Adolescents and carers using mindfulness Therapy To END depression

WP3 RCT + WP4 Mechanisms
Protocol V1.3: 20.06.2024

Ethics Approval Date: XXX

1. TITLE PAGE

Title

Full title	**Is Mindfulness for Adolescents and Carers (MAC) plus treatment as usual (TAU) more effective and cost-effective compared to TAU alone; how does it work and for whom does it work best? A Randomised Controlled Trial (RCT) with embedded economic evaluation and study of mechanisms.**
Short title	**ATTEND: Adolescents and carers using mindfulness Therapy To END depression. WP3 RCT and WP4 Mechanisms.**

Research Reference Numbers

NIHR Portfolio number	NIHR204413
ISRCTN registration WP3+4	ISRCTNXXXX
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CPMS ID WP3+4	ATTEND RCT 59026
Linked applications reference numbers	
WP2 SLaM CAMHS Clinical Audit Approval	TBC
WP2 Cambridge Psychology REC No.	TBC
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CPMS ID WP5	ATTEND Implementation 58950

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Trial Sites

Pilot	
1	East of England
2	London
3	Devon
4	Sussex
+ Full Trial	
5	Oxford
6	Nottingham

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Programme Co-ordination

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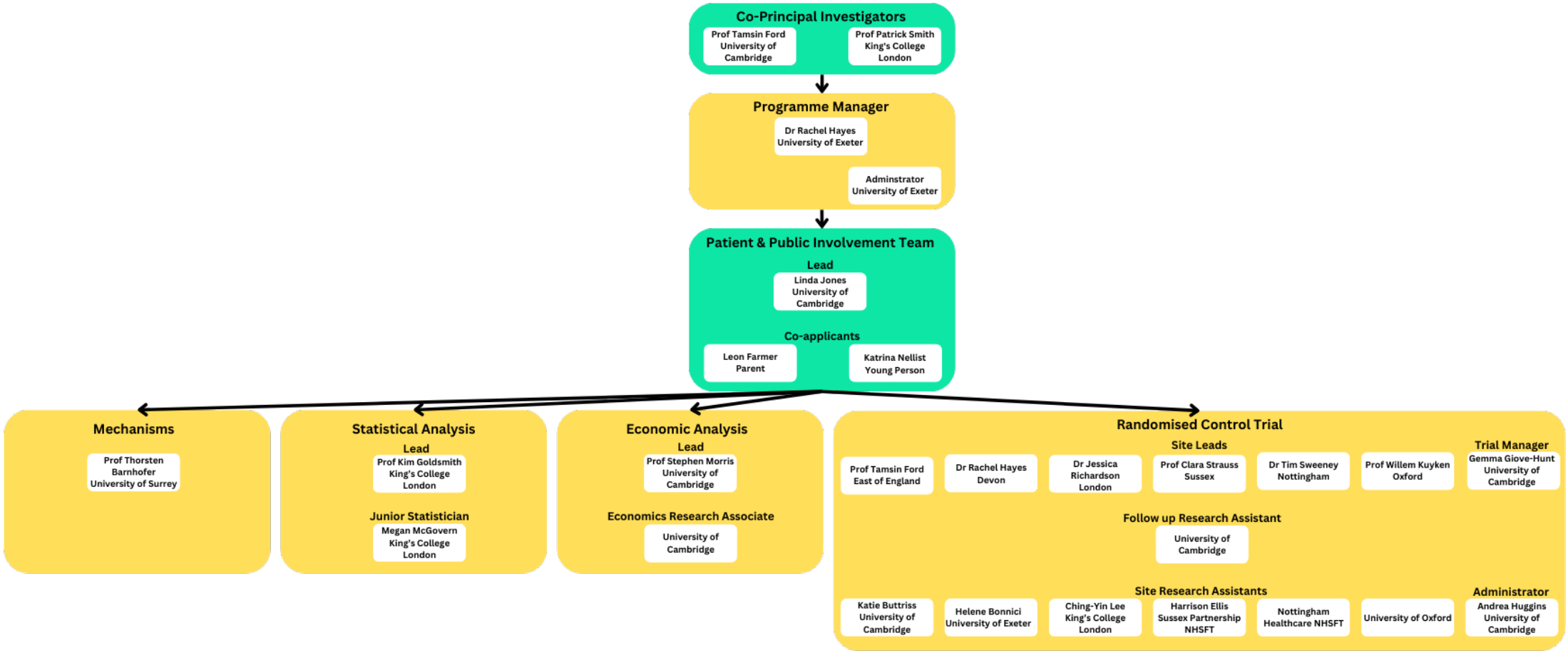
Figure 1: WP3 + 4 Organisation Chart



2. SIGNATURE PAGE

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

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

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

	Name	Position	Signature	Date
Trial Sponsor	Stephen Kelleher	CPFT Senior R&D Manager		
Chief Investigators	Tamsin Ford	Professor of Child and Adolescent Psychiatry		
	Patrick Smith	Reader in Clinical Psychology		

General Information This protocol describes the ATTEND programme and provides information about the procedures for entering participants into the trial. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance to the Programme Manager Dr Rachel Hayes (R.A.Hayes@exeter.ac.uk).

3. CONTENTS PAGE

4. LIST OF ABBREVIATIONS + DEFINITIONS

BPI	Brief Psychosocial Intervention
CACE	Complier Average Causal Effect analysis
CAMHS	Child and Adolescent Mental Health Services (NHS)
CAPA	Choice and Partnership Approach
CBT	Cognitive Behavioural Therapy
CC	Care Co-ordinators
CPFT	Cambridgeshire and Peterborough Foundation Trust
CRATE	Clinical Records Anonymisation and Text Extraction
CRIS	Clinical Record Interactive Search
DMEC	Data Monitoring and Ethics Committee
DPT	Devon Partnership Trust
Dyads	Parent/Carer-child pair
HRQL	Health-related quality of life
IPT	Interpersonal Psychotherapy
KCTU	King's College London Clinical Trials Unit
MAC	Mindfulness for Adolescents and Carers intervention
MBCT	Mindfulness-Based Cognitive Therapy
MBIs	Mindfulness-Based Interventions
MHST	Mental Health Support Teams
MYRIAD	MY Resilience In ADolescence
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
P/C	Parent/Carers
PDG	Programme Development Grant (NIHR)
PGfAR	Programme Grant for Applied Research (NIHR)
PPIE	Patient and Public Involvement and Engagement
QALYs	Quality-adjusted life years
RCT	Randomised Control Trial
SLaM	South London and Maudsley Trust
TAU	Treatment As Usual
TRS	Treatment Recording Sheet
TSC	Trial Steering Commitee
WP	Work Package
YP	Young People

5. STUDY SUMMARY

Table 1: Study Summary

Programme title	ATTEND: Adolescents and carers using mindfulness Therapy To END depression.
Work Packages full title	Is Mindfulness for Adolescents and Carers (MAC) plus treatment as usual (TAU) more effective and cost-effective compared to TAU alone; how does it work and for whom does it work best? A Randomised Controlled Trial (RCT) with embedded economic evaluation and study of mechanisms.
Funder and ref.	National Institute for Health Research, Programme Grant for Applied Research (NIHR PGfAR): **NIHR204413**
Programme co-sponsors	Cambridge and Peterborough NHS Foundation Trust University of Cambridge
Programme rationale	The prevalence of depression among adolescents is high and has increased over the last 20 years (Sadler et al., 2017)(Sadler et al., 2017). Depression is associated with significant distress and impairment in adolescence, including school failure, self-harm, and substance misuse; and adolescent depression predicts worse mental and physical health outcomes, and occupational functioning (Costello & Maughan, 2015)(Costello & Maughan, 2015). Current treatments for adolescent depression show modest effect (Costello & Maughan, 2015)(Costello & Maughan, 2015). This is problematic because treatment non-response and residual symptoms strongly predict recurrent depression (Costello & Maughan, 2015)(Costello & Maughan, 2015), while each depressive episode increases the risk of subsequent recurrence (Costello & Maughan, 2015; Weisz et al., 2017)(Costello & Maughan, 2015; Weisz et al., 2017). Effective methods to treat residual symptoms and prevent relapse are therefore critical (Mehta et al., 2014; Mental Health Taskforce, 2016; Weisz et al., 2017)critical (Mehta et al., 2014; Mental Health Taskforce, 2016; Weisz et al., 2017). Among adults, Mindfulness Based Cognitive Therapy (MBCT) is a NICE-recommended treatment for recurrent depression (Kuyken et al., 2016)(Kuyken et al., 2016). A similar mindfulness-based intervention could be efficacious for depressed adolescents, but we currently lack evidence (Dunning et al., 2022)(Dunning et al., 2022). We have adapted MBCT specifically for adolescents with depression. Key features of our MAC intervention include theory-driven targeting of maintenance factors and a parallel intervention for carers. This protocol relates to Work Packages 3 and 4 of an NIHR funded Programme Grant for Applied Research (PGfAR) and comprises of an RCT to test the effectiveness of MAC, with an embedded economic evaluation to explore the cost effectiveness of MAC and costs beyond the lifetime of the study, as well as a mechanism study to understand how MAC works and who is most likely to benefit from MAC.
Programme aims	The PGfAR has two distinct components that address development and evaluation respectively. To reduce the potential influence of MAC developers on evaluation (Parsons et al., 2017)(Parsons et al., 2017), the programme is co-led by Smith (WPs 1 & 2) and Ford (WPs 3, 4 & 5), supported by universal Programme Manager (Hayes). This protocol relates to two work packages (WP3+4) out of a total of five work packages (WP) and an

	embedded PPIE stream, which combined form the larger ATTEND Programme Grant for Applied Research. Each WP addresses distinct but with interconnected objectives: • **WP1 Training:** Improve our training programme for MAC therapists. • **WP2 App:** Co-produce two apps that can encourage and support mindfulness practice as well as provide a mechanism for teenagers to record their mood more frequently in real time. • **WP3 RCT:** Test whether MAC works to reduce symptoms of depression in teenagers by comparing the outcomes of teenagers who receive MAC with those who don't. We also want to find out if MAC is value for money by comparing the costs of services that young people and carers access. • **WP4 Mechanisms:** Find out how MAC might work and for whom it works best by exploring characteristics related to outcome and changes in how teenagers think and relate to others after receiving MAC. • **WP5 Implementation:** Understand how best we can start using MAC across the country should it be effective. • **Embedded PPIE:** Co-applicants with lived experience of MAC and the PPIE lead will convene several user involvement groups which will support all five of the work packages.
RCT + Mechanisms study design	Our PGfAR will refine, evaluate, and optimise implementation of MAC for young people and their carers using cutting edge efficient methodologies by drawing on a hybrid effectiveness implementation trial design and advanced modelling methods that aim to address the following question: **Could MAC improve recovery among 15–18-year-olds with low mood or depression who fail to completely respond to first line treatment or relapse rapidly?** **WP3 comprises a two-arm, pragmatic, parallel-group, superiority, individually randomised controlled hybrid type I clinical and cost-effectiveness trial** of MAC plus Treatment as Usual (TAU) versus TAU alone, among N=480 15–18-year-olds who have received a previous evidence-based intervention for depression or anxiety, and who continue to experience significant symptoms of low mood or have relapsed. Our focus in this protocol is to test the effectiveness of MAC as an intervention. This does not include the therapist training (WP1), the App for home practice (WP2), or the different care pathways or implementation (WP5), which have their own protocols and ethics where applicable. Our **economic analysis** will evaluate the cost and cost-effectiveness of MAC plus TAU compared to TAU alone from NHS/personal social services, education, and societal perspectives. **WP4 Mechanisms:** In line with guidelines on evaluation of complex interventions (Skivington et al., 2021)(Skivington et al., 2021), we will investigate treatment moderators and mediators. This WP aims to provide a more nuanced understanding of: • who is likely to benefit, • how change is achieved, and • how mechanisms of change are best facilitated.
Number of sites	Seven sites across England; six physical and one virtual. 1) East of England 2) London 3) Devon 4) Sussex 5) Oxford

	6) Nottingham 7) Remote site
Sample size	480 young person/carer dyads. 240 per arm: MAC + TAU vs TAU
Participant inclusion criteria	**Young People Inclusion** • Aged 15 to 18 years old at the time of recruitment. • Completed at least one evidence-based treatment for anxiety, low mood or depression. • Primary presenting problem of unresolved or relapsed low mood, depression, or anxiety who are currently experiencing some symptoms of low mood as evidenced by a score of 20 or above on the 33 item MFQ. • Readiness to engage in a group-based mindfulness-based intervention, which would include the ability to focus and participate in a group for up to 1 hour 45 minutes; capacity to think flexibly and reflect on one's own experiences; and the willingness to practice everyday mindfulness and learn formal meditation for up to 15 minutes per day. **Carer Inclusion** • A carer of a young person who has consented to take part in the study.
Participant exclusion criteria	**Young People Exclusion** • Current active management required for suicidal risk, self-harm or eating disorder. • A score of <20 on the MFQ33 • Current psychosis or PTSD. **Carer Exclusion** • A carer of a young person who has not consented to take part in the study.
Summary of trial intervention	**Mindfulness for Adolescents and their Carers (MAC)** MAC consists of eight, weekly, group-based sessions of between 1 hour 30 minutes and 1 hour 45 minutes duration after a pre-class orientation interview. Among adults, Mindfulness Based Cognitive Therapy (MBCT) is a NICE-recommended treatment for recurrent depression (Kuyken et al., 2016)(Kuyken et al., 2016). A similar mindfulness-based intervention could be efficacious for depressed adolescents, but we currently lack evidence (Dunning et al., 2022)(Dunning et al., 2022). We have adapted MBCT specifically for adolescents with depression. Key features of our intervention include theory-driven targeting of maintenance factors and a parallel group intervention for the young people's parents or carers.
Intervention duration	8 sessions over 8 weeks
Follow-up duration	Young people will also be invited to complete the short form (13 items) of the Moods and Feelings Questionnaire (SMFQ; (Angold et al., 1995)(Angold et al., 1995) fortnightly via a web-based outcome measurement system. Follow up data at 14 weeks and 12-months post-randomisation will also be completed (see **Figure 5**).
RCT duration	WP3 (RCT) + WP4 (Investigating patients' experience and testing moderators and mediators of treatment effects) will: • recruit from June 2024 to December 2025, • with the final cohort of 12-month follow-up assessments occurring in December 2026, • with an internal pilot and a Stop-Review-Go checkpoint in March 2025 (see **Figure 10**).

Outcome Measure

Primary Outcome: Short Moods and Feelings Questionnaire (SMFQ) (Angold et al., 1995)(Angold et al., 1995) completed at fortnightly intervals from randomisation until 12 months post randomisation.
We intend to estimate the difference in AUC by including an intervention arm by fortnight interaction term, allowing the extraction of fortnightly/follow-up visit intervention arm difference estimates, and then the calculation of the appropriate linear combination of these estimates (i.e. using the trapezium rule).
Other outcomes are listed in the summary table below, with full details provided in the main body of the protocol.

Construct	**Young People Completed**	**Parent/Carer Completed**	**Timepoint Data Collected**		
			T0: B/L	**T1:3.5m F/U**	**T2:12m F/U**
Eligibility					
PTSD screen	CRIES-8 (Perrin et al., 2005)(Perrin et al., 2005)		At intake assessment		
Current low mood	33 item MFQ (COSTELLO & ANGOLD, 1988; Daviss et al., 2006)		At intake assessment		
Baseline Outcomes					
Current depression and anxiety severity	RCADS 25 (Ebesutani et al., 2012)(Ebesutani et al., 2012)		X		
Past trauma and adversity	YCAS (Schlechter et al., 2021)(Schlechter et al., 2021)	YCAS (Schlechter et al., 2021)(Schlechter et al., 2021)	X		
Respondent Background		**Own and child's** Race/ethnicity, family, current living situation[c] **Child's** DOB, gender, current medication for anxiety or depression, past treatment for depression and anxiety[c] **Own** occupation, personal history of depression, education background	X		

	Site option	Face-to-face or remote		X		
	Primary outcome					
	YP Depression	SMFQ (Angold et al., 1995)(Angold et al., 1995)		Repeated at 2 weekly intervals throughout follow-up		
	Secondary outcomes					
	P/C Depression		PHQ-8 (Kroenke et al., 2009a)(Kroenke et al., 2009a)	Repeated at 2 weekly intervals throughout follow-up		
	YP Depression	33 item MFQ (Costello & Angold, 1988; Daviss et al., 2006)		X	X	X
	Anxiety	RCADS 25 (Ebesutani et al., 2012)(Ebesutani et al., 2012)	GAD-7 (Spitzer et al., 2006)(Spitzer et al., 2006)	X	X	X
	Quality of Life[a]	EQ-5D-5L (Devlin et al., 2018a)(Devlin et al., 2018a)	EQ-5D-5L (Devlin et al., 2018a)(Devlin et al., 2018a)	X	X	X
	Coping	1 bespoke question	1 bespoke question	X	X	X
	Parent – young people relationship quality[b]	PARS (Burke et al., 2021)(Burke et al., 2021)	PARS (Burke et al., 2021)(Burke et al., 2021)	X	X	X
	Health Economics Measures					
	Services and personal costs		**Child's** resource use bespoke questionnaire[c]	X	X	X
	Quality of Life[a]	EQ-5D-5L (Devlin et al., 2018a)(Devlin et al., 2018a)	EQ-5D-5L (Devlin et al., 2018a)	X	X	X
	Mediators					
	Decentring and wider mindfulness	CHIME-A (C. Johnson et al., 2017)	CHIME-S (Karl et al., 2024)	X	X	X
	Self-Compassion	SCS-SF (Raes et al., 2011)	SCS-SF (Raes et al., 2011)	X	X	X
	Emotion Regulation	ERQ (Gross & John, 2003)	ERQ (Gross & John, 2003)	X	X	X
	Rumination	Rumination sub-scale of CRSQ	Brooding and Reflection sub-	X	X	X

		(Abela et al., 2002)	scales of RSS (Treynor et al., 2003)			
	Parent – young people relationship quality[b]	PARS (Burke et al., 2021)	PARS (Burke et al., 2021)	X	X	X
	Experience of MAC	Qualitative interviews with a sub-set of MAC participants				X
	Type and duration of mindfulness practice	Weekly records of mindfulness practice (MAC arm only)	Weekly records of mindfulness practice (MAC arm only)			
		Bespoke question about recent meditation practice	Bespoke question about recent meditation practice	X	X	X
	[a] Quality of life is both a secondary outcome and used in the health economic analysis. **[b] PARS is both a secondary outcome and a mediator.** [c] In situations where a parent/carer does not consent to their own involvement in the study, we would ask the young person to complete the information about their background, service and personal cost use.					
Expected impacts	Impacts include knowledge generation and tangible outputs, such as MAC and the MAC training curriculum, two Apps (one for young people, one for parents/carers), MAC implementation plan and toolkit, and specifically for WP3+4, RCT data linked to administrative health and education data that would support longer term follow up. We will mobilise knowledge with our lived experience team via social media, podcasts, and blogs modified to suit the needs and interests of different stakeholders including service-users and practitioners.					

6. PLAIN ENGLISH SUMMARY

Background:

In the UK about 140,000 15–19-year-olds experience depression. An estimated 35,000 young people access NHS treatment for depression, of which,

- about 14,000 do not respond.
- A further 8,000 are likely to experience depression again after initial successful treatment.

Teenagers who still have symptoms after treatment for low mood, depression or anxiety, or who relapse quickly, need more treatment options.

These young people have a high risk of substance-misuse, self-harm, school, or relationship difficulty, as well as poor adult mental and physical health. Parenting a teenager with depression is stressful and can damage family relationships. Teenagers whose parents have depression are more likely to develop mental health problems in adulthood.

Mindfulness-Based Cognitive-Therapy (MBCT) combines training in mindfulness meditation with principles from cognitive therapy. It teaches skills to recognise early warning signs of depression, avoid repetitive thinking patterns that make depression more likely, and respond in ways that protect mental health. Although MBCT is recommended for adults who have experienced three or more depressive episodes, MBCT for teenagers is relatively untested.

We developed Mindfulness for Adolescents and Carers (MAC) as a version of MBCT adapted to be more engaging for teenagers. MAC aims to help teenagers recover from depression and the parallel parent/carer group aims to support parents and carers to cope better.

Aims:
We want to see if MAC supports recovery and prevents relapse amongst 15-18-year-olds who risk developing recurrent depression as adults.

Methods:
Our research has work packages as follows:

1. Finalise our therapist-training programme.
2. Co-produce two Apps to encourage and measure mindfulness practice.
3. a) Recruit 480 teenagers, and their parents/carers will be invited too. Half will access MAC and half will access the standard NHS treatment currently available. This will allow us to compare the differences between the two groups on depression and other outcomes.
   b) Compare the two group's treatment costs, with their symptoms 9 months after treatment, to assess whether MAC is value for money.
4. Find out how MAC works and who benefits the most by exploring changes in how teenagers and parents feel, think, and relate to each other.
5. Understand how best we can scale up MAC across the NHS.

This protocol refers to work packages 3 and 4 only.

Public and Patient Involvement and Engagement (PPIE):

- Young people and parents with experience of MBCT designed the MAC materials and helped to design our research.
- Two co-applicants with lived experience and our PPIE lead will coordinate PPIE throughout the Programme.
- We will recruit 3-4 young people to join them as well as establishing the Research Advisory Groups of young people and parents.
- Each part of the programme will have dedicated support from 4 young people with lived experience.

Dissemination:
We will share our findings with different audiences. Examples will include blogs, podcasts, videos, social media, websites, and both self-help and professional networks.

7. PATIENT AND PUBLIC INVOLVEMENT

Farmer and Nellist were co-applicants on the Programme Development Grant (PDG) and core members of the PDG project team, attending monthly meetings to discuss progress and future development. They have met with the research team intermittently over a period of six years and have been integral in the

development of the manual for MAC and all our feasibility studies. They have assisted and advised on who should be referred into the groups and how they should be approached, how the study should be explained, what are the most important outcomes to measure, which questionnaires ask the most appropriate questions and what is the most appropriate comparator.

In addition, we sought advice about the PDG from CAMHS advisory groups at the Institute of Psychiatry, Psychology and Neuroscience and South London and Maudsley NHS Trust as well as our Devon based advisory group to broaden the diversity of our advisers. These sessions focused on adaptations to MAC in relation to remote working and whether these should remain in the trial, and a discussion of our findings and next steps.

Jones became involved in this application at Stage 1 of the current application. She has supported Farmer and Nellist in developing the PPIE programme of work. Nellist and Farmer have attended the programme development meetings and actively contributed to decisions about study design well as writing the PPIE sections of the application.

Jones, Farmer, and Nellist will form the core PPIE leadership group. Each WP has a clearly defined PPIE element and representative lead. Jones will co-ordinate and support all the PPIE work and representatives, and a formal communication plan created. Work package leads will also be responsible for updating the core team and PPIE will be a standing item on monthly whole team meetings.

We are recruiting to two diverse Research Advisory Groups (RAG) of experts by experience, one composed of parents or carers and one of young people in the age range 14 to 18. They will advise researchers on approaching potential participants and be involved with core group training, interpretation of results, dissemination advice, and coproduction of dissemination materials. We intend to over recruit to the RAGs, aiming to have a rolling membership of 12 people in each RAG, so that people with lived experience can vary the extent of their commitment over the research programme as the other demands on their time and availability vary. We realise that people are busy, and their circumstances will change during the Programme and want to be able to accommodate this whilst ensuring continuity of PPIE activities. Fluctuating availability is particularly an issue for young people, who are likely to face public examinations and major transitions, such as leaving home for college or work over the course of the programme.

All PPIE time and travel expenses for face-to-face meetings have been costed. Recruitment will be through multimedia (both online and offline methods), as well as through our clinicians, such as previous MBCT groups attendance, CAMHS, or through local contacts. The PPIE Lead will give full support and will arrange any individual's needs (accessibility, training etc). Examples include 'zoom' practice calls and glossary/dictionary provision. Private computers in a local library can be booked for those not able to meet from home.

8. BACKGROUND

The problem

The prevalence of depression among young people increased during the previous two decades (Sadler et al., 2017) with further evidence of deterioration in young people's mental health in the UK since the onset of the Covid-19 pandemic (Newlove-Delgado et al., 2021). Prevalence estimates vary depending on the age, population, and methods used, the time- period studied, and impairment criteria applied. A pre-pandemic meta-analysis of 41 studies in 27 countries suggests that the world-wide prevalence of depression was 1.7 to

3.9% (Polanczyk et al., 2015) among children and young people under the age of 18 years, while a 2021 meta-analysis of 29 studies from 11 countries provides an alarming estimate of 21.2 to 29.7% in the same age group (Racine et al., 2021). In the latter study, prevalence estimates were higher in data collected later in the pandemic, as well as among girls and older teenagers. Mental health conditions cost the UK economy almost £18 billion per year in 2019/2020, emphasising the potential of prevention (Mcdaid et al., 2022).

Young people who function poorly in their mid-to-late-teens pay a heavy developmental price as education, occupation and child-bearing related decisions during these years can drastically alter life trajectory. In this developmental period, young people often develop attitudes and habits in relation to diet, exercise, sexual activity, and substance use that profoundly influence future health (Sawyer et al., 2012). Depression in adolescence predicts school-failure, substance-misuse, self-harm, and poorer occupational function, as well as poorer adult mental and physical health, particularly among young people who experience repeated episodes (Costello & Maughan, 2015). Insufficient treatment response significantly increases the risk of relapse (Costello & Maughan, 2015; Weisz et al., 2017), while between 34% and 75% of young people relapse within five years. Each depressive episode also increases the risk of subsequent recurrence (Costello & Maughan, 2015).

Mental health interventions for young people are underexplored, particularly for anxiety and depression, which has become a major focus of research funders (Dubicka & Bullock, 2017; Mental Health Taskforce, 2016). Treatment non-response and residual symptoms strongly predict recurrent depression among young people, yet current evidence on relapse prevention has been researched mostly following full initial recovery (Cox et al., 2012; Kennard et al., 2009). The Cochrane review of relapse prevention in young people reported that medication reduced the proportion who relapsed from two-thirds to 40% (Kennard et al., 2009), while psychological approaches were less frequently studied and showed similarly modest effects.

Effective methods to treat residual symptoms and prevent relapse are therefore critical, which is why they are listed among the top 10 priorities for depression research according to the James Lind Alliance (Mehta et al., 2014; Mental Health Taskforce, 2016; Weisz et al., 2017). In addition to the alleviation of psychological distress to young people and their families, recovery and its maintenance during adolescence could improve educational, occupational, and social outcomes as well as their health in adulthood. Furthermore, our feasibility work suggests potential "spillover" effects on the mental health of parents, with potentially substantial cost-savings across all public sector services (Ford et al., 2020; Racey et al., 2018).

Existing evidence

A large body of evidence demonstrates that maladaptive responses to negative mood, such as rumination or worry, may be key mechanisms in the onset and maintenance of depressive symptoms (Schäfer et al., 2017). Analyses suggest that poor mental health relates to both a general psychopathology factor, best understood as a reflection of the extent of impairment or dysfunction in a person's life, and a bi-factor model, which includes an internalising psychopathology factor characterised by an increased propensity to respond to stress and negative mood with maladaptive repetitive thinking (Caspi et al., 2014; Farb et al., 2018). Such responses are likely to become increasingly automatic and habitual with recurrent exposure to symptoms of depression and may drive relapse. Interventions that improve the young person's ability to respond adaptively to stress and negative mood may thus be key to fostering recovery, although there is little research into mechanisms in this age-group.

Mindfulness-based Cognitive Therapy (MBCT) is a NICE-recommended treatment for recurrent depression in adults (Kuyken et al., 2016). It was designed to prevent depressive relapse by reducing unhelpful ways of reacting to stress and negative mood, including maladaptive patterns of repetitive thinking; it comprises an

8-week group-based programme that combines mindfulness practice with cognitive behavioural elements (Kuyken et al., 2016). MBCT aims to teach people to recognise these patterns and to respond in more adaptive ways. There is now a substantial body of evidence for its effectiveness and cost-effectiveness in relapse prevention for depression among adults (Kuyken et al., 2016); with evidence suggesting that the preventative effects of the intervention are increased among people who are suffering from residual symptoms. Importantly, research shows that the utilisation of core skills is maintained, and often increases, after the completion of MBCT, which suggests a lasting potential for buffering responses to negative mood and stress (Farb et al., 2018).

There is an increasing interest in MBIs for children and young people, although enthusiasm is running ahead of the evidence (Dunning et al., 2022). A recent meta-analysis of 68 randomised controlled trials of universal and targeted Mindfulness-based Interventions (MBIs) with under- 19s reported tentative evidence for improved anxiety/stress and social behaviour, but also considerable heterogeneity in interventions, populations and outcomes, plus moderate risk of bias (Dunning et al., 2022). Moreover, the 23 trials that tested MBIs as a targeted or indicated intervention were small, included heterogeneous conditions, and failed to follow-up beyond the intervention. MYRIAD, the largest and most rigorous included study, reported that a universal school-based didactic curriculum delivered to 12- to 15-year-olds did not prevent depression or improve well-being but did improve school climate and reduce teacher burnout (Kuyken et al., 2022). Exploratory subgroup analysis suggested that older teenagers, those practising mindfulness skills and those taught by the most competent teachers may have derived benefit and the investigators recommended that future research should explore indicated MBCT with young people who choose to engage (Montero-Marin et al., 2022). The investigators also suggested that future research would need to consider in more detail the impact of contextual and implementation factors on programme outcomes (Kuyken et al., 2022).

Adaptation of MBCT for young people needs to accommodate the contributing factors specific to adolescent mental health in order to optimise treatment response. How young people cope is strongly influenced by their family context for many reasons; indeed, we have demonstrated a bi-directional relationship over time for depression between parents and children (K. Wilkinson et al., 2021). Given the evidence for intergenerational transmission of depression (Hammen et al., 2012), working with both parents and adolescents may amplify the effectiveness and cost-effectiveness of an intervention to support recovery from depression among those vulnerable to recurrent episodes.

Drawing on the above evidence and theory, we have developed and piloted the MAC programme for young people who have completed a first line psychological intervention for depression or anxiety within CAMHS with a parallel version of the intervention for carers. In our feasibility work, more than half the attending carers had a personal history of depression, and approximately a quarter of whom were taking antidepressants (Racey et al., 2018). Parent involvement was strongly endorsed by young people, carers, and the referring clinicians and, although primarily designed to support young people's mindfulness practice, given its association with treatment response (C. Crane et al., 2014), parents reported that the parallel group supported them through the emotional impact of caring for a child with poor mental health. Carers, as well as young people, reported statistically significant reductions in rumination and improvements in self-compassion and de-centring (Racey et al., 2018). A parallel group for carers would seem to be a particularly powerful approach to support recovery from depression among highly vulnerable young people who have relapsed or not responded fully to initial treatment, and for whom intergenerational transmission is likely to have played a significant role in their presentation. It may also improve carer mental health (K. Wilkinson et al., 2021).

As summarised above, we consulted Young People's Mental Health Advisory Groups in Exeter and London and gathered qualitative information from participating young people and carers during our PDG and feasibility work. We developed and delivered a training programme for CAMHS practitioners to teach MAC. Newly trained practitioners delivered MAC in our pilot trial: and we demonstrated acceptability and feasibility of MAC and the proposed research procedures. The Covid-19 disruption required remote MAC groups and revealed strong and disparate preferences for remote or face-to-face delivery, which we intend to explore further.

9. TRIAL OBJECTIVES AND PURPOSE

Purpose of research

This programme has huge potential impact for depression treatment in the NHS and is a non-commercial trial funded by the National Institute of Health Research as part of a PGfAR. In the short term, we anticipate that young people and their parents who access MAC will experience reduced psychological distress and improved function. In the longer term the prevention of future depressive episodes may profoundly improve young people's life chances, both in the UK and internationally. Effective implementation combined with potentially reduced depression among the parents and carers could significantly reduce the million referrals to IAPT for depression each year and the rapidly escalating prescriptions for antidepressants, particularly among young people and emerging adults (Heald et al., 2020). The burden of depression is enormous, while effective interventions potentially release substantial economic benefits with an estimated cost-benefit ratio of between three and five to one (Chisholm et al., 2016). Reduced number and frequency of depressive episodes among parents and young people in the longer term may release extensive cost savings related to improved productivity through reduced absenteeism, presenteeism and sickness benefit claims. Today's young people with residual symptoms or rapid relapse are tomorrow's adults with repeated depression and importantly, tomorrow's parents. Improving current and future parents' mental health may reduce the intergenerational transmission of depression.

Aims and objectives

The research aims to answer the following questions:

PGfAR WP3 RCT:

1) Is MAC plus TAU more effective in producing a sustained reduction of symptoms of depression in adolescents compared to TAU?
2) Is MAC plus TAU cost-effective compared to TAU?
3) Does MAC plus TAU impact the following secondary outcomes:
    a. For Young people:
        i. Anxiety
        ii. Quality of life
        iii. Ability to cope
        iv. Perceived quality of family relationship

    b. For Parent/Carers:
        i. Depression
        ii. Anxiety
        iii. Quality of life

iv. Ability to cope
v. Perceived quality of family relationship

PGfAR WP4 mechanisms:

4) What characteristics moderate the effect of MAC?
5) Does MAC work through its intended psychological mechanisms (such as increases in the ability to decentre and mindfulness skills)? And if yes, what are the exact pathways?
6) Do changes in process variables (such as decentring and mindfulness) transfer to influence outcome across the young person-carer dyad? If yes, what are the exact pathways?
7) Are outcomes of the MAC intervention related to the amount of mindfulness practice that participants engage in?
8) How is the learning from the trial intervention reflected in participants actual responses to negative mood (as assessed using second-person methods to analyse subjective reports)?
9) What are the experiences of young people and their carers with the intervention?

10. STUDY DESIGN

We will conduct a two-arm, pragmatic, parallel-group, superiority, individually randomised controlled hybrid type I clinical and cost-effectiveness trial of MAC and TAU versus TAU among 15–18-year-olds, with an internal pilot study involving only 4 of the 6 sites for the first year to ensure feasibility of recruitment.

The traditional research pipeline that encourages a staged approach to moving an intervention from efficacy trials to the real world can take a long time. To address this issue, hybrid effectiveness-implementation designs were codified to promote examination of both effectiveness and implementation outcomes within a study (Curran et al., 2012; Landes et al., 2019). This type 1 hybrid trial focuses primarily on clinical effectiveness outcomes of the intervention while exploring the "implementability" of the intervention (which is addressed in WP5's protocol).

Site selection

Pilot sites:

- Devon,
- Sussex,
- London,
- East of England.
- The remote option will recruit from all sites and run in parallel.

Full trial sites as above but including:

- Nottingham,
- Oxford.

Sites were chosen to reflect a range of environments from:

- **Culturally and ethnically diverse cities**. More than a third of Nottingham's population are from ethnic minorities, with large Black and Asian communities, while a quarter of people living in Oxford were born outside the UK according to 2021 census data. Our London site provides CAMHS and school-based

mental health support teams to Lambeth, Croydon, Lewisham, and Southwark, which are highly ethnically diverse.

- **The Levelling Up white paper** classes the Lewisham and Southwark as among the most "left behind" areas, as is Great Yarmouth in the East of England (Levelling Up the United Kingdom Executive Summary, n.d.). Indeed, the East Midlands and East of England cover areas with particularly high community needs, for example Fenland and Peterborough (OCSI, 2020) .
- **Rural and semi-rural areas** (Sussex, Devon, and East of England) face a different set of challenges with service access, while the latter two have the highest prevalence in England of depression in young people (Sadler et al., 2017).
- **Experience with MBI from established centres** vary among sites, from extensive experience of implementation (Oxford, London, Sussex), through to very limited experience (East of England).
- **Remote.** We will include people who prefer remote treatment from all six geographical sites and then randomise them to the different treatment arms. This opens the treatment to those who may struggle with face-to-face or otherwise choose not to join. Our PDG necessarily involved remote delivery as it ran during the Covid-19 Pandemic. Some young people and parents expressed a strong preference and our advisory groups recommended that we retain this option for the PGfAR. We will therefore deliver one remote group with each cohort, randomising those who express a preference for this mode of delivery from all the sites. Administratively, it will be treated as an additional site.

The pilot would commence in June 2024, involving each of the pilot sites delivering two MAC groups, one in the Autumn 2024 and one in the Spring 2025. Providing we meet the STOP/REVIEW/GO criteria in Spring 2025, the final two trial sites will open for recruitment and all six sites will deliver two MAC groups, one in Autumn 2025 and one in Spring 2026 (see Figure 11). The remote option will recruit from all sites and run in parallel.

11. PARTICIPANT SELECTION

MAC is a second-line clinical intervention, so recruitment and delivery will be from the most appropriate service for each local area:

- CAMHS,
- Mental Health Support Teams (MHSTs), including:
    - Educational Mental Health Practitioners (EMHPs),
    - Children's Wellbeing Practitioners,
    - Counsellors or nurses based in schools/school-based mental health teams,
    - Other community wellbeing teams.

Subject inclusion and exclusion criteria

Table 2: Inclusion and exclusion criteria with justification

Young Person Inclusion Criteria	Identifier	Justification
Aged 15 to 18 years old at the time of recruitment.	Research team.	We have increased the minimum age from 14 in the PDG. The mean age in our feasibility work was 16.4 years, and 14-year-olds were more likely to struggle to engage than their older peers (Racey et al., 2018). Similarly, the

		recently completed MY Resilience In ADolescence (MYRIAD) study suggests that older teenagers may be more likely to derive benefit (Montero-Marin et al., 2022). The upper age limit relates to the most common age boundary between most CAMHS and adult mental health services.
Completed at least one evidence-based treatment for anxiety or depression.	Referring clinician.	MAC is a second line treatment and should only be offered after one psychosocial treatment for depression or anxiety has been delivered.
Primary presenting problem of unresolved or relapsed low mood, depression or anxiety who are currently experiencing some symptoms of low mood as evidenced by a score of 20 or above on the 33 item MFQ (COSTELLO & ANGOLD, 1988; Daviss et al., 2006)	Research team.	Comorbidity with any of the problems in the Exclusion Criteria below would not necessarily exclude a young person provided their score at recruitment on the 33 item MFQ (COSTELLO & ANGOLD, 1988; Daviss et al., 2006) is 20 or above
Readiness to engage in a group-based mindfulness-based intervention. This includes the ability to focus and participate in a group for up to 1 hour 45 minutes; capacity to think flexibly and reflect on one's own experiences; and the willingness to practice everyday mindfulness and learn formal meditation for up to 15 minutes per day.	Referring clinician.	This is a requirement to be able to engage in the treatment.
Carer Inclusion Criteria: A carer of a young person who has consented to take part in the study.	Research team.	Young people will be included regardless of whether one or both carers wish to attend the parallel carer groups. Likewise, parents/carers would be able to continue to attend should the young person withdraw from the study.

Young Person Exclusion Criteria	**Identifier**	**Justification**
Current active management required for suicidal risk, self-harm or eating disorder.	Referring clinician.	Would struggle to engage with, and derive benefit from, a group-based MAC intervention from experience of feasibility and PDG.
Current psychosis.		
Current PTSD.	CRIES-8 administered by Research team.	
A score of <20 on the MFQ33	MFQ33 administered by Research team	MAC is designed to treat depression and low mood, therefore are using a cutoff score of 20 or above, as it is often used to indicate clinically significant depressive symptoms.
Carer Exclusion Criteria: A carer of a young person who has not consented to take part in the study.	Research team.	The parent group is primarily about supporting the young people's mindfulness practice.

Patient withdrawal/discontinuation from MAC

While we will encourage the young people and parent(s) to attend in tandem, it would be unethical to refuse a willing young person access to the study if their parent was unable or unwilling to attend with them. Likewise, while a parent or carer would only be recruited if their child was initially willing to attend because the parent group is primarily about supporting the young people's mindfulness practice, we would still encourage them to continue should their child withdraw from the trial. Outcome measures will still be taken regardless of any withdrawal from MAC, unless the young person/carer formally withdraws from the trial. More details in the later section COMPLIANCE AND WITHDRAWAL.

12. PARTICIPANT RECRUITMENT

Participant recruitment routes

1. The Clinical Team and the Clinical Research Network will identify potential participants by active screening of caseloads. Research Assistants in each site will provide support by answering any eligibility queries but will not have access to identifiable information.
2. Participants will also be recruited via practitioner referrals.
3. Any participants that contact the study email address directly via word-of-mouth or from seeing promotional materials will be asked to provide their name, date of birth, and the city/town they live in. The relevant site's Research Assistant with the local Clinical Team and Clinical Research Network will then screen their case notes for eligibility.
4. One method of recruitment will be via NHS Trust research databases, each approved and operated by the relevant NHS Trust. The database will be queried to find patients that are likely to meet the study's eligibility criteria. For patients that have specifically consented to the following (either in advance or having been approached by their primary clinical team), the Trust will provide the patient's details to the research team and authorize the research team to view the patient's records and to contact the patient to discuss participation in the study. Researchers will not be given identifiable information without the patient's specific consent. Study participation itself would require the patient's further consent.

Eligibility assessment

Before contacting potential participants, eligibility for inclusion is established by the referring clinician who will be provided with comprehensive details of participant inclusion and exclusion criteria. As well as this, we have produced a recruitment poster for the referring clinicians (**Appendix a**) as a brief, quick eligibility criteria guide and to remind them to refer participants. The only exceptions to this are the administration of the Child Revised Impact of Events Scale (CRIES-8) (Perrin et al., 2005) and the 33 item MFQ (COSTELLO & ANGOLD, 1988; Daviss et al., 2006), which will be administered by the Research Team during the intake assessment after permission to contact has been provided (**Figure 5**). Please see details further below.

Provision of PIS

Potential eligible participants that have been identified will be provided with a short, written summary (**Appendix b**) in the format of a printable or email leaflet from the referring clinician, local CRN support, or clinical care team which have recruited them. This information is also formatted as a poster, which we intend to put up in clinic and GP waiting rooms, school pin-boards, and other public places. It includes a QR code

which links to the study website, which holds the full Participant Information Sheet (**Appendix d**), should they independently want to find out more. We've also made this short summary available as a short information video (**Appendix c**), which we will request to play in clinic or GP waiting rooms if they have a TV screen, can email to potential participants, and share to social media to increase visibility of the trial. This has been written in consultation with the PPIE RAG. We also propose using a short information film solely produced by young people, summarising the study verbally using real people. At the time of writing this version of the protocol this second video has not been produced, and once it has, we will update the protocol with details of this.

Detail of enrolment procedure

1. If a young person expresses an interest in the study, the young person (aged 16 to 18) or parent/carer (for young person aged 15) will be asked to return a Permission to Contact Form (**Appendix e**) either directly to the study team or provide permission for the person who referred them to return it.
2. When a permission to contact form is received by the study team, a Research Assistant will contact the young person and parent/carer to explain more about the study and answer any questions.
3. If the young person is still interested, they will be sent the full Participant Information Sheet (PIS) (**Appendix d**) and the Privacy Notice (**Appendix n**), and a time will be arranged to complete an intake assessment.
4. During the intake assessment the study will be fully explained to the young person and their parent/carer before written informed consent is obtained by the Research Assistant via REDCap. The Research Assistant will also ask the young person to complete the CRIES-8 and MFQ screens. The CRIES-8 is a screening tool used to identify possible post-traumatic stress disorder. We have included this tool as it is not uncommon for clinicians to be unaware of traumatic events in a young person's life. It is necessary that young people are currently experiencing low mood and this will be assessed through the MFQ. All other exclusion criteria require other services to be involved, and therefore the referring clinician would be aware of these.

CRIES-8 (Perrin et al., 2005)
The Child Revised Impact of Events Scale CRIES-8; (Perrin et al., 2005) is a brief child-friendly measure designed to screen children at risk for posttraumatic stress disorder (PTSD) (Perrin et al., 2005). Each item is rated on a four-point scale (Not at all, Rarely, Sometimes, Often), scored 0, 1, 3, 5. The total score indicates the severity of a child's post-traumatic stress reactions with a range from 0 to 65. Perrin et al., 2005 reported Cronbach's alpha to be 0.80 for the total scale and 0.70, 0.73, and 0.60 for the intrusion, avoidance, and arousal subscales, respectively (Perrin et al., 2005). A score of 17 and above has been suggested as the most effective cut-off score for screening cases of PTSD (Perrin et al., 2005), and therefore any young people above this threshold would not be eligible to take part.

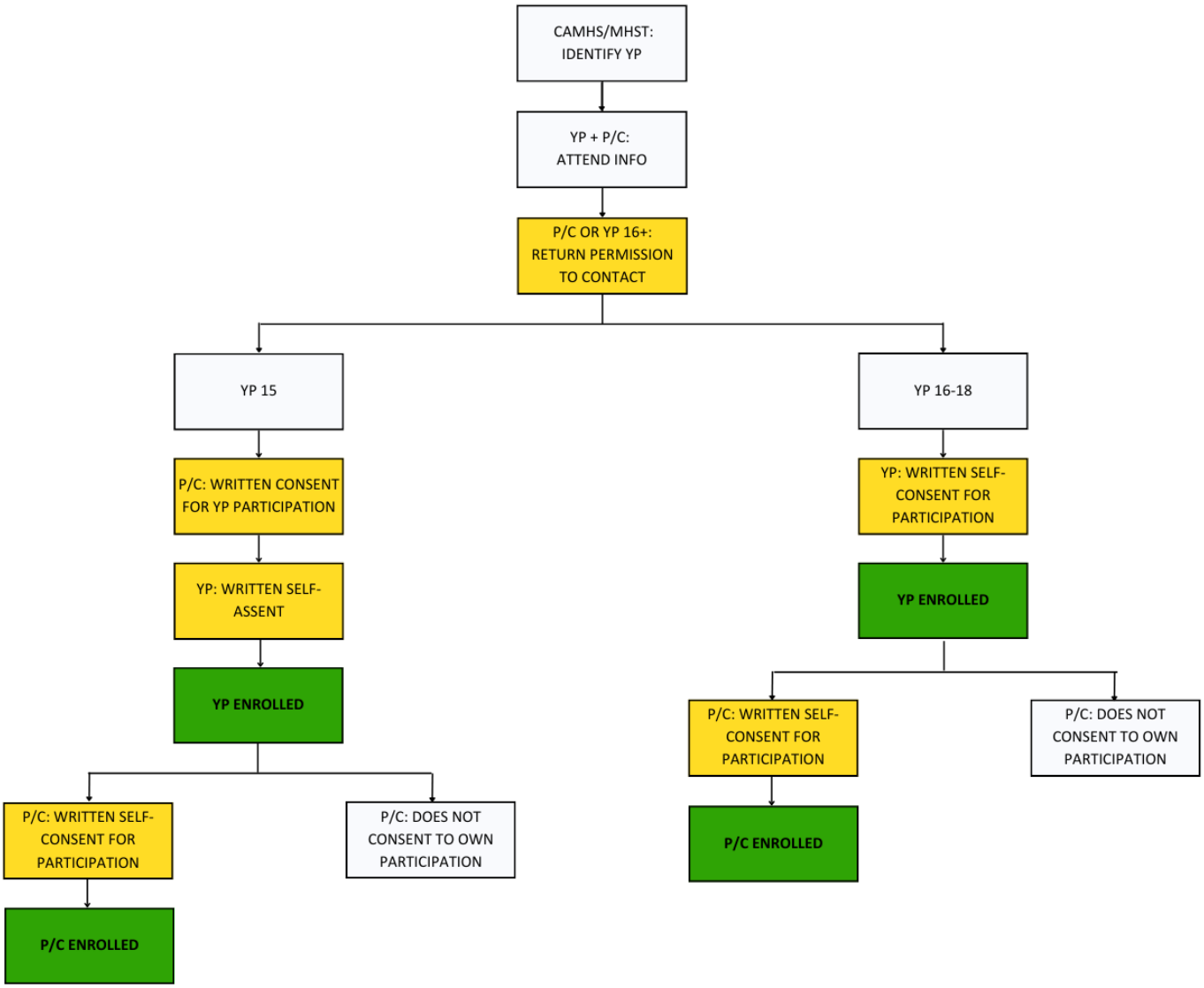
Moods and Feelings Questionnaire
The MFQ is a 33-item self-report scale designed to assess depressive symptoms in children and adolescents aged 8 to 18 years. It covers various domains of depression, including mood, anhedonia, and cognitive symptoms. Respondents rate each item based on how they have been feeling or acting recently, with choices ranging from 0 to 2. The total score ranges from 0 to 66, with higher scores indicating greater levels of depressive symptoms. A cutoff score of 20 or above is often used to indicate clinically significant depressive symptoms (Cooper & Goodyer, 1993). The MFQ has demonstrated good internal consistency (α = .89 to .95) and test-retest reliability (r = .79 to .91). Additionally, it has been shown to have good convergent and discriminant validity when compared with other measures of depression.

Gaining participant consent via REDCap

Informed written consent will be provided by parents or carers for their own participation (**Appendix f**), and that of their child if aged 15 (**Appendix g**). However, as many of the younger teenagers will be Gillick competent and because it is good practice, young people aged 15 will also be asked to provide informed written assent (**Appendix h**). As the trial length is 12 months, once 15-year-old participants reach 16 years of age during the study, we will ask them to provide informed written consent. Young people aged 16 to 18 will be able to provide informed written consent for their own participation without the need for parent/carer written consent (**Appendix i**).

While we will encourage the young person and their carer to both consent to the study, it would be unethical to refuse a willing young person access to the study if their carer was unable or unwilling to consent to their own involvement in the research study. If a young person aged 15 wishes to participate in the research study without the involvement of their carer, it will still be necessary for the carer to provide written consent that their child is able to enrol in the study. Parents/carers are only eligible for the study if their child enrols but can stay on if their child enrols then decides to not continue during the trial. **Figure 2** presents a schematic of the various routes for joining the trial.

Figure 2: Pathway to enrolment in the ATTEND RCT



Payment of participants

Both young people and parent/carers will be offered a small incentive for the completion of research measures as detailed in **Table 3**.

Table 3: Incentives offered to participants for the completion of Outcome Measures.

	Young person	**Carer**
Completion of Baseline Measures	£15	£15
Completion of Follow-up 1 Measures	£15	£15
At Follow-up 2: Completion of fortnightly measures	£15	£15
Completion of Follow-up 2 Measures	£15	£15
Total	**£60**	**£60**

13. THE INTERVENTION

Patients in the MAC arm will still access TAU, alongside the MAC intervention. However, our PDG indicated that YP in the MAC arm received less mental health intervention than those randomised to TAU (PDG Competition 25 Panel B Programme Development Grants Final Report Form Project Title A Combined Mindfulness-Based Approach for Adolescent Non-Responders to First-Line Treatments of Depression or Anxiety and Their Carers: Establishing Feasibility of Implementation and Delivery Reference Number NIHR201024 Contracting Organisation Cambridgeshire and Peterborough NHS Foundation Trust Approved Duration 12 Current Duration 16, n.d.), and we expect to find similar results during the current study.

Figure 3: Logic model for the mechanisms of actions of the MAC intervention.

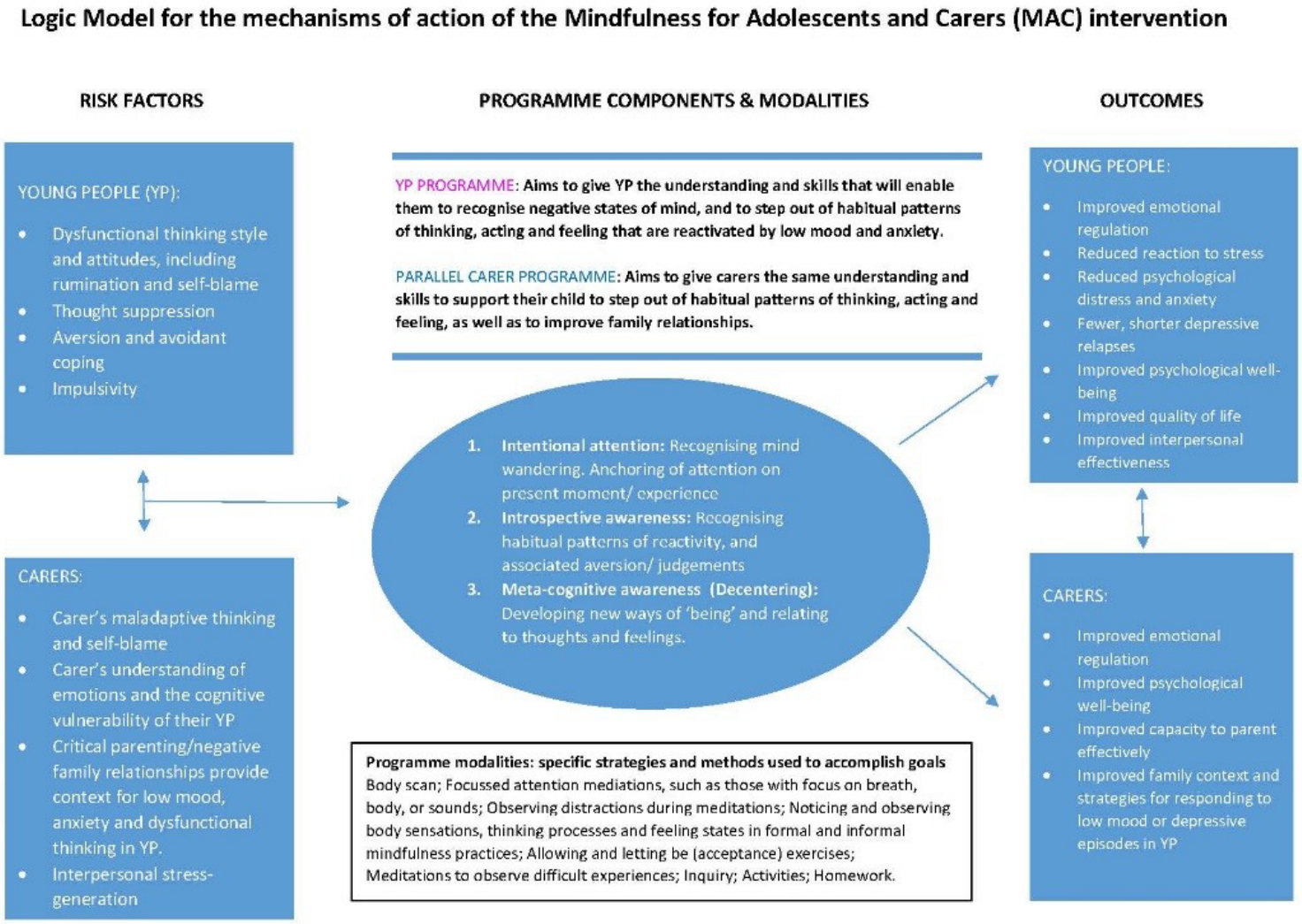


Table 4: TIDieR criteria to describe the Mindfulness intervention to be assessed in ATTEND

BRIEF NAME			
Mindfulness for Adolescents and their Carers (MAC)			
WHY			
Mindfulness-based cognitive therapy (MBCT) for adults was designed to prevent depressive relapse by reducing unhelpful ways of reacting to stress and negative mood, including maladaptive patterns of repetitive thinking; it comprises of an 8-week group-based programme that combines mindfulness practice with cognitive behavioural elements (Kuyken et al., 2016). MBCT aims to teach people to recognise these patterns and to respond in more adaptive ways. There is now a substantial body of evidence for its effectiveness and cost-effectiveness in relapse prevention for depression among adults (Goldberg et al., 2018; Kuyken et al., 2016); these meta-analyses suggest that the preventative effects of the intervention are increased among people who are suffering from residual symptoms. Importantly, research shows that the utilisation of core skills is maintained, and often increases, after the completion of MBCT, which suggests a lasting potential for buffering responses to negative mood and stress (Farb et al., 2018). There is growing interest in the application of mindfulness-based approaches with young people and some tentative but low-quality evidence to support their use in clinical populations (Tan, 2016). Drawing on the above evidence and theory, we have developed and piloted an 8-session programme for young people who have completed a first line psychological intervention for depression or anxiety but are not sufficiently well enough to be discharged from their clinical service. Given the importance of family context in influencing young people's recovery (Sander & McCarty, 2005), we have included a parallel version of the intervention for carers. Our theory of change is illustrated in our Logic Model (**Figure 3**).			
WHAT			
Materials: The therapists will be provided with a manual which lists all the resources needed to undertake each session. MAC PAC Resources:			
Session 1: Becoming Aware - Register - Snacks and drinks - Food item like raisin/ grapes for everyone & tissues - Flip chart/ whiteboard and pens - Journal for writing down notes and practice	***Session 2: Mind Chat*** - Register - Snacks and drinks - Sound links - Whiteboard or flipchart and pens - GBO sheets from last week - MAC booklet with handouts and home experience record - Cup and jug of water	***Session 3: The Body as an Anchor*** - Register - Snacks and drinks - Ball - GBO sheets from last week - MAC booklet with handouts and home experience record - Yoga Mats - Art sheets and pens	***Session 4: Reacting or Responding*** - Register - Snacks and drinks - Pleasant and unpleasant food items and tissues - Whiteboard or flipchart and pens - GBO sheets from last week - MAC booklet with handouts and home experience record

- MAC booklet with hand-outs - GBO sheets			(hotcross bun sheet included)
Session 5: Being with Stress - Register - Snacks and drinks - Video for Aikido exercise - Whiteboard or flipchart and pens - GBO sheets from last week - MAC booklet with handouts and home experience record	***Session 6: Thoughts are not Facts*** - Register - Snacks and drinks - Bubbles - GBO sheets from last week - MAC booklet with handouts and home experience record	***Session 7: Taking Care of Yourself*** - Register - Snacks and drinks - Music tracks - GBO sheets from last week - MAC booklet with handouts and home experience record - Game e.g. dobble/ soundlilicous/ charades	***Session 8: Relating Mindfully and Moving Forward*** - Register - Snacks and drinks - GBO sheets from last week - MAC booklet with handouts and home experience record - Letter, pens, and envelopes - Glitter jar content (for each person- glass jar, glitter glue, hot water, food colouring, tubs of glitter) - Stones/ jewels for end meditation
As with other mindfulness-based interventions, MAC includes daily formal and informal mindfulness practices for both young people and carers. This between-session practice will be supported by two bespoke mobile Apps that have been developed specifically for the MAC intervention. The two Apps, (one for parent/carers and one for young people) have been guided by our PPIE co-applicants, and broader input from young advisors and parent/carers throughout development. The Apps include content that is fun, engaging, interesting, and relevant for a diverse range of potential users including young people and carers. The Apps include audio-recordings of all MAC-specific mindfulness practices, and short exercises to help bring mindfulness awareness into everyday life, they are easily accessible in the App, and simple and intuitive to use. Participants will have the option to set practice reminders using push notifications if they wish to, but this will not be a requirement. The Apps are going through a separate Clinical Audit approval process.			
Procedures: An individual orientation session serves to brief each adolescent-carer dyad on the aims and structure of the treatment. The themes (learning intentions) of each session are explicit, and the skills are taught sequentially over the course. Skills-teaching in the small group setting is highly experiential, with sessions comprising short exercises, formal and informal mindfulness practices, as well as group discussion. In addition to groups for young people, MAC includes parallel groups for carers or parents. Carer groups follow the same sequential pattern of skills teaching as the adolescent groups, are similarly experiential, and over the same period.			
WHO PROVIDED			

Depending on therapists' previous experience, MAC groups will be facilitated by either one or two therapists who will receive regular supervision during the delivery of the treatment, further details below. MAC therapists will require competency in both mindfulness and working with young people and their carers, and therefore we will invite therapists who meet the following minimum criteria:

i) have a core professional training meaning they can work therapeutically with depressed children and young people,
ii) have experience of running group-based interventions for young people or carers,
iii) have their own personal mindfulness practice following attendance at either an 8-week MBCT or MBSR group,
iv) desirably, have experience leading or co-leading a Mindfulness Based Intervention (MBI), ideally with level 1 MBI teacher training.

Therapists will all need to attend specific MAC training which will involve a 5-day training workshop that will include built-in practice and feedback sessions. We will provide weekly online supervision to group leaders. Supervision is especially crucial when practitioners first deliver after training in a new approach.

Detailed data about applicants' previous experience of work with children and young people and their willingness to engage in mindfulness will be gathered to judge suitability of the candidates for the training.

HOW

The intervention will be held in-person in groups, with one site per cohort being remote via videoconferencing.

WHERE

In-person groups will be held in central locations to maximise attendance, with both young people and parent/carer groups at the same location. Where possible these two groups will run simultaneously to aid travel for the young person and their parent/carer, however, where this is not possible, they will occur in the same week. In person groups will only involve participants from the same site joining together.

Remote groups will be conducted using NHS approved software, for example MS Teams or Zoom. Participants will be encouraged to have their video cameras on during the MAC sessions since we know this improves engagement and this will be emphasised during the orientation meeting. Remote groups will involve participants from multiple sites and will run once enough participants have selected this as an option. All materials that would usually be given in person to participants will be posted to participants' homes or emailed, depending on preference. Remote and in person MAC groups will cover exactly the same content in exactly the same order, their only difference being their mode of delivery.

WHEN and HOW MUCH

The interventions will consist of 8 weekly group-based sessions of 1 hour 30 to 45 minutes duration and a pre-class interview of 1 hour duration conducted with each dyad of a young person and their parent/carer and allowing for individual therapist contact with both. Participants of both groups will be asked to engage

in regular daily home practice consisting of guided meditation and generalisation exercises aimed at helping participants utilise mindfulness skills in daily life.
HOW WELL
- Therapist completed supervision forms indicate issues that therapists wanted guidance about. - Session checklists will be used to record if all elements of a session were delivered as intended. - Data from the practice Apps will indicate the number and duration of practice sessions conducted by YP and parents/carers. **Supervision** Therapists will take part in 9 supervision sessions: Week 0 before orientation and session 1 begins, through to week 9 after the final session has been delivered. Therapists will access remote group supervision with experienced MAC therapists. The 60-minute supervision would comprise 45 minutes on the young person intervention and 15 minutes on carer intervention, with a strong focus on overlap. A brief pre-supervision form will be developed, which therapists will complete to highlight demands to discuss at supervision. **Session checklists** Competence and fidelity will be assessed by applying the MBI-TAC (R. S. Crane et al., 2012) to video recordings of the weekly sessions. Attendance will indicate dosage received by YP and parents. In addition, session checklists will be used to record if all elements of a session were delivered as intended.

Summary of TAU

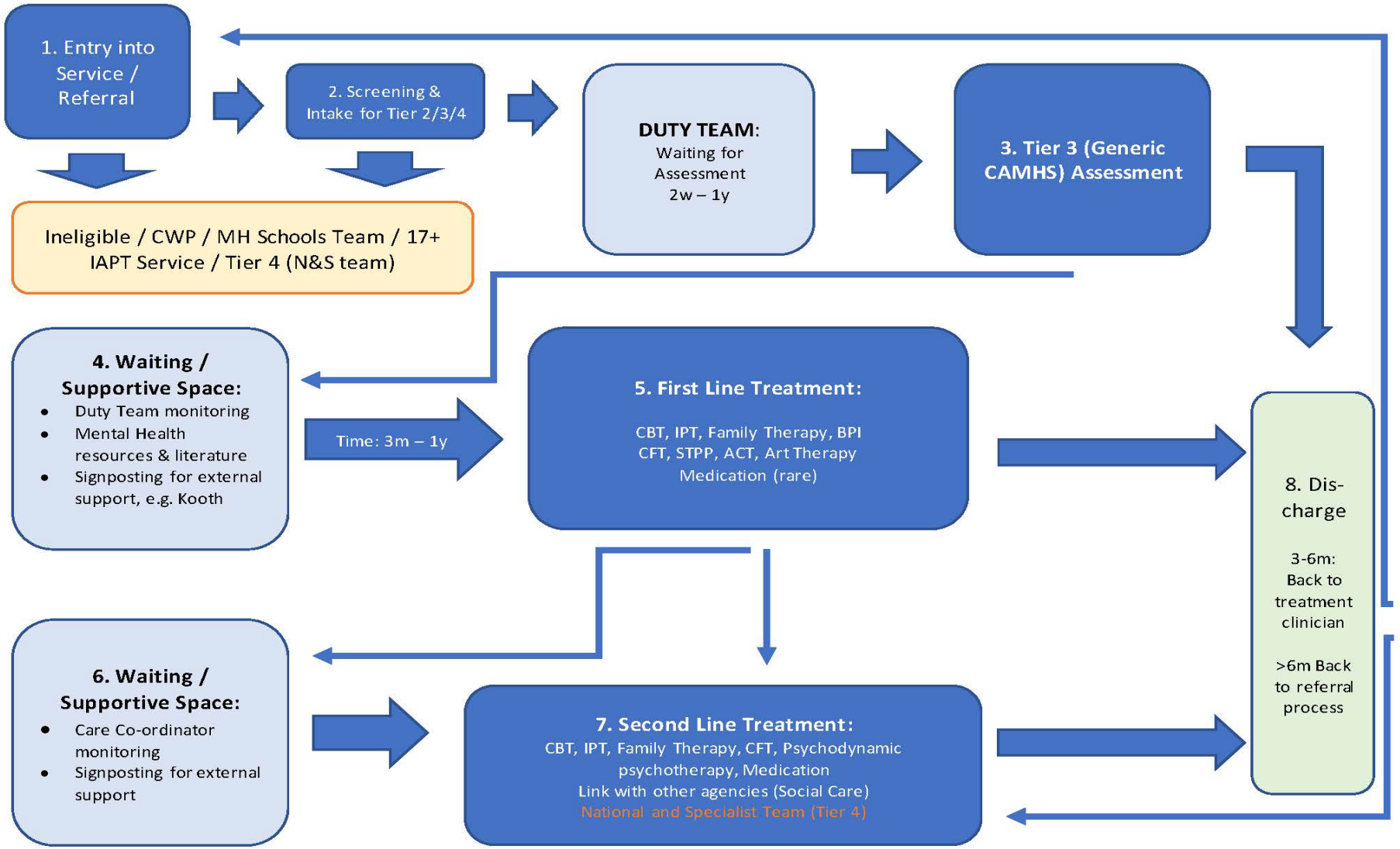
Young people, carers and practitioners strongly recommended TAU as the optimal comparator during extensive discussion in the feasibility work and PDG. In contrast to common assumptions, TAU was also the most potent comparator (smaller effect sizes) compared to active and waiting-list controls in a recent meta-analysis of psychological interventions for children over five decades (Weisz et al., 2017).

The characterisation of TAU was part of our PDG. The electronic case-record audit found that young people with depression attending CAMHS in Cambridge and London were typically girls, and commonly had comorbidities, particularly anxiety. Most referrals came from primary care, though many also were through Accident and Emergency Departments. Most young people received weekly therapy, commonly Cognitive Behavioural Therapy (CBT), but also Supportive, Family, and Interpersonal Therapies. Total time spent in the service was variable, but in some cases exceeded two years. Most young people were discharged because their treatment had been completed, often back to primary care. These results echoed an earlier audit of care pathways in Devon. The PDG found a consistent pattern of clinical pathways from young people, parents and case managers about the care pathway and TAU, despite significant variability across and within sites (**Figure 4;**) (PDG Competition 25 Panel B Programme Development Grants Final Report Form Project Title A Combined Mindfulness-Based Approach for Adolescent Non-Responders to First-Line Treatments of Depression or Anxiety and Their Carers: Establishing Feasibility of Implementation and Delivery Reference Number NIHR201024 Contracting Organisation Cambridgeshire and Peterborough NHS Foundation Trust Approved Duration 12 Current Duration 16, n.d.). The TAU arm received more treatment, including Family Therapy and Interpersonal Therapy than those in the MAC arm. Clinicians often continued with less frequent “check ins” and psychiatric medication reviews as needed with young people allocated to MAC.

Interviews with case-managing clinicians highlighted areas where the services received by young people differed from the organisational offer described by services. While there was significant variation in the specific support offered to young people, general Supportive Therapy, CBT, and Systemic Family Therapy were common first line treatments. The most commonly reported treatment in interviews was Supportive Therapy, which was confirmed by data from the Treatment Recording Sheet (TRS). The typical referral and treatment pathway that was found during the PDG is summarised in **Figure 4:** Typical CAHMS pathway.

We will not be controlling or changing the participants' TAU, we have requested from sites that both arms be offered their usual care, regardless of being in this trial.

Figure 4: Typical CAMHS pathway



14. OUTCOMES

Outcome measures (**Appendices j and k**) were chosen in close collaboration with young people and parents to reflect target psychopathology, key therapeutic components, and clinical processes. Participants will need to have completed all intake and baseline measures before they are randomised.

- Young people will then complete the Short Mood and Feelings Questionnaire SMFQ; (Angold et al., 1995) every fortnight for 12 months.
- Parents/carers will then complete the Generalised Anxiety Disorder GAD-7; (Spitzer et al., n.d.-a) every fortnight for 12 months.

The full complement of measures as listed in **Table 5** will be completed by both groups 14 weeks and 12 months after randomisation. If participants withdraw from treatment, we will continue to request outcome measures from them for the 12-month follow-up, unless they choose to formally withdraw from the trial completely.

Table 5: Outcome Measures

Construct	Young People Completed	Parent/Carer Completed	Timepoint Data Collected		
			T0: B/L	T1: 3.5m F/U	T2: 12m F/U
Eligibility					
PTSD screen	CRIES-8 (Perrin et al., 2005)		At intake assessment		
Current low mood	33 item MFQ (COSTELLO & ANGOLD, 1988; Daviss et al., 2006)		At intake assessment		
Baseline Outcomes					
Current depression and anxiety severity	RCADS 25 (Ebesutani et al., 2012)		X		
Past trauma and adversity	YCAS (Schlechter et al., 2021)	YCAS (Schlechter et al., 2021)	X		
Respondent Background		**Own and child's** Race/ethnicity, family, current living situation[c] **Child's** DOB, gender, current medication for anxiety or depression, past treatment for depression and anxiety[c] **Own** occupation, personal history of depression, education background	X		
Site option	Face-to-face or remote		X		

Primary outcome					
YP Depression	SMFQ (Angold et al., 1995)		Repeated at 2 weekly intervals throughout follow-up		
Secondary outcomes					
P/C Depression		PHQ (Kroenke et al., 2009b)	Repeated at 2 weekly intervals throughout follow-up		
YP Depression	33 item MFQ (COSTELLO & ANGOLD, 1988; Daviss et al., 2006)		X	X	X
Anxiety	RCADS 25 (Ebesutani et al., 2012)	GAD-7 (Spitzer et al., n.d.-b)	X	X	X
Quality of Life[a]	EQ-5D-5L (Devlin et al., 2018b)	EQ-5D-5L (Devlin et al., 2018b)	X	X	X
Coping	1 bespoke question	1 bespoke question	X	X	X
Parent – young people relationship quality[b]	PARS (Burke et al., 2021)	PARS (Burke et al., 2021)	X	X	X
Health Economics Measures					
Services and personal costs		**Child's** resource use bespoke questionnaire[c]	X	X	X
Quality of Life[a]	EQ-5D-5L (Devlin et al., 2018b)	EQ-5D-5L (Devlin et al., 2018a)	X	X	X
Mediators					
Decentring and wider mindfulness	CHIME-A (C. Johnson et al., 2017)	CHIME-S (Karl et al., 2024)	X	X	X
Self-Compassion	SCS-SF (Raes et al., 2011)	SCS-SF (Raes et al., 2011)	X	X	X
Emotion Regulation	ERQ (Gross & John, 2003)	ERQ (Gross & John, 2003)	X	X	X
Rumination	Rumination sub-scale of CRSQ (Abela et al., 2002)	Brooding and Reflection sub-scales of RSS (Treynor et al., 2003)	X	X	X
Parent – young people relationship quality[b]	PARS (Burke et al., 2021)	PARS (Burke et al., 2021)	X	X	X
Experience of MAC	Qualitative interviews with a sub-set of MAC participants				X
Type and duration of mindfulness practice	Weekly records of mindfulness practice (MAC arm only)	Weekly records of mindfulness practice (MAC arm only)			

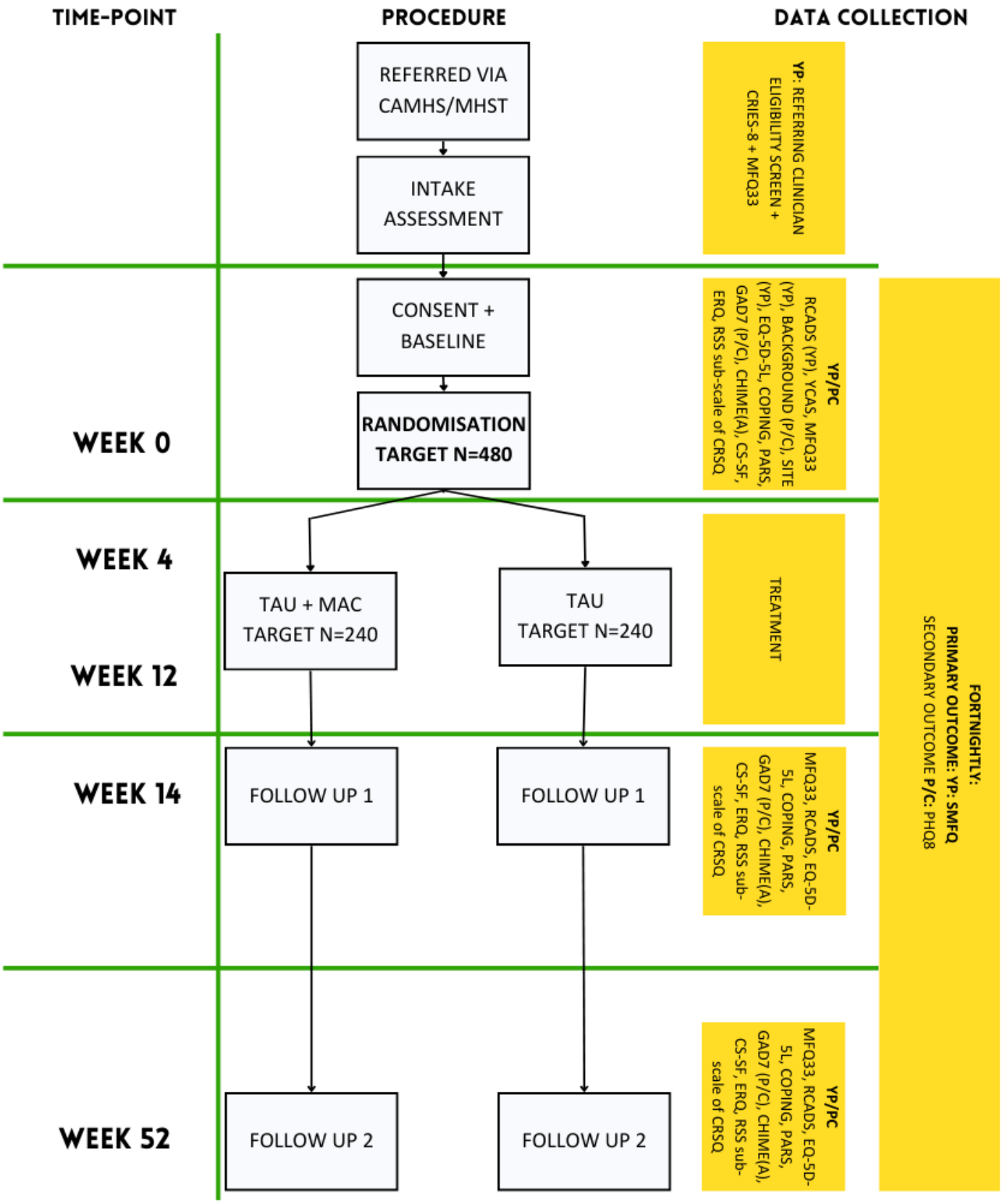
	Bespoke question about recent meditation practice	Bespoke question about recent meditation practice	X	X	X

[a] Quality of life measured using the EQ-5D-5L is both a secondary outcome and used in the health economic analysis.

[b] PARS is both a secondary outcome and a mediator.

[c] In situations where a parent/carer does not consent to their own involvement in the study, we would ask the young person to complete the information about their background, service and personal cost use.

Figure 5: Schematic diagram of the trial design, procedures, stages, and data collection



Primary outcome measure

The **primary clinical outcome will be the mean difference in depression** measured using the Short Moods and Feelings Questionnaire (SMFQ); (Angold et al., 1995) over the 12 months follow-up period using an Area Under the difference Curve (AUC) analysis of the fortnightly and follow up measures, as this better reflects the maintenance of recovery than a single data point at 12 months. We selected the SMFQ (Angold et al., 1995) as our primary outcome as it is recommended to monitor response to treatment by the National Institute of Clinical Excellence in Health and Social Care guidance (NICE, 2019) and has been shown to be sensitive to improvement in previous UK-based RCTs of interventions for depression in young people (Goodyer et al., 2008, 2017; Stallard et al., 2012).

Baseline moderators of treatment effects

To gather important information about participants' backgrounds we will ask about the following characteristics:

- the severity of depression and/or comorbid anxiety at baseline as measured by the RCADS (Ebesutani et al., 2012),
- exposure to childhood trauma as measured by the YCAS (Schlechter et al., 2021)
- ethnicity,
- age group (15 to 16 versus 17 to 18).

Youth and Childhood Adversity Scale (YCAS) (Schlechter et al., 2021)
The YCAS (Schlechter et al., 2021) is a 13-item measure of early adversity, assessing the experience (yes/no) and severity of adverse events (7-point Likert scale: 1-Not at all traumatic, 4-Somewhat traumatic, 7-Extremely traumatic). Total scores can be generated to reflect the total number of adverse events experienced or also incorporate the severity of these events (higher scores indicate greater number of experiences or severity of early adverse events, respectively). Both approaches yield a reliable, valid, and psychometrically sound measure.

Secondary outcome measures

The secondary outcomes will be expressed as the mean differences between the MAC + TAU versus TAU arms at 14 weeks and 12 months post-randomisation.

Collected every fortnight:

Patient Health Questionnaire eight-item depression scale PHQ-8; (Kroenke et al., 2009a)
The PHQ-8(Kroenke et al., 2009a; Kroenke & Spitzer, 2002) evaluates 8 of the 9 DSM-IV depression diagnostic criteria, omitting the question about suicide and self-harm. Patients are asked how many days in the last 2 weeks they experienced different symptoms (0-1 days = 0, 2-6 days = 1, 7-11 days = 2, 12-14 days = 3). The maximum score is 24, with higher scores indicating greater symptom severity. Scores ≥10 are taken to signify clinical level major depression and when this cut off is used, sensitivity and specificity are both 88% (Corson et al., 2004; Kroenke et al., 2001; Kroenke & Spitzer, 2002). In line with the SMFQ, this will be analysed over the 12 months follow-up period using an Area Under the difference Curve (AUC), as this better reflects levels of depression throughout the period rather than one single data point.

Collected at T0, T1 and T2 only:

Revised Child Anxiety and Depression Scale Short Form RCAD-SF; (Ebesutani et al., 2012)

The RCAD-SF (Ebesutani et al., 2012) is a 25-item questionnaire that measures anxiety (15 items) and depression (10 items). Items are scored on a 4-point Likert scale (Never, Sometimes, Often or Always) with higher scores indicating greater levels of psychopathology. Both the depression and anxiety sub-scales show good internal and external validity with good reliability in both a clinical and school-based sample (Ebesutani et al., 2012). The RCADS will be used as a Baseline Moderator (T0) to measure depression severity for stratification, and also be used at T1 and T2 as a secondary outcome measure for anxiety. It will not be used to analyse depression outcomes in young people, as that is measured using the SMFQ as the primary outcome.

Moods and Feelings Questionnaire 33 MFQ 33; (COSTELLO & ANGOLD, 1988; Daviss et al., 2006)
The MFQ is a 33-item self-report scale designed to assess depressive symptoms in children and adolescents aged 8 to 18 years. It covers various domains of depression, including mood, anhedonia, and cognitive symptoms. Respondents rate each item based on how they have been feeling or acting recently, with choices ranging from 0 to 2. The total score ranges from 0 to 66, with higher scores indicating greater levels of depressive symptoms. A cutoff score of 20 or above is often used to indicate clinically significant depressive symptoms (Cooper & Goodyer, 1993). The MFQ has demonstrated good internal consistency (α = .89 to .95) and test-retest reliability (r = .79 to .91). Additionally, it has been shown to have good convergent and discriminant validity when compared with other measures of depression (COSTELLO & ANGOLD, 1988; Daviss et al., 2006).

Generalized Anxiety Disorder 7 GAD 7; (Spitzer et al., n.d.-a)
The GAD-7 (Spitzer et al., n.d.-a) is 7-item scale measuring symptoms of anxiety and worry. Items are rated on a 4-point Likert scale (0-3; maximum score 21), with higher scores reflecting greater symptom severity. Scores ≥10 indicate clinical levels of anxiety. The scale is reported to have excellent internal consistency (α = .89) and good convergent validity (S. U. Johnson et al., 2019; Löwe et al., 2008). Sensitivity and specificity are between 89-74% and 82-54%, respectively when a cut off of 10 is used (Beard & Björgvinsson, 2014).

Ability to 'cope'
Following consultation with our Patient and Public Intervention (PPI) group, we will ask a bespoke question about participants' perception of their ability to cope with life on a 5-point Likert scale.

Parent-Adolescent Relationship Scale PARS; (Burke et al., 2021)**.**
Critical Dimensions of the parent–adolescent relationship will be assessed from multiple perspective using the Parent Adolescent Relationship Scale (Burke et al., 2021). The PARS is a 20-item measure that comprises three subscales: connectedness, shared activities, and hostility. Initial research has demonstrated good discriminant and convergent validity (Burke et al., 2021).

Mediators

Collected at T0, T1, T2:

PARS (Burke et al., 2021) (above) is also a mediator.

CHIME-S (Karl et al., 2024)/**CHIME A** (C. Johnson et al., 2017)
The Comprehensive Inventory of Mindfulness Experiences CHIME; (Karl et al., 2024) is an established self-report questionnaires available in parallel versions for adults (Bergomi et al., 2014; S. Wilkinson et al., 2023) and adolescents (C. Johnson et al., 2017). The CHIME-S and CHIME-A cover mindfulness as a complex construct consisting of the following facets (subscales):

- Awareness of Internal Experience,

- Awareness of External Experience,
- Acting with Awareness,
- Accepting and Nonjudgmental Orientation,
- Decentring and Nonreactivity,
- Openness to Experience,
- Relativity of Thoughts, and
- Insightful Understanding.

They will be administered at all main trial assessment points for all individuals, young people, and carers.

Self-Compassion Scale Short Form SCS-SF; (Raes et al., 2011)
The SCS-SF (Neff, 2016; Raes et al., 2011) is a 12 item self-report measure of self-compassionate responding in the event of failure and distress. Items are rated on a five-point scale from 1 (almost never) to 5 (almost always). The measure has excellent internal consistency (α = .89) as well as good convergent, divergent, content and face validity (Raes et al., 2011) .

Emotion Regulation Questionnaire ERQ; (Gross & John, 2003)
The ERQ (Gross & John, 2003) uses a 10-item scale to measure 2 different emotion regulation strategies: cognitive reappraisal (6 items) and expressive suppression (4 items). Items are rated on a 7-point Likert scale from 1–7, with higher scores indicating greater agreement with items. The cognitive reappraisal facet negatively predicts psychological distress and alexithymia, whilst expressive suppression is positively correlated with these characteristics (Preece et al., 2020). Across samples, the two ERQ facets show adequate to excellent internal consistency (cognitive reappraisal α = .89-.90; expressive suppression α = .76-.80 (Preece et al., 2020)).

Ruminative Responses Scale Brooding and Reflection Sub-Scales RRS-BR; (Treynor et al., 2003)
Rumination will be assessed using the Ruminative Responses Questionnaire (Treynor et al., 2003) at all points of assessment on all individuals in the trial. The full RRS (Treynor et al., 2003) is a 22-item scale to measure-symptom focused, self-focused and cause-focused responses to depressive mood. Since depressive mood is being measured elsewhere, we will only use the brooding and reflection sub-scales which comprise 10 items in total. Items are rated from 1 (almost never) to 4 (almost always). Internal consistency is excellent (α = .90), and test-retest reliability is adequate (r = .67;(Treynor et al., 2003).

Children's Response Styles Questionnaire Rumination Sub-Scale CRSQ-R; (Abela et al., 2002)
The full CRSQ (Abela et al., 2002) is 25-item scale measuring responses to depressive symptoms. It includes 3 scales (ruminative, distractive, and problem-solving responses) which are scored individually by taking the mean (1-4) of items from that scale. Higher scores indicate a higher likelihood of responding in a given manner to depressive symptoms. Internal consistency across subscales is moderate to high (α = .51-.84) and scores are predictive of level of depressive symptoms, self-control, and perceived helplessness, (Abela et al., 2002; Treynor et al., 2003). Since our focus is on rumination, we will only use the 13 item sub-scale that measures rumination.

Collected weekly during the 8-week intervention (MAC arm only)

Measuring engagement with mindfulness practice
Participants will be asked to record their daily mindfulness practice, either directly via the app or on paper diary cards. We will measure number of times both formal and informal mindfulness has been practiced as well as recording which practices were used. Whilst self-report will be the primary source of this data, we will

cross reference this with metrics recorded directly via the app, for example, the dates, duration, and frequency of log-ons as well as how often each audio recorded mindfulness practice was played.

Health Economic Measures

Cost components included in the health economic analysis will comprise:

- Detailed costs of the MAC intervention,
- Other NHS and social service use during the 12-month within-study period, including:
    - CAMHS, primary care, social care, and community care contacts,
    - prescribed medications,
    - hospital inpatient admissions and outpatient attendances,
- School attendance and other education-related contacts
- Informal care costs incurred by participants, parents and carers and families, including time taken off work.

The intervention costs will comprise the costs of:

- training the trainers,
- staff time to deliver MAC classes and pre-class orientation interviews,
- non-staff costs associated with delivery of MAC classes (e.g., life or virtual room hire),
- the costs of delivering the app, and
- provision of information materials for participants and families.

The volume of resource use for the non-intervention cost components will be measured in the trial using a bespoke retrospective questionnaire based on a modified version of the Client Service Receipt Inventory, completed by participants for a 12-month period at baseline, 14 weeks, and 12-months post-baseline for each individual participant. These questionnaires will cover the previous 3-month period at baseline and 3 months, and the previous 9-month period at 12 months.

When parents/carers have consented to take part we will ask them to complete this information on behalf of their child. If the young person's parent/carer has not consented for their own involvement, then we will ask the young person themselves to complete this questionnaire.

EQ-5D-5L Quality of Life (Devlin et al., 2018a)

The EQ-5D-5L (Rabin & Charro, 2001) describes health status in 5 health dimensions, with 5 levels of each. The patient reports their present health state by ticking the level of each dimension that currently applies to them. They then rate their current health state from 0-100 (best possible health state). This measure has good convergent and divergent validity with other health questionnaires (J. A. Johnson & Pickard, 2000).

Treatment Recording Sheet TRS; (Bearsley-Smith et al., 2008)
We will also measure public and charitable sector services accessed and health-related quality of life for both young people and carers for economic evaluation. Researchers will support practitioners to complete the revised TRS (Bearsley-Smith et al., 2008) (**Appendix L**) for any other therapy or psychological intervention provided, to allow for comparison of treatment strategies and intervention content for all those randomised to MAC or TAU during the 12-month follow-up period post randomisation for the cost-effectiveness. The TRS is a non-validated measure collecting clinicians' report monthly for each young person and is used to record specific intervention strategies (e.g., goal setting, supportive listening, family therapy) provided to young

people and/or parents/families during sessions, and the frequency with which they are provided. We have revised it following feedback from clinicians in the PDG.

Routinely Collected Data

Given that the utilisation of core mindfulness skills in adults is maintained, and often increases, after the completion of MBCT (Farb et al., 2018), we will explore attitudes to data linkage to support longer-term follow up. Specifically, we will seek permission to link trial data to education data from schools, apprenticeships, and higher education to explore attendance, attainment, and exclusion, plus Hospital Episode Statistics and the Mental Health Dataset to explore future health service contacts.

Qualitative Analyses to Investigate the Experience of the Intervention

We will use qualitative analyses to explore young people's and carer's experience of the intervention more widely. As described above, previous research in young people has used varying degrees of practice requirements and a major focus of this qualitative analysis will therefore be on factors influencing such engagement and its relationship with subjectively experienced dynamics of change.

We will investigate young people and carer's views on:

1) acceptability of the mindfulness-based intervention and mindfulness practice,
2) the changes they experience and their utilisation of mindfulness skills, and
3) the broader impact of the mindfulness-based intervention on their family relationships and their lives more widely.

After the last follow-up (12-month post-randomisation) of the pilot trial, a subsample of 20 to 24 young people in the MAC intervention arm (or until data saturation has been reached), will be invited to a qualitative interview. Recruitment will be purposive, including patients across all sites, and seeking to achieve maximum variation in relation to:

1) completion/non-completion of treatment,
2) response/non-response to treatment (defined as reaching a score below the clinical threshold for depression on the RCADS (Ebesutani et al., 2012)), and
3) recruitment site (to examine contextual factors).

Carers of these young people will be invited for separate interviews.

Practice data and written feedback from the intervention app will be used to inform subsampling and will also provide us with the opportunity to explore any unanticipated experiences and effects in more depth. In collaboration with the PPIE members of our team, we will develop, and pilot test, a semi-structured topic guide (**Appendix mi and mii**).

Interviews will be video recorded, transcribed verbatim, and anonymised. Thematic analysis of interview transcripts will be conducted using a Framework approach (Richie et al., 2014), involving the coding and sorting of textual units according to both deductive and inductively derived categories, and the use of matrices to review the coded data, investigate commonalities and differences and search for patterns. Coding and data management will be facilitated by NVivo software.

Exploration of subjective experiences of decentring and mindfulness relating to negative mental events

To better understand the ways in which young people and their carers utilise decentring and mindfulness skills, we will complement questionnaire assessments by asking a subgroup of young people and their carers

to participate in micro-phenomenological interviews, in which they will be asked to describe their subjective experience of dealing with negative mental events (see qualitative analyses below).

The micro-phenomenological approach (Petitmengin et al., 2019) is based on the observation that mental activities are often not immediately accessible to reflective consciousness and uses specific prompts and questions to help participants become aware of the unrecognised or "pre-reflective" part of their experience. The interviews will focus on a singular experience of relating to a negative mental event. Participants will be guided to identify such an event and "evoke" the experience of responding to it while reporting on increasingly finer details in an iterative process.

Interviews will be recorded and transcribed, questions and answers numbered, general statements eliminated, and the remaining content chronologically reorganised to reconstitute the temporal course of the experience. We will follow recommendations for micro-phenomenological analysis by Petitmengin, Remilliey, and Valenzuela-Moguillansky (Petitmengin et al., 2019) first to identify minimal units of meaning and secondly, to abstract from these units to derive generic structures of experience. This will allow us to compare structures between young people and carers as well as between subgroups (completion/non-completion, responders/non-responders) within these two groups (**Appendix mi and mii**).

15. STATISTICAL CONSIDERATIONS

Randomisation

Table 6: Randomisation Summary

Randomised design	Individual patient
Type of randomisation to be used	Randomly permuted varying length blocks, stratified by:
Stratification variables	- Site - Young person currently taking a therapeutic does of antidepressant: Yes/No - Young person's total RCADS score above a T score of 70 versus a score 70 or below
Ratio allocation between treatment arms	1:1 ratio
How randomisation will be implemented and approach to conceal allocation	A web-based randomisation system designed and maintained by the King's College London Clinical Trials Unit (KCTU) for the duration of the project. Access will be restricted via usernames and passwords to appropriate research team members, and the system will be hosted on a dedicated server within KCL.
Define the circumstances under which randomisation codes may be broken and the procedure for doing it	As this is not a drug trial, and it is not possible to blind the participants and certain trial team members to allocation, we will not need a special procedure for code breaking. We do not anticipate serious adverse reactions, but if there is a serious adverse event and there is a need for a blinded member of the trial team to know if an individual is in the MAC group, the individual, their carer, or one of the trial therapists can provide this information.

Following written consent, participants will be randomised in a 1:1 ratio to one of the two treatment arms (TAU, or MAC + TAU). A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL. The system will employ block randomisation with randomly varying block sizes and will be stratified by i) site, ii) if the young person is taking a therapeutic dose of antidepressants or not and iii) if their RCADS (Ebesutani et al., 2012) score at baseline indicates that they have severe depression or not. The details needed for randomisation will be held in a dedicated database. Only the Programme Manager, Trial Manager and Programme Administrators (unblinded) will have access to the randomisation system (or their nominated backup in times of absence; the nominated backup will not be another member of the blinded team but will be a team member whose role on the delegation log specifies this role as contingency Trial Manager).

Sample size calculation

Our power calculation suggests that 480 participants (240 per arm, MAC allocation=20 groups) will allow us to detect an effect size of 0.3 with 90% power, allowing for 20% attrition. The calculation assumed using a two-sided independent samples t-test of the difference between arms, alpha = 0.05, assuming a MAC group size of 12, intraclass cluster correlation of 0.05, i.e. a design effect / inflation of 1 + [12 – 1] x 0.05 = 1.55 (Williams et al., 2008), one baseline and two post-randomisation measures with correlation rho = 0.5 = deflation factor of 0.5 (Machin et al., 2009), and 20% attrition (Kennard et al., 2009;(Mental Health Taskforce, 2016). The calculation was done using the Gpower software, with methods from Killip et al used to hand-calculate the cluster effect for MAC group (Killip, 2004).

We selected this effect size in part because the mean effect size for depression was 0.29 across multiple measures and interventions in a meta-analysis of psychological interventions in children and young people over the last five decades (Weisz et al., 2017). We also note the MFQ (COSTELLO & ANGOLD, 1988) specifically was sensitive to improvement in previous UK-based RCTs of interventions for depression in young people (Goodyer et al., 2008, 2017). Goodier's studies (NG134 2019 Evidence Review A, 2019a;Goodyer et al., 2017) suggest a five-point between group reduction on the MFQ represents the minimally clinically important difference for the assessment of superiority. The ADAPT study found a MFQ standard deviation of 14.6, equating this to an effect size of 0.34 (Goodyer et al., 2008). This suggests our power estimate is conservative, as does the fact that two MAC groups we ran in London after the PDG completed found larger MFQ correlations over time of rho~0.8, whereas we chose to use the more conservative rho = 0.5. To build in a buffer and be conservative, we based our sample size calculation on an effect size of 0.3. While 0.3 represents a small effect size, given the impact of prolonged depression during adolescence and the potential impact of escape from future episodes, combined with the number of young people who could benefit and spillover effects among carers, even this small effect would bring large potential patient and societal benefits. The calculation was simplified with respect to AUC to minimise the complex data structure assumptions made, however, we expect the AUC model with fortnightly measures to increase efficiency, so the sample size is likely also conservative from this point of view.

Blinding

- **The senior statistician and senior health economist** will not have access to the randomisation list or REDCap database at any point in the trial to remain fully blinded until review of the first draft of the statistical/health economic reports for checking, when they will become fully unblinded.

- Similarly, **the Chief Investigator and Principal Investigators** in each trial centre will remain fully blinded until they review the finalised statistical report, when they will become fully unblinded.
- **The Junior Statistician and Junior Health Economist** will be fully blinded until sign-off of the statistical and health economic analysis plans, after which they will be fully unblinded so they can inspect and utilise app usage/intervention-related data.
- **The Programme Manager, Trial Manager and the Trial Administrators** will be unblinded.

The only individuals that will be able to summarise/see data by arm prior to the review of the statistical report are the Junior Statistician, Junior Health Economist, and the members of the Data Monitoring Committee. We presume that the Data Monitoring Committee will remain partially blinded and will prepare the closed report accordingly.

No serious harms associated with taking part in the intervention are expected, therefore a formal procedure for unblinding any blinded staff during the study is not needed.

Table 7: Blinding Summary

Roles	Individual-level	Method of blinding OR justification for unblinding	Group-level	Method of blinding OR justification for unblinding
Programme Manager	U	Assigns participants to randomisation groups (is not recruiting or assessing participants)	B	No access to randomisation list or data summarised at group-level
Trial Manager	U	Assigns participants to randomisation groups (is not recruiting or assessing participants)	B	No access to randomisation list or data summarised at group-level
Trial Administrator	U	Assigns participants to randomisation groups (is not recruiting or assessing participants)	B	No access to randomisation list or data summarised at group-level
Study Participants	U	Only unblinded to their own allocation (we are unable to blind participants due to the nature of the intervention)	B	No access to randomisation list or data summarised at group-level
Referring Clinician	U	No access to data at the individual level		
Trial Therapists	U/P	Only unblinded to those seen for therapy (required for providing MAC). Information	B	No access to randomisation list or data summarised at group-level

Roles	Individual-level	Method of blinding OR justification for unblinding	Group-level	Method of blinding OR justification for unblinding
		about other therapists' participants may be mentioned in therapy supervision but is minimised.		
Therapist Supervisor	U/P	Usually blinded (not told of group assignments), unless participant details need to be conveyed for safety or wellbeing purposes	B	No access to randomisation list or data summarised at group-level
Data Collectors / Outcome Assessors	B	Not told of group assignment, participants asked to conceal this, but blinding assessed *	B	No access to randomisation list or data summarized at group-level
Trial Statistician	B	No interaction with individual participants	U	Access to full randomisation list required for data monitoring & analysis. NB only unblinded after an initial draft of the SAP has been signed
Senior Statistician	B	No interaction with individual participants	B	No access to full randomisation list *
Chief Investigators	B	Usually blinded, unless participant details need to be conveyed for safety or wellbeing purposes	B	No access to randomisation list or data summarised at group-level
Independent Members of DMEC	B	No interaction with individual participants	U/P	The level of DMEC blinding will be at their discretion but will likely see data split by group at least a partially blinded level.
TSC	B	No interaction with individual participants	B	No access to randomisation list or data summarised at group-level

U = unblinded, B = blinded, P = partially blinded (i.e., see data split by groups labelled as A/B).
* After data has all been collected, the database locked, the data have been analysed and a first draft of the statistical report has been prepared, the senior statistician will become unblinded to carry out final checks on the analysis code and statistical report.

16. STATISTICAL ANALYSIS

General

Statistical methods are described briefly here. A comprehensive Statistical Analysis Plan (SAP) will be developed and agreed with the Trial Steering Committee (TSC) before any analysis is carried out. The SAP will describe statistical procedures in detail. Please see Section 14 for a description of the measures.

The main analysis will follow the intention to treat (ITT) principle as much as possible (Sullivan et al., 2018;White et al., 2012). We will outline this as our main estimand with further detail in the Statistical Analysis Plan. The analysis will be carried out by the Junior Statistician under the guidance of the Senior Statistician. Analysis will progress once all data have been cleaned and the database locked.

Baseline variables will be summarised by arm and overall, using mean and standard deviation or median and 25th and 75th percentiles for normally distributed/non-normally distributed continuous variables or ordinal variables, and frequencies and percentages for categorical variables. There will be no statistical testing of, or presentation of p-values relating to, differences between the arms.

Primary outcome

The difference between the arms on the primary SMFQ outcome will be estimated using a linear mixed effects analysis of covariance (adjusting for baseline) model, with the fortnightly SMFQ measures as dependent variables, accounting for repeated measures and therapy group clustering and including intervention arm and the stratification variables as independent variables. We intend to estimate the difference in AUC by including an intervention arm by fortnight interaction term, allowing the extraction of weekly/follow-up visit intervention arm difference estimates, and then the calculation of the appropriate linear combination of these estimates (i.e. using the trapezium rule). We may also explore time as a continuous variable in models.

Secondary complier average causal effect (CACE) analyses of the SMFQ primary outcome using instrumental variable/structural equation modelling methods will estimate the treatment effect in those that attend at least 4 MAC sessions (Dubicka & Bullock, 2017) and of those that complete 50% or more of the mindfulness practice (C. Crane et al., 2014), possibly with an exploration of methodology for extending the CACE analysis to the AUC models.

Secondary outcome

The fortnightly PHQ-8 secondary carer outcome will be analysed in the same way as described for the primary outcome. The differences in the other secondary outcomes between intervention arms at 14 weeks and 12-months post-randomisation will be estimated using similar models to that for the primary and PHQ-8 secondary outcome, with 14 week- and 12-months measures of the outcome as dependent variables, and an appropriate link function depending on the form of the variable. Rather than calculating the AUC for these variables, we will include an intervention arm by time point interaction term and extract the differences for each at 14 weeks, and 12 months.

Sub-group (baseline moderator) analysis

Baseline moderators (young people: RCADS score, YCAS score, race/ethnicity, gender, age, on a therapeutic dose of medication for the treatment of depression or anxiety or not, preference for face-to-face or remote) will be analysed by replacing the intervention arm by fortnight interaction term with a baseline variable by intervention arm by fortnight interaction term in the main analysis model described for the primary MAC outcome. If this interaction term suggests there are different effects by different levels of the moderators,

the AUC will be re-estimated for appropriate levels of the moderator. We note that subgroup analyses are not powered for, and so will be exploratory.

Missing Data

Missing data due to loss to follow-up or withdrawal will be accounted for under a missing at random assumption in the mixed effects models estimated using maximum likelihood. To make the missing at random assumption more plausible, we will assess whether baseline variables predict missing data, and included these in the analysis models if so. We may consider multiple imputation if post-randomisation variables predict missing data, and/or missing not at random sensitivity analyses; if so, these will be outlined in more detail in the SAP.

17. MEDIATION ANALYSIS

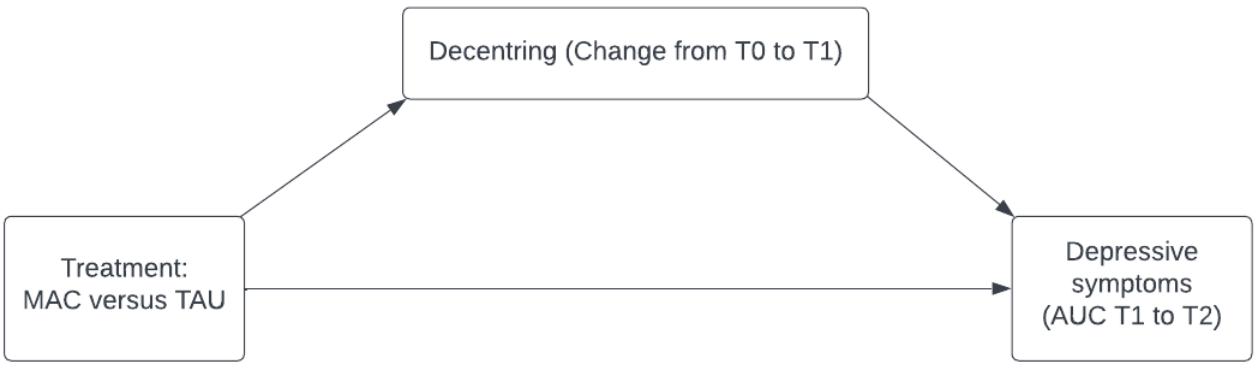
Decentring

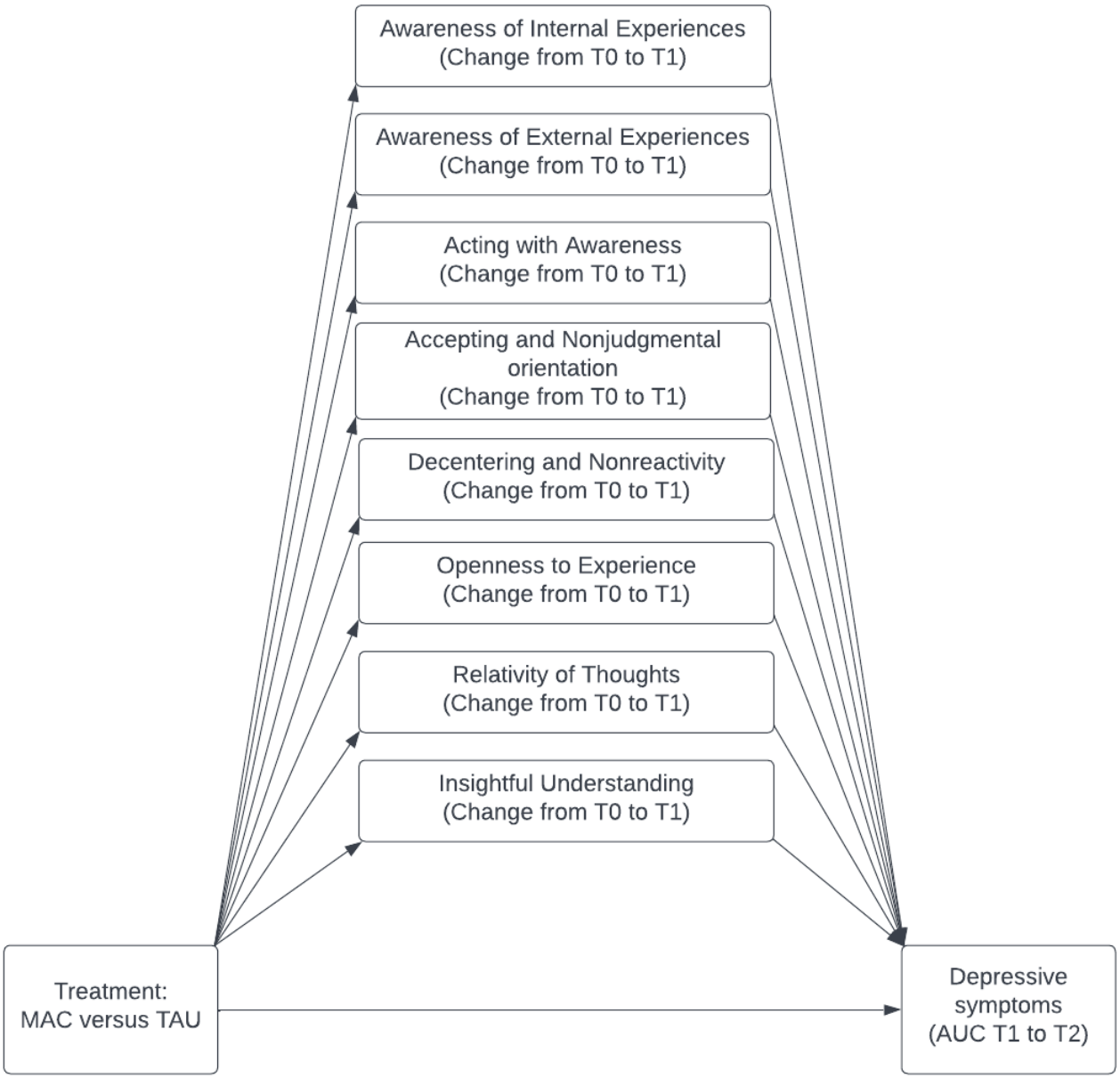
To investigate the purported core mechanisms of the treatment, we will test whether treatment-related changes on the Decentring and Nonreactivity scale of the CHIME/CHIME-A questionnaire mediate change in depressive symptoms in both young people and carers.

Mindfulness skills

To investigate the role of general mindfulness skills, we will investigate whether treatment-related increases in mindfulness skills across all facets of the CHIME/CHIME-A mediate levels of depressive symptoms (i.e., total CHIME/CHIME-A scores across all subscales). To explore the relative contributions of treatment-related changes in mindfulness facets (all the CHIME/CHIME-A subscales) to the mediation of the primary treatment outcome, we will run multiple parallel mediator models using a stepwise approach to enter the different subscales to identify the most relevant facets in both groups, as shown in **Figure 6**.

Figure 6: Graphical representation of mediator models used to investigate the role of general mindfulness skills





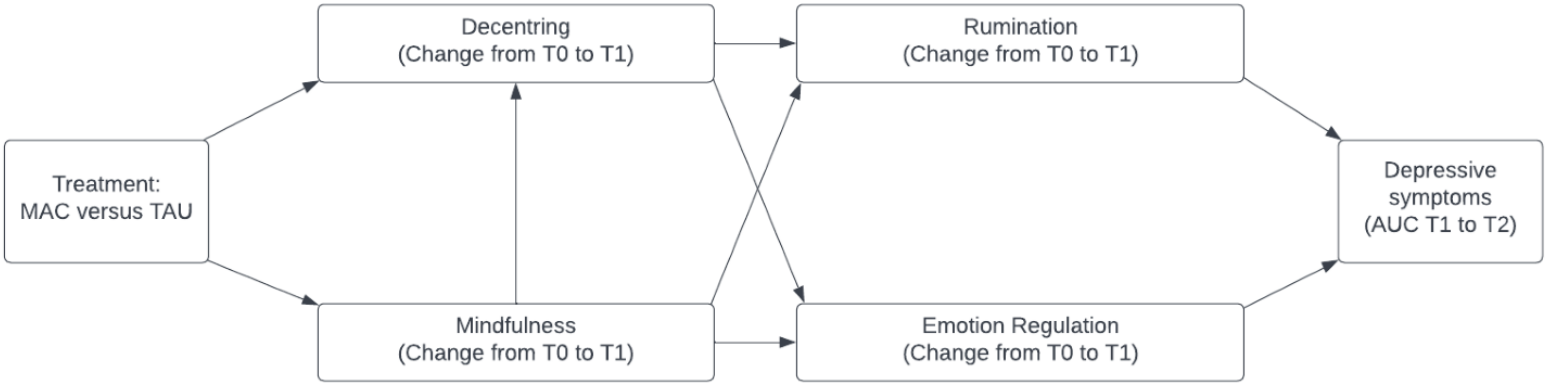
Self-compassion

While not explicitly listed in our logic model, we will also investigate potential mediating effects of self-compassion, a characteristic that is integral to the attitudinal components of mindfulness and has previously been shown to increase following MBIs.

Sequential mediation pathways

Including cognitive targets of decentring and mindfulness skills: To better understand how increases in decentring and general mindfulness skills may impact on symptoms, we will explore pathways in a more comprehensive model that includes cognitive target variables, separately in young people and in adults. Based on previous research, this model assumes that decentring is particularly suited for reducing ruminative tendencies (Wu et al., 2022; Ishikawa et al., 2018), while general mindfulness skills not only support the ability to decentre but benefit emotion regulation more widely (Desrosiers et al., 2014). That is, we assume two separate sequential pathways, one in which decentring reduces rumination thereby reducing symptoms and another in which mindfulness increases emotion regulation skills thereby reducing symptoms, as shown in **Figure 7**.

Figure 7: Graphical representation of sequential mediation models used to investigate the role of decentring and general mindfulness skills



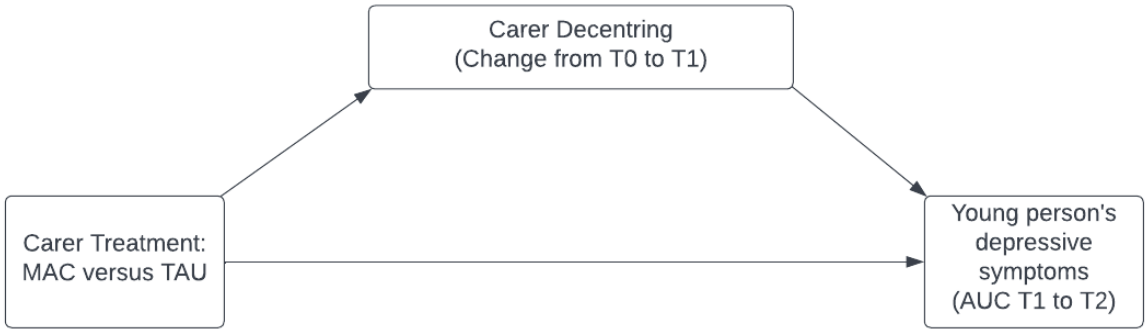
Transfer across the young person-carer dyad

A unique characteristic of our mindfulness-based approach is the use of parallel interventions for young people and their carers to address the interrelated nature of mental health within the family. Parental psychopathology and emotion dysregulation represent an important risk for the development of depression in children and young people (Zhang et al., 2020) and there is increasing evidence that carers shape emotion regulation processes in children across development through several different mechanisms (Silvers, 2022; Martin & Ochsner, 2016).

Decentring and mindfulness

To test such transfer and investigate the degree to which improvements in regulation in carers influence outcome in young people, we will run analyses to investigate mediation of treatment outcome in young people through changes in carer's ability to decentre, more specifically, and mindfulness skills, more generally. As shown in **Figure 8**, we hypothesise that treatment-related increases in carer's ability to decentre and general mindfulness skills will both have a significant mediating influence on young people's symptoms during follow-up.

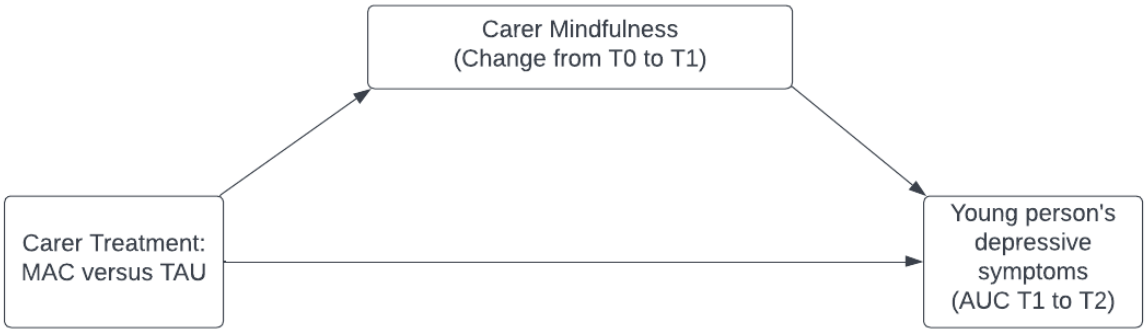
Figure 8: Graphical representation of mediator models used to investigate the role of changes in carers decentring and general mindfulness and the impact this may have on young people's symptoms

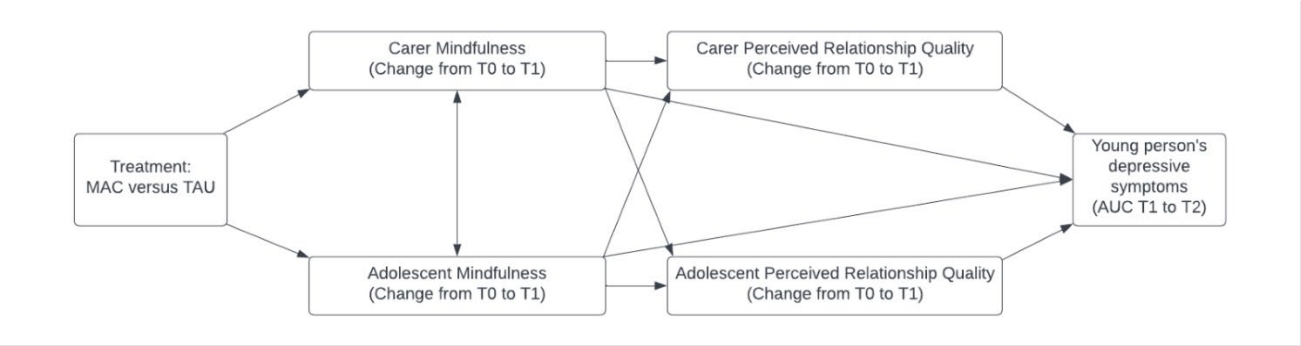


Sequential mediation pathways including mindfulness and relationship quality

Transfer may occur through several mechanisms, including modelling of emotion regulation skills or indirect influences on parenting behaviours and the wider emotional context within the family, which we assume to become reflected in changes in perceived adolescent-carer relationship quality. To explore these mechanisms in more detail, we will test pathways within a comprehensive model considering potential influences of mindfulness skills on perceived relationship quality, as shown in **Figure 9**. Relationship quality will be assessed from both the young person's and the parent's perspective using the Parent-Adolescent Relationship Scale (Burke et al., 2021), administered to all individuals in the trial.

Figure 9: Graphical representation of sequential mediation models used to investigate the role of family relations, mindfulness skills and young person's symptoms





Mediation of the effect of practice in the intervention arm only

We will test, in young people and in parent/carers, whether the degree to which they engage in practice during the intervention is related to changes in decentring and mindfulness skills over the period of the intervention, and to levels of symptoms measured using the SMFQ. We assume that regular practice is necessary for effective development of the treatment-related skills that serve to reduce depression and will test the hypothesis that effects of practice on depressive symptoms during follow-up are mediated through changes in decentring and general mindfulness skills during the intervention, both in young people and in adults who participated in MAC. We will use similar methods to those described above for the other mediation modelling, but will just model data from the individuals in the MAC arm, i.e., those for whom we can measure engagement in practice.

Mediation analysis methods

Mediation will be evaluated using structural equation modelling and/or causal mediation analysis methods adjusting for the stratification variables and baseline measures where appropriate (i.e., adjusting for baseline measures of mediator and outcome in mediator models (Dunn et al., 2015) and using appropriate modelling methods (i.e., temporally ordered mediator and outcome, longitudinal models where appropriate). Given previous research on MBCT that has provided evidence for the importance of acquisition of therapy-related skills across the intervention period (C. Crane et al., 2014), as well as their refinement and continued utilisation after the end of the intervention (Segal et al., 2019), we will run separate sets of analyses to test mediation of outcome at the end of intervention and at the end of follow-up. We may explore the extension of this methodology to repeated measures/AUC models. If we find significant baseline moderators of treatment effect, we may explore whether there is mediated moderation (Dunn et al., 2015; Muller et al., 2005). All mediation models will use raw mediator and outcome scores adjusted for baseline scores, rather than change scores (Landau et al., 2018).

18. HEALTH ECONOMIC ANALYSIS

Our economic analysis will evaluate the cost and cost-effectiveness of MAC plus TAU compared to TAU alone from NHS/personal social services, education, and societal perspectives. To do this we will:

- Undertake a detailed analysis of the costs of MAC,
- Evaluate the within-trial impact of MAC on
    - Resource use and costs,

  - Health-related quality of life,
  - Quality-adjusted life-expectancy,
- Model the long-term impact of depression in childhood on a range of outcomes using longitudinal datasets,
- Evaluate the cost-effectiveness of the intervention in the short-term and long-term from
  - NHS,
  - Education,
  - Personal social services,
  - Societal perspectives.

An economic analysis is warranted given the non-zero cost of MAC and its potential impact on depression and associated costs. Our analysis will conform to accepted economic evaluation methods (National Institute for Health and Care Excellence (NICE); (NICE Health Technology Evaluations: The Manual NICE Process and Methods, 2022). We will estimate costs and cost-effectiveness for the 'within-trial' period, and, using modelling, over a lifetime time horizon. Costs will be assessed from the perspective of the NHS and personal social services (PSS; base case analysis), and also from a wider societal perspective (secondary analysis). A Health Economic Analysis Plan will be presented to the Trial Steering Committee for approval before data lock and prior to any analysis being undertaken.

The resource use data collected in the trial will be valued using UK unit costs (in 2022/2023 £). Unit costs will be identified from published sources, including the:

- British National Formulary (https://bnf.nice.org.uk/),
- Unit Costs of Health and Social Care (https://www.pssru.ac.uk/project-pages/unit-costs/),
- Prescription Cost Analysis (https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data), and
- National Schedule of NHS Costs (https://www.england.nhs.uk/national-cost-collection/).

Health Economic outcome measures

- Quality-adjusted life years (QALYs) accrued by participants (QALYs are the recommended outcomes for economic evaluations in the UK (NICE Health Technology Evaluations: The Manual NICE Process and Methods, 2022),
- The trial primary outcome (SMFQ-measured depression),
- Other trial secondary outcome measures including those for parents and carers.

QALYs will be calculated based on the following collected during the trial:

- Health-related quality of life (HRQL) data, and
- Mortality data.

HRQL will be measured using the EQ-5D-5L, which we will collect for a 12-month period at baseline (randomisation) and 14 weeks- and 12-months post-randomisation for each individual participant. This period will cover the period during which the MAC sessions occur, and time thereafter.

Utility scores will be computed from the EQ-5D-5L descriptive system data using recommended algorithms for the UK population at the time of analysis. Participant-specific utility profiles will be constructed assuming a straight-line relation between each of the participant's EQ-5D-5L utility scores at each of the three follow-up points. If any participants die within the 12-month period, they will be assigned a utility score of zero at the date of death and thereafter. The QALYs experienced by each participant from baseline to 12 months will

be calculated as the area underneath the utility profile. Unit costs will be taken from standard published sources.

The cost-effectiveness measures in the within-trial (12-month) model will be the:

- Incremental cost per case of SMFQ-measured depression avoided (cost-effectiveness analysis, CEA),
- Incremental cost per quality-adjusted life year (QALY) gained (cost-utility analysis, CUA), and
- Cost consequences analysis (CCA) presenting the costs associated with the intervention and the full range of trial secondary outcome measures.

This analysis will be closely aligned with the analysis of effectiveness in the main trial in WP3. Multiple imputation by chained equations will be used to deal with missing EQ-5D-5L and resource use values (Faria et al., 2014). Subsequent analyses of imputed data will include variance correction factors to account for additional variability introduced into parameter values as a result of the imputation process (Little & Rubin, 2014). In the CEA and CUA, cost-effectiveness will be calculated as the mean cost difference between the intervention versus control, divided by the mean difference in outcomes (SMFQ-measured depression, QALYs) to give incremental cost-effectiveness ratios (ICERs). In the CUA we will also calculate cost-effectiveness measures based on net monetary benefits and incremental net monetary benefits (iNMBs). Non-parametric methods for calculating confidence intervals around the ICER and iNMB based on bootstrapped estimates of the mean cost and QALY differences will be used (A. H. Briggs et al., 1997). The bootstrap replications will also be used to construct a cost-effectiveness acceptability curve, which will show the probability that MAC is cost-effective at 12 months for different values of the NHS' willingness to pay for an additional QALY. We will subject the results to extensive deterministic (one-, two- and multi-way) sensitivity analysis. We will also undertake separate cost-effectiveness calculations for pre-specified subgroups of the trial population, as defined in the main trial statistical analysis plan. Theoretical and empirically derived subgroups include the include severity of depression and/or comorbid anxiety at baseline, exposure to childhood trauma, ethnicity, and age group (15 to 16 versus 17 to 18).

Lifetime cost-effectiveness of MAC

These will be calculated in terms of the incremental cost per QALY gained (lifetime CUA) and longer-term costs and spill-over effects associated with childhood depression, measured in terms of health, lifestyles and behaviours, educational attainment, employment, earnings (lifetime CCA). We will construct a de novo cost-effectiveness model, since reviews of economic evidence suggest that no long-term economic models of the management of depression in children exist (*NG134 2019 Evidence Review A*, 2019b). Assuming this remains the case at the time of analysis, we will model long-term costs and outcomes associated with depression in childhood using UK longitudinal datasets (e.g., National Child Development Study, NCDS, English Longitudinal Study of Aging, ELSA, Avon Longitudinal Study of Parents and Children, ALSPAC) coupled with secondary cost and HRQL evidence from published sources. This will replicate an approach that we have used previously to model the long-term costs and consequences of child maltreatment from health and societal perspectives (Conti et al., 2021). We will use regression analysis to predict longitudinal outcomes of measures of depression in childhood available in NCDS, ELSA and ALSPAC. The outcomes we select to model will be identified from a scoping review of reviews of the literature but are likely to include relapses of depression at older ages, and impacts on:

- Anxiety,
- Other mental health problems,
- Smoking,
- Alcohol abuse,

- Educational attainment,
- Marital status,
- Labour market outcomes (employment and earnings) and
- Welfare services use.

This analysis will allow us to predict the impact of childhood depression on the incremental probability of each outcome at the different ages used as follow-up points in the longitudinal studies. We will linearly interpolate the probabilities between these ages to produce tables of risk probabilities for every outcome for all ages across the life course. Annual costs for each outcome will be obtained, identifying published cost estimates from previous UK cost or cost of illness studies where possible, from searches of the literature, including:

- PubMed,
- NHS Economic Evaluations Database,
- EconLit and
- Google Scholar.

HRQL impacts associated with each outcome, and by age group where possible, will be obtained from a review of utilities from the CEA Registry Database at Tufts University (CEA Registry Database at Tufts University https://cevr.tuftsmedicalcenter.org/databases/cea-registry).

This analysis will result in estimates of the lifetime cost and QALY impacts of depression in childhood; these will be incorporated into the economic modelling based on differences in depression found in the trial (SMFQ-measured depression, the primary outcome). We will undertake deterministic (one-, two- and multi-way) and probabilistic sensitivity analysis, the latter assuming appropriate distributions and parameter values (A. Briggs et al., 2006).

In addition, we will combine data on incremental costs with epidemiological data on projected numbers and undertake a budget impact analysis to evaluate what the total cost impact of rolling out the use of the MAC intervention were it to be scaled up. We will use the probabilistic sensitivity analyses to undertake a value of information analysis (A. Briggs et al., 2006) to evaluate the potential economic value of future research on the use of MAC. We will discuss how best to utilise and present the findings of the economic analysis in WP5 to inform implementation of the MAC intervention.

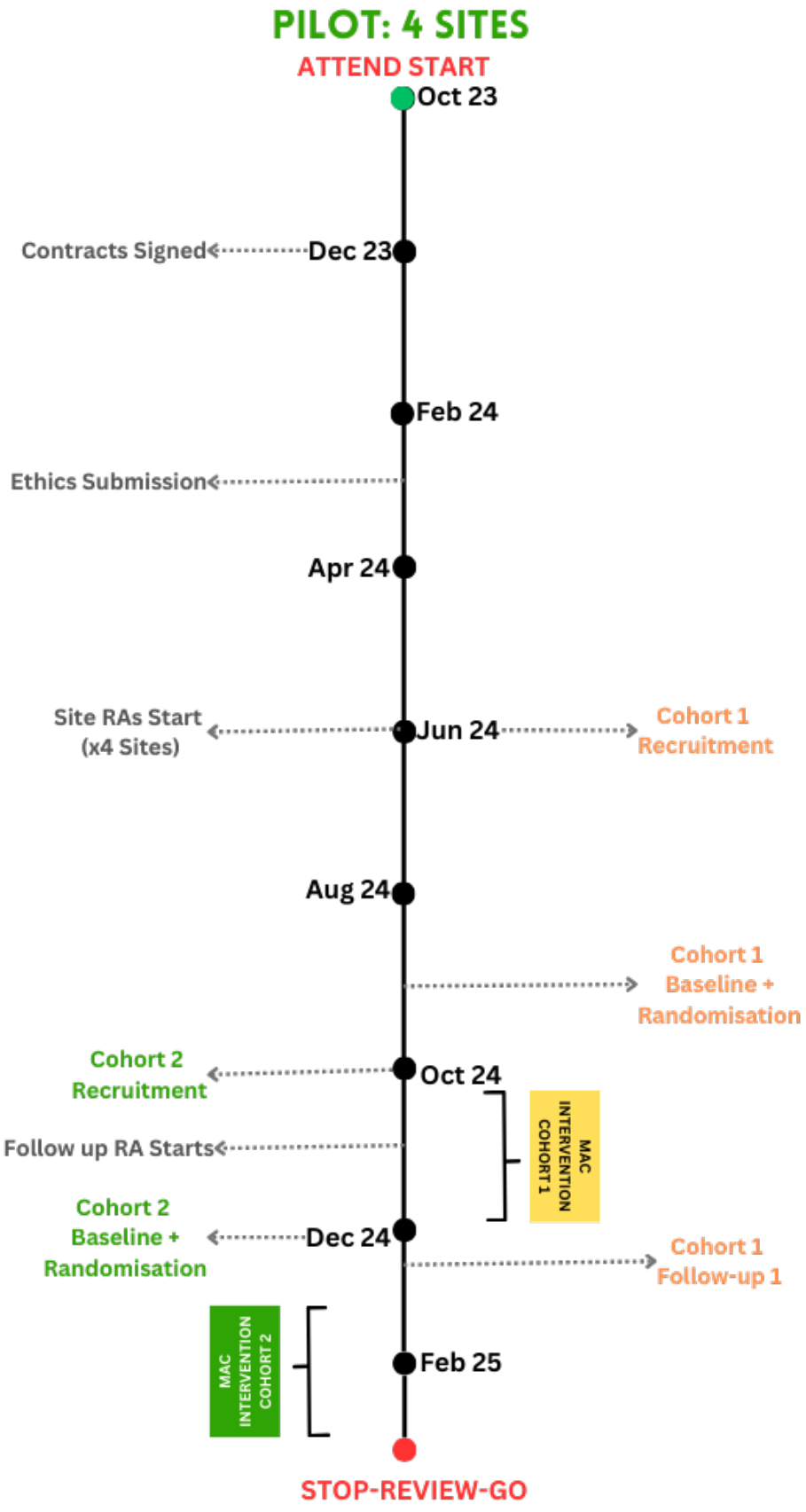
19. TRIAL TIMELINE

The study will start with an internal pilot RCT of two groups in each of the four sites (East of England, London, Devon, and Sussex) and one remote group; groups will be run in the Autumn 2024 and Spring 2025 academic terms. Should we meet our STOP/REVIEW/GO criteria, the full RCT would then bring on two additional sites (Oxford and Nottingham) and run a further 2 MAC groups in all six sites plus a remote group during the Autumn 2025 and Spring 2026 terms. Eight to twelve weeks are allowed for recruitment, and randomisation will occur within a month of the groups beginning. We have deliberately avoided running MAC groups during the summer terms since our experience indicates poor uptake while young people are preoccupied by examinations (see **Figure 10**).

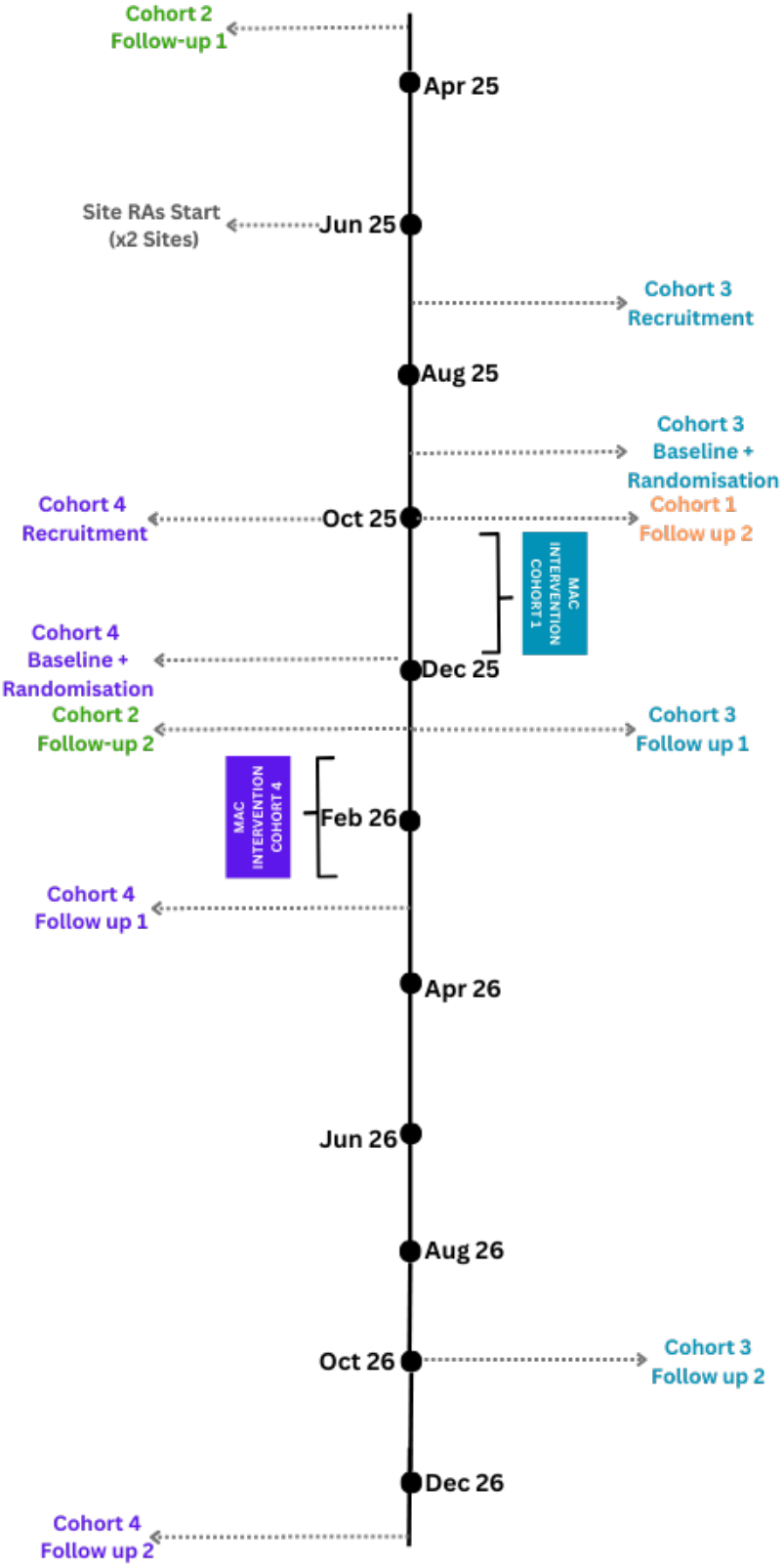
Participants' levels of depression will be measured using the SMFQ for young people and PHQ-8 for parent/carers fortnightly for 12 months following randomisation. All participants will also complete a full set

of measures at baseline, just after the MAC finishes (14 weeks post-randomisation) and 12 months post randomisation. Further details of how this work fits with the rest of the programme from the timeline are included in the Gantt chart (**Figure 11**)

Figure 10: RCT Milestones

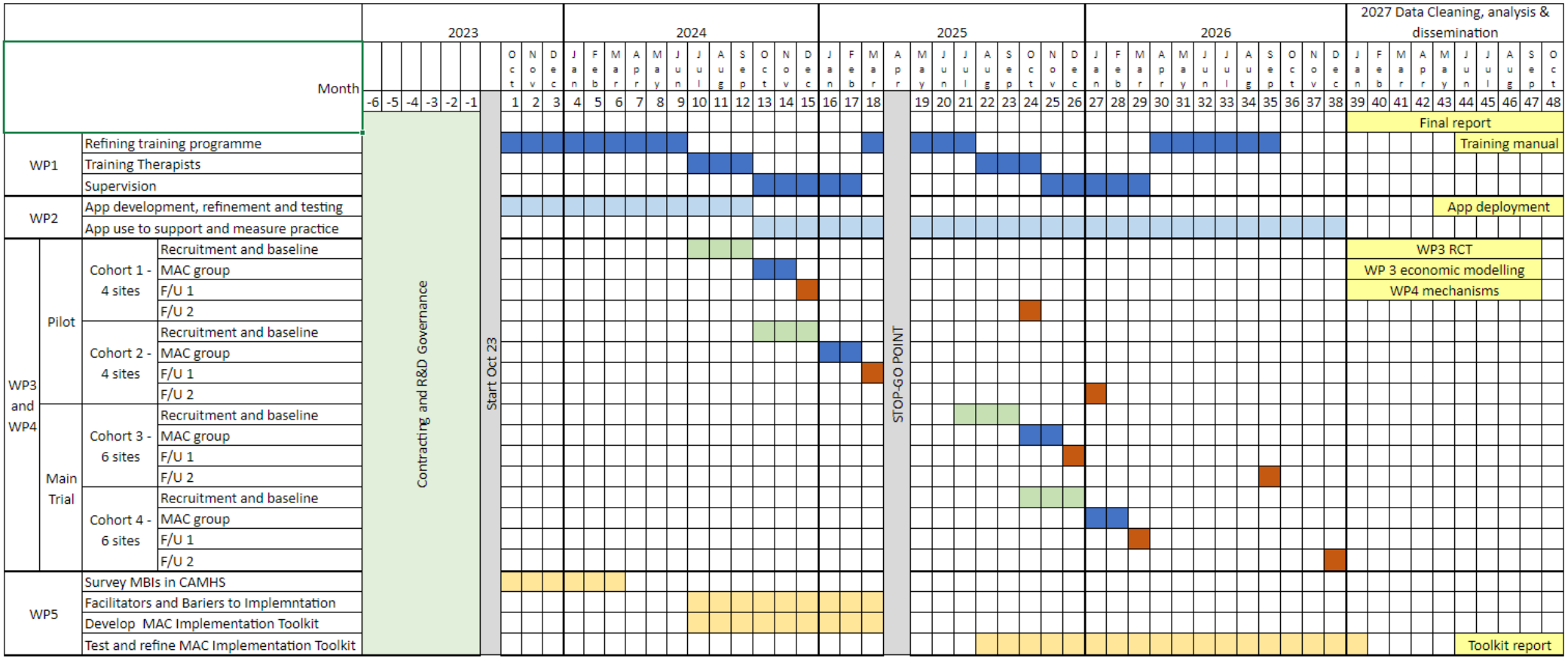


MAIN TRIAL: 6 SITES



2027: ECONOMIC MODELLING, MECHANISMS, ANALYSIS, DISSEMINATION

Figure 11: Whole Programme Gantt



20. CRITERIA FOR EARLY TERMINATION OF THE TRIAL

The trial has the following stop-review-go criteria based on recruitment, uptake of intervention, and drop out, that may lead to premature discontinuation of the trial.

STOP / REVIEW / GO criteria:

1. Mean recruitment of 40 adolescents per geographical site (target 48, stop if < 36),
2. Mean of 9 adolescents commence MAC from each site for each cohort of groups (target 12, stop if < 6),
3. Mean of 36 adolescents complete SMFQ at 3 months per site (target 40, stop if < 28).

Values in the review zones (36-39 recruited, 6 to 8 commenced, 28-39 retained) would require exploration for the potential to improve and continue with advice from the funders and the Trial Steering Committee.

21. DATA MANAGEMENT

Methods used to maximise completeness of data

We have worked with our PPIE collaborators and will continue to do so as well as with the newly formed Research Advisory Groups (RAGs) to support the development of standardised operating procedures on how we approach young people and families to ensure that the outcomes we are collecting are easy to complete and most relevant for the trial. We have built in regular checks on data completeness, including employing a researcher who will work across all sites to remind participants when follow-ups are due and gently reminding participants of overdue follow-ups. The participant incentive for taking part is offered in staggered payments that fall after each period of data collection (see **Table 3**).

Methods for ensuring secure storage of data

- All data will be collected and held in accordance with GDPR.
- Each young person, carer, and therapist will be assigned a unique identifier, which will be stored separately to all research data.
- Data collection will be managed by the CAM:IDE Team (University of Cambridge) and stored on servers located at the University West Site Data Centre.
- Identifiable data will be held in a REDCap server database, hosted on the ISO 27001 certified, NHS Toolkit compliant SafeHaven.
- Access to data will be restricted to the ATTEND research team.
- Levels of access will be set by assigning team members to defined User Roles within REDCap, to control both the blinding and restrict access to identifiable data.
- Deidentified data sets will be provided to Study Statisticians by the CAM:IDE Data Managers as required.
- Participants will be given the Privacy Notice (**Appendix n**) when consenting to take part.

Data collection methods

Scheduling of participant follow ups and the data collection will be carried out by Team Members allowed access to identifiable data (see **Table 7**), directly from the REDCap Database on the SafeHaven.

Both the fortnightly collection of the SMFQ or PHQ-8 for carers, and the Baseline and Follow-up measures will be achieved using the MyCap phone app, the data being returned directly to REDCap on the SafeHaven. Once initiated, scheduling and text message reminders are completely automated. Web links or paper forms can be provided for participants who prefer this, or without access to a phone. In the case of paper copies

being used, this data will be entered onto REDCap by one of the research team and then double checked by a different member of the research team. The paper copy of completed measures will then be securely scanned and uploaded to the participant's REDCap record. The original paper copy will be confidentially shredded. An additional variable will be added to the trial database to indicate if paper copies have been used so that it is easy to identify this form of data entry. The Apps will use secure end-to-end encryption and data security and handling will be General Data Protection Regulation (GDPR) compliant and will only be available for use by project participants.

We need to collect certain identifiable data in order to contact participants to arrange assessment and pass on important information. We are collecting the following participant identifiable data:

- Name
- Address
- Email
- Phone number
- GP name and address
- CAMHS/mental health service caseworker name and contact details.

This identifiable data will be obtained either via the Permission to Contact Form (**Appendix e**), in which case a member of the research team will enter it into the REDCap trial database or entered directly by the participant into REDCap.

Should this data be provided in paper format, it will be securely scanned and uploaded to REDCap with the original paper copy being confidentially shredded. Any identifiable data will be stored securely and separately from research data.

How long data will be stored for

The identifiable data listed above will be stored for the duration of the study on the SafeHaven platform. This is a prevention trial and so we hope to undertake a longer term follow up to see how benefits accrue during the next ~10 years (or when our youngest participant is 25) by linking to administrative datasets via their identifiable data, to compare key outcomes (attendance at school, A level results, post school education/training, admissions to A&E and further mental health treatment) to see if they differ between the intervention and control arms. Therefore, we offer participants the option to consent to the retention of their name, address, and date of birth following the study's completion, until we establish linkage with the National Pupil Database and various NHS England datasets, including HMRC, DWP, Hospital Episode Statistics, and the Mental Health Dataset. Our intention is to conduct this linkage post-trial, and five and ten years later, pending funding and the necessary ethical approvals which we will submit as an amendment. After this linkage, the identifiable information will be promptly deleted. Participants retain the right to opt out via the consent form. Ford and Smith hold overall responsibility for data storage and disposal of data from this project.

Data access

The de-identified research data will be as accessible as possible to other researchers who wish to use it, with requests being granted by the ATTEND Core Team as a group, using the standard ATTEND Publication Proforma. This also avoids duplication. Details in the ATTEND Dissemination Policy.

22. COMPLIANCE AND WITHDRAWAL

Intervention compliance

Whilst our primary analysis will be Intention-To-Treat, we will also run secondary complier average causal effect (CACE) analyses of the SMFQ primary outcome in young people. We will use the following criteria to determine if an 'adequate dose' of MAC has been received by the young person:

- **Attend at least 4 MAC sessions**(Dubicka & Bullock, 2017)

End of Trial definition

The end of the trial will be considered as the date on which the last participant has completed their follow-up assessment or qualitative component. The sponsor will notify the main Research Ethics Committee of the end of the trial within 90 days of its completion or within 15 days if the trial is terminated early.

Archiving

There is no requirement for physical archiving since all data will be stored electronically. Any information collected on paper will be securely scanned and confidentially shredded. All electronic data will remain encrypted, and password protected and saved in a study specific SharePoint hosted by the University of Cambridge.

Trial Governance

Ford and Smith, as joint Chief Investigators will assume responsibility for the financial management and delivery of the trial, supported by Hayes as Programme Manager and Giove-Hunt as Trial Manager. Ford will lead the Core Trial Team of PPIE Collaborators, Site Leads, RCT Researchers, Trial Statistician, Junior Statistician, Trial Health Economist and Junior Health Economist who will meet monthly via teleconference. These meetings will be used to monitor progress against the proposed timeline, to discuss recruitment and coordinate findings between the different work-streams as they arise and to discuss and solve possible risks or barriers to the delivery of the project. Weekly researcher meetings will be led by Giove-Hunt as the Trial Manager to keep track of the day-to-day running of the RCT.

Our independent Steering Committee is chaired by Dr Sara Evans-Lacko, Associate Professor, of the Care Policy and Evaluation Centre, London School of Economics and the Committee's role will be to provide critical scrutiny to the conduct of the programme overall and they will meet at least annually with the option of convening more frequently if required. Data Monitoring and Ethics Committee (DMEC) meetings will take place shortly prior to each TSC meeting. The Trial Statistician will request data extracts prior to the DMEC meeting and prepare open and closed DMEC reports (see **Table 7** for information regarding blinding) summarising data quality and safety information. The Chair of the DMEC will be provided to the TSC after each meeting.

Risk Management

This trial will inevitably involve participants who are vulnerable by virtue of their age and mental health. The latter may also apply to parent/carers. It is therefore essential that we have strong standardised operational procedures to ensure participant safety should risk of harm to self or others become evident, or if safe-guarding concerns emerge. Clinical responsibility for all young people will remain with their referring clinician. We will ensure that one person with Level 3 child protection training is available during office hours at all times to support Junior Researchers who are concerned about participants, as well as liaising closely with the referring clinician teams and ensuring that junior staff have basic child protection and risk management training.

Should young people or carers disclose a risk of harm to self or others a separate Risk Protocol will be actioned (**Appendix o**). This Risk Protocol will involve the completion of a standardised pro forma which will be signed by the local site lead and sent to the Trial Manager within 24 hours. The Trial Manager will complete a Serious Adverse Event form (SAE) (**Appendix o**) sending a copy to the Trial Steering Committee and to the East of England – Cambridge South Research Ethics Committee (24/EE/0091). The Participant Information Sheet (**Appendix d**) informs young people and carers that if they disclose information of potential harm to themselves or someone else, we will need to break confidentiality.
Although young people will be referred to the study from clinical services in health or school settings and may remain linked to these services during the study, some young people may be discharged during the follow-up period, and we will therefore need additional procedures in place to ensure the safety of this group. Service organisation varies between our sites, so we will prepare site specific standardised operating procedures in partnership with the involved teams. Where local services are unable to maintain clinical responsibility for young people, this role will be fulfilled by the young person's General Practitioner (GP). We will also record details of the parent/carer's GP in case we need to notify them of any risk to their patient.

Ford and Smith, with the support of Hayes and Giove-Hunt, will be responsible for identifying and managing risks and potential barriers. They will undertake a formal risk assessment and maintain a risk register. Risk or barriers to delivery will be a standing item for all team meetings to ensure the early identification of any issues arising, and to enable us to take timely remedial or mitigating action. If difficulties were not rapidly resolvable, we would inform the Trial Steering Committee and our grant manager at NIHR as appropriate.

Research ethics approval

We have received multi-centre ethical approval from the East of England – Cambridge South Research Ethics Committee (ref number 24/EE/0091) and local research governance approval for all sites (Devon Partnership Trust, South London and Maudsley Trust, Sussex Partnership NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, and Oxford Health NHS Foundation Trust). The study personnel, management group and independent Trial Steering Committee, chaired by Dr Sara Evans-Lacko will ensure that the study is conducted within appropriate NHS and professional ethical guidelines, ensuring that Good Clinical Practice guidelines are observed at all times. The core research team will all complete Good Clinical Practice Training and we will ensure that any Junior Researchers supporting the trial are also trained.

We intend to publish this protocol via a publicly available Open Science Framework. For any amendment to the trial, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body for them to issue approval for the amendment. Any amendments will be handled in line with the HRA IRAS amendments protocol, and our sponsor will submit a valid notice of amendment to the REC for consideration and follow the HRA IRAS processes.

23. FINANCING AND INSURANCE

Cambridgeshire and Peterborough NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the study caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the study, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the study (**Appendix r**). Further information and evidence of indemnity is available from the University's Research Operations Office.

24. REPORTING AND DISSEMINATION

We will mobilise knowledge from all WPs via social media, podcasts, blogs, and brief written summaries modified to suit the needs and interests of different stakeholders, including young people, parents, the public, practitioners in mental health and other services working with young people. We plan to discuss how best to present our findings with the Science Media Centre, and to provide policy briefings for service providers, commissioners, and policymakers. Our lived experience leads will support the young people and parent advisers who express an interest to actively contribute or lead the development of dissemination materials. Likewise, dissemination will be co-delivered with our young people and carer advisers and will leverage professional networks, such as the Association of Child and Adolescent Health, a multidisciplinary organisation devoted to evidence-based mental health care with a national network of branches and a widely disseminated newsletter.

Our training package and Implementation Toolkit would support NHS and third sector capacity to deliver MAC and MAC training at scale should MAC prove effective and cost-effective. Implementation will be facilitated by Richardson and Payne's leadership roles in the Children and Young People's Mental Health (CYP-MH) Programmes (previously known as CYP IAPT). The collaborative work of the Exeter and Oxford Mindfulness Centres has successfully embedded MBCT into adult NHS mental health services, including NICE guidelines and the Increasing Access to Psychological Therapy services and training. We anticipate similar pathways would be available to support training and dissemination for MAC. Likewise, the Implementation Toolkit will inform and support the rapid roll-out of MAC at scale, should CAMHS, school-based mental health support teams or the third sector be commissioned to deliver MAC at scale.

The co-applicants and all researchers involved in the wider ATTEND PGfAR will have access to the final full dataset produced by the research proposed in this protocol. A data sharing agreement will be drawn between all the institutions where co-investigators on the ATTEND PGfAR are based. All participant information documents will outline the intended use of the data in the research.

25. DIVERSITY CONSIDERATIONS

We expect to have to work harder to engage underserved populations and are actively linking with the established avenues of communication in all sites with their underserved populations, such as the NIHR Applied Research Centre East of England's "populations in focus".

As a second line therapy, participants will come to the trial through services, meaning that we will have limited power to counter any inequalities in initial access. However, we will systematically scan records to encourage referrals from underserved groups and have broadened our recruitment to school based mental health support teams, counsellors and nurses, and community well-being teams in an effort to reach a more diverse population. We will monitor equity of access by recording participants' relevant demographic information (including protected characteristics) at registration. We will report these data fully, and where possible we will compare the background demographics of our sample to those of the relevant local clinical

and/or community populations. This will be monitored throughout the trial, including the demographics of participants who have refused to take part. This information will guide our actions below to ensure we are focusing our outreach to the correct underrepresented groups. To address potential barriers, we have included in the PPIE funding:

- A Research Advisory Group which will consist of a mix of people with different ethnicities, socio-economic backgrounds, and from LBGTQ+ communities. Part of their role will be to check all recruitment procedures and documents to make sure that these are inviting and relatable.
- Funding for professional translators for better chance of engaging hard-to-reach groups. Unfortunately, we are not able to confirm all questionnaires will have validated translations. The MAC intervention will also be conducted in English. However, as the young people are of school-age and living in Britain, it is likely they have a good enough grasp of English to take part in MAC and complete the measures. We are aware that their parents may not have as good a level of English, and in these cases will utilise translators to ensure they are clear on the study before consenting their child to take part, even if they may not be able to join in the parent/carer sessions themselves.
- Funding is included in the PPIE budget for outreach to the different communities, including travelling into the community to speak about the project. We will include some incentives for the local leads/volunteers to be the point of contact for the PPIE representative to engage with.
- We will use the local contacts stated above to have a phone call with the identified participants of the diverse groups, to go through the trial and any questions (we would ensure consent to be contacted is gained prior via the usual channel). We hope the relatability with someone who is local and belonging to the same group/community will mean populations who may not normally take part would be more willing to try.

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Appendices

A: Recruitment Poster for Referring Clinicians

B: PIS Short Written Summary

C: PIS Video of Short Written Summary

D: PIS Full

E: Permission to Contact Form

F: Consent: Parent/Carer

G: Consent: YP Aged 15 – Parents

H: Assent: YP Aged 15

I: Consent: YP Aged 16+

Ji: YP: Questionnaire Booklet

Jii: YP: Fortnightly Questionnaire

Jiii: YP: CRIES–8 and site preference

K: P/C: Questionnaire Booklet

L: Treatment Recording Sheet

Mi: Qualitative Interview Topic Guide: Parent/Carers

Mii: Qualitative Interview Topic Guide: Young People

N: Participant Privacy Notice

O: Risk Protocol

P: Safeguarding Report Form

Qi: Template GP Letter: Young People

Qii: Template GP Letter: Parent/Carers

R: Insurance Details

S: Template Invite Email: First contact from researcher

T: Recruitment Poster (All pilot sites)

Ui: Template CRN Letter: 15 + Parent/Carers

Uii: Template CRN Letter: 16 +