 8.0% (34/424) withdrawing consent for further follow-up and 0.9% (4/424) dying during the trial; the pattern of missing data was similar across interventions. The flow of participants through the trial is depicted in *Figure 3*.

Missing data

The missing data rates for each time point are shown in *Table 6*.

Baseline characteristics

Of the 424 randomised participants, 212 were allocated to receive MBCT-TS and 212 were allocated to receive m-ADM. As indicated in *Table 7*, baseline characteristics were balanced between the two groups with the possible exception of gender. As we know of no strong evidence that gender moderates MBCT treatment outcomes[28] we did not add gender to the primary analysis model. It is interesting to note that the psychiatric history of these participants differs in a number of ways from the history of those randomised in the pilot trial (*Table 8*),[28] with PREVENT participants reporting lower BDI scores and fewer comorbidities and a smaller proportion previously attempting suicide. A much larger percentage of the PREVENT participants also previously accessed psychiatric treatment, which is likely to be the result of the recent significant progress made in improving the accessibility of evidence-based mental health services in the UK.[4,15,16]

Treatment adherence in each trial arm and the extent to which patients followed invitations to (dis)continue m-ADM are reported in *Table 9*; > 75% of patients adhered to treatment as intended. Details of the ADM that was taken are provided in *Appendix 2*.

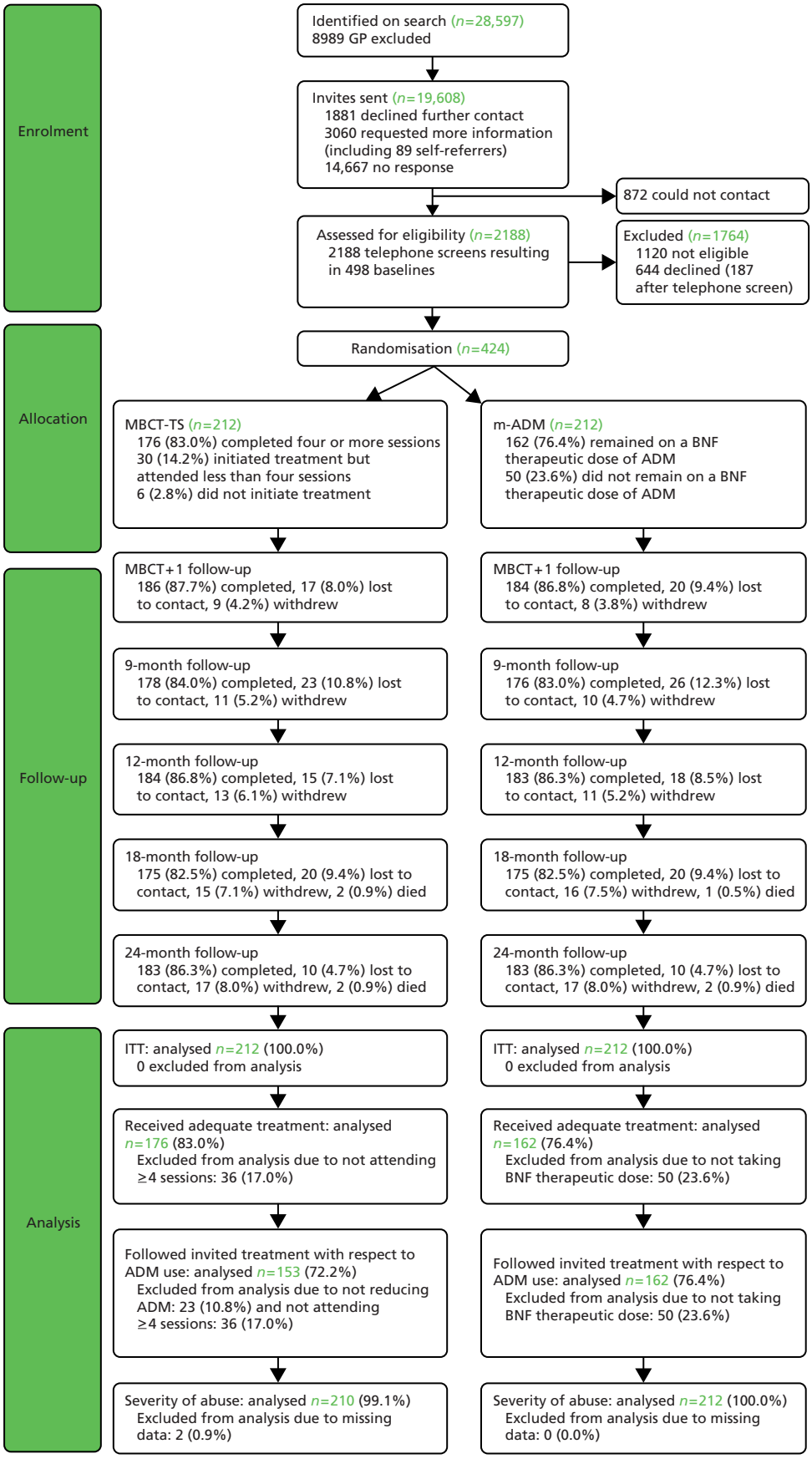

FIGURE 3 The CONSORT flow chart illustrating the flow of participants into the PREVENT trial.

TABLE 6 Rates of missing data at each time point

Outcome	Number of participants					
	Baseline	MBCT+1	9 months	12 months	18 months	24 months
Primary outcome: days till relapse/recurrence,* n *(%)						
Valid cases	–	402 (95)	398 (94)	395 (93)	387 (91)	383 (90)
Censored prior to 24 months	–	22 (5)	26 (6)	29 (7)	37 (9)	41 (10)
Secondary outcomes						
Depression-free days, *n* (%)						
Valid cases	–	402 (95)	396 (93)	392 (92)	377 (89)	366 (86)
Data missing	–	22 (5)	28 (7)	32 (8)	47 (11)	58 (14)
Residual depressive symptoms, *n* (%)						
BDI-II						
Valid cases	416 (98)	348 (82)	293 (69)	324 (76)	291 (69)	336 (79)
Individual missing items within valid cases	16 (0.2)	2 (0.03)	3 (0.05)	0	2 (0.03)	0
Participants who contributed no data	8 (2)	76 (18)	131 (31)	100 (24)	133 (31)	88 (21)
GRID-HAMD						
Valid cases	424 (100)	369 (87)	352 (83)	365 (86)	348 (82)	366 (86)
Individual missing items within valid cases	0	0	0	0	0	0
Participants who contributed no data	0	55 (13)	72 (17)	59 (14)	76 (18)	58 (14)
Psychiatric comorbidity: SCID, *n* (%)						
Valid cases	424 (100)	–	–	392 (92)	–	366 (86)
Data missing	0	–	–	32 (8)	–	58 (14)
Medical comorbidity: MSCL, *n* (%)						
Valid cases	416 (98)	–	–	323 (76)	–	336 (79)
Individual missing items within valid cases	0	–	–	0	–	7 (0.02)
Participants who contributed no data	8 (2)	–	–	101 (24)	–	88 (21)
Quality of life: WHOQOL-BREF, *n* (%)						
Valid cases	414 (98)	348 (82)	292 (69)	323 (76)	290 (68)	336 (79)
Individual missing items within valid cases	36 (0.3)	15 (0.2)	8 (0.1)	5 (0.1)	4 (0.1)	3 (0.03)
Participants who contributed no data	10 (2)	76 (18)	132 (31)	101 (24)	134 (32)	88 (21)
EQ-5D-3L						
Valid cases	413 (97)	347 (82)	293 (69)	324 (76)	291 (69)	336 (79)
Individual missing items within valid cases	2 (0.1)	0	0	1 (0.1)	0	0
Participants who contributed no data	11 (3)	77 (18)	131 (31)	100 (24)	133 (31)	88 (21)

MBCT+1, assessment point 1 month after the end of MBCT treatment in the MBCT arm and at the equivalent time point in the m-ADM arm.

TABLE 7 Baseline characteristics of the trial participants

Characteristic/variable	MBCT-TS ($n = 212$)	ADM ($n = 212$)
Demographic characteristics		
Female, *n* (%)	151 (71)	174 (82)
White, *n* (%)	210 (99)	210 (99)
Age (years)		
Mean (SD)	50 (12)	49 (13)
Range	22–78	20–79
Marital status, *n* (%)		
Single	42 (20)	38 (18)
Married, cohabiting or civil partnership	125 (59)	140 (66)
Separated, divorced or widowed	44 (21)	33 (16)
Missing	1 (0)	1 (0)
Level of education, *n* (%)		
No educational qualifications	10 (5)	10 (5)
Some school qualifications	36 (17)	45 (21)
High school and/or vocational qualification	84 (40)	92 (43)
University degree/professional qualification	77 (36)	61(29)
Missing	5 (2)	4 (2)
Religion, *n* (%)		
Christian	133 (63)	139 (66)
Other	10 (5)	4 (2)
None	68 (32)	68 (32)
Missing	1 (0)	1 (0)
Salary (£ sterling)		
Mean (SD)	19,930 (13,387)	18,024 (13,582)
Range	1200–72,000	792–80,000
Social class, *n* (%)[a]		
Class 0	96 (45)	76 (36)
Class 1	53 (25)	52 (25)
Class 2	22 (10)	38 (18)
Class 3	5 (2)	6 (3)
Class 4	0 (0)	2 (1)
Class 5	35 (17)	37 (17)
Not classified	1 (0)	1 (0)

TABLE 7 Baseline characteristics of the trial participants (*continued*)

Characteristic/variable	MBCT-TS ($n = 212$)	ADM ($n = 212$)
Stratification variables		
Depressive symptomology at randomisation, *n* (%)		
Asymptomatic	163 (77)	162 (76)
Symptomatic	49 (23)	50 (24)
Recruitment site, *n* (%)		
Bristol	33 (16)	31 (15)
Exeter and East Devon	72 (34)	76 (36)
North and Mid Devon	55 (26)	54 (25)
South Devon	52 (25)	51 (24)
Psychiatric characteristics		
Current depressive symptomology, mean (SD)		
GRID-HAMD score	4.8 (4.3)	4.6 (4.3)
BDI-II score	13.8 (10.2)	14.5 (10.1)
Previous major depressive episodes, *n* (%)		
Fewer than six episodes	120 (57)	106 (50)
Six or more episodes	92 (43)	106 (50)
Age (years) at first depression onset, mean (SD)	24.4 (11.5)	25.4 (13.3)
Time (months) since last depressive episode, mean (SD)	21.2 (27.0)	17.1 (23.0)
No. of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD)	0.5 (0.9)	0.7 (0.9)
Received outpatient psychiatric or psychological treatment, *n* (%)	103 (49)	108 (51)
Attempted suicide, *n* (%)	48 (23)	53 (25)
No. of previous suicide attempts, mean (SD)	1.7 (1.1)	1.9 (1.5)
Severity of reported childhood abuse, *n* (%)		
High	105 (50)	111 (52)
Low	105 (50)	101 (48)
Missing	2 (1)	0 (0)
Quality of life, mean (SD)[b]		
How would you rate your quality of life?	3.7 (0.8)	3.7 (0.8)
How satisfied are you with your health?	2.9 (1.0)	3.1 (1.0)
Physical	14.5 (6.5)	14.4 (5.1)
Psychological	12.6 (2.6)	12.3 (2.6)
Social	13.4 (3.4)	13.1 (3.4)
Environment	15.0 (2.4)	15.1 (2.6)
Health-related quality of life (EQ-5D-3L tariffs), mean (SD)	0.760 (0.268)	0.778 (0.211)

a Social class was determined according to the UK Office for National Statistics and the range was from professional and managerial occupations (class 1) to semiroutine and routine occupations (class 5); class 0 represents those who have never worked, the long-term unemployed, students or retired people [see www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/index.html (accessed 20 July 2015)].
b Data determined on the basis of the WHOQOL-BREF assessment.

TABLE 8 Baseline characteristics of the pilot trial participants[28]

Characteristic/variable	MBCT ($n = 61$)	m-ADM ($n = 62$)
Demographic characteristics		
Female, *n* (%)	47 (77)	47 (76)
White, *n* (%)[a]	60 (98)	62 (100)
Age (years)		
Mean (SD)	48.95 (10.55)	49.37 (11.84)
Range	26–66	21–72
Marital status, *n* (%)		
Single	4 (7)	9 (15)
Married or cohabiting	42 (69)	40 (65)
Separated, divorced or widowed	15 (25)	13 (21)
Level of education, *n* (%)		
No educational qualifications	9 (15)	17 (27)
Some school qualifications	16 (26)	16 (26)
High school and/or vocational qualification	24 (39)	15 (24)
University degree/professional qualification	12 (20)	14 (23)
Religion, *n* (%)		
None	12 (20)	16 (26)
Christian	46 (75)	45 (73)
Other[b]	3 (5)	1 (2)
Social class, *n* (%)[c]		
Class 1	22 (36)	23 (37)
Class 2	15 (25)	12 (19)
Class 3	7 (11)	7 (11)
Class 4	6 (10)	2 (3)
Class 5	11 (18)	17 (27)
Psychiatric characteristics		
Depression, mean (SD)		
HRSD score, mean (SD)	5.62 (4.3)	5.76 (4.69)
BDI-II score, mean (SD)	18.51 (10.91)	20.15 (12.86)
Depression diagnosis at intake, *n* (%)		
In full remission	42 (69)	41 (66)
In partial remission	19 (31)	21 (34)
Previous episodes of depression		
Mean (SD)	6.43 (3.04)	6.35 (2.91)
Median	6	6
≥ 10 episodes, *n* (%)	23 (38)	19 (31)
Number of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD)	0.83 (0.96)	1.04 (1.11)
Age (years) at first depression onset, mean (SD)	26.34 (11.7)	26.11 (12.65)

TABLE 8 Baseline characteristics of the pilot trial participants[28] (*continued*)

Characteristic/variable	MBCT ($n = 61$)	m-ADM ($n = 62$)
Time (months) since last depressive episode, mean (SD)	24.20 (27.74)	18.68 (23.89)
Severity of last depressive episode (no. of DSM-IV symptoms recorded), mean (SD)	7.27 (1.3)	7.04 (1.35)
Attempted suicide, *n* (%)	20 (33)	22 (35)
Number of previous attempts		
Mean (SD)	0.69 (1.37)	0.66 (1.05)
Range	0–7	0–4
Previous psychiatric treatment, mean (SD)	17 (28)	13 (21)
Quality of life, mean (SD)[d]		
Physical	22.64 (5.59)	23.0 (5.18)
Psychological	17.8 (3.82)	18.03 (3.63)
Social	9.52 (2.32)	9.27 (2.65)

HRSD, Hamilton Rating Scale for Depression.
a The non-white participant was British Asian.
b There was one Muslim in the m-ADM group and one Bahai, one Buddhist and one spiritualist in the MBCT group.
c Social class was determined according to the UK Office for National Statistics and the range was from professional and managerial occupations (class 1) to semiroutine and routine occupations (class 5) [see www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/index.html (accessed 20 July 2015)]. Data were missing for one case in the m-ADM arm of the trial.
d Data determined on the basis of the WHOQOL-BREF assessment.

TABLE 9 Adherence to treatment in each trial arm

Treatment adherence	*n* (%)
m-ADM	
Remained on therapeutic dose	162 (76)
Did not remain on therapeutic dose	50 (24)
MBCT-TS	
Participants who did not initiate MBCT treatment	6 (3)
Participants who initiated MBCT treatment	206 (97)
Number of sessions attended	
Mean	6
Mode	8
SD	2.4
Completed four or more MBCT sessions	176 (83)
ADM use among patients who attended four or more MBCT sessions	
No reduction in ADM dose	23 (13)
Reduction in ADM dose	29 (17)
Discontinued ADM	124 (71)

Primary outcome

Intention-to-treat analysis

We observed little or no clustering in primary or secondary outcomes by therapist. As model results accounting for clustering by therapist were identical to those obtained for the primary ITT analysis, outcome findings without consideration of therapist clustering are reported.

With respect to the primary outcome, the primary ITT analysis showed no evidence of a reduction in the hazard of relapse/recurrence with MBCT-TS compared with m-ADM (HR 0.89, 95% CI 0.67 to 1.18; $p = 0.43$), with 44% (94/212) of the MBCT-TS patients relapsing compared with 47% (100/212) of the m-ADM patients (*Figure 4*).

Secondary analyses

Two secondary analyses of the primary outcome were undertaken to explore the impact of variations in intervention adherence in the MBCT-TS and m-ADM groups.

There was a non-significant reduction in the hazard of relapse/recurrence with MBCT-TS compared with m-ADM at 24 months in those participants who received an adequate dose of treatment (HR 0.79, 95% CI 0.58 to 1.08; $p = 0.14$), with 46% (81/176) of the MBCT-TS patients relapsing compared with 49% (80/162) of the m-ADM patients (*Figure 5*). In this subgroup, the m-ADM group included more women and participants with a greater number of comorbidities than the MBCT-TS group (see *Appendix 3*).

There was a non-significant reduction in the hazard of relapse/recurrence with MBCT-TS compared with m-ADM at 24 months in participants who followed the invited treatment with respect to ADM use (HR 0.77, 95% CI 0.56 to 1.06; $p = 0.10$), with 46% (70/153) of the MBCT-TS patients relapsing compared with 49% (80/162) of the m-ADM patients (*Figure 6*). In this subgroup, the m-ADM group included younger participants, lower earners, more women and participants with a greater number of comorbidities than the MBCT-TS group (see *Appendix 4*). Given their non-randomised nature, these secondary analyses are prone to selection bias and confounding.

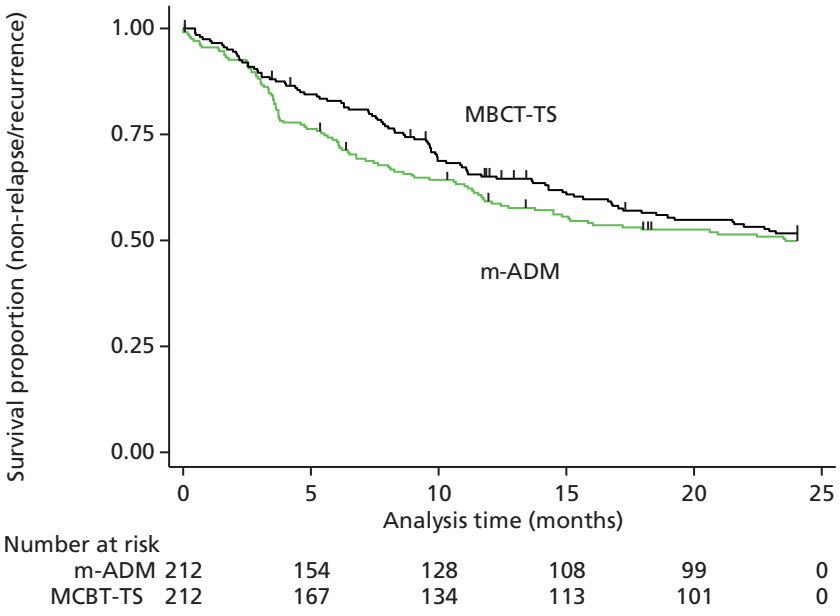

FIGURE 4 Survival (non-relapse/recurrence) curves comparing relapse/recurrence of major depression for the MBCT-TS and m-ADM groups over the 24-month follow-up period for ITT participants.

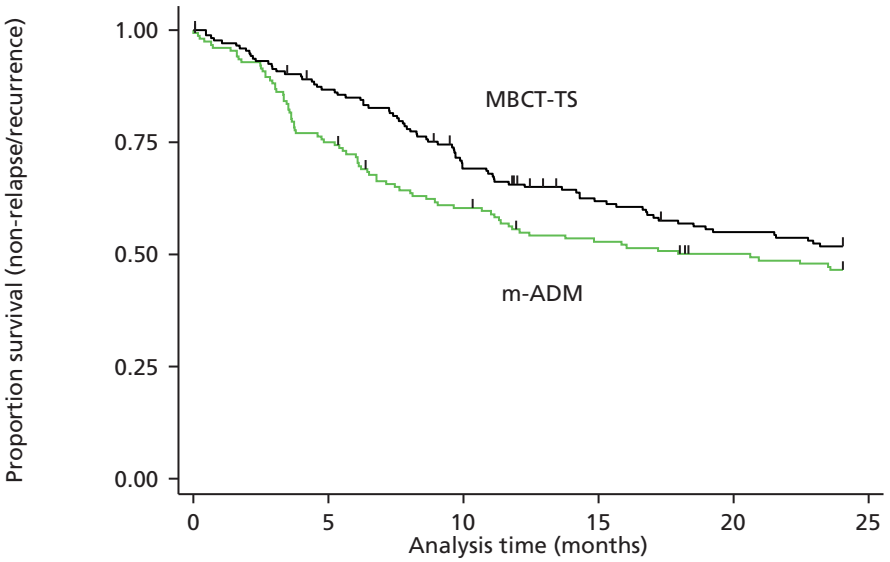

FIGURE 5 Survival (non-relapse/recurrence) curves comparing relapse/recurrence of major depression for the MBCT-TS and m-ADM groups over the 24-month follow-up period for those participants who received an adequate dose of treatment.

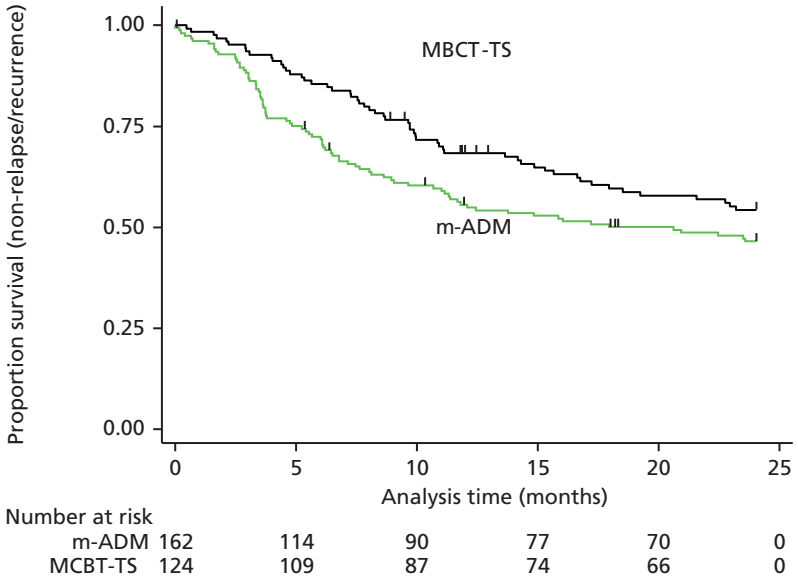

FIGURE 6 Survival (non-relapse/recurrence) curves comparing relapse/recurrence of major depression for the MBCT-TS and m-ADM groups over the 24-month follow-up period for those participants who followed the invited treatment with respect to ADM use.

There was no difference in treatment effect on the primary outcome across either stratification variable subgroup (severity of depression at baseline or centre) (*Table 10*). However, there was evidence of a significant interaction between the severity of reported childhood abuse and treatment group (HR 0.53, 95% CI 0.29 to 0.95; $p = 0.03$). Specifically, compared with ADM-m, MBCT-TS reduced the risk of relapse/recurrence for participants with a higher severity of reported childhood abuse (MBCT-TS 47% vs. ADM-m 59%) whereas there was a slightly higher risk of relapse/recurrence with MBCT-TS in the lower severity of reported childhood abuse subgroup (MBCT-TS 42% vs. ADM-m 35%) (see *Table 10*). Comparing the baseline characteristics of those with high and low severities of reported childhood abuse we find a number of differences. Participants who reported a more abusive childhood had had more previous psychiatric treatments, including more hospitalisations, had experienced more previous episodes of depression and made more suicide attempts, had a greater chance of a familial history of both suicide and mental illness and were more likely to smoke (see *Appendix 5*). Given their non-randomised nature, these secondary analyses are prone to selection bias and confounding

Secondary outcomes

With respect to the secondary outcomes, there was again no evidence of MBCT-TS's superiority over m-ADM (*Table 11*). Furthermore, none of the secondary outcome treatment effects at any follow-up point exceeded a standardised mean difference of 0.4. The health economics outcomes are reported in full in *Chapter 5*.

TABLE 10 Treatment effect subgroup analyses

Subgroup	Stratified HR (95% CI)	Interaction HR (95% CI), *p*-value
Depression severity		
Asymptomatic (HRSD score < 8)[a]	0.83 (0.60 to 1.15)	1.27 (0.68 to 2.39), 0.46
Symptomatic (HRSD ≥ 8)	1.06 (0.62 to 1.18)	
Centre		
South Devon[a]	0.61 (0.33 to 1.13)	1.75 (0.70 to 4.39)
Bristol	1.60 (0.54 to 2.12)	1.81 (0.83 to 3.96)
Exeter and East Devon	1.10 (0.68 to 1.81)	1.37 (0.61 to 3.08), 0.47[b]
North and Mid Devon	0.84 (0.49 to 1.43)	
Childhood abuse		
Lower risk[a]	1.31 (0.83 to 2.04)	0.53 (0.29 to 0.95), 0.03
Higher risk	0.69 (0.47 to 1.00)	

HRSD, Hamilton Rating Scale for Depression.
a Reference subgroup.
b *p*-value for treatment–centre interaction across centres.

TABLE 11 Intention-to-treat repeated measures analyses at 1 month post treatment and 9, 12, 18 and 24 months' follow-up for the MBCT-TS and m-ADM groups for the secondary outcomes: complete case and imputed data sets

		Baseline		MBCT+1		9 months		12 months		18 months		24 months			
Outcome	Group	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	*p*-value[a]	*p*-value[b]
Depression-free days	m-ADM											607.4 (196.4)	212	0.66	0.63
	MBCT-TS											607.4 (203.7)	212		
Residual depressive symptoms															
BDI-II score	m-ADM	14.4 (10.1)	206	13.9 (10.9)	174	10.5 (9.7)	142	11.3 (9.2)	157	11.3 (10.7)	149	11.9 (10.7)	167	0.18	0.21
	MBCT-TS	13.8 (12.4)	210	9.9 (9.7)	174	11.0 (10.5)	151	10.7 (10.0)	167	11.7 (10.6)	142	11.6 (10.9)	169		
GRID-HAMD score	m-ADM	4.6 (4.3)	212	7.4 (6.3)	183	5.6 (6.4)	175	4.7 (5.2)	181	5.3 (6.1)	174	4.7 (5.7)	183	0.76	0.55
	MBCT-TS	4.8 (4.3)	212	6.3 (5.6)	186	6.0 (5.5)	177	5.7 (5.7)	184	5.7 (5.7)	174	4.7 (4.8)	183		
Psychiatric and medical comorbidity															
Psychiatric comorbidities	m-ADM	0.7 (1.0)	212					0.1 (0.4)	196			0.3 (0.6)	183	0.91	0.90
	MBCT-TS	0.5 (0.9)	212					0.1 (0.3)	196			0.3 (0.7)	183		
MSCL score	m-ADM	21.7 (13.8)	206					19.3 (13.7)	156			21.7 (16.3)	167	0.42	0.43
	MBCT-TS	22.8 (14.0)	210					21.0 (14.0)	167			22.2 (14.6)	169		

continued

TABLE 11 Intention-to-treat repeated measures analyses at 1 month post treatment and 9, 12, 18 and 24 months' follow-up for the MBCT-TS and m-ADM groups for the secondary outcomes: complete case and imputed data sets (*continued*)

		Baseline		MBCT+1		9 months		12 months		18 months		24 months			
Outcome	Group	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	*p*-value[a]	*p*-value[b]
Quality of life															
WHOQOL: Q1 overall perception of quality of life	m-ADM	3.7 (0.8)	205	3.8 (0.9)	173	3.9 (0.8)	141	3.9 (0.9)	157	3.9 (0.9)	149	3.8 (1.0)	167	0.07	0.03
	MBCT-TS	3.7 (0.8)	209	3.8 (0.8)	174	3.7 (0.9)	151	3.7 (0.9)	166	3.7 (0.9)	141	3.7 (0.9)	169		
WHOQOL: Q2 overall perception of health	m-ADM	3.1 (1.0)	205	3.2 (1.0)	173	3.2 (1.0)	141	3.3 (1.0)	157	3.3 (1.1)	149	3.2 (1.0)	167	0.97	0.90
	MBCT-TS	2.9 (1.0)	209	3.1 (1.0)	174	3.1 (1.1)	151	3.2 (1.1)	166	3.2 (1.0)	141	3.1 (1.0)	169		
WHOQOL domain 1: physical health	m-ADM	12.3 (2.6)	205	14.3 (3.0)	173	14.8 (3.2)	141	14.7 (3.3)	157	14.7 (3.3)	149	14.9 (5.5)	167	0.07	0.02
	MBCT-TS	12.6 (2.6)	209	14.3 (3.3)	174	14.2 (3.3)	151	14.1 (3.4)	166	13.9 (3.5)	141	13.9 (3.5)	169		
WHOQOL domain 2: psychological	m-ADM	12.3 (2.6)	205	12.6 (2.8)	173	13.4 (2.7)	141	13.3 (2.7)	157	13.3 (3.0)	149	13.1 (3.0)	167	0.55	0.68
	MBCT-TS	12.6 (2.6)	209	13.4 (2.6)	174	13.3 (3.0)	151	13.3 (2.9)	166	12.9 (2.8)	141	13.1 (2.9)	169		
WHOQOL domain 3: social relationships	m-ADM	13.1 (3.4)	205	13.3 (3.4)	173	14.0 (3.4)	141	14.2 (3.3)	157	14.2 (3.4)	148	13.9 (3.5)	167	0.96	0.81
	MBCT-TS	13.4 (3.4)	209	13.8 (2.9)	174	13.7 (3.4)	151	13.9 (3.5)	166	14.0 (3.4)	141	13.7 (3.3)	169		
WHOQOL domain 4: environment	m-ADM	15.1 (2.6)	205	15.3 (2.5)	173	15.7 (2.3)	141	15.6 (2.6)	157	15.7 (2.6)	149	15.7 (2.7)	167	0.14	0.04
	MBCT-TS	15.0 (2.4)	209	15.21 (2.4)	174	15.4 (2.6)	151	15.2 (2.6)	166	15.3 (2.6)	141	14.9 (2.6)	169		
EQ-5D-3L tariff	m-ADM	0.778 (0.211)	202	0.760 (0.226)	173	0.773 (0.234)	142	0.764 (0.248)	156	0.768 (0.243)	149	0.757 (0.266)	166	0.13	0.07
	MBCT-TS	0.760 (0.268)	209	0.727 (0.295)	174	0.735 (0.256)	151	0.721 (0.293)	167	0.723 (0.282)	142	0.715 (0.310)	169		

MBCT+1, assessment point 1 month after the end of MBCT treatment in the MBCT arm and at the equivalent time point in the m-ADM arm.
a *p*-values reported are the treatment group × time interaction contrasts of marginal linear predictions for observed data.
b *p*-values reported are the treatment group × time interaction contrasts of marginal linear predictions for including imputed data.
All models adjusted for baseline depression severity category on Hamilton and centre.

Adverse events

A total of 10 serious adverse events were reported and are summarised in *Table 12*. Following discussion with the centre principal investigators and confirmation from the DMC we concluded that there was no reason to believe that any of the serious adverse events were intervention or trial related.

Over the 24 months there was no difference in the total number of suicidal ideations reported between the MBCT-TS group ($n = 44$ events) and the m-ADM group ($n = 46$ events) (rate ratio 0.94, 95% CI 0.64 to 1.38; $p = 0.75$).

TABLE 12 Serious adverse events reported over the 24-month follow-up of the trial

Event	Date reported
MBCT-TS arm	
Attempted suicide	5 November 2010
Death from lung cancer	11 September 2012
Death from pancreatic cancer	14 November 2012
Non-fatal stroke	27 February 2013
Attempted suicide	2 July 2013
Non-fatal hemotympanum resulting in a blood clot	19 July 2013
m-ADM arm	
Completed suicide	15 June 2012
Death from hyperischaemic heart disease	19 July 2012
Attempted suicide	8 March 2013
Non-fatal hysterectomy because of cancer and admitted to hospital for 2 nights	14 May 2013

Chapter 5 Economic evaluation

Introduction

Aim

The aim of the economic evaluation was to assess the cost-effectiveness of MBCT-TS compared with m-ADM in patients with recurrent major depressive disorder, in full or partial remission, in primary care over 24 months. The economic evaluation followed the methods developed in the pilot trial[28] and was carried out alongside the main RCT.[78,83]

Methods

Perspective

In the first instance the economic evaluation took a NHS/Personal Social Services (PSS) perspective, which is recommended by NICE[84] and covers the use of all hospital, community health and social services. In addition, as depression is known to impact on an individual's ability to work, resulting in substantial losses in the workplace,[85] we also widened our perspective to include productivity losses resulting from time off work and reduced productivity at work because of illness.

Method of economic evaluation

The primary economic analysis is focused on the policy question and is therefore a cost-effectiveness analysis with outcomes expressed as relapse/recurrence prevented. A secondary cost–utility analysis was also undertaken in which outcomes were expressed as QALYs, as recommended by NICE.[84]

Outcomes

The primary outcome for the study was time to recurrence of depression and is detailed in *Chapter 3*. For the purpose of the economic evaluation we created a binary outcome based on whether or not a relapse/recurrence had occurred.

Quality-adjusted life-years were calculated from EQ-5D scores at baseline, 1 month after treatment and 9, 12, 18 and 24 months' follow-up. The EQ-5D is a non-disease-specific measure for describing and valuing health-related quality of life.[86] The measure includes a rating of own health in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a rating of own health by means of a visual analogue scale (a 'thermometer') (score 0–100). It has been established that the EQ-5D can be used with confidence in economic evaluations for common mental health disorders.[87] The health states from the EQ-5D were given a utility score using responses from a representative sample of adults in the UK.[88] From these, QALYs were calculated using the area under the curve approach as defined by the utility values at baseline and each follow-up. It was assumed that changes in utility score over time followed a linear path.[89] QALYs in the second year were discounted at a rate of 3.5% as recommended by NICE.[84]

Calculation of costs

The calculation of costs was separated into the identification, measurement and valuation of relevant resources. All unit costs are for the financial year 2011/12, uprated when necessary using the Hospital and Community Health Services Index.[90] Costs in the second year were discounted at a rate of 3.5% as recommended by NICE.[84]

Identification of resources

We identified relevant resources based on the results of the pilot trial[28] and in discussion with study clinicians and patient representatives. We collected resource use in the following domains:

- delivery of the MBCT-TS intervention
- use of NHS secondary care services:
  - inpatient stays (mental health and all medical specialties)
  - outpatient appointments (mental health and all medical specialties)
  - accident and emergency attendances
- use of NHS primary care services:
  - GP (in surgery, at home and by telephone)
  - practice nurse
  - other community nurse (for example district nurse, health visitor, midwife)
  - support and recovery (STAR) or health-care support worker
  - community psychiatric nurse
  - community psychiatrist
  - community occupational therapist
  - community art/music/drama therapist
- use of medication in the following areas:
  - antidepressants
  - sleeping tablets
  - mood stabilisers/antipsychotic
  - painkiller
- use of social care and voluntary sector services:
  - social worker
  - marriage counselling service
  - advice service, for example Citizen's Advice Bureau
  - helpline, for example Samaritans/Mind
  - day centre/drop-in centre
- costs to patients and their carers
  - travel to trial MBCT-TS sessions
- productivity costs
  - time off work (absenteeism) and reduced productivity at work (presenteeism).

Measurement of resources

Delivery of the MBCT-TS intervention

Throughout the trial, the MBCT-TS therapists recorded details of attendance and non-attendance at group sessions for each study participant and these were used as the basis for the calculation of the total cost of the intervention.

Contact with general practitioners and antidepressant medication

Information on the numbers and types of contact with GPs and on prescriptions for ADM for the 24-month follow-up period was collected through a search of GP records by research assistants blind to randomisation status.

Use of all other health, social and voluntary sector services and out-of-pocket costs

Data on use of all other services included in the study were collected using the Adult Service Use Schedule (AD-SUS; see *Appendix 6*). The AD-SUS has been developed in several mental health trials and was further modified and successfully employed in the pilot trial.[28] Information about the study participants' use of services was collected in interviews with a researcher at baseline and at 1 month post treatment and 9, 12, 18 and 24 months' follow-up. At baseline, information covered the previous 3 months. At each of the follow-up interviews, service use since the previous interview was recorded; in this way the entire period from baseline to the final follow-up was covered. The AD-SUS asks participants for the number and duration of contacts with various services and professionals. In addition to the researcher-completed component of the AD-SUS, we also created a self-complete section that asked participants about their use of non-trial psychological therapies, sleeping tablets, mood stabilisers and painkillers and any out-of-pocket costs associated with their attendance at a MBCT-TS group. The self-complete questionnaire was included to ensure that the researchers maintained blindness to randomisation allocation at each follow-up.

Productivity losses

Information about time off work (absenteeism) and reduced productivity whilst at work (presenteeism) was collected by researchers alongside the AD-SUS using the productivity questions of the WHO Work Performance Questionnaire.[91]

Valuation of resources

A unit cost was applied to each resource use to calculate the total cost of resources used by each study participant.

Trial MBCT-TS sessions

We used the approach developed by the Personal Social Services Research Unit (PSSRU) at the University of Kent[92] for the calculation of the unit cost of the MBCT-TS group intervention. Trial therapists were on band 7 of the Agenda for Change salary scale and employer's national insurance, superannuation contributions and overheads were added to the average salary. We collected information from trial therapists on the time that they spent running the MBCT-TS sessions and the time that they spent on other activities and calculated a direct–indirect ratio of 1 : 0.67. MBCT-TS sessions lasted for 2 hours and there were 12 participants allocated to each group. We thus calculated the cost per participant per session at £14 (*Table 13*). Although there is no clear agreement on how the costs of group interventions should be allocated,[93] we decided to calculate the cost of the intervention on the basis of allocation to a MBCT-TS group, regardless of whether or not the individual attended, because if participants did not attend they were not replaced.

TABLE 13 Unit cost schema for MBCT-TS

Unit	Unit cost 2011/12 (£ per year)
Salary	37,800
Salary oncosts including employers' national insurance and superannuation contribution	9532
Overheads	
Management, administration and estates	9140
Non-staff	19,865
Capital overheads	2682
Working time	42.7 weeks per annum, 37.5 hours per week
Ratio of direct face-to-face to indirect time	1 : 0.67
Length of sessions	2 hours
Total	£49 per hour, £82 per direct contact hour, £165 per session, £14 per participant per session

Source: Curtis.[90]

Antidepressants and other medication

Medication costs were calculated using daily dose information and the cost of the generic drugs as listed in the BNF.[94]

Secondary care services

The unit costs for all hospital services were taken from the National Schedule of NHS Reference costs for 2012.[95] The costs used in the analysis are summarised in *Table 14*.

Primary care services and social care and voluntary services

For NHS primary care services and social care and voluntary services we used costs contained in Curtis.[90]

Costs to patients

The cost of travel to MBCT-TS treatment groups was calculated by multiplying mileage information by estimates of running costs from the UK Automobile Association [see www.theaa.com/motoring_advice/running_costs (accessed 17 March 2015)].

Productivity costs

For productivity losses, absenteeism costs were calculated using the friction cost approach[96] and presenteeism costs were calculated using the method set out by Kessler *et al.*[91]

TABLE 14 Unit costs applied to economic data

Service	Unit	Cost (£)
MBCT-TS	Per session	14.00
Medication	Per daily dose	Various
Inpatient	Per night	496.48–585.58
Outpatient	Per appointment	60–234
Accident and emergency	Per attendance	108–157
Ambulance	Per attendance	214
GP surgery	Per minute of patient contact	2.78
GP home	Per home visit minute	3.55
GP telephone	Per minute of patient contact	2.78
Practice nurse	Per minute of face-to-face contact	0.75
District nurse, health visitor, midwife	Per home visit minute	1.05
Community psychiatric nurse	Per minute of face-to-face contact	1.12
Community psychiatrist	Per minute of patient contact	1.93
Clinical psychologist	Per minute of patient contact	2.27
Occupational therapist	Per minute of patient contact	0.67
Physiotherapist	Per minute of patient contact	0.50
Counselling	Per minute of patient contact	1.08
Art/drama/music therapist	Per minute of patient contact	0.67
Chiropodist	Per minute of patient contact	0.50
Dietician	Per minute of patient contact	0.67
Social worker	Per minute of patient contact	2.60
Support worker	Per minute of patient contact	0.47
Advice service	Per minute of patient contact	0.47
Day centre	Per user per session	37.00

Data analysis

Complete case analysis was used in the economic evaluation.

Resource use

Resource use by study participants is reported as the mean by group and as a percentage of the group who had at least one contact. Differences in the use of services between randomised groups at 24 months' follow-up are reported descriptively and are not compared statistically to avoid problems associated with multiple testing and because the focus of the economic evaluation was on a quantitative analysis of cost and cost-effectiveness.

Difference in costs

Differences in mean costs between randomised groups at 24 months' follow-up were analysed using standard parametric *t*-tests with the validity of the results confirmed using bias-corrected, non-parametric bootstrapping (repeat resampling).[97] Despite the skewed nature of cost data, this approach is recommended to enable inferences to be made about the arithmetic mean.[98]

Cost-effectiveness and cost–utility analyses

The primary economic analysis focused on the policy question: MBCT-TS compared with m-ADM at 24 months and assessed cost-effectiveness in terms of cost per relapse/recurrence prevented. A secondary cost–utility analysis was undertaken using QALYs calculated from the EQ-5D measure of quality of life. Initially, ICERs – the difference in mean cost divided by the difference in mean effect – were calculated.[99] Because ICERs are calculated from four sample means and are therefore subject to statistical uncertainty, repeat resampling (bootstrapping) from the cost and outcomes data was used to generate a distribution of mean costs and effects for each of the relapse/recurrence and QALY outcomes.[100] These distributions were used to calculate the probability that each of the treatments is the optimal choice, subject to a range of possible maximum values (the ceiling ratio, λ) that a decision-maker might be willing to pay for a unit improvement in outcome. To explore the uncertainty that exists around estimates of mean costs and effects and the uncertainty regarding the maximum value of λ, cost-effectiveness acceptability curves (CEACs) are presented by plotting these probabilities for a range of possible values of λ.[101,102] CEACs show the probability that MBCT-TS is the more cost-effective of the two options for different values of λ. These analyses were run allowing for stratification variables (recruitment locality and participants' symptomatic status).

Sensitivity analyses

A number of sensitivity analyses were carried out to test the robustness of the assumptions made:

1. The discount rate was varied from 0% to 6%.
2. The impact of missing data was considered using single imputation of individual missing values using multiple covariates.

Results

Data completeness

At 24 months, full service use data for the entire follow-up period were available for 180 participants in the m-ADM group and 181 participants in the MBCT-TS group, which was 85% of the total number randomised.

Resource use

Trial MBCT-TS sessions

Full details of the MBCT-TS sessions are provided in *Chapter 2* and associated costs are summarised in *Table 13*.

Antidepressants and other medication

For details of the use of ADM see *Table 9*. The use of other medication is summarised in *Table 15*, which shows that similar proportions of both the MBCT-TS group and the m-ADM group used painkillers (61%) and sleeping tablets (15–16%).

Secondary care, primary care, social care and voluntary sector services

The use of secondary care, primary care, social care and voluntary sector services was broadly similar across both randomised groups over 24 months' follow-up and there is no evidence that treatment allocation had any substantial impact on the scope or intensity of service use.

Productivity losses

Over 24 months' follow-up the mean number of days off work was 9.8 in the m-ADM group and 11.0 in the MBCT-TS group.

TABLE 15 Service use (unit) over 24 months' follow-up

	MBCT-TS			m-ADM		
Service use	Mean	SD	% using at least once	Mean	SD	% using at least once
Inpatient stay (nights)	0.70	3.87	14.81	0.89	2.79	20.14
Outpatient appointments (number)	4.79	9.21	67.11	4.29	6.29	67.63
Accident and emergency (attendances)	0.59	1.25	30.20	0.60	1.09	33.09
Ambulance (calls)	0.07	0.34	4.70	0.72	0.26	7.19
GP (contact)	12.13	12.51	95.30	9.66	8.44	99.28
Other community health-care services (contact)	1.27	4.43	87.92	6.99	17.22	86.33
Social care, local authority and voluntary services (contact)	1.58	4.81	22.82	2.55	7.55	18.71
Use of painkillers			61.26			60.85
Use of sleeping tablets			15.09			15.57
Days off work over follow-up	11.01	32.66	43.40	9.76	27.06	51.89

Total costs

Changes over time

Changes in total cost per week over follow-up are summarised in *Figure 7* (NHS/PSS perspective) and *Figure 8* (societal perspective). The charts demonstrate that costs were fairly consistent between groups and over time, suggesting that randomisation to MBCT-TS or m-ADM had little impact on the cost of health and social care services and productivity losses.

Total costs at follow-up

Total costs over follow-up are summarised in *Table 16*, including a breakdown of costs by service-providing sector. From a NHS/PSS perspective, the mean total cost over 24 months' follow-up was £2360 in the m-ADM group and £2485 in the MBCT-TS group; the mean difference in costs was not statistically significant ($p = 0.80$). From a societal perspective the mean total cost over 24 months' follow-up was £2755 in the m-ADM group and £3204 in the MBCT-TS group; again, the mean difference in costs of £449 was not statistically significant ($p = 0.68$).

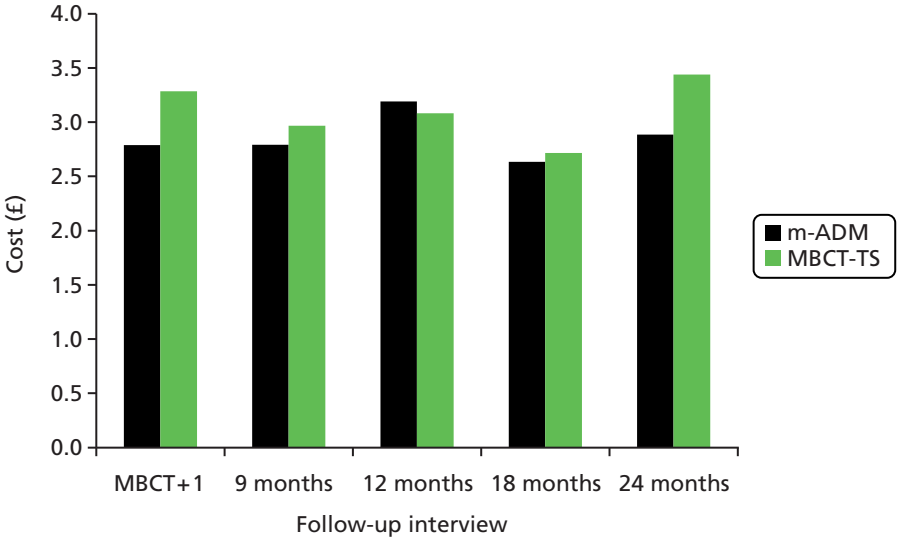

FIGURE 7 Average cost per week at each follow-up using a NHS/PSS perspective.

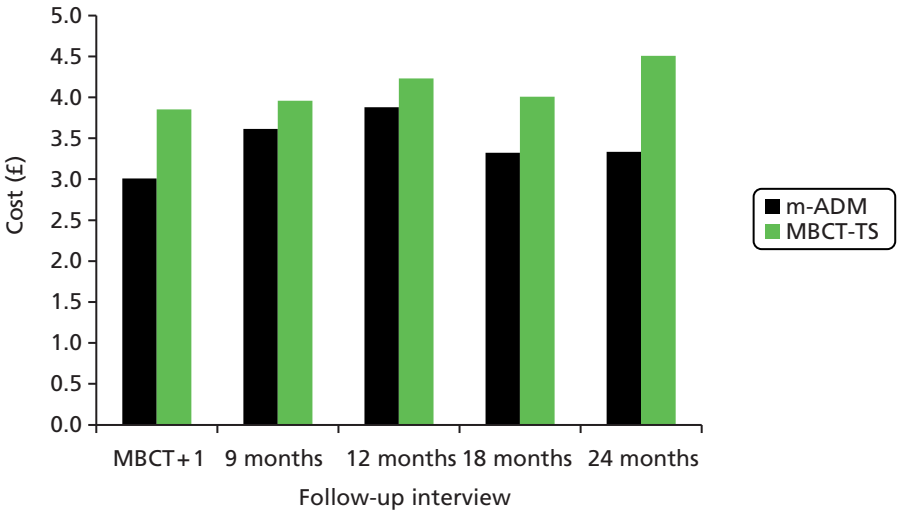

FIGURE 8 Average cost per week at each follow-up using a societal perspective.

TABLE 16 Total costs (£) and outcomes over 24 months' follow-up by randomised group

Cost category	MBCT-TS ($n = 181$)		m-ADM ($n = 180$)		Mean difference	95% CI	*p*-value
	Mean	Mean	Mean	SD			
MBCT-TS	112.00	112.00	0.00	0.00			
Antidepressants	40.10	72.13	69.79	168.48			
Hospital and community services	2332.43	4065.88	2290.62	4190.65			
Total health-care costs (NHS/PSS)	2484.52	4077.31	2360.41	4205.58	124.11	–749.98 to 972.57	0.80
Out-of-pocket costs to patients	56.76	168.29	83.33	283.12			
Productivity losses ($n = 265$)	504.26	1881.49	310.54	761.06			
Societal costs ($n = 252$)	3204.05	4011.91	2754.92	4465.07	449.14	–842.18 to 1286.26	0.68
Relapse/recurrence (%) ($n = 402$)	47	47	50	50	–3		
QALYs ($n = 213$)	1.49	1.49	1.53	0.35	–0.04		

Outcomes

Health-related quality of life

Mean EQ-5D health state scores are summarised in *Figure 9*. The graph shows that the average health state score was between 0.7 and 0.8 for both groups for the entire period between baseline and 24 months' follow-up and that there is very little difference between the groups. The resultant QALYs over follow-up are summarised in *Table 16*; the difference of –0.04 between the groups was not statistically significant ($p = 0.42$, adjusted by stratification variables).

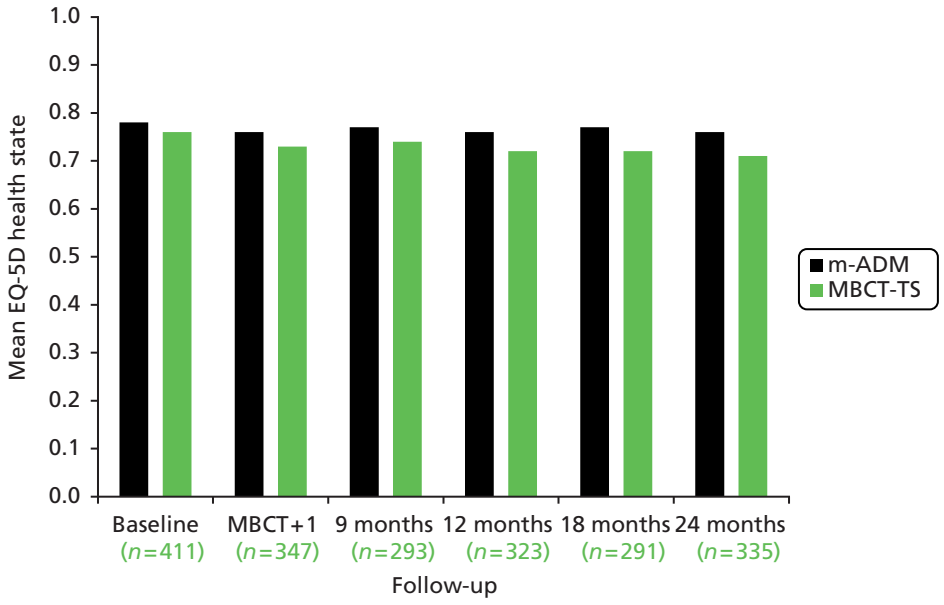

FIGURE 9 Mean EQ-5D health state scores over follow-up.

Relapse/recurrence

Detailed information on the relapse/recurrence outcome measure is provided in *Chapter 4*. For the purpose of the economic evaluation we used the percentage of individuals who relapsed in each of the randomised groups. In the m-ADM group 50% had a relapse/recurrence over follow-up and in the MBCT-TS group this figure was 47% (see *Table 16*).

Cost-effectiveness

Relapse/recurrence

In terms of relapse/recurrence, costs were higher in the MBCT-TS group and outcomes better, generating an ICER (the additional cost of one intervention compared with another divided by the additional effects) of £4955 from the NHS/PSS perspective and £17,930 from the societal perspective, including productivity losses and patient costs. The ICER indicates that an additional £4955 (from the NHS/PSS perspective) or £17,930 (from the societal perspective) would need to be invested to generate a unit reduction in the percentage of participants who relapse.

Non-parametric bootstrapping from the cost and effectiveness data was used to generate a joint distribution of incremental mean costs and effects for the treatments under comparison to explore the probability that each is the optimal choice, subject to a range of maximum values (λ) that a decision-maker might be willing to pay for improvements in outcomes. *Figures 10* and *11* illustrate the scatterplots of the bootstrapped cost and effectiveness pairs for MBCT-TS compared with m-ADM, from the NHS/PSS and societal perspectives respectively. The points in the scatterplot fall in all four quadrants of the cost-effectiveness plane suggesting that there is no clear conclusion to be made regarding cost-effectiveness in terms of relapse/recurrence. It is important to note that, as positive values of relapse/recurrence correspond with worse outcomes, the usual interpretation of the quadrants of the cost-effectiveness plane is reversed with respect to the *x*-axis so that points that fall to the left of 0 denote better outcomes for MBCT-TS and those that fall to the right denote worse outcomes. Statistical uncertainty around the ICER was explored through the calculation of CEACs, shown in *Figure 12*, which demonstrate that the probability of MBCT-TS being more cost-effective than m-ADM does not rise above 43%.

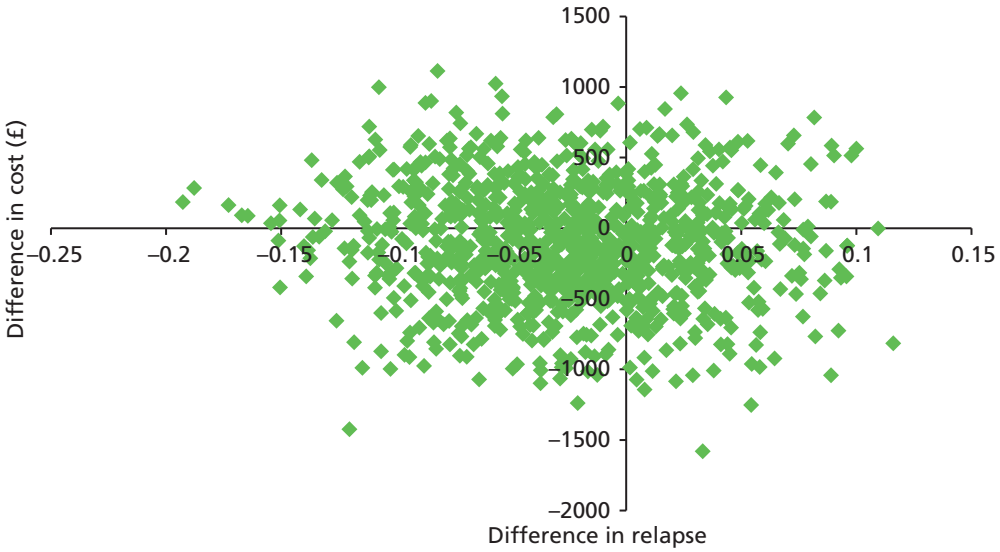

FIGURE 10 Scatterplot showing the bootstrapped mean differences in costs and effects of MBCT-TS compared with m-ADM using relapse/recurrence and service costs.

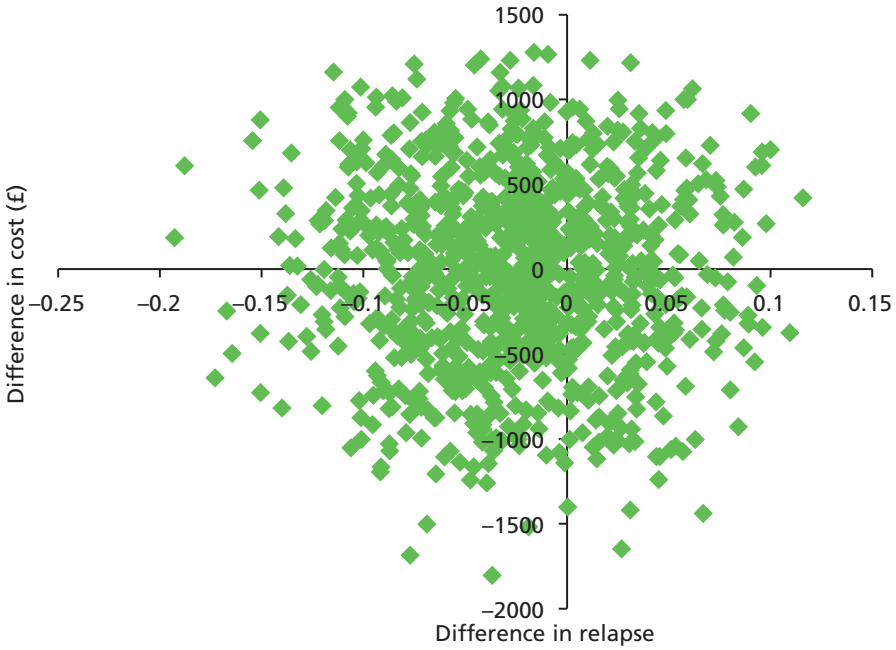

FIGURE 11 Scatterplot showing the bootstrapped mean differences in costs and effects of MBCT-TS compared with m-ADM using relapse/recurrence and societal costs.

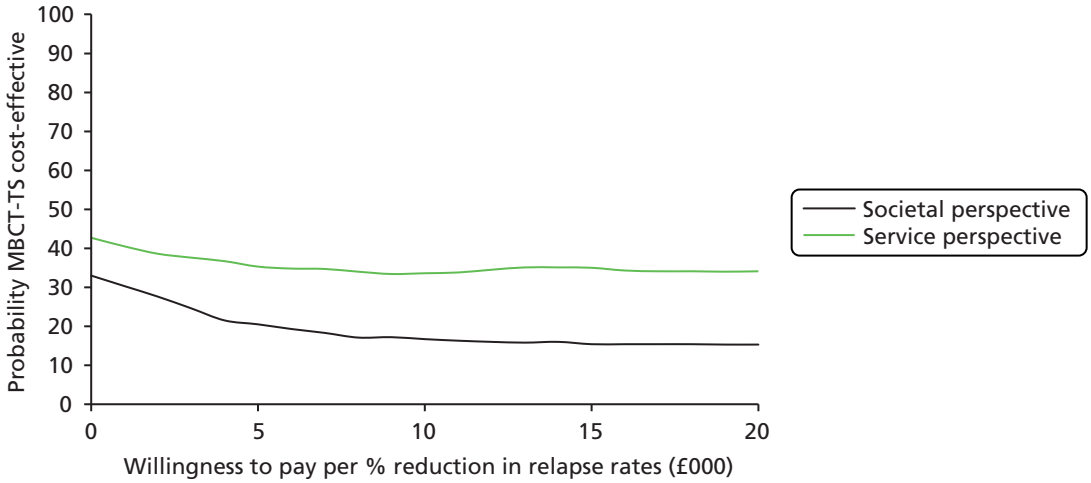

FIGURE 12 Cost-effectiveness acceptability curves showing the probability that MBCT-TS is cost-effective compared with m-ADM for different values that a decision-maker is willing to pay for a unit reduction in the percentage of patients who undergo relapse/recurrence.

Quality-adjusted life-years

In terms of QALYs, costs were higher in the MBCT-TS group and outcomes slightly worse, suggesting that MBCT-TS was dominated by m-ADM. The scatterplots in *Figures 13* and *14* show points falling mainly in the north-west quadrant (outcomes worse and costs higher) and south-west quadrant (outcomes worse and costs lower). The probability that MBCT-TS is more cost-effective than m-ADM, shown in the CEACs in *Figure 15*, does not rise above 52%.

Sensitivity analysis

Imputation of missing data and variation in the discount rate from 0% to 6% made no difference to the results, as summarised in *Table 17*.

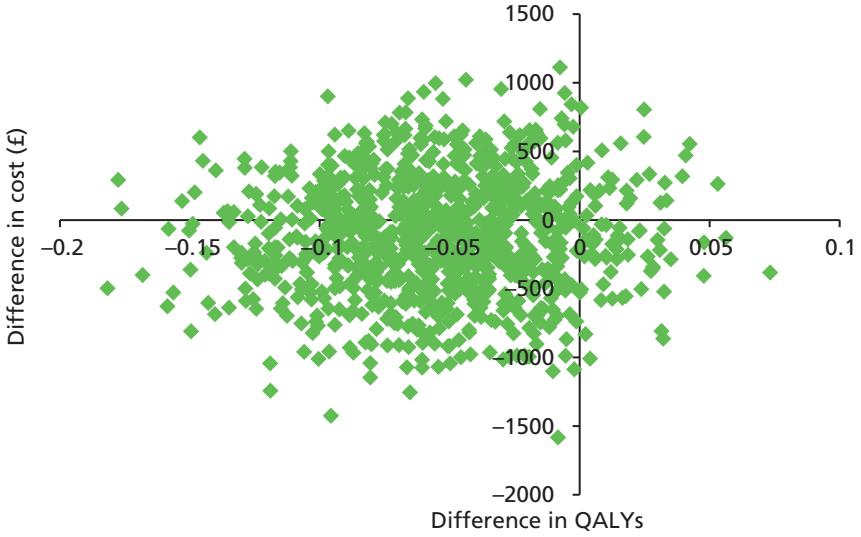

FIGURE 13 Scatterplot showing the bootstrapped mean differences in costs and effects of MBCT-TS compared with m-ADM using QALYs and service costs.

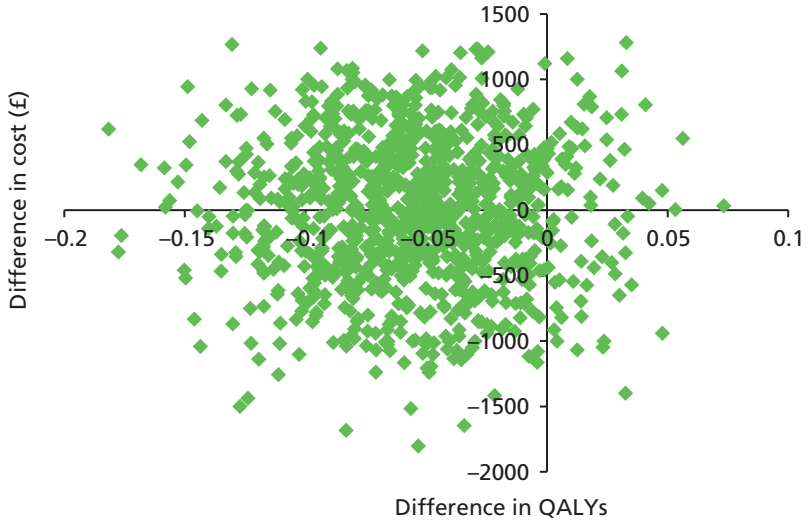

FIGURE 14 Scatterplot showing the bootstrapped mean differences in costs and effects of MBCT-TS compared with ADM-T using QALYs and adjusted societal costs.

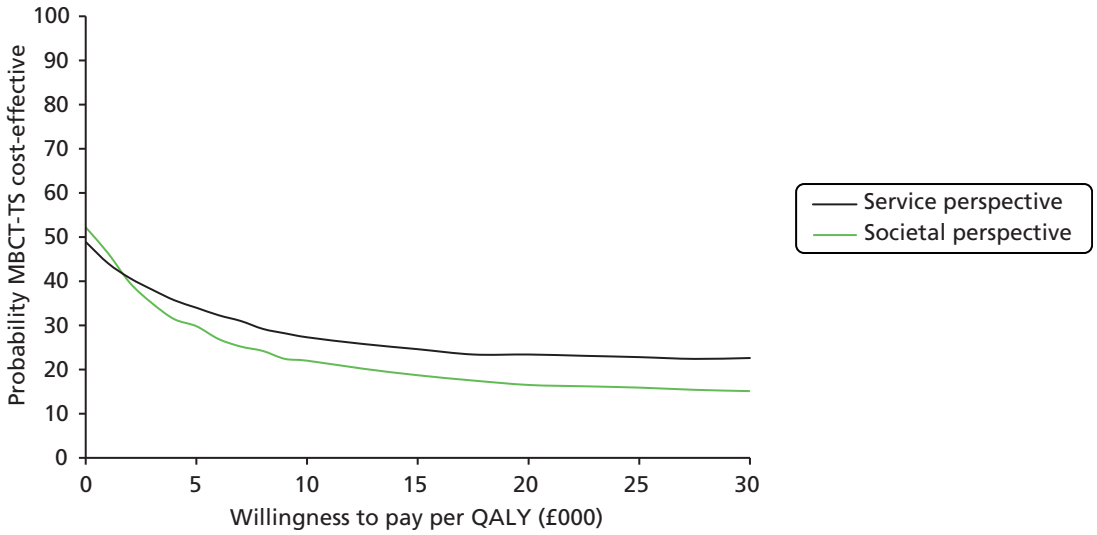

FIGURE 15 Cost-effectiveness acceptability curves showing the probability that MBCT-TS is cost-effective compared with m-ADM for different values that a decision-maker is willing to pay for a QALY.

TABLE 17 Total costs and QALYs with discount rate varied from 0% to 6%

Cost category and discount rate	MBCT-TS ($n = 181$)		m-ADM ($n = 180$)		Mean difference	95% CI	*p*-value
	Mean	SD	Mean	SD			
Total NHS/PSS costs (£), discount rate 0%	2439.98	3992.68	2319.75	4120.03	107.96	–735.63 to 951.55	0.80
Total societal costs (£), discount rate 0%	3007.99	3970.62	2747.60	4468.00	214.72	–844.97 to 1274.42	0.69
Total NHS/PSS costs (£), discount rate 6%	2516.34	4137.95	2389.46	4267.05	113.68	–760.28 to 987.64	0.80
Total societal costs (£), discount rate 6%	3035.53	4041.78	2760.14	4468.15	227.27	–840.25 to 1294.78	0.68
QALYs, discount rate 0%	1.48	0.48	1.52	0.35	–0.05	–0.16 to 0.07	0.42
QALYs, discount rate 6%	1.46	0.47	1.5	0.35	–0.05	–0.16 to 0.06	0.42
Multiple imputation of missing data, NHS/PSS costs (£)	2423.68	3780.54	2348.59	3903.41	67.13	–668.39 to 802.65	0.858
Multiple imputation of missing data, societal costs (£)	2934.68	3177.99	2692.53	3595.67	229.16	–417.93 to 876.25	0.487

Chapter 6 Quantitative process–outcome evaluation

Introduction

Aim

The trial sought to address the following explanatory question: 'Is an increase in mindfulness skills the key mechanism of change of MBCT?' We approached this question using embedded process–outcome studies across the trial arms.

An important first step in establishing mechanisms of action is to identify whether or not the selected mechanism variables mediate the effects of the target treatment (MBCT-TS) on outcome.[103] In other words, (1) are those mechanisms differentially altered by the treatment and (2) do those mechanisms explain all or part of the effect of treatment on outcome?

This chapter reports our meditational analyses examining whether changes in mindfulness as measured by the Five Factor Mindfulness Questionnaire (FFMQ)[104] from pre treatment (baseline) to post MBCT (1-month post-treatment follow-up point) mediate the effects of treatment arm on clinical outcome over the course of the trial.

Establishing mediation

To establish mediation requires attention to several key aspects of study design[103,105,106] that have been instantiated in the PREVENT trial. First, MBCT is compared with a treatment that works but not through the same mechanism of action (m-ADM),[107] thus allowing a test of effects specific to MBCT. Second, assessment of change in the hypothesised mediator occurred (1) during MBCT and (2) before the assessment of outcome. For the current approach we assessed change in mindfulness at baseline and immediately following MBCT and depressive relapse/recurrence over 24 months of follow-up was the dependent variable in our mediation analyses. Finally, the design requires that all those in the intervention arm received an adequate dose of the intervention to properly test the hypothesis that MBCT's impact on the hypothesised mechanism (mindfulness) mediates outcome. Therefore, only patients who attended four or more sessions were included in the mediational analyses.

Hypothesis

Based on our previous work[37] and on the theoretical and clinical rationale of MBCT, we predicted that enhanced mindfulness over the active treatment period would significantly mediate outcome, with those participants evidencing larger gains in mindfulness faring better. We did not predict an interaction with treatment arm (see *Mediation approach*).

Methods

Measurement of mindfulness

As noted, mindfulness in the PREVENT trial was measured using the FFMQ.[104] The FFMQ is a 39-item measure that assesses five facets of a general tendency to be mindful in daily life: observing, describing, acting with awareness, non-reactivity to inner experience and non-judging of inner experience. Items are rated on a 5-point Likert scale, with higher scores indicating a greater tendency to be mindful. The FFMQ was administered at the baseline and 1-month post-treatment assessment points.

Analytic approach

Selection of the sample

Analyses that address mediation of treatment-specific effects require an adequate treatment dose.[103] In the PREVENT trial an adequate dose of MBCT was defined as participation in four of eight MBCT sessions. As relapse/recurrence is the primary outcome it is also necessary that participants have not relapsed prior to the post-MBCT assessment point. Finally, participants need to have full data on mindfulness skills (the FFMQ) at baseline and post treatment as well as full data on GRID-HAMD-assessed depression at baseline and post treatment. Participants satisfying all of these criteria make up the mediation sample.

Mediation approach

We used the mediation analytical framework recommended by Kraemer *et al.*[105] for RCTs. This comprises a regression approach in which treatment group (T), the mediator (M) and the treatment by mediator interaction term (T × M) are the independent variables. We examined the outcome of relapse/recurrence using Cox proportional hazards regression.[108] Within this regression approach, for M to be a mediator of treatment, M must be an event occurring during or after treatment that is significantly altered by treatment and temporally precedes the outcome. M must also then show a main effect and/or an interactive effect with treatment on outcome, that is, the M and/or T × M terms in the regression should be significant. Treatment need not have a significant overall or main effect on outcome.[105]

A main (but not interactive) effect of mediation is therefore when treatment significantly changes the mediator but the effect of the mediator on outcome does not significantly differ across treatment types. In the present analysis, if MBCT-TS differentially improves mindfulness skills and any such improvement translates into a better outcome, but the relationship between improvement and outcome does not differ between MBCT-TS and m-ADM, this would be a main, but not interactive, effect of mediation. In contrast, an interactive effect of mediation is when treatment significantly changes not only the mediator but also the relationship between the mediator and outcome such that it is significantly different for the alternative treatments. In the present study, if treatment significantly affects the acquisition of mindfulness skills, but the relationship between change in mindfulness across treatment and outcome is then significantly different between the m-ADM group and the MBCT group, this would be an interactive effect of mediation.

To ensure that any mediation effects found in the current analyses were present over and above the influence of levels of depression, our regression models included change in depression severity on the Hamilton Rating Scale for Depression (HRSD) from baseline to 1-month post treatment when evaluating mediation, on the first step in the regression analysis.

Calculating change in mindfulness

Development of mindfulness as a potential mediator was computed as change over time, that is, from baseline to 1-month post treatment. We calculated standardised residualised change scores for the mindfulness variables using a simple linear regression model in which time 1 scores predicted time 2 scores.[35,109] The standardised residuals were then used in the mediation analyses. However, we report raw score equivalents when appropriate for ease of comprehension.

Results

Selection of the sample

The full treatment-adherent sample consisted of 388 participants (MBCT-TS $n = 176$; m-ADM $n = 212$). However, 68 participants relapsed before the 1-month post-treatment assessment point and were, therefore, not included in these mediation analyses. This reduced the sample to 320 participants (MBCT-TS $n = 156$; m-ADM $n = 164$). A further 60 participants did not complete the FFMQ and/or GRID-HAMD at baseline and/or 1-month post treatment, giving a mediation sample of 260 participants (MBCT-TS $n = 135$; m-ADM $n = 125$). The baseline characteristics of the mediation sample are provided in *Table 18*.

TABLE 18 Baseline characteristics of the mediation sample

Characteristic/variable	MBCT-TS ($n = 135$)	m-ADM ($n = 125$)
Demographic characteristics		
Female, *n* (%)	96 (71)	102 (82)
White, *n* (%)	133 (99)	123 (98)
Age (years)		
Mean (SD)	52 (11)	50 (13)
Range	25–78	20–79
Marital status, *n* (%)		
Single	23 (17)	19 (15)
Married, cohabiting or civil partnership	88 (65)	90 (72)
Separated, divorced or widowed	24 (18)	16 (13)
Missing	0 (0)	0 (0)
Level of education, *n* (%)		
No educational qualifications	9 (7)	6 (5)
Some school qualifications	19 (14)	25 (20)
High school and/or vocational qualification	56 (41)	57 (46)
University degree/professional qualification	50 (37)	36 (29)
Missing	1 (1)	1 (1)
Religion, *n* (%)		
Christian	85 (63)	82 (66)
Other	9 (7)	4 (3)
None	41 (30)	39 (31)
Missing	0 (0)	0 (0)
Salary (£ sterling)		
Mean (SD)	21,054 (14,649)	17,961 (12,910)
Range	1200–72,000	1200–75,000
Social class, *n* (%)[a]		
Class 0	56 (41)	47 (38)
Class 1	37 (27)	29 (23)
Class 2	14 (10)	24 (19)
Class 3	4 (3)	4 (3)
Class 4	0 (0)	0 (0)
Class 5	24 (18)	21 (17)
Not classified	0 (0)	0 (0)

continued

TABLE 18 Baseline characteristics of the mediation sample (*continued*)

Characteristic/variable	MBCT-TS ($n = 135$)	m-ADM ($n = 125$)
Stratification variables		
Depressive symptomology at randomisation, *n* (%)		
Asymptomatic	105 (78)	99 (79)
Symptomatic	30 (22)	26 (21)
Recruitment site, *n* (%)		
Bristol	26 (19)	21 (17)
Exeter and East Devon	48 (36)	47 (38)
North and Mid Devon	38 (28)	28 (22)
South Devon	23 (17)	29 (23)
Psychiatric characteristics		
Current depressive symptomology, mean (SD)		
GRID-HAMD score	4.6 (4.3)	4.2 (4.1)
BDI-II score	13.0 (10.0)	13.3 (9.4)
Previous major depressive episodes, *n* (%)		
Fewer than six episodes	78 (58)	70 (56)
Six or more episodes	57 (42)	55 (44)
Age (years) at first depression onset, mean (SD)	26.2 (12.4)	27.5 (14.2)
Time (months) since last depressive episode, mean (SD)	21.5 (25.3)	18.2 (23.9)
Number of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD)	0.4 (0.7)	0.6 (0.8)
Received outpatient psychiatric or psychological treatment, *n* (%)	66 (49)	59 (47)
Attempted suicide, *n* (%)	23 (17)	27 (22)
Number of previous attempts, mean (SD)	1.7 (1.0)	1.5 (0.9)
Severity of reported childhood abuse, *n* (%)		
High	61 (45)	55 (44)
Low	74 (55)	70 (56)
Missing	0 (0)	0 (0)
Quality of life, mean (SD)[b]		
How would you rate your quality of life?	3.7 (0.8)	3.9 (0.7)
How satisfied are you with your health?	2.9 (1.0)	3.2 (0.9)
Physical	14.4 (5.2)	14.7 (2.8)
Psychological	12.7 (2.6)	12.7 (2.4)
Social	13.4 (3.5)	13.6 (3.1)
Environment	15.2 (2.4)	15.6 (2.2)
Health-related quality of life (EQ-5D tariffs)	0.786 (0.243)	0.798 (0.193)

a Social class was according to UK Office for National Statistics and the range was from professional and managerial occupations (class 1) to semiroutine and routine occupations (class 5); class 0 represents those who have never worked, the long-term unemployed, students or retired people [see www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/index.html (accessed 20 July 2015)].
b Data determined on the basis of the WHOQOL-BREF assessment.

Mindfulness

Baseline and 1-month post-treatment FFMQ data for the mediation sample are presented in *Table 19*. The first criterion of mediation is whether treatment significantly changes the mediator.[105] We examined this by entering the FFMQ subscales as dependent variables together in a mixed-model multivariate analysis of variance (MANOVA) with time (baseline, 1-month post treatment) as the repeated measure and group (MBCT-TS, m-ADM) as the between-subjects variable. Multivariate output (broadly reflecting FFMQ total scores) showed significant main effects of group (Wilks' $\lambda = 0.92$, $F_{5,254} = 4.20$, $p < 0.001$, $\eta_p^2 = 0.08$) and time (Wilks' $\lambda = 0.67$, $F_{5,254} = 24.63$, $p < 0.001$, $\eta_p^2 = 0.33$), qualified by a significant time × group interaction (Wilks' $\lambda = 0.88$, $F_{5,254} = 7.05$, $p < 0.001$, $\eta_p^2 = 0.12$), consistent with a greater increase in mindfulness in the MBCT-TS group. Univariate output revealed the same significant interactions for all of the subscales (F-values > 4.12, p-values < 0.05, $\eta_p^2 > 0.015$).

Mediation

To examine mediation effects we included the different FFMQ subscales and the FFMQ total score in separate Cox regression analyses as outlined in the analysis plan. Main effect (M) and interaction (T × M) terms for these mediation analyses are presented in *Table 20*. There was no support for a relationship between change in mindfulness and risk of relapse/recurrence over 24 months. Following the approach to establishing mediation of Kraemer *et al.*,[105] there was no support for the hypothesis that change in mindfulness is the key mechanism of action of MBCT-TS.

Follow-up analyses within the MBCT-TS group

To further explore the patterns in the data we performed supplementary analyses focused on only those participants within the MBCT-TS arm (who also met the criteria for inclusion in the mediation sample) ($n = 135$). We again used Cox proportional hazard regressions, this time without the treatment arm variable on step 1 and without the interactions between treatment and the FFMQ variables on step 3. We therefore examined whether or not changes in FFMQ scores from baseline to 1-month post treatment in the MBCT-TS group significantly predicted relapse/recurrence over 24 months. The results are presented in *Table 21*. As can be seen, there was no significant relationship between FFMQ changes across treatment and relapse/recurrence, even within the MBCT-TS group.

TABLE 19 Mean (SD) data for the potential mediator variables

	Baseline		MBCT+1	
Variable	MBCT-TS ($n = 135$)	m-ADM ($n = 125$)	MBCT-TS ($n = 135$)	m-ADM ($n = 125$)
FFMQ Total	120.12 (18.75)	119.94 (16.19)	133.44 (18.26)	123.57 (16.20)
FFMQ Observe	24.20 (5.46)	23.66 (5.66)	28.64 (4.99)	24.94 (5.45)
FFMQ Describe	26.11 (6.70)	26.51 (6.72)	27.81 (6.28)	26.60 (6.04)
FFMQ Awareness	21.12 (4.92)	21.58 (4.79)	22.64 (4.29)	22.03 (4.22)
FFMQ Non-judgement	25.07 (6.56)	25.51 (6.07)	27.93 (6.26)	26.19 (5.54)
FFMQ Non-reactivity	20.36 (5.01)	19.42 (4.46)	23.02 (3.98)	20.51 (3.96)

MBCT+1, assessment point 1 month after the end of MBCT treatment in the MBCT arm and at the equivalent time point in the m-ADM arm.

TABLE 20 Cox regression to test potential mediators in the prediction of relapse/recurrence at 24 months' follow-up by examining main and interactive effects of treatment and change in hypothesised mediators

Variable	Wald	*p*-value	Exp (B)
ΔGRID-HRSD	3.40	0.07	1.20
Treatment	1.57	0.21	1.31
ΔFFMQ Total	0.03	0.87	1.02
ΔFFMQ Total × treatment	0.40	0.83	0.86
ΔFFMQ Observe	0.04	0.85	0.98
ΔFFMQ Observe × treatment	1.66	0.20	0.75
ΔFFMQ Describe	0.07	0.79	1.03
ΔFFMQ Describe × treatment	0.01	0.93	0.98
ΔFFMQ Awareness	0.03	0.86	0.98
ΔFFMQ Awareness × treatment	0.001	0.98	1.01
ΔFFMQ Non-judgement	0.70	0.41	1.10
ΔFFMQ Non-judgement × treatment	0.32	0.57	1.13
ΔFFMQ Non-reactivity	0.72	0.40	0.91
ΔFFMQ Non-reactivity × treatment	1.42	0.23	0.77

Δ, standardised residualised change in a variable from baseline to MBCT+1 (the assessment point 1 month after the end of MBCT-TS treatment in the MBCT-TS arm and at the equivalent time point in the m-ADM arm); treatment, MBCT-TS vs. m-ADM.
Treatment and ΔGRID-HRSD were entered on step 1 of each regression. Reported values of each control for the effects of the other. ΔFFMQ variables were entered on step 2 of separate regressions. Reported values control for the effects of treatment and ΔGRID-HRSD. The ΔFFMQ × treatment interaction term variables were entered on step 3 of the separate regressions. Reported values control for the effects of treatment, ΔGRID-HRSD and the relevant ΔFFMQ variable.

TABLE 21 Main effects of FFMQ variables in the prediction of relapse/recurrence at 24 months' follow-up for the MBCT-TS group only ($n = 135$)

Variable	Wald	*p*-value	Exp (B)
ΔGRID-HRSD	0.13	0.71	1.06
ΔFFMQ Total	0.24	0.62	0.94
ΔFFMQ Observe	1.03	0.31	0.87
ΔFFMQ Describe	0.00	0.98	1.00
ΔFFMQ Awareness	0.10	0.75	0.96
ΔFFMQ Non-judgement	0.60	0.44	0.11
ΔFFMQ Non-reactivity	2.87	0.09	0.79

Δ, standardised residualised change in a variable from baseline to MBCT+1 (the assessment point 1 month after the end of MBCT-TS treatment in the MBCT-TS arm and at the equivalent time point in the m-ADM arm).
ΔGRID-HRSD was entered on step 1 of each regression. ΔFFMQ variables were entered on step 2 of separate regressions. Reported values for ΔFFMQ variables control for the effects of ΔGRID-HRSD.

Discussion

The analyses presented in this chapter sought to address the following explanatory question: 'Is an increase in mindfulness skills the key mechanism of change of MBCT-TS?' We approached this question by examining whether or not change in mindfulness from baseline to 1 month post MBCT-TS (or the equivalent time point in the m-ADM arm), as measured by the self-report FFMQ, was a significant mediator between trial arm (MBCT-TS or m-ADM) and outcome as assessed by depressive relapse/recurrence over 24 months.

We found no support in the data for either main or interactive mediation effects, somewhat contrasting with our earlier finding from the PREVENT pilot trial[37] that change in mindfulness (assessed using a different measure) mediated effects on residual symptoms of depression at 12 months.

Supplementary analyses examined whether or not change in mindfulness was significantly associated with clinical outcome (time to relapse/recurrence) within the MBCT-TS group alone. Again, we found no support for this prediction.

Future work will systematically explore whether or not there are any mediating effects of mindfulness on secondary trial outcomes or whether or not any putative mediating effects are moderated by key demographic variables (e.g. exposure to childhood abuse).

Chapter 7 Barriers to participation in the PREVENT trial: a qualitative exploration

Introduction

Qualitative research within RCTs can provide a patient-centred and in-depth perspective on the implementation of complex interventions and on trial processes and outcomes.[110] The PREVENT trial offers an opportunity to build on previous qualitative work on MBCT in three important ways: (1) the follow-up period (2 years) is longer than that in many other studies; (2) participant experiences can be explored across larger numbers than in previous qualitative studies; and (3) these large numbers provide opportunities for purposive sampling. Previous qualitative work on MBCT has included very small numbers[111,112] and sociodemographically homogeneous samples.[30] As a consequence, analysis has tended to focus on commonalities, with little exploration of variations in experiences of MBCT. The large number of participants in the PREVENT trial allows exploration of both similarities and variations in their experiences.

One area of focus for the qualitative exploration was the acceptability of MBCT-TS (other qualitative work within the PREVENT trial that is not reported here is listed at the end of the chapter). There are several reasons for interest in acceptability issues: (1) attrition between possible case identification and recruitment in MBCT trials is typically high;[28] (2) between 7% and 25% of people do not complete the full MBCT course and a 15% dropout rate from MBCT is typical;[24,25,28] and (3) there are wide variations in the extent to which people engage with mindfulness practices that are assumed to be the vehicle of change.[112] Existing evidence about the acceptability of MBCT is limited[111] and there is no published evidence on the acceptability of MBCT-TS. Little is known about several elements of acceptability: why people choose not to participate in MBCT; reasons for dropout from treatment; and why people fail to engage with or continue mindfulness practices. The research reported here focuses on the first of these issues, namely barriers to participation in MBCT-TS within the PREVENT trial, at the point of initial invitation into the trial (other acceptability questions are addressed by data not reported here).

Methods

Development of data collection tools drew on the perspectives of both PREVENT MBCT therapists and members of the trial LEG (see *Chapter 3*). This helped to enhance the relevance and acceptability of data collection to patients and ensured that it was informed by the clinical judgements of MBCT therapists.

Reasons for declining participation at initial contact

Initial letters of invitation to participate in the PREVENT trial sent to potentially eligible patients identified by GP practices provided a return envelope and reply form. This form allowed people who did not want to participate to write their reasons for this, in response to the following prompt:

> *It helps us to plan research in the future if we know the reasons why this trial did not appeal to you. We would be very grateful if you could write these reasons below, but we want to stress that this is not something you have to do; we respect that this may be a private decision that you do not want to share.*

Space for up to four lines of text was provided. Basic demographic information was also collected using this form.

Telephone interviews with non-participants

The reply form referred to in the previous section also asked people who declined to participate in the trial to indicate if they would be willing to conduct a brief telephone interview on their reasons for declining. Of the 2157 individuals who indicated that they were not interested in participating in the trial, 290 (13%) agreed to be interviewed and a sample of 16 was selected. Sampling was based on initial content analysis of the first 50 written responses about reasons for non-participation provided on reply forms. Based on this, we aimed to construct a sample of 16 interviewees using the following criteria: ADM issues – at least four; therapy issues – at least four; lifestyle issues – at least four; others – up to four, including at least one each from 'research issues' and 'symptom issues'. We aimed to recruit from all of the four sites and to ensure that a spread of basic demographic characteristics was included. This strategy ensured that the diversity of the larger sample of people who gave reasons for non-participation was reflected in the sample of people interviewed.

A smaller number of people declined trial participation after the initial telephone screening ($n = 187$; see *Figure 3*). We aimed to conduct six to eight semistructured telephone interviews with members of this group, with at least one person from each site in the sample. This subsample allowed exploration of any impact of receiving additional information during a telephone screening interview on people's reasons for non-participation.

Telephone interviews for both of these groups were conducted within 1 month of the person declining trial participation. They began with an initial open question about reasons for declining participation and subsequently asked about the reasons identified by analysis of written responses provided on reply forms. This included questions on participation in research, randomisation preferences, the nature of MBCT and expectations of ADM use associated with each arm of the trial.

Data analysis

Written responses were transcribed verbatim into Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA). Content analysis was used to classify responses into basic categories of reasons for non-participation. A collaborative approach to analysis was adopted by a small team of researchers who worked together to establish, define and agree on content analysis categories using a subset of data before these categories were used to analyse the complete data set.

Telephone interviews were audio recorded and transcribed, with any identifying information removed. Data were analysed using thematic analysis[113] in NVivo 10 software (QSR International, Warrington, UK). The analytical strategy combined inductive and deductive approaches. Reasons for declining that were used to categorise written response data were used as a starting point for data exploration. These were added to as data analysis progressed, and main themes were divided into subthemes to capture complexity and variation. A collaborative approach involving team working among a small group of researchers enhanced the validity of the analytical process.

Results

Reasons for declining participation at initial contact

From a total of 19,608 invitations sent, 2157 people (11%) indicated that they were not interested in participating in the PREVENT trial either by declining any further contact or after further discussion with a member of the research team. Within this sample, 1535 (71%) participants were female and the average age was 58.6 years (range 20–91 years; missing data for 25 cases). The sample was spread across the different geographical areas: South Devon $n = 490$ (23%); North and Mid Devon $n = 788$ (37%); Exeter and East Devon $n = 580$ (27%); and Bristol $n = 299$ (14%). These characteristics are similar to those of the final sample of PREVENT trial participants (see *Table 7*) with the exception that the PREVENT trial population was younger on average (mean age 49 years). Education and marital status are not reported as fewer than half of the respondents provided this information.

Because a minority of people gave more than one reason for not participating, responses added up to an overall number of 2402 instances of coding. Of these, 120 codings (5%) were coded not eligible for participation (mainly when participants did not fulfil trial inclusion criteria such as having three episodes of depression or a diagnosis other than depression). Hence their responses were excluded from further analysis. Furthermore, some 1109 (46%) codings did not reveal any reasons, yielding a final number of valid codings of 1173 (49%).

Content analysis produced 10 categories of reasons, the distribution of which within the data is shown in *Figure 16*. We further categorised these reasons into four broad areas as follows:

i. intervention-related issues – these are about use of ADM, therapy-related issues and the group-based nature of the intervention
ii. personal circumstances – three categories of reasons relating to personal circumstances were found: lifestyle issues, time issues and medical issues
iii. symptom-related issues – reasons relating to current symptoms and feelings of being in recovery
iv. research-related and other issues.

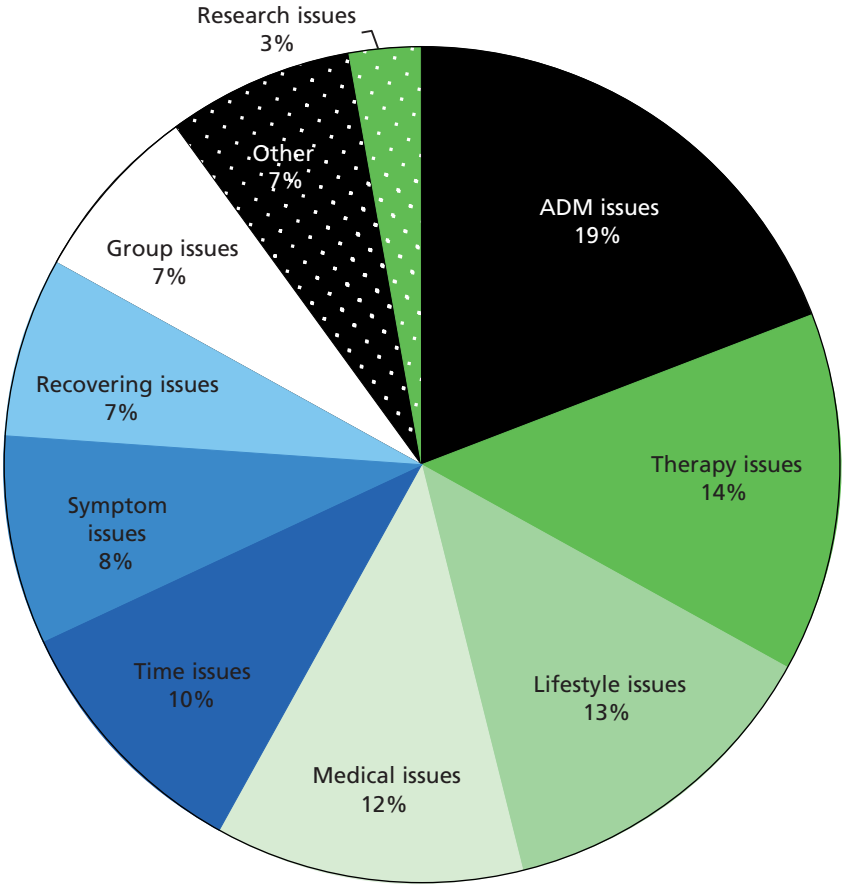

FIGURE 16 Frequencies of reasons for non-participation provided in written responses on invitation reply forms.

Intervention-related issues

The most commonly cited reasons for non-participation were related to the treatment interventions provided in the PREVENT trial. Together these accounted for 40% of all reasons given. Within this, the largest category related to use of ADM (19% of all responses). Most commonly, people reported that they did not want to stop taking ADM (49% of ADM reasons). Other reasons were that people were no longer taking ADM (24%), were currently coming off ADM (9%) and were happy with their current ADM use (11%). The second most common category of reasons overall related to therapy issues (14% of all responses). In total, 23% of responses in this category related to people having previously tried talking therapies and a further 17% of responses related to reports that past therapy had not helped. Some reported that they were currently receiving a different kind of therapy (19%) and others reported wanting to avoid bringing up bad memories (16% of responses in this category). Related to this, a third category of responses was about reluctance to participate, or anxiety about participating, in group-based therapy (7% of all responses).

Personal circumstances

In total, 35% of responses described personal circumstances as a barrier to participation. The category of lifestyle issues accounted for 13% of responses. Specific reasons within this category included feeling too old (23%), moving house or relocating (17%), transport difficulties (14%) and feeling that participation would mean taking on too much (15%). Health-related barriers were also common (given in 12% of responses overall). Most frequently, people reported their own physical or health difficulties as a reason preventing participation (47%), but caring for others (21%) and illness or death of a family member (15%) were also cited. In total, 10% of responses overall cited lack of time, with one-quarter of these participants specifically stating that they would be unable to take time off work.

Symptom-related issues

Symptom-related reasons for non-participation were cited in 15% of responses. Specific reasons within this included considering that they suffered from anxiety more than depression (18%), feeling that they did not suffer from depression (14%), that they were currently depressed (17%), that they were currently feeling well or recovering (27%) or that they already had strategies in place to manage their depression (12%).

Research-related and other issues

The final 10% of responses referred to research-related issues (3%) and miscellaneous other reasons that could not be categorised in other ways (7%). Just over half of the research-related reasons were that people did not want to be involved in research or had concerns about this. Another common reason was already being involved in research, currently or in the past.

Telephone interviews with non-participants

Telephone interviews were conducted with 16 people who declined to participate having received an initial invitation letter and six people who declined to participate after telephone screening. Demographic information for these subgroups in comparison with that for PREVENT trial participants is provided in *Table 22*.

TABLE 22 Demographics of declining samples and the final PREVENT trial sample

Demographic characteristics	Pre-screen decliners ($n = 16$)	Post-screen decliners ($n = 6$)	PREVENT participants ($n = 424$)
Age (years)			
Mean (SD)	56.8 (11.1)	59.0 (11.8)	49.4 (12.3)
Range	40–72	44–77	20–79
Missing, *n*	1	1	0
Female, *n* (%)	13 (81)	5 (83)	325 (77)
Recruitment site, *n* (%)			
Exeter and East Devon	3 (19)	1 (17)	148 (35)
North and Mid Devon	6 (38)	2 (33)	109 (26)
South Devon	5 (31)	2 (33)	103 (24)
Bristol	2 (13)	1 (17)	64 (15)
Marital status, *n* (%)			
Single	2 (13)	0 (0)	80 (19)
Married or living together	10 (63)	2 (33)	264 (62)
Separated, divorced or widowed	2 (13)	1 (17)	77 (18)
Missing	2 (13)	3 (50)	3 (1)
Employment status, *n* (%)			
Employed	5 (31)	3 (50)	240 (57)
Unemployed or retired	9 (56)	1 (17)	178 (42)
Missing	2 (13)	2 (33)	6 (1)

Table 22 shows that the main differences between these non-participant samples and the PREVENT trial participants are that there are slightly higher proportions of women in the non-participant samples and the non-participant samples are older on average. The two non-participant subsamples are broadly similar to each other.

Analysis identified nine broad thematic areas within the interview transcripts, with subthemes within each. The frequency of coding across interviews using these themes is show in *Table 23*.

Table 23 shows the application of a theme at any point in an interview transcript but does not provide further information on how often or where themes were used in interview transcripts or the relative weights or meanings attached to these. To explore these more complex issues, a distinction was made between reasons for non-participation provided in response to an initial open question at the beginning of the interview ('Could you tell me the reason or reasons why you are not interested in taking part in this research study') and reasons provided later in the interview in response to prompts about barriers to participation identified from written replies. It was assumed that reasons given in response to the first open question would usually be the most important for an individual. The distribution of themes and subthemes for first question responses and later parts of the interview and the co-existence of themes within interview transcripts is shown in *Appendix 7*. Details of each of the thematic areas are reported below in descending order of frequency with which they occur as 'principal' reasons for declining participation (i.e. in response to the initial open question). Exploration of these did not detect any obvious differences between the two subsamples of interviewees (those interviewed before telephone screening and those interviewed after). Accordingly, findings from the two subgroups are reported together, yielding a total sample of 22 interviews.

TABLE 23 Frequency of themes and subthemes within interview transcripts

Theme	Subthemes	Pre-screen ($n = 16$)	Post-screen ($n = 6$)	Total ($n = 22$)
Taking part in a research trial	No concerns	15	5	20
	Safety and reliability concerns	4	1	5
	Wanting to help others	2	2	4
	Previously taken part in research	2	1	3
ADM-related issues	Wants to remain on ADM	14	6	20
	Wants to come off ADM	7	2	9
	Does not want to take ADM for 2 years	1	0	1
	Not regularly taking ADM	1	0	1
Being randomised to a trial arm	Would like to choose group	9	4	13
	Would like to be in the ADM group	7	2	9
	Would like to be in the therapy group	2	2	4
	No worries about randomisation	3	1	4
Time issues	Not the right time	9	4	13
	2 years is too long	2	0	2
	Working full time	1	1	2
Attitudes to psychological intervention	Had therapy before	7	4	11
	Previous therapy unhelpful	3	3	6
	Previous therapy helpful	4	1	5
	Therapy and ADM complementary	2	0	2
MBCT-related issues	Meditation is a good idea	7	4	11
	Not keen on meditation	4	1	5
	Conflicts with religious interests	1	0	1
Being in a group	Unhappy with group therapy	9	1	10
	No concerns about group therapy	3	2	5
Lifestyle and medical barriers	Too unwell	3	2	5
	Cannot travel to sessions	3	1	4
	Too old	1	1	2
Symptom-related issues	Not depressed enough	5	1	6
	Depression is contextual	4	3	7
	Depression because of chemical imbalance	2	1	3
	Worried about relapsing	4	0	4

Antidepressant medication-related issues

The most prominent reasons for declining participation were related to ADMs. Concerns about ADMs were raised by all of the interviewees, nearly half of whom ($n = 10$) discussed ADMs in response to the initial open question. For the majority (18/22), the principal concern was about potentially stopping or reducing their ADM. Most people felt that they needed to take ADM, or were well when they were taking it, and they did not want to jeopardise this or risk relapse/recurrence if randomised to the treatment arm.

> *When I read through the literature I believe um it w- . . . t'was about stop taking medication and um I wasn't really prepared to do that because it has taken me a long time to sort of get the balance right um and that would I think that would I didn't want to stop and jeopardise that was I think that was um what I recall.*
>
> *2007*

For nine people, the concerns around ADMs related to the fact that they would like to eventually come off their medication. For some of these people the risk of being randomised to the m-ADM arm, and feeling that this would entail a loss of choice or flexibility, was a bigger concern.

> *In agreeing to this I'd have to agree to keep taking my medication for you know the next 2 years. It may be that I wanna come off my medication in a year or so's time you know so that was an issue. Um you know um so . . . you know I'd feel I'm sort of trapped on medication as it were you know, err, I may not want to be trapped on medication or I might feel that at some point in the fairly near future it might not be a bad idea to come off . . . I have a feeling if I committed to this then that would um that would maybe cramp my options a bit.*
>
> *2001*

Three people described having already started to reduce their ADMs and their hopes that they would be able to stop taking them in the near future.

Time issues

The second most common reasons for non-participation involved time-related issues, with more than half (13/22) mentioning time constraints at some point in the interview and 10 people citing time constraints in response to the initial open question. Reasons related to people's circumstances and predominantly included not having enough time for the study or it not being the right time in their lives. Two people worked full-time and as such were not able to attend MBCT sessions that were mostly run during working hours. Of those who were employed, nearly all mentioned time constraints as a reason for declining, whereas only half of those who were retired discussed this. Those who were married also tended to give time constraints as a reason for declining. Two people declined as they felt that 2 years was too long a time to be involved in a research study.

> *Um it is time, it is purely because I just don't have the time. I've taken on so many other new commitments which are quite essential commitments you know jobs and things like that that really need enough time to commit to properly. And rather than start it and give it up, it's probably best not to start it.*
>
> *3005*

> *I mean primarily I haven't got time. Um I work 2 days a week um, I've got an elderly mother I look after and I look after my grandson as well so in the literature that you sent out you said about going to group meetings and things like that. I haven't got time to do it basically.*
>
> *2005*

Lifestyle and medical barriers

Ten people cited practical or medical reasons for non-participation, of whom six gave such reasons in response to the first open question. Five respondents said that they were unable to participate in the PREVENT trial because of physical health problems that meant they felt unable to commit to attending treatment. For four people, travelling to and from sessions was a barrier. Two people felt that they were too old to take part, although the exact reasons for this remained unstated:

> I: *To begin with it would be really helpful if you could tell me the reason or reasons why you are not interested in taking part in this research study.*
>
> 2013: *Er it's not so much not interested, er I wouldn't like to put it like that really, but the fact is I can hardly get about anyway myself 'cause I walk on sticks, I've had problems with my back and also my husband has recently been diagnosed with heart problems and so he's not well himself. So he's the one that does the driving and all that so it's something I don't really want to be doing at this point in time.*
>
> *No no my general view is that at this stage in my life because of my age I really don't need to take part.*
>
> *3008*

Being in a group

Ten individuals reported feeling uneasy with the idea of group-based treatment or said that they would feel more comfortable with one-to-one contact. Four of these people gave this reason in response to the first question.

> *When my depression is really bad . . . and you're sort of crying out for help um it's very . . . the thought of . . . being within a group of people you know um is quite daunting in a way, at the best of times. . . . I really didn't want to be in a group situation with people who were potentially my neighbours or the people who worked in the café or the bank, you know, locally to me.*
>
> *2014*
>
> *You know I d- you know I I think there are a lot of people out there that probably feel the same as me, but I realise that and I don't really think I want to . . . go into a group (.2) you know I, I – just one of those things, I just don't want to do it really.*
>
> *2009*

However, the group-based nature of MBCT was not a universal barrier and five individuals said that they would not mind taking part in group-based therapy.

> *But when you're talking to a stranger sometimes if they can gain your confidence then you feel as though you can talk to them more and tell exactly how you're feeling. But I think that um group therapy is a good thing actually.*
>
> *2013*

Attitudes to psychological intervention

Half of the individuals interviewed (11/22) had some previous experience of psychological therapy, of whom six had found this unhelpful.

> *Because I've had therapy in the past, counselling sessions actually, the reason I considered this is because the counselling session didn't actually help, going back over and over again on all the issues and actually why I was upset and feeling unhappy actually just made me feel more upset than happy. So I found that wasn't particularly beneficial for me, and I had a, you know, sort of aversion to therapy to do with one particular therapy incidence.*
>
> *3005*

Of the six that found psychological therapy unhelpful, three mentioned negative experiences of therapy in the past in response to the first open question. The most common forms of therapy experienced were CBT and counselling. One person had received hypnotherapy and another had seen a psychiatrist.

Mindfulness-based cognitive therapy-related issues

The nature of MBCT treatment was seen as a barrier to participation by some respondents but as a facilitator by a larger proportion of respondents. Half of the individuals interviewed thought that therapy incorporating meditation was a good idea. Some mentioned that they already practised some form of meditative techniques such as breathing exercises, yoga or t'ai chi and so were open to the meditative aspects of MBCT.

> *Um I think it sounds very good, I've tried meditating in the past and you know err breathing techniques and stuff and the idea of it sounds really good.*
>
> *2007*

However, five people expressed concerns about meditation forming a large part of MBCT and appeared sceptical of its benefits.

> *I've tried yoga in the past and tried to meditate. My problem with that is I just I find it very hard and I end up making mental lists of all the different things I have to do and my mind doesn't switch off.*
>
> *3006*

Only one person cited the nature of MBCT as a significant barrier in response to the first question. This person's concerns centred on perceived incompatibilities with religious beliefs.

> *No I think it was to do with somebody like you ringing up and explaining what was going to happen, and I wasn't happy with it because I'm a Christian and it didn't hold with my beliefs I think. It was err, I felt it was very based on Eastern religions, Eastern philosophy and that, and that was uncomfortable. I thought the meditation where you've got to clear your mind I'm not happy with that anyway, and I just felt it was more like younger based, and I think that's what concerned me more than anything.*
>
> *2010*

Symptom-related issues

Twelve participants discussed symptom issues as a barrier to participation, although only one person cited this in response to the first question. Six people said that they did not consider themselves to be depressed enough or were no longer suffering from depression. Seven people described their depressive symptoms as contextual or a consequence of specific life stressors. As such, they felt that their symptoms did not warrant psychological therapy.

> *I've always been a person in c- basically in control of myself I mean m- much of my trouble was caused all the work rather than anything else you know? Particularly when I took them [ADMs] before I don't remember when that was now um but it was caused too much work.*
>
> *2002*

Four people said that they had concerns about relapsing as a consequence of reducing their ADM during MBCT-TS treatment.

> *I have twice in the past tried to come off the tablets um you know it was quite a long time ago, and after I'd got down to a certain dose I became ill again and you know it's not something I want to happen, you know me taking 3 weeks off of work, which um is never good for me or the department you know. With a responsible job you can't um you can't really do that.*
>
> *2006*

Being randomised to a trial arm

Only one person cited trial randomisation as a barrier to participation in response to the first open question.

> *I just saw it as an opportunity, and I think if I'd been in a group that wasn't actually receiving the help, in the other test group [m-ADM] I would find it very disappointing and it may even affect me and I'd feel maybe unfairly treated perhaps. Whereas I should have been looking at it as a research project, um I was probably looking at it as some sort of therapy for me really.*
>
> *3003*

However, when asked later in the interview about being randomised to MBCT or m-ADM, 13 people said that they would prefer to have a choice rather than be randomised. Of these, nine said that they would like to be placed in the m-ADM group and the remainder said that they would choose to receive MBCT. Only four respondents did not mind which trial arm they were placed in.

Taking part in a research trial

In response to a question about taking part in research generally, the majority of respondents (20/22) either had no concerns about taking part in a research study or said that they would be happy to do so if the circumstances were right for them. Four people said that they would take part in research to help other people and three individuals had previously taken part in a trial.

> *I'm absolutely fine with that, taking part in a research study, I don't have any problem with that at all.*
>
> *2007*

Five people voiced concerns about the safety and reliability of research. These ranged from concerns about data confidentiality to concerns about the qualifications and professionalism of research staff.

> *I guess it's to do with things around privacy and confidentiality of data, stuff to do with that and to do with the uses to which data might be put in the future by persons unknown, as it were, you know, or authorities of note. There is an issue for me with that, but it wouldn't necessarily put me off taking part in something like this, but it is a nagging issue I feel, personally yeah.*
>
> *2001*

Discussion

Barriers to participation in the PREVENT trial

It is difficult to collect reliable data on why people choose not to participate in research or treatment and hence there is little good evidence on this issue. Our attempts to do so yielded data from < 5% of the total sample who were sent initial invitation letters. It is not possible to judge how representative this subsample is of the larger number of people who were invited to take part, in terms of either their sociodemographic and clinical characteristics or their reasons for not wanting to participate.

Given these sample-related caveats, data from reply forms allowing people to decline participation in the PREVENT trial and provide brief reasons for this suggest that views on the interventions being tested within the PREVENT trial were a principal barrier to participation. Overall, these accounted for 40% of the reasons given at this early stage, with ADM issues – most typically people being reluctant to consider stopping their ADM – being commonly cited (19%). A large proportion of people (21%) also expressed a reluctance to engage with therapy or a group-based intervention (although this was not always about therapy per se as some people reported already receiving another form of therapy). A further 33% of responses cited personal circumstances as barriers to participation. These included health issues, time constraints, caring commitments and transport issues.

Data from telephone interviews allowed more in-depth exploration of reasons for non-participation. Interviewees were carefully selected to be broadly representative of the larger non-participant group according to reasons given on reply forms. Reasons provided in brief written responses were replicated in these data and no new themes were detected. The same four broad clusters of reservations were expressed: intervention-related concerns, personal circumstances, symptom-related issues and research-related concerns. However, a richer understanding of these reasons was obtained and features that were attractive or at least acceptable, as well as those perceived to be barriers to participation, were discussed. This highlights that barriers are not universal. Many respondents had no problems with the prospect of participating in research, psychological therapy and treatment that incorporates meditation practices. Smaller numbers did not object to group-based treatment or being randomised. Interview data also shed light on relationships between these themes. In particular, concerns about randomisation appeared to be primarily motivated by preferences relating to ADM use.

Taking the findings from these two substudies together, the principal barrier to participation in the PREVENT trial at the point of recruitment appeared to be expectations surrounding ADM use. This applies to both arms of the trial. For most people, their concerns centred on being randomised to MBCT-TS, as they did not consider themselves to be in a position to taper their ADM. Although ADM tapering is presented as an invitation rather than a requirement by MBCT-TS therapists, the *perceived* expectation of this presented a considerable barrier at this point. For a smaller group of people, reluctance to participate related to being randomised to the m-ADM arm, as this carries an expectation of continuing on ADM for 2 years, a prospect that may not be acceptable to many.

Preferences for ADM use appeared to be the principal reason why randomisation within the PREVENT trial was off-putting to many, as it is perceived to remove choice and flexibility. This may be a particularly large barrier within the PREVENT trial, which involved a 2-year follow-up period, and for a participant group with long-term mental health problems who may have developed functional self-management strategies based on experiential knowledge of ADMs that they are reluctant to disrupt. As such, randomisation without taking account of patient preferences runs counter to the promotion of self-management, patient choice and expertise by experience that features in much current policy rhetoric in health and mental health. Randomisation appeared to be the principal barrier to research participation as few other concerns about involvement in research were expressed and the majority of interviewees were positive about participating in research.

Other than ADM-related issues, several identified aspects of the acceptability of MBCT-TS may apply equally to MBCT. The expected time commitment and the group-based nature of treatment appear to be two important perceived barriers at the point when people are deciding whether or not to participate. The considerable time commitment of MBCT participation and home-based practice may not be compatible with many people's life circumstances. Although the group-based nature of treatment is off-putting to some, previous research on MBCT has found that initial concerns about group work are often replaced by recognising the value of sharing experiences in a safe environment during and following treatment.[111,114] For a significant minority, physical health may be a barrier to participation. Although negative experiences of, or expectations of, talking therapies were cited as reasons for non-participation by some, the nature of MBCT did not seem to be a concern for most at this stage. A small number of interviewees found the prospect of meditation off-putting, but a larger number expressed interest in or positive views of a meditation-based treatment.

There are some suggestions than non-participants may be older than participants (average age of 59 years for written response data participants and 57 years for interviewees compared with 49 years for PREVENT participants). Interestingly, feeling too old as a reason for non-participation appeared in a small number of both written responses and telephone interviews.

Findings can contribute to informing both clinical practice and future research trials on MBCT. The external validity of RCTs can be undermined by low recruitment rates. These data provide a window on reasons for the relatively low recruitment rate in the PREVENT trial (424 from an initial total of 19,608 people invited). Exploring barriers to participation and their impact on the composition and characteristics of trial participant groups is an important aspect of interpreting trial results. Findings also have implications for clinical practice in highlighting features of MBCT-TS and MBCT that may prevent people who are offered this treatment from taking it up. This counters the tendency in previous qualitative research to focus on the benefits of MBCT for those who engage meaningfully with treatment,[30] at the expense of exploring the experiences of others who do not engage. Awareness of these barriers may help practitioners to put in place strategies to overcome reluctance to commence therapy and may help to increase the accessibility of mindfulness-based treatments.

Other qualitative studies within the PREVENT trial

As well as the data reported in this chapter, two further sources of qualitative data were collected within the PREVENT trial with the aim of addressing the following research questions:

1. *The acceptability of MBCT-TS.* We conceptualise acceptability as dynamic and related to various levels of knowledge and experience of MBCT-TS at different stages of recruitment and participation. Further data analysis will focus on barriers to and facilitators of MBCT-TS at later stages of participation, during and after treatment.
2. *Mechanisms of change in MBCT.* This extends previous qualitative work[30] in two ways, first by using larger numbers and purposive sampling and second by drawing on insights from quantitative studies of change mechanisms.[37] Qualitative explorations of processes that have been identified as mediating outcome, such as self-compassion and reactivity, may strengthen understanding of how MBCT works.
3. *Participants' attitudes towards and experiences of ADM with and without MBCT (including ADM tapering and continuation)*. Monitoring of ADM usage within the PREVENT trial suggests considerable variability in adherence, especially in the MBCT arm (see *Chapter 4*). No previous qualitative work has been carried out on experiences of combining MBCT with ADM tapering.

The following two sources of qualitative data were collected:

1. *Feedback booklets.* All trial participants were asked to provide written accounts of their experiences in feedback booklets provided at two time points: 1 month post MBCT-TS (or the equivalent time point for those in the m-ADM arm) and at 24 months' follow-up. This design helps avoid the influence of memory biases, allows longitudinal comparisons and ensures equipoise. Four feedback booklets were created (1 month post MBCT-TS, 24 months post MBCT-TS, 1 month post m-ADM, 24 months post m-ADM). Members of the LEG provided feedback about the wording of booklet questions, the choice of issues covered and the time needed to complete them. To ensure sensitivity to the range of participants' experiences, the design of the 24-month booklets was informed in part by responses obtained at the 1-month time point. Booklets covered the following topics:

    i. 1 month post MBCT-TS: (i) attitudes towards and experiences of taking and reducing ADM; (ii) experiences of taking part in MBCT-TS and MBCT-TS practices; (iii) the impact of MBCT-TS
    ii. 24 months post MBCT-TS: (i) experiences of MBCT-TS reunions; (ii) carrying out mindfulness practices; (iii) the impact of continued MBCT-TS practice; (iv) ongoing experiences of medication use and possible tapering in relation to MBCT-TS impact
    iii. 1 month post m-ADM: (i) acceptability of using ADMs in general; (ii) perceived effectiveness of ADMS; (iii) experiences of ADM continuation within the trial
    iv. 24 months post m-ADM: (i) attitudes to and experiences of continuing to take ADMs during the trial; (ii) deviations from the ADM use protocol during the trial; (iii) reasons for and impacts of any changes.

2. *End-of-trial interviews.* Semistructured interviews were designed to explore experiences during the follow-up period of use of ADMs and MBCT-based techniques, in relation to each other, during periods of wellness and depressive relapse/recurrence and during transitions between them. The research team, informed by responses from a sample of 1-month post-MBCT-TS feedback booklets and feedback from the trial LEG, developed interview topic guides. Interviews were structured around discussion of periods of wellness, early signs of depressive relapse/recurrence (referred to in interviews as 'wobbles') and depressive relapses/recurrences. For each of these, questions explored the use and value of mindfulness techniques, use of ADMs and use of a combination of mindfulness techniques and ADMs. The final section of the interview asked about the broader impacts of participation in the trial on other life domains, sense of self and views of depression. A sample of 40 interviewees was constructed according to principles of maximum variation sampling, aiming to access a range of participant positions and characteristics relevant to the research questions.[115] Interviewees were selected evenly across the four study sites and to broadly reflect the sociodemographic characteristics of the full trial sample. In addition, we sampled according to treatment response (depressive relapse/recurrence or not) and medication usage during follow-up (four categories: stopped, stopped and resumed, reduced but never stopped and did not reduce or stop). Face-to-face interviews were conducted in participants' homes and lasted between 45 minutes and 1 hour.

These data collection strategies will enable a combination of depth of understanding within a purposively selected sample and breadth of data collected from all PREVENT trial participants. The 2-year follow-up period of the PREVENT trial allows exploration of how MBCT-TS impacts on people's depressive symptoms and lives over a much longer time period than has previously been studied. Careful sampling of respondents for end-of-trial interviews ensures that this data set is genuinely reflective of the range of relapse/recurrence, ADM use and MBCT-TS experiences across trial participants. Analysis of these data sources will be reported in subsequent published papers, adding complexity and further understanding to the trial's results.

Chapter 8 Discussion and conclusions

Principal findings

The overarching aim of the PREVENT trial was to establish whether or not MBCT-TS provides an effective alternative relapse/recurrence prevention approach to m-ADM in primary care settings for patients with a history of recurrent depression. Specifically, we asked a primary policy research question: 'Is MBCT-TS superior to m-ADM in terms of a primary outcome of preventing depressive relapse/recurrence over 24 months?' Secondary outcomes were depression-free days, residual depressive symptoms, psychiatric and medical comorbidities, quality of life and cost-effectiveness. The study was conducted in line with both CONSORT guidance[74–76] and our published protocol.[78,83] Participant recruitment, flow and data completeness were above estimated thresholds. We are, therefore, able to answer the key research questions.

There was no evidence for the superiority of MBCT-TS over m-ADM for patients with recurrent depression in terms of either the primary outcome of time to depressive relapse/recurrence over 24 months or any of the secondary outcomes (see *Chapter 4*). The cost-effectiveness analysis does not support the hypothesis that MBCT-TS is more cost-effective than m-ADM, in terms of either relapse/recurrence or QALYs (see *Chapter 5*).

In a predefined subgroup analysis,[83] we found that time to relapse/recurrence at 24 months for participants with a higher severity of reported childhood abuse was delayed in the MBCT-TS arm, compared with the m-ADM arm.

Finally, the first results from our process studies suggest that, although changes in mindfulness were greater in the MBCT-TS group than in the m-ADM group, they did not mediate time to relapse/recurrence at 24 months (see *Chapter 6*). In terms of acceptability, the qualitative analyses suggest that people have views about (dis)/continuing their ADM that can serve as a facilitator and barrier to taking part in a trial that requires either continuation for 2 years or discontinuation (see *Chapter 7*).

Research findings in context

Relapse/recurrence rates in people with three or more previous episodes are as high as 80% over 2 years.[6] Moreover, meta-analyses consistently suggest that m-ADM reduces the relative risk of relapse/recurrence by two-thirds compared with placebo, a halving of the absolute risk.[9] Therefore, it is likely that MBCT would provide benefits over and above either no treatment or pill placebo.

Outcomes were comparatively good across both treatment arms in the PREVENT trial in terms of relapse/recurrence over the 2 years of follow-up compared with those in previous trials (i.e. MBCT-TS 44%, m-ADM 47%). Moreover, PREVENT trial participants reported residual depressive symptoms within the minimal range and quality of life in the range 'good' at each follow-up point. This suggests that participants in both arms experienced relatively good mental health and quality of life over the follow-up period.

Before the PREVENT trial, only two small studies had compared MBCT-TS with m-ADM. In our pilot trial with 123 participants, MBCT-TS ($n = 62$) was compared with m-ADM ($n = 61$) over 15 months' follow-up.[28] The relapse/recurrence rate was 47% for MBCT-TS and 60% for m-ADM. In a second study, 84 patients with recurrent depression who had remitted on ADM were randomised to MBCT-TS, m-ADM or pill placebo.[51] Relapse/recurrence rates observed over 18 months of follow-up did not differ between MBCT-TS (28%) and m-ADM (27%; $p = 0.93$) and both MBCT-TS and m-ADM were superior to placebo (71%; $p = 0.007$).

Since the start of the PREVENT trial, a key systematic review and meta-analysis has been published that included six RCTs comparing MBCT with usual care, m-ADM or placebo (including the two previously described trials) ($n = 593$). The pooled estimate from this review shows that MBCT reduces the risk of relapse/recurrence compared with usual care or placebo (risk ratio 0.66, 95% CI 0.53 to 0.82).[116]

Since this systematic review/meta-analysis, several additional large-scale trials of MBCT have been published[117–119] or are due to be published soon.[120] The Staying Well After Depression (SWAD) trial compared MBCT with cognitive psychoeducation plus usual care and usual care alone in 274 participants currently in remission but reporting at least three previous episodes of depression.[117] The SWAD trial reported no significant effect of treatment on risk of depressive relapse/recurrence over the 12-month follow-up (MBCT vs. psychoeducation: HR 0.88, 95% CI 0.58 to 1.35; MBCT vs. usual care: HR 0.69, 95% CI 0.42 to 1.12). In another recent RCT, 203 non-depressed adults with a history of three or more previous episodes of depression were randomised to MBCT plus depression relapse active monitoring (i.e. training in self-management of depression and monthly monitoring of symptoms) ($n = 101$) or active monitoring alone ($n = 102$).[119] The DARE trial found no significant difference between the two treatment arms for the primary outcome of time to first relapse/recurrence over 24 months, although there was some evidence that proportionally fewer people relapsed in the MBCT arm than in the active monitoring alone arm (odds ratio 0.68, 95% CI 0.38 to 1.23). It is noteworthy that the absolute rates of relapse/recurrence in the usual care arms of these two more recent trials are lower than those seen in earlier RCTs. In total, 66% relapsed in the usual care arms in the Piet and Hougaard systematic review[116] compared with approximately 50% in the usual care arms in the DARE[119] and SWAD[117] trials at 12 months' follow-up.

Economic evaluation found group-based MBCT-TS to be a relatively inexpensive intervention compared with individual therapies. In line with previous results from our pilot study,[28] there was little difference in the use of other health and social services between the groups, resulting in only a small difference in the total costs of care over 24 months between the two groups. Coupled with small, non-significant differences in outcome, MBCT-TS failed to demonstrate cost-effectiveness compared with m-ADM.

Consistent with an emergent pattern of findings,[117] MBCT may confer most benefit to patients at greatest risk of relapse/recurrence. Earlier trials[24,25] and NICE guidance[8] suggest that MBCT is indicated for patients who have a history of three or more previous episodes of depression. In the SWAD trial,[117] a subgroup analysis compared participants reporting greater or lesser childhood adversity. For participants reporting greater childhood adversity MBCT conferred better protection against relapse/recurrence than both psychoeducation and usual care (MBCT vs. psychoeducation: HR 0.61, 95% CI 0.34 to 1.09; MBCT vs. treatment as usual: HR 0.43, 95% CI 0.22 to 0.87). The PREVENT trial results replicate the SWAD finding and converge with those of earlier studies suggesting that patients at greatest risk of depressive relapse/recurrence may benefit most from MBCT. Trials of other psychosocial approaches have shown that more intensive psychosocial treatments result in greater protection for those most at risk. For example, in a two-arm RCT with 21 months' follow-up, relapse/recurrence rates were 51% for maintenance CBT and 60% for psychoeducation but, among those at greatest risk, CBT conferred greater protection than psychoeducation.[121] A reported history of abuse and adversity is associated with worse outcomes among people who suffer depression.[122] Perhaps MBCT confers resilience in this group at highest risk because patients learn skills that address some of the underlying mechanisms of relapse/recurrence, a question that we will seek to explore in a subsequent publication from this trial. Future trials of MBCT need to focus on the question of the effectiveness and mechanism of action of MBCT for those at differing risk of relapse/recurrence, with broad and robust measures of risk.

Strengths and limitations

Strengths of the PREVENT trial include the following.

- The pragmatic main study question is of high relevance to the NHS. The study answered an important clinical question of high relevance to GPs and patients at risk of depressive relapse/recurrence.
- The trial was a multicentre RCT conducted in accord with both CONSORT guidance and our published protocol/statistical analysis plan.
- This is the largest trial of MBCT for recurrent depression to date. Good recruitment/retention rates and low levels of missing data mean that the trial was adequately powered and able to answer the primary research question.
- The study benefited from a comprehensive economic evaluation, providing evidence to support resource allocation decision-making of both clinical and policy relevance.
- Treatment fidelity with respect to both arms of the trial was designed into the trial and high levels of fidelity ensured high internal validity.
- The 2-year follow-up allowed assessment of the impact of MBCT-TS over a time period that was comparable to or longer than that in all MBCT trials completed to date.
- A parallel process evaluation was undertaken to provide contextual understanding and examine the mechanism of action of MBCT.

Limitations of the PREVENT trial include the following.

- Our recruitment strategy involved searching primary care databases and inviting patients who were currently taking m-ADM rather than recruiting patients who were discussing their options with their GP for preventing relapse/recurrence.
- The design included neither a usual care nor an attention control arm. The absence of an attention control arm means that any effects of MBCT-TS or m-ADM cannot be inferred to be specific to these treatments.
- The m-ADM arm included active monitoring of adherence by the research team and in this sense might best be represented as enhanced m-ADM.

The pragmatic nature of the trial resulted in a proportion of patients in both arms not complying with the invitation to (dis)continue ADM. We undertook a per-protocol analysis to examine the impact on the primary outcome inference compared with ITT analysis. This is both a strength (pragmatism and generalisability) and a limitation (the ADM was not completely controlled). Finally, the sample consisted of a group at high risk of depressive relapse/recurrence,[123] currently taking ADM, who were open both to considering a group-based psychosocial treatment and to (dis)continuing their ADM. This is both a strength and limitation of the study. The findings of the PREVENT trial are therefore generalisable to only those individuals who are in equipoise about the type of preventative treatment that they choose, that is, m-ADM or switch to psychosocial intervention and reduce their ADM.

Implications for practice

Depression is a major public health problem that tends to run a recurrent course, producing substantial decrements in health and well-being. The cost of mood disorders to the UK economy is substantial. Most of the prevalence, burden and cost of depression is a consequence of recurrent depression and could be offset through providing a range of psychosocial low- and high-intensity treatments.[4]

Mindfulness-based cognitive therapy with support to taper/discontinue ADM may confer ongoing protection for patients who would like an alternative to m-ADM. Many patients with recurrent depression may have been on m-ADM for many years and for a variety of reasons would prefer to learn skills that they can use to stay well. The results further suggest that psychosocial treatments such as MBCT and CBT[117,121,124] offer added value for patients who need them most, that is, those at highest risk of depressive relapse/recurrence. The investment of effort by these patients in learning the skills taught in psychosocial treatments such as CBT and MBCT pays off. However, for patients at low risk, treatments such as psychoeducation or m-ADM, which require less patient commitment and cost, may be indicated. This has significant potential to improve prevention by maximising the delivery of treatments through stratified approaches, which also have the potential to improve patient choice. As patients with recurrent depression select options to stay well in the long term, these findings taken together with the broader emergent literature suggest a number of alternatives. It is clear that m-ADM is an effective mainstream approach. For patients at low risk of relapse low-intensity interventions may be indicated and for patients at high risk high-intensity treatments such as MBCT may be indicated.

Future research

There are several key areas for future research:

- Given the completion of the PREVENT trial and the recent publication of other large RCTs, an updated meta-analysis is indicated to re-examine evidence for MBCT as a strategy for the prevention of depressive relapse/recurrence in the context of alternative treatments that include usual care, other active treatments such as m-ADM and additive therapy approaches (e.g. MBCT plus m-ADM). An alternative strategy would be to conduct a large cohort study or effectiveness study to examine the effectiveness of MBCT and m-ADM in various real-world scenarios.
- Furthermore, an individual patient data meta-analysis of published trials would help address the question of which specific patient subgroup MBCT is best indicated for. There is emerging evidence that MBCT is most effective for those at highest risk of relapse/recurrence and an individual patient data analysis could provide the empirical evidence to address this question.
- Studies have tended to operationalise risk in somewhat different ways (e.g. early adversity, unstable remission, a greater number of previous episodes, early age of onset) and, although these risk factors overlap, future research should examine how and through what mechanism risk is conferred and resilience learned.
- In addition to further analysis of the process data from the PREVENT trial and recently completed large MBCT RCTs, future trials need to incorporate process studies and consider dismantling designs to further unpack MBCT's mechanism of action. This could enhance the specificity and efficacy of MBCT.
- Given the current NICE guidance that MBCT should be offered to patients with three or more previous episodes of depression, and the limited availability of MBCT within the NHS, research is needed to explore the facilitators and barriers to implementation. This National Institute for Health Research-funded work is in progress.[22]

Conclusions

In a large, rigorous yet pragmatic RCT we have demonstrated that MBCT-TS is not superior to m-ADM over 2 years of follow-up for patients with recurrent depression. Benchmarked against epidemiological data, both treatments were associated with enduring positive outcomes in terms of relapse/recurrence, residual depressive symptoms and quality of life. This study provides important evidence that MBCT-TS may confer ongoing protection for patients who would like an alternative to m-ADM. The results further suggest that psychosocial treatments, such as MBCT and CBT,[117,121,124] offer added value for patients who need them most, that is, those at highest risk of depressive relapse/recurrence. However, studies have tended to operationalise risk in somewhat different ways (e.g. early adversity, unstable remission, a greater number of previous episodes, early age of onset) and, although these risk factors overlap, future research should examine how and through what mechanism risk is conferred and resilience learned. In the interim, the implication is that, for patients at low risk, treatments such as psychoeducation or m-ADM, which require less patient commitment and cost, may be indicated, whereas for patients at highest risk more intensive treatments such as MBCT may be indicated. This has significant potential to improve prevention by maximising the delivery of treatments through stratified approaches, which also have the potential to improve patient choice.

Acknowledgements

We thank the National Institute for Health Research Health Technology Assessment programme for funding the trial, our programme manager Alexa Cross for her support of the project and Professor Tom Walley for his advice in the early set phase. We are grateful to all of the practitioners and GP surgery staff who took part in this research. We would also like to thank the research workers and therapists who worked on this trial: Claire Brejcha, Jessica Cardy, Aaron Causley, Suzanne Cowderoy, Alison Evans, Felix Gradinger, Surinder Kaur, Paul Lanham, Jonathan Richards, Pooja Shah, Harry Sutton, Rachael Vicary, Alice Weaver, Jenny Wilks and Matthew Williams. AW acted as Acting Trial Manager during RH's maternity leave. CB, AE, SC and JW were trial therapists. All researchers contributed to data collection. FG, MW, PS and AC all contributed to the qualitative data analysis. We would like to thank Trish Bartley for her input to the MBCT therapist training and MBCT fidelity checks. We would like to thank Beverley Herring, Naomi Gilbert and other service users who brought their personal lived experience of depressive illness to advise on the direction of the trial and provide training for the research assessors. We wish to acknowledge the SCID and GRID-HAMD training that Sandra Kennell-Webb provided to our research staff. We are grateful to members of our TSC (Chris Leach, Richard Moore and Glenys Parry) and DMC (Paul Ewings, Andy Field and Joanne MacKenzie) for their valuable advice and support during the project. We would also like to thank Shadi Beshai who completed some of the final research assessments. Contribution to funding is also acknowledged for RB, WK and RT from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for the South West Peninsula. The Mental Health and Primary Care Research Networks provided additional support for trial recruitment. We also acknowledge the support provided by the Department of Health and local primary care trusts in meeting the excess treatment and service support costs associated with the trial. Most importantly, we are grateful to the participants for taking part in this trial.

Finally, we would also like to thank the following colleagues who have contributed to the PREVENT study through the recruitment and retention of patients or the provision of administrative support: Rebecca Amey, Miriam Cohen, Alice Garrood, Nora Goerg, Anna Hunt, Sarah Lane, Mary Sharkey, Cara Simmance, Holly Sugg, Lucy Wootton and other undergraduates and researchers who provided support to the trial.

Contributions of authors

Willem Kuyken, **Sarah Byford**, **Richard Byng**, **Tim Dalgleish**, **Glyn Lewis**, **Rod Taylor**, **Edward Watkins**, **David Kessler** and **Nicola Morant** were responsible for the original proposal, securing funding for the trial and drafting the original protocol.

Willem Kuyken as chief investigator had overall responsibility for the management of the study and the Exeter site and **Glyn Lewis** and **David Kessler** as co-investigators had responsibility for the Bristol site.

Willem Kuyken provided training and supervision for the trial therapists.

Rachel Hayes, **Willem Kuyken**, **Rod Taylor** and **Sarah Byford** wrote the statistical analysis plan.

Rod S Taylor conducted the main analyses and **Sarah Byford** and **Barbara Barrett** the health economics analyses. **Richard Byng** provided support for intervention development and delivery.

Rachel Hayes, **Sarah Byford** (see *Chapter 5*), **Tim Dalgleish** (see *Chapter 6*), **Willem Kuyken**, **Nicola Morant** (see *Chapter 6*) and **Rod Taylor** (see *Chapter 4*) wrote the initial draft of the report.

All authors contributed to, and approved, the final manuscript.

Data sharing statement

Non-identifiable data will be made available following an application to the corresponding author Professor Willem Kuyken.

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Appendix 1 Serious adverse event form and suicidal thoughts protocol

Serious adverse event form

NHS
National Patient Safety Agency

National Research Ethics Service

REPORT OF SERIOUS ADVERSE EVENT (SAE)

The Chief Investigator should report any SAE that is both related to the research procedures and is unexpected. Send the report to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event. For further guidance see: *http://www.nres.npsa.nhs.uk/applicants/review/after/safety.htm*.

1. Details of Chief Investigator

Name:	Prof Willem Kuyken
Address:	Mood Disorders Centre School of Psychology Washington Singer Laboratories University of Exeter Perry Road, Exeter EX4 4QG
Telephone:	01392 724659
Email:	w.kuyken@exeter.ac.uk
Fax:	01392 264623

2. Details of study

Full title of study:	Preventing depressive relapse/recurrence in NHS settings through mindfulness-based cognitive therapy (MBCT)
Name of main REC:	South West Research Ethics Committee
Main REC reference number:	**09/H0206/43**
PCT number:	**(NHS Devon) 0739**
Research sponsor:	University of Exeter
Sponsor's reference for this report: (if applicable)	

3. Type of event
Please categorise this event, ticking all appropriate options:

Death ☐	Life threatening ☑	Hospitalisation or prolongation of existing hospitalization ☑
Persistent or significant disability or incapacity ☐	Congenital anomaly or birth defect ☐	Other ☐

Report of Serious Adverse Event, version 3.0, April 2007

4. Circumstances of event

Date of SAE:	
Location:	
Describe the circumstances of the event: *(Attach copy of detailed report if necessary)*	
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	**Causality:** **Expectedness:**

5. Declaration

Signature of Chief Investigator:	
Print name:	Professor Willem Kuyken
Date of submission:	

6. Acknowledgement of receipt by main REC (please insert name):

The South West Research Ethics Committee Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back to Chief Investigator (or other person submitting report)
Copy to be kept for information by main REC.

Report of Serious Adverse Event, version 3.0, April 2007

Suicidal thoughts protocol

Disclosure of Suicidal Thoughts Protocol

PREVENT Policy Statement

GPs are responsible for the on-going clinical care of participants. Therefore, all trial staff directly involved with research participants, including MBCT therapists, have a duty of care to ensure that the GP is aware of any suicidal thoughts expressed by participants.

Researchers must initiate the suicidal thoughts protocol each time a participant expresses potentially significant suicidal thoughts or thoughts of self harm above a certain level. This may be as a result of responses to questionnaire items or the participant may disclose information during an interview that leads the researcher to believe that there are thoughts of suicide or harm to self or others. In both instances, the researcher should inform the participant's GP and notify the site Clinical Lead (or nominated deputy).

Therapists are expected to use their clinical judgement to assess the seriousness of risk and follow normal clinical procedures with respect to communicating disclosure to the participant's GP. Therapists may contact the study team to seek advice from the Clinical Lead and/or to determine history of previous disclosure. Therapists **must** communicate any disclosure made to GPs to the trial manager.

Symptoms of depression include low self-esteem, feelings of hopelessness, thoughts of self harm, and suicide ideation, particularly with severe episodes. Consequently, the questionnaires administered to trial participants include items to detect these thoughts. Participants may also disclose information during an interview or therapy session leading the researcher/therapist to believe that there is potentially a significant suicidal risk. It is important that participants discuss these thoughts with an appropriate health professional to ensure access to necessary support.

In the case of PREVENT, GPs are responsible for the on-going clinical care of participants. Therefore, researchers and therapists have a duty of care to ensure that the GP is aware of any potentially significant suicide ideation expressed by participants.

It is expected that therapists will use their clinical judgement to assess the seriousness of risk and follow normal clinical procedures with respect to communicating disclosure to the participant's GP. In addition, therapists may contact the study team to seek advice from the clinical lead and/or to determine history of previous disclosure. Therapists must communicate any disclosure made to GPs to the trial manager.

Researchers are not clinically trained and should receive adequate training/supervision and work within their competence. If a participant discloses any potentially significant thoughts of suicide or self-harm, researchers should complete a Suicidal Thoughts Report (below) and inform the participant's GP of the nature of information disclosed.

Definition of 'Potentially Significant Suicidal Thoughts'

In the PREVENT study, significant suicidal thoughts are identified by:

1. A response of 2 or above to question 9 (suicidal thoughts or wishes) on the **BDI** questionnaire.

Q9.
0. I don't have any thoughts of killing myself
1. I have thoughts of killing myself, but I would not carry them out
2. **I would like to kill myself**
3. **I would kill myself if I had the chance**

OR

2. A rating of 3 or above on the **GRID-HAMD** question number 3.

Q3. Suicide
This past week, have you had any thoughts that life is not worth living, or that you'd be better off dead? What about having thoughts of hurting or even killing yourself?
0. Absent
1. Feels life is not worth living
2. Wishes he/she were dead or any possible thoughts of death to self
3. **Suicidal ideas of gesture**
4. **Attempts at suicide**

OR

3. Patients who disclose information during the **SCID** interview (face-to-face or telephone) that they have had recurrent thoughts of death or suicide at a similar level to those described in items 1 and 2 above.

OR

4. Information disclosed at any other time that would indicate significant suicidal thoughts

Researcher Action required

Before conducting an assessment with a participant (either telephone or face-to-face), the researchers should review all previous data on suicidal thought and ensure that contact details for the site Clinical Lead (or nominated deputy) are current. When assessments are being conducted over the telephone it is important that the researcher has accurate information about where the participant is calling from so that if needed this can be forwarded to the participant's GP and/or emergency services.

Whenever a researcher becomes aware that a participant has thoughts of suicide, the researcher should reinforce the importance of maintaining a dialogue with his/her GP and ask for permission to pass the information to his/her GP. Suggested scripts can be found in Figure 1.

If the participant agrees to this communication, the researcher should telephone the participant's GP within 48 hours* to pass on the information obtained. If the participant's GP is not available then the researcher should ask to speak to the duty doctor. The researcher should make it clear to the GP that no clinical risk assessment has been performed and that clinical responsibility for the study participants remains with the GP. A letter counter-signed by the site Clinical Lead should be sent to the GP confirming this notification. A copy of this letter should be filed in the Participant Contact File. If the participant does not agree to their GP being informed, the researcher should contact the site Clinical Lead to discuss.

The researcher will also complete a Suicidal Thoughts Report (below) and files this in the Participant's Research File. This report should not contain any information that could identify the patient.

*If the participant discloses something to the researcher that leads them to believe the participant to be in immediate danger of acting on suicidal thoughts, the researcher must immediately contact the participant's GP. If it not possible to speak to the participant's GP the researcher should request to talk to the duty GP. If the assessment is being conducted outside of office hours the researcher should contact the Crisis Team. Once this contact has been completed, the researcher should contact the site Clinical Lead to inform them of the situation. If possible, this contact should be made whilst the participant is still with the researcher, if this is not possible the researcher must make every effort to obtain a contact telephone number and address for the participant.

If the assessment is being carried out over the telephone there are instructions at the end of this protocol detailing how to call another person using a VOIP phone without cutting off the participant.

A letter should be sent to the participant's GP, copying in the participant, detailing the disclosure made and the resulting action taken.

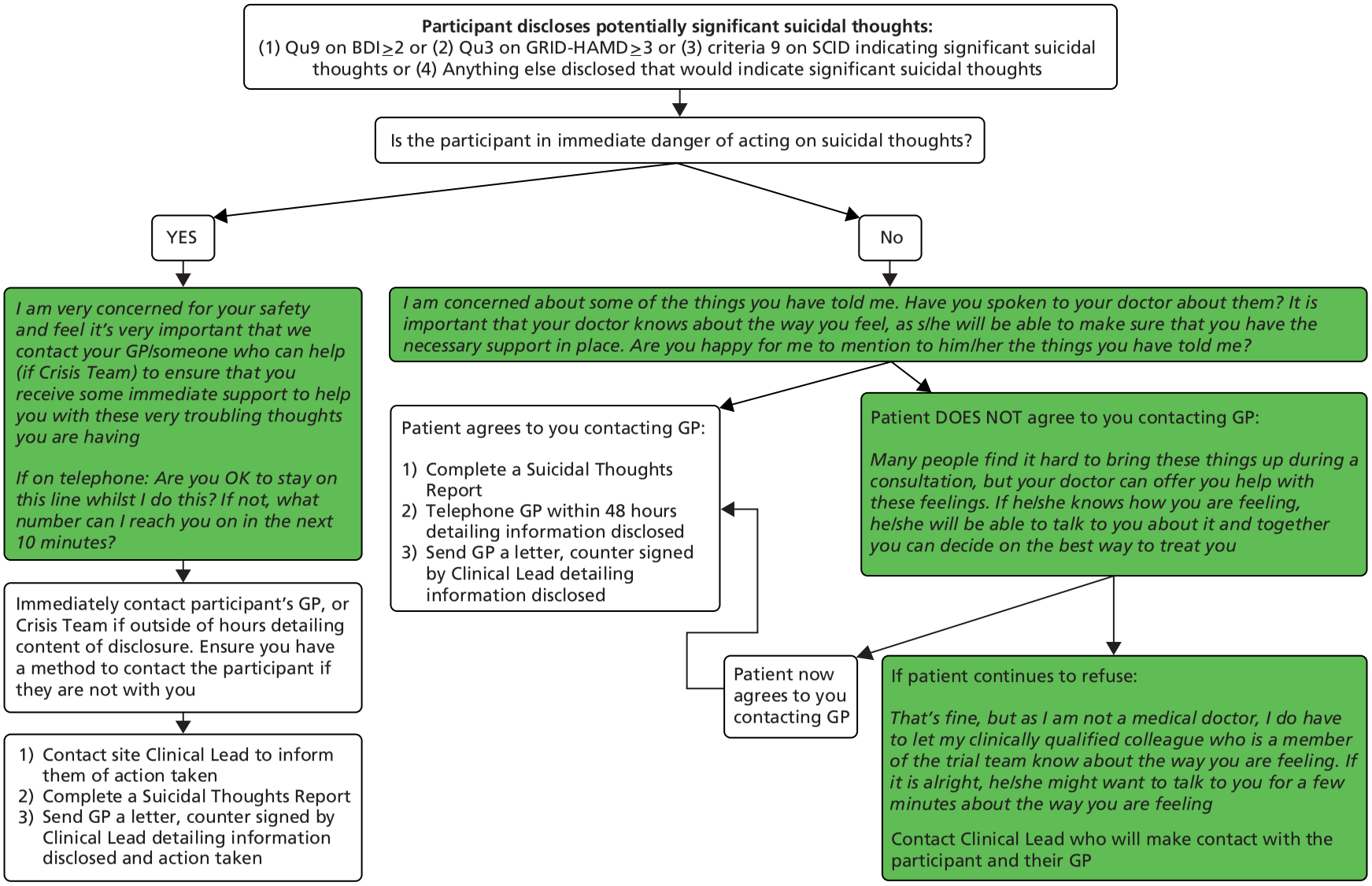

FIGURE 17 Researcher action required – including suggested scripts.

Suicidal Thoughts Report – File in Research File

Participant ID (Do not include any identifiable information): Date:

Time period: Telephone Screen / Baseline /Rand Assessment / MBCT+1month / 9m / 12m / 18m / 24m

BDI suicide item score:
Hamilton suicide item score:
Suicide risk information: *Include whether the participant has reported any of the following:* • *History of previous suicide attempts* • *Current suicidal ideation* • *Suicide plans / preparations* • *Escalation in suicidal ideation* • *Protective factors* • *Regular contact with GP?* *Date reported: ___/___/___*
Additional notes / actions taken: *As part of the PREVENT protocol, suicide risk is **managed** by the patient's GP.* *Date action taken: ___/___/__*

Researcher: _____ Signed: _____ Date: ___/___/___

Clinical Lead: _____ Signed: _____ Date: ___/___/___

GP Risk Letter – Copy filed in Patient Contact File

Surgery Address

Date

Dear Dr _____

POTENTIAL SUICIDE RISK

Re: Participant Name _____ DOB

As you know, PATIENT NAME, is taking part in the PREVENT trial comparing mindfulness-based cognitive therapy with antidepressant medication for the treatment of recurrent depression. As part of this research I speak with him/her on a number of occasions to assess his/her wellbeing and depressive symptoms. I am writing to update you about our discussions/meeting today.

As part of the assessment we ask about depression using a standardised interview and questionnaire. PATIENT NAME reported that he / she ……(verbal report / score on relevant item). I have not undertaken a formal assessment with PATIENT NAME but I have recommended that he / she arrange to make an appointment to come and see you to discuss this further.

As ever, the clinical management of this patient remains your responsibility, but it is part of our study protocol to inform you of any suicidal thoughts disclosed to ourselves so that you can take account of them in your clinical management of this patient.

Yours sincerely,

Site Researcher **Supervised by Site Clinical Lead**

Cc: Participant
=

Appendix 2 Antidepressants prescribed

TABLE 24 Total number of weeks that each antidepressant was prescribed over the 24-month follow-up period

Antidepressant	m-ADM	MBCT-TS
Agomelatine	64	0
Amitriptyline	660	350
Citalopram	7311	4258
Clomipramine	224	0
Dosulepin	212	376
Doxepin	0	16
Duloxetine	222	156
Escitalopram	272	128
Fluoxetine	2915	2493.5
Flupentixol	24	0
Fluvoxamine	0	12
Lofepramine	324	224
Mirtazapine	919	622
Moclobemide	0	14
Nortriptyline	0	200
Paroxetine	394	653
Sertraline	1668	1538
Trazodone	144	0
Venlafaxine	1225	1087
Other	0	32

Appendix 3 Baseline characteristics of participants who received an adequate dose of treatment

TABLE 25 Baseline characteristics of participants who received an adequate dose of treatment

Characteristic/variable	MBCT-TS ($n = 176$)	m-ADM ($n = 162$)	Difference test
Demographic characteristics			
Female, *n* (%)	122 (69)	136 (84)	$\chi^2(1) = 10.00$; $p = 0.002$
Ethnicity, *n* (%)			$\chi^2(3) = 4.01$; $p = 0.26$
White	174 (99)	160 (99)	
Other (including three categories)	2 (1)	2 (1)	
Age (years)			$t(336) = -1.21$; $p = 0.23$
Mean (SD)	51 (12)	50 (12)	
Range	22–78	24–79	
Marital status, *n* (%)			$\chi^2(5) = 7.18$; $p = 0.21$
Single	30 (17)	22 (14)	
Married, cohabiting or civil partnership	107 (61)	115 (71)	
Separated, divorced or widowed	39 (22)	24 (15)	
Missing	0 (0)	1 (1)	
Level of education, *n* (%)			$\chi^2(6) = 8.50$; $p = 0.20$
No educational qualifications	10 (6)	7 (4)	
Some school qualifications	24 (14)	36 (22)	
High school and/or vocational qualification	71 (40)	72 (44)	
University degree/professional qualification	69 (39)	44 (27)	
Missing	2 (1)	3 (2)	
Religion, *n* (%)			$\chi^2(7) = 5.04$; $p = 0.66$
Christian	109 (62)	103 (64)	
Other	10 (6)	3 (2)	
None	57 (32)	55 (34)	
Missing	0 (0)	1 (1)	
Salary (£ sterling)			$t(190) = -1.92$; $p = 0.06$
Mean (SD)	20,560 (13,707)	16,884 (12,777)	
Range	1200–72,000	792–75,000	

continued

TABLE 25 Baseline characteristics of participants who received an adequate dose of treatment (*continued*)

Characteristic/variable	MBCT-TS ($n = 176$)	m-ADM ($n = 162$)	Difference test
Social class, *n* (%)[a]			$\chi^2(5) = 7.39$; $p = 0.19$
Class 0	72 (41)	58 (36)	
Class 1	49 (28)	38 (23)	
Class 2	19 (11)	31 (19)	
Class 3	5 (3)	4 (2)	
Class 4	0 (0)	2 (1)	
Class 5	31 (18)	28 (17)	
Not classified	0 (0)	1 (1)	
Stratification variables			
Depressive symptomology at randomisation, *n* (%)			$\chi^2(1) = 0.03$; $p = 0.87$
Asymptomatic	136 (77)	124 (77)	
Symptomatic	40 (23)	38 (23)	
Recruitment site, *n* (%)			$\chi^2(3) = 0.61$; $p = 0.90$
Bristol	32 (18)	25 (15)	
Exeter and East Devon	62 (35)	57 (35)	
North and Mid Devon	45 (26)	42 (26)	
South Devon	37 (21)	38 (23)	
Psychiatric characteristics			
Current depressive symptomology, mean (SD)			
GRID-HAMD score	4.7 (4.2)	4.7 (4.4)	$t(336) = -0.14$; $p = 0.89$
BDI-II score	13.4 (10.3)	14.3 (9.9)	$t(329) = 0.79$; $p = 0.43$
Previous major depressive episodes, *n* (%)			
Fewer than six episodes	98 (56)	76 (47)	
Six or more episodes	78 (44)	86 (53)	
Age (years) at first depression onset, mean (SD)	24.8 (11.8)	24.8 (12.3)	$t(336) = 0.02$; $p = 0.98$
Time (months) since last depressive episode, mean (SD)	21.5 (25.0)	18.6 (25.4)	$t(336) = -1.05$; $p = 0.30$
Number of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD)	0.5 (0.8)	0.6 (0.9)	$t(336) = 2.06$; $p = 0.04$
Received outpatient psychiatric or psychological treatment, *n* (%)	86 (49)	87 (54)	$\chi^2(1) = 1.58$; $p = 0.21$
Attempted suicide, *n* (%)	34 (19)	42 (26)	$\chi^2(1) = 2.30$; $p = 0.13$
Number of previous attempts, mean (SD)	1.7 (1.2)	2.0 (1.6)	$t(73) = 0.73$; $p = 0.47$
Severity of reported childhood abuse, *n* (%)			$\chi^2(1) = 0.12$; $p = 0.73$
High	88 (50)	84 (52)	
Low	88 (50)	78 (48)	
Missing	0 (0)	0 (0)	

TABLE 25 Baseline characteristics of participants who received an adequate dose of treatment (*continued*)

Characteristic/variable	MBCT-TS ($n = 176$)	m-ADM ($n = 162$)	Difference test
Quality of life, mean (SD)[b]			
How would you rate your quality of life?	3.7 (0.8)	3.7 (0.9)	$t(327) = 0.05$; $p = 0.96$
How satisfied are you with your health?	2.9 (1.0)	3.1 (1.0)	$t(327) = 1.25$; $p = 0.21$
Physical	14.3 (4.8)	13.9 (2.8)	$t(327) = -0.90$; $p = 0.37$
Psychological	12.7 (2.6)	12.2 (2.6)	$t(327) = -1.70$; $p = 0.09$
Social	13.4 (3.5)	13.1 (3.4)	$t(327) = -0.87$; $p = 0.39$
Environment	15.1 (2.4)	14.9 (2.6)	$t(327) = -0.81$; $p = 0.42$
Health-related quality of life (EQ-5D tariffs)	0.773 (0.252)	0.762 (0.219)	$t(325) = -0.43$; $p = 0.67$

a Social class was according to UK Office for National Statistics and the range was from professional and managerial occupations (class 1) to semiroutine and routine occupations (class 5); class 0 represents those who have never worked, the long-term unemployed, students or retired people [see www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/index.html (accessed 20 July 2015)].
b Data determined on the basis of the WHOQOL-BREF assessment.

Appendix 4 Baseline characteristics of participants who did follow invited treatment with respect to antidepressant medication use

TABLE 26 Baseline characteristics of participants who did follow invited treatment with respect to ADM use

Characteristic/variable	MBCT-TS ($n = 153$)	m-ADM ($n = 162$)	Difference test
Demographic characteristics			
Female, *n* (%)	105 (69)	136 (84)	$\chi^2(1) = 10.28$; $p = 0.001$
Race, *n* (%)			$\chi^2(2) = 2.95$; $p = 0.23$
White	152 (99)	160 (99)	
Other (including two categories)	1 (1)	2 (1)	
Age (years)			$t(313) = -1.85$; $p = 0.07$
Mean (SD)	52 (12)	50 (12)	
Range	25–78	24–79	
Marital status, *n* (%)			$\chi^2(5) = 6.72$; $p = 0.24$
Single	23 (15)	22 (14)	
Married, cohabiting or civil partnership	96 (63)	115 (71)	
Separated, divorced or widowed	34 (22)	24 (15)	
Missing	0 (0)	1 (1)	
Level of education, *n* (%)			$\chi^2(6) = 7.10$; $p = 0.31$
No educational qualifications	10 (7)	7 (4)	
Some school qualifications	22 (14)	36 (22)	
High school and/or vocational qualification	63 (41)	72 (44)	
University degree/professional qualification	56 (37)	44 (27)	
Missing	2 (1)	3 (2)	
Religion, *n* (%)			$\chi^2(7) = 4.31$; $p = 0.74$
Christian	91 (59)	103 (64)	
Other	8 (5)	3 (2)	
None	54 (35)	55 (34)	
Missing	0 (0)	1 (1)	
Salary (£ sterling)			$t(175) = -1.84$; $p = 0.07$
Mean (SD)	20,657 (14,444)	16,884 (12,777)	
Range	1200–72,000	792–75,000	

continued

TABLE 26 Baseline characteristics of participants who did follow invited treatment with respect to ADM use (*continued*)

Characteristic/variable	MBCT-TS ($n = 153$)	m-ADM ($n = 162$)	Difference test
Social class, *n* (%)[a]			$\chi^2(5) = 6.46$; $p = 0.26$
Class 0	65 (42)	58 (36)	
Class 1	39 (25)	38 (23)	
Class 2	17 (11)	31 (19)	
Class 3	3 (2)	4 (2)	
Class 4	0 (0)	2 (1)	
Class 5	29 (19)	28 (17)	
Not classified	0 (0)	1 (1)	
Stratification variables			
Depressive symptomology at randomisation, *n* (%)			$\chi^2(1) = 0.02$; $p = 0.88$
Asymptomatic	116 (76)	124 (77)	
Symptomatic	37 (24)	38 (24)	
Recruitment site, *n* (%)			$\chi^2(3) = 1.68$; $p = 0.64$
Bristol	27 (18)	25 (15)	
Exeter and East Devon	57 (37)	57 (35)	
North and Mid Devon	42 (27)	42 (26)	
South Devon	27 (18)	38 (24)	
Psychiatric characteristics			
Current depressive symptomology, mean (SD)			
GRID-HAMD score	4.8 (4.2)	4.7 (4.4)	$t(313) = -0.33$; $p = 0.74$
BDI-II score	13.8 (10.4)	14.3 (9.9)	$t(306) = 0.45$; $p = 0.65$
Previous major depressive episodes, *n* (%)			
Fewer than six episodes	84 (55)	76 (47)	
Six or more episodes	69 (45)	86 (53)	
Age (years) at first depression onset, mean (SD)	25.3 (12.0)	24.8 (12.3)	$t(313) = -0.37$; $p = 0.71$
Time (months) since last depressive episode, mean (SD)	20.5 (23.7)	18.6 (25.4)	$t(313) = -0.68$; $p = 0.50$
Number of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD)	0.4 (0.7)	0.6 (0.9)	$t(313) = 2.33$; $p = 0.02$
Received outpatient psychiatric or psychological treatment, *n* (%)	72 (47)	87 (54)	$\chi^2(1) = 2.35$; $p = 0.13$
Attempted suicide, *n* (%)	30 (20)	42 (26)	$\chi^2(1) = 1.95$; $p = 0.16$
Number of previous attempts, mean (SD)	1.8 (1.2)	2.0 (1.6)	$t(69) = 0.50$; $p = 0.62$
Severity of reported childhood abuse, *n* (%)			$\chi^2(1) = 0.15$; $p = 0.70$
High	76 (50)	84 (52)	
Low	77 (50)	78 (48)	
Missing	0 (0)	0 (0)	

TABLE 26 Baseline characteristics of participants who did follow invited treatment with respect to ADM use (*continued*)

Characteristic/variable	MBCT-TS ($n = 153$)	m-ADM ($n = 162$)	Difference test
Quality of life, mean (SD)[b]			
How would you rate your quality of life?	3.7 (0.8)	3.7 (0.9)	$t(305) = -0.14$; $p = 0.89$
How satisfied are you with your health?	3.0 (1.0)	3.1 (1.0)	$t(305) = 0.86$; $p = 0.39$
Physical	14.3 (5.0)	13.9 (2.8)	$t(305) = -0.92$; $p = 0.36$
Psychological	12.7 (2.6)	12.2 (2.6)	$t(305) = -1.69$; $p = 0.09$
Social	13.6 (3.5)	13.1 (3.4)	$t(305) = -1.29$; $p = 0.20$
Environment	15.2 (2.5)	14.9 (2.6)	$t(305) = -1.08$; $p = 0.28$
Health-related quality of life (EQ-5D tariffs)	0.775 (0.256)	0.762 (0.219)	$t(303) = -0.50$; $p = 0.62$

a Social class was according to UK Office for National Statistics and the range was from professional and managerial occupations (class 1) to semiroutine and routine occupations (class 5); class 0 represents those who have never worked, the long-term unemployed, students or retired people [see www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/index.html (accessed 20 July 2015)].
b Data determined on the basis of the WHOQOL-BREF assessment.

Appendix 5 Baseline characteristics of participants who scored high and low on severity of childhood abuse

TABLE 27 Baseline characteristics of participants who scored high and low on severity of childhood abuse

Characteristic/variable	Lower severity of childhood abuse ($n = 206$)	Higher severity of childhood abuse ($n = 216$)	Difference test
Demographic characteristics			
Female, *n* (%)	162 (78.6)	161 (74.5)	$\chi^2(1) = 0.99$; $p = 0.32$
Ethnicity, *n* (%)			$\chi^2(3) = 4.23$; $p = 0.24$
White	202 (98.1)	216 (100.0)	
Other (including three categories)	4 (2.0)	0 (0.0)	
Age (years)			$t(420) = 1.02$; $p = 0.31$
Mean (SD)	50.9 (13.2)	48.9 (11.4)	
Range	20–79	21–74	
Marital status, *n* (%)			$\chi^2(5) = 9.47$; $p = 0.09$
Single	36 (17.5)	44 (20.4)	
Married, cohabiting or civil partnership	130 (63.1)	134 (62.0)	
Separated, divorced or widowed	39 (18.9)	38 (17.6)	
Missing	1 (0.5)	0 (0.0)	
Level of education, *n* (%)			$\chi^2(6) = 3.27$; $p = 0.78$
No educational qualifications	13 (6.3)	7 (3.2)	
Some O levels/GCSEs	38 (18.4)	43 (19.9)	
Some AS/A levels	21 (10.2)	21 (9.7)	
NVQ or other vocational qualification	61 (29.6)	72 (33.3)	
University bachelor's degree	42 (20.4)	47 (21.8)	
University master's degree	10 (4.9)	10 (4.6)	
University professional training or PhD	16 (7.8)	13 (6.0)	
Missing	5 (2.4)	3 (1.4)	

continued

TABLE 27 Baseline characteristics of participants who scored high and low on severity of childhood abuse (*continued*)

Characteristic/variable	Lower severity of childhood abuse ($n = 206$)	Higher severity of childhood abuse ($n = 216$)	Difference test
Religion, *n* (%)			$\chi^2(7) = 8.63$; $p = 0.28$
Atheist	7 (3.4)	11 (5.1)	
Christian	142 (68.9)	130 (60.2)	
Muslim	1 (0.5)	0 (0.00)	
Spiritualist	3 (1.5)	1 (0.5)	
Buddhist	1 (0.5)	1 (0.5)	
Other	3 (1.5)	4 (1.9)	
Agnostic	5 (2.4)	3 (1.4)	
None	43 (20.9)	66 (30.6)	
Missing	1 (0.5)	0 (0.0)	
Smokes, *n* (%)			$\chi^2(1) = 5.23$; $p = 0.02$
Yes	34 (16.5)	56 (25.9)	
Missing	3 (1.5)	0 (0.0)	
Salary (£ sterling)			$t(231) = -0.26$; $p = 0.80$
Mean (SD)	18,687 (13,938)	19,147 (13,091)	
Range	792–80,000	1200–72,000	
Social class, *n* (%)[a]			$\chi^2(5) = 7.86$; $p = 0.16$
Class 0	82 (39.8)	89 (41.2)	
Class 1	43 (20.9)	62 (28.7)	
Class 2	38 (18.4)	22 (10.2)	
Class 3	6 (2.9)	5 (2.3)	
Class 4	1 (0.5)	1 (0.5)	
Class 5	35 (17.0)	37 (17.1)	
Not classified	1 (0.5)	0 (0.0)	
Stratification variables			
Depressive symptomology at randomisation: *n* (%)			$\chi^2(1) = 0.78$; $p = 0.38$
Asymptomatic	162 (79)	162 (75)	
Symptomatic	44 (21)	54 (25)	
Recruitment site, *n* (%)			$\chi^2(3) = 10.38$; $p = 0.02$
Bristol	28 (13.6)	36 (16.7)	
Exeter and East Devon	76 (36.9)	72 (33.3)	
North and Mid Devon	64 (31.1)	45 (20.8)	
South Devon	38 (18.4)	63 (29.2)	

TABLE 27 Baseline characteristics of participants who scored high and low on severity of childhood abuse (*continued*)

Characteristic/variable	Lower severity of childhood abuse ($n = 206$)	Higher severity of childhood abuse ($n = 216$)	Difference test
Psychiatric characteristics			
Current depressive symptomology, mean (SD)			
GRID-HAMD score	4.2 (4.2)	5.1 (4.3)	$t(420) = -2.18$; $p = 0.03$
BDI-II score	12.9 (9.6)	15.3 (10.5)	$t(413) = -2.44$; $p = 0.02$
Previous major depressive episodes, *n* (%)			
Fewer than six episodes	126 (61.2)	100 (46.3)	
Six or more episodes	80 (39)	116 (54)	
Age (years) at first depression onset, mean (SD)	28 (13)	22 (12)	$t(420) = 4.31$; $p < 0.0001$
Time (months) since last depressive episode, mean (SD)	17 (23)	21 (27)	$t(420) = -1.7$; $p = 0.09$
Severity of last depressive episode (no. of DSM-IV symptoms recorded), mean (SD)	6.5 (1.1)	7.1 (1.2)	$t(420) = -5.67$; $p < 0.0001$
Number of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD)	0.5 (0.9)	0.7 (0.95)	$t(420) = -1.72$; $p = 0.09$
Ever been hospitalised for emotional or psychiatric reason? *n* (%)			$\chi^2(1) = 19.896$; $p < 0.0001$
Yes	11 (5.3)	43 (19.9)	
Missing	2 (1.0)	1 (0.5)	
Ever received outpatient psychiatric or psychological treatment? *n* (%)			$\chi^2(1) = 2.78$; $p = 0.10$
Yes	95 (46.1)	115 (53.2)	
Missing	2 (1.0)	6 (2.8)	
Ever made a suicide attempt? *n* (%)			
Yes	30 (14.6)	70 (32.4)	$\chi^2(1) = 18.12$; $p < 0.0001$
Number of previous attempts, mean (SD)	1.6 (0.78)	1.9 (1.4)	$t(97) = -1.28$; $p = 0.21$
Family history of mental illness or alcohol or drug abuse, *n* (%)			$\chi^2(2) = 20.36$; $p < 0.0001$
Yes	77 (37.4)	121 (56.0)	
No	114 (55.3)	74 (34.3)	
Not sure	12 (5.8)	21 (9.7)	
Missing	3 (1.5)	0 (0.0)	
Quality of life, mean (SD)[b]			
How would you rate your quality of life?	3.7 (0.8)	3.6 (0.8)	$t(411) = 1.96$; $p = 0.05$
How satisfied are you with your health?	3.1 (1.0)	2.9 (1.0)	$t(411) = 1.57$; $p = 0.12$
Physical	14.4 (2.9)	14.5 (7.6)	$t(411) = -0.04$; $p = 0.97$
Psychological	12.7 (2.6)	12.2 (2.6)	$t(411) = 1.91$; $p = 0.06$
Social	13.9 (3.2)	12.7 (3.5)	$t(411) = 3.46$; $p = 0.001$
Environment	15.4 (2.3)	14.7 (2.6)	$t(411) = 2.87$; $p = 0.004$

a Social class was according to UK Office for National Statistics and the range was from professional and managerial occupations (class 1) to semiroutine and routine occupations (class 5); class 0 represents those who have never worked, the long-term unemployed, students or retired people [see www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/index.html (accessed 20 July 2015)].
b Data determined on the basis of the WHOQOL-BREF assessment.

Appendix 6 Adult Service Use Schedule

TO BE COMPLETED BY RESEARCHER:

ID Number			
Date of baseline interview:	dd	mm	20 yy

Instructions

We want to know about your use of psychological treatments and certain medications commonly taken by people with depression for the *three months* preceding this interview.

Please try and complete this form without discussing your answers with the researcher.

Medication

NB See opposite page for list of common medications in each category to guide you.

1. Have you been prescribed an antidepressant over the last three months?

Yes ☐ Go to question 2 No ☐ Go to question 9

2. What is the name of the antidepressant and your daily dose (see list opposite)? *Example: Fluoxetine 20mg*

3. How many weeks have you been **prescribed** this antidepressant over the last three months? ☐ Weeks

4. In an average week, how many days do you **actually take** this medication? ☐ Days

We realise that there are lots of reasons why people do not like and sometimes do not take the medication which is prescribed to them. We are interested in your experience. Please answer the questions thinking about ***the last three months***.

5. Did you ever forget to take your antidepressant medication?

Yes ☐ No ☐

6. Were you careless at times about your antidepressant medication?

Yes ☐ No ☐

7. When you felt better did you sometimes stop taking your antidepressant medication?

Yes ☐ No ☐

8. Sometimes when you feel worse do you stop taking your antidepressant medication?

Yes ☐ No ☐

9. Have you been prescribed a sleeping tablet or medication for anxiety over the last three months?

Yes ☐ Go to question 10 No ☐ Go to question 13

10. What is the name of this medication and your daily dose (see list opposite)? *Example: Diazepam 2mg*

11. How many weeks have you been **prescribed** this medication over the last three months? ☐ Weeks

12. In an average week, how many days do you **actually take** this medication? ☐ Days

13. Have you taken a painkiller over the last three months (prescribed by doctor or bought from chemist)?

Yes ☐ Go to question 14 No ☐ Go to question 18

14. What is the name of the painkiller and your daily dose (see list opposite)? *Example: Codeine 30mg*

15. Is this painkiller prescribed by your doctor? ☐ Yes Go to qu. 12 ☐ No Go to qu. 13

16. Over the last three months, how many weeks have you been prescribed this painkiller ☐ Weeks

17. In an average week, how many days do you take these pain killers? ☐ Days

MEDICATION

Antidepressants:

Amitriptyline/Triptafen	Flupentixol/Fluanxol	Paroxetine/Seroxat
Amoxapine/Asendis	Imipramine/Tofranil	Phenelzine/Nardil
Citalopram/Cipramil	Isocarboxazid	Reboxetine/Edronax
Clomipramine	Lofepramine/Gamanil	Sertraline/Lustral
Dosulepin/Dothiepin/Prothiaden	Maprotiline/Ludiomil	Tranylcypromine
Doxepin/Sinequan	Mianserin	Trazodone/Molipaxin
Escitalopram/Cipralex	Mirtazepine/Zispin	Trimipramine/Surmontil
Fluoxetine/Prozac	Moclobemide/Manerix	
Fluvoxamine/Faverin	Nortriptyline/Allegron/Motival	

Sleeping tablets/medication for anxiety:

Alprazolam	Meprobamate
Buspirone/Buspar	Nitrazepam
Chlorazepate/Tranxene	Oxazepam
Chlordiazepoxide	Temazepam
Diazepam	Zapelon/Sonata
Flurazepam/Dalmane	Zolpidem/Stilnoct
Loprazolam	Zopiclone/Zimovane
Lorazepam	
Lormetazepam	

Examples of painkillers:

Alka-Selzer	Hedex	Solpadeine
Anadin	Ibuprofen	Tramadol/Zamadol
Aspirin	Lemsip	
Buprenorphine/Transtec	Morphine	
Codeine	Nefopam/Acupan	
Dihydracodeine	Neurofen	
Dipapnone/Dicolnal	Night nurse	
Disprin	Panadol	
Fentanyl/Durogesic	Paracetamol	
Hedex	Paracetamol with co-codamol	

Psychological treatments

18. Have you had any psychological treatments or counselling over the last 3 months, excluding marriage guidance and art/drama/music therapy?

Yes ☐ Go to question 19 No ☐ Go to question 33

Details of first therapist:

19. What is the name of your therapist?

20. How many sessions have you had with your therapist in the last three months? Number of sessions

21. What was the average duration of each session with your therapist? Minutes

22. Was your therapy individual (one-to-one) or group therapy? ☐ Individual ☐ Group

23. How did you travel to your therapy?

Train/Bus ☐ Go to question 24
Car/motorcycle ☐ Go to question 25
Walk/Cycle ☐ Go to question 26

24. If you used public transport, what was the one-way fare? £

25. Approximately how many miles was the journey one-way? Miles

Details of second therapist, if applicable:

26. What is the name of your second therapist?

27. How many sessions have you had with your second therapist in the last three months? Number of sessions

28. What was the average duration of each session with your second therapist? Minutes

29. Was your second therapy individual (one-to-one) or group therapy? ☐ Individual ☐ Group

30. How did you travel to your second therapy?

Train/bus ☐ Go to question 31
Car/motorcycle ☐ Go to question 32
Walk/cycle ☐ Go to question 33

31. If you used public transport, what was the one-way fare? £

32. Approximately how many miles was the journey one-way? Miles

END OF QUESTIONNAIRE **THANK YOU FOR COMPLETING THIS QUESTIONNAIRE**

Preventing depressive relapse/recurrence in NHS settings through mindfulness-based cognitive therapy (PREVENT) - adult SERVICE USE Schedule (ad-sus), Interview

ID Number	

Date of interview:	dd	mm	20 yy

Period(s) covered (tick all that apply)	
Baseline	
3-month	
9-month	
12-month	
18-month	
24-months	
If previous interviews missed, this schedule should cover the entire period from previous to current interview date. Please tick all periods that apply	

Instructions

This schedule should be given in *interview*.

The schedule covers:
- At baseline, the patient's use of services for the *three months* preceding the interview
- At any follow-up point, the patient's use of services *since the previous interview*

If the patient was not interviewed at an earlier follow-up point, this schedule can be used to cover the entire period from previous to current interview – please tick all periods that apply.

Please tell the patient that you want to know about their use of all services *except* psychological interventions and medications. Please ask the patient not to mention any psychological treatments or medications received and tell them that details of these treatments will be collected in a separate schedule to be completed by the patient.

Section A: Hospital Services

A1 – Have you had a hospital admission *(if baseline)* **in the last three months /** *(if follow-up)* **since you were last interviewed approximately [X] months ago?**

1	Yes	Go to A2
0	No	Go to A3
666	*Research worker unable to evaluate*	Go to A3
999	*Not completed*	Go to A3

A2 – If yes, record details below

Hospital code	Speciality code	Details if hospital=92 (other) and/or speciality code=28 (other)	Number of nights

A3 – Have you been to hospital for an outpatient/day patient appointment *(if baseline)* **in the last three months /** *(if follow-up)* **since you were last interviewed approximately [X] months ago?**

1	Yes	Go to A4
0	No	Go to A5
666	*Research worker unable to evaluate*	Go to A5
999	*Not completed*	Go to A5

A4 - If yes, record details below

Hospital code	Speciality code	Details if hospital=92 (other) and/or speciality code=28 (other)	Number of appointments

A5 – Have you attended an accident and emergency (A&E) department *(if baseline)* **in the last three months /** *(if follow-up)* **since you were last interviewed approximately [X] months ago?**

1	Yes	Go to A6
0	No	Go to B1
666	*Research worker unable to evaluate*	Go to B1
999	*Not completed*	Go to B1

A6 - If yes, record details below

Hospital code	Details	Admitted	Ambulance	Number of contacts
		Yes/no	Yes/no	
		Yes/no	Yes/no	
		Yes/no	Yes/no	
		Yes/no	Yes/no	

Section B: Community-based health, social and complementary services

B - Which of the following community based professionals or services have you had contact with *(if baseline)* **in the last three months /** *(if follow-up)* **since you were last interviewed approximately [X] months ago?**

		Number of contacts	Average duration in minutes per contact
1	General practitioner – surgery		
2	General practitioner – home		
3	General practitioner – telephone		
4	Practice nurse (nurse in GP surgery)		
5	District nurse, health visitor, midwife		
6	Community psychiatric nurse in the community		
7	Psychiatrist in the community		
8	Occupational therapist in the community		
9	Art/drama/music therapy in the community		
10	Social worker		
11	Marriage counselling service e.g. Relate		
12	Advice service e.g. Citizen's Advice Bureau		
13	Helpline e.g. Samaritans, MIND		
14	Day centre/drop-in centre		
15	Chiropractor/osteopath		
16	Homeopathy		
17	Acupuncture		
18	Other – give details		
19	Other – give details		
20	Other – give details		

Section C: Employment and time off work

C1 – What is your current occupational status?

1	Full-time employment (30+ hours per week)	Go to C3	7	Voluntary worker	Go to C2
2	Part-time employment (<30 hours per week)	Go to C3	8	Unemployed & looking for work	Go to C2
3	Employed & currently unable to work	Go to C3	9	Unemployed & not looking for work (e.g. housewife)	Go to C2
4	Part-time employment & part-time student	Go to C3	10	Unemployed & unable to work for medical reasons	Go to C2
5	Full-time student	Go to C2	11	Medically retired	Go to C2
6	Part-time student	Go to C2	12	Retired	Go to C2

666	*Research worker unable to evaluate*	Go to C2			
999	*Not completed*	Go to C2			

C2 – Have you been in paid employment *(if baseline)* **in the last three months /** *(if follow-up)* **since you were last interviewed approximately [X] months ago?**

0	No	END
1	Yes	Go to C3
666	*Research worker unable to evaluate*	
999	*Not completed*	

C3 – What is your approximate gross pay per year (before tax) for your current or most recent employment?

1	Under £5,000	8	£35,001-£40,000
2	£5,001-£10,000	9	£40,001-£45,000
3	£10,001-£15,000	10	£45,001-£50,000
4	£15,001-£20,000	11	£45,001-£50,000
5	£20,001-£25,000	12	£50,001-£75,000
6	£25,001-£30,000	13	£75,001-£100,000
7	£30,001-£35,000	14	£100,001 +
666	*Research worker unable to evaluate*		
999	*Not completed*		

C4 – How many DAYS have you been absent from work due to illness *(if baseline)* **in the last three months /** *(if follow-up)* **since you were last interviewed approximately [X] months ago?**

1	Days	Number of days
666	*Research worker unable to evaluate*	
999	*Not completed*	

C5 – How many HOURS does/did your employer expect you to work in a typical 7-day week for your current or most recent employment? If it varies, estimate the average. If more than 97, enter 97.

1	Hours	Number of hours
666	*Research worker unable to evaluate*	
999	*Not completed*	

C6 – Have you been in paid employment in the last four weeks?

0	No	END
1	Yes	Go to C7
666	*Research worker unable to evaluate*	
999	*Not completed*	

C7 – Please think about your work experiences over the past 4 weeks (28 days). In the past 4 weeks (28 days), how many days did you…

1	miss an entire work day because of problems with your physical or mental health? Please include only days missed for your own health.	Number of days
2	miss an entire work day for any other reason (including holiday)?	Number of days
3	miss part of a work day because of problems with your physical or mental health? Please include only	Number of days

	days missed for your own health.	
4	miss part of a of a work day for any other reason (including holiday)?	Number of days
666	*Research worker unable to evaluate*	
999	*Not completed*	

C8 – About how many HOURS altogether did you work in the past 4 weeks (28 days)? See examples for calculating hours worked below

1	Hours	Number of hours
666	*Research worker unable to evaluate*	
999	*Not completed*	

C9 – On a scale from 0 to 10 where 0 is the worst job performance anyone could have at your job and 10 is the performance of a top worker, how would you rate the usual performance of most workers in a job similar to yours? Place a ✓ in the circle below the number that best describes this.

Worst performance *Top performance*

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

C10 – Using the same 0-to-10 scale, how would you rate your usual job performance over the past year or two? Place a ✓ in the circle below the number that best describes this.

Worst performance *Top performance*

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

C11 – Using the same 0-to-10 scale, how would you rate your overall job performance on the days you worked during the past 4 weeks (28 days)? Place a ✓ in the circle below the number that best describes this.

Worst performance *Top performance*

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

Examples for Calculating Hours Worked in the Past 4 weeks
40 hours per week for 4 weeks = 160 hours
35 hours per week for 4 weeks = 140 hours
40 hours per week for 4 weeks with 2 8-hour days missed = 144 hours
40 hours per week for 4 weeks with 3 4-hour partial days missed = 148 hours
35 hours per week for 4 weeks with 2 8-hour days missed and 3 4-hour partial days missed = 112 hours

Employment and time off work section taken from the WHO Health Productivity Questionnaire (HPQ), questions B5-B11.

End of interview.

AD-SUS designed by Sarah Byford at the Institute of Psychiatry
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Appendix 7 Distribution of themes in telephone interviews

TABLE 28 Distribution of themes in telephone interviews

Theme	Subtheme	2012	2006	2004	2005	2007	2015	3006
ADM issues	Wants to remain on ADM	✗	✗	✗	✗	✗	✗	✗
	Wants to come off ADM	✗			✗			
	Not wanting to take ADM for 2 years							
	Not regularly taking ADM							
	Worried about relapse	✗					✗	
Time issues	Not the right time	✗	✗	✗	✗			✗
	Study too long							
	Working full time		✗					
Attitudes to psychological intervention	Had therapy before	✗		✗	✗		✗	
	Previous therapy unhelpful	✗			✗			
	Previous therapy helpful			✗			✗	
	Therapy and ADM complementary					✗		
MBCT issues	Meditation is a good idea			✗	✗	✗		
	Not keen on meditation	✗						✗
	Conflicts with religious views							
Being in a group	Unhappy with group therapy				✗			✗
	No concerns about group therapy			✗				
Lifestyle and medical barriers	Too unwell			✗				
	Cannot travel to sessions	✗		✗				✗
	Too old							
Symptom issues	Depression because of chemical imbalance							
	Not depressed enough	✗						
	Depression is contextual		✗	✗				
Taking part in research	No concerns	✗	✗	✗	✗	✗	✗	✗
	Safety/reliability concerns							✗
	Wanting to help others							
	Previously taken part in research							
Being randomised	Would like to choose group			✗			✗	✗
	Would like ADM arm			✗			✗	✗
	Would like MBCT arm							
	No worries about randomisation							

Shaded boxes represent reasons for non-participation given in response to the first open question.

3008	2009	2010	2001	2002	2003	3005	3007	2013	3004	2011	3003	2008	2014	2016
✗		✗	✗	✗		✗	✗	✗	✗	✗	✗	✗		✗
	✗	✗	✗			✗			✗	✗		✗	✗	
		✗												
	✗		✗			✗								
				✗										
		✗	✗	✗	✗	✗	✗		✗			✗		
			✗	✗										
								✗	✗					
✗		✗				✗				✗	✗	✗	✗	✗
✗						✗				✗	✗			✗
		✗				✗							✗	
		✗												
	✗					✗	✗	✗	✗		✗		✗	✗
		✗		✗						✗				
		✗												
	✗		✗	✗	✗					✗		✗	✗	
								✗	✗					
							✗	✗			✗			✗
				✗										
✗	✗													
				✗			✗					✗		
✗	✗			✗										✗
		✗		✗							✗		✗	✗
	✗		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
		✗	✗								✗		✗	✗
		✗						✗	✗		✗			
			✗				✗	✗						
	✗			✗	✗	✗	✗		✗	✗	✗	✗	✗	✗
				✗	✗		✗			✗				✗
	✗					✗			✗		✗	✗	✗	
		✗				✗		✗						✗

EME
HS&DR
HTA
PGfAR
PHR

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