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Complete List of Authors:	Ewais, Tatjana; Mater Misericordiae Brisbane Ltd, Mater Young Adult Health Centre; University of Queensland, School of Medicine Begun, Jake; Mater Misericordiae Brisbane Ltd, Mater Young Adult Health Centre; University of Queensland, School of Medicine Kenny, Maura; University of Adelaide, School of Medicine; Mindfulness Training Institute Chuang, Kai-Hsiang; UQ Queensland Brain Institute; University of Queensland Barclay, Johanna; Mater Misericordiae Brisbane Ltd, Mater Medical Research Institute; University of Queensland Kisely, Steve; University of Queensland,
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PROTOCOL FOR A PILOT RANDOMISED CONTROLLED TRIAL OF MINDFULNESS BASED COGNITIVE THERAPY IN YOUTH WITH INFLAMMATORY BOWEL DISEASE AND DEPRESSION

Tatjana Ewais[1,2,3], Jakob Begun[1,2], Maura Kenny [5,6], Kai-Hsiang Chuang[2,4], Johanna Barclay[1,2], Steve Kisely[2]

Correspondence: Tatjana Ewais, e-mail: t.ewais@uq.edu.au , tel:617 3216 5800**;** Word count: 3806

ABSTRACT

Introduction

Inflammatory Bowel Disease (IBD) is a chronic auto-inflammatory disease of the gastrointestinal tract with peak age of onset during adolescence and young adulthood. Adolescents and young adults (AYAs) with IBD experience higher depression rates compared to peers who are well or have other chronic conditions. Mindfulness-based interventions are of particular interest because of their potential to improve both the course of IBD and depression.

Methods and analysis

This study is a parallel design, single blinded, pilot randomised controlled trial (RCT) of mindfulness-based cognitive therapy (MBCT) in AYAs with IBD and depression. The trial aims to recruit 64 participants who will be randomly allocated to MBCT or treatment as usual (TAU). The primary outcome measure is the depression subscale score from the Depression, Anxiety and Stress Scale (DASS). Secondary outcomes include anxiety, stress, posttraumatic growth (PTG), IBD-related quality of life (QoL), illness knowledge, medication adherence, mindfulness, IBD activity, inflammatory markers, microbiome and brain neuroconnectivity changes. All outcomes other than neuroimaging will be collected at three time points-at baseline, at therapy completion and at twenty weeks. Neuroimaging will be conducted at baseline and at therapy completion. Outcomes will be assessed by blinded outcome assessors.

Discussion

The findings from this study will provide information regarding the feasibility and efficacy of an IBD-focused and developmentally-informed MBCT program in AYAs with IBD and depression, elucidate mechanisms of action of mindfulness intervention and provide data to enable design and sample size calculation for a future large RCT of MBCT in this cohort.

Ethics and dissemination

The protocol has been approved by the Mater Hospital Human Research Ethics Committee (HREC) and University of Queensland HREC. Trial findings will be published in peer-reviewed journals and presented at scientific conferences.

Registration details: Australian and New Zealand Clinical Trials Registry (ANZCTR) Trial ID-ACTRN12617000876392, Universal Trial Number (UTN)-U1111-1197-7370.

Keywords: Mindfulness, Inflammatory bowel disease, Depression, Young adult, Randomised controlled trial.

Strengths and limitations of this study

- This study will be the first RCT of MBCT in AYAs with IBD, a cohort with a peak age of IBD onset
- Outcome measures will include psychological measures as well as inflammatory markers, disease activity and neuroimaging, and will potentially contribute to explaining the mindfulness intervention mechanisms of action.
- The results from this study will be used to inform the design and sample size calculation of a future large RCT.
- The study will be run as a pilot RCT because variability in the effect sizes of mindfulness interventions and unknown effect size in this population make it difficult to estimate the sample size accurately.
- The pilot nature of the study will enable assessment of the intervention feasibility as well as recruitment and attrition rates specific to this intervention and this cohort.

INTRODUCTION

Inflammatory bowel disease is an immune-mediated condition characterised by chronic inflammation of the gastrointestinal tract (large and small bowel) and frequent extra-intestinal symptoms [1, 2]. The peak age of onset is between the ages of 15 and 29, thus interrupting a crucial developmental stage and impacting on relationships, education and employment opportunities [3]. Adolescents and young adults with IBD experience depression rates that are three times higher than in general population and higher than depression rates in youth with other chronic diseases [4-6]. They frequently experience impaired health-related quality of life and delayed social development compared to their peers [5].

Depression in IBD

The relationship between depression and IBD is bidirectional in that IBD can both cause and exacerbate depression while depression can precede the onset of IBD, as well as worsen its course and prognosis. A recent systematic review has shown that depression increases the risk of exacerbation and recurrence of symptoms of IBD [7]. There are a number of ways that depression and IBD interact including common risk factors and shared underlying immune system abnormalities with depression increasingly being conceptualised as an inflammatory disease [8]. Given the magnitude of the depression impact on IBD course and their reciprocal relationship, it is important to recognise and treat depression in IBD early [9]. Despite the impact of depression on the course of IBD, research into treatments for depression in these patients has been sparse and limited by poor methodological quality. Antidepressant medications have shown promise in treating depression and anxiety associated with IBD as well as improving IBD symptoms although further studies with better methodological quality are needed [10]. Their use is also limited by gastro-intestinal side effects and patient preference [10]. Psychosocial interventions with the most evidence include cognitive behavioural therapy, hypnosis and mindfulness-based interventions [10, 11]. However, the evidence for psychological therapies in IBD has been mixed, with best results seen in improvement of depression and quality of life and non-significant improvements seen in IBD symptoms and disease activity [10, 11].

Mindfulness Interventions and Mindfulness Based Cognitive Therapy

Mindfulness-based interventions are therapeutic interventions based on mindfulness, a meditative practice that teaches non-judgmental awareness of one's current experience. Accumulating evidence suggests that these interventions are associated with reduced depression and anxiety levels and improved QoL in individuals with IBD [11, 12] . Mindfulness-based cognitive therapy, an eight-week manualised group program which combines mindfulness with cognitive therapy [13], has been shown to be effective for treatment of depression [14] as well as prevention of depressive relapse [15], and has recently been modified for use in IBD [16]. Mindfulness-based cognitive therapy is traditionally delivered in 8 weekly sessions of 2-hour duration to groups of 8-12 participants. Research has shown that MBCT and other mindfulness programs are associated with changes in neural structure and function in brain regions important for improved emotional well-being (experience dependent neuroplasticity) [17], suggesting possible neural mechanisms for mindfulness attenuating symptoms associated with mental health disorders [18]]. A recent meta-analyses of mindfulness studies indicated that mindfulness can also modify immune activity, with the authors concluding that "mindfulness meditation may be salutogenic for immune system dynamics, but additional work is needed to examine these effects"[19].

To date there have been only a few published studies exploring the potential utility of mindfulness interventions in individuals with IBD and only one RCT of MBCT, conducted in adults with IBD, with the mean age of 49. This RCT reported a significant improvement in depression and trait anxiety and small, not statistically significant, improvements in IBD disease activity and QoL [16]. However, no biological markers were measured to detect potential changes in inflammation and brain function in these studies. To further investigate the effectiveness and feasibility of this novel therapy in young adult IBD patients and elucidate its mechanism of action, we will conduct a pilot RCT of MBCT, and measure changes in psychological outcomes as well as inflammatory biomarkers and brain connectivity following the intervention.

Hypotheses

1. MBCT intervention will improve depression scores
2. MBCT will decrease anxiety, stress and maladaptive coping and increase QoL, posttraumatic growth (PTG), mindfulness, medication adherence and perceived health care empowerment
3. MBCT will change the structural and functional connectivity in default mode and executive control networks
4. MBCT intervention will be associated with decreased inflammatory burden and improved microbiome
5. MBCT intervention will be feasible as indicated by sessions attendance and completion of home practices

Study Aims

Using 64 volunteer individuals (aged 16-29) with IBD and depression, we will explore the feasibility and benefits of IBD-focused, developmentally informed MBCT program on depressive symptoms in youth living

with IBD and comorbid depression. Secondary aims are to explore the potential benefits of the MBCT on additional outcomes including:

- anxiety, stress, QoL, medication adherence, perceived health care empowerment, coping patterns, illness perceptions and PTG
- Biological markers of IBD
- Brain structure and function using functional MRI (fMRI) performed on a sub-group of 16 intervention and 16 control subjects.

Specific aims related to the pilot nature of the study are the following:

- To determine the feasibility of the mindfulness program by measuring the participants' attendance and their compliance with home mindfulness practices,
- To adapt the MBCT intervention to young adult IBD patients while measuring the intervention delivery fidelity,
- To use the findings to elucidate mindfulness mechanisms of action, and
- To use data from this pilot RCT to inform the design and sample size calculation for a large RCT.

METHODS AND ANALYSIS

Study Design

This is a parallel, single blinded, pilot RCT of an adapted MBCT program for AYAs with IBD and depression versus treatment as usual (TAU). The design adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement recommendations and CONSORT extensions for pilot trials[20, 21]. We followed the Standard Protocol Items for Randomised Trials (SPIRIT) statement recommendations in writing the trial protocol [22, 23]. The flow of the participants through the study is shown in Figure 1.

Recruitment Strategies

Participants will be recruited from the IBD outpatient services at Mater Young Adult Health Centre in Brisbane and surrounding IBD clinics via a specified referral pathway. The recruitment strategy was developed in discussion with the IBD multidisciplinary team including gastroenterologists, IBD nurses and allied health staff. Recruitment will be initiated during outpatient appointments and those who are interested will meet with the research assistant who will explain the study in more detail, conduct the initial screening and obtain informed consent. After participants consent, they will attend an interview to confirm the clinical diagnosis of depression and other inclusion criteria and ensure that there are no exclusion criteria to participation. Recruitment and enrolment will be conducted in groups of 16-24 participants with 8-12 participants per MBCT group which will suit the clinical nature of the group and provide optimal support.

Participant Selection

Since this is a study of MBCT in AYAs with IBD and depression, main eligibility criteria will include age, IBD diagnosis and depression diagnosis. Complete inclusion and exclusion criteria are listed in box 1 and box 2.

Box 1 Inclusion Criteria

- Young adult (aged 16-29)
- Able to verbally communicate and write in English
- Able to give informed consent (for youth aged 16-18 both the participant and their parent/guardian)
- Confirmed diagnosis of Crohn's disease or ulcerative colitis
- Confirmed clinical diagnosis of depression corresponding to DASS depression subscale scores between 10-27
- Attending the IBD outpatient clinic at the Mater Young Adult Health Centre Brisbane
- Have access to internet-enabled computer
- Able to do light exercise because this program involves a mindful movement component
- Able to commit to attend the eight weekly sessions of two hours' duration
- Able to commit to do home practice of up to 45 minutes per day over the 8 weeks of the study as this is a requirement of the program
- No change in antidepressant medication (dose or type) within three months of trial onset

Box 2 Exclusion criteria

- Individuals who do not have conversational or written English
- Individuals who may have limited or no capacity for self-care
- Individuals who have no depression or have extremely severe levels of depression or anxiety
- Individuals with major mental illness other than depression as its treatment and symptoms could interfere with their ability to participate in program (e.g. current psychotic symptoms, PTSD)
- Individuals with a history of or current alcohol or drug dependency
- Individuals scheduled for major surgery in the next 3 months as this would impact on their ability to attend the program for its entire duration
- Individuals who have been started on antidepressants or changed their antidepressant dose within three months of the study onset
- Individuals enrolled or participating in another psychological therapy study or pharmacological study within the last six months or intending to participate during this study duration
- Exacerbation of IBD symptoms (flare) as this will make it difficult for participants to attend weekly sessions and complete home practice

Randomisation

Randomisation will be conducted by an off-site statistician not involved in patient recruitment or assessment, using random allocation software, after participants have provided written consent. Group allocation to MBCT (intervention group) or TAU (control group) will be conducted in a 1 :1 ratio. The statistician will be given de-identified patient details generated by a researcher not involved in the recruitment, assessment or treatment. The statistician will generate the allocation schedule using the software and return it to the same researcher who will then match the participants' codes to their details and reveal the allocation.

To ensure a balanced composition between groups in terms of age, gender and depression levels, stratified randomisation will be performed using the *ralloc* function in the Stata statistical package. Patients will be stratified by two categories for gender, age and depression scores. Within each stratum, patients will be allocated to MBCT or TAU. Because of limited resources, only 50% of participants, (n=32) will be randomly allocated to have neuroimaging (fMRIs), using the same statistical package. Participants will be recruited and allocated in groups of 16-24 participants in order to accommodate the clinical nature of the group and provide sufficient numbers. Participants and those delivering the intervention will not be blinded due to the nature of the intervention, however, research personnel involved in assessing the outcomes and data analysis will be blinded.

Adapted MBCT Program

MBCT program which will be used in this trial closely follows the original MBCT curriculum designed by Segal, Williams and Teasdale [13] with adaptations used to introduce IBD-specific education and developmentally informed practices. Adapted manual includes education about IBD-specific stress responses and "gut-brain axis" as well as adapted mindfulness practices.

The program will be delivered by an experienced mindfulness teacher who completed teachers' level training in Mindfulness-based Stress Reduction (MBSR) and MBCT, delivered several mindfulness courses and maintained personal practice for five years. Supervision during the study will be provided by a senior MBCT supervisor who is a founding member of Mindfulness Training Institute of Australia. Fidelity of the delivered intervention will be appraised by assessing video-recordings of the sessions by the study MBCT supervisor and discussing the adherence to session content and delivery in supervision. Feasibility will be assessed from sessions attendance rates and home practices completion rates.

Participants will be given the adapted MBCT manual and encouraged to engage in mindfulness practices for 45 minutes per day. They will be given a USB with guided mindfulness practices to do at home. They will be sent weekly group emails with summary of the discussions from the previous session and ideas on how to troubleshoot any barriers to practicing at home. They will be asked to record their home mindfulness practices daily in the home practice record form.

An example of the MBCT program session content-session 1 summary

Theme: Awareness and automatic pilot

1. Establish the orientation of the class
2. Ground Rules
3. Pair up and introduce yourselves to each other and then to the group
4. Raisin exercise
5. Additional or alternative exercise-describing picture postcards
6. Feedback and discussion of raisin exercise and introduction to automatic pilot
7. Body scan practice & inquiry, starting with short breath focus, feedback
8. Home Practice, starting with short breath focus, discuss and assign practices for the coming week
9. Discuss in pairs: timing for home practice, dealing with obstacles, meaning centred goal setting; setting an intention
10. Session 1 handouts (including Home Practice record forms to be collected next week)
11. Summary of session 1, end the class with a short 2-3-minute breath focus, followed by poem

Data Collection and Analysis

Participants will be asked to complete questionnaires and provide blood and stool samples at baseline (week 0), on completion of the eight-week therapy program or TAU (week 8) and at 20 weeks after baseline. The data gained from the research will be stored in a re-identifiable format with linkage of the data to patient details only able to be performed by the study research assistant. Study data will be stored and accessible from the University of Queensland's institutional repository, UQ eSpace.

Research assistant will complete a screening and recruitment sheet with details of all patients approached regarding the study, enrolled and excluded at each stage of the recruitment process and reasons for this. MBCT group facilitator will complete weekly attendance sheets to enable the calculation of attendance and attrition rates. This data will inform the recruitment strategies for a future large RCT. An Analysis of Covariance will be used to analyse continuous outcomes available at baseline and weeks 8 and 20. We will use intention to treat analysis and multiple imputation models for missing data whenever possible.

Safety Considerations—Data Safety and Monitoring Board

Participation in the program is very low risk although for some people, discussions about their health may be mildly upsetting. There have been no reports of significant adverse side effects of MBCT in literature with a recent meta-analysis which canvassed all completed MBCT studies for adverse events confirming that no adverse events were reported[24]. Safety reporting will be done in keeping with Good Clinical Practice guidelines including the reporting of all adverse events and serious adverse events (SAEs), both related and unrelated to the study, throughout the study duration. Participants will be screened and carefully selected for

their suitability for the program. They will be asked about *any* perceived adverse events, whether or not these may be related to the mindfulness intervention, and this information recorded in the trial database.

All serious adverse events will be reported within 24 hours to the Mater and UQ HRECs. All aspects of safety, recruitment and quality control of the data will be monitored by the Mater and UQ HRECs and there will be no separate Data Safety and Monitoring Board involved. Participants will continue to receive standard medical and psychosocial care both during and after the conclusion of the trial.

Sample size calculation

Based on researcher experience, we expect 64 patients to be available to participate in the study, with a drop-out rate of 15%. We expect that around 54 participants will complete the study (n=27 intervention group; n=27 control group). This sample size provides 80% power to identify large (Cohen's D = 0.8) effects. However, given the effects sizes variability for mindfulness studies, we have decided to run this study as a pilot RCT to assess the intervention's feasibility and effectiveness, as well as provide data for establishing sample size numbers for a definitive large RCT. The proposed sample size of 54 is in keeping with guidelines for pilot studies which recommend a sample size of at least 40 and for effectiveness studies,30 participants per arm of the study [25].

Outcomes

All outcome tools chosen for the study are valid, reliable and routinely used in the setting of IBD and chronic illness.The primary outcome measure will be the depression subscale score from the Depression, Anxiety and Stress Scale (DASS) [26]. Remission and recovery rates will be calculated from the available DASS scores. Depression, Anxiety and Stress Scale (DASS) is a self-report instrument comprising of three scales designed to measure three negative emotional sates of depression, anxiety and stress. All three scales of the DASS have been shown to have high internal consistency and meaningful discriminations in a variety of clinical and research settings . There are two versions of the DASS questionnaire, DASS 42 with 14 items per scale and DASS 21 with 7 items per scale. The short version, DASS 21, will be used in the study as it has shown comparable validity to the long version and it will pose lesser burden to complete it for the participants.

Secondary outcomes will include anxiety and stress scores on DASS, posttraumatic growth scores on PTGI, IBD related quality of life (SIBDQ,10), illness knowledge, perception and coping (CCKNOW, IPQ and COPE), medication adherence and self-efficacy, healthcare empowerment (MAQ, SEAMS, HCEI), and mindfulness (FFMQ). Posttraumatic Growth Index (PTGI) is is a 21-item-questionnaire measuring growth and positive changes that individuals experience following traumatic events [27]. Posttraumatic growth has been recognised as a meaningful treatment goal for people with IBD and PTGI has been identified as a validated screening tool in individuals with IBD and other chronic illnesses and [28].Short Inflammatory Bowel Disease Quality of Life questionnaire(SIBDQ) is a 10-item-questionaire which is a validated and reliable instrument for assessing health related quality of life in IBD patients [29]. The Crohn's and Colitis Knowledge Score

(CCKNOW), Brief Illness Perception Questionnaire (Brief IPQ) and Brief (COPE) are brief, validated questionnaires for assessing illness knowledge, perception and coping, commonly used in clinical practice and research in IBD population [30-32] . Morisky 4-Item Medication Adherence Questionnaire (MAQ), Self-efficacy for Appropriate Medication Use Scale (SEAMS) and Health Care Empowerment Inventory (HCEI) are also brief, validated and reliable self-report questionnaires used to assess medication adherence, self-efficacy, and healthcare empowerment, in IBD population [33-35] . The Five Facet Mindfulness Questionnaire (FFMQ) is a validated screening tool assessing mindfulness as a multifaceted construct [36] .

Secondary outcomes will also include IBD disease activity questionnaires (SCAI, HBI), biological markers of inflammation both systemic (CRP, ESR, IL-6) and IBD-specific (faecal calprotectin, small intestinal ultrasound), microbiome analysis as it reflects IBD activity, and neuroconnectivity changes (fMRIs). We are measuring inflammation markers and neuroconnectivity as research has shown that mindfulness practices can attenuate inflammation and improve neuroconnectivity, and changes in these parameters combined with changes in psychological outcomes could contribute to explaining mindfulness mechanism of action.

Discussion

This study is the first RCT of a mindfulness-based intervention in AYAs with IBD and depression, a vulnerable group of young patients with a high burden of IBD and significant long-term impairments in multiple areas of functioning. The study will be using an adapted MBCT program for young adults with IBD which, if proven feasible, may become integrated into the early intervention pathways for IBD. The intervention could contribute to altering disease progression, reduce disabling symptoms, and improve long-term outcomes in this group of young patients.

The study will explore feasibility of the adapted MBCT program by recording sessions attendance and completion rates of home mindfulness practices. It will assess the effectiveness of the MBCT program by measuring its impact on various psychological and physical outcomes of IBD and depression, including biological markers of inflammation and brain connectivity. The study has the potential to validate this type of intervention, improve patient outcomes in young IBD sufferers and translate this approach to other chronic illness patient groups. The inclusion of biologic measures of disease activity and functional neuro-imaging will allow additional insights into the relationship between IBD and depression, and mindfulness' mechanism of action.

STUDY STATUS

The study was approved by the ethics committees of the Mater Hospital and The University of Queensland in June 2017. An amendment to the protocol was approved in January 2018 (version 3, date 18/01/2018), extending the upper age range to 29, and replacing the Hospital Anxiety and Depression Scale (HADS) with the PTGI to measure post-traumatic growth. The upper age range was extended in order to match the peak age range of IBD onset, and the HADS was replaced because depression and anxiety were already measured by the DASS. The study is currently in the recruitment stage, with completion expected by the end of 2019. The

study paper will be published in a peer reviewed journal and a lay summary of the findings provided to each of the participants.

Authors' affiliations

1.Mater Health, Raymond Terrace, South Brisbane, Queensland, Australia

2.University of Queensland, St Lucia, Brisbane, Queensland, Australia

3.Griffith University, Gold Coast, Queensland, Australia

4.. Queensland Brain Institute, St Lucia, Brisbane, Queensland, Australia

5. The University of Adelaide, Adelaide, South Australia, Australia

6. Mindfulness Training Institute Australia, Sydney, Australia

Authors' Contributions

Study protocol was conceived and designed by TE and critically revised by SK,JB,MK, KC and JBA. Drafting of the paper was completed by TE. Critical revision of the manuscript was done by SK.

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Competing interests

None

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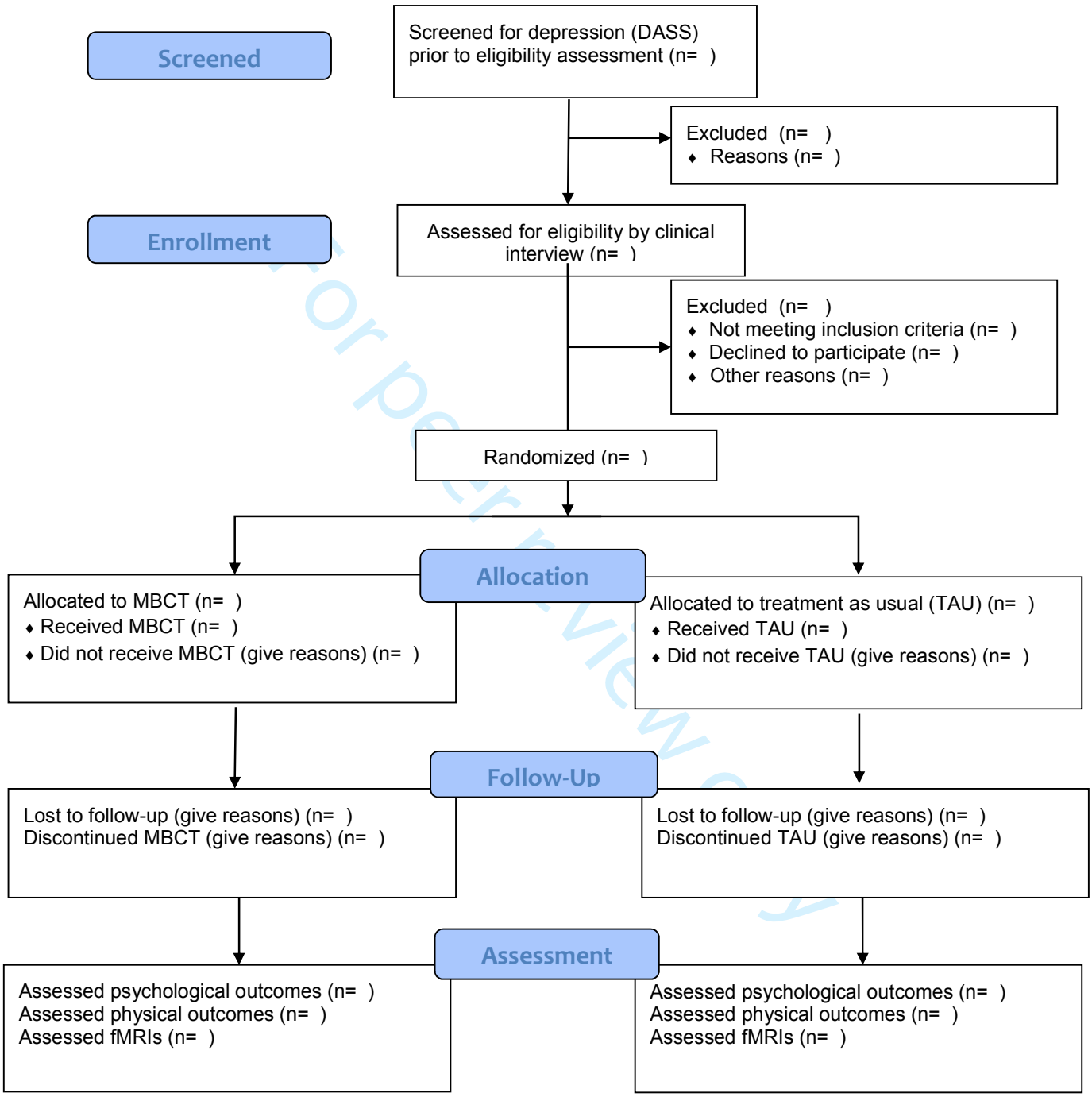
Figure 1 CONSORT Extension for Pilot and Feasibility Trials Flow diagram showing the flow of the participants through the study



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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-10
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	10
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	10

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	3-4, 8-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7,13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	6

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	na
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1,7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Data access	#29	Statement of who will have access to the final trial dataset,	7

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	7-8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	10
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	na
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	na

BMJ Open

PROTOCOL FOR A PILOT RANDOMISED CONTROLLED TRIAL OF MINDFULNESS BASED COGNITIVE THERAPY IN YOUTH WITH INFLAMMATORY BOWEL DISEASE AND DEPRESSION

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Complete List of Authors:	Ewais, Tatjana; Mater Misericordiae Brisbane Ltd, Mater Young Adult Health Centre; University of Queensland, Faculty of Medicine Begun, Jake; Mater Misericordiae Brisbane Ltd, Mater Young Adult Health Centre; University of Queensland, Mater Research Institute-UQ Kenny, Maura; University of Adelaide, Faculty of Health and Medical Sciences; Mindfulness Training Institute Chuang, Kai-Hsiang; University of Queensland, Queensland Brain Institute Barclay, Johanna; University of Queensland, Mater Research Institute-UQ Hay, Karen; QIMR Berghofer Medical Research Institute Kisely, Steve; University of Queensland, Faculty of Medicine; Metro South Hospital and Health Service, Princess Alexandra Hospital
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Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, Depression & mood disorders < PSYCHIATRY, Mindfulness, Young Adult, Randomised controlled trial

PROTOCOL FOR A PILOT RANDOMISED CONTROLLED TRIAL OF MINDFULNESS BASED COGNITIVE THERAPY IN YOUTH WITH INFLAMMATORY BOWEL DISEASE AND DEPRESSION

Tatjana Ewais[1,2,3], Jake Begun[1,4], Maura Kenny [6,7], Kai-Hsiang Chuang[5], Johanna Barclay[4], Karen Hay[8], Steve Kisely[2,9]

Correspondence: Tatjana Ewais, e-mail: tatjanaewais@gmail.com, tel:617 3216 5800; Word count: 4003

ABSTRACT

Introduction

Inflammatory Bowel Disease (IBD) is a chronic auto-inflammatory disease of the gastrointestinal tract with peak age of onset during adolescence and young adulthood. Adolescents and young adults (AYAs) with IBD experience higher depression rates compared to peers who are well or have other chronic conditions. Mindfulness-based interventions are of particular interest because of their potential to improve both the course of IBD and depression.

Methods and analysis

This study is a parallel design, single blinded, pilot randomised controlled trial (RCT) of mindfulness-based cognitive therapy (MBCT) in AYAs with IBD and depression. The trial aims to recruit 64 participants who will be randomly allocated to MBCT or treatment as usual (TAU). The primary outcome measure is the depression subscale score from the Depression, Anxiety and Stress Scale (DASS). Secondary outcomes include anxiety, stress, posttraumatic growth (PTG), IBD-related quality of life (QoL), illness knowledge, medication adherence, mindfulness, IBD activity, inflammatory markers, microbiome and brain neuroconnectivity changes. All outcomes other than neuroimaging will be collected at three time points-at baseline, at therapy completion and at twenty weeks. Neuroimaging will be conducted at baseline and at therapy completion. Mixed effects linear and logistic regression will be used to analyse continuous and dichotomous outcomes respectively. Participants' experiences will be explored through focus groups, and thematic analysis used to generate relevant themes.

Ethics and dissemination

The protocol has been approved by the Mater Hospital Human Research Ethics Committee (HREC) and University of Queensland HREC. Trial findings will be published in peer-reviewed journals and presented at scientific conferences.

Registration details: Australian and New Zealand Clinical Trials Registry (ANZCTR) Trial ID-ACTRN12617000876392, Universal Trial Number (UTN)-U1111-1197-7370.

Keywords: Mindfulness, Inflammatory bowel disease, Depression, Young adult, Randomised controlled trial

Strengths and limitations of this study

- This study will be the first RCT of MBCT in AYAs with IBD, a cohort with a peak age of IBD onset.
- Outcome measures will include psychological measures as well as inflammatory markers, disease activity and neuroimaging, and will potentially contribute to explaining the mindfulness intervention mechanisms of action.
- The results from this study will be used to inform the design and sample size calculation of a future large RCT.
- The study will be run as a pilot RCT because variability in the effect sizes of mindfulness interventions and unknown effect size in this population make it difficult to estimate the sample size accurately.
- The pilot nature of the study will enable assessment of the intervention feasibility in this cohort.

INTRODUCTION

Inflammatory bowel disease is an immune-mediated condition characterised by chronic inflammation of the gastrointestinal tract and frequent extra-intestinal symptoms [1, 2]. The peak age of onset is between the ages of 15 and 29, thus interrupting a crucial developmental stage and impacting on relationships, education and employment opportunities [3]. Adolescents and young adults with IBD experience depression rates that are three times higher than in general population and higher than depression rates in youth with other chronic diseases with reported rates of current depression of up to 25% [4-6]. They frequently experience impaired health-related quality of life and delayed social development compared to their peers [5].

Depression in IBD

The relationship between depression and IBD is bidirectional in that IBD can both cause and exacerbate depression while depression can precede the onset of IBD, as well as worsen its course and prognosis. A recent systematic review has shown that depression increases the risk of exacerbation and recurrence of symptoms of IBD [7]. There are a number of ways that depression and IBD interact including common risk factors, decrease in treatment adherence and health promoting behaviours, and shared underlying immune system abnormalities [8]. Despite the impact of depression on the course of IBD, research into treatments for depression in these patients has been sparse and limited by poor methodological quality. Antidepressant medications have shown promise in treating depression and anxiety associated with IBD as well as improving IBD symptoms although further studies with better methodological quality are needed [9]. Psychosocial interventions with the most evidence include

cognitive behavioural therapy, hypnosis and mindfulness-based interventions [10, 11]. However, the evidence for psychological therapies in IBD has been mixed, with best results seen in improvement of depression and quality of life and non-significant improvements seen in IBD symptoms and disease activity [10, 11].

Mindfulness Interventions and Mindfulness Based Cognitive Therapy

Mindfulness is a particular state of awareness described as "paying attention in a particular way: on purpose, in the present moment and non-judgmentally" [12]. Mindfulness-based interventions are therapeutic interventions based on core mindfulness principles and containing various mindfulness practices. They have been proven effective in treating depression and anxiety in diverse clinical populations including those with chronic illness [13, 14]. Furthermore, by improving depression and anxiety which are known predictors of treatment non-adherence and poor engagement [15], mindfulness interventions can lead to improved treatment adherence, health care empowerment and improvement in the course of chronic illness.

Research has shown that mindfulness programs are associated with changes in neural structure and function in brain regions important for improved emotional well-being (experience dependent neuroplasticity) [16], suggesting possible neural mechanisms for mindfulness attenuating symptoms associated with mental health disorders [17-19]. A recent systematic review of the impact of mindfulness interventions on the immune system parameters indicated that mindfulness can also modify immune activity, with the authors concluding that "mindfulness meditation may be salutogenic for immune system dynamics, but additional work is needed to examine these effects", (page 1)[20].

Accumulating evidence from mindfulness studies in IBD populations suggests that these interventions are associated with reduced depression and anxiety levels and improved QoL in individuals with IBD [10, 21] . Mindfulness-based cognitive therapy, an eight-week manualised group program combining mindfulness with cognitive therapy and delivered in weekly sessions of two hours duration[22], has been shown to be effective for treatment of depression [23] as well as prevention of depressive relapse [24], and has recently been modified for use in IBD [25]. Recent studies suggest that MBCT may be particularly helpful in individuals with significant baseline depressive symptoms, with larger treatment effect in this cohort, and further reduction of depressive symptoms over time[23, 26] .

To date there have been only a few published studies exploring the potential utility of mindfulness interventions in individuals with IBD and only one RCT of MBCT, conducted in adults with IBD, with the mean age of 49. This RCT reported a significant improvement in depression and trait anxiety and small, not statistically significant, improvements in IBD disease activity and QoL [25]. However, no biological markers were measured to detect potential changes in inflammation and brain function in these studies. To further investigate the effectiveness and feasibility of this novel therapy in young adult IBD patients and elucidate its mechanism of action, we will conduct a pilot RCT of MBCT, and measure

changes in psychological outcomes as well as inflammatory biomarkers and brain connectivity following the intervention.

Hypotheses

1. MBCT intervention will be feasible and acceptable as indicated by sessions attendance, completion of home practices, recruitment and attrition rates, and participants' MBCT group experiences
2. MBCT intervention will result in significantly improved depression scores post intervention
3. MBCT will decrease anxiety, stress and maladaptive coping and increase QoL, posttraumatic growth (PTG), mindfulness, medication adherence, self-efficacy, health care empowerment, illness knowledge and perceptions
4. MBCT intervention will be associated with decreased inflammatory burden and improved microbiome
5. MBCT will change the structural and functional connectivity in default mode network (medial prefrontal cortex, posterior cingulate cortex) and executive control network (dorsolateral prefrontal cortex and frontoparietal regions)

Study Aims

Using 64 volunteer individuals (aged 16-29) with IBD and depression, we will explore the feasibility and benefits of IBD-focused, developmentally informed MBCT program on depressive symptoms in AYAs living with IBD and comorbid depression. Secondary aims are to explore the potential benefits of the MBCT on additional outcomes including:

- anxiety, stress, coping, QoL, PTG, mindfulness, medication adherence, self-efficacy, health care empowerment, and illness knowledge and perceptions
- Biological markers of IBD
- Brain structure and function using functional MRI (fMRI) performed on a sub-group of 16 intervention and 16 control subjects.

Specific aims related to the pilot nature of the study are the following:

- To determine the feasibility of the mindfulness program by measuring the participants' attendance, compliance with home mindfulness practices, recruitment and attrition rates, and MBCT group experiences
- To adapt the MBCT intervention to young adult IBD patients while measuring the intervention delivery fidelity
- To use the findings to elucidate mindfulness mechanisms of action, and
- To use data from this pilot RCT to inform the design and sample size calculation for a future large RCT

METHODS AND ANALYSIS

Study Design

This is a parallel, single blinded, pilot RCT of an adapted MBCT program for AYAs with IBD and depression versus treatment as usual (TAU). The design adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement recommendations and CONSORT extensions for pilot trials[27, 28]. We followed the Standard Protocol Items for Randomised Trials (SPIRIT) statement recommendations in writing the trial protocol [29, 30]. The flow of the participants through the study is shown in Figure 1.

Recruitment Strategies

Participants will be recruited from the IBD outpatient services at Mater Young Adult Health Centre in Brisbane and surrounding IBD clinics via a specified referral pathway. Recruitment will be initiated during outpatient appointments and those who are interested will meet with the research assistant who will explain the study in more detail, conduct the initial screening and obtain informed consent. Screening questionnaires will be made available in electronic and paper form, and email and text reminders will be used, to minimise the burden to participants and facilitate recruitment. After participants consent, they will attend an interview to confirm the clinical diagnosis of depression and other inclusion criteria and ensure that there are no exclusion criteria to participation. The intake interview will be unstructured clinical interview conducted by the principal investigator who is a psychiatrist by training, and who will assess whether participants meet the criteria for a major depressive disorder as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM–5) [31]. Recruitment and enrolment will be conducted in groups of 16-24 participants with 8-12 participants per MBCT group which will suit the clinical nature of the group and provide optimal support.

Participant Selection

Since this is a study of MBCT in AYAs with IBD and depression, main eligibility criteria will include age, IBD diagnosis and depression diagnosis. Complete inclusion and exclusion criteria are listed in box 1 and box 2.

Box 1 Inclusion Criteria

- Young adult (aged 16-29)
- Able to verbally communicate and write in English
- Able to give informed consent (for youth aged 16-18 both the participant and their parent/guardian)

- Confirmed diagnosis of IBD
- Confirmed clinical diagnosis of depression and DASS depression subscale score of 10 and above
- Attending the IBD outpatient clinic at the Mater Young Adult Health Centre Brisbane
- Have access to internet-enabled computer
- Able to do light exercise because this program involves a mindful movement component
- Able to commit to attend the eight weekly sessions of two hours' duration
- Able to commit to do home practice of up to 45 minutes per day over the 8 weeks of the study as this is a requirement of the program
- No change in antidepressant medication (dose or type) within three months of trial onset

Box 2 Exclusion criteria

- Individuals who do not have conversational or written English
- Individuals who may have limited or no capacity for self-care
- Individuals who have no depression or have extremely severe levels of depression (e.g. associated with acute suicidal thoughts and /or delusional beliefs and other psychotic symptoms)
- Individuals with major mental illness other than depression as its treatment and symptoms could interfere with their ability to participate in program (e.g. current psychotic symptoms, PTSD)
- Individuals with a history of or current alcohol or drug dependency
- Individuals scheduled for major surgery in the next 3 months as this would impact on their ability to attend the program for its entire duration
- Individuals who have been started on antidepressants or changed their antidepressant dose within three months of the study onset
- Individuals enrolled or participating in another psychological therapy study or pharmacological study within the last six months or intending to participate during this study duration
- Exacerbation of IBD symptoms (flare) as this will make it difficult for participants to attend weekly sessions and complete home practice

Randomisation

Randomisation will be conducted by an off-site statistician not involved in patient recruitment or assessment, using random allocation software, after participants have provided written consent. The statistician will be given de-identified patient details generated by a researcher not involved in the recruitment, assessment or treatment. The statistician will generate the allocation schedule using the software and return it to the same researcher who will then match the participants' codes to their details and reveal the allocation.

To ensure a balanced composition between groups in terms of age, gender and depression levels, stratified randomisation will be performed by user-written RALLOC module [32], in the Stata statistical package [33]. Patients will be stratified by two categories for gender, age and depression scores. Within each stratum, patients will be allocated to MBCT or TAU. Because of limited resources, only 50% of participants, (n=32) will be randomly allocated to have neuroimaging (fMRIs), using the same statistical package. Participants will be recruited and allocated in groups of 16-24 participants in order to accommodate the clinical nature of the group and provide sufficient numbers. Participants and those delivering the intervention will not be blinded due to the nature of the intervention, however, research personnel involved in assessing the outcomes and data analysis will be blinded.

Adapted MBCT Program

MBCT program which will be used in this trial closely follows the original MBCT curriculum designed by Segal, Williams and Teasdale [22], and consists of eight, weekly sessions of approximately two hours duration. The adaptations will introduce IBD-specific education about stress and "gut-brain axis" and developmentally informed and IBD-adapted mindfulness practices. The program will be delivered by an experienced mindfulness teacher who is a mental health clinician with teachers' level training in Mindfulness-based Stress Reduction (MBSR) and MBCT, and who has delivered several mindfulness courses and maintained personal practice for five years. Supervision during the study will be provided by a senior MBCT supervisor who is a founding member of Mindfulness Training Institute of Australia. Fidelity of the delivered intervention will be appraised by assessing video-recordings of the sessions by the study MBCT supervisor and discussing the adherence to session content and delivery in supervision. Feasibility of the program will be assessed from sessions attendance, home practices completion rates, recruitment and attrition rates, and participants' MBCT group experiences which will be explored through post-intervention focus groups. We will conduct three focus groups with 6-8 participants in each group in keeping with recommendations for running a minimum of three to four groups to enable conducting across groups analysis of patterns and themes [34], and recommended group size for clinical populations. Consecutive sampling will be used by inviting all participants who completed MBCT groups (5 out of 8 sessions as this is the accepted benchmark), via email and phone, until required numbers are recruited.

Participants will be given the adapted MBCT manual and a USB with guided mindfulness practices, and encouraged to engage in mindfulness practices for 45 minutes per day. They will be asked to record their home mindfulness practices daily in the home practice record form.

Data Collection and Analysis

Participants will be asked to complete questionnaires and provide blood and stool samples at baseline (week 0), on completion of the eight-week therapy program or TAU (week 8) and at 20 weeks after baseline. The data gained from the research will be stored in a re-identifiable format with linkage of the data to patient details only able to be performed by the study research assistant.

Research assistant will complete a screening and recruitment sheet with details of all patients approached regarding the study, enrolled and excluded at each stage of the recruitment process and reasons for this. MBCT group facilitator will complete weekly attendance sheets to enable the calculation of attendance and attrition rates in the intervention group. These data will inform the recruitment strategies for a future large RCT.

This is a repeated measures study so mixed effects linear regression modelling will be used to assess the effect of the intervention on continuous, approximately normally distributed outcome measures (depression, anxiety and stress scores, and inflammation levels). Stratification variables (gender, age group and baseline depression level) will be controlled for in the analyses. In addition, a logistic mixed effects model will be used to assess the effect of the intervention on clinical remission (binary outcome, defined as DASS less than 10). We will conduct intention to treat analysis as well as per protocol analysis. Finally, the proportions lost to follow-up will be reported and compared between groups.

In terms of the qualitative data, focus groups will be audio-recorded, transcribed and analyzed using thematic analysis, a widely used and flexible qualitative research method for identification, analysis and reporting of key themes and patterns within the data [35]. An inductive thematic analysis approach will be used, as it fits our aim of exploring AYAs experiences of MBCT group and novelty of the topic being investigated. The data will be analysed iteratively and inductively until coherent and distinct themes develop, and thematic saturation is achieved, as indicated by no new codes and themes emerging.

Safety Considerations

There have been no reports of significant adverse side effects of MBCT in literature with a recent meta-analysis which canvassed all completed MBCT studies for adverse events confirming that no

MBCT-related adverse events were reported[26]. Safety reporting will be done in keeping with Good Clinical Practice guidelines including the reporting of all adverse events and serious adverse events (SAEs), both related and unrelated to the study, throughout the study duration. Participants will be screened and carefully selected for their suitability for the program. They will be asked about any perceived adverse events, whether or not these may be related to the mindfulness intervention, and this information recorded in the trial database.

All serious adverse events will be reported within 24 hours to the Mater and UQ HRECs. All aspects of safety, recruitment and quality control of the data will be monitored by the Mater and UQ HRECs and there will be no separate Data Safety and Monitoring Board involved. Participants will continue to receive standard medical and psychosocial care both during and after the conclusion of the trial.

Sample size calculation

Based on researcher experience, we expect 64 patients to be available to participate in the study, with a drop-out rate of 15%. This sample size provides 80% power to identify large (Cohen's D = 0.8) effects. However, given the effects sizes variability for mindfulness studies, we have decided to run this study as a pilot RCT to assess the intervention's feasibility and effectiveness, as well as provide data for establishing sample size for a definitive large RCT. The proposed sample size is in keeping with guidelines which recommend a sample size of at least 40 for pilot studies and for effectiveness studies, 30 participants per arm of the study [35].

Outcomes

All outcome tools chosen for the study are valid, reliable and routinely used in the setting of IBD and chronic illness. The primary outcome measure will be the depression subscale score from the Depression, Anxiety and Stress Scale (DASS) [36].

Depression, Anxiety and Stress Scale (DASS) is a self-report instrument comprising of three scales designed to measure three negative emotional sates of depression, anxiety and stress. All three scales of the DASS have been shown to have high internal consistency and meaningful discriminations in a variety of clinical and research settings. The short version, DASS 21, will be used in the study as it has shown comparable validity to the long version and it will pose lesser burden to complete it for the participants.

Secondary outcomes will include anxiety and stress scores on DASS, coping patterns on COPE, IBD related quality of life (SIBDQ,10), posttraumatic growth scores on PTGI, mindfulness (FFMQ), medication adherence, self-efficacy and healthcare empowerment (MAQ, SEAMS, HCEI), illness knowledge and perception (CCKNOW, IPQ). Short Inflammatory Bowel Disease Quality of Life questionnaire(SIBDQ) is a 10-item-questionaire which is a validated and reliable instrument for

assessing health related quality of life in IBD patients [37]. Posttraumatic Growth Index (PTGI) is a 21-item-questionnaire measuring growth and positive changes following traumatic events [38], and it has been identified as a validated screening tool in individuals with IBD [39]. The Five Facet Mindfulness Questionnaire (FFMQ) is a validated screening tool assessing mindfulness as a multifaceted construct [40] . The Crohn's and Colitis Knowledge Score (CCKNOW), Brief Illness Perception Questionnaire (Brief IPQ) and Brief COPE are short, validated questionnaires for assessing illness knowledge, perception and coping, commonly used in clinical practice and research in IBD population [41-43] . Morisky 4-Item Medication Adherence Questionnaire (MAQ), Self-efficacy for Appropriate Medication Use Scale (SEAMS) and Health Care Empowerment Inventory (HCEI) are also brief, validated and reliable self-report questionnaires used to assess medication adherence, self-efficacy, and healthcare empowerment, in IBD population [44-46] .

Secondary outcomes will also include IBD disease activity questionnaires (SCAI, HBI), biological markers of inflammation, both systemic (CRP, ESR, IL-6) and IBD-specific (faecal calprotectin, small intestinal ultrasound), microbiome analysis as it reflects IBD activity, and neuroconnectivity changes (fMRIs). We are measuring inflammation markers and neuroconnectivity as research has shown that mindfulness practices can attenuate inflammation and improve neuroconnectivity, and changes in these parameters combined with changes in psychological outcomes could contribute to explaining mindfulness mechanism of action.

Patient and public involvement

Patients' views informed the study design and they were obtained during the study conception from Mater Consumer Youth Consultancy Group members who provided feedback regarding the study. Participants' group experiences and burden of the intervention will be assessed through focus group interviews and informal feedback. Patients will not be involved in recruitment and conduct of the study. Results from this study will be disseminated to each participant as a lay summary of the findings and through presentations at consumer consultancy forums.

Discussion

This study is the first RCT of a mindfulness-based intervention in AYAs with IBD and depression, a vulnerable group of young patients with a high burden of IBD and significant long-term impairments in multiple areas of functioning. In keeping with research evidence of larger treatment effect of MBCT in individuals with significant baseline depressive symptoms, the study will recruit participants with clinical diagnosis of depression.

The study will be using an adapted MBCT program for AYAs with IBD which, if proven feasible, may become integrated into the early intervention pathways for IBD. The intervention could contribute to altering disease progression, reduce disabling symptoms, and improve long-term outcomes in this group of patients.

The study will explore feasibility of the adapted MBCT program by recording sessions attendance, completion rates of home mindfulness practices, recruitment and attrition rates, as well as participants' MBCT group experiences assessed through focus groups. It will assess the effectiveness of the MBCT program by measuring its impact on various psychological and physical outcomes of IBD and depression, including biological markers of inflammation and brain connectivity. The study has the potential to validate this type of intervention, improve patient outcomes in young IBD sufferers and translate this approach to other chronic illness patient groups. The inclusion of biologic measures of disease activity and functional neuro-imaging will allow additional insights into the relationship between IBD and depression, and mindfulness' mechanism of action.

STUDY STATUS

The study was approved by the ethics committees of the Mater Hospital and The University of Queensland in June 2017. An amendment to the protocol was approved in January 2018 (version 3, date 18/01/2018), extending the upper age range to 29, and replacing the Hospital Anxiety and Depression Scale (HADS) with the PTGI. Additional amendment to protocol was approved in October 2018 (version 4, date 11/10/2018), removing the upper limit of the DASS from inclusion criteria. The study is currently in the recruitment stage, with completion expected by the end of 2019.

Authors' affiliations

1. Mater Young Adult Health Centre, Mater Health, South Brisbane, Queensland, Australia
2. Faculty of Medicine, University of Queensland, St Lucia, Brisbane, Queensland, Australia
3. School of Medicine, Griffith University, Gold Coast, Queensland, Australia
4. Mater Research Institute-UQ, Faculty of Medicine, University of Queensland, St Lucia, Brisbane, Queensland, Australia
5. Queensland Brain Institute, University of Queensland, St Lucia, Brisbane, Queensland, Australia
6. Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia
7. Mindfulness Training Institute Australia, Sydney, Australia
8. QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia
9. Princess Alexandra Hospital, Metro South Addiction and Mental Health Service, Brisbane, Queensland, Australia

Authors' Contributions

Study protocol was conceived and designed by TE and critically revised by SK, JB, MK, KH, KC and JBA. Drafting of the paper was completed by TE. All authors edited the manuscript.

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Competing interests

None

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Figure legends

Figure 1 CONSORT Extension for Pilot and Feasibility Trials Flow diagram showing the flow of the participants through the study

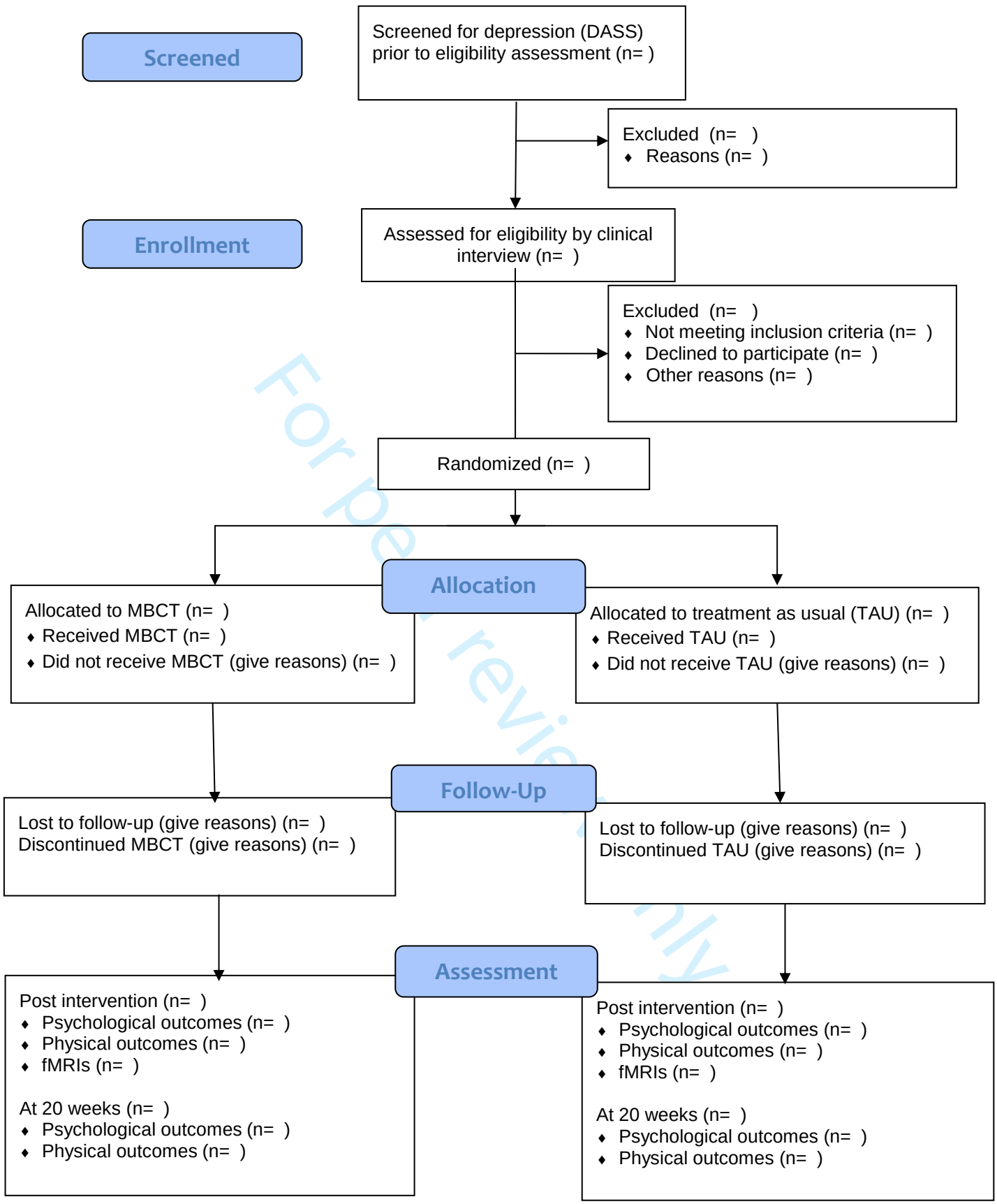

Figure 1 CONSORT Extension for Pilot and Feasibility Trials Flow diagram showing the flow of the participants through the study

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-11
Protocol version	#3	Date and version identifier	11
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	11

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-3,5
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3, 7-9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7-9

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5,8, fig.1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5,7,10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8-9
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8-9

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8-9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8-9
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8-9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8-9,11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5,8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8,10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8,10
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1,10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	1
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a