EMDR for Depression

A randomised controlled trial evaluating the efficacy and mechanisms of eye movement desensitisation and reprocessing therapy (EMDR) compared with treatment as usual for adults with depression in primary care

Protocol version:	V3.0 06-Nov-2025
IRAS project ID:	338392
REC Reference:	South West – Frenchay, 25/SW/0087
Sponsor:	University of Bristol 2025 - 883
ISRCTN:	13955131
Funder (NIHR EME):	160513
NIHR RDN Portfolio:	CPMS 60219

This protocol has regard for the HRA guidance

KEY TRIAL CONTACTS

Chief Investigator	Professor Nicola Wiles, Professor of Epidemiology Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, Clifton, Bristol BS8 2PN Tel: 0117 331 3358 Email: Nicola.Wiles@bristol.ac.uk
Co-investigators	Professor David Kessler, Professor of Primary Care Mental Health, Population Health Sciences, University of Bristol Professor Katrina Turner, Professor of Primary Care Research, Population Health Sciences, University of Bristol Professor Tim Peters, Professor of Primary Care Health Research, Bristol Dental School, University of Bristol Dr Stephanie MacNeill, Associate Professor in Medical Statistics, Population Health Sciences, University of Bristol Professor Stanley Zammit, Emeritus Professor of Psychiatric Epidemiology, Population Health Sciences, University of Bristol Dr Charlotte Archer, Research Fellow in Primary Care Mental Health, Population Health Sciences, University of Bristol Ms Debbie Tallon, Research Programme Manager, Population Health Sciences, University of Bristol Dr Gemma Hammerton, Senior Lecturer in Epidemiology and Medical Statistics, Population Health Sciences, University of Bristol Dr Kirsty Garfield, Senior Research Fellow in Health Economic Evaluation, Population Health Sciences, University of Bristol Professor Glyn Lewis, Professor of Epidemiological Psychiatry, Division of Psychiatry, UCL Division of Psychiatry Professor Kate Walters, Professor of Primary Care and Epidemiology, Primary Care and Population health, UCL Institute of Epidemiology and Health Care Professor Oliver Robinson, Professor of Neuroscience and Mental Health, UCL Institute of Cognitive Neuroscience Professor Quentin Huys, Professor of Computational Psychiatry, Division of Psychiatry, UCL Division of Psychiatry Professor Athene Lane, Professor of Trials Research, Population Health Sciences, University of Bristol Professor Barney Dunn, Professor of Clinical Psychology, Health and Community Sciences, University of Exeter Medical School

	Professor Rupert Payne, Professor of Primary Care and Clinical Pharmacology, Health and Community Sciences, University of Exeter Medical School Mr Garry Hendy, PPI Co-Applicant
Trial Management	Bristol Trials Centre, University of Bristol
Lead Statistician	Associate Professor Stephanie MacNeill, University of Bristol
Web address	https://eyed.blogs.bristol.ac.uk

Table of Contents

1 FUNDING AND SUPPORT IN KIND

FUNDING AND SUPPORT IN KIND	**Financial and non-financial support given**
NIHR EME National Institute for Health Research, Efficacy & Mechanism Evaluation Address: University of Southampton Alpha House, Enterprise Road Southampton, SO16 7NS (UK) Telephone: 023 8059 4303 Email: eme@nihr.ac.uk	Grant funding
Bristol Trials Centre Population Health Sciences, Bristol Medical School, University of Bristol 1-5 Whiteladies Road Bristol, BS8 1NU Telephone: 0117 455 1230 Email: btc-mailbox@bristol.ac.uk	Methodological expertise and trial management
University of Bristol Key contact: Anna Brooke Address: Research and Enterprise Development University of Bristol, Senate House Tyndall Ave Bristol, BS8 1TH Telephone: 0117 455 3545 Email: research-governance@bristol.ac.uk	Sponsorship
Bristol, North Somerset and South Gloucestershire (BNSSG) Integrated Care Board (ICB) Address: 360 Bristol – Three Six Zero, Marlborough Street Bristol, BS1 3NX Telephone: 0117 9002323 Email: bnssg.research@nhs.net	Host

2 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ARC	Applied Research Collaboration
BDI-II	Beck Depression Inventory (second edition)
BNSSG	Bristol, North Somerset and South Gloucestershire
BTC	Bristol Trials Centre
CACE	Complier Average Causal Effect
CAPC	Centre for Academic Primary Care
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CIS-R	Clinical Interview Schedule – Revised
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
CTQ	Childhood Trauma Questionnaire
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DSA	Data Sharing Agreement
EDI	Equality, Diversity, and Inclusion
eISF	Electronic Investigator Site File
EOI	Expression of Interest
EMDR	Eye Movement Desensitisation and Reprocessing
ETC	Excess Treatment Cost
eTMF	Electronic Trial Master File
EU	European Union
GAD-7	Generalised Anxiety Disorder-7
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
IAPT	Improving Access to Psychological Therapies
ICD-10	International Classification of Diseases (10th revision)
ICB	Integrated Care Board
ICECAP-A	Icepop Capability measure for Adults
ICH-GCP	International Council for Harmonisation's Good Clinical Practice
IMD	Index of Multiple Deprivation
IMP	Investigational Medicinal Product
IQR	Interquartile Range
ITQ	International Trauma Questionnaire
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
LEC-5	Life Events Checklist for DSM-5
LEG	Lived Experience Group

MCID	Minimum Clinically Important Difference
MH-ALL	Mental Health Research for All
NHS	National Health Service
NHS-TT	NHS Talking Therapies
NICE	National Institute for Health and Care Excellence
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PIL	Patient Information Leaflet
PPI	Patient and Public Involvement
PPIE	Patient and Public Involvement and Engagement
PTSD	Post-Traumatic Stress Disorder
QALY	Quality Adjusted Life Years
R&D	Research & Development
RCT	Randomised Controlled Trial
RDN	Research Delivery Network
RDSF	Research Data Facility Storage
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDV	Standard Data Verification
SEM	Structural equation modelling
SLE	Stressful life events
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SSC	Service Support Costs
SUD	Subjective Units of Distress
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	Usual Care
UCL	University College London
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust
USM	Urgent Safety Measure
UK	United Kingdom
UoB	University of Bristol
VAS	Visual Analogue Scale
VOC	Validity of Cognition
WM	Working memory
WSAS	Work and Social Adjustment Scale

3 TRIAL SUMMARY

Trial Title	A randomised controlled trial evaluating the efficacy and mechanisms of eye movement desensitisation and reprocessing therapy (EMDR) compared with treatment as usual for adults with depression in primary care.
Short title	EMDR for depression (EYE-D)
Chief Investigator	Professor Nicola Wiles Professor of Epidemiology University of Bristol, UK
Sponsor	University of Bristol (UoB)
Funder	Efficacy and Mechanism Evaluation (EME), National Institute for Health and Care Research (NIHR)
Trial Design	Two parallel group multicentre randomised controlled trial (RCT) with allocation at the level of the individual
Trial Participants	Primary care patients with depression
Target sample size	380
Target number of GP practices	90
Intervention	12-18 sessions of EMDR (weekly 60-90 mins individual in-person)
Follow up duration	52 weeks post randomisation
Inclusion criteria	Aged ≥18 years; have a BDI-II score ≥14; meet ICD-10 depression criteria; and willing to discuss past stressful experiences related to their depression.
Exclusion criteria	PTSD/complex PTSD, substance abuse problems (including alcohol dependence), bipolar disorder, schizophrenia, psychosis, dissociative disorder, moderate/severe personality disorder or dementia; receiving psychotherapy or secondary care for depression at eligibility screening; who have a history of repeated contacts with secondary care services or community mental health teams; who have a history of repeated self-harm; who cannot complete self-administered questionnaires in English; or who are participating in another trial of an intervention for mental health.
Primary objectives	Efficacy: To determine the efficacy of EMDR (in addition to Usual Care (UC)) in improving depressive symptoms in primary care patients with depression, compared with UC.
Primary efficacy outcome	The primary outcome is depressive symptoms on the Beck Depression Inventory (BDI-II) at 26 weeks post-randomisation

Secondary objectives	Efficacy: To determine the efficacy of EMDR at 26 weeks in terms of: 1) Proportional change in depressive symptoms 2) Remission of depressive symptoms 3) Measures of anxiety and depression used in NHS Talking Therapy services 4) Impairment in functioning 5) Health-related quality of life and capability These outcomes will also be measured at 52 weeks
Internal pilot	The study includes a 6-month internal pilot to ensure that we are able to recruit to the main trial as planned, and that participants are engaging with the intervention as expected. Aim: To have randomised a total of 36 participants from at least 10 GP practices by month 7 of participant recruitment.
Study duration	Grant contract start date: 1st March 2025 Anticipated duration: 50 months Anticipated end date: 30th April 2029

3.1 Plain English Trial summary

Depression is a common and disabling illness. Many people with depression have experienced traumatic and stressful life events. These may include physical, sexual or emotional abuse, death of a loved one, job loss or relationship breakdown. These experiences can affect an individual's beliefs about themselves, which can lead to depression or make it worse. Current treatments for depression do not focus on the memories linked to these past experiences. We may be able to better treat depression by targeting these memories and beliefs.

A therapy called eye movement desensitisation and reprocessing therapy (EMDR) is an effective treatment for post-traumatic stress disorder. It may also help treat depression. The theory behind EMDR is that symptoms continue or are made worse because memories of past life experiences were not fully processed at the time of the event. EMDR is a way of helping reprocess these memories to lessen their impact.

During EMDR, the patient is asked to think about the memory of a past experience and a negative belief linked to that memory. At the same time, they make left-to-right eye movements by following the therapist's finger as they move it from side-to-side. The therapist may also ask the patient questions about their past experience. The eye movements are thought to help fully process the memory. Eye movements continue until the memory is less distressing, and a more helpful self-belief emerges.

Small studies suggest that EMDR may reduce depressive symptoms. However, no large, high-quality studies have been done so we don't know if EMDR is a useful treatment for depression. We want to do a large study of 380 people to see if EMDR can help people with depression and to understand how it works. We will ask people with depression if they are willing to take part and to be put into one of two groups at random (like flipping a coin). One group will receive 12 to 18 sessions of one-to-

one EMDR therapy, in addition to usual GP care, and the other group will see their GP as usual but will not receive any EMDR therapy. People who take part will be contacted by a researcher six times over a year. They will be asked to fill in a questionnaire about their symptoms each time. By comparing depressive symptoms for the two groups, we will find out if EMDR helps people with depression. To understand how EMDR works, we will ask people in the study if their memories become less vivid and distressing, and if their beliefs about themselves change over time. Patients and therapists will be asked about their views and experiences of EMDR as a depression treatment.

In the UK, most patients with depression are treated by their GP in primary care. We will work with GP practices to recruit patients for this study. We will invite patients from 90 general practices to take part. We will invite people of different ages, genders, backgrounds and ethnicity so the results apply as widely as possible.

We are involving people who have experienced depression in each stage of the research, so that the study's design and delivery is shaped by patient views, and findings are shared with public and patient groups in ways that are easy to understand. The results of our study will also be shared with other researchers, GPs, and the people who decide what health services are needed.

This is an important study because depression is very common, and memories of stressful experiences may be part of why many people experience depression.

4 BACKGROUND AND RATIONALE

4.1 Evidence explaining why this research is needed now

Depression is a common condition in primary care, with a prevalence estimated as 13.2% in 2022/23 [1]. It is one of the leading causes of disability [2] and lost work-days [3], and represents a great burden to patients, the NHS and society. By 2026, the total costs of services for depression in England are estimated to be £3 billion and, with lost employment, total economic costs £12.2 billion [4]. Only 40-50% of patients respond to the most common treatments (antidepressants and cognitive behavioural therapy, CBT) [5, 6]. Novel approaches to treating depression are needed, especially if they act via different mechanisms to existing treatments.

Eye-movement desensitisation and reprocessing therapy (EMDR) is a NICE-recommended trauma-focused psychological intervention for post-traumatic stress disorder (PTSD) [7]. The protocol has been adapted for depression [8]. It emphasises the importance of eliciting and reprocessing dysfunctionally stored (or pathogenic) memories that predispose to and maintain depression.

Many people with depression talk about distressing past events. Stressful life events (SLEs) (e.g. job loss, bereavement) or traumatic experiences (e.g. childhood abuse and neglect, accidents and assaults) are associated with an increased risk of depression and poorer prognosis [9-14]. There is some evidence that individuals with a history of childhood maltreatment are less likely to respond to depression treatments, [11, 13] but others found no such differences [15].

Pathogenic memories may arise after stressful past events. Targeting memories linked to depression using EMDR provides a new avenue for treatment and aligns with guidance to discuss stressful experiences in the initial primary care consultation [16], but, to date, there is no robust evidence of efficacy [17].

4.2 Mechanism of action

It is unclear how EMDR works [18]. Whilst CBT teaches people skills to change unhelpful thoughts and behaviours, EMDR focuses on reprocessing pathogenic memories to reduce their emotional salience and enable more positive beliefs and behaviours to emerge.

The adaptive information processing model [19] underpinning EMDR posits that there is an innate system that processes memories in an adaptive way so that the emotional salience of an upsetting memory usually decreases with time. After an upsetting event, memories are stored as a sensory representation (emotional memory). As connections are made with contextual information (e.g. it's over, others say it's not my fault), it becomes stored as a contextual representation (factual memory), without the distress, physiological arousal and body sensations when recalling what happened [20]. An inadequate shift from sensory to contextual representation results in pathogenic memories. Recall of pathogenic memories is not under voluntary control and can be triggered by internal or external stimuli resulting in a re-experiencing of the cognitive, emotional and physical states associated with the original distressing event [19, 21]. It is postulated that depression can arise and be maintained by stimuli triggering pathogenic memories (e.g. of parental separation) and associated beliefs (e.g. I am inadequate) [8].

The working memory (WM) hypothesis [18] is the leading theory of how EMDR enables the shift from emotional to factual memory and has empirical support [22]. A central element of EMDR is bilateral stimulation where patients make eye movements whilst recalling the memory (dual task). The dual task demand on WM limits the scope for emotional overactivation that can impair memory processing. Hence patients with lower WM capacity may benefit more from EMDR.

It is hypothesised that, as processing occurs, the vividness and emotional intensity of memories decreases, and global (not just memory-specific) self-beliefs become more positive (e.g. I am good enough). This shift in beliefs is aided through therapeutic interweaves (e.g. Socratic questioning, third-person perspective, imagery) and leads to symptom reduction (as occurs when treating PTSD). Yet, no studies of EMDR for depression have examined changes in emotional salience, negative beliefs and other PTSD symptoms as mediators of treatment effect, nor have they examined whether WM capacity affects treatment response.

Lack of understanding of mechanisms has led to scepticism about EMDR. Future efficacy studies need to incorporate a mechanistic study to provide empirical evidence of how EMDR for depression works and for whom. This would allow the potential for improving the effectiveness of EMDR by optimising content and/or delivery, provide hypotheses for targeting treatment, and may lead to novel therapies using newly identified mechanisms.

4.3 Setting and comparator to establish efficacy

Antidepressants and CBT-based therapies are common interventions in primary care, but these are not acceptable or effective for all depressed patients. EMDR is a novel intervention focused on pathogenic memories of distressing events that may underlie depression. Unlike CBT, EMDR does not require individuals to directly challenge beliefs or behaviours, or complete 'homework', so it may be more acceptable to those who find homework difficult and a barrier to engagement. EMDR probably acts via a different mechanism than existing treatments, so combining EMDR with current treatments could improve outcomes. But first, we need to establish if EMDR is an efficacious treatment for depression and understand how it works.

Depression is usually managed in primary care. Whilst, if efficacious, EMDR would probably be offered by NHS primary care talking therapy services (NHS-TT) (formerly IAPT), a trial in this setting could not answer the efficacy question. If recruiting from a talking therapy service, the comparator would, by definition, be an established treatment, most often CBT, and the trial designed as a non-inferiority comparison. This would not answer the question of whether EMDR is an efficacious treatment for depression. Moreover, less than one-third of those with depression will be seen in NHS talking therapy services by 2023/24 [23] and hence a trial recruiting from talking therapy services would exclude more than 70% of those with depression in primary care. As an intensive therapy, EMDR may be viewed as a further-line treatment [16], but we need to know if EMDR is of benefit before targeting treatment (e.g. for medication non-responders). Hence, this study has been designed with the key question as whether EMDR is an efficacious treatment for depression compared with care as usual delivered by GPs in primary care. This is the best comparator and setting for a trial to definitively establish the efficacy of EMDR. A wait-list design is not an option as a network meta-analysis of trials of CBT for depression found that this is harmful compared with usual care for depression [24].

To date, there is evidence that EMDR may reduce depressive symptoms in individuals whose primary problem is depression [17, 25], but no definitive evidence of efficacy or mechanisms of action from large randomised controlled trials (RCTs). Given the high burden of depression, this research is highly relevant to primary care, aligns with NHS strategy [26], and, if EMDR is efficacious, may result in substantial health gains for individuals and increase productivity.

RESEARCH QUESTIONS, OBJECTIVES AND OUTCOMES

4.2 Aim:

To establish the efficacy of EMDR (in addition to usual GP care (UC)) compared with UC for adult patients with depression in UK primary care.

An embedded mechanistic study will determine whether reductions in depression are mediated via key memory-processing mechanisms and if working memory capacity is associated with treatment response. A nested qualitative study will examine the acceptability of EMDR for depression, the application of EMDR for depression compared to PTSD, further explore mechanisms, and identify possible causes of differing responses that could explain trial results. An intervention costing exercise will estimate the cost of delivering EMDR in the NHS.

4.3 Efficacy objectives

4.3.1 Primary efficacy objective

Efficacy: To determine the efficacy of EMDR (in addition to UC) in improving depressive symptoms in primary care adult patients with depression, compared with UC. The primary outcome is depressive symptoms on the Beck Depression Inventory (BDI-II) at 26 weeks post-randomisation (post-treatment).

4.3.2 Secondary efficacy objectives

Efficacy: To determine the efficacy of EMDR at 26 weeks post-randomisation in terms of:

1.) Proportional change in depressive symptoms (BDI-II)
2.) Remission of depressive symptoms (BDI-II score <10)
3.) Measures of anxiety and depression used in NHS talking therapy services (PHQ-9 and GAD-7)
4.) Impairment in functioning (WSAS)

5.) Health-related quality of life and capability (EQ-5D-5L and ICECAP-A)
These outcomes will also be measured at 52 weeks along with the continuous BDI-II score.

4.4 Mechanistic objectives

4.4.1 Primary mechanistic objectives

To determine whether reductions in:

1.) Vividness and emotional intensity of depression-related memories;
2.) Negative self-beliefs; and
3.) Re-living, avoidance and hyper-arousal symptoms linked to past stressful events

measured during treatment (16 weeks) mediate the effect on depression at 26 weeks.

4.4.2 Secondary mechanistic objective

To determine whether baseline working memory capacity is associated with treatment response at 26 weeks.

4.5 Qualitative Objectives

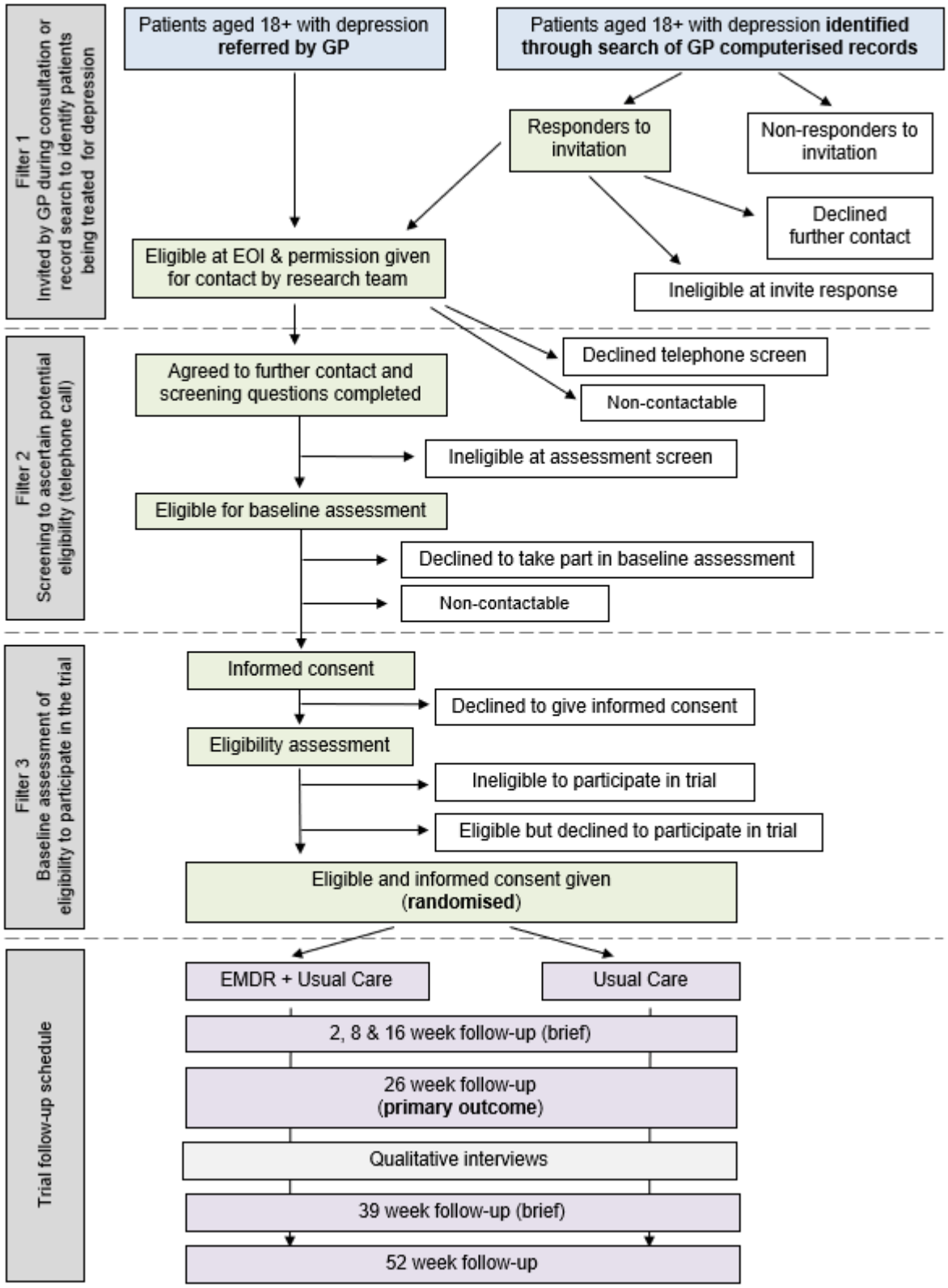
1.) To understand patients' and therapists' views and experiences of UC and EMDR as treatments for depression.
2.) To explore patients' and therapists' views on how EMDR affected the intensity of memories, self-beliefs and symptoms linked to past stressful events.
3.) To explore EMDR trainers', therapists' and their supervisors' views on similarities and differences between EMDR for depression and EMDR for PTSD
4.) To identify possible reasons for variation in treatment outcomes, any adverse effects and unintended consequences associated with EMDR, and how these could be addressed.

4.6 Intervention costing objectives

An intervention costing exercise will estimate the cost of delivering EMDR in the NHS.

5 TRIAL DESIGN AND SETTING

5.1 Trial schema



5.2 Trial design

EYE-D is a two parallel group multi-centre, individually randomised, controlled trial with an internal pilot and embedded mechanistic and qualitative studies and intervention costing exercise.

A remote (web) randomisation service will ensure allocation concealment. Randomisation will be stratified by centre and minimised on baseline antidepressant use and depression severity (section 6.5 randomisation). Given the nature of the intervention, it will not be possible to blind participants to treatment allocation. Self-reported outcomes will avoid observer bias. Attrition bias will be minimised through regular contact with participants as advised by our lived experience group (section 12). The recruitment processes outlined (section 6.3) mirror those used in our previous successful primary care depression trials that have recruited to target [27-30]. We have included an internal pilot (section 5.4) to ensure that we are able to recruit as planned and that participants are engaging with the intervention.

5.3 Inclusivity and diversity

Patient eligibility will not be restricted by age (except excluding those aged <18 years), sex, gender, marital status, ethnicity, pregnancy, religion, sexual orientation, or socio-economic status. The number of people affected by poor mental health is highest in communities living in some of the most disadvantaged areas. However, these individuals are less likely to use mental health services and are under-represented in mental health research. Whilst our three recruiting centres (Bristol, Exeter and UCL) are located in the South of England, 'heat maps' of regional research activity show that our University centres are located in areas of unmet mental health need (recruitment per 1,000 prevalence: West of England (Bristol) 7.1; South West Peninsula (Exeter) 5.0; North West London (UCL): 11.5 compared with South London: 57.1) [31]. Moreover, our three recruiting centres are diverse e.g. self-reporting non-white British ethnicity: England & Wales: 19.0%; Bristol 18.9%; Exeter 9.7%; London 63.2%; and living in social housing: England & Wales: 17.1%; Bristol 18.7%; Exeter 16.6%; Camden 33.7% (https://www.ons.gov.uk/peoplepopulationandcommunity). This will enable us to recruit from practices providing care for under-served groups to ensure that a more representative and inclusive sample is recruited [32, 33].

We have carefully considered the primary reasons for under-representation [34]: (1) language; (2) access and (3) trust. Potential participants will be provided with information leaflets to ensure that the nature of the study, and what is entailed, is clearly set out. We will work with our lived experience group (LEG) (PPI and section 12) to ensure that patient-facing materials are clear, accessible and transparent in relation to confidentiality, anonymity and data recording to help participants build trust in the research team. As part of the baseline assessment, we will collect demographic data in order to describe the population recruited. Using mailed invitations (as well as in-consultation referral) will also help us reach those not in frequent contact with their GP.

In our recent INTERACT trial (unpublished data), 19% of participants from the Bristol and London sites self-reported non-white British ethnicity (Bristol: 9% n=25/278; London: 45% n=45/99) demonstrating the inclusion of a more diverse population compared with our earlier depression trials (CoBalT; 2% [30]; MIR: 3% [29]; PANDA: 11% [28]; ANTLER: 5%) [27].

We will use guidance from the NIHR INCLUDE project [33] to improve inclusion and Trial Forge guidance [32] to recruit and retain individuals from ethnic minority groups. We will build on colleagues' experiences of improving diversity in research [35] through established connections with local communities in order to maximise engagement and utilise existing resources to promote research participation (e.g. 'why take part in research' video) [36]. One of our LEG members has

agreed to work with us as Equality, Diversity and Inclusion (EDI) Ambassador to ensure a diverse population is represented in the study. Our diverse LEG will help diversify our PPI activities to ensure that different groups and their voices shape the trial. We will seek their advice about how best to: (1) build trust with local communities; (2) advertise in their communities; and (3) create summary/easy-read versions of study recruitment materials to improve access for people with lower literacy or people for whom English is not their first language. Our LEG members will also inform our dissemination routes.

We will recruit via GP practices that serve diverse populations, for example, via the 'GPs at the Deep End' network which was established by colleagues in Bristol and includes 17 practices that serve patients from the most deprived and ethnically diverse areas in Bristol [37] as well as targeting practices with index of multiple deprivation (IMD) scores 1-3 (i.e. lowest three deciles) to increase diversity in all centres. We will also partner with local initiatives working to support diverse communities with research participation (e.g. Health Ambassadors working in the Bristol area [38]; the Mental Health Research for All (MH-ALL) programme led by NIHR ARC North Thames [39] and the South West Mental Health Gap Practice Research Network (Exeter) [40]. In addition, through their established links, the Centre for Academic Primary Care (CAPC) Patient and Public Involvement and Engagement Advisor will support us in developing relationships with the Research Engagement Networks on Diversity (REND) whose focus is on increasing diversity in research participation [34, 41, 42].

Participants will be required to give informed consent and to complete six follow-ups (at 2, 8, 16, 26, 39 and 52 weeks) during the course of their year-long study involvement. Thirty people will be invited to take part in an individual interview with a researcher (section 6.15). As advised by our PPI group (PPI: proposal development) two early contacts at 2 and 8 weeks will help build trust and engagement with the study to maximise longer-term retention.

Whilst remote (videocall/telephone) trial appointments may be convenient and enable participation for some (e.g. those living in more remote areas; with disabilities or caring responsibilities; or those working/studying full-time); for others digital exclusion or mistrust of digital approaches may be barriers to participation [34]. Hence, as advised by our PPI group, remote and in-person appointments will be offered for follow up. There will also be the option of completing a questionnaire independently online (section 6.12). Participants will be asked their preference for the mode of contact for follow-ups.

Trial participants will be asked if they would like to be sent a regular newsletter to update them on study progress. They will also be asked if they would like to be sent a plain English summary of the findings. The newsletters and summary will be co-produced with our LEG to ensure accessibility. Although many people take part in depression research for altruistic reasons [43, 44] our PPI group advised offering participants shopping vouchers in recognition of the time taken to complete follow-up questionnaires. We will therefore offer participants £10 for the short follow-ups at 8, 16 and 39 weeks; and £20 for the longer follow-ups at 26 and 52 weeks. We are not offering a voucher at the initial 2-week follow-up as this will be a brief contact (phone/email) to check in and answer any questions that have arisen about participation. Participants will also be offered a £20 shopping voucher for taking part in an interview.

5.4 Internal pilot

There will be a 6-month internal pilot to ensure that we are able to recruit to the main trial as planned and that participants are engaging with the intervention as expected.

EMDR is a novel intervention for patients with depression. Therefore, it is important to examine treatment engagement during the initial stages of the trial to ensure that patients are engaging with the treatment as anticipated and so that we can address any issues through sites and staff/therapist training. During this pilot, short telephone interviews will be held with individuals who were invited to take part in the trial but decline to do so (section 6.15). Such 'decliner' interviews can indicate how recruitment processes and documents can be improved to encourage engagement, and can provide another standpoint from which to evaluate acceptability of the trial and intervention being assessed.

Recruitment will start in one centre (Bristol, the lead centre) in order to most efficiently refine the trial processes and working instructions, and identify and address difficulties that we might encounter. We have used this approach in our previous trials that have successfully recruited to target – CoBalT [30], MIR [29], PANDA [28], ANTLER [27] and, more recently, INTERACT [44]. Bristol was selected for the pilot as we have close links with the Research Delivery Network (RDN) team that covers a wide geographic area including rural and urban, and affluent and deprived areas. Prior to the start of the internal pilot, we will engage with the Bristol RDN teams to ensure local approvals are in place and that we can approach local GP practices early.

Starting recruitment at one site will increase the efficiency of later site set-up by ensuring that the other sites start when trial processes and working instructions have been refined, and databases have been finalised, thus ensuring successful roll-out. Furthermore, in our previous trials, we have found that the recruitment rate and intervention engagement in the lead site provides a very good estimate of the future recruitment and engagement rates in the other sites.

Centre set-up for UCL and Exeter will therefore start in month 5 of the internal pilot (Appendix 1: month 13), with a two-month period of training for their EMDR therapists. This will run concurrently with the set-up and recruitment of GP practices.

The Trial Steering Committee (TSC) will be closely involved in monitoring the progress of the internal pilot and will be provided with a report at the end that details progress against the progression criteria.

Criteria to judge success of the internal pilot

We anticipate recruiting 6-7 patients per centre per month once recruitment is established. In our experience, recruitment builds over the early months of a trial, and we would expect to reach our recruitment target by the end of the internal pilot period. The pilot will only take place in one centre (Bristol). We will employ a traffic-light system to judge the success of our internal pilot (Table 1).

Table 1: Internal pilot progression criteria

Progression criteria	Red (Stop)	Amber (Review)	Green (Go)
1. Number of 'greenlit' GP practices in Bristol	<6 practices	6-9 practices	≥10 practices
2. Number recruited in Bristol at end of internal pilot	<18 patients (<50% of expected)	18-35 patients (50-99% of expected)	≥36 patients (100% of expected)
3. Emerging recruitment trajectory in Bristol at end of internal pilot (e.g. months 4 to 6)	≤3 patients per month	4-5 patients per month	6-7 patients per month
4. Engagement with intervention	<50% of those randomised to EMDR will have received at least 2 sessions with a therapist	50-69% of those randomised to EMDR will have received at least 2 sessions with a therapist	≥70% of those randomised to EMDR will have received at least 2 sessions with a therapist

If we achieve 100% of our target for recruitment of patients AND 70% of those randomised are engaging with the intervention (defined as having received at least 2 sessions with a therapist), have 10 or more 'greenlit' practices, AND our emerging recruitment trajectory is as expected, then we will continue with the study (all green = Go).

If we recruit less than 50% of our recruitment target AND less than 50% of patients are engaging with the intervention AND have fewer than 6 practices 'greenlit' AND our emerging recruitment trajectory is ≤3 patients per month, then we would stop the trial.

If any of the criteria are in the amber zone, we will discuss with our TSC, funder, Sponsor, Data Monitoring Committee (DMC) and LEG whether we should make changes to recruitment/therapy processes and if we should continue. For example, if we have not recruited at least 36 patients but our emerging recruitment trajectory is as expected, greater emphasis will be placed on the latter within the review, so long as the former is in the amber range.

These progression criteria are realistic based on our experience. The criteria to judge recruitment success (2 & 3) were informed by guidance [45] that advises a focus on recruitment rates rather than just absolute numbers. The fourth target is based on data from: (1) the EDEN trial [46] that found that three out of 40 depressed patients (8%) randomised to EMDR did not start treatment; and (2) our previous psychotherapy trials [30, 45, 47], in which 12-19% attended less than 2 sessions.

We will recruit patients from 30 general practices at each of the three sites. During the internal pilot period, we expect to recruit at least 36 patients (Table 1). A further 344 patients will be recruited during the main 18-month recruitment period across the three sites. This equates to a target of 6 – 7 patients/month/site (344/3 sites/18m). This is achievable based on our experience.

5.5 Setting

General practices in Bristol, London and Exeter and surrounding areas. In the UK, primary care is the setting where most depression is managed. Practices providing care for under-served groups [33] will be included, and guidance used to recruit and retain individuals from diverse backgrounds [32].

5.6 Trial population

Adults with depression in primary care.

5.6.1 Eligibility criteria

5.6.1.1 Inclusion criteria

Participants may enter the study if ALL of the following apply:

- Aged ≥18 years
- Have a BDI-II score ≥14
- Meet ICD-10 depression criteria
- Are willing to discuss past stressful experiences related to their depression.

5.6.1.2 Exclusion criteria

Participants may not enter the study (i.e. may not be randomised) if ANY of the following apply:

- Have a diagnosis of PTSD/complex PTSD
- Have a substance use disorder (including alcohol dependence) within the last 12 months
- Have bipolar disorder, schizophrenia or psychosis
- *Have a current diagnosis of moderate/severe personality disorder
- Have a dissociative disorder
- Have dementia
- Are currently under secondary care for depression (including those referred but not yet seen) at eligibility screening
- *Have a history of repeated contacts with secondary care services or community mental health teams
- *Have a history of repeated self-harm
- Are currently receiving psychotherapy for depression at eligibility screening
- Unable to complete self-administered questionnaires in English
- Taking part in another trial of an intervention for mental health

**Criteria at the discretion of the clinical PI who will use judgement in deciding if patient should be excluded based on these factors.*

5.6.2 Co-enrolment in other research studies

Co-enrolment in EYE-D and other mental health related interventional studies is not permitted due to potential impact on the study objectives and patient burden and safety. If the centre team become aware that a participant has enrolled in another trial whilst taking part in EYE-D, they should inform the central research team (UoB) but they would not automatically be withdrawn from the study.

5.7 Intervention

5.7.1 Description of intervention

Those randomised to the intervention group will receive 12-18 sessions of EMDR (weekly 60-90 mins individual in-person) [8]. The number and duration of sessions mirrors that provided in NHS talking therapy (NHS-TT) services for primary care patients with PTSD. Therapy will take place face-to-face in person, in GP practices or other local NHS clinics, or at local University centres. Participants in the intervention arm will also continue to be cared for as usual by their GP.

EMDR-Europe accredited therapists with comparable experience to those working as EMDR therapists within NHS talking therapy services will be recruited. All therapists will be employed by the study or seconded to the study from local NHS Trusts/services. Therapists will be experienced in delivering EMDR for PTSD but will likely also be familiar with the client group (depression) through

their prior clinical work. Therapists will be employed approximately two months before they start delivering therapy to trial participants to ensure that they are familiar with trial procedures and the EMDR depression (DeprEnd) protocol [8]. Training will be provided by two of the EMDR protocol authors (Hofmann & Lehnung, EMDR-Institut Deutschland) who are collaborators. As part of their training, therapists will start treating at least two patients ('training cases') to learn how to apply the DeprEnd protocol in practice, before treating trial participants (see section 5.7.2 Therapist training cases for details). During the trial, therapists will receive weekly group supervision from EMDR-Europe accredited consultants. Therapists will be provided with detailed training manuals and working instructions e.g. for risk assessment and management.

The expectation is that the therapy sessions will take place weekly, but this will be treated pragmatically.

It is possible that patients and therapists may reach an 'agreed end' of therapy in less than 12 sessions, where clinically appropriate.

In exceptional circumstances, it may be clinically appropriate for therapists to offer additional therapy sessions (e.g. to enable safeguarding issues to be adequately and sensitively addressed). The justification for additional sessions will be discussed with the Clinical Supervisor where possible, agreed with the Clinical PI, and logged in the clinical notes.

Participants will be asked for their (optional) consent for the research team to have access to their therapy notes and for sessions to be audio-recorded for research purposes. Information on past event(s) worked on during EMDR will be extracted for those randomised to receive the intervention. Depression scores collected at EMDR therapy sessions, Subjective Units of Distress (SUDs) scores and scores on the validity of cognition (VOC) scale may also be collected from therapy notes (with consent).

5.7.2 Therapist training cases

Each therapist working on the study will start by treating at least two patients (training cases) to learn how to apply the DeprEnd protocol in practice. A small number of practices will screen and approach these patients in-consultation, and refer them for this purpose. Alternatively, practices may identify potential training cases via a medical record search, and send them an invitation letter and reply slip by post. Adapted referral and recruitment materials will be used for this purpose. If the two training case patients do not engage with therapy, more patients may need to be recruited for the therapist to be trained. This will be recorded by the central research team, and at the discretion of the EMDR supervisors. Training case patients will not be counted towards the total recruitment target.

These patients must meet the same trial eligibility criteria, and will be screened and undergo baseline in the usual way, except they will be consented using a different consent form and PIL designed specifically for the training case patients. This will explain that the patient will be receiving a course of therapy that is not part of the trial. The baseline data set will be reduced to only eligibility confirmation, and no follow up data will be collected other than audio-recordings of the therapy sessions for the supervisors (and trainers, where appropriate) to review this content for clinical supervision. The GP will be kept informed of their patient in the usual way. Their data will not be analysed as part of the main trial dataset.

5.7.3 Attendance at EMDR sessions

Attendance at EMDR sessions will be recorded by the therapist on the REDCap database. Therapists will monitor the participant's therapy sessions and attendance. A participant may be discharged from treatment by their therapist if they do not engage with therapy. This is at the discretion of the therapist. We have included a qualitative study within our trial (section 6.15) in order to investigate therapists' and patients' views and experiences of delivering/receiving EMDR for depression. Participants who are discharged from therapy or who withdraw from therapy will still be invited to complete follow-up assessments and, if sampled, a qualitative interview with the research team, unless they have explicitly indicated that they wish to withdraw from the trial.

5.7.4 Fidelity to the EMDR model

EMDR therapy sessions will be audio-recorded for the purposes of clinical supervision. These audio-recordings may be reviewed by the therapist, their clinical supervisor and the EMDR trainers (if required).

Participants will provide optional consent to allow the audio-recordings of their EMDR therapy sessions to be used for research purposes. Amongst those who have given permission, recordings will be randomly sampled for evaluation of fidelity to the EMDR model by independent EMDR experts using a recognised EMDR rating scale, for example [48].

All recordings will be indexed by study number only and stored securely on the local University network drive.

During the study, those randomised to receive EMDR will receive this in addition to usual care from their GP. There will be no restrictions on the treatment offered by the GP; for example, they may prescribe antidepressant medication or refer to psychological services as appropriate.

5.7.5 Post-therapy arrangements

Once a participant has completed their EMDR sessions, their GP will be informed as the professional with clinical responsibility. The patient's GP will also be informed if they withdraw from therapy or are discharged for non-attendance.

5.7.6 Trial comparator – usual care

Participants allocated usual care will continue to receive treatment as usual from their GP. This may include referral to local psychological services provided by NHS talking therapies (NHS-TT) or antidepressant medication, as appropriate. There will be no restrictions on the treatment options that can be offered to this group. However, we will record other treatments received (as part of the follow-up questionnaires and data from medical records) and describe these for both groups at the end of the trial.

5.8 Efficacy Outcomes

5.8.1 Primary efficacy outcome

The primary efficacy outcome is depressive symptoms at 26 weeks post-randomisation measured using the Beck Depression Inventory (BDI-II) as a continuous variable.

5.8.2 Secondary efficacy outcomes

Secondary efficacy outcomes will include proportional change in depressive symptoms (on the BDI-II), remission of depressive symptoms (BDI-II score<10), symptoms of depression and anxiety measured using instruments used in NHS-TT services (score on PHQ-9 and GAD-7), impairment in

functioning (WSAS), quality of life (EQ-5D-5L) and capability (ICECAP-A) at 26 weeks post-randomisation, together with these outcomes and the continuous score on the BDI-II (primary outcome) measured at 52 weeks post-randomisation. Data on the PHQ-9 and GAD-7 will also be collected as part of the brief follow-ups at 2, 8, 16 and 39 weeks post-randomisation.

Mechanistic measures are described in section 6.6.

5.8.3 Estimands

Estimand component	**Definition**
Population	Adults with depression in primary care, as laid out in eligibility criteria, section 5.6
Treatment condition	EMDR (in addition to UC) compared with UC alone, regardless of treatment discontinuation (treatment policy)
Primary Endpoint	BDI-II score at 26 weeks post-randomisation, 5.8.1, adjusted for baseline BDI-II score
Summary measure	Difference in mean depression scores at follow-up, adjusted for baseline, section 10.1
Handling of intercurrent events	The intercurrent event "treatment discontinuation" is addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.

5.8.4 Target sample size (with calculation/justification)

The established minimum clinically important difference (MCID) for BDI-II is a 23% reduction ([49]). Assuming a mean BDI-II at follow-up in usual care of 22.0/24.5 (SD 13.5/13.1)([30],[47]), this translates to 5.1-5.6 BDI-II points or an effect size of 0.378 (based on a standard deviation of 13.5). 149 are therefore needed per group for 90% power at the 2-sided 5% significance level. 380 participants will be recruited, allowing, conservatively, for a correlation of 0.20 between baseline and 6-month BDI-II scores and 25% attrition at 26 weeks (based on our past experience & our recent NIHR funded INTERACT trial (ISRCTN13112900 [44]). Early contact with the participants will maximise retention (as advised by PPI) and we will use guidance to help retain individuals from diverse backgrounds [32] and build on colleagues' experiences of improving diversity in research (section 5.3). Sample size is not inflated to account for clustering by therapist given little evidence of this in our previous trials [30, 47]

6 TRIAL PROCEDURES

6.1 Recruitment of participating centres & GP practices

Recruitment will take place in general practices linked to the three University trial centres, Bristol, Exeter and London, and will be supported by local Research Delivery Networks (RDNs).

6.1.1 Training for the recruiting centres and GP practices

Research staff at the Bristol, London and Exeter centres will receive training from the Co-ordinating Centre, and centre Lead Investigators as appropriate.

Each collaborating GP practice will receive information and advice on all trial recruitment procedures prior to the start of recruitment. This will be provided to Bristol centre GP practices by the Trial Manager, with the assistance of other members of the trial team as appropriate. Guidance will be provided to collaborating GP practices at the London and Exeter centres by the local trial team with assistance from the Bristol centre as required. A training log will be maintained within the Trial Master File.

6.1.2 GP practice recruitment process

The University of Bristol will follow its "Green Light" process, in order for the trial Sponsor to document the preparedness of each collaborating centre (Bristol, London, and Exeter) to conduct recruitment locally.

Following training from, and with the support of, their local centres and local researchers, general practices will recruit autonomously using methods similar to those successfully employed in previous studies (CoBalT [30], IPCRE5SS [47], MIR [29], INTERACT [44]). Their primary role will be to identify and invite patients to consider trial participation. Practices will receive NHS Service Support Costs and Research Cost payments to reimburse them for these activities.

The study has been adopted onto the NIHR portfolio. All the participating centres are linked with local RDN research teams. These research teams will be approached to provide support with recruitment activities.

6.2 Trial advertising

The study will be advertised in GP practices and listed on the NIHR Be Part of Research Website.

6.3 Screening and identification of participants

6.3.1 Identification

Method 1: record search

GP practices will conduct a search of their computerised records for potentially eligible patients (defined as those who are aged 18 years or over, who have been diagnosed with depression). Practices will be asked to exclude those who do not meet the eligibility criteria (section 5.6.1.1). The record search will be conducted using primary care diagnostic codes. Practices will be given the opportunity to manually screen the resulting list.

Potentially eligible patients will then be mailed an invitation to participate by the GP practice, asking for their permission to be contacted by the research team. The summary Participant Information Leaflet (PIL) will be posted alongside the mail out invitation. This will include direction to the full PIL. These materials will also be available on the study website. Patients who have not responded after two weeks may be sent one reminder letter by the practice. Invited patients interested in taking part in the trial will be asked to complete an expression of interest form and return it by post or to complete the form online.

Patients will be able to respond anonymously if they wish to decline participation, and will be able to provide a reason for declining. Decliners will be asked to indicate whether they are willing to be interviewed briefly over the telephone about their reasons for declining, and if so, to add their contact details to the form. Some practices may opt to send invites via text messages (with a link to the website that presents the summary PIL and a form to express interest).

Method 2: in consultation

GPs (or other primary care health care professionals) can identify patients in consultation that they think might be suitable for the trial.

Patients may also see a poster advertising the study at the practice and ask their GP about taking part. The GP will introduce the trial and ask the patient for their permission to be contacted by the research team (verbal permission can be taken during telephone and videocall consultations). The GP will provide the summary PIL and complete a referral form for these patients.

The GP practice Index of Multiple Deprivation (IMD) score will be recorded for consented patients in order to better describe the characteristics of collaborating practices and inclusion of those serving diverse populations.

6.3.2 Screening

Primary care patients who have been referred, or expressed interest via any recruitment method, will be telephoned by a researcher from the local centre. The researcher will briefly explain the study, check that a summary PIL has been received, and answer any questions the patient may have.

With verbal consent, the researcher will then proceed with the telephone screening questionnaire to confirm patient suitability for a baseline appointment. This will include questions about the key inclusion/exclusion criteria (section 5.6.1). The screening call is likely to take around 15 minutes. If telephone screening is not practical for the patient (e.g. if they are hard of hearing) we will make adaptations where possible (e.g. offer screening via post/email).

If a patient meets the screening criteria, they will be offered a detailed eligibility screening appointment (baseline assessment) with the researcher to explain the trial, conduct the baseline assessment, establish eligibility and obtain written informed consent for trial participation. The full PIL will be provided upon booking the baseline appointment.

6.3.3 Baseline assessment

This appointment will usually last between 1-2 hours and will take place remotely, with the patient completing online questionnaires on their own smartphone, tablet or computer, and the researcher providing support via telephone or videocall. Alternatively, where resources permit, the appointment may take place in-person at the patient's home, GP practice, the local research centre, or other mutually convenient location. The local researcher will explain the study in more detail, answer questions the patient may have, and obtain written informed consent (section 6.4). The researcher will check whether the participant's circumstances have changed since they completed the screening questionnaire in order to check they are still eligible for a baseline assessment.

Potentially eligible patients will be asked to complete several questionnaires. These will include the BDI-II as a measure of their depressive symptoms and the computerised version of the Clinical Interview Schedule – revised version (CIS-R) [50] to establish whether they meet ICD-10 criteria for a depressive episode. Additional information will be gathered on socio-demographic details (age, sex,

gender, ethnicity, marital status) and markers of socio-economic status (employment status, housing situation, financial stress). Patients will also be asked for relevant medical history including: co-morbidities and history of depression and treatment including antidepressant medication and adherence. They will be asked if they are willing for their summary data to be passed to their GP.

Patients who score 14 or more on the BDI-II, and have an ICD-10 primary diagnosis of depression on the CIS-R will be told they are eligible to enter the trial. Eligible participants will be asked to complete further questionnaires including: the Patient Health Questionnaire (PHQ-9) [51] and General Anxiety Disorder questionnaire (GAD-7) [52] which are brief measures of depression and anxiety used in NHS talking therapy (NHS-TT) services, and measures of quality of life (EQ-5D-5L), function (Work and Social Adjustment Scale [53] (WSAS)); and capability (ICECAP-A) [54].

As part of the baseline appointment, those who are eligible will be asked about adverse childhood experiences (using the childhood trauma questionnaire (CTQ) [55]) and stressful or traumatic events in adulthood (using a measure of stressful life events taken from the Adult Psychiatric Morbidity surveys [56] which has been widely used in previous depression trials [9], and the Life Events Checklist (LEC-5) that asks about traumatic events [57]).

Patients will be asked to describe (in a few words) the experience that they associate most strongly with their depression and asked to rate the vividness and emotional intensity of the memory associated with that event (using a visual analogue scale (VAS) (0-10)). Patients will only be asked to provide enough detail about the experience so that they know which experience they should be thinking about when asked to re-rate these questions as part of the follow-up questionnaires. They will not need to discuss the event in detail. Symptoms of re-living, avoidance and hyper-arousal related to that experience will be measured using the International Trauma Questionnaire (ITQ) [58]. In addition, the number and strength of negative self-beliefs will be recorded using a list adapted from an existing checklist [19].

6.3.4 Re-screening

Patients who do not meet the eligibility criteria at telephone screen or baseline may be eligible for rescreening. For example, those who are currently receiving a course of therapy could be rescreened once this course has ended. Patients who do not meet the BDI-II or ICD-10 criteria at baseline could be offered a rescreen as long as one month had elapsed since their original baseline appointment. The telephone screening questionnaire would also be repeated in order to identify any other changes since the original screen, which could make them unsuitable to take part. Ineligible patients would be advised that they can re-contact the study team to request one rescreen, as long as one month had elapsed since the original screen, and the study was still recruiting.

6.4 Consent

Prior to commencing the baseline assessment, the researcher will obtain written informed consent from the patient relating to their participation in the trial. Informed consent will be obtained either via an online consent ‘e-consent’ method, or via paper-based informed consent.

Paper-based informed consent will be used if the researcher is meeting with the patient in-person and this option is preferred, or if the patient wishes to complete the baseline via telephone call and is not able to complete an electronic consent. If paper consent is required, two copies of the consent form will be sent to the participant with a pre-paid envelope. The patient will complete both forms

and return them to the local researcher to countersign. The participant will then be sent one of the fully signed forms for their records.

Patients completing the assessment via e-consent will receive an electronic copy of their e-consent form via email. A copy will also be sent to the patient's GP if they are eligible to take part in the study.

Participants will be reminded that they are free to withdraw from the trial at any time without giving reason and without prejudicing their further treatment. We will seek consent to use data collected up to the point of withdrawal, and this will be explained in the information sheet. In addition, in line with open access data requirements, information may also be used to support other research in the future and may be shared anonymously with other researchers. This will be explained in the information sheet.

Consent will also be sought for details of the participant to be shared with the qualitative researcher so that they can be approached about taking part in an interview. Taking part in an interview will be optional. Full details of the integrated qualitative research are detailed separately; see Section 6.15.

As part of the baseline consent procedure, patients who give informed consent for trial participation will be asked to indicate whether they would be willing to be contacted about future related research. All participants will also be asked to provide (optional) consent for the research team to access their medical records in order to collect data on treatments and consultations in primary care. Intervention participants will be asked for their (optional) consent for the research team to have access to their EMDR therapy notes from their time in the study, and for audio-recordings of their EMDR sessions to be used for research purposes.

6.5 Randomisation

Individuals will only be randomised after: (a) written informed consent (wet ink or eConsent) has been received; (b) baseline assessments have been completed; and (c) eligibility is confirmed by the local researcher.

The randomisation sequence will be generated by Sealed Envelope™. Randomisation will be stratified by centre and minimised on baseline antidepressant use (Yes; No) and depression severity (baseline (BDI-II score): 14-27; 28-36; 37-63). Stratifying by centre will ensure a balance in terms of local differences and proportionate workload for therapists. The minimisation variables are important prognostic indicators and hence minimising will ensure a balance between the two groups. Participants will be randomised to one of two treatment groups on a 1:1 ratio, that is either EMDR therapy in addition to usual care (intervention arm) or usual care (control arm). The researcher will inform the participant of the allocation during the baseline appointment where possible, or by telephone/email shortly afterwards.

The local researcher will sign into the secure online randomisation system, find the individual's (participant's) unique record and enter the necessary minimisation variables; they will then receive confirmation of the randomised allocation (EMDR or UC). The local research team will inform the EMDR therapist if a patient has been allocated to them. Confirmation of the participant's treatment allocation will be emailed to the local researcher at the coordinating centre and the University of Bristol study mailbox, for the attention of the Trial Manager. The allocation will be recorded on the trial database. The local research team will send written confirmation of the allocation to the participant's GP.

6.6 Embedded Mechanistic Study

The embedded mechanistic study will determine whether reductions in depression are mediated by key memory-processing mechanisms and if working memory capacity is associated with treatment response. The specific objectives were set out in section 4.6.

6.6.1 Mechanistic Measures

Potential mediators will be measured during treatment at 16 weeks post-randomisation:

1) VAS (0-10) for vividness and emotional intensity of depression-related memories;

2) number, and strength, of negative self-beliefs; and

3) symptoms of re-living, avoidance and hyper-arousal linked to past distressing events.

The timing of 16 weeks allows: (1) time to start therapy after randomisation (mean: 3 weeks in previous trials [30, 44]; (2) session cancellations by patients; and (3) the processing phase of EMDR to begin (phase 4 of 8). In a trial of a similar length intervention (12-18 sessions) [30], by 12 weeks participants had only had an average of 5 sessions.

To determine whether reductions in depression are mediated via key memory-processing mechanisms, it will be necessary to ask individuals to provide brief details about the past stressful experience that they associate (most strongly) with their depression at baseline. They will be prompted to think about this memory when they are rating the vividness and emotional intensity of depression-related memories at 16 weeks. Similar scales have been used previously in studies examining the WM hypothesis [22].

The number, and strength, of negative self-beliefs will be measured based on a list of negative and positive cognitions in the EMDR manual [19]. Symptoms of re-living, avoidance and hyper-arousal will be measured using the ITQ [58]. Repeat measurements at 26 weeks will enable mediation analyses of 52 week outcomes. We will examine the test re-test reliability of the list of negative self-beliefs by asking participants to repeat those questions at one of the follow-up appointments (either 26 or 52 weeks).

Memory vividness depends on the detail, sharpness and strength with which memories are being actively represented and processed in WM [59]. EMDR is thought to reduce the resources available for detailed memory representation and processing by using up both visuospatial and processing resources. The amount of WM resources available for vivid memory representation depends on both the individual's capacity in the first place, and the fraction of the resource taken up by EMDR. If WM capacity is large, then EMDR is unlikely to lead to sufficient reduction in WM to prevent distressingly vivid reconstruction.

WM capacity will be measured at baseline using a short (15 - 30 minutes) battery of standardised measures. Two aspects of WM capacity are most likely to be relevant: visuospatial capacity, and processing capacity. Visuospatial capacity will be measured using a spatial memory 'Corsi' task where individuals are shown a pattern of blocks on a screen. A spatial sequence of these blocks illuminates, which they then need to recreate. The capacity of spatial WM is determined by performance at increasing sequence lengths. Processing capacity will be measured using an N-back task where individuals have to recall letters in a constantly changing string of single letters on a screen. The individual has to indicate if a given letter is the same as the letter N trials earlier. We will assess how well individuals perform at increasing N to determine their maximal N. Finally, we will examine to

what extent the effects of objective WM capacity might be captured by subjective memory capacity by asking participants a short set of questions about their memory.

6.6.2 Sample size: Primary mechanistic hypothesis

We used the methods by Vittinghoff and Neilands [60], implemented using the R package medssp, to estimate the power to detect mediation of the intervention effect by a standardised continuous post-randomisation measure of the mediator (e.g. visual analogue scale) assuming: a standardised total effect of 0.378 (based on the MCID as stated above); no exposure-mediator confounding (given the intervention will be randomised); moderate confounding for the mediator-outcome association (correlation of 0.3); and a medium standardised effect size (square root of R2 = 13%) for the exposure-mediator association. For a sample size of 285 (based on 25% attrition), we have 87.2%, 87% and 79.4% power to detect an indirect effect of 40%, 30% and 20% respectively.

6.7 Emergency contact procedure for participants

The participant's GP will retain clinical responsibility for them throughout their participation in the trial. Details of what a participant should do if they experience any problems or adverse effects whilst taking part in the trial is detailed in the PIL.

If a symptom is troublesome (as explained in the PIL) participants are advised to seek medical help in the normal way (e.g., dialling 111 or contacting their GP). In an emergency they should phone the emergency services or attend an Emergency Department. There will also be information provided about helplines participants can choose to access for mental health support 24/7, which will be available on the study website, or on paper if required.

Participants receiving EMDR will complete a measure of depressive symptoms (PHQ-9) for each session which will be shared with their therapist. This will completed via REDCap survey shortly ahead of the session, or completed in person at the beginning of each session. If this is completed on paper, the therapist will enter this into the database following the therapy session. A safety protocol outlines the procedure to follow if a therapist is concerned about the risk, such as increased suicidality. Further details on the safety protocol are outlined in section 7.1.

6.8 Schedule of assessments and data collection

Table 2 specifies the timepoints for outcome data collection. All timepoints are counted from randomisation.

Table 2: Schedule of assessments and research data collection

			STUDY PERIOD						
	Pre-baseline	At randomisation	Post-randomisation						
Data collection timepoint	**Identification /Screening**	**Baseline Appointment**	**2 weeks**	**8 weeks**	**16 weeks**	**26 weeks**	**39 weeks**	**52 weeks**	**End of study**
ENROLMENT:									
EOI Form	●								
Phone Screen	●								
Informed consent		●							
Socio-demographics		●							
CIS-R		●							
History of depression and treatment		●							
History of stressful/traumatic experiences and willing to work on memories		●							
LEC-5		● [A]							
CTQ		● [A]							
Life Events checklist		● [A]							
Stressful experience linked to depression (description and age at event)		● [A]							
Social support		● [A]							
Long-term health conditions		● [A]							
Self-report memory		● [A]							

Cognitive (working memory) tasks	● [A]						
Reasons for taking part	● [A]						
Future contact	● [A]						
Consent to pass information to GP	● [A]						
Random allocation	● [A]						
INTERVENTION:							
EMDR Sessions* [B]		←	—	—	→		
PHQ9, SUDs and VOC* [B]		←	—	—	→		
ASSESSMENTS:							
BDI-II (primary outcome)	●				●		●
PHQ-9	● [A]	●	●	●	●	●	●
GAD-7	● [A]	●	●	●	●	●	●
Global rating of change			●	●	●	●	●
Negative self-beliefs	● [A]		●	●	●	●	●
ITQ (shortened)	● [A]		●	●	●	●	●
Vividness/Intensity of memories	● [A]		●	●	●	●	●
Grounding question	● [A]		●	●	●	●	●
Your EYE-D EMDR therapy	● [B]						
Antidepressant medication	● [A]		●	●	●	●	●
WSAS	● [A]				●		●
EQ-5D-5L	● [A]				●		●
ICECAP-A	● [A]				●		●
Other treatments received (cCBT/talking therapy)			●	●	●	●	●

Use of healthcare services (ModRUM)		●	●	
Medical note data collection				●

*Time period is an approximation of when EMDR sessions are expected to take place; [A]Only completed if patients are eligible at this point [B]Intervention group only

6.9 Blinding and unblinding

Given the nature of the intervention, it will not be possible to blind participants to treatment allocation. Self-reported outcomes will avoid observer bias.

The wider Trial Management Group (TMG) will be blinded to aggregate data by treatment group with only the reporting of follow-up rates presented to the TMG by arm. This is to monitor potential discrepancies in follow-up rates. The site and clinical site leads, one of the two trial statisticians and trial/data management staff from the University of Bristol, trial therapists and supervisors of trial therapists will be unblinded for practicalities of delivering the trial and intervention. Two statisticians based at the University of Bristol will support this trial. The senior (lead) statistician will be blinded throughout the trial. The second trial statistician will perform all disaggregated analyses according to a pre-specified SAP and will attend closed Data Monitoring Committee (DMC) meetings as required. Clinicians (PIs), other researchers and centre staff will not be blinded.

6.10 Change in participation status

Participants can choose to withdraw for any reason at any time during their involvement in the trial. Participants can withdraw from: (a) EMDR sessions, and/or (b) providing data to the trial, at any time for any reason without affecting their usual care. Clinical site leads can also decide to withdraw participants based on clinical opinion at any time during the trial. A participant may be discharged from treatment by their therapist if they do not engage with therapy.

Where possible, any data collected up to the point of withdrawal will be retained for analysis, as advised in the PIL. Participants who withdraw from a) EMDR sessions, will be asked if they are still willing to provide follow-up data and/or take part in a qualitative interview if applicable. If a participant withdraws from b) providing data to the trial, no further data will be collected – this includes the collection of health resource use data from the patient's medical notes at the end of the trial. They will not be approached for future follow-up questionnaires or qualitative interviews.

Withdrawals will be recorded on the REDCap database, including reasoning for withdrawal, if provided.

Participants who commence concurrent psychological therapy after randomisation to the intervention arm will **not** be withdrawn from the intervention or study by the trial team, though they would be advised against commencing concurrent therapy. Participants in the intervention arm will **not** be withdrawn from the intervention or study due to lack of efficacy.

6.11 Retention strategies & participant payments

Participants will be followed up (by videocall or in person) at 26 and 52 weeks. Brief follow-ups (telephone/videocall) at 2 & 8 weeks will be used to maximise trial retention (as advised by PPI) and at 16 weeks to collect data on mediators and depressive symptoms. A brief 39-week follow-up will aid longer-term retention. At baseline, participants will be asked their preference for mode of contact for these follow-up appointments. They will also have the option of completing follow-up questionnaires online independently or by post.

If full questionnaire data collection is not feasible, the researcher will attempt to collect a measure of depressive symptoms (BDI-II or PHQ-9 as appropriate to the time point), current use of antidepressant medication, and receipt of other psychological treatments as a minimum.

If the researcher is unable to contact the participant for any of the follow ups, the researcher will send a brief postal questionnaire, or a link to an online version of the questionnaire.

Participant appointments will be confirmed by email or letter. If questionnaires are sent by post, a brief covering letter and pre-paid envelope will also be included. If patients do not respond to postal or online questionnaires within two weeks, a reminder letter, email or text will be sent. Up to 3 reminders will be sent in total.

Upon receipt of completed questionnaires at 8, 16 & 39 weeks, the central research team will offer participants a £10 gift voucher (i.e. £10 per time-point). £20 vouchers will be offered for the longer follow-ups at 26 & 52 weeks (£70 potential total). No vouchers will be offered for the initial 2-week follow-up as this will be a brief contact (phone/email) to check in and answer any questions that have arisen about participation, and record brief details of symptoms of depression/anxiety.

A £20 voucher will also be offered for taking part in a qualitative interview.

6.12 Communication with participants

Trial participants will be asked if they want to be sent a regular newsletter via email to update them on study progress. This will also be uploaded to the study website. Participants will also be asked if they want to be sent a plain English summary of the findings.

6.13 End of trial

Participants end their involvement with the trial when their last planned interaction with the study is complete (or efforts to complete this have been unsuccessful), in this case the 52 week questionnaire, or when they have discontinued their participation in the study.

The end of trial will be when the last participant has completed their involvement with the trial, all data collection is complete and any data queries have been resolved, the database has been locked, and subsequent planned data analyses have been completed.

6.14 Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, CI, Regulatory Authority or Funder based on new safety information or for other reasons given by the DMC, regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC, who will advise on whether to continue or discontinue the trial and make a recommendation to the Funder.

If the trial is prematurely discontinued, no new participants will be recruited, and a decision on data collection on active participants will be made in discussion with the TSC/DMC and Sponsor.

6.15 Integrated qualitative research

6.15.1 Aims and Objectives

The qualitative study will examine the acceptability of EMDR for depression, the application of EMDR for depression compared with PTSD, further explore mechanisms and identify possible causes of differing responses that could explain the trial results. Specific objectives are detailed in section 4.5. It will entail conducting in-depth interviews with trial participants, individuals who are approached to

take part in the trial but decline to so, and the EMDR trainers, supervisors and therapists involved in the trial.

The qualitative researcher will be employed by Bristol Trials Centre and will conduct the qualitative interviews. They will conduct the qualitative analysis in collaboration with the qualitative lead, also based at the University of Bristol.

6.15.2 Consent

Participants recruited to the main trial will be asked to consent to being approached for interview as part of their baseline consent. The possibility of being interviewed as part of the trial will be mentioned in the main study PIL. The aim will be to interview a sample of participants shortly after they have completed their primary outcome measures for the trial at 26-weeks post-randomisation. The qualitative researcher employed on the trial will be informed by the trial team who has completed their 26 week follow up. The qualitative researcher will email or post participants sampled for interview an information leaflet about the qualitative study. The researcher will then contact them two weeks later, by telephone, to explain more about the interview, answer any questions and, if they agree, arrange a convenient time and preferred method (e.g., phone/video) to conduct the interview.

During the pilot for the main trial, short telephone interviews will be held with up to 10 individuals who were invited to take part in the trial but decline to do so. These 'decliners' will be individuals who have received a letter inviting them take part in the trial, having been identified via systematic searches of GP practice records of depression. The trial invite letter will be accompanied by a reply slip, which the individual will be asked to complete and return (or complete online), indicating whether they are willing to be contacted by a researcher to discuss participation in the trial. If they do not want to take part, they will be asked to indicate this and complete a short questionnaire. This questionnaire will ask for their age, gender and reason(s) for declining participation, using a series of closed responses and one open 'other' category. These items will be based on previous research [61, 62]. The reply slip (or online form) will also ask individuals whether they would be willing to take part in a short telephone interview to discuss their reasons for declining in more detail. The qualitative researcher will approach a purposeful sample of decliners, explain more about the interview, answer any questions, and, if they agree, arrange a convenient time and preferred method (e.g., phone/video) to conduct the interview. The aim will be to interview decliners within a month of them returning the reply slip. This will provide another standpoint from which to assess the acceptability of EMDR and indicate ways to maximise recruitment.

Therapists, clinical supervisors, and EMDR trainers will be informed about the interviews through their respective information leaflets, which will be provided ahead of arranging an interview. When the interviews are due to be held, the qualitative researcher will telephone the therapists, supervisors and trainers to answer any questions they might have and to arrange an interview.

As all of the interviews will be conducted remotely, verbal consent to participate will be taken. It will be obtained by the qualitative researcher immediately prior to interview and will be audio recorded. This will involve the researcher reading out standard consent form statements and, if appropriate, the participant verbally agreeing to them. The researcher will complete the consent form on behalf of the participant, sign and date it, and email a copy of the completed consent form to the individual. The audio recorded excerpts will be retained for auditing purposes in line with trial archiving policies.

6.15.3 The interviews

To examine the application of EMDR for depression, prior to training trial therapists, or shortly thereafter, a paired in-depth interview will be held with the EMDR trainers to understand how the DeprEnd (EMDR for depression) protocol [8] is tailored EMDR to depression management, and what they think are the similarities and differences in the application of EMDR to depression compared with PTSD, in terms of mechanisms of actions (particularly in relation to the WM hypothesis), and events worked on. In addition, trial therapists will be interviewed on a one-to-one basis within approximately two weeks of completing training, to explore the same issues, and to assess their expectations of delivering EMDR in the trial. The trainers' interview will last up to an hour. The therapist interviews will last up to 30 minutes.

To further examine the application of EMDR and its mechanisms, and to explore its acceptability as a depression treatment, in-depth interviews will also be held with participants within a month of them completing their primary (trial) outcomes (with, depending on data saturation, up to 20 intervention (including those who do not complete therapy) and 10 UC), and with all trial therapists and supervisors once therapy is completed at their trial site. These interviews will last about an hour and will explore interviewees' views and experiences of UC and EMDR for depression, and their views on how EMDR affects the intensities of memories, self-beliefs and symptoms linked to distressing events. Having supported the therapists during the trial, supervisors will also be asked what they think are the similarities and differences in the application of EMDR to depression compared with PTSD.

'Decliners' and trial participants will be purposefully sampled across sites on the basis of gender, ethnicity, age and socio-economic background. Trial participants will also be sampled to achieve maximum variation in relation to baseline antidepressant use and depression severity, change in BDI-II score and, for the EMDR group, treatment adherence. All interviews will be held by telephone or videocall to encourage participation, and because it is now acknowledged that remote interviews can result in data of the same quality and value, as those held in person [63]. Consent will be taken immediately prior to interview as detailed in section 6.15.2.

Topic guides will be used to ensure consistency across the interviews. For the trial participants, there will be two guides: one to use with individuals allocated to EMDR plus usual care, and one to use with individuals allocated to receive usual care only. Guides will be developed in parallel to ensure areas common to different groups of interviewees are included in each guide. This will aid triangulation of trainers', supervisors', therapists', and patients' accounts during the analysis phase. Trainers, therapists and supervisors will be asked to complete a brief demographic questionnaire after their interview, so that the sample can be described when disseminating results.

Interviews will be audio recorded, transcribed verbatim and anonymised. Trial participants will be given a £20 voucher for taking part in an interview. The supervisors, therapists, trainers and decliners will not be given a voucher or paid for taking part in an interview.

6.15.4 Safeguarding during qualitative research

We will ensure that participants are not subjected to undue distress during the qualitative component of the trial. To mitigate this, the GCP-trained interviewer will be experienced in sensitive interviewing, will adhere to the safety working instructions and will conduct the interviews according

to trauma-informed research guidelines to ensure participants feel safe and empowered throughout the research process [64]. The interview will only continue if participants are happy to proceed and engage with the interview topic. If the researcher feels a participant is becoming distressed, they will ask the participant if they wish to have a break or discontinue the interview and will offer support. Participants will also be offered a leaflet with the contact details of support networks, or the researcher may contact the local clinical PI if necessary.

6.15.5 Qualitative Analysis

Data collection and analysis will proceed in parallel, so that analytical insights from earlier interviews can shape later data collection. Transcripts will be analysed thematically [65] to allow comparisons to be made within and across the datasets and to highlight themes and views associated with specific areas e.g. the process through which EMDR affects the emotional salience of memories. This analysis will entail transcripts being read and re-read by members of the research team to familiarise themselves with the data, identify themes and develop a coding frame. Once the coding frame has been agreed, transcripts will be imported into the software package NVivo to allow electronic coding and data retrieval. Following this, data pertaining to each code will be summarised in tables using an approach based on Framework analysis [66]. Each data set will be analysed separately before the views and experiences of therapists, patients etc are compared.

6.16 Intervention costing exercise

This study presents a unique opportunity to collect valuable information on the costs associated with EMDR, which will be of key interest to policymakers and inform future NICE decision making regarding the potential value of EMDR as a treatment for depression.

To estimate the cost of delivering EMDR in the NHS, the duration of each EMDR session and the therapist job role will be recorded on study data collection forms completed by the therapist after each session. Additionally, details of therapist supervision, including the roles of both the therapist and supervisor and the duration of supervision sessions, will be collected. Unit costs for therapists and supervisors will be derived from national sources such as the Unit Costs of Health and Social Care [67]. EMDR delivery costs will be calculated per session and per participant and presented using descriptive statistics (mean and standard deviation).

Although an economic evaluation is not funded as part of this grant, the necessary data for such an evaluation will be collected. Health-related quality of life and capability will be measured using the EQ-5D-5L and ICECAP-A, collected at baseline, 26 and 52 weeks. Resource-use data will be collected via self-report at 26 and 52 weeks, covering NHS talking therapy services, primary and secondary health care, social care, informal care, patient expenses (including travel, private and alternative care/treatments and over-the-counter medications), and time off work. With participant consent, primary care consultations and prescribed medication data will be collected via primary care medical records. Subject to further funding, cost effectiveness will be assessed in future through a cost-utility analysis, using the EQ-5D-5L to estimate quality-adjusted life years, and in a cost-effectiveness analysis, using the ICECAP-A to estimate years of full capability equivalent.

7 SAFETY RECORDING AND REPORTING

7.1 Risk Management

7.1.1 Risk Management by therapists

Trial therapists will be experienced in managing clinical risk, as this is an essential and core component of the work of mental health practitioners. Clinical risk includes risk of suicide, self-neglect, harm to self and/or others and requires practitioners to help clients manage their behaviour in relation to these sorts of risks. Trial therapists will be provided with a risk policy to promote a thorough, consistent and high standard of practice with regards to clinical risk assessment and management, to ensure that those risks are managed safely and effectively.

Whilst the patient's GP maintains overall clinical responsibility for the care of the patient, it is expected that therapists will use their clinical judgement to assess the seriousness of all risks, including risks to self and others. As part of the initial therapy session, therapists will be expected to carry out a risk assessment. Therapists will follow the Therapist Risk Policy and Procedure with regards to managing risk which may include contacting the patient's GP, their clinical supervisor or the local principal investigator with clinical responsibility (clinical PI) (or nominated deputy clinician), or other local services as appropriate. Therapists may also contact the study team to determine history of previous disclosure. Subsequent risk assessments will be triggered by PHQ9 question 9 responses collected as part of therapy, or clinical concern and will be more focused. Actions taken in response to such concerns will be clearly documented in line with the above policy.

Therapists must inform the study team of any incident (including adverse events) that result in serious harm to the participant or to others and ensure that the incident is fully documented and reported as described in section 7.8.

7.1.2 Risk policy for researchers

Should a trial researcher become concerned for the safety of a participant (for example, if the participant expresses suicidal ideation or recent self-harm at any point during participation, including during the screening call or interview) or be concerned about the safety of others, the researcher will follow the study's detailed Patient Safety and Disclosure Working Instructions for researchers, and seek advice from the local Principal Investigator with clinical responsibility (local Clinical PI) or nominated deputy clinician. If suicidal ideation is expressed, the researcher would speak to the participant about this, encourage the participant to speak to their own GP and seek permission from the patient to pass the clinical information to the GP. Should the participant refuse permission (or not respond to attempts to contact them to request permission), the local Clinical PI would assess the risk information and attempt to call the participant if necessary. The local Clinical PI would break confidentiality and pass information to the participants GP without the participant's consent if this was deemed necessary to protect the safety of the participant and only if the participant continued to decline to give permission for their GP to be contacted (or did not respond to attempts to contact them to request permission). This policy would be explained in the patient information leaflet (PIL).

7.2 Safety Definitions

Adverse Event

An adverse event (AE) is any untoward or undesirable medical occurrence in a subject receiving treatment according to the protocol. This includes occurrences which are not necessarily caused by or related to administration of the research procedures. An adverse event can therefore be any

unfavourable and unintended sign, symptom or disease temporally associated with the use of the intervention or research procedures whether or not considered to be related to the intervention/research procedures.

Adverse events that might be expected to occur at a higher rate in this group of participants include episodes of self-harm not requiring hospital admission and worsening of depression sufficient to require referral to a clinician. Although these AEs are expected, they will still be reported as data in this study. Variations in mood, including worsening of depression that does not lead to self-harm or hospitalisation, are commonly seen during therapy and would not be reported as individual adverse events. Expected events are listed in full in section 7.9.

There may be more AE reports in the intervention group as a result of their regular contact with the study team (i.e. receipt of up to 18 EMDR sessions with the study therapist, and more regular completion of the PHQ-9 and related participant safety risk assessments as part of therapy). This will be taken into consideration when interpreting the pattern of AEs.

Adverse Reaction

An adverse reaction (AR) is any undesirable experience that has happened to a subject that is suspected to be caused by the intervention.

Serious Adverse Event

A serious adverse event (SAE) is any adverse event which:

- results in death,
- is / was life threatening*,
- requires hospitalisation or prolongs an ongoing hospitalisation**,
- results in persistent or significant disability or incapacity,
- consists of a congenital anomaly or birth defect,

Other important medical events that may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above should also be classed as an SAE.

**"Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

***"Hospitalisation" is defined as an unplanned overnight stay. Note, however, that the patient must be formally admitted – waiting in outpatients or an Emergency Department would not count as hospitalisation (even though this can sometimes be overnight). Planned hospital stays would not be counted as SAEs, nor would time in hospital for "social reasons" (e.g. respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting unless complications occur.*

There may be more SAE reports in the intervention group as a result of their regular contact with the study team (i.e. receipt of up to 18 EMDR sessions with the study therapist, and more regular completion of the PHQ-9 and related participant safety risk assessments as part of therapy). This will be taken into consideration when interpreting the pattern of SAEs.

Suspected Serious Adverse Reaction (SSAR)

A suspected serious adverse reaction (SSAR) is any serious adverse event that is suspected (possibly or probably or definitely) to be related to the intervention.

Non-IMP Suspected Unexpected Serious Adverse Reaction (Non-IMP SUSAR)

An SAE that occurs in a non-IMP trial and is:

- "Related" – that has, possibly, probably or definitely resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol (or above) as an expected occurrence.

All AEs will be assessed for seriousness, causality (relatedness) and expectedness by a clinical PI or nominated deputy clinician. The clinical PI at each centre will also record whether an event is considered to be related to the participant's mental health. We will develop a detailed, study-specific standard operating procedure for reporting and recording adverse events in line with the Sponsor's requirements. This will be in place prior to the commencement of recruitment activities.

7.3 Classification of severity (intensity)

Mild event:	An event that is easily tolerated by the participant, causing minimal discomfort a not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event:	An event that prevents normal everyday activities.

7.4 Classification of relatedness (causality)

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

7.5 Risk adaptive approach

This study is following a risk-adaptive approach to safety reporting because the intervention being studied has already been proven to be safe and is already in use for PTSD.

7.6 Safety reporting period

Adverse events/reactions will be recorded and reported from the point of consent (baseline assessment) until the 12-month follow-up assessment or point of withdrawal from the study.

7.7 Identification of AEs

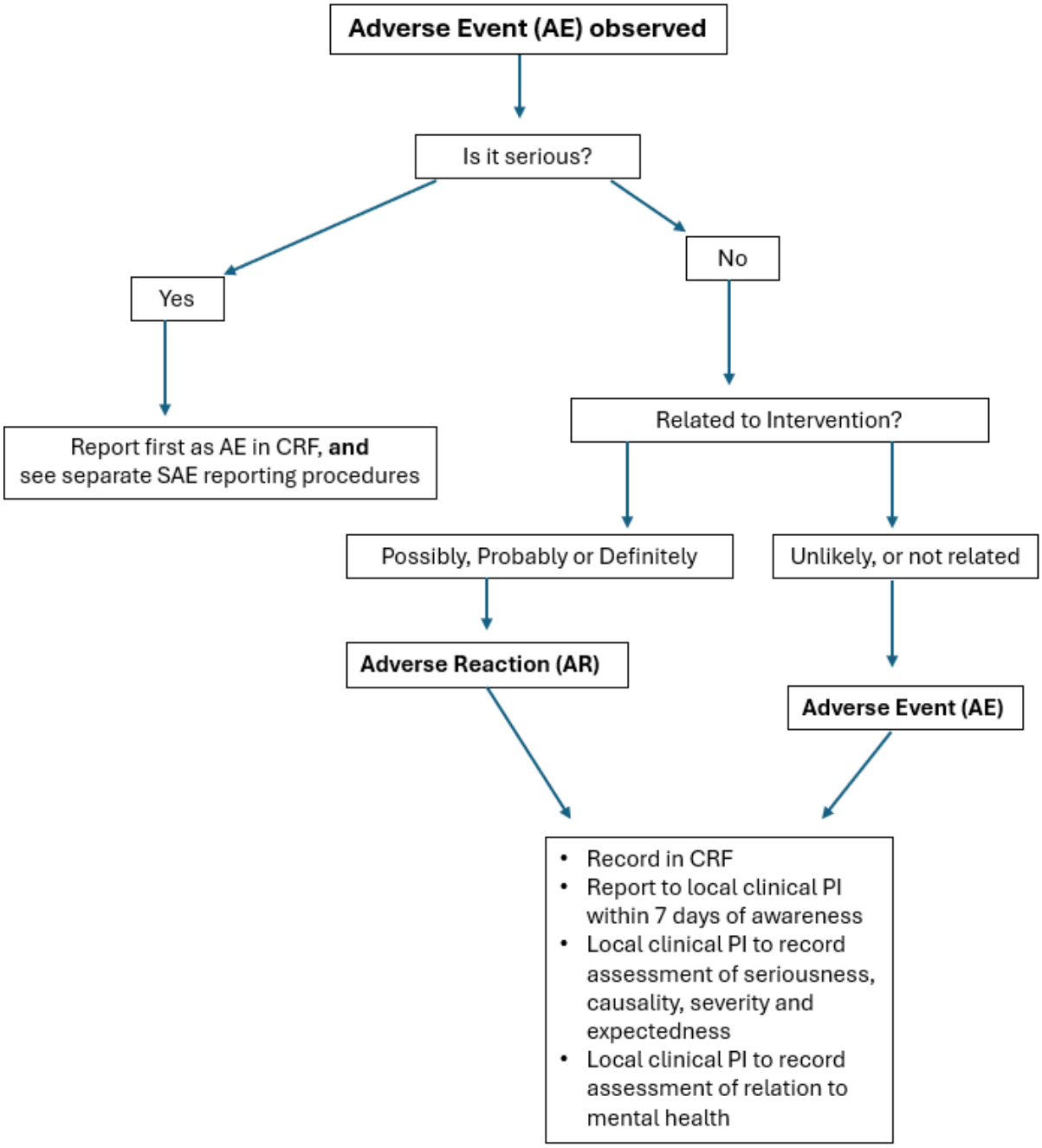
AEs are expected to occur throughout the course of the trial. Local researchers are responsible for recording AEs for their participants during the trial.

We anticipate that some AEs may be identified during EMDR appointments for participants allocated to the intervention. Up until the 52 week follow up, AEs may also be detected via researcher contact to encourage questionnaire completion, or via completion of study questionnaires (across both UC and EMDR groups). We will not actively monitor for events outside of study questionnaires. However, the central and/or local research team will report any AEs that occur should they become aware, as below.

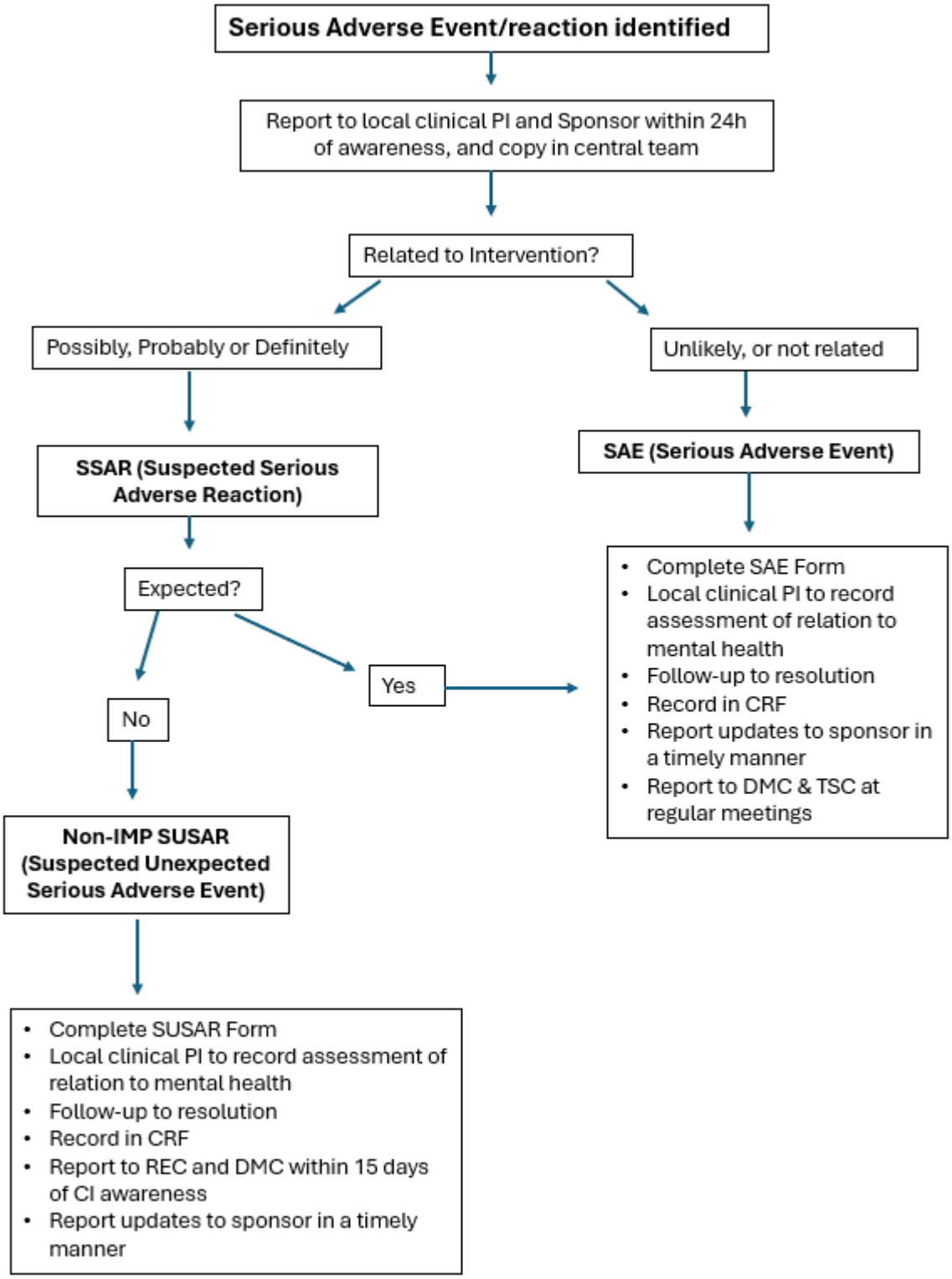
We anticipate that most AEs will be identified via study questionnaires. For example, participants will be asked about suicidal thoughts as part of the PHQ-9 and BDI-II questionnaires, and about hospital treatment as part of the 26 week and 52 week questionnaires; their responses and other disclosures may lead to further investigation in relation to AE reporting. The central and/or local team will communicate with clinical PI and GP practices if additional information is required, e.g., to ascertain the nature and severity of an AE. If the study team become aware of an AE, they will assess and log this according to trial recording and reporting procedures; see below.

7.8 Reporting overview

7.8.1 Adverse Events Overview



7.8.2 Serious Adverse Events Overview



**refers to the initial notification to University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) on behalf of the Sponsor.*

All safety information, including information relating to safety events that are not subject to expedited reporting, will be closely monitored by the DMC throughout the trial. The DMC will be provided with a report at least annually (unless specified by the DMC).

7.9 Expected events

Expected events are clinical outcomes that routinely occur when delivering the intervention.

Expected AEs and SAEs that are a more common occurrence in this study population regardless of the study are listed below. Although these events are expected, they will still be reported in this study.

- Self-harm
- Self-harm leading to hospitalisation
- Suicide attempts
- Suicide attempts leading to hospitalisation
- Worsening of depression which requires referral to a clinician
- Worsening of depression leading to hospitalisation

All AEs will be assessed for seriousness, severity, causality and expectedness by a clinical PI or nominated deputy clinician. Relatedness to mental health will also be assessed. We will develop a detailed, study-specific standard operating procedure for reporting and recording adverse events in line with the Sponsor's requirements. This will be in place prior to the commencement of recruitment activities.

7.10 Responsibilities

Centre Clinical Principal Investigator:

- Will check individual reports of AEs and use medical judgement in assigning seriousness, severity, causality and whether the event/reaction was expected, and whether the event was related to the participants mental health. If the local Clinical PI is not available this role will be delegated to a deputy clinician, or clinical PI from another centre.
- Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator:

- Maintain oversight of the safety of participants in the trial, including an ongoing review of the risk/benefit. A clinical PI (or deputy) will provide clinical advice to the CI in this regard.

Sponsor:

University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) will monitor safety information on behalf of the Sponsor. UHBW will be given the opportunity to review the trial AE reporting SOP prior to the start of the trial.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, the group will periodically review safety data and liaise with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, group will periodically review overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

The TSC and DMC will advise the trial team on the frequency of review of individual and cumulative SAEs.

7.11 Notification of deaths

All deaths will be reported to the Sponsor irrespective of whether the death is related to disease progression, the intervention, or an unrelated event.

7.12 Pregnancy reporting

We do not plan to report or follow-up pregnancies in this trial.

7.13 Urgent safety measures

The Sponsor and investigator may take appropriate urgent safety measures (USM) to protect a research participant from an immediate hazard to their health and safety. This USM can be taken before seeking approval from the competent authorities and ethics committee.

The main research ethics committee must be notified by email within three days. Information should include that such measures have been taken and the reasons why. The Sponsor will then follow-up with written notification within three days of the action being taken, i.e. in the form of an amendment, describing the event, the measures taken and justification for the measures taken. Where the USM requires an amendment to study documentation, this should be submitted as a substantial amendment as soon as possible and marked as being in response to USM. A copy of the USM notification should be submitted with the amendment.

If the Principal Investigator (and not the Sponsor) has instigated the USM, the Sponsor should be notified immediately so that they can assess and report the USM within the timelines required.

NHS R&D offices will require notification in accordance with local policies/procedures. Where applicable, oversight committees (such as the DMC) should review information relating to USM and report any recommendations to all relevant parties. The funder should be updated on all developments and actions as soon as possible.

8 DATA MANAGEMENT

8.1 Data collection

8.1.1 Data Sources

A full list of source data and location will be maintained in the Data Management Plan (DMP). Data extracted from GP records and sent to the central research team such as healthcare use, will also form part of the source data for this trial.

Data will be collected using electronic/paper case report forms (CRFs). Direct data entry to eCRFs will be done using REDCap. If paper CRFs are used these will be entered into the database as soon as possible.

Baseline consent will be documented using online or paper consent forms, and verbal consent will be taken (and audio-recorded) for qualitative interviews, with a consent form signed by the researcher on the participants behalf.

Screening, baseline, and follow-up data will be collated using validated and bespoke electronic and paper questionnaires. Where trial data has been collected on paper questionnaires, these questionnaires will be considered primary source documents, and data will be entered into the REDCap database by trial staff. Similarly, where patients or researchers have entered data directly onto electronic questionnaires, this will be saved directly to the REDCap database, and will be source data. Any paper copies will be stored in a secure locked cabinet in an access-controlled area.

Therapy data such as types of events worked on in therapy, depression scores, SUDs scores and scores on the VOC scale will be collected during EMDR sessions and recorded on the database as clinical data. Where consent is given, these data will be used for research purposes.

Audio recordings of therapy sessions will be deleted at the end of the study once the independent assessment of fidelity of the intervention has been completed.

Audio recordings of qualitative interviews will be deleted at the end of the trial, after being used to check the accuracy of interview transcripts and post analysis. All transcripts will be anonymised and stored for potential future use.

At the end of the follow-up period, health care resource data will be collected from patients' primary care notes. This data will either be captured electronically, or transcribed from care notes onto bespoke CRFs, prior to being entered into the study database.

The trial databases will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance.

8.1.2 Data System

REDCap will be used to capture and store study data for the trial. REDCap is a web-based electronic central data management system which is built and supplied by Vanderbilt.

The BTC systems team have standard operating procedures (SOPs) to ensure there is a structured approach to designing, building, testing and validating the database prior to release.

Access to the trial REDCap database is managed at an individual level via delegation logs and requires a password that must meet the minimum format requirements.

Participant personal identifiers will be stored securely. Participants will be informed of data storage and security processes in the Patient Information Leaflet.

The database contains audit trails to record all changes to the data and who actioned the changes, user permissions and when access was granted and revoked. The database is held on UoB servers that are automatically backed up daily by UoB IT and stored securely.

In the event of a study amendment, updates to the study database will be coordinated through changes to the relevant specification documents. Specification updates will be discussed between the study team (including the statistician) and the CI.

8.2 Data quality

Throughout the trial, data integrity, accuracy and completeness of data collection will be monitored and reported in compliance with good clinical practice (GCP) guidelines. This may include source data verification, use of automated data validation rules, data cleaning, training and risk-based monitoring (further details of which can be found in section 9.2). Periodic data reviews will be carried out and audit trails will be maintained.

Qualitative data transcripts will be checked for accuracy using the audio-recordings.

8.3 Essential document storage and security

Essential documentation, as specified by the Sponsor, will be stored in an eTMF and eISF. Read only access to the relevant systems can be provided for inspection purposes.

Access to the eTMF and eISF will be restricted and access will be approved and monitored by the BTC trial team. All systems where essential documentation is held are automatically backed up daily by UoB IT teams and stored securely.

8.4 Essential document archiving

Essential documentation, as specified by the sponsor, and source data (including REDCap database) will be kept for at least 10 years after the end of the trial. Documents will be kept at the University of Bristol and/or participating centres for this time. At the end of the archiving period, documents will be destroyed by confidential means. All non-essential documentation will be destroyed securely prior to archiving.

Where trial data are stored in a paper format, these records will be identified by a label bearing the name and duration of the trial and clearly stating the 'do not destroy before' date. Where electronic records are in use, local centre policy will be followed.

Participant personal identifiers will be archived where they form part of the essential documentation and will be destroyed at the end of the archiving period.

A study archiving plan will be developed, to include the TMF and ISF, in accordance with the BTC archiving procedure which require Sponsor and CI oversight. Centres will retain access to their ISF throughout the archiving period and the trial archive will be available for inspection purposes.

Data held at the University of Bristol will conform to the University of Bristol Data Security Policy and be held in compliance with the UK General Data Protection Regulation (GDPR), tailored by the Data Protection Act 2018. All centres should send all consent forms, paper questionnaires and other trial documentation to the University of Bristol at the end of the trial, for central archiving.

8.5 Database lock and exports

At the point of data lock all user access to the database will be changed to read-only to prevent any changes to the data. A final data extract will be produced for analysis and a copy archived with restricted access.

8.6 Database archiving

The database export created at the point of database lock will be stored on secure UoB servers for the duration of the archive period. The REDCap database will then be archived following REDCap standard procedures. The BTC systems team have protocols in place to retrieve the database from archive for inspection purposes, if required.

8.7 Data sharing

Members of the TMG will develop a data sharing policy consistent with UoB policy.

All data sharing will comply with the consent provided by participants and adheres to data protection legislation.

A data sharing plan will be developed at the outset of the trial. This will describe who will have access to the full dataset, and the process of requesting access to the full dataset.

9 RISK REVIEW AND MONITORING

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available on request for monitoring and audit by the Sponsor, the relevant REC and for inspection by regulatory authorities.

9.1 Risk Assessment

The risk assessment process is a careful examination of what could cause harm, who/what could be harmed and how, and risks to the study integrity. Reasonably foreseeable risks associated with a research study, and actions to control the risks so far as is reasonably practicable, will be identified and documented as soon as possible in a study specific risk assessment.

The risk assessment documentation and any subsequent revisions should be kept in the TMF. The risk assessment should be an ongoing process. Each time there are changes to the perceived risks and mitigating circumstances these must be agreed by the TMG and CI and documented.

9.2 Monitoring

Monitoring is defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

The purpose of monitoring is to verify that:

- The rights and well-being of the participants are protected;
- The reported study data are accurate, complete and verifiable from source documents;
- The conduct of the study complies with the currently approved protocol, GCP and the applicable regulatory requirements.

Study monitoring activities should be identified based on the study-specific risk assessment and will be documented in a Monitoring Plan. This will be developed in consultation with the Sponsor based on the trial risk assessment.

9.3 Monitoring of study by Sponsor

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available on request for monitoring and audit by the Sponsor (or BTC if they have been delegated to monitor) and the relevant REC.

University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) may be used to externally monitor the trial on behalf of the Sponsor.

9.4 Monitoring of study by BTC

The Sponsor usually delegates some monitoring activities to the central trial team at BTC. Checks of the following would be typical:

- Informed Consent process and documentation
- Inclusion and Exclusion criteria verification
- Completed source documents and CRFs, data completeness and other types of data queries
- Study procedures and / or intervention compliance
- Safety documentation and adverse event reporting
- Protocol deviations

The BTC will carry out regular central monitoring and audit of compliance of centres with Good Clinical Practice (GCP) and trial-specific data collection procedures described in the protocol. The trial database will have in-built validation and the TMG will review the completeness of the data throughout the trial. The BTC will not check CRFs or other source data against the data entered to the trial database, unless there are good reasons to visit a centre to complete a monitoring visit (e.g. the central monitoring highlights a problem).

The quality of the study data may be monitored through centralised database monitoring. Validation checks are documented in the database specification document. Data completeness and accuracy checks may be run through the study databases. Data queries are usually reported via the study database and may be supplemented by additional independent data checks carried out by the study statistical team.

Other study monitoring activities may also be carried out, e.g. remote centre monitoring, on site (centre) monitoring.

The plan will include elements of self-monitoring at centres (e.g. checking of site file documentation, safety reporting, and consent form reviews) and database checking and source data verification (SDV) checks. The results of self-monitoring will be shared with the CI/PI and Sponsor as appropriate. Areas of concern will be followed up and this may involve a site visit.

9.5 Training of recruiting sites and GP practices

Initiation training

Before the trial commences at each participating centre, training will be organised by Bristol Trials Centre (BTC). The training provided will ensure that site research personnel fully understand the protocol, case report forms (CRFs) and the practical procedures (working instructions) for the trial including using the data capture systems. These sessions may be provided virtually or on-site. They may include training videos and manuals as well as a site initiation meeting. Initial training and any subsequent training e.g. for new staff members will be documented.

Training for GP practices will also be organised by Bristol Trial Centre, ensuring that site staff fully understand the screening criteria, referral procedure, and the record search and Docmail processes for mail outs.

Each GP practice recruiting to the trial will receive information and advice on all trial recruitment procedures prior to the start of recruitment. This will be provided to collaborating Bristol practices by the Trial Manager, with the assistance of other members of the trial team as appropriate. Guidance will be provided to London and Exeter centre GP practices by the local trial team with assistance

from the Bristol centre as required. A training log will be maintained within the Trial Master File (TMF). Participating centres will be informed of amendments by the Bristol Trials Centre, who will pass this information on to GP practices as required.

Investigators' responsibilities

Investigators must ensure that local research approvals have been obtained and any required contractual agreements have been signed off by all parties before recruiting any participants. Investigators will be required to ensure compliance to the protocol and completion of the CRFs. Investigators will be required to allow access to trial documentation or source data on request for monitoring visits and audits performed by the Sponsor, BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their team of any amendments to the trial documents approved by the HRA/REC that they receive and ensure that the changes are complied with.

9.6 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed. Accidental protocol deviations will be documented and reported to the CI and Sponsor in line with the Sponsor's reporting requirements. They will also be reported to the DMC. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, DMC and the TMG.

Sponsor specific procedures will be followed for the reporting of any breaches. All protocol breaches will be reported to the Sponsor as soon as possible after they occur/are identified. The Sponsor will determine whether it constitutes a serious breach, requiring onward reporting to the REC.

9.7 Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to affect to a significant degree:

a. the safety or physical or mental integrity of the subjects of the trial; or

b. the scientific value of the trial.

In the event that a serious breach is suspected, the Sponsor will be notified as soon as possible and within 24 hours of becoming aware of the event. The serious breach will be reviewed by the Sponsor in collaboration with the CI. The Sponsor will determine whether it constitutes a serious breach, requiring onward reporting to the REC. If appropriate, the Sponsor will report it to the REC and the relevant NHS host organisation within seven calendar days of become aware of the serious breach.

Reports of misconduct or malpractice will be dealt with according to the University of Bristol's Regulations on Research Misconduct, Preventing harm in research (safeguarding) and Whistleblowing policies. These policies can be found on the University of Bristol website.

10 ANALYSES

10.1 Statistical analysis

Analyses will be directed by a pre-specified Statistical Analysis Plan (SAP) and will be in line with CONSORT reporting guidelines for clinical trials. The SAP will be prepared and approval sought from the TSC prior to database lock. The analysis plan will be published on the University of Bristol Research Portal. All analyses (unless otherwise stated) will be conducted on an intention to treat

(ITT) basis. Continuous data will be summarised as mean and SD or median and inter-quartile range (IQR) if distributions are skewed. Categorical data will be summarised as number and percentages.

10.1.1 Efficacy Analysis

In the primary efficacy analyses, we will compare groups 'as randomised' using linear regression adjusting for stratification/minimisation variables and baseline measurement of the outcome (BDI-II score).

Secondary analyses will adjust for any substantial baseline imbalances in key prognostic factors based on descriptive statistics. Impact of process measures (e.g. involvement in EMDR/other interventions) will be explored. Repeated measures analyses will incorporate outcomes over 52 weeks. An interaction between treatment group and time will formally assess whether effects are sustained or emerge later. A Complier Average Causal Effect (CACE) analysis is planned to estimate the treatment effect among compliers who attend an adequate number of EMDR sessions (defined as ≥9 sessions by 26 weeks). We will explore any potential therapist effects using a fully heteroscedastic mode [68]l. Sensitivity analyses will examine impact of missing data. A priori subgroup analyses will explore possible differential treatment effects based on baseline depression chronicity and severity by including an interaction term between treatment allocation and each factor.

Model validity will be checked using standard methods; if a model is a poor fit, alternative models or transformations will be explored.

10.1.2 Mechanistic analysis

To determine whether reductions in depressive symptoms are mediated via the proposed mechanisms (vividness and emotional intensity of depression-related memories, negative self-beliefs and symptoms of re-living, avoidance and hyper-arousal), we will use a cutting-edge counterfactual framework based on the parametric g-formula [69]. This can accommodate both continuous (e.g., depressive symptoms, BDI-II score) and binary outcomes (e.g., remission), multiple mediators, and potential intermediate confounders (e.g., depressive symptoms during therapy). With continuous outcomes, we will also use traditional mediation (products of coefficients within a structural equation modelling (SEM) framework) to compare results with the counterfactual approach, and estimate the path specific effects via each mediator.

We will identify potential baseline/intermediate confounders using Directed Acyclic Graphs. Despite the exposure being randomised, there may still be mediator-outcome confounders (e.g. prognostic factors, baseline measures of the mediators and outcome) which will be measured and included. We will compare findings using other methods making different assumptions to strengthen causal inference (e.g., instrumental variable (IV) methods which address mediator-outcome confounding and measurement error in the mediators through identifying covariates which moderate the effect of treatment on the mediators [70, 71]). If strong moderators of the effect of treatment on the mediators cannot be identified to use as an IV, we will examine the sensitivity of the results to the assumption of no unmeasured mediator-outcome confounders [72-74]. Finally, we will decompose CACE into the complier average natural direct effect and the complier average causal mediated effect via each of the proposed mechanisms using IV SEM [75]. This will allow us to examine the role of treatment receipt (e.g. attending an adequate number of EMDR sessions) on the outcome (e.g. depressive symptoms) via the mediators using randomisation as an IV.

If the WM hypothesis is correct, then EMDR will be more effective in those with lower WM capacity. So, we predict a negative relationship between WM capacity and baseline to post-treatment symptom reduction in the EMDR group. We will report a two-tailed correlation between baseline

WM capacity (three continuous measures) and change in depressive symptoms on the BDI-II between baseline and 26 weeks. We will also explore associations using suitable regression models and undertake exploratory analyses testing for an interaction between baseline WM (for each of the three measures) and treatment allocation. Analysing each of the three measures of WM separately will help us understand which aspects of WM are important. Tests for interaction will be interpreted with caution given that they will be underpowered.

10.2 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants and after data lock. Safety data will be reported to the DMC at a frequency to be agreed, together with any additional analyses the committee requests.

11 TRIAL OVERSIGHT

11.1 Day-to-day management

The trial will be managed by the Bristol Trials Centre (BTC). The BTC is a fully registered UK Clinical Research Collaboration (UKCRC) Unit. University of Bristol will act as Sponsor. Day-to-day management of the trial will be overseen by the Chief Investigator (CI) and BTC staff. The CI and BTC team will work with the co-applicants to prepare the final protocol and submissions for regulatory approvals; REC & HRA. The BTC will prepare all trial documentation and data collection forms, and design and implement the data management systems. The Trial Manager will be the contact point to provide support and guidance to the participating centres and GP practices throughout the trial.

11.2 Host organisation: NHS Bristol, North Somerset and South Gloucestershire (BNSSG) ICB

NHS Bristol, North Somerset and South Gloucestershire (BNSSG) Integrated Care Board (ICB) is the host organisation. They will ensure NHS engagement and their Research Team will support the project. The Host will be responsible for delivering the contract, including financial obligations and will work with the Sponsor to monitor and manage supplier contracts.

11.3 Trial Management Group (TMG)

The trial will be managed by a trial management group (TMG), which will meet approximately monthly for the duration of the study. The TMG will comprise of all investigators, including the PPI co-applicant. Other members of the research team will be invited to attend as required. The TMG will have responsibility for the day-to-day management of the trial and will report to the Trial Steering Committee (TSC).

11.4 Data Monitoring Committee (DMC)

An independent DMC will be established to review safety data during the trial and will advise on any interim analyses if appropriate. Membership, responsibilities, and reporting mechanisms of the DMC will be formalised in a DMC charter. The DMC will usually meet jointly with the TSC before recruitment in the trial begins and then approximately every six months or as agreed with the DMC during the course of the trial. It is anticipated that the DMC will comprise of independent members including a Chairperson, Statistician and expert in the clinical and/or academic field of this research. The CI, Trial Manager, Lead and Unblinded Statistician and any other TMG members agreed by the DMC chair will attend the open session only and the Unblinded Statistician will attend both open and

closed sessions. The DMC will usually meet prior to the TSC and will provide their recommendations to the TSC Chairperson.

11.5 Trial Steering Committee (TSC)

A TSC will be established, in line with funder requirements, to oversee the conduct of the trial. Membership, responsibilities, and reporting mechanisms of the TSC will be formalised in a TSC Terms of Reference. The TSC will make recommendations during the trial to the TMG and will advise on key decisions. Meeting minutes will be sent to the funder. It is anticipated that the TSC will comprise of independent members including a Chairperson, Statistician, relevant experts in the clinical and academic field of this research, and PPI representative(s). The CI, a clinical co-investigator, Trial Manager and Lead Statistician will represent the TMG as observers, the attendance of any other TMG members will be agreed by the TSC chair. Sponsor, the ICB and funder contact will all be invited to these meetings as observers. Anyone not directly involved in the study team but from the same institution may attend as non-independent members, with the agreement of the TSC Chair. The TSC will meet before recruitment to the trial begins and then approximately every six months or as agreed with the TSC during the trial.

11.6 Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator (CI), Regulatory Authority, or Funder, based on new safety information or for other reasons provided by the DMC or TSC, regulatory authority, or ethics committee.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC, who will advise on whether to continue or discontinue the trial and make a recommendation to the Funder. If the trial is prematurely discontinued, no new participants will be recruited and a decision on data collection for active participants will be made in discussion with the Funder, TSC, DMC and Sponsor.

12 PATIENT AND PUBLIC INVOLVEMENT (PPI)

PPI (Patient and Public Involvement) work was incorporated into the project in accordance with HRA guidance to ensure that public perspectives informed the design, conduct, and dissemination of the research. A lived experience advisory group (LEG) (n=5) was established for the grant application of EYE-D and met on three occasions to discuss the proposed study. They were enthusiastic in their support for evaluating EMDR as a treatment for depression and understanding how EMDR works.

The group discussed recruitment methods and talked about the importance of the participant information leaflet and being clear about who would be eligible to take part and the focus on past traumatic experiences and depression to minimise the likelihood of individuals dropping out once recruited. Based on this discussion, the entry criteria for the study now includes a requirement for participants to be willing to discuss past stressful experiences. This suggestion aligns with requirements in NHS primary care talking therapy services in terms of accessing EMDR for PTSD.

The group reflected on whether recruitment should take place in general practice or NHS talking therapies services. There was concern that if recruitment took place in talking therapy services, then it would be excluding people who had not sought help via that service. The group suggested that if the aim of the study is to understand if, and how, EMDR works for depression, then it was important that the trial was open to as many people as possible, so that it was more representative of the population with depression.

The group discussed the proposed follow-up schedule for the trial – initially proposed as four contacts (at 13, 26, 39 and 52 weeks). The group felt that there should be more contact initially, to help build links with the research team and engagement with the study and advised adding two early follow-ups for all participants – an initial phone call at 1-2 weeks, and a further contact at 8 weeks. The group also said that it would be important to offer the option of in-person follow-up appointments for trial participants as this is important for building trust in the research team and for participants to feel comfortable answering questions in an open manner. The suggested two additional contacts and the option for remote or in-person appointments have been incorporated into the study design.

The group also suggested expanding membership of the PPI group for the study to include a more diverse group including those who have not previously been involved with research. The group discussed PPI involvement more generally, and talked about the importance of contributors having a clear timeline for when PPI and trial activities are scheduled to take place. They also described how it was important that research teams maintain contact with PPI group members throughout the duration of the study and suggested regular updates to the PPI group would be useful. All of these suggestions have been adopted in the trial design. Three members of the group contributed to writing the plain English summary. One member of this group has joined the research team as a co-applicant and a second member will act as EDI Ambassador.

The PPI lead and PPI co-applicant will facilitate involvement of the Lived Experience advisory Group (LEG) throughout the project. More members have been recruited, and the LEG will now comprise 8-10 members and includes a diverse membership.

All potential LEG members will have the opportunity to discuss the study and decide on the level of involvement that is appropriate for them. If online meetings are a barrier to LEG membership, the PPI lead will support individuals to contribute in other ways. This may include attending community settings to provide support or access to online technology, use of telephone calls or meeting in person.

The LEG will develop patient-facing materials, advise on recruitment and retention, co-develop interview topic guides and study newsletters, discuss results and advise on dissemination strategies (e.g. infographics, participant summaries) (section 14). In addition to the usual dissemination routes (academic papers and conference presentations), we aim to develop connections with relevant community organisations to disseminate findings more widely. We will also work with the Bristol Centre for Academic Primary Care (CAPC) PPI group and CAPC communications officer who are skilled in adapting research output for participants and for a wider audience.

The PPI lead will maintain a log of PPI activities to capture the impact of these activities in the final report.

Four meetings will be held at the beginning of the project. The initial meeting will cover introductions, checking and setting group expectations and discussion of the protocol. The second and third will focus on documentation, with the group helping to develop patient-facing materials (e.g. study invitations, PILs and questionnaires). The fourth will focus on topic guides for the qualitative study. There will be an additional two meetings early in the study to discuss issues related to recruitment and retention. All LEG members will be sent regular updates to keep them informed of the study progress.

Regular newsletters will be co-produced with the LEG and sent to study participants. There will be two meetings to discuss the qualitative interview data, findings and interpretation. A meeting will be held to discuss the quantitative data, further exploratory analyses, and dissemination. There will be a final meeting to co-produce an easy-to-read infographic for public dissemination. PPI co-applicant will join the trial management group (TMG) that will meet monthly during the study. We will also recruit one or two PPI members to join the independent TSC that meets twice a year for the study duration.

Through the CAPC, ARC West and People in Health West of England, PPI members will have access to peer support, resources and training to support their role.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Governance and legislation

This trial will be conducted in accordance with:

- The principles of Good Clinical Practice, as set out in the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- UK Policy Framework for Health and Social Care Research
- Data Protection Act 2018
- UK General Data Protection Regulation

Before any NHS site (GP practice) can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes along with other documentation required for the sponsor or designee to grant sites with a greenlight letter.

Approved amendments will be submitted to participating NHS Integrated Care Boards (ICBs) for information or approval, as required.

GCP training and trial specific training for research staff members will be at a level commensurate with their involvement within the trial. Informed consent to participate in the trial will be sought and obtained according to GCP guidelines.

The Concordat to Support Research Integrity will be followed.

13.2 Research Ethics Committee review and reports

Ethics review of the protocol and other trial related patient facing documents will be carried out by an NHS Research Ethics Committee (REC) and the Health Research Authority (HRA).

All correspondence with the HRA/REC will be retained in the Trial Master File (TMF). The CI will notify the REC of the end of the trial and if the trial is ended prematurely (including the reasons for the premature termination). Within one year of the end of the trial, the CI will submit a final report with the results to the REC.

13.3 Peer review

The EYE-D trial has been reviewed by the funder at the application stage. As part of this, the proposal was assessed by the funding panel and was subject to external peer review.

The protocol and ongoing trial will be reviewed by the independent TSC and DMC, and by the funder as part of the annual progress review.

13.4 Amendments

Any amendments to the protocol or other trial related participant facing documents will be approved by the Sponsor (and where necessary the funder) before being submitted to the REC/HRA for approval prior to implementation.

It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC, in accordance with the legislation and HRA processes. All amendments will be documented on the HRA amendment tool regardless of substantiality. Approved amendments will be sent to participating centres by Bristol Trials Centre, for sending onto GP practices as required.

13.5 Financial and other competing interests

The research team must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

13.6 Indemnity

The necessary trial insurance is provided by the Sponsor. The PIL provides a statement regarding indemnity.

14 DISSEMINATION POLICY

A publication policy will be developed following the BTC template, with authorship models agreed in advance with the TMG.

The findings will be disseminated by usual academic channels, i.e. presentation at national and/or international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to participants, where available.

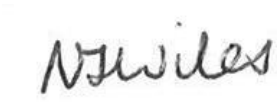
Where possible, information will be disseminated to participating GP practices and participants in line with timelines for academic audiences (i.e. participant and GP practices being informed of the study results on or shortly after the date the academic paper is published). Before dissemination materials are drafted, PPI members should be consulted on the proposed methods for dissemination to non-academic audiences.

15 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 UK Policy Framework for Health and Social Care Research, the Sponsor's SOPs, and other regulatory requirements as amended. 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 clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature:



Name (please print): Nicola J Wiles Date: 12.11.2025

Senior Statistician:

Signature:

Name (please print): Stephanie MacNeill Date: 17/11/2025

16 REFERENCES

1. NHS England. *NHS Mental Health Implementation Plan 2019/20 - 2023/24*. 2019; Available from: https://www.longtermplan.nhs.uk/publication/nhs-mental-health-implementation-plan-2019-20-2023-24/.
2. GBD 2019 Disease and Injuries Collaborators, *Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019.* Lancet, 2020. **396**: p. 1204-1222.
3. Health and Safety Executive. *Health and safety at work. Summary statistics for Great Britain 2018*. 2018; Available from: https://www.hse.gov.uk/statistics/overall/hssh1718.pdf.
4. McCrone, P., et al., *Paying the price: the cost of mental health care in England to 2026*. 2008, King's Fund: London.
5. Cuijpers, P., et al., *The effects of psychotherapies for depression on response, remission, reliable change and deterioration: a meta-analysis.* Acta Psychiatrica Scandinavica, 2021. **144**(3): p. 288-299.
6. Trivedi, M.H., et al., *Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice.* American Journal of Psychiatry, 2006. **163**: p. 28-40.
7. National Institute for Health and Care Excellence. *Post-traumatic stress disorder (PTSD). NICE guideline (NG116)*. 2018; Available from: https://www.nice.org.uk/guidance/ng116.
8. Hofmann, A., et al., *Treating depression with EMDR therapy. Techniques and interventions*. 2023, New York: Springer Publishing Company.
9. Buckman, J.E.J., et al., *Life events and treatment prognosis for depression: A systematic review and individual patient data meta-analysis.* Journal of Affective Disorders, 2022. **299**: p. 298-308.
10. Monroe, S.M. and K.L. Harkness, *Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective.* Psychological Review, 2005. **112**(2): p. 417-445.
11. Nanni, V., R. Uher, and A. Danese, *Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis.* American Journal of Psychiatry, 2012. **169**(2): p. 141-151.
12. Humphreys, K.L., et al., *Child maltreatment and depression: A meta-analysis of studies using the Childhood Trauma Questionnaire.* Child Abuse & Neglect, 2020. **102**.
13. Nelson, J., et al., *Childhood maltreatment and characteristics of adult depression: meta-analysis.* Br J Psychiatry, 2017. **210**(2): p. 96-104.
14. Norman, R.E., et al., *The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis.* PLoS Med, 2012. **9**(11): p. e1001349.
15. Childhood Trauma Meta-Analysis Study Group, *Treatment efficacy and effectiveness in adults with major depressive disorder and childhood trauma history: a systematic review and meta-analysis.* Lancet Psychiatry, 2022. **9**: p. 860-873.
16. National Institute for Health and Care Excellence. *Depression in adults: treatment and management. NICE guideline [NG222]*. 2022; Available from: https://www.nice.org.uk/guidance/ng222.
17. Carletto, S., et al., *Eye movement desensitization and reprocessing for depression: a systematic review and meta-analysis.* European Journal of Psychotraumatology, 2021. **12**(1): p. 1894736.
18. Landin-Romero, R., et al., *How Does Eye Movement Desensitization and Reprocessing Therapy Work? A Systematic Review on Suggested Mechanisms of Action.* Frontiers in Psychology, 2018. **9**: p. 1395.

19. Shapiro, F., *Eye movement desensitization and reprocessing (EMDR) therapy: Basic principles, protocols and procedures*. 3rd edition ed. 2018, New York: Guilford Press. 568.
20. Brewin, C.R., et al., *Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications.* Psychological Review, 2010. **117**(1): p. 210-232.
21. Solomon, R.M. and F. Shapiro, *EMDR and the Adaptive Information Processing Model Potential Mechanisms of Change.* Journal of EMDR Practice and Research, 2008. **2**(4): p. 315-325.
22. Wadji, D.L., C. Martin-Soelch, and V. Camos, *Can working memory account for EMDR efficacy in PTSD?* BMC Psychology, 2022. **10**: p. 245.
23. Kendrick, T., et al., *Management of depression in adults: summary of updated NICE guidance.* British Medical Journal, 2022. **378**: p. 1-7.
24. Lopez-Lopez, J.A., et al., *The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis.* Psychological Medicine, 2019. **49**: p. 1937-1947.
25. Yan, S., et al., *The Effectiveness of Eye Movement Desensitization and Reprocessing Toward Adults With Major Depressive Disorder: A Meta-Analysis of Randomized Controlled Trials.* Frontiers in Psychiatry, 2021. **12**: p. 11.
26. NHS England. *The NHS Long Term Plan*. 2019 11/10/2022]; Available from: www.longtermplan.nhs.uk.
27. Lewis, G., et al., *Maintenance or Discontinuation of Antidepressants in Primary Care.* New England Journal of Medicine, 2021. **385**(14): p. 1257-1267.
28. Lewis, G., et al., *The clinical effectiveness of sertraline in primary care and the role of depression severity and duration (PANDA): a pragmatic, double-blind, placebo-controlled randomised trial.* The Lancet Psychiatry, 2019. **6**(11): p. 903-914.
29. Kessler, D.S., et al., *Mirtazapine added to SSRIs or SNRIs for treatment resistant depression in primary care: phase III randomised placebo controlled trial (MIR).* British Medical Journal, 2018. **363**: p. k4218.
30. Wiles, N., et al., *Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial.* Lancet, 2013. **381**(9864): p. 375-84.
31. NIHR. *NIHR Three Research Schools Mental Health Research Programme 2021-2024, Appendix 1*. 2021 [cited 2025 02/05/2025]; Available from: https://www.spcr.nihr.ac.uk/files/news/fellowship-guidance-notes_nihr-three-research-schools_mental-health-programme_sept-21.
32. Dawson, S., et al., *Trial Forge Guidance 3: randomised trials and how to recruit and retain individuals from ethnic minority groups - practical guidance to support better practice.* Trials, 2022. **23**.
33. NIHR. *Improving inclusion of under-served groups in clinical research: Guidance from the NIHR-INCLUDE project*. 2020; Available from: https://www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435.
34. NHS England. *Increasing diversity in research participation: a good practice guide for engaging with underrepresented groups*. 2023 14/12/2023]; Available from: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2023/02/B1905-increasing-diversity-in-research-participation-v2.pdf.pdf.
35. Centre for Academic Primary Care. *10 tips for improving diversity in research*. 2024 [cited 2025 02-May-2025]; Available from: https://capcbristol.blogs.bristol.ac.uk/2024/04/18/10-tips-for-improving-diversity-in-research/.
36. Centre for Academic Primary Care. *Why take part in research?* 2023 [cited 2025 02/05/2025]; Available from: https://www.bristol.ac.uk/primaryhealthcare/researchthemes/why-take-part-in-research/.
37. University of Bristol. *GPs at the Deep End Bristol* 2025 [cited 2025 02/05/2025]; Available from: https://deependgps.bristol.ac.uk/.

38. NIHR Applied Research Collaboration West. *Four new Health Ambassadors recruited to help diversify local research participation*. 2023 [cited 2025 02-05-2025]; Available from: https://arc-w.nihr.ac.uk/news/four-new-health-ambassadors-recruited-to-help-diversify-local-research-participation/.
39. NIHR Applied Research Collaboration North Thames. *Mental Health Research for All: Inclusion of diverse experiences in mental health and care research*. [cited 2025 02/05/2025]; Available from: https://www.arc-nt.nihr.ac.uk/research/projects/mental-health-research-for-all/.
40. University of Exeter. *The South West Mental Health Gap Practice Research Network* [cited 2025 02/05/2025]; Available from: https://www.exeter.ac.uk/research/mooddisorders/groups/southwestmentalhealthgappracticeresearchnetworkprn/.
41. Bristol Health Partners. *New funding awarded which aims to drive up diverse participation in research to help narrow region's health gap*. 2023 [cited 2025 02/05/2025]; Available from: https://www.bristolhealthpartners.org.uk/news/new-funding-awarded-which-aims-to-drive-up-diverse-participation-in-research-to-help-narrow-regions-health-gap/.
42. NHS England. *Embedding research in the NHS*. [cited 2025 02/05/2025]; Available from: https://www.england.nhs.uk/aac/what-we-do/embedding-research-in-the-nhs/.
43. Simmonds, B., et al., *Patients' experiences of participating in a large-scale trial of cognitive behavioural therapy for depression: a mixed methods study.* Family Practice, 2013. **30**(6): p. 705-711.
44. Tallon, D., et al., *Integrated therapist and online CBT for depression in primary care (INTERACT): study protocol for a multi-centre randomised controlled trial.* Trials, 2023. **24**: p. 421.
45. Avery, K.N.L., et al. *Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies*. BMJ Open, 2017. **7**, DOI: 10.1136/bmjopen-2016-013537.
46. Ostacoli, L., et al., *Comparison of Eye Movement Desensitization Reprocessing and Cognitive Behavioral Therapy as Adjunctive Treatments for Recurrent Depression: The European Depression EMDR Network (EDEN) Randomized Controlled Trial.* Frontiers in psychology, 2018. **9**: p. 74.
47. Kessler, D., et al., *Therapist-delivered internet psychotherapy for depression in primary care: a randomised controlled trial.* Lancet, 2009. **374**: p. 628-634.
48. Korn, D.L., et al. *EMDR Fidelity Rating Scale (EFRS)*. 2023 [cited 2024 06/01/2024]; Available from: https://emdrresearchfoundation.org/research-grants/emdr-fidelity-rating-scale/.
49. Kounali, D., et al., *How much change is enough? Evidence from a longitudinal study on depression in UK primary care.* Psychological Medicine, 2020. **52**(10): p. 1875-1882.
50. Lewis, G., et al., *Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers.* Psychological Medicine, 1992. **22**(2): p. 465-486.
51. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* Journal of General Internal Medicine, 2001. **16**(9): p. 606-613.
52. Spitzer, R.L., et al., *A brief measure for assessing generalized anxiety disorder. The GAD-7.* Archives of Internal Medicine, 2006. **166**: p. 1092-1097.
53. Mundt, J.C., et al., *The Work and Social Adjustment Scale: a simple measure of impairment in social functioning.* British Journal of Psychiatry, 2002. **180**: p. 461-464.
54. Mitchell, P.M., et al., *Assessing the validity of the ICECAP-A capability measure for adults with depression.* BMC Psychiatry, 2017. **17**: p. 46.
55. Bernstein, D.P., et al., *Development and validation of a brief screening version of the Childhood Trauma Questionnaire.* Child Abuse and Neglect, 2003. **27**(2): p. 169-190.
56. McManus, S., et al., *Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014*. 2016: Leeds.

57. Weathers, F.W., et al. *The Life Events checklist for DSM-5 (LEC-5)*. 2013 [cited 2023 11/07/2023]; Available from: Instrument available from the National Center for PTSD: https://www.ptsd.va.gov/professional/assessment/te-measures/life_events_checklist.asp.
58. Cloitre, M., et al., *The International Trauma Questionnaire: development of a self-report measure of ICD-11 PTSD and complex PTSD.* Acta Psychiatrica Scandinavica, 2018. **138**(6): p. 536-546.
59. Baddeley, A.D. and J. Andrade, *Working memory and the vividness of imagery.* Journal of Experimental Psychology: General, 2000. **129**(1): p. 126-145.
60. Vittinghoff, E. and T.B. Neilands, *Sample Size for Joint Testing of Indirect Effects.* Prevention Science, 2015. **16**(8): p. 1128-1135.
61. Fox, F., et al., *Patients' reasons for declining a primary care trial online therapy: a mixed methods study.* BJGP Open, 2025: p. BJGPO.2024.0272.
62. Brown, G., et al., *Barriers to recruiting ethnic minorities to mental health research: a systematic review.* International Journal of Methods in Psychiatric Research, 2014. **23**(1): p. 36-48.
63. Saarijärvi, M. and E.-L. Bratt, *When face-to-face interviews are not possible: tips and tricks for video, telephone, online chat, and email interviews in qualitative research.* European Journal of Cardiovascular Nursing, 2021. **20**(4): p. 392-396.
64. Alessi, E. and S. Kahn, *Toward a trauma-informed qualitative research approach: Guidelines for ensuring the safety and promoting the resilience of research participants.* Qualitative Research in Psychology, 2022. **20**: p. 1-34.
65. Braun, V. and V. Clarke, *Using thematic analysis in psychology.* Qualitative Research in Psychology, 2006. **3**: p. 77-101.
66. Ritchie, J. and L. Spencer, *Qualitative data analysis for applied policy research*, in *Analysing qualitative data*, A. Bryman and R.G. Burgess, Editors. 1994, Routledge: London. p. 173-194.
67. Jones, K., Weatherly, H. L. A., Birch, S., Castelli, A., Chalkley, M. J., Dargan, A., Findlay, D., Forder, J., Gao, M., Hinde, S., Markham, S., Premji, S., & Teo, H., *Unit Costs of Health and Social Care 2023*, Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York), Editor. 2024: Kent, UK.
68. Roberts, C. and S.A. Roberts, *Design and analysis of clinical trials with clustering effects due to treatment.* Clinical Trials, 2005. **2**(2): p. 152-162.
69. De Stavola, B.L., et al., *Mediation analysis with intermediate confounding: structural equation modeling viewed through the causal inference lens.* American Journal of Epidemiology, 2015. **181**(1): p. 64-80.
70. Dunn, G., et al., *Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: a methodological research programme.* Health Technology Assessment, 2015. **19**(93): p. 1-115.
71. Emsley, R., G. Dunn, and I.R. White, *Mediation and moderation of treatment effects in randomised controlled trials of complex interventions.* Statistical Methods in Medical Research, 2010. **19**(3): p. 237-270.
72. Smith, L.H. and T.J. VanderWeele, *Mediational E-values: Approximate sensitivity analysis for unmeasured mediator-outcome confounding.* Epidemiology, 2019. **30**(6): p. 835-837.
73. VanderWeele, T.J. and Y. Chiba, *Sensitivity analysis for direct and indirect effects in the prescence of exposure-induced mediator-outcome confounders.* Epidemiology, biostatistics and public health, 2014. **11**(2): p. e9027.
74. VanderWeele, T.J., *Bias formulas for sensitivity analysis for direct and indirect effects.* Epidemiology, 2010. **21**(4): p. 540-551.
75. Park, S. and E. Kürüm, *A two-stage joint modeling method for causal mediation analysis in the presence of treatment noncompliance.* Journal of Causal Inference, 2020. **8**(1): p. 131-149.

17 APPENDIX 1: Gantt Chart

Timeline	2025											
	J	F	M	A	M	J	J	A	S	O	N	D
Month			1	2	3	4	5	6	7	8	9	10
Phase 1: set-up												
Recruit PPI, set-up oversight & trial management committees												
PPI design trial paperwork and finalise protocol												
Apply and obtain necessary approvals and SSCs and ETCs							*					
Develop and test database for data collection and randomisation system												
Obtain local approvals needed for Bristol start												
Recruit Bristol researcher & finalise SOPs												
Start recruiting GP practices												
Recruit Bristol therapists												
Therapist training in Bristol												
Recruit therapists at other centres												
Phase 2: Internal pilot												
Recruit participants in Bristol												
PPI & management group; review processes & procedures												
2, 8, 16 week follow-ups												

Timeline	2026											
	J	F	M	A	M	J	J	A	S	O	N	D
Month	11	12	13	14	15	16	17	18	19	20	21	22
Phase 2: Internal pilot												
Recruit participants in Bristol												
Local researchers start at other centres & obtain local approvals and SSCs												
Recruit GP practices at other centres												
Therapist training at other centres												
PPI & management group; review processes & procedures												
Interviews with decliners												
2, 8, 16 week follow-ups												
Review of 'stop-go' criteria by TSC				*								
Phase 3: Main trial												
Participant recruitment starts at other centres and continues in Bristol												
Interviews with decliners												
26 week follow-ups												
39 week follow-ups												
52 week follow-ups												
Qualitative interviews with trial participants												

Timeline	2027											
	J	F	M	A	M	J	J	A	S	O	N	D
Month	23	24	25	26	27	28	29	30	31	32	33	34
Participant recruitment at all centres										*		
Follow-ups continue (2, 8, 16, 26, 39 & 52 wks)												
Qualitative interviews with trial participants												

Timeline	2028											
	J	F	M	A	M	J	J	A	S	O	N	D
Month	35	36	37	38	39	40	41	42	43	44	45	46
16 week follow-ups		*										
26 week follow-ups				*								
39 week follow-ups							*					
52 week follow-ups										*		
Data collection from medical records												
Qualitative interviews with trial participants												
Interviews with therapists & supervisors												

Timeline	2028											
	J	F	M	A	M	J	J	A	S	O	N	D

Month	35	36	37	38	39	40	41	42	43	44	45	46
Qualitative analysis and reporting												
Data cleaning & analysis: efficacy & mechanisms & intervention costing exercise												

Timeline	2029			
Month	J 47	F 48	M 49	A 50
Qualitative analysis and reporting				
Analysis and report writing – efficacy & mechanisms & intervention costing exercise				*
Dissemination of results				

18 Amendment History

Amendment number (i.e. REC amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
N/A ahead of initial approval	V1.0	02-Jul-25	V2.0	02-Sep-25	Updated in line with REC recommendations: • Confirmation of who is carrying out qualitative analysis • Description of how reports of malpractice will be handled • Correction of inaccuracy in estimands table section 5.83	18-Sep-2025
01	V2.0	02-Sep-25	V3.0	06-Nov-25	• Timeframe of quali trainer interviews updated • Addition of collecting IMD rank of GP practice • Correction of researcher risk policy document name	*tbc*