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Full title: An international randomised factorial trial of therapist-supported online cognitive behavioural therapy for the reduction of repetitive negative thought (overthinking, rumination, worry) in adults: the Calming Minds study

Short title: Therapist-supported online cognitive behavioural therapy for reduction of repetitive negative thought: the Calming Minds study

The Calming Minds Study

PROTOCOL

Version 2.0 15/12/2025

IRAS number:	356635
ISRCTN reference:	ISRCTN10569526
Funder reference:	UNS141804
Sponsor reference:	24-25-37

This study forms part of a wider Wellcome Trust programme grant titled “Understanding the mechanisms driving the reduction of repetitive negative thought”.

Format of the protocol

This study will be delivered in the UK and the USA. The study is sponsored by the University of Exeter in the UK, and **Exeter, UK is the ‘Lead Site’**. Throughout the main body of this protocol, sections are structured such that information that applies to the Lead Site comes first. All sections then contain a **“USA-specific detail” sub-section** which describes any differences from the Lead Site that apply to the USA only.

This protocol has regard for the HRA guidance and order of content

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and in accordance with the UK Policy Framework for Health and Social Care Research, the Data Protection Act (2018), the principles of Good Clinical Practice (GCP) and the Sponsor's (and any other relevant) SOPs.

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 and serious breaches of GCP from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

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PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol version no.	Protocol date	Author(s) of changes	Details of changes made
Non-notifiable amendment 1	2.0	15/12/25	Katie Joyce	- Figure 1: Corrections to align with Table 2 - Section ix: Removed mention of allocated therapist/coach being automated by the REDCap database. - Section 2 & 12: Updated/clarified definition of 'worsening symptoms' throughout - Loosened referenced to obtaining HRA approval throughout, as the HRA confirmed this is not required. - Table 3: Clarified the definition of 'Day 0' for each of the timepoints in the footer, corrected the collection of self-reported gender to be on the screening questionnaire. - Section 8.1 and Table 3: Added collection of the participants route of access to the study - Section 8.3 and Table 3: clarified that the period for completing baseline questionnaires can be extended in extenuating circumstances, updated threshold for extending EMA completion period - Section 8.4: Added details about what the participant's randomisation email will contain - Section 8.5: Specified that the schedule for mPath follow-up surveys and EMA will start when the participant reinstalls mPath, added a reminder email for missed micro-assessments/engagement prompts - Section 10: Updated the selection criteria for process evaluation interviews - Section 15 & 17.7: Correction to reflect that participants will now receive two mPath invitation codes - Section 17.5: Removed a duplicate item from the list of example non-compliances - Section 17.7: Corrected archiving retention period to 10 years, as per section 14.4

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Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

i. LIST OF CONTENTS

SIGNATURE PAGE **2**

PROTOCOL AMENDMENT HISTORY **3**

KEY STUDY CONTACTS **3**

I. LIST OF CONTENTS 6
II. LIST OF ABBREVIATIONS 8
III. STUDY SUMMARY 9
IV. FUNDING AND SUPPORT IN KIND 10
V. ROLE OF STUDY SPONSOR AND FUNDER 11
VI. ROLE OF THE COORDINATING CLINICAL TRIALS UNIT (CTU) 12
VII. ROLES OF TRIAL OVERSIGHT COMMITTEES AND GROUPS 12
VIII. KEY WORDS: 13
IX. PATIENT JOURNEY AND FLOW CHART 14
1. RATIONALE 17
2. ASSESSMENT AND MANAGEMENT OF RISK 20
3. OBJECTIVES AND OUTCOME MEASURES / ENDPOINTS 22
3.1. Primary objectives 22
3.2. Secondary objectives 23
3.3. Outcome measures 24
4. STUDY TREATMENTS 29
4.1. Intervention arm 29
4.2. Control arm 30
5. TRIAL DESIGN 30
5.1. Design considerations for minimising bias 32
6. STUDY SETTING 33
7. PARTICIPANT ELIGIBILITY CRITERIA 33
7.1. Inclusion criteria 33
7.2. Exclusion criteria 34
8. STUDY CONDUCT 35
8.1. Participant recruitment 41
8.2. Consent 44
8.3. Baseline data collection 45
8.4. Randomisation procedure 47
8.5. Follow up data collection 48
8.6. End of study 49
9. STUDY TREATMENT DELIVERY 49
10. PROCESS EVALUATION 50
11. PARTICIPANT WITHDRAWAL 50
12. SAFETY MONITORING 52
12.1. Definitions 53
12.2. Assessing causality of serious adverse events 55
12.3. Reporting Serious Adverse Events 55
12.4. Risk management following notification of potential harm to others 56
13. STATISTICS AND DATA ANALYSIS 58

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

13.1. Target sample size and justification 58
13.2. Planned recruitment rate 58
13.3. Statistical analysis plan 58
13.4. Interim analysis and criteria for the premature termination of the study 60
13.5. Participant analysis population(s) 60
13.6. Procedure(s) to account for missing or spurious data 60
13.7. Other statistical considerations 60
14. DATA MANAGEMENT 61
14.1. Data collection tools and source document identification 61
14.2. Data handling and record keeping 61
14.3. Access to Data 62
14.4. Archiving 63
15. MONITORING, AUDIT & INSPECTION 63
16. PUBLIC AND PATIENT INVOLVEMENT 64
17. ETHICAL AND REGULATORY CONSIDERATIONS 65
17.1. Research Ethics Committee (REC) review 65
17.2. Confidentiality Advisory Group (CAG) review 65
17.3. Peer review 65
17.4. Regulatory Compliance 65
17.5. Protocol compliance 66
17.6. Notification of Serious Breaches to GCP and/or the protocol 67
17.7. Data protection and patient confidentiality 67
17.8. Financial and other competing interests 70
17.9. Indemnity 70
17.10. Amendments 70
17.11. Post trial care 71
17.12. Access to the final study dataset 71
18. DISSEMINATION POLICY 72
18.1. Dissemination policy 72
18.2. Authorship eligibility guidelines and any intended use of professional writers 72
19. REFERENCES 72

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
EAB	External Advisory Board
EMA	Ecological Momentary Assessment
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
HRA	Health Research Authority
ISRCTN	International Standard Randomised Controlled Trials Number
LEAP	Lived Experience Advisory Panel
LMU	Ludwig Maximilian University, Munich
PI	Principal Investigator
PIS	Participant Information Sheet
PWP	Psychological Wellbeing Practitioner
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RUSAE	Related Unexpected Serious Adverse Reaction
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCLA	University of California, Los Angeles
UKCRC	UK Clinical Research Collaboration

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

iii. STUDY SUMMARY

Full title	An international randomised factorial trial of therapist-supported online cognitive behavioural therapy for the reduction of repetitive negative thought (overthinking, rumination, worry) in adults: the Calming Minds study
Short title	Therapist-supported online cognitive behavioural therapy for reduction of repetitive negative thought: the Calming Minds study
Trial acronym	The Calming Minds Study
Trial design	Large scale, component-mechanism selection factorial experiment
Trial participants	A diverse population of adults from different countries (UK, USA). **Inclusion** Living in UK or USA. Aged 18+ years. Access to a suitable smartphone/device and internet. Elevated repetitive negative thought (RNT). **Exclusion** Concurrent psychotherapy. Current diagnosis of alcohol or substance abuse/dependence. Current or past diagnosis for bipolar disorder or psychosis. Taking antidepressants or anxiolytic medications at a stable dose for less than six weeks. Current severe PTSD. Suicidal thoughts and self-harm.
Planned sample size	2192 Participants
Treatment duration	16 weeks
Follow up duration	52 Weeks
Planned study period	55 Months (12 months set-up, 24 months recruitment, 12 months follow-up, 7 months data cleaning, analysis and write up)
Primary protocol objectives	To delineate the causal mechanisms underpinning reduction in RNT, a characteristic of the most common mental health conditions. Our specific inter-related research questions are: (a) What are the causal mechanisms that underpin effective cognitive-behavioural interventions to reduce RNT?

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

	(b) What are the active ingredients within RNT-focused cognitive-behavioural therapy (RF-CBT) that effectively manipulate these mechanisms, and, thereby, reduce RNT?
Secondary protocol objectives	See Table 1, section 3.3.5.
Interventions	Content from the established rumination-focused CBT (RF-CBT) treatment delivered online with telephone/video-conference support from a Psychological Wellbeing Practitioner (PWP; UK) /coach (USA). The online material teaches skills through text, graphics, audio, animated video, and quiz content, all designed with cognitive principles to facilitate memory, and already includes RF-CBT components; Absorption-Be Present, Tackling Habits-Break Habit, Be Specific, Self-Compassion- Be Kind. For the factorial trial, we will adapt the content based on Lived Experience feedback and proof-of-principle experiments including user-centred design and will programme the multiple conditions necessary to manipulate the different components/mechanisms. A component-mechanism selection experiment using a balanced orthogonal factorial design will manipulate the 4 components described above at high versus low levels (effect coded: high level coded +1 versus low level coded -1; i.e. ½ of sample randomized to high level of factor; ½ randomised to low level) to differentially engage respective mechanisms and test their causal effects on RNT. In practice, this means that there will be 16 different variants of the digital RF-CBT intervention ranging from a version that is high in all the factors of interest (Be Present, Be Kind, Be Specific, Break Habit) to a version that is low in all factors of interest (i.e., a basic psychoeducation version), and all combinations in between. The intervention will be delivered via the MyDataHelps digital platform for which each randomised participant will be issued an account to access the specific variant of modules they have been allocated.

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL SUPPORT GIVEN
The Wellcome Trust	£5,037,110.00

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

v. ROLE OF STUDY SPONSOR AND FUNDER

Sponsor

The study sponsor will ensure that the research team has access to resources and support to deliver the research as proposed and that responsibilities for management, monitoring and reporting of the research are in place prior to the study commencing. The sponsor will ensure that there is agreement on recording, reporting and reviewing significant developments as the research proceeds and approve any modifications to design, obtaining requisite regulatory authority approval.

The sponsor will assume responsibility for operating the management and monitoring systems of the research.

Prior to the study commencing the sponsor will be satisfied that:

- The research will respect the dignity, rights, safety and well-being of participants and the relationship with healthcare professionals.
- Where appropriate the research has been reviewed and approved by an NHS research ethics committee and/or the health research authority approval programme, and an appropriate institutional review board or equivalent at international sites.
- The Chief Investigator, and other key researchers have the requisite expertise and have access needed to conduct the research successfully.
- The arrangements and resources proposed for the research will allow the collection of high quality, accurate data and the systems and resources will allow appropriate data analysis and data protection.
- Organisations and individuals involved in the research agree the division of responsibilities between them.
- Arrangements are in place for the sponsor and other stakeholder organisations to be alerted to significant developments during the study, whether in relation to the safety of individuals or scientific direction.
- There are arrangements for the conclusion of the study including appropriate plans for the dissemination of findings.

The sponsor will play no role in the design of this study and will have no role in data analysis or interpretation or writing up of findings of the study.

Funder

The research funder (“Wellcome”) has the responsibility to ensure that there is a proper use of the funds they control. The funder has reviewed the study plan and established that the research, is worthwhile, and of high scientific quality. The research funder has assessed the experience and expertise of the chief investigator, other key researchers on the programme and has deemed that there is appropriate infrastructure for the research to be carried out. The funder will be sent all outputs prior to dissemination, but the final decision on the content or whether to submit works for publication is the decision of the Chief Investigator

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

vi. ROLE OF THE COORDINATING CLINICAL TRIALS UNIT (CTU)

Exeter Clinical Trials Unit (ExeCTU), University of Exeter, is the Clinical Trials Unit responsible for the day-to-day management of the study. Responsibilities of ExeCTU, the Sponsor, the Chief Investigator (CI) and external collaborators at UCLA and Ludwig Maximilians University, Munich (LMU) are defined in detail in a separate task allocation document.

vii. ROLES OF TRIAL OVERSIGHT COMMITTEES AND GROUPS

Trial Steering Committee (TSC)

The Calming Minds Study TSC role will be to:

- Review the study protocol before the study starts, along with monitoring and supervision of the study's progress including;
    - Monitor the conduct, performance and technical content of the study and progress.
    - Critically assess the results of the study.
    - Modify or authorise modifications to the implementation of the as necessary from time to time.

Full terms of reference for the TSC will be described in a separate Charter.

The TSC shall be comprised of a minimum of five independent persons ("Members") including:

- An experienced researcher who shall act as chair of the TSC (the "TSC Chair"); and
- An independent statistician.

The remaining Members will be selected according to the funding body guidelines, and the identity of the remaining Members (and their successors) will be agreed jointly between Wellcome and the Sponsor.

The Chief Investigator and senior trial statistician will join the TSC as non-independent members.

Representatives of the Sponsor, Wellcome Trust and the research team will be invited to attend meetings of the TSC as observers but will not have voting rights.

Data Monitoring and Ethics Committee (DMEC)

The Data Monitoring and Ethics Committee (DMEC) will comprise three independent professional members, including an independent statistician who will act as Chairperson. The Chief Investigator, senior statistician, programme manager and members of the ExeCTU study team will be invited to attend the open sessions of DMEC meetings but will not be voting members. The senior statistician will attend closed sessions of DMEC meetings.

The DMEC will monitor accumulating study data, including safety, and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or early closure of the study. Further details of the roles and responsibilities of the DMEC are documented in the DMEC charter.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

External Advisory Board (EAB)

The External Advisory Board (EAB) will be formed of experts relevant to the field of study, including people with lived experience along with academic and clinical experts.

The EAB will provide oversight of the leadership team of the wider Calming Minds programme, which includes workstreams outside of this study.

The EAB will have oversight of all aspects of the wider Calming Minds programme and will provide advice to the Chief Investigator . For the purposes of this study, recommendations from the EAB concerning the study will be communicated to the TSC. The TSC and the Funder will have the final say on decisions directly pertaining to amendments or stopping of the study.

Trial Management Group (TMG)

The Trial Management Group (TMG) will be composed of the Chief Investigator, collaborators at UCLA and LMU, co-applicants, trial statisticians, the programme manager, the trial manager, data manager(s) and a Sponsor representative. The TMG is responsible for writing the protocol and participant-facing materials, obtaining relevant approvals from an NHS REC and the HRA as required, coordinating with recruitment agencies and sites, reviewing the statistical analysis plan, ensuring the study is conducted according to the principles of GCP and the UK Policy Framework for Health and Social Care and ensuring the UCLA site has obtained institutional review board (IRB) approval and performs the research in compliance with applicable U.S. federal regulations, local laws, and policies including the Health Insurance Portability and Accountability Act (HIPAA). The TMG will meet regularly (approximately every month) to manage the study, monitor safety, key performance indicators and discuss and resolve emerging issues. Members of the TMG will analyse the data, interpret the analyses, write reports to the funder and write and submit manuscripts to peer-reviewed journals.

LEAP

The Lived Experience Advisory Panel (LEAP) is comprised of approximately 20 individuals (actual number of members will vary across the course of the project) aged 18+ with experience of Repetitive Negative Thought (RNT), and experience of engaging with formal therapy or self-help tools to reduce their RNT. Panel members are not required to have a clinical diagnosis of anxiety or depression, and there are no exclusion criteria around comorbidity. Panel members are a mix of female, male and people who identify outside the gender binary. Panel sessions will be held throughout the study, either online or in person, and vary in group size depending on the task and individual preference. LEAP members have collectively co-produced the programme name, the logo, and provided feedback on the therapeutic intervention. The panel will review and provide feedback on participant materials for the study (e.g., information sheets and recruitment pathways), discuss the study promotion and recruitment, and continue to provide feedback on the intervention for the duration of the study. Panel members will be involved in interpreting the results of the study and designing materials to communicate the results to participants and the public.

viii. KEY WORDS:

Repetitive Negative Thinking (RNT), Anxiety, Depression, Overthinking, Worry, Rumination

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

ix. PATIENT JOURNEY AND FLOW CHART

See Figure 1 and the below text for an overview / summary of the full participant journey through the study. Further details on each element of the study are provided later in the protocol.

We will recruit through an online and publicly advertised screening website. In the UK, we will also promote the study within the NHS including via the NIHR Mental Health Mission Mood Disorder Clinics (of which Exeter is one site) and, subject to costs and their agreement to support the study, the NIHR BioResource and NHS DigiTrials.

Potential participants will be directed to an online screening platform (REDCap) where they will self-assess their eligibility for the study. Those who are ineligible will be directed to appropriate exit screens and provided with signposting to appropriate support. Those who are eligible will be directed to complete an electronic consent form hosted within the electronic data capture system (EDC; REDCap Academic). Once full informed consent is provided, participants will be directed to a page outlining three parallel processes (more detail in section 8.3):

i) Participants will be able to request a call from a member of the research team to answer any questions about the project, help with set-up and completing EMA and baseline assessments (optional)
ii) Participants will be required to complete the full baseline assessment questionnaires, demographic data and contact details for the study within 4 weeks from consent (mandatory).
iii) Participants will complete a concurrent process of baseline ecological momentary assessment (EMA)[1,2] as delivered via the m-Path app.

Participants who complete the baseline assessments and EMA to the level required (see sections 8.3 & 8.4 for details) will be randomised into the study to receive one of 16 variations of online cognitive behavioural therapy (CBT), made up of 6 modules. Randomised participants will count toward the sample size.

The randomisation allocation will be automatically communicated to the MyDataHelps online platform (which hosts the online CBT) and the participant will be sent an email with details of how to set up their user account to access their variant of the intervention modules. The participant will have up to 16 weeks post-randomisation to complete the intervention modules – these 16 weeks are the 'intervention period'. Access to the online platform will remain available to participants during the follow up period for the study.

Participants will have a minimum of 3 (maximum 6) contact sessions with a Psychological Wellbeing Practitioner (PWP; UK) or coach (USA) to support their use of the online CBT. The therapy team will be informed of the randomisation allocation via automated email from REDCap. The PWP/coach will contact the participant to arrange the first contact session (typically via videoconference; by telephone as alternative). Further details on the intervention are described in section 4.1.

During the intervention period, because putative mediators need to be measured early, intensively, and briefly (to minimize participant burden), participants will complete a 5-minute online micro-assessment during weeks 1, 2, 3, 4, 5, 7, 9 and 11, 13 and 15 of the intervention period. The micro-assessments will be completed via the m-Path app. In the weeks when the mediators are not assessed, participants will be asked to complete a single-item measure of RNT and a single-item measure of treatment progress in order to maintain engagement with the app and the study.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

At 16-weeks and 52-weeks post-randomisation, participants will receive a link within an email to complete follow-up questionnaires via REDCap. Participants will also complete another 10 (or 14) days of EMA via the m-Path app at 16-weeks post-randomisation. Further details on all follow-up are in section 8.5.

A subset of participants will be selected for two qualitative interviews, one at 16- and one at 52-weeks post randomisation (if they consent to this). Selected participants will be contacted online or via telephone by a post-doctoral researcher employed on the grant.

USA-specific detail

In the USA, the study will be delivered by UCLA with recruitment of students from Imperial Valley Community College. Recruitment will follow previously successful methods, further described in Section 8.1.

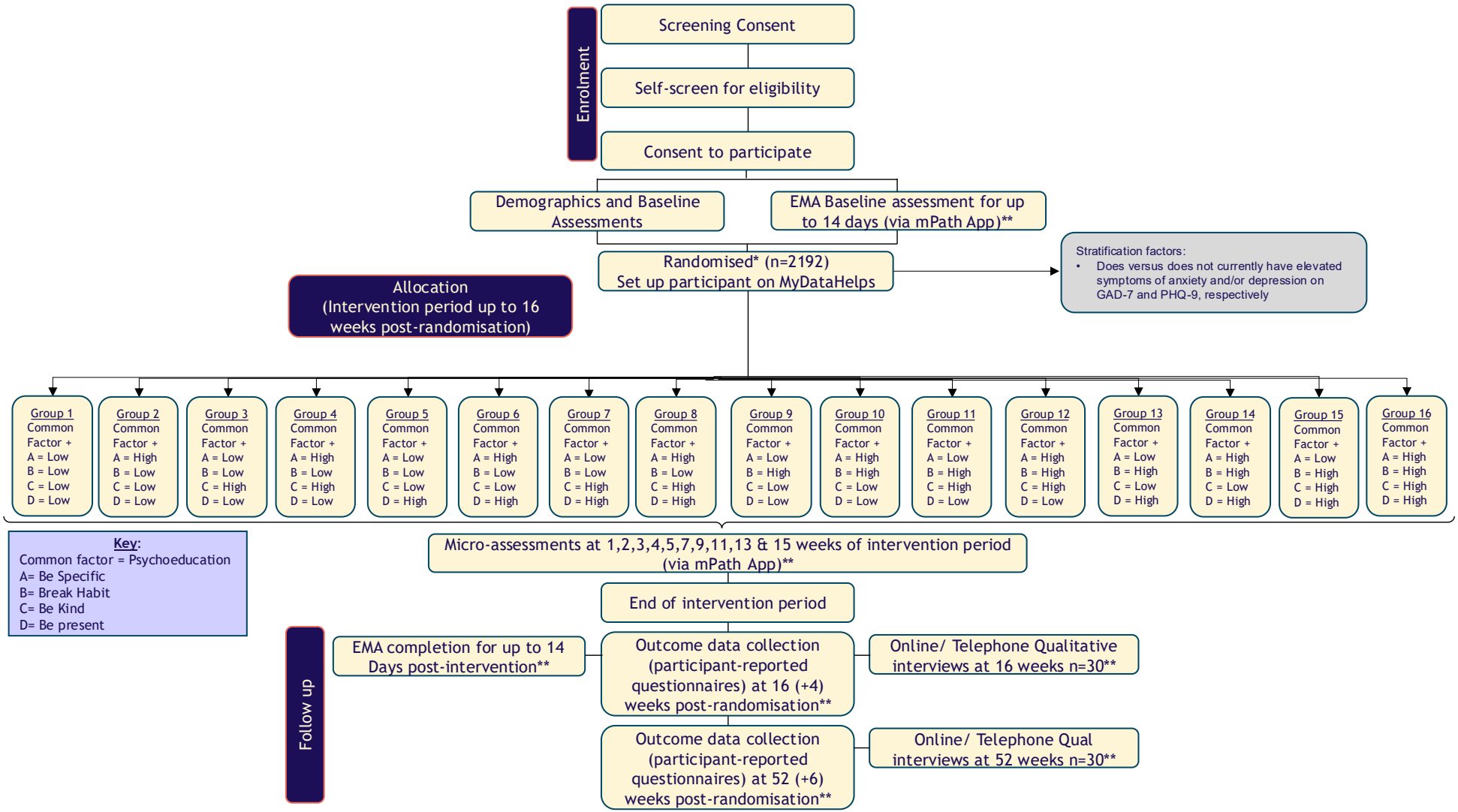
A key difference between the USA and the UK is that the USA will not utilise PWPs in the delivery of the intervention. UCLA will instead use coaches to undertake tasks that would have been undertaken by a PWP. The training and competence requirement for coaches is detailed in section 4.1.

Important: Wherever 'PWP' is written in the main body of the protocol this refers to the UK only; a 'coach' will perform the same task in the USA unless detailed otherwise in the related 'USA-specific detail' for that section.

A separate research team at UCLA will manage the USA-based participants and will obtain ethical approval from a local Institutional Review Board (IRB).

UCLA will utilise a separate but equivalent parallel instance of REDCap Academic for data collection and randomisation. There will be no qualitative interviews conducted for participants in the USA.

Figure 1: Participant flow diagram



**Randomisation enabled once all baseline data complete and a minimum of 60% baseline EMA complete.*
***Participant payments offered upon completion of key data timepoint.*

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

1. RATIONALE

The study is focused on depression and anxiety as our primary mental health problems to address (although we recognise that targeting RNT may have transdiagnostic benefit for other disorders).[3] Depression and anxiety together are a major global health challenge[4]: both highly prevalent, disabling, and recurrent disorders with enormous individual, societal, and economic burden[5]. Although effective treatments exist (e.g., antidepressants, cognitive-behavioural therapy (CBT)), there remains significant scope to increase their long-term efficacy. For example, for depression there is substantive (≥40%) partial/non-response, high relapse/recurrence rates (50-80%) and limited sustained recovery[6]. The corresponding rates for partial/non-response and return of fear are similar for anxiety disorders[7]. Increases in the availability and efficacy of both acute and preventive interventions are critical if we are to tackle the global burden of anxiety and depression. Reducing RNT (worry, rumination) is robustly identified as an active ingredient in psychological interventions for anxiety and depression in systematic reviews[3] including the recent Wellcome Trust Active Ingredients report[8]. In treatment studies, reductions in RNT are associated with positive treatment outcomes for anxiety and depression[9-11]. Conversely, when RNT does not improve, symptoms of depression and anxiety also do not improve, and are likely to worsen over time[3,9-11]. Clinicians, leading therapy researchers and people with Lived Experience identify reducing RNT as an integral part of therapy[8].

Moreover, there is extensive evidence that RNT is a transdiagnostic vulnerability factor that contributes to the onset and maintenance of anxiety and depression (and eating disorders; substance/alcohol abuse), is elevated in those experiencing interpersonal stress, family histories of mental health difficulties, socioeconomic disadvantage, stressful life transitions, bullying or abuse and acts as a common mediator between these risk factors and later psychopathology (see reviews [3,12-14]).

Longitudinal studies have robustly found that RNT prospectively predicts the onset and symptom levels of depression and anxiety[15,16], and comorbidity between anxiety and depression symptoms/disorders[16,17] even after accounting for baseline symptoms. RNT increases risk of symptom persistence (OR=1.4-1.9 for depression) and risk of relapse (OR=2.7-3.0)[16]. Experimental studies manipulating RNT implicate it as playing a causal role in exacerbating and prolonging distress and in impairing problem solving[13]. Reducing RNT has thus been identified as a target for early intervention and prevention[3,12-14].

A specific version of CBT, titled rumination-focused CBT (RF-CBT), has proven to be especially effective for RNT (developed and evaluated by applicants Watkins, Ehring). A recent meta-analysis[18] of 36 randomised controlled trials (RCTs) involving 3307 patients concluded that treatments that explicitly target RNT may be most effective at reducing RNT and “in particular RNT-focused CBT may have a more pronounced effect on RNT than other types of interventions” (Spinhoven et al., 2018, p. 71[18]). Of the treatments targeting RNT, RF-CBT had the largest effect size (g=0.76)[18] and reduced both worry and rumination. Multiple RCTs have demonstrated that RF-CBT:

(1) reduces depression: improving outcomes for patients with medication-refractory residual depression when added to ongoing treatment as-usual (TAU; antidepressant medication)[19]; large effect size RF-CBT + medication versus medication d=0.94, 95% CI 0.06-1.82, numbers-needed-to-treat [NNT]=2.1, compared to standard CBT + medication versus medication d=0.3, 95% CI -0.3- 1.10; NNT=5.95;

(2) outperforms standard group CBT in reducing depression[20] for adult outpatients with depression and;

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

(3) prevents future depression and anxiety in young people with elevated RNT whether delivered in groups or digital online treatment[21,22].

An independent trial found that group-delivered RF-CBT improved depressed mood and reduced RNT relative to a waiting list condition in patients with residual depression, with treatment gains maintained over one-year follow-up[23]. These RCT outcomes confirm that RF-CBT is an efficacious treatment with significant promise for early intervention/ Prevention.

We distinguish between the active components of therapy, operationalized as the active elements or ingredients within a therapy that produce clinical benefit, which could be therapist-based, client activities, specific techniques/procedures, or related to therapy structure and delivery, versus the active mechanisms of the therapy, operationalized as the underlying change processes that causally underpin therapeutic benefit. In these terms, there is strong evidence to consider components within a treatment that reduce RNT as an active ingredient, and change in RNT as an active mechanism, in the treatment of anxiety and depression. We note that RF-CBT, like many psychological interventions, is a complex intervention that includes multiple components including therapy content and techniques, the interaction between the therapist and patient, and patient activities. Each of these components is a potential “active ingredient” that may reduce RNT via one or more distinct mechanisms. With many different components, there could be several mechanistic pathways to reducing RNT, such that different specific mechanisms may underpin change in RNT. However, to date, the individual active treatment ingredients within RF-CBT and their mechanistic pathways to reducing RNT have not been tested[8,24] and the component/s and mechanism/s which causally drive the reduction in RNT remain unknown. There are calls for dismantling studies or equivalent[8,24] to understand how treatments targeting RNT work.

We therefore seek to delineate:

(a) which components within CBT designed to target RNT (using RF-CBT as a model) are active ingredients that reduce RNT;

(b) what distinct mechanisms are causally manipulated by these active ingredients;

(c) which distinct mechanisms mediate the effect of active ingredients on RNT, and, thereby;

(d) identify what are the causal mechanisms underpinning effective CBT interventions driving reduction in RNT.

Drawing on extant theory and evidence, we hypothesize multiple candidate (potentially complementary) psychological mechanisms that may causally reduce RNT, each with corresponding treatment component(s) within CBT, and specifically within RF-CBT, designed to engage each specific mechanism (CBT *components, each a potential active ingredient, indicated in parentheses*) – see also Table 2:

1. Shifting from unhelpful abstract to helpful concrete processing style, with evidence that manipulating processing style improves problem-solving and reduces emotional reactivity[15,25,26], and training concrete thinking alone reduces RNT[27,28] (corresponding component/active ingredient in RF-CBT is *increasing specific contextualised detail in description of events and plans*).

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

2. Breaking RNT-as-a-habit by establishing new, more adaptive habits, with evidence that RNT is a habit[29,30] and learning new habits reduces RNT[28,31] (corresponding component(s) in RF-CBT: *identify warning signs, stimulus control, implementation intentions, repeatedly practise alternative strategies*).
3. Replacing self-criticism with self-compassion, identified as a potential active ingredient[8] (corresponding component(s) in RF-CBT: *validation of patient experience by psychoeducation that normalises and explains RNT; validation of patient experience by therapist; learning self-compassion skills*).
4. Improving attentional focus to present-moment experience, with evidence that mindfulness and task absorption counteract RNT[8,31,32](corresponding component(s) in RF-CBT: *absorption in direct experience; attentional training*).
5. Generating explanations for symptoms and difficulties, which reduces the search for understanding, insight and certainty shown to drive RNT[13,14] (corresponding component(s) in RF-CBT: *individualised rationale, psychoeducation, therapist empathy and understanding*).

We note that some of these elements are shared with general CBT and are not specific to RF-CBT but that each is a component in the overall RF-CBT package that has the strongest evidence for effectively reducing RNT. There is both good empirical evidence and strong theoretical rationales to support each of these hypothesized mechanisms.

The proposed research will advance knowledge in relation to:

(a) How the change in RNT plays a causal role in the resolution and prevention of mental health problems, by examining the effects of manipulating RNT via components of RF-CBT and by examining reduction of RNT, assessed in multiple ways (self-report, EMA) as a short and long-term mediator of reductions in anxiety and depression.

(b) How different psychological mechanisms play a causal role in reducing RNT, by the differential provision of treatment components intended to engage specific hypothesized candidate mechanisms to determine which components (or which combination of components) and mechanisms underpin change in RNT. Because we will test the different mechanisms at the same time within an innovative methodological framework, we will advance knowledge of how these different mechanisms interact in resolution of RNT and mental health problems for the first time.

(c) How CBT works to reduce RNT, more specifically, identifying what are the active ingredients within RF-CBT that reduce RNT. The manipulation of treatment components enables us to test simultaneously which components reduce RNT and which mechanisms causally underpin this reduction. This approach therefore addresses calls for dismantling studies or equivalent[8,24] to understand how treatments targeting RNT work and for “testing of the presence or absence of individual elements in rigorous study designs” (Institute of Medicine, 2015, p3-10)[33].

The Potential for Impact

The research will have considerable direct impact and transform treatment, prevention, and early intervention options for people with anxiety and depression because it is focused on:

a) understanding the active ingredients within RF-CBT that reduce RNT;
b) understanding the causal mechanisms underpinning reduction in RNT, an identified active ingredient in treating and preventing anxiety and depression;

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

c) using this understanding to refine, strengthen and optimise our interventions for RNT;
d) developing a scalable digital intervention platform to make evidence-based interventions accessible, ready to be used as a massive open online intervention (MOOI)[34].

To significantly transform early intervention and prevention options, it is necessary to:

a) have an effective evidence-based intervention with considerable scale and reach, and;
b) be able to easily identify those people who would benefit from an early or preventive intervention.

This research programme will deliver both. At project end, we anticipate having an enhanced intervention for RNT that could be delivered in a massive open online format. Moreover, it is easy to screen for elevated worry and rumination (e.g., by self-report) and these are non-stigmatising concepts that individuals easily recognise and are motivated to seek help for. To support future implementation and impact, we will also explore the views of relevant stakeholders involved in the potential delivery and implementation of digital interventions. The research also has potential to explore how different contexts impact on the diverse population of individuals with elevated RNT under different circumstances and from different contexts, including from different countries (UK, USA), different cultural and socioeconomic backgrounds, and those who do versus do not currently have elevated symptoms of anxiety and depression. The inclusion of the USA and in particular of Latinx lower socio-economic population at Imperial Valley College enables assessment of generalisability of the intervention, and potentially provides proof-of-principle of relevance to a diverse range of participants. The location (UK versus USA) and caseness or not for anxiety or depression will be used as stratification variables in our randomisation design, enabling us to examine them as potential moderators of outcome in exploratory analyses.

Further, the research has potential to identify and validate markers of which individuals may respond to a specific active ingredient and to examine moderated mediation. Baseline measures will include those that have predicted treatment outcome in prior studies: demographics, mental health history, symptoms, stress, personality, cognitive and behavioural measures. For example, theories of RNT predict that levels of executive functioning would moderate ability to switch processing style and break RNT-as-a-habit, and that histories of chronic stress or early adverse events would moderate breaking RNT-as-a-habit[3]. For the majority of participants, we will also have ecological momentary assessment (EMA), providing detailed contextual information on patterns in the relationships between mood, RNT, and daily behaviour. These data open the opportunity for future analyses to examine possible moderators of response to specific components within RF-CBT and to develop individualised treatment rules (e.g., via machine learning methods) that can predict which components an individual should receive (see for example our involvement in[35]). Because there may be considerable individual differences in response to each treatment component, knowing who responds optimally to which treatment component may enable us to personalize within the treatment package and, thereby, transform treatment outcomes.

2. ASSESSMENT AND MANAGEMENT OF RISK

With respect to the safety and wellbeing of participants, before the start of the study, approval will be sought for the study protocol, informed consent forms and other documents from an NHS research ethics committee (REC) and the Health Research Authority in the UK. The intervention provided will be therapist-supported digitally delivered cognitive-behavioural therapy. There are few potential risks to participants. In general, this psychological intervention, when delivered appropriately, is unlikely to

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

be harmful to participants, and is relatively safe, with no unexpected side effects, although a small percentage of patients can deteriorate during psychological interventions. This is a NICE recommended therapy. There are considerable potential benefits from receiving RF-CBT as it is proven on average to reduce worry, rumination, anxiety and depression. The risk is no more than normal standard practice with digital CBT routinely provided in the NHS.

There is no known health risk associated with any of the assessments or interventions proposed. We anticipate that the supported digital CBT will on average improve wellbeing and reduce symptoms. Nonetheless, we will assess for potential harms. The research team will be provided with a standard operating procedure and trained to assess and manage risk in order to safeguard participants, including referral to local treatment services, and access to a designated clinician to support them.

The initial screening process for the study will exclude anyone reporting current or past severe psychiatric disorder (current or past diagnosis or treatment for psychosis or bipolar disorder; current severe PTSD or alcohol/substance abuse or dependence) and those reporting elevated suicidality (scoring 1 or more on item 9 of the PHQ-9 and then answering yes to automated follow-up questions asking about plans or intentions regarding suicide). The screening tool will automatically signpost these individuals towards appropriate guidance and help, including general information on the presenting symptom, recommended actions to keep themselves safe, advice to seek medical help from their GP or relevant local clinician/service and direct links to relevant national sources of help. The form will enable the person to volunteer their contact details and GP details if they would like to receive a phone call from a member of the research team, and potentially be referred to their GP. Excluded individuals will still be able to access other treatment outside the study.

Participants who report risk (e.g. suicidal thoughts) or significant worsening symptoms on the follow-up assessments or during contacts with PWPs will also receive automated messaging recommending actions and signposting. Significant worsening symptoms is defined as a deterioration of movement across two or more score categories on the GAD7 or PHQ-9 from baseline to 16-weeks or from baseline to 52-weeks follow-up. At the point of automated signposting, participants can request contact from a study PWP or contact a study PWP via e-mail or telephone to seek advice. PWPs will follow standard risk management protocols that include contacting the individual, assessing their situation and status (e.g., standardised checklist concerning suicidal or self-harm thoughts, plans, intentions, preparation, barriers, and safety measures), providing safeguarding, safety plans and guidance, and, as necessary, referring to relevant clinical services, including contacting participants GP, crisis teams, or acute emergency services as necessary. This procedure has been successfully used in prior trials which received ethical approval including both local institutional approval and NHS approval.

Similar standard operating procedures including risk assessment, signposting to relevant sources of help and bringing in relevant clinically qualified members of the team (clinical psychologists, psychological wellbeing practitioners in UK), will be used by research staff if participants report worsening of symptoms or suicidality during interviews or contacts with research staff.

The study has been designed in collaboration with a Lived Experience Advisory Panel (LEAP) who have advised on all aspects of the intervention.

A detailed risk assessment has been completed by Exeter Clinical Trials Unit and will be maintained throughout the study.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

Information about possible benefits and risks of participation will be described in the Participant Information Sheet (PIS).

USA-specific detail

The study will be reviewed and approved by an Institutional Review Board at UCLA, USA.

Digital CBT is widely available for patients and is frequently incorporated into research studies in the USA.

Coaches, supervised by a licensed clinician, will support participants recruited in the USA.

For participants recruited in the USA, automated signposting to support services will be tailored to services specific to the local study population in the USA. USA-based participants will be students at the Imperial Valley Community College (IVC), so services will include the student support services already available through the College.

During screening, if individuals indicate the exclusion criteria of active suicidality, severe PTSD or diagnosis of bipolar disorder, substance abuse or psychosis they will be provided with contact information for the college health centre counselling services, as well as community emergency resources.

If, during the study, participants indicate suicidality on self-report assessments, they will be provided with information about community and emergency resources. Additionally, study staff may provide participant contact information to the IVC Behavioral Intervention Team (BIT) for their team to conduct independent follow up with students. Participants will be informed of this potential for information sharing in the informed consent signed before study enrollment.

If a participant discloses suicidality during an encounter with study staff, study staff will provide the participant with information about community and emergency resources, and report to the Coaching Supervisor. Additionally, study staff may provide participant contact information to the IVC Behavioral Intervention Team (BIT) for their team to conduct independent follow up with students.

If during the course of the study a participant's responses to surveys indicate a significant worsening of symptoms, they will be provided with contact information for the IVC health center, as well as community and emergency resources. This is defined as a deterioration of movement across two or more score categories on the GAD7 or PHQ-9 from baseline to 16-weeks or from baseline to 52-weeks follow-up.

3. OBJECTIVES AND OUTCOME MEASURES / ENDPOINTS

We aim to better understand the mechanisms and active treatment components that underpin the effective reduction of RNT (e.g., worry, rumination), a proven major active ingredient and mediator in the treatment of anxiety and depression.

3.1. Primary objectives

The objective of this study is to delineate the causal mechanisms underpinning reduction in RNT, a characteristic of the most common mental health conditions. Our specific inter-related research questions are:

(a) What are the causal mechanisms that underpin effective cognitive-behavioural interventions to reduce RNT?

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

(b) What are the active ingredients within RNT-focused cognitive-behavioural therapy (RF-CBT) that effectively manipulate these mechanisms, and, thereby, reduce RNT?

3.2. Secondary objectives

Secondary objectives are to:

1. To compare the changes in anxiety and depression symptoms in participants across the treatment period with respect to the main effect of each treatment component and their interactions
2. To compare the changes in diagnostic status in participants across the treatment period with respect to the main effect of each treatment component and their interactions
3. Examine potential moderators of treatment outcome by condition and to examine potential personalisation.

Exploratory analyses will consider how different contexts (baseline characteristics, e.g., country, socioeconomic status, level of current symptoms) have an impact on the efficacy of targeting RNT and the efficacy of the specific components (active ingredients) and seek to identify markers that can predict whether an individual will respond to each of the specific component factors within the intervention. These potential markers include baseline assessment and EMA. Critically, and uniquely, this design affords us data that can be used to develop personalized treatment matching not between different treatments but rather to select and match the relevant components within a treatment approach (e.g., identifying who may benefit most from targeting RNT-as-a-habit versus increased self-compassion), with transformative potential for individualising treatment and, thereby, improving outcomes. There is emerging evidence that matching treatment correctly to the individual can significantly improve outcomes. As an exploratory first step, we will test which pre-treatment measures moderate the differential effects of each factor.

Because individual predictors are usually weak and underpowered, an improved approach is to use composite models that combine individual moderators to produce Individualised Treatment Rules (ITRs) that can guide the selection of active ingredients (components) most likely to be helpful for each individual. Machine learning approaches have been validated as a means to develop effective composite models. It has been estimated that between n=350-500 patients per arm is estimated to be sufficient to provide stable estimates of ITRs. As such, the factorial trial will be sufficiently powered to examine potential ITRs for each main factor, enabling the identification of rules to predict who will benefit most from which treatment component, which has the potential to transform intervention efficacy. Identifying ITRs is a key step towards precision treatment personalisation and to prepare for definitive future trials that test whether treatment allocation using ITRs improves outcomes relative to random allocation or usual clinical practice. In addition, a potential benefit of using a digital intervention coupled with EMA is that if successful prediction models that utilise EMA can be derived and tested, the efficacy of the open access digital therapy intervention for RNT could be further enhanced by accompanying it with EMA apps that support ongoing selection of the intervention components most likely to be effective for a given individual.

Baseline measures will include those that have predicted treatment outcome in prior studies: demographics, symptoms, stress, personality, cognitive measures. For example, theories of RNT predict that levels of executive functioning would moderate ability to switch processing style and break RNT-as-a-habit, and that histories of chronic stress or early adverse events would moderate breaking RNT-as-a-habit. We will also have ecological momentary assessment (EMA)[1,2], providing detailed contextual information on patterns in the relationships between mood, RNT, and daily behaviour.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

These data open the opportunity for future analyses to examine possible moderators of response to specific components within RF-CBT and to develop individualised treatment rules (e.g., via machine learning methods) that can predict which components an individual should receive. Because there may be considerable individual differences in response to each treatment component, knowing who responds optimally to which treatment component may enable us to personalize within the treatment package and, thereby, transform treatment outcomes.

4. Examine the mechanism and factors related to implementation

To inform understanding of mechanisms and barriers and facilitators of sustained implementation within a mixed model approach, semi-structured online or telephone interviews will be conducted with 30 UK trial participants at 16 weeks and 12 months, matching quantitative data collection points. Qualitative data will be analysed using realist-informed thematic analysis, with NVivo v14, to deductively investigate each of these areas but we will also include an inductive approach to identify any novel findings. See Section 11 Process Evaluation for details.

5. Development and examination of linguistic Natural Language Processing markers

The study will include collection of text material from participants both within baseline and follow-up assessments (tasks to describe problems and concerns) and during the online intervention package. This material will be analyzed for linguistic markers of changes in relevant mechanisms (e.g., specific versus abstract descriptions of events, more self-critical versus more self-compassionate language) using establishing linguistic feature analysis and the use of machine learning and AI to train and test models. We will explore whether these markers can be provided in real-time in order to provide ongoing feedback to participants within the intervention to support their learning of skills.

3.3. Outcome measures

3.3.1. Primary outcome

The primary outcome will be change in RNT as indexed by the Perseverative Thinking questionnaire[36] from baseline to post-treatment (16 weeks) as recommended in the Wellcome Review of Active Ingredients section on RNT[8].

3.3.2. Secondary outcomes

The following secondary outcomes will be measured using standardised validated measures at baseline, and post-treatment at 16 weeks and 52 weeks post-randomisation via participant survey on REDCap:

1. Change in anxiety measured with GAD-7[37]
2. Change in depression measured with PHQ-9[38]
3. Change in mental wellbeing measured with WEMWBS (Warwick-Edinburgh Mental Wellbeing Scale short-form[39])
4. Change in levels of rumination measured with RRS-Brooding subscale[40]
5. Change in levels of worry measured with PSWQ (Penn State Worry Questionnaire short-form)[41]
6. Change in social functioning measured with WSAS (Work and Social Adjustment Scale)[42]

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

The following secondary outcome will only be measured at baseline and at 16 weeks post-randomisation (captured by the mPath app):

7. Change in RNT in everyday life measured with EMA[1] (aggregrate person-level ratings of RNT across 10 day period; variability of RNT; relationship of RNT to mood state & contextual events; automaticity of RNT, based on EMA items). This provides an ecologically valid measure, in the real-world, of extent of RNT and how it changes pre-to-post intervention.

We will also assess incidence of major depressive episodes and generalized anxiety disorder across the 12-month follow-up using standardized structured online measures (adapted Lifetime history of depression and anxiety disorders (adapted LIDAS)[43] for depression, adapted GAD for anxiety (based on Roemer et al., 1995[44]) enabling us to test which factors have long-term effects on RNT and on the prevention of first incidence or recurrence of episodes of depression and anxiety, providing direct data to inform transformation of early interventions.

3.3.3. Process measures (putative mediators)

A series of measures will be used to ascertain potential change in the hypothesised mechanisms of interest (abstract to specific concrete processing; self-criticism to self-compassion; increased present moment focus; breaking the RNT habit).

These measures will include:

- Self-report standardised questionnaire measures completed at baseline, 16 weeks, and 12 months (see Table 3 for full details). These include (with associated mechanism in parentheses):
  - Overgeneralisation subscale of Attitudes towards self-scale[45,46] (abstract to concrete processing)
  - Self-criticism subscale of Attitudes towards self-scale[45,46] (self-criticism)
  - Adapted self-report habit index[47] (breaking the RNT habit)
  - Self-compassion scale short-form[48] (self-compassion)
  - Problem clarification, self-efficacy/mastery subscales from Bern post session report[49,50] (to assess insight and understanding and general sense of control)
  - 5 facet Mindfulness Questionnaire (short form, 2 subscales to assess present-moment focus)[51]
  - Flow Proneness Questionnaire[52] (leisure only subscale to assess present moment focus)
- Specific analysis of the EMA data – for example to examine the change in level of RNT; the extent to which RNT is associated with low mood (index of habit), the extent of present moment focus in EMA; the extent to which RNT is associated with particular situations or cues (index of habit).
- Micro-assessments during the intervention period providing very brief, repeated measures of putative mediators, taking 2–item versions of measures above. These repeated frequent measurements will enable us to assess changes in putative mediators across time enabling factorial mediation analysis with temporal precedence and to determine if treatment components impact one or more mechanisms, and which change in putative mechanisms is associated with active components and mediates improvement in RNT.

- Linguistic analysis of instructed writing tasks (e.g., asking participants to describe a problem; describe an example of RNT) at baseline and 16 weeks follow-up. Such linguistic analysis enables measurement of how abstract or specific text is, how positive or negative text is, how self-related and repetitive text is, thus providing a behavioural index of the mechanisms of self-compassion and level of processing (abstract vs concrete). Linguistic analysis of text provided by participants will include manual coding for level of abstraction, and the use of well-established vocabulary dictionaries (e.g., Linguistic Inquiry and Word Count software) that can generate counts of particular word categories (e.g., first-person singular pronouns to assess the self-referential thinking associated with rumination; proportion of positive versus negative emotion words to capture shift away from negative evaluation; proportion of abstract versus concrete nouns and verbs as determined from normative linguistic measures), successfully used in our prior research. Building on these established approaches, we will explore automated evaluation of these dimensions using Natural Language processing models (e.g. BERT sentiment decoders, LLAMA) trained to predict the above dimensions in a corpus of text. If viable, we will apply this linguistic analysis to the text provided within the exercises and open text boxes in the treatment platform, which may enable us to gain further insight into therapeutic process, track session-by-session change in these indices and test if these linguistic indices predict outcomes.
- Linguistic analysis of text generated during the intervention – as above

3.3.4. Exploratory analysis

There are no exploratory outcomes. As noted above, there will be exploratory analyses of moderators of effects of outcomes – see secondary objectives.

3.3.5. Table of objectives and outcomes

Table 1: Table of objectives and outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary Objective: To delineate the causal mechanisms underpinning reduction in RNT, a characteristic of the most common mental health conditions. Our specific inter-related research questions are: (a) What are the causal mechanisms that underpin effective cognitive-behavioural interventions to reduce RNT? (b) What are the active ingredients within RNT-focused	Primary outcome: Change in RNT as indexed by the Perseverative Thinking Questionnaire[36] from baseline to post-treatment (16 weeks). Secondary outcomes: Change in levels of rumination measured with RRS-Brooding[40] subscale.	- Baseline - 16 weeks post-randomisation - 52 weeks post-randomisation - Baseline - 16 weeks post-randomisation - 52 weeks post-randomisation

cognitive-behavioural therapy (RF-CBT) that effectively manipulate these mechanisms, and, thereby, reduce RNT? This includes comparing the effects on proposed mechanisms across the treatment period with respect to the main effect of each treatment component and their interactions.	Change in levels of worry measured with PSWQ (Penn State Worry Questionnaire – short-form)[41]. Change in RNT in everyday life measured with EMA. <u>Process-mechanisms will be assessed by change in:</u> - Overgeneralisation subscale of Attitudes towards self-scale (abstract to concrete processing)[45,46]; - Self-criticism subscale of Attitudes towards self-scale (self-criticism)[45,46]; - Adapted self-report habit index (breaking the RNT habit)[47]; - Self-compassion scale short-form (self-compassion)[48]; - Problem clarification, self-efficacy/mastery subscales from Bern post session report[49,50]; - 5 facet Mindfulness Questionnaire (short form, 2 subscales to assess present-moment focus)[51]; - Flow Proneness Questionnaire (leisure only subscale to assess present moment focus)[52]; - Brief micro-assessments during therapy course.	- Baseline - 16 weeks post-randomisation - 52 weeks post-randomisation - Baseline - 16 weeks post-randomisation - Baseline - 16 weeks post-randomisation
<u>Secondary Objectives</u>		

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

To compare the changes in anxiety and depression symptoms in participants across the treatment period with respect to the main effect of each treatment component and their interactions	<u>Secondary outcomes:</u> Change in anxiety measured with GAD-7[37] Change in depression measured with PHQ-9[38] Change in mental wellbeing measured with WEMWBS[39] Change in social functioning measured with WSAS[42]	- Baseline - 16 weeks post-randomisation - 52 weeks post-randomisation
To compare the changes in diagnostic status in participants across the treatment period with respect to the main effect of each treatment component and their interactions	<u>Secondary outcomes:</u> Incidence of major depressive episodes and generalized anxiety disorder using adapted LIDAS[43] for depression and adapted GAD[44] for anxiety.	- Baseline - 16 weeks post-randomisation - 52 weeks post-randomisation
Examine potential moderators of treatment outcome by condition and to examine potential personalisation.	As primary and secondary outcomes above.	- Baseline - 16 weeks post-randomisation - 52 weeks post-randomisation
Examine the mechanism and factors related to implementation.	Process evaluation semi-structured interviews.	- 16 weeks post-randomisation - 52 weeks post-randomisation
Development and examination of linguistic Natural Language Processing markers.	Use of text material from participants, coding and analysed for linguistic markers of mechanisms of interest.	- Baseline - 16 weeks post-randomisation

Refer also to the tabulated schedule of assessments (Section 8).

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

4. STUDY TREATMENTS

4.1. Intervention arm

Participants will be randomised into different variants of an online CBT intervention, such that they receive different combinations of four different intervention components (at either high versus low levels, giving 16 different variants). All interventions include a default core common content (e.g., psychoeducation about RNT and CBT approaches to coping) so that all participants receive a minimal-level intervention (i.e., there is not a no-treatment control), delivered via the MyDataHelps digital platform. Participants will receive a course of online CBT designed to target RNT taking up to 16 weeks to complete, consisting of different randomised intervention components. Building on lessons from our previous trials[53,54], each intervention component will be present and interleaved throughout the entire course of therapy (rather than in discrete modules) to increase patient exposure to each ingredient and strengthen effective dose. See Section 5, Table 2, for an overview of the intervention components. Access to the online platform will remain available to participants during the follow up period for the study.

All participants will receive PWP(UK)/ coach(USA) support delivered via video conference/telephone and within the MyDataHelps platform (i.e., supported use of the intervention).

Participants will need to provide an email address to be set up with an account on MyDataHelps. There is evidence that supported digital interventions (i.e., those with support from a clinician or coach) outperform unsupported ones, with improved retention and adherence[55]. In the UK, the support will be provided by psychological wellbeing practitioners (PWP), which is a well-established workforce for delivery of blended digital therapies used for low-intensity CBT in the IAPT Talking Therapies workforce.

The intervention will consist of 6 sessions in the MyDataHelps digital platform to be worked through over up to 16 weeks and supported by a minimum of 3 contacts with a PWP(UK)/ coach(USA). These contacts will typically last 20-30 minutes and focus on motivating, supporting and encouraging the participant to work through online material, dealing with any questions arising and tackling any problems or trouble-shooting.

The UK Psychological Wellbeing Practitioners (PWPs) will be certified via competency-based training at supporting digital interventions (e.g., behavioural activation) and managing risk. The USA coaches will have similar competency-based training in supporting digital interventions and managing risks. All PWPs and coaches will also be trained to be familiar with the content of the Calming Minds intervention, receive regular clinical supervision from an experienced clinician and will be trained to deliver all combinations of the intervention.

There will be standardised processes to ensure fidelity (including PWP self-rating of sessions). PWPs will follow up and reschedule sessions if missed or not attended by participant up to 3 times. It is planned that the minimum number of contact sessions would be 3, as detailed below. Participants can have additional sessions if needed up to a maximum of 6 sessions total.

- Session 1: An orientation session occurring close to when participant is set up on MyDataHelps to explain the intervention and to check the participant is able to access and use the platform, and to answer any questions.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

- Session 2: A second session after the start of the intervention (after 1st online session is completed) to motivate ongoing use of the intervention as possible.
- Session 3: A third session approx. halfway through the intervention course (after 3rd online session is completed) to encourage participants to complete as much of the intervention as possible.

The trial management team will monitor the number of contact sessions with participants and online sessions started and completed, and maintain a record of inability to schedule sessions (with reasons) and sessions which were scheduled but unattended by the participant. The proportion of participants receiving less than 3 contacts for any reason during the intervention period will be monitored and reported.

USA-specific detail

In the USA, coaches will be undergraduate students or recent graduates who undergo local competency-based training similar to that provided for PWPs. Coaches are not equivalent to therapists and should not be referred to as such. Coaches will be supported by a local experienced lead clinician. The local trial management team at UCLA will monitor the number of contact sessions with USA participants and report to the lead team at University of Exeter for central oversight of contact session frequency.

Participants in the USA will have the option to access a Spanish translated version of the intervention in MyDataHelps, however coaching will only be available in English.

4.2. Control arm

There is no control arm in this study. All participants will be offered at least a minimum level of intervention in each of the different factorial variants described in section 4.1.

5. TRIAL DESIGN

This is an international factorial, randomised trial of a therapist-supported digital CBT intervention for people aged 18 and over with elevated RNT, with primary outcome collection at baseline, and at 16-weeks and 52- weeks post-randomisation. Participants and PWPs/coaches will be unblinded to the allocation.

A component-mechanism selection experiment using a balanced orthogonal factorial design will manipulate 4 components at high versus low levels (effect coded: high level coded +1 versus low level coded -1; 50% of sample randomized to high level of factor; 50% randomised to low level – see details in Section 4.1), to differentially engage respective mechanisms and test their causal effects on RNT (see Table 2)[56].

Factorial designs systematically experimentally manipulate multiple components or factors of interest simultaneously. Factorial designs have several advantages over comparative RCTs, component (dismantling or additive) designs, and single factor designs[56].

In effect-coded analysis of a balanced 2^k factorial experiment (in contrast to dummy coding), we have equal power to detect any regression coefficient of a given size (main effect or interaction), the main and interaction effects are completely uncorrelated, and the presence of interaction effects does not

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

reduce power for the estimation of main effects. In a factorial mediation analysis, a joint significance test (causal steps approach) enables us to test if a manipulated component/ingredient changes RNT and changes each putative mediator and if each assessed putative mediator is associated with change in RNT[57].

We hypothesize that at least one of the intervention components will be an active ingredient such that the presence of that component will outperform absence of that component in reducing RNT across 16 weeks in a high RNT adult sample.

We further hypothesize that at least one of the intervention components will be an active ingredient such that the presence of that component will outperform absence of that component in reducing anxiety (GAD7) and depression (PHQ-9) across 16 weeks in a high RNT adult sample.

Based on the benefits of the design, we will explore whether there are any two-way interactions between components such that their combination has either additional benefit or reduced benefit relative to their occurrence alone.

Table 2: Illustrative example of factorial trial (4 factors=2^4) to test mechanisms to reduce RNT

	RNT-Focussed CBT Components				
	Manipulated				Fixed
Conditions	**Increased specificity & concreteness (Be Specific)**	**Targeting RNT as a habit (Break Habit)**	**Self-compassion (Be Kind)**	**Absorption in direct experience (Be Present)**	**Psychoeducation**
1.	-1	-1	-1	-1	+1
2.	+1	-1	-1	-1	+1
3.	-1	-1	+1	-1	+1
4.	+1	-1	+1	-1	+1
5.	-1	-1	-1	+1	+1
6.	+1	-1	-1	+1	+1
7.	-1	-1	+1	+1	+1
8.	+1	-1	+1	+1	+1
9.	-1	+1	-1	-1	+1
10.	+1	+1	-1	-1	+1
11.	-1	+1	+1	-1	+1
12.	+1	+1	+1	-1	+1
13.	-1	+1	-1	+1	+1
14.	+1	+1	-1	+1	+1
15.	-1	+1	+1	+1	+1
16.	+1	+1	+1	+1	+1

Note. Every manipulated component factor occurs an equal number of times at high and low levels (i.e., balanced). Effect coded; for each component factor 50% of participants are randomised to high level (coded +1) and 50% randomised to low level (coded -1). All factors are orthogonal to each other, except for psychoeducation about RNT and coping, which is the default element common to all conditions received by participants.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

5.1. Design considerations for minimising bias

5.1.1. Randomisation

Randomisation will be in equal allocation (i.e., 1:1 for high level versus low level for all factors) using an independent computerised randomisation programme (REDCap Academic). The randomisation system and randomisation code will be designed and written by the senior statistician at ExeCTU. Randomisation will be stratified by location (UK versus USA) and those above or below caseness on PHQ-9 (depression; PHQ ≤ 9 versus >9) or GAD7 (anxiety; ≤9 versus >9) to investigate acute treatment versus prevention.

PWP (UK) / coach (USA) allocation will be independent of randomisation to treatment arm and occurs with allocation concealment i.e., selection of next PWP/coach to take on next randomised patient occurs before the randomisation of next patient is known; all PWPs/coaches will provide all 16 variants of the intervention, with the assumption that, given the large numbers randomised, this will become balanced over the course of the study, with this balance monitored and adjusted if necessary - to ensure that the main effects of intervention factors are independent of PWP/coach allocation.

USA-specific detail

The USA will utilise a separate but equivalent parallel randomisation system (REDCap Academic) to that used in the UK, with a separate randomisation list provided by ExeCTU (UK).

5.1.2. Blinding

As is common for psychotherapy studies, neither study participants nor PWPs/coaches will be blind to treatment condition allocation – although given the factorial trial and that all participants receive a variant of internet CBT, participants may not necessarily be knowledgeable of the specific components being manipulated.

Outcome assessors (e.g., members of the study team who support participants with questionnaires over the telephone or follow-up on automated data collection, where necessary) and trial managers will be blind to treatment allocation. If an outcome assessor becomes unblinded then they will be replaced by an alternative researcher, where possible and this will be documented. All unblinding incidents will be reported to the oversight committees in routine reports. Because all participants will receive a variant of the intervention the impact of outcome assessor unblinding on outcome integrity is likely to be very low.

The trial statistician completing the analysis will be blinded throughout, while the senior statistician will be unblinded after the statistical analysis plan is signed off.

The qualitative interviewer and members of the process evaluation team will be unblinded, as they will sample and interview participants about mechanisms based on treatment allocation amongst other sampling criteria.

USA-specific detail

The blinding plan is equivalent in the USA, with exception that the trial statisticians and qualitative interviewer are based in the UK and equivalent roles will not be performed at UCLA.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

6. STUDY SETTING

This is a multicentre study, with nationwide recruitment in the UK (led from University of Exeter, UK) and recruitment from Imperial Valley Community College in the USA (led by UCLA, USA).

The study will be delivered online, with the intervention supported by virtual contact with trained PWPs/coaches (phone or video call or messaging). Participants will self-screen, provide informed consent and complete baseline and follow-up outcome data using REDCap Academic and the mPath App (for EMA and online micro-assessments). The intervention will be delivered using the MyDataHelps digital platform.

Professor Ed Watkins, at the University of Exeter will lead the study and recruitment in the UK, with a team of research fellows and trained PWPs and with support from the Exeter Clinical Trials Unit (ExeCTU).

A central trial manager based at ExeCTU will be responsible for monitoring study progress at all sites.

USA-specific detail

The Co-Investigator, Professor Michelle Craske at UCLA shall lead recruitment in the USA, and manage the local research team with providing the coach support, risk management and monitoring local study progress (recruitment, treatment progress, retention) and ensuring all relevant local permissions have been gained.

UCLA hold the licence to the MyDataHelps platform.

7. PARTICIPANT ELIGIBILITY CRITERIA

7.1. Inclusion criteria

Participants must satisfy ALL of the following criteria to be enrolled in the study, and will be excluded in sequence if an individual does not meet a criterion during screening (to minimise participant burden):

1. Lives in the UK or USA
2. Aged 18 and over
3. Access to a suitable smart phone/device to use the m-Path app and MyDataHelps intervention (i.e. MyDataHelps requires iOS 16.4 or later. iOS 16.4 is compatible with all iPhone models starting from the iPhone 8 and later. For Android devices, MyDataHelps requires Android version 8.0 or higher.)
4. Elevated RNT based on the following assessment scores – scoring in top quartile in one and in top tercile for the other based on prior studies:
   - RRS brooding[40] score above 12 (top quartile) and PSWQ-short form[41] score above 24 (top tercile) OR
   - RRS brooding[40] score above 11 (top tercile) and PSWQ-short form[41] score above 26 (top quartile)

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

7.2. Exclusion criteria

Participants who self-report meeting ANY of the following criteria at time of recruitment will be excluded from study participation:

1. Concurrent psychotherapy
2. Current self-reported diagnosis of any of the following conditions, including receiving or waiting for treatment:
   - Alcohol abuse/dependence
   - Substance abuse/dependence
3. Self-reported diagnosis of current or history of bipolar disorder or psychosis at any time
4. Taking antidepressants or anxiolytic medications at a stable dose for less than six weeks
5. Severe post-traumatic stress disorder (PTSD, assessed as a score of 17 or higher in total for the first six questions AND a score of 2 or higher on the seventh question of the adapted International Trauma Questionnaire[58]; ITQ)
6. Suicidal thoughts and self-harm assessed by a combination of PHQ-9[38] **question 9** score of 1 or higher and a yes to question R1a and/or R1B, and a yes to either question R2 and/or R3 (detailed below):
   - *R1a = In the last 2 weeks have you been experiencing regular thoughts about suicide?*
   - *R1b = In the last 2 weeks have you been experiencing regular thoughts about self-harm?*
   - *R2 = In the last 2 weeks have you had any intention to hurt or kill yourself?*
   - *R3 = In the last 2 weeks have you made any plans to harm yourself or end your life?*

People who are excluded from the study will be provided with information signposting them to relevant advice or support. If a person indicates that they have intention to, or made plans to, hurt or kill themselves in the past 2 weeks the screening form will enable the person to volunteer their contact details and GP details if they would like to receive a phone call from a member of the research team, and potentially be referred to their GP.

The PWPs will follow a separate risk management protocol to assess and support any individuals who are identified as being at risk during the study.

USA-specific detail

For participants recruited in the USA, automated signposting to support services will be tailored to services specific to the local study population in the USA.

During screening, if individuals endorse the exclusion criteria of active suicidality, severe PTSD or diagnosis of bipolar disorder, substance abuse or psychosis they will be provided with contact information for the college health center counseling services, as well as community emergency resources.

8. STUDY CONDUCT

Table 3: Schedule of assessments

	Pre-baseline	**Baseline**	**Allocation**	**Post-allocation**																
TIMEPOINT (*t*) unit = Days	Undefined	*t*-28[g]	*t*0	***Intervention period***															***Follow-up 1***	***Follow-up 2***
				t+ 7[a]	*t*+ 14[a]	*t*+ 21[a]	*t*+ 28[a]	*t*+ 35[a]	*t*+ 42[a]	*t*+ 49[a]	*t*+ 56[a]	*t*+ 63[a]	*t*+ 70[a]	*t*+ 77[a]	*t*+ 84[a]	*t*+ 91[a]	*t*+ 98[a]	*t*+ 105[a]	*t+112 days*[b]	*t+365 days*[c]
ENROLLMENT																				
Consent to screen	X																			
Email (duplicate participant check)	X																			
Eligibility screen:																				
Route of access to the study	X																			
Age	X																			
Demographics (self-reported gender)	X																			
Smart phone/device availability	X																			
Current psychotherapy	X																			
Antidepressants or anxiolytic medications	X																			
RRS-Brood[40]	X																		X	X
PSWQ-shortform[41]	X																		X	X
Alcohol abuse/dependence, substance abuse/dependence (current diagnosis or treatment)	X																		X	X

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

	Pre-baseline	Baseline	Allocation	Post-allocation															
TIMEPOINT (*t*) unit = Days	Undefined	*t*-28[g]	*t*0	***Intervention period***														***Follow-up 1***	***Follow-up 2***
				t+ 7[a]	*t*+ 14[a]	*t*+ 21[a]	*t*+ 28[a]	*t*+ 35[a]	*t*+ 42[a]	*t*+ 49[a]	*t*+ 56[a]	*t*+ 63[a]	*t*+ 70[a]	*t*+ 77[a]	*t*+ 84[a]	*t*+ 91[a]	*t*+ 98[a]	*t*+ 105[a]	*t*+112 days[b]	*t*+365 days[c]
Lifetime diagnosis or treatment of bipolar disorder, psychosis	X																		X	X
PTSD (adapted ITQ[58])	X																		X	X
PHQ-9[38] + risk questions (suicidality)[f]	X																		X	X
Informed consent to participate	X																			
SMS verification legitimate participant check	X																			
ASSESSMENTS																				
Name, address, GP details and additional demographics, including employment, education, and marital status		X																		
Diagnostic assessment including current mental health diagnoses (last 6-12 months)		X																		
Neurodivergence, disability, long term health conditions		X																		

	Pre-baseline	Baseline	Allocation	Post-allocation															
TIMEPOINT (*t*) unit = Days	Undefined	*t*-28[g]	*t*0	***Intervention period***														***Follow-up 1***	***Follow-up 2***
				t+ 7[a]	*t*+ 14[a]	*t*+ 21[a]	*t*+ 28[a]	*t*+ 35[a]	*t*+ 42[a]	*t*+ 49[a]	*t*+ 56[a]	*t*+ 63[a]	*t*+ 70[a]	*t*+ 77[a]	*t*+ 84[a]	*t*+ 91[a]	*t*+ 98[a]	*t*+ 105[a]	*t*+112 days[b]	*t*+365 days[c]
Perseverative Thinking Questionnaire[36] (PTQ; primary outcome)		X																	X	X
GAD-7[37]		X																	X	X
Medical history & concomitant medications		X																	X	X
WEMWBS Short Form[39]		X																	X	X
WSAS[42]		X																	X	X
Adapted LIDAS[43]		X																	X	X
Adapted GAD[44]		X																	X	X
Intervention use and experience																			X	
Treatment and hospitalisations																			X	X
Mechanism Measures:																				
Self-Compassion Scale[48] (self-kindness, common humanity, self-judgement subscales)		X																	X	X

	Pre-baseline	Baseline	Allocation	Post-allocation															
TIMEPOINT (*t*) unit = Days	Undefined	*t*-28[g]	*t*0	***Intervention period***														***Follow-up 1***	***Follow-up 2***
				t+ 7[a]	*t*+ 14[a]	*t*+ 21[a]	*t*+ 28[a]	*t*+ 35[a]	*t*+ 42[a]	*t*+ 49[a]	*t*+ 56[a]	*t*+ 63[a]	*t*+ 70[a]	*t*+ 77[a]	*t*+ 84[a]	*t*+ 91[a]	*t*+ 98[a]	*t*+ 105[a]	*t*+112 days[b]	*t*+365 days[c]
5 Facet Mindfulness Questionnaire[51] (short form, 2 subscales)		X																	X	X
Self-Reported Habit Index[47] for RNT		X																	X	X
Attitudes towards self scale[45,46] (overgeneralisation and self criticism subscales)		X																	X	X
Self efficacy/mastery & problem clarification[49,50]		X																	X	X
Flow Proneness Questionnaire[52] – leisure subscale only		X																	X	
Linguistic Analysis		X																	X	
EMA assessment of RNT (via mPath)		X																	X	
Moderators:																				
Childhood loss		X																		
Early adversity (including Childhood Trauma Screener[59]; CTS)		X																		
Adult trauma and stress		X																		

	Pre-baseline	Baseline	Allocation	Post-allocation															
TIMEPOINT (*t*) unit = Days	Undefined	*t*-28[g]	*t*0	***Intervention period***														***Follow-up 1***	***Follow-up 2***
				t+ 7[a]	*t*+ 14[a]	*t*+ 21[a]	*t*+ 28[a]	*t*+ 35[a]	*t*+ 42[a]	*t*+ 49[a]	*t*+ 56[a]	*t*+ 63[a]	*t*+ 70[a]	*t*+ 77[a]	*t*+ 84[a]	*t*+ 91[a]	*t*+ 98[a]	*t*+ 105[a]	*t*+112 days[b]	*t*+365 days[c]
(including adapted adverse events questionnaire[46])																			
Sleep[60]		X																	
UCLA Loneliness Short[61]		X																	
Big Five Inventory-10[62]		X																	
Cognitive Failures Questionnaire 2.0[63]		X																	
Avoidance and Activation[64]		X																	
Need for closure scale (avoidance and predictability subscales)[65,66]		X																	
Discrimination scale[67]		X																	
INTERVENTION/TREATMENT PERIOD																			
Allocation			X																
Intervention (via MyDataHelps)			→																
During intervention micro-assessments:																			
PHQ-2				X	X	X	X	X		X		X		X		X		X	
GAD-2				X	X	X	X	X		X		X		X		X		X	

	Pre-baseline	Baseline	Allocation	Post-allocation															
TIMEPOINT (*t*) unit = Days	Undefined	*t*-28[g]	*t*0	***Intervention period***														***Follow-up 1***	***Follow-up 2***
				t+ 7[a]	*t*+ 14[a]	*t*+ 21[a]	*t*+ 28[a]	*t*+ 35[a]	*t*+ 42[a]	*t*+ 49[a]	*t*+ 56[a]	*t*+ 63[a]	*t*+ 70[a]	*t*+ 77[a]	*t*+ 84[a]	*t*+ 91[a]	*t*+ 98[a]	*t*+ 105[a]	*t*+112 days[b]	*t*+365 days[c]
Condensed (2-3 item version) of self report and brief problem description measures of mechanisms and brief outcome measures of RNT				X	X	X	X	X		X		X		X		X		X		
mPath engagement prompts									X		X		X		X		X			
OTHER ACTIVITIES																				
Researcher / PWP (UK) / Coach (USA) contact points		X[d]		X[e]			X[e]					X[e]								
Withdrawals, including free text reasons		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Participant contact log	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Qualitative interview																			X[h]	X[h]
Adverse events			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Suicide Risk assessment	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		

a = Schedule begins when participant reinstalls mPath with code provided at point of randomisation, +4 day window for completion, b = Schedule begins from randomisation for all assessments other than EMA which begins when participant reinstalls mPath with code provided at point of randomisation, +4 week window for completion, c = Schedule begins from randomisation, +6 week window for completion, d = Researcher contact to help participant set up and use mPath App, e = Minimum of 3 sessions planned for approximately at the start of the intervention, 1/3 through and 2/3 through the intervention. Additional sessions may also be scheduled based on participant need. Ad-hoc interactions between PWPs/coaches and participants will also occur in response to identification of potential risk/safety events, f = Participant will complete PHQ-9 and if scoring 1 or more on question 9, additional suicide risk questions will be presented, g = Maximum 28 days to complete baseline questionnaires (this period may be extended in extenuating circumstances if requested by a participant). Minimum time to complete baseline is 10 days to allow sufficient time to complete the EMA, h = subset of UK participants only.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

8.1. Participant recruitment

We will have several streams of advertising and recruitment ongoing simultaneously. Participants will be asked to specify how they heard about the study during the screening questionnaire, to enable us to assess which streams are proving most successful through the trial.

Social media and other public advertising (UK only)

We will run recruitment advertising campaigns across popular online platforms such as Google, Facebook, Spotify, Instagram and TikTok. These social media adverts will be targeted at our population of interest based on user viewing habits (e.g., users who view or follow content related to mental health). Social media campaigns will be managed by a third party provider. Adverts will include a URL/QR code which interested individuals will use to access a landing page (which will allow monitoring of the source of the link followed) from which they will be directed to the full participant information sheet (PIS), a participant information video and a screening survey on REDCap Academic.

The study will also be advertised publicly on the Calming Minds project website through which members of the public will be able to access the full PIS and screening tool. We may also advertise via radio, directing to our website. We will engage with mental health charities for study promotion.

NHS mental health clinics (e.g. Mental Health Mission Mood Disorder Clinics) will also display NHS REC-approved posters and provide leaflets with brief details of the study, including the URL/QR code to access the PIS and self-completed screening survey. We will not actively recruit through NHS clinics; staff at the clinics will not screen patients, provide the PIS, take informed consent or undertake any study related assessments. The clinics will be solely for advertising the study.

NIHR Bioresource (UK only)

The NIHR BioResource [https://bioresource.nihr.ac.uk/centres-programmes/mental-health-bioresource/] is a recallable resource of over 250,000 volunteers, with and without health conditions who have agreed to take part in health-related research. We will apply to use this resource to recruit (final decision on use of this resource will be subject to costs and their agreement to support the study). Within the NIHR Bioresource we would be sending invitations to participants aged 18 years and over who are part of the Genetics Links to Anxiety and Depression (GLAD) study resource and participants of the wider BioResource who are identified as having anxiety and/or depression. Participants in the GLAD trial have been referred through clinics and through self-referral with all participants having mild to moderate anxiety and depression. NIHR BioResource will create a list of potential participants based on our inclusion/exclusion criteria, which is then input into a database. Staff at NIHR BioResource have ethical approval to send out invites (either by email or post), which summarise the study, what's involved, next steps, how to register (including the URL/QR code to the screening survey), contact details for the research team, and they also include a BioResource-specific participant information sheet. If a potential participant is interested in the study, they will use the provided URL to access the self-complete screening survey (REDCap Academic). The research team at University of Exeter will not receive personal identifiable information from participants of the BioResource prior to them completing the screening survey (where they will input an email address).

NHS DigiTrials (England only)

We will potentially use NHS DigiTrials [https://digital.nhs.uk/services/nhs-digitrials] to send information about the study to potentially suitable/interested people (subject to costs and their agreement to support the study). Through NHS DigiTrials we will obtain support under Regulation 5 of the Health

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

Service (Control of Patient Information) Regulations 2002 (equivalent to section 251 of the NHS Act 2006) to screen individual medical records against relevant and reviewed eligibility criteria (e.g. criteria that can be clinically coded) and selected demographic variables in order to target people who are most likely to be interested in the study. We will apply to the Confidentiality Advisory Group for support with accessing potential participants through NHS DigiTrials. The research team at University of Exeter will not receive personal identifiable information from patients invited through NHS DigiTrials prior to them self-screening for the study. The DigiTrials team at NHS England will identify suitable people and send out an invitation letter (via post, email and/or SMS) on behalf of the research team. If a contacted person is interested in the study, they will use the provided URL to access the PIS and the self-complete screening survey.

USA-specific detail

The research team at UCLA will recruit participants from Imperial Valley Community College to widen the diversity of the sample and increase generalisability of our findings, particularly to lower socio-economic and more marginalized and underserved populations. Imperial Valley is a rural area of California that borders Mexico, and is a predominantly Latinx community (85.8%), with rates of poverty (18%) and per capita income ($18,064) significantly worse than US national averages (11.4% and $35,384 respectively). Imperial Valley Community College serves this community, with a predominantly Hispanic student population (92%), with high rates of financial stress, food insecurity, low mood and anxiety, and a reported need for help for emotional needs. 500 students from Imperial Valley College will be recruited over 18 months.

In collaboration with Imperial Valley Health Services, a group of student ambassadors will be hired to promote study recruitment through the methods deemed effective given their knowledge of the student body. Examples of recruitment efforts may include tabling at outdoor events, sending out college-wide emails, posting a banner on the college website, staff trained to refer relevant students, creating social media campaigns and presentations during classes, giving lectures to student organisations, emailing and text messaging, posting physical flyers or banners, attending town hall meetings, and creating video testimonials about participation.

Recruitment materials used in the USA will have relevant IRB approvals.

8.1.1. Eligibility screening

Interested participants will access the study via a URL/QR code (provided on the social media post/poster/leaflet/invitation letter/study website/participant information sheet) which will direct them to a landing page (simple web page) provided by a third-party vendor. The landing page will contain brief information about the study and ask the participant if they wish to proceed to screening. The purpose of the landing page is to enable the research team to monitor metrics on the source of the URL the participant clicked so we can identify the most effective methods of recruiting into the study. The landing page will include a ReCAPTCHA feature that attempts to limit usability by “bot farms” (ReCAPTCHA is a free, widely used technology that detects the difference between human users and “bots”).

If the participant agrees to continue to the screening tool they will click a URL which will take them to REDCap Academic where they will be able to access the Participant Information Sheet (PIS) and a summary Participant Information Video (participants who received an invitation from NIHR BioResource will also have received a PIS with their invitation letter). It will not be mandated that the individual has to read the PIS or watch the video before proceeding with the screening process but

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

they will be required to complete a light touch consent to provide the screening data. This will involve reading a brief statement on the purposes of collecting screening data, and how their data will be protected. If the individual is willing to continue, they select 'I agree' (or similar). Participants will be asked to provide an email address at this stage for the following purposes: 1) if a screening survey or consent form is partially completed a survey link can be emailed to the individual inviting them to continue, 2) to email a copy of the PIS and completed consent form to the individual with instructions for the next steps, and 3) we can identify if the same people are entering the study multiple time.

For screening, individuals will complete an online survey of the eligibility criteria. Screening will be step-wise, so if a person is excluded on a criterion, they will not need to complete any further questions. Screening questions will be presented in order of seriousness (starting with the least serious) to avoid asking potentially distressing questions if a person is clearly ineligible (e.g. under 18 years old or does not meet the criteria for RNT). The screening process will include completing the RSS, PSQW short form and PHQ-9 validated questionnaires and if a person is eligible and consents to take part, the data from these questionnaires will be included as baseline data so participants do not have to repeat the questionnaires. Screening data will be self-reported. The research team will not undertake checks with healthcare services to verify the data provided is accurate (e.g., will not check for a diagnosis of depression or bipolar disorder in an individuals' medical record). The screening form will not collect personal identifiable data other than email address for purposes noted above, however some non-identifiable demographic data (age and self-reported gender) will be collected at screening so we can monitor whether the study is disproportionately screening out individuals from a particular demographic. If a potential participant clicks away from the screening process they will be sent a link by email which they can follow to return to the survey later.

Potential participants who, after self-screening, meet all the inclusion criteria and none of the exclusion criteria will be invited to provide informed consent to take part in the study. This will be electronic consent via REDCap Academic (see section 8.2 Consent).

USA-specific detail

UCLA will not utilise the UK landing webpage. Interested individuals will navigate directly to the REDCap Academic which will contain the PIS, video and screening forms.

8.1.2. Payment

Participants will be offered an online shopping voucher for the value of £30 for completion of each of the activities listed below.

- Completion of baseline data AND a minimum of 60% of the baseline EMA
- Completion of 6 or more of the micro-assessments during the intervention period
- Completion of the 16-week post-randomisation data AND a minimum of 60% of the follow-up EMA
- Completion of the 52-week post-randomisation data
- Participation in a 16-week post-randomisation qualitative interview (a selected subset of overall sample)
- Participation in a 52-week post-randomisation qualitative interview (a selected subset of overall sample)

Vouchers for participants in the UK will be monitored and administered by the University of Exeter.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

USA-specific detail

Participants will be offered online shopping vouchers up to a total of $200 for the completion of the above listed activities (excluding the qualitative interviews which will not be conducted in the USA). Payments to participants in the USA will be monitored and administered by the trial management team at UCLA.

8.1.3. Recording screening and recruitment information

Potential participants will self-identify and self-enrol into the study using the online screening and e-consent tool, individuals will not be directly screened and approached by health or social care providers. Screening and recruitment data will be collected and stored in REDCap Academic.

The electronic data capture system (EDC; REDCap Academic) will maintain an auditable record of initiated screening forms, completed screening forms, numbers eligible/ineligible (including reasons for ineligibility), number and proportion of eligible people who provide informed consent, number and proportion who complete the baseline assessment, and number and proportion who are randomised into the study.

During the screening process, we will attempt to collect anonymised demographic data including age, and self-reported gender. By collecting this data we will be able to monitor whether we are disproportionately screening out a subset of the population.

USA-specific detail

The USA will host a separate equivalent instance of REDCap Academic within which participants from Imperial Valley Community College will enter their information. The USA instance of REDCap will be available with Spanish language translation.

8.2. Consent

The consent process will be completed in two stages. Prior to screening, potential participants will be asked to agree to a series of short statements explaining that we will collect their email address and answers to the screening questions as part of the screening process (the statement will detail the reason for collecting this data and how long we will keep it for).

To deter disingenuous enrolment which is common in online enrolment (e.g., bot farms or imposter participants (people who attempt to enrol multiple times for disruptive or monetary reasons)), each potential participant will only be able to screen themself with their email address once. In cases where individuals have a genuine need to rescreen themselves, e.g. they were not eligible previously but may be now, they will be prompted to contact the research team and this will be manually overridden allowing them to screen themselves again. While this may not entirely prevent duplicate or disingenuous enrolment, it will act as a deterrent.

Once a potential participant has completed the screening process and is eligible to take part in the study, they will again be presented with the participant information sheet and the participant

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

information video on screen. The potential participant will then be invited to complete an electronic consent form within REDCap Academic. They will have up to 2 weeks to complete the consent form after being confirmed eligible, if 2 weeks lapses, they would have to complete the screening process again to ensure they are still eligible. If they click away from the consent process they will be sent a link by email which they can follow to return later and they will be sent up to two email reminders to return to the consent form during the two week window.

The transfer from the screening forms to the PIS and the consent form will be continuous and the participant will not be required to navigate to a different system, ensuring a smooth and minimally burdensome process. To further deter disingenuous enrolment and to ensure accurate contact details are available, eligible individuals consenting to the study will be asked to enter their mobile phone number as part of the consent process. An SMS will be sent to the phone number with a verification code that they will need to enter on screen. Once the code is entered correctly (and consent form fully completed) the individual will be permitted to proceed into the study.

Participants who provide informed consent will be automatically sent a copy of their completed consent form by email and have the option to download it directly. A copy will also be stored in REDCap Academic.

As part of the consent process, participants will be able to opt in to receiving newsletter updates about the Calming Minds project by email, receiving an email summary of the aggregate results once the study has finished and being contacted for future research they may be eligible for. They will also be able to opt in to completing two interviews to discuss their experience of the therapy (see Section 10 for details about the interviews).

The trial management team at Exeter will be responsible for monitoring consent forms and ensuring consent is completed appropriately for participants in the UK.

USA-specific detail

Participants in the USA will be required to have an Imperial Valley Community College email address to demonstrate that they are genuine participants and not a “bot”. To limit opportunity for duplicate enrolment, each participant will only be able to enrol with their email address once.

The trial management team at UCLA will be responsible for monitoring consent forms and ensuring consent is completed appropriately for participants in the USA.

8.3. Baseline data collection

Once a participant has provided informed consent to take part in the study, they will receive a copy of the PIS, their completed consent form and information on what to do next, as detailed below. Instructions will be detailed on screen and emailed to the participant for later reference.

1. OPTIONAL: Participants will be given the option to request contact with a member of the Calming Minds Research team, via an automated request form via REDCap, to help explain any questions and to get set up on the mPath app required for the study. This is not mandatory allowing participants to work through the process on their own if desired but provides an opportunity for support and contact with a team member, which may improve overall engagement. The research team in each country will receive notification of the participant

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

request for contact and will send an email and SMS text message introducing themselves and provide a booking schedule for a video-conference call and contact details for the research team. The intention is that the same researcher will also be available to follow up participants to improve retention. Meeting with a researcher is not critical/mandatory to proceed to randomisation[55]. Including a meeting with a real person is proven to improve engagement and retention in digital trials and it also provides a potential means to screen out "fake participants" and "bots". The researchers may follow-up participants who haven't completed the baseline or the EMA, and get in touch to encourage them to complete or check for difficulties – e.g. messages that they have one more week to complete baseline assessment or EMA.

2. MANDATORY: Participants will be able to directly proceed to complete the baseline assessment questionnaires in REDCap Academic and will also receive an automated email and SMS text message with a link to the survey in REDCap Academic, allowing them to complete at their discretion / pause and return to complete as needed. Participants will be given up to 4 weeks post-consent to complete baseline data collection (this period may be extended on a case-by-case basis if requested by a participant who has extenuating circumstances). During the designated time window, participants will receive emails and SMS text message reminders prompting them to complete the baseline surveys. Data collected at baseline are detailed in Table 3, Section 8.

3. MANDATORY: In parallel, participants will receive information required to install the m-Path App on their smart phone which is required for the ecological momentary assessment (EMA) measures[1,2]. These are another way of assessing their RNT in the real-world, as a means to measure its frequency and occurrence in daily life and as a way of providing information to their PWP (UK)/coach (USA), who will have a 'view only' user account on mPath to see data entered by participants. Participants do not need to provide any personal identifiable data to set up m-Path but will be provided with a unique invitation code. Once installed, participants will be asked to complete EMA (via m-Path) for 10 consecutive days. Participants will receive 6 prompts each day from the app to complete brief questions asking about RNT, mood, stress and habit, at pseudo random intervals throughout the day. There is a dashboard so participants can view the data they are entering in the EMA. Participants will need to complete a minimum of 60% of total EMA prompts (i.e., 36 prompts) to be able to proceed to randomisation. Any participant who has completed <20% of prompts (i.e., 12 or fewer) after 10 days is unlikely to be engaged in the study and will not proceed to randomisation. Any participant who has completed ≤20% and <60% of prompts by day 10, could raise this completion level sufficiently with more time and will therefore be given 4 additional days to complete a minimum of 36 EMA prompts on the m-Path app. If they complete a minimum of 36 prompts by the end of the additional 4 days, they will be able to proceed to randomisation. Participants will be sent emails to notify them of their status as required (e.g. reminder to start if not yet started, being allowed more time, not enough completed to proceed).

Progress on completing the EMA will be monitored by the research team at LMU. LMU will provide regular reports to the ExeCTU and UCLA study team of their participants (identified by unique invitation code (as a proxy for participant ID (PID) number)) including: a list of participants signed up to the app, the date the first prompt was sent to each participant and summary data to indicate completion rates at various stages of the EMA process. The reports will be used to send reminders/status updates to participants about their progress with the prompts, and to update

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

REDCap that a participant has either met the threshold for randomisation or has not met the threshold and will not proceed with randomisation.

USA-specific detail

No differences from lead site.

8.4. Randomisation procedure

Participants will be randomised online using the REDCap Academic randomisation software. Participants who complete the screening process, provide informed consent, complete the baseline dataset and assessments, including a minimum of 36 EMA prompts, will be eligible to be randomised.

Randomisation will be completed following submission of the required data. Upon randomisation, an automated email notification will be sent to the Chief Investigator, the trial manager/trial management team (at ExeCTU), the PWPs (UK)/coaches (USA) and the participant. The email notification to the PWPs/coaches will contain the randomised allocation (The PWP/coach will be assigned prior to knowledge of the allocation group). All other recipients will receive blinded notifications. The participant's email will contain instructions for the next steps, including how to reinstall mPath with a new invitation code to start the series of follow-up surveys, and to anticipate a set up email from MyDataHelps and contact from the PWP/coach.

There will not be a process for emergency unblinding of a participant's allocation because PWPs/coaches will already know the allocation. In the event that a participant is at risk of self-harm or suicide, their management will not be dictated by knowledge of their allocated group. Participants will be managed according to a standard operating procedure for managing people at risk, irrespective of intervention allocated or received.

Randomisation will be managed by discrete REDCap instances in the UK and the USA. Each country will have separate randomisation lists provided by the senior trial statistician based at ExeCTU (see Section 5.1.1 Randomisation). Stratification factors will be pulled directly from the baseline data entered into REDCap by the participant. Stratification will be location (UK versus USA) and caseness or not for depression (PHQ-9 ≤ 9 versus >9) or anxiety (GAD-7 ≤ 9 versus >9).

The randomisation allocation will be automatically communicated to the MyDataHelps platform via an API, including the participant ID number and email address. This will ensure the participant only has access to the specific variants of the modules as per their allocation. The email address is necessary for the participant to set up their account on MyDataHelps. During account set-up, the participant will also be able to volunteer their name and phone number if they wish to receive personalised messages (i.e., reminder prompts) directly from MyDataHelps.

Randomisation to particular intervention condition will be independent of allocation to study PWP/coach. Allocation to PWP/coach will be conducted independently and with concealment of randomisation (i.e. PWPs/coaches will be allocated to next sets of patients before randomisation is known). All PWPs/coaches will provide all variants of the online therapy, with the assumption that across the study this will be balanced given the randomisation to intervention condition and large numbers of participants per PWP/coach.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

8.5. Follow up data collection

8.5.1. Weekly micro-assessments (during the intervention stage)

At week 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, participants will receive prompts to complete brief questionnaires (micro-assessments) via the mPath App. The schedule for these questionnaires will start from the day the participant reinstalls mPath with their second invitation code, provided to them at the point of randomisation. The questionnaires collected during the micro-assessments will include condensed (2-3 item versions) of self-report and brief problem description measures of mediators, as well as brief outcome measures of RNT, anxiety (GAD2), depression (PHQ2), as detailed in Table 3. Participants will also be prompted to complete two brief questions in weeks that the full micro-assessment is not required (weeks 6, 8, 10, 12 and 14). This is to maintain engagement and to keep m-Path live on their phones (i.e., prevent the App from being put to sleep by the operating system).

Participants will have a +4 day window each week to complete the micro-assessments, after which the assessment will no longer be accessible to the participant. If any of the micro-assessments or engagement prompts are not completed, the participant will be sent an email to increase their engagement with the app and reminding them to open the m-Path app to ensure future survey notifications are received (i.e. to avoid the app going into sleep mode).

During the intervention period we will also collect data on engagement with the intervention (see Section 9 for more details).

8.5.2. 16 weeks post-randomisation

At 16-weeks post randomisation, participants will receive an automated SMS text message and an email with a link to complete the follow up questionnaires as surveys via REDCap Academic. On week 16 participants will also be invited to complete EMA for another 10-14 days (see the EMA thresholds under the Baseline Section 8.3) via the m-Path App. The schedule for the EMA will start from the day the participant reinstalls mPath with their second invitation code, provided to them at the point of randomisation. The questionnaires and data collected at 16 weeks post-randomisation are detailed in Table 3.

Participants will have a +4 week window to complete the questionnaires. During the 4-week window, participants will receive up to 3 SMS text messages and 3 email reminders to prompt them to complete the questionnaires. Participants who have not completed the questionnaires after receiving the reminders may be telephoned up to three times by the research team (postgraduate researchers) to encourage and support the participant to complete the questionnaires. The researchers will support participants in completing the assessments during the call, understand any barriers to completion, directly send them the link to complete the assessment if needed, and as a final step only collect the primary outcome data directly over the phone.

If a participant completes one of the questionnaires with data that indicates they could be at risk of self-harm and/or suicide, additional questions about their immediate risk will be triggered. A separate study risk protocol will be followed under these circumstances.

8.5.3. 6 months post-randomisation

No data will be collected 6 months post randomisation but as there is a large gap between the 16-week and 52-week data collection timepoints participants will be sent a 6-month email as a simple

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

touch point to keep the participant engaged. This will act as a reminder that we will be in contact with them to complete their final questionnaires at 52-weeks after randomisation.

8.5.4. 52 weeks post randomisation

At 52-weeks post randomisation, participants will receive an automated SMS text message and an email with a link to complete the follow up questionnaires as surveys via REDCap Academic. The questionnaires and data collected at 52 weeks are detailed in Table 3.

Participants will have a +6week window to complete the questionnaires. During the 6 week window, participants will receive up to 3 SMS text messages and 3 email reminders to prompt them to complete the questionnaires. Participants who have not completed the questionnaires after receiving the reminders may be telephoned up to three times by the research team (postgraduate researchers) to encourage the participant to complete the questionnaires, support in completing the assessments during the call, understand any barriers to completion, directly send them the link to complete the assessment if needed, and as a final step only collect the primary outcome data directly over the phone.

If a participant completes one of the questionnaires with data that indicates they could be at risk of self-harm and/or suicide, additional questions about their immediate risk will be triggered. A separate study risk protocol will be followed under these circumstances.

8.6. End of study

The study will end for a participant once their 52-week follow-up questionnaires and data collection are complete, or sooner if the participant opts to withdraw their consent to participate before the end of the study.

The study will end overall once all follow-up are complete (or if not completed, when the final follow-up window has expired), the data has been checked and cleaned and both instances of the REDCap Academic EDC have been locked in the UK and the USA, respectively.

9. STUDY TREATMENT DELIVERY

The intervention is primarily an online digital platform (MyDataHelps) delivering modules of CBT that participants complete in a self-directed manner. The intervention is accessed through a web browser/app. See section 8.4 for details of how the allocation is communicated to the platform and how the participant accesses it.

The intervention is supported by a minimum of three sessions with a PWP (UK)/coach (USA) (see Section 4.1 for details) delivered by video or telephone call.

Adherence to the digital intervention will be measured by collecting data on; a. number of PWP/coach contacts attended, b. number of online CBT sessions completed, and c. number and frequency of tools (self-practice element in app) completed as a minimum, with more detailed analyses examining completion of specific sections within the online sessions. The target would be for participants to complete at least 50% of the online sessions (i.e., 3 of 6). A contact log will document interactions between PWPs/coaches and participants and the reasons for any missed contact sessions.

USA-specific detail

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

Coaches in the USA will be responsible for setting up their local participants on MyDataHelps and conducting the contact sessions.

10. PROCESS EVALUATION

To inform understanding of mechanisms and barriers and facilitators of sustained implementation within a mixed model approach, semi-structured online or telephone interviews will be conducted with 30 UK study participants around the 16 weeks and 12 months timepoints. These will be conducted after the participant has completed their follow-up questionnaires (or the time window for completion has elapsed) for the relevant follow-up timepoint. The same participants will be interviewed at both timepoints where possible; when attrition occurs, we will make up the sample with further participants. The sampling strategy will include participants who have received at least three of the different intervention components to enhance our ability to investigate interactions between elements. Within this criteria, we will also sample for those who make the most/least progress on the core outcome measures (measured through EMA/PTQ), as well as sampling for maximum variation in t, socio-economic group, age, and ethnic heritage. Interviews will examine engagement with the digital platform, acceptability, experiences of any PWP support, how different mechanisms of impact operate to produce outcomes, and any contextual factors.

Qualitative data will be analysed using realist-informed thematic analysis, with NVivo v14, to deductively investigate each of these areas but we will also include an inductive approach to identify any novel findings. Participants who drop out of the intervention will be invited to complete a brief online form with an open question about their reasons for withdrawing; these data will be analysed using framework analysis. We will analyse metrics of digital intervention use (reach, dose, frequency and attrition). Mixed methods analysis will then use matrix and joint-display tables to integrate qualitative and quantitative data (including from psychological measures collected for the study) at case level for each participant and at the intervention level.

11. PARTICIPANT WITHDRAWAL

Participants are able to withdraw from some of all aspects of the study at any time. We will ask for the reason(s) for their withdrawal but participants do not have to provide a reason. The study will adopt the principles of the PerSEVERE guidance[68] to enable participants flexibility with their participation where it is practical and reasonable to do so. In accordance with regulatory guidance, data that have already been collected will continue to be retained and used in the analysis (this does not include any data collected as part of the qualitative interviews which participants can request deletion of up to the point that the analysis of the data has begun, approximately 2 weeks after each interview).

Participants who withdraw after consent but before randomisation will not count toward the sample size and we will continue to recruit until the target sample size is met with randomised participants.

Participants who withdraw after randomisation will count toward the target sample size and will not be replaced.

Randomised participants can change their participation in the study in the following flexible ways:

- Opt out of the intervention
- Opt out of the follow-up data collection
- Opt out of any qualitative interviews they consented to but have not yet taken part in

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

- Stop contact from the research team (only if withdrawn from all other components of the study)

Participants who have either completed or opted out of the intervention AND have opted out of follow-up data collection will not be monitored by the research team for risk. The research team will be acting strictly in a research capacity in the study and will not be considered a 'healthcare provider' responsible for providing support or services that would normally be provided by the NHS or other health and social care services. Only participants in active follow-up will be monitored for risk.

When a participant opts to withdraw from one or more component of the study a member of the research team will attempt to contact them to gather more information about which elements of the trial they wish to opt out of. The participant will then be asked to provide freetext reason for their withdrawal via a survey via REDCap Academic, this will be optional. If a participant notifies the research team via any method that they wish to opt out of the study, but declines to complete a Change in Participation form, a member of the research team will complete a form on behalf of the participant and document the communication with the participant in which the request was received. The form will capture whether it was the participant or a member of the research team who completed it.

Randomised participants who opt out of the intervention will have the option to opt back in under their original consent, but only if still within their original intervention time window. Once the participant has reached the 16-week post-randomisation follow-up timepoint, they will not be able to opt back into the intervention. Once the intervention time window has passed, participants will, by default, no longer be able to opt out of the intervention.

Randomised participants who opt out of follow-up data collection will have the option to opt back in under their original consent, providing they have not exceeded the window for the final follow-up at 52-weeks post-randomisation. Participants who opted out after the 16-week follow-up window has expired, and then opt back into the study, will not be able to retrospectively complete the 16-week follow-up data.

Participants will be able to change the communication preferences for study updates and summary study results at any time by contacting the research team. Even if a participant withdraws from active participation in the study, their previously specified communication preferences will be retained unless they actively change them.

The research teams will only withdraw participants under limited circumstances, as detailed below:

- The participant is strongly suspected to be an imposter participant (i.e., a person/bot who has disingenuously enrolled in the study, potentially for financial benefit). Clear documentation will be recorded to capture reasons for believing the participant is an imposter.
- The participant displays threatening or abusive behaviour toward a researcher/PWP/coach. In this situation, the participant would be withdrawn from the intervention and interview (if consented to it) but may still complete follow-up if willing.
- The participant is found to be ineligible (post-consent) in such a way that the intervention is not suitable for them and it would be in their best interest to withdraw.
- The participant loses capacity to consent during their participation in the study.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

The CI or site lead will be required to assess and approve any withdrawals of participants proposed by the local research team/PWP/coach. All withdrawals and reasons for them will be reported to and monitored by the TMG, DMEC and TSC.

Randomised participants who are lost to follow-up (i.e. have not completed any or parts of the intervention and/or have not completed follow-up data and who the research team have not been able to make contact with) will not be categorised as withdrawn.

12. SAFETY MONITORING

There is no known health risk associated with any of the assessments or the CBT modules included in the intervention. As such, the risk associated with participation in this study is deemed to be low. Further, we anticipate that the interventions will on average reduce symptoms and improve well-being. CBT is a widely used intervention in NHS and non-NHS settings.

The initial screening process will exclude anyone self-reporting a history of severe psychiatric disorder, alcohol/substance abuse and those reporting elevated suicidality. These individuals will be automatically guided towards appropriate information and sources of help. This process means that individuals likely to have significantly increased risk (e.g., for self-harm and suicidality), and/or for whom more intensive psychological and psychiatric treatment is appropriate, will not be included in the study.

Other than the intervention failing to produce an effect, there is nothing in the literature to suggest possible adverse effects of the assessments and interventions for the participants involved. Versions of components within the intervention have been previously used with no detected harmful effect.

As with all psychological interventions, individuals reflect on their difficulties, which can produce temporary increases in distress, but no more than would commonly occur in daily life. The likeliest outcome for users who do not find the intervention of benefit, or who do not get on well with the assessments, is their disengagement from it. In addition, all participants receive more intensive monitoring, with processes to identify and direct all relevant participants to potential sources of help.

As part of our policy for addressing risk and prioritising the welfare of participants, participants are provided with links to online support, the opportunity to request contact from the study team, and automatic signposting to help and guidance if reporting risk (e.g., suicidal thoughts, as indexed in items within the Patient Health Questionnaire-9 (PHQ-9) on the screening or follow-up questionnaires) or significant worsening symptoms suggesting a need for help. These messages include general information on the presenting symptom, recommended actions to make themselves safe, and advice to seek medical help, and direct links to relevant national sources of help. These sources of support will be tailored by participating country. For this purpose, significant worsening symptoms is defined as a deterioration of movement across two or more score categories on the GAD7 or PHQ-9 from baseline to 16-weeks or from baseline to 52-weeks follow-up. At the point of automated signposting, participants can request contact from a study PWP or contact a study PWP via e-mail or telephone to seek advice.

The main indicator of harm will be the completion of the PHQ-9 questionnaire by the participants at baseline and at 16-weeks and 52-weeks post-randomisation. Questionnaires will be automatically screened for signs of severe distress (for example, defined reports of suicidal ideation), with automatic programmed questions following up to ascertain aspects of risk and to automatically provide users

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

with recommended advice and signpost towards help (GP, local hospital, crisis teams, relevant charities; e.g., website link to the Samaritans). Other indicators would be reports of worsening symptoms or suicidality in direct contact from participants to the research team or in contact with the study PWP (UK)/coach (USA). For participants at 16-weeks, elevated reports of suicidality (as per definition at screening, i.e., endorsing automated follow-up questions 2 or 3) will be followed up by the associated PWP, following an established risk protocol.

PWPs/coaches will maintain a risk log separate from the research database to document interactions with participants who are (or potentially are) 'at risk' and any actions taken to support, guide and/or refer them on to other services. The risk log will not be considered 'research data', but instead will be data pertaining to the clinical care of the participant

In addition, the number of participants who report significant worsening symptoms of anxiety, or worsening symptoms of depression (as defined above) will be reported to the DMEC, TSC and TMG via regular reports. For all participants, we will include brief open questions at 16-week follow up to assess potential harm from the intervention (e.g., "Have you had any problems with the study treatment? Has any aspect made you feel worse?"), whilst minimizing participant burden. If harm is indicated in these questions, the PWPs will be automatically notified to review the freetext answers and discuss any concerns with the site lead within 3 working days. Number of participants indicating harm in these questions will be reported to the oversight committees via routine reports.

Individuals reporting severe levels of symptoms or meeting diagnostic criteria for depression will be offered guidance to seek appropriate help from their GP or relevant clinical service, should this seem necessary.

For those who are randomised into the study and then indicate risk there will be the option to request contact from a PWP to seek advice. This advice will include guidance for the participant to seek appropriate help from their GP or other relevant services, should this seem necessary. PWPs will be trained in and provided with a protocol to assess risk including standard useful responses in these circumstances. The University of Exeter (UK) study site has a designated site lead/senior clinical psychologist and psychological wellbeing practitioners who will be available as a resource to researchers to provide guidance on clinical issues arising from participants either through standardised measures or contacts initiated by the participant. An equivalent series of expertise is available at UCLA (USA).

If a PWP/coach has serious concerns about a participant, where appropriate, after discussion with a supervisor (e.g. site lead; clinically qualified supervisor), the clinician or PWP/coach will contact the participant (by email or telephone) to review the situation, provide guidance and offer to write a referral letter, subject to participant consent. These procedures will be made explicit in all information sheets and will be detailed in a separate risk protocol. Any concerns detected this way will be recorded on a risk log. The same process will be activated in response to any concerns raised by participants at other times, either spontaneously or in responses during the assessments.

12.1. Definitions

Because the current intervention is digital self-help with PWP(UK)/ coach(USA) support, rather than a medicinal product and involves no biological agent, it is not appropriate to report all adverse events (defined as any untoward medical occurrence). Rather, as a psychological intervention, appropriate adverse events would include those related to mental state and behaviour. We will therefore not report

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

non-serious adverse events but will report serious adverse events (SAEs) within all intervention groups under our own study-specific definition (see **Table** 1).

As this is a low risk study with no known adverse events associated with the intervention, all related adverse events are unexpected of the intervention.

Table 1**:** Definitions of adverse events

Term	Definition
AE	Any unintentional, unfavourable clinical sign or symptom, or any new illness or disease or the deterioration of existing disease or illness (not recorded/reported in this study).
SAE	For the purposes of this study, a Serious Adverse Event (SAE) is defined as any of the following events: • Death (including suicide). • Suicide attempt. • New self-harm or an increase in frequency, intensity or duration of self-harm (self-harm is defined as anything with the intention to harm self without the intention to end life including but not limited to; cutting, burning, scratching, hitting). • Serious accident or violent incident requiring emergency medical assistance (including presentation at Accident and Emergency, hospital treatment or ambulance/paramedic callout). • Referral to crisis care or admission to psychiatric hospital. • Admission to A&E for overdose or excessive alcohol or drug use.
Related Unexpected SAE (RUSAE)	Any event which meets one or more of the above SAE criteria AND is assessed as being likely to have been caused by the intervention.

All SAEs will be reported to ExeCTU on a SAE form within REDCap. This must be completed within 24 hours of the investigator becoming aware of the event. All SAEs will be onward reported to the Sponsor by ExeCTU. SAEs which are categorised as unrelated to the intervention will be reported monthly by provision of a trial management group (TMG) report.

SAEs which are categorised as related to the intervention (Related Unexpected SAE (RUSAE)) will be reported to the Sponsor using a SAE template report form produced by ExeCTU. ExeCTU will report RUSAEs to the Sponsor as soon as reasonably practicable after becoming aware of the event, taking into account that the Sponsor must report the event to the REC within 15 calendar days.

SAEs may be detected by the research team via interaction with the participant and some will be detected by data submitted by participants on the assessment forms in which case, it may not always be possible to obtain full details of an event before submitting the initial report. The research team (typically PWP) will endeavour to make contact with the participant by email and telephone to obtain as much detail as possible and signpost to relevant support if appropriate. All attempted and actual contacts will be documented on a contact log.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

12.2. Assessing causality of serious adverse events

Causality of SAEs will be assessed by a trained PWP or the chief investigator/site lead in the UK, and the site lead (or clinically qualified delegate) in the USA. Members of the research team who assess causality will be required to complete safety training and will be provided with a study-specific safety work instruction to follow.

SAEs will be assessed for causality within 2 working days of the research team being notified of the event.

12.3. Reporting Serious Adverse Events

SAEs will be reported from randomisation up until 20 weeks post randomisation (i.e. 16-week follow-up plus the 4-week window allowed for completion of questionnaires).

In a bid to commit to data minimisation (especially of sensitive category data), we will not respond to or report SAEs for non-randomised participants. Depending on the attrition rate during completion of baseline assessments, the number of individuals who do not convert to randomisation could be significant, and therefore beyond the capacity of the research team to follow-up events. Only randomised participants (i.e. those offered the intervention) will be monitored for safety.

In the event a member of the research team becomes aware of a (potential) SAE, a PWP will endeavour to contact the participant by telephone and/or email to enquire about the safety and well-being of the participant, determine whether a SAE has occurred and offer support as described in Section 12. If a SAE has not occurred, the PWP/coach will document it on the risk log, but no further data will be collected.

In the event of a SAE the PWP or site lead will complete a SAE report form on REDCap Academic to capture key information about the event. This will include:

- Event name (brief term describing the event)
- Reason for being an SAE
- Date of occurrence (estimated if exact date unknown)
- Date research team became aware of event
- Detailed description of the event and any actions taken
- Status of the event (ongoing, resolved, death)
- Intensity (mild, moderate, severe)
- Causality (relationship to the study intervention)
- Name and signature of person assigning causality

If a SAE is categorised as related to the intervention, a statement will appear on the SAE form informing the research team that the event is a Related Unexpected SAE (RUSAE) and must be reported to the Sponsor, DMEC and REC following the expedited timeframe (15 days for the DMEC and REC).

If the SAE is ongoing at the time of the initial report, follow-up report forms will be completed until the event is resolved, the participant has died, or the Sponsor and CI agree that no further follow-up is required. Where possible, efforts will be made to ensure any ongoing SAEs are resolved prior to database lock.

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If an event is recorded as an SAE in the first instance but it is later determined that the event did not meet the definition of an SAE, the event will be marked as withdrawn in the REDCap database, but the data will not be removed. There will be no further follow up of such events.

Serious adverse events (SAE) will be reported to the TMG monthly. The Chief Investigator will review aggregate SAE data monthly through receipt of the TMG report and will determine whether there are any safety concerns arising which could have implications for other participants. This will be documented in TMG meeting minutes. If the event was a death, or resulted in death, the Chief Investigator will review the event and determine the potential safety implications for other study participants within one week of the event.

SAEs categorised as related to the intervention (RUSAEs) will be reported to the DMEC and the Research Ethics Committee who provided favourable opinion for the study within 15 days of the research team becoming aware of the event.

Aggregate SAE data will be reported to the DMEC and TSC biannually as part of their oversight of the study.

12.4. Risk management following notification of potential harm to others

If a participant indicates through any means of communication that they or someone else could be at risk of harm, the study team (typically PWP) will follow a dedicated risk management protocol and may onward report the information to the appropriate authorities, including the police. If this happens, personal identifiable data of the participant and the person at risk of harm may need to be provided to the relevant authority(s). This information will be included in the participant information sheet.

USA-specific detail

Coaches will manage participant risk under supervision of the lead clinical psychologist/site lead.

In the USA, coaches will not make causality assessments. The site lead at UCLA (or clinically qualified delegate) will assess SAEs for causality as soon as practically possible.

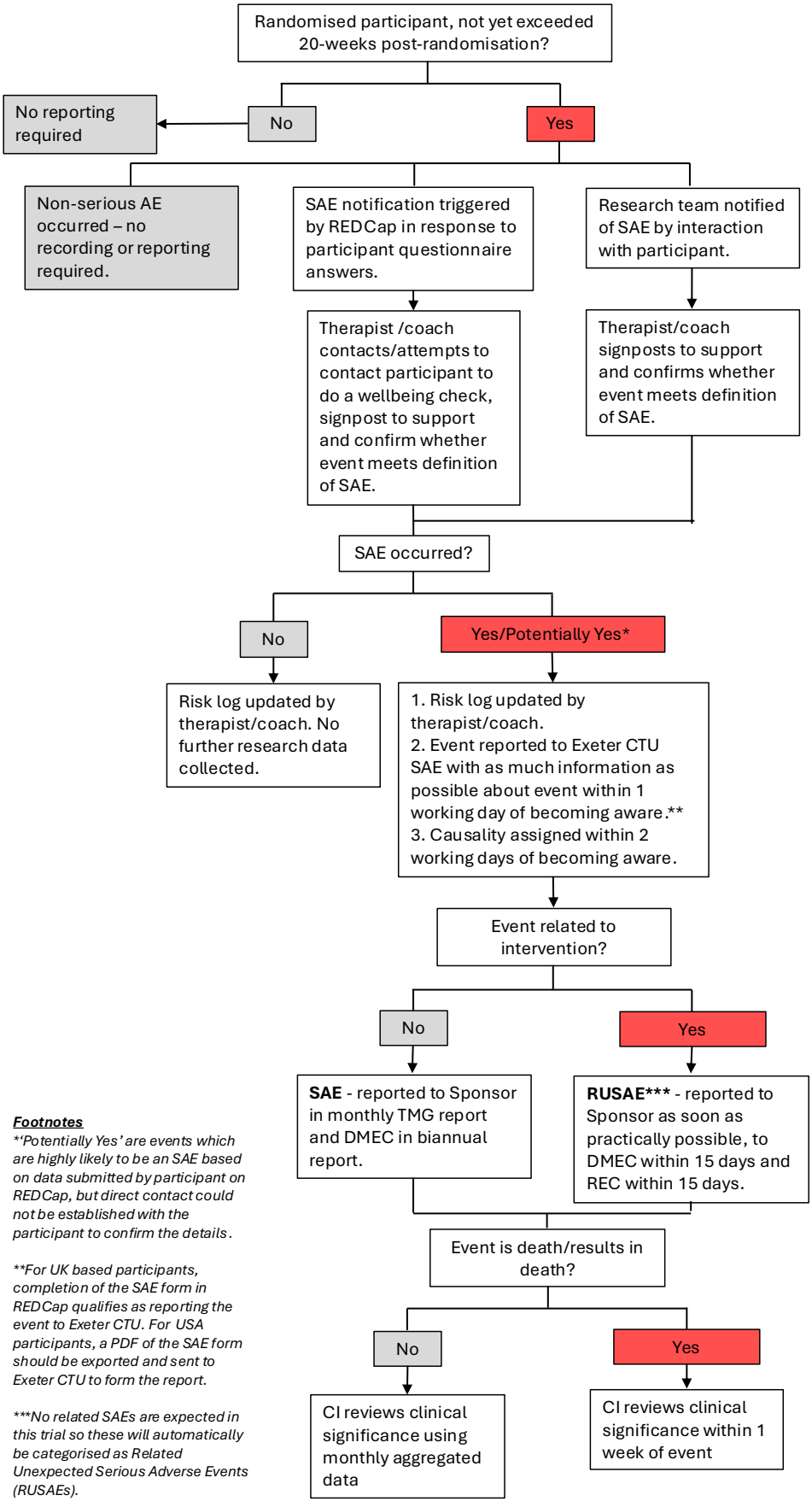
Participants based in the USA will not be referred on to the equivalent of a GP in the event of an SAE or other adverse event.

If a USA-based participant discloses an SAE to staff, staff will send participants a follow-up survey to ask participants to self-report the details about the reported SAE. If a USA-based participant reports an SAE in their survey responses, they will automatically be presented with additional questions to collect the details of the SAE. This information will then be transcribed into the template SAE form and provided to the site lead for causality assessment. Staff may additionally provide the participant with resources for college, community and emergency services available to them, as appropriate.

As safety data will be entered into the UCLA instance of REDCap, ExeCTU will not have direct access to SAE reports in the database. Therefore, PDF copies of all SAE reports are required to be provided to Exeter Clinical Trials Unit within 24 hours (1 working day) of UCLA team becoming aware of the event.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

Figure 2: Safety reporting flowchart



Footnotes

**'Potentially Yes' are events which are highly likely to be an SAE based on data submitted by participant on REDCap, but direct contact could not be established with the participant to confirm the details.*

***For UK based participants, completion of the SAE form in REDCap qualifies as reporting the event to Exeter CTU. For USA participants, a PDF of the SAE form should be exported and sent to Exeter CTU to form the report.*

****No related SAEs are expected in this trial so these will automatically be categorised as Related Unexpected Serious Adverse Events (RUSAEs).*

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

13. STATISTICS AND DATA ANALYSIS

13.1. Target sample size and justification

To detect a Minimum Clinically Important Difference of Standardized Mean Difference (SMD) (Cohen's d) = 0.20 (i.e., a small effect size below which any effect is unlikely to be an important mechanism or specific ingredient) with 90% power at α=0.05 in main effect of treatment component(s) requires N=1054 (n=527 per level of each factor). Conservatively estimating 52% dropout attrition posttreatment, we require N≈2192 for Analysis of Variance (or equivalent) to test main effects and two-way interactions.Recruitment rates from our prior online trials confirm this target is feasible.

13.2. Planned recruitment rate

2192 participants over 24 months

13.3. Statistical analysis plan

Analysis will be undertaken in line with the factorial trial extension to the CONSORT agreement for the reporting of trials[69]. Primary inferential analyses, using a treatment policy estimand, will compare the main effects across outcomes using multilevel mixed models adjusting for baseline score, first order interactions, and PWP/coach effect (random effect).

The extent of missing data will be considered and where necessary, in agreement with Trial Steering Committee (TSC), imputation methods will be used (led by co-investigator Taylor) to handle missing data whilst minimising bias. These assumptions will further be tested through a sensitivity analyses.

The study statistical analysis plans will be prepared before any formal analyses and reviewed and approved by Data Monitoring and Ethics Committee (DMEC) and TSC. The trial statistician will remain blind to allocation until primary analyses are completed. However, given the complexity of this study and to facilitate communication with the DMEC the senior statistician (Taylor) will be unblinded once the Statistical Analysis Plan (SAP) is approved by the DMEC and TSC and has been signed off with the intention that this is achieved prior to the randomisation of the first participant.

13.3.1. Summary of baseline data and flow of patients.

The baseline data being collected in the study is summarised in the Schedule of Events (Table 3). The eCRF for the collection of the baseline data is available as a separate approved document. The baseline data will be collected after the screening and consent, other than those items listed under the 'eligibility screen' heading which will be collected as part of the screening survey. The measures are detailed fully in separately approved assessment documents for the various timepoints. The flow of patients throughout the study is outlined in Figure 1.

13.3.2. Primary outcome analysis

The primary analysis will investigate the between factors difference change in RNT from baseline to post-treatment (16 weeks).The primary outcome will be reported descriptively (mean and standard deviations (SD)) and inferential comparisons will be reported between the levels of the treatment factors (High versus Low levels in Be specific, Break Habit, Be Kind, Be present) adjusting for the first order interactions.

All analysis will be based on a treatment policy estimand and will include participants with primary outcome data at 16 weeks, we will adjust for the stratification variables (location (UK or USA), caseness or not for anxiety or depression) and if necessary adjust for any significant imbalance in baseline participant characteristics (if there is >1SD difference in mean or >10 percentage points for categorical data and the variable is thought to be predictive of outcome).

Analysis will be using an adjusted multilevel mixed model to investigate the effect of the four treatment factors and their first order interactions.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

13.3.3. Secondary outcome analysis

A range of exploratory secondary analyses will be undertaken including but not limited to those specified below with the full analysis being specified in the statistical analysis plan.

8 Weekly Micro Assessments

In addition to the endpoints at 16 and 52 weeks the study also includes multiple weekly micro assessments in order to assess change in hypothesized mechanisms-of-change over time during the course of therapy (recognising that change often happens in first half of therapy), and thereby, test if (a) manipulated treatment components influence hypothesized mechanisms and/or alternative mechanisms (e.g. does presence of Be Kind increase self-compassion more than absence); (b) track any such change over time; (c) enable a test of mediation across multiple time points and with prospective analysis of whether any changes in process measures predicts change in RNT and mediates the effect of factors on change in RNT.

The micro-assessments will be analysed using a repeated measures analysis of variance to assess change in hypothesized mechanisms-of-change over time during the course of therapy as specified prior.

Analysis of PWP/coach effect

The study is supported by a relatively small number of PWPs (UK) and coaches (US). With the initial number employed expected to be fewer than 10. All PWPs and coaches will also be expected to deliver all intervention arms and the PWP/coach will be selected for the participant prior to randomisation. All steps will be taken to minimise the PWP/coach effect and to ensure that it is balanced across treatment conditions. However, as part of our secondary analysis we will still investigate the PWP/coach effect and its potential for impacting on the outcome.

52 Week follow-up analysis

Where possible we will obtain long-term follow-up (52 weeks) on all participants. Analysis will be analogous to the primary analysis using an adjusted multilevel mixed model to investigate the effect of the four treatment factors and their first order interactions.

13.3.4. Subgroup analyses

Primary and secondary analyses will be extended to explore potential subgroup effects by including additional interaction terms between the factor allocation. The study is powered to detect overall difference between the factors with the inclusions of the first order interactions and therefore insufficiently powered to definitively investigate subgroup analysis. The results may, however, be of exploratory value. Results will be presented using confidence intervals, as well as a global p value for the interaction between the treatment factor and each of our identified sub-groups (adjusted for the first order treatment factor interactions) and they will be interpreted with due caution. Our identified subgroups are:

1. Country (UK, USA)
2. Caseness (as defined by standard thresholds on GAD-7 for anxiety and PHQ-9 for depression)

13.3.5. Adjusted analysis

All analysis will be based on a treatment policy estimand and will include participants with primary outcome data at 16 weeks, we will adjust for the stratification variables (location (UK or USA), caseness or not for anxiety or depression) and if necessary adjust for any significant imbalance in baseline participant characteristics (if there is >1SD difference in mean or >10 percentage points for categorical data and the variable is thought to be predictive of outcome).

13.3.6. Sensitivity analysis

All of the analyses will be presented with appropriate confidence intervals for their parameters and estimates. The inclusions of further sensitivity analyses will be dependent on the assumptions made in

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

the models (e.g. the need for data imputation, inclusion of additional interaction terms) and will be undertaken following agreement from the Trial Steering Committee and where appropriate specified in the statistical analysis plan.

13.4. Interim analysis and criteria for the premature termination of the study

There is no planned interim analysis or criteria for the premature termination of the study based on efficacy. However, the DMEC will receive regular and timely information related to study safety and are at liberty to request analysis of interim data including reporting any concerns to the TSC regarding the continuation of the study.

13.5. Participant analysis population(s)

Analysis will be undertaken on three participant populations:

- All-randomised population: Any participant randomised into the study, regardless of whether they received study treatment (intention-to-treat)
- All-treated population: Any participant randomised into the study that received any amount of study treatment
- Protocol-compliant population: Any participant who was randomised and received the protocol required treatment exposure and required protocol processing

With the primary analysis based on a treatment policy estimand and therefore based on the all-randomised population. The results of the analysis on the all-treatment and protocol compliant populations will be used to provide insight related to the primary analysis.

13.6. Procedure(s) to account for missing or spurious data

The data will be collected and stored to both highlight and minimise the chances of missing or spurious data. Patterns of missing outcome data at follow-up will be extensively investigated. Imputation models will be used to impute missing primary and secondary outcome data and any explanatory variables at all follow-up time points. Results for the between group comparisons based on these imputed data sets will be presented in addition to the primary analysis described. Propensity for missingness and potentially spurious values associated with baseline characteristics will be investigated; imputation models will include treatment allocation as well as stratification variables, baseline variables, and any variables associated with missingness or included in the models as covariates due to baseline imbalance. The potential for introducing bias through the imputation of missing data will be extensively considered and where appropriate highlighted.

13.7. Other statistical considerations.

No formal p-value adjustment will be made for multiple testing; the results of the treatment policy estimand analyses will be interpreted first, and the results of the additional analyses interpreted in this light. The focus of the analysis will be on the four treatment factor comparisons. However, the first order interactions will also be investigated and reported on. Interpretation of results will draw focus on confidence intervals rather than emphasising p-values.

Given the complexity of the study the lead statistician will be unblinded following the sign-off of the statistical analysis plan. However, the primary analyses will be performed by a statistician who remains blinded to group allocation and will be presented as such to the investigators. The results will be discussed and interpreted prior to the unblinding of group allocations. Additional analyses will then be performed following unmasking.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

14. DATA MANAGEMENT

Data management activities are summarised in this section. Detailed data management activities are described in a separate Data Management Plan (DMP).

14.1. Data collection tools and source document identification

Study data will primarily be collected online. The source data will be the eCRFs held in REDCap Academic, the MyDataHelps platform, and the mPath app. All data will be provided directly by the participant with the following exceptions:

- Data reported by a participant over the telephone that is entered into the eCRF by the research team (e.g. in the case that a participant does not complete the questionnaires and receives a reminder phone call from the research team, and the participant opts to complete the questionnaires over the phone).
- SAE report eCRFs will be completed by the PWPs (UK)/coaches (USA)/site leads
- Change of participation status eCRFs will be completed by the research team.
- The participant contact log/appointment log will be completed by the research team/PWPs (UK)/coaches (USA).

A full audit trail will be maintained on REDCap Academic, including the date and time data was first recorded, by whom if the user is a staff user (i.e., not a participant) and a full history of amendments made to the original data. Any data that would ordinarily be participant-reported that was entered into the eCRF by a PWP/coach/researcher will be specified so that the source is clearly distinguishable. For the data entered into the m-Path app an audit trail will be automatically logged of the time that each survey or reminder is sent, received, accessed and completed. The entered data cannot be edited by staff or participants on m-Path once it has been submitted.

This is a decentralised trial, with research sites defined at the country level. Each participating country will hold and be in control of their respective data.

PWPs/coaches will maintain risk logs separate to the REDCap database, but this will not be included as ‘research data’.

Data collected as part of qualitative interviews with participants will be audio-recorded via Teams or Zoom, or using an encrypted GDPR-compliant audio-recording device. Audio-recordings will be the source of the interview-generated data and will be stored until interview analysis is complete. Audio-recordings will be transcribed into Word documents by a third-party transcription service.

USA-specific detail

Only USA-based participants and coaches/members of the research team based at UCLA will be able to enter data into the USA instance of REDCap Academic. Researchers/PWPs at the lead site in the UK will not have access to the USA instance of REDCap Academic.

14.2. Data handling and record keeping

A full data management plan (DMP) will be implemented for the study. The DMP can be viewed upon request to the Sponsor (Research Ethics, Governance & Compliance Office, University of Exeter). An

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

international data sharing agreement will be in place for the study to facilitate the sharing of data between University of Exeter (UK), UCLA (USA) and LMU (Germany).

EMA and micro-assessment data from m-Path will be transferred to ExeCTU at least 6-monthly and stored securely on a SharePoint site with restricted access. LMU will report completion data to ExeCTU at least monthly to facilitate the sending of reminders, production of oversight reports and payment of participants for completion of activities.

The research team at UCLA will provide regular (approximately monthly) pseudonymised exports of both completion data from MyDataHelps and data from their instance of REDCap to the research team at ExeCTU for the purpose of reporting to oversight committees. These exports will not contain any personal identifiable data and will be transferred to ExeCTU via a SharePoint site, managed by ExeCTU, with access restricted to the study team.

14.3. Access to Data

Participants will be granted access to enter their data using REDCap surveys. They will not have user access to REDCap and will not be able to log in to view, amend or delete previously submitted data. Participants will be able to view and delete their previously submitted data collected via the m-Path app, but will not be able to amend data in m-Path once submitted. Participants will set up a user account on MyDataHelps which they will be able to access for the duration of their intervention period.

User access to REDCap will be restricted to staff members working on the study with a genuine business need. User permissions will be set as appropriate for the individuals role on the study. ‘Read Only’ access will be granted to representatives of the Sponsor research governance team and regulatory bodies upon request for audit and inspection purposes, in line with participant consent.

LMU will have access to the pseudonymised data collected in mPath. Secure transfer of data from mPath to ExeCTU for the purposes of study monitoring and reporting will be made at least 6-monthly.

Participants personal email address will be communicated to MyDataHelps which is managed by UCLA and hosted on a server in the USA. This is for the purpose of setting up their user account to access the intervention. During account set up on MyDataHelps participants will be given the option to volunteer their name and phone number for the purpose of receiving personalised messages from the platform directly related to their completing the intervention.

PWPs/coaches may have ‘read-only’ accounts on m-Path and MyDataHelps to view completion data for their respective participants (UK/USA) if required for appointments.

Qualitative research data collected as part of the interviews for the process evaluation will be stored on a restricted SharePoint site hosted by the University of Exeter, with access granted to authorised members of the research team who need to collect, review or analyse the qualitative data. This will include the original audio-recordings and the pseudonymised transcribed documents. Access to the pseudonymised transcribed documents and pseudonymised quantitative data will be provided to the lead process evaluation researcher at the University of Southampton.

The SMS text messaging service provider will receive the participant’s telephone number and the wording for the follow-up and reminder text messages. Their text messaging data centre is located in the United States. Participants do not have to respond to any text messages so no data will be sent

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

back via the SMS service provider. No other identifiable information will be shared with the SMS service provider. By linking directly into REDCap, REDCap will be used to store logs and records of communications with participants and the SMS service provider will delete their logs and not hold data after it has been fed back into REDCap.

USA-specific detail

In the USA, to enable day-to-day management and monitoring of the study, members of the research team at UCLA (coaches) and members of the study team responsible for coordinating the study locally will have access to the US REDCap instance, with permissions set as appropriate for their role. The local lead investigator will have data entry access to SAE report forms. Access will not be granted to the Sponsor for audit and inspection due to institutional limitations on external accesses, however, pseudonymised data exports will be regularly transferred to ExeCTU and can be monitored by the Sponsor if required.

LMU will notify the research team at UCLA of completion status for participants in relation to EMA and the weekly micro-assessments to facilitate the sending of reminders and voucher payments for those participants. This summary data will be transferred to UCLA via a SharePoint site, managed by ExeCTU, with access restricted to the study team.

14.4. Archiving

The TMF and complete dataset will be prepared by Exeter Clinical Trials Unit and provided to the Sponsor for archiving. Study documents will be archived for 10 years after the end of the study. After 10 years, all personal identifiable data will be securely destroyed upon authorisation from the Sponsor. The anonymised dataset will be stored indefinitely for the purposes of future research and made available on an open access database.

USA-specific detail

UCLA will be responsible for archiving their instance of REDCap Academic in line with their institutional policy. Copies of all essential documents will be provided to ExeCTU for preparation and collation, prior to final archiving by the Sponsor. Data collected in the USA will be archived locally for an indefinite period in line with approval from the local UCLA IRB.

15. MONITORING, AUDIT & INSPECTION

A detailed monitoring plan will be agreed between the Chief Investigator, Exeter Clinical Trials Unit, UCLA and the Sponsor. The monitoring plan will be based on the risk assessment that will be reviewed periodically and in response to amendments to the study protocol.

Monitoring will be conducted by a combination of remote and central monitoring, led by the Exeter Clinical Trials Unit. A regular report will be compiled and circulated to the TMG for the purposes of their oversight of the study.

The Sponsor and/or regulatory authorities may audit or inspect any aspect of the study at any time during the study.

A DMEC and TSC will review data completeness, data quality and accumulating safety data at agreed intervals throughout the study. The DMEC will view unblinded disaggregated data.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

A postdoctoral research fellow at LMU will monitor the completeness of the mPath data and provide the teams at UCLA/ExeCTU regular reports of their participants (identified by unique invitation codes (as a proxy for participant ID (PID) number)) including: a list of participants signed up to the app, the date the first prompt was sent to each participant and summary data to indicate completion rates at various stages of the EMA process. The reports will be used to send reminders/status updates to participants about their progress with the prompts, and to update REDCap that a participant has either met the threshold for randomisation or has not met the threshold and will not proceed with randomisation. LMU will also provide regular reports on the number and proportion of weekly mediator surveys that are due, partially completed, fully completed or fully incomplete after the relevant time window has closed. Data from mPath will be securely transferred to the University of Exeter and UCLA using a SharePoint site managed by ExeCTU.

The team at UCLA will provide approximately monthly pseudonymised exports of completion data from MyDataHelps to the research team at ExeCTU for the purpose of reporting to oversight committees. These data will be securely transferred to the University of Exeter using a SharePoint site managed by ExeCTU.

A copy of the monitoring plan and risk assessment is available upon request to Exeter Clinical Trials Unit.

USA-specific detail

As the Sponsor and the trial management team at University of Exeter will not have direct access to the REDCap instance at UCLA, deidentified data exports will be provided to ExeCTU on a monthly basis. ExeCTU staff will also be able to access a summary data dashboard for the UCLA REDCap that will provide details of the numbers and proportions (where applicable) of screened, recruited, randomised and withdrawn participants as well as an overview of data completeness (including numbers due to complete follow-up, percentage completed, incomplete and window still open, incomplete and window closed) at each time point. The site lead at UCLA will be responsible for ensuring appropriate monitoring of research activities in the USA and the delegation of monitoring duties within the local trial management team.

16. PUBLIC AND PATIENT INVOLVEMENT

Our Lived Experience Advisory Panel (LEAP) (described in detail in Section vii) are formed of a diverse membership of experts-by-experience. Experts-by-experience will be involved at all stages of the study, from proposal development through to study design, delivery, oversight (through membership of the TMG) and dissemination. The LEAP is supported by a postdoctoral research fellow at the University of Exeter.

People with lived experience identified RNT as an essential therapeutic target for anxiety and depression in Wellcome Trust Active Ingredient reports[8].

The study is acceptable from the perspective of experts-by-experience. During the development of the funding proposal, the research design, recruitment and methodology were reviewed with five members of Exeter clinical Lived Experience Group and a lived experience collaborator was actively involved in developing the funding proposal. Further, for the intervention design, the final selection of mechanisms to test was co-developed with our LEAP.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

All experts-by-experience who contribute to the study will be appropriately reimbursed for their involvement.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. Research Ethics Committee (REC) review

Before commencing the study, approval of the protocol and participant-facing materials will be obtained from an NHS research ethics committee (REC) and the Health Research Authority (HRA), as required. Amendments to the study documents will also be submitted the REC and HRA for approval, as required. Evidence of all support, approvals and significant correspondence will be filed in the trial master file (TMF).

The Chief Investigator will notify the REC of the end of the study, or the premature termination of the study if applicable, using the appropriate declaration form. Within one year of the end of the study, the Chief Investigator will submit a summary report to the REC using the appropriate form. The Chief Investigator may delegate these responsibilities to ExeCTU to complete under the oversight of the Chief Investigator.

USA-specific detail

In the USA, the study and all subsequent amendments will be approved by the Institutional Review Board (IRB) of the participating organisation (UCLA Medical School). Participant materials provided by University of Exeter will be adapted to be specific to the USA and will be submitted to the UCLA IRB. The research team at UCLA will also produce their own participant recruitment materials where relevant such as recruitment emails and banners for students.

17.2. Confidentiality Advisory Group (CAG) review

The study will potentially involve inviting people to participate through NHS DigiTrials (dependent on costs and their approval to support the study). If NHS DigiTrials is agreed to be used, support will be sought from the Confidentiality Advisory Group (CAG) under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 (also known as section 251 of the National Health Service Act 2006).

17.3. Peer review

The study has been extensively independently peer-reviewed as part of the competitive funding application made to the Wellcome Trust. The Sponsor, University of Exeter, have also reviewed the study as part of the exercise to support the funding bid and act as Sponsor for the study. The protocol will also be reviewed by the TSC prior to starting the study.

17.4. Regulatory Compliance

This study will adhere to the UK Policy Framework for Health and Social Care Research, and follow guidance set out by the HRA and the Sponsor.

USA-specific detail

Relevant legislation in the USA will be adhered to for all study activities conducted in the USA. UCLA has established policies, including Policy 991, to assure full compliance with all federal regulations,

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

state laws, and University of California policies governing the participation of Human Subjects in Research. The Office of Human Research Protection Program (OHRPP) ensures the safety and welfare of research participants in human research conducted at UCLA. All research activities at UCLA will be reviewed by the OHRPP, and research operations and analysis will adhere to relevant regulations.

17.5. Protocol compliance

The study will be monitored to check for compliance with the protocol using remote and central monitoring methods. Non-compliances may also be detected through ad-hoc interactions with participants and study staff.

Non-compliances are classified as follows:

- Deviation: A change or departure from the approved trial protocol, other key trial documents, GCP and/or applicable regulatory requirements that is not likely to affect the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.
- Violation: Failure to comply with the approved trial protocol, other key trial documents, GCP and/or regulatory requirements which has the potential to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.
- Serious Breach: A non-compliance that is likely to affect to a significant degree the safety or physical or mental integrity or rights of the trial participants, or the scientific value of the trial.

The majority of the data collected is participant-reported data. Non-compliance with the protocol as a direct result of participant non-engagement (e.g. a participant not completing some or all of their questionnaires) will not be reported as a non-compliance but the number and proportion of incomplete questionnaires will be summarised as aggregate data and monitored by the TMG and oversight committees.

Examples of non-compliances which will require a non-compliance report will include (but are not limited to):

- Failure to randomise an eligible, consenting participant who completes all required baseline data (meeting the randomisation criteria) for any reason other than participant withdrawal
- from the study.
- Technical failure to communicate randomisation from REDCap to MyDataHelps.
- Participant gaining access on MyDataHelps to a variant of CBT components that differs to that which they were randomised to.
- Failure to comply with safety reporting processes as specified in Section 12.
- Entry of personally identifiable data into REDCap by a member of the study team outside the designated contact details fields. For example, including identifiable information in an SAE report form would constitute non-compliance. Correcting contact information that a participant has already provided in relevant contact details fields is allowed.

Non-compliances will be recorded/reported via a report form within REDCap. A monthly report will be produced for the TMG and the Sponsor representative including aggregate summary data on participant screening, consent, randomisation, intervention delivery, follow-up completeness and safety. The report will include summary tables of non-compliances.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

A detailed monitoring plan will be written for the study.

USA-specific detail

As the Sponsor organisation will not have real time access to data collected in the USA, responsibility for monitoring and reporting non-compliances (referred to locally as deviations) for participants in the USA will be the responsibility of the research team at UCLA. UCLA will follow institutional guidelines for reporting to their IRB - UCLA IRB requires the reporting of only those non-compliances (referred to locally as deviations) which pose increased risk to subjects or others, or are deemed to significantly, adversely impact the rights or welfare of participants or the integrity of the data. The study team will be responsible for monitoring participant completion rates, contacting participants who are missing data, and ensuring data completion.

Non-compliances should also be recorded in a report form on REDCap.

17.6. Notification of Serious Breaches to GCP and/or the protocol

When a non-compliance is reported to ExeCTU, the Trial Manager will review the event in the first instance and where required obtain input from or escalate to the CTU's Quality Assurance Manager in accordance with ExeCTU SOP_019_TM Non-Compliance, Serious Breach Reporting and Research Misconduct. If there is the potential for the event to be a serious breach, the report will be forwarded by ExeCTU to the Sponsor. The Sponsor will be responsible for deciding if the non-compliance meets the criteria of a serious breach. In the event of a serious breach, the Sponsor will report the event to the REC within 7 days of ExeCTU becoming aware of the event, and if applicable other relevant approval bodies. The Chief Investigator, with support from ExeCTU, will report the serious breach to the TSC and DMEC as outlined in their respective charters.

USA-specific detail

Serious breaches occurring in the USA will be subject to reporting to their local regulatory authorities. The lead investigator at UCLA will be responsible for ensuring appropriate management of serious breaches.

17.7. Data protection and patient confidentiality

This study will be conducted in a way that protects the rights and dignity of the participants. Throughout the study (e.g. in oversight reports) and at the end of the study (e.g. when reporting the results), data will be reported anonymously so that it will not be possible to identify any individual taking part.

Each participant will be assigned a unique ID number (participant ID number (PID)) automatically generated by REDCap upon initiation of screening. Consented participants will also be issued two unique invitation codes to access to the mPath app (one after consent, and one after randomisation). The invitation codes will be used to monitor participants use of the app.

Personal identifiable data will be collected for the purposes of contacting participants and will only be accessible to authorised members of the research team (via REDCap academic). Personal data will only be used for reasons relevant to the research as outlined in the participant information sheets and will be stored for 10 years after the end of the study before being destroyed.

Participants personal email address will be communicated to MyDataHelps which is hosted on a server in the USA for the purposes of setting up their user account to access the intervention. During

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

account set up on MyDataHelps participants will be given the option to volunteer their name and phone number for the purpose of receiving personalised messages from the platform directly related to their completing the intervention. An international data sharing agreement between University of Exeter and UCLA will cover the data transfer. Pseudonymised MyDataHelps completion data will be securely transferred to the University of Exeter using a SharePoint site hosted by University of Exeter. Personal identifiable data of UK participants will be removed from MyDataHelps at the end of the study, the process for this will be detailed in the Data Management Plan.

Data collected via the mPath app will not contain personal identifiable data and cannot be linked back to an individual without access to the participants REDCap record, access to which will be limited to people with a legitimate need for their role. ExeCTU and UCLA will be able to link mPath data back to their participants by linking their invitation codes to their PID. Third parties who only have access to mPath, but not REDCap, will not be able to identify individual participants. Data from mPath will be securely transferred to the University of Exeter using a SharePoint site hosted by University of Exeter.

Data will be managed by the UKCRC registered Exeter Clinical Trials Unit (ExeCTU) in accordance with data protection legislation, which includes the UK Data Protection Act 2018, the General Data Protection Regulation (UK GDPR) 2018, and Data (Use and Access) Act 2025. Access to the EDC system (REDCap Academic) web interface will be over Hyper Text Transfer Protocol Secure (HTTPS) / Transport Layer Security (TLS) version 1.2 as a minimum and it will be ensured that web traffic to and from the REDCap server is encrypted. University of Exeter will host REDCap Academic in Amazon Webservices (AWS). Amazon Relational Database Service (RDS) will be encrypted. Amazon RDS encrypted database instances use the industry standard AES-256 encryption algorithm to encrypt the data on the server that hosts the Amazon RDS database instances. The AWS global infrastructure is designed and managed according to security best practices as well as a variety of security compliance standards. AWS provides on-demand access to security and compliance reports and select online agreements through AWS Artefact. Standards include ISO 27001 and ISO 9001.

Audio-recordings of interviews will be initially stored on an encrypted audio recorder or as a Teams video/audio file and then transferred to a secure area on University of Exeter servers accessible only to authorised members or the research team. Voice recorders will be stored in a secure place (locked cupboard/drawer and within a locked office when researcher not present). Recordings on a voice recorder will be uploaded to a secure university of Exeter folder at the earliest opportunity and, once checked, files will be deleted from the recorder. A third party transcription service will be used to transcribe the audio-recordings. A data sharing and confidentiality agreement will be put in place between the transcription service provider and the University of Exeter. Audio and transcription files will be transferred between the University of Exeter and the transcription company via secure file transfer, and transcriptions returned will be pseudonymised by removing details such as names of individuals and saved on a secure University of Exeter server. Quotes used in the reporting of findings will not contain any information that would identify an individual.

The data controller for the study is the Sponsor, the University of Exeter.

USA-specific detail

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

UCLA will host a separate instance of REDCap Academic on an AWS hosted in the USA. University of Exeter will not have direct access to the UCLA REDCap instance and will not receive any participant identifiable information on participants recruited in the USA. De-identified REDCap data will be transferred to University of Exeter via a SharePoint site, managed by ExeCTU, with access restricted to the study team. The final merged dataset will only be accessible to authorised members of the study team at University of Exeter.

All research activities conducted by investigators at UCLA will follow policies of the UCLA Office of the Human Research Protection Program (OHRPP) regarding protection of privacy, confidentiality, and data security.

All study personnel are required to have up-to-date training in Human Subjects Research and the Health Insurance Portability and Accountability Act (HIPAA), and all studies with direct access to participants or access to identifying information in the research database are listed on the site IRB. All study personnel are required to comply with policies of the UCLA OHRPP regarding protection of privacy, confidentiality, and data security.

Prospective participants are directed to a study website, where they can first complete online screening to determine initial eligibility. Individuals who are eligible to participate, based on the online screening, will be asked to provide signed consent using the REDCap eConsent framework. UCLA will host a separate instance of REDCap Academic on an AWS hosted in the USA.

After signing consent, data are collected electronically through REDCap, through an application installed on the participant's phone called MyDataHelps, and through an application installed on the participant's phone called m-Path.

Each participant will be assigned a unique coded identifier when they are enrolled in the study by the online registration system. Only this coded identification number will be associated with the participant's data. Personally identifying information will be maintained in the UCLA participant database and REDCap, both of which are in secure environments overseen by the UCLA Health Information Technology Security team. Study databases have strict security provisions, including but not limited to multiple firewalls, separate servers, and data encryption protocols.

Data collected through the MyDataHelps app are collected under the participant's unique coded identifier. UCLA personnel meeting requirements listed above have access to the study dashboard on servers hosting MyDataHelps, and information about participant engagement in the MyDataHelps app (under the participant's coded identifier) are automatically transferred from the app platform to REDCap via secure data transfer workflow.

Data from mPath will not contain any personal identifiable data and will be securely transferred to UCLA using a SharePoint site hosted by University of Exeter.

University of Exeter will not have direct access to the UCLA REDCap instance and will not receive any participant identifiable information on participants recruited in the USA. Exports are constructed from the REDCap database to ensure inclusion of only de-identified fields. The data will be archived electronically and maintained in a secure environment.

Only de-identified data will be shared with study collaborators. De-identified REDCap data will be transferred to University of Exeter via a SharePoint site, managed by ExeCTU, with access restricted to the study team. The final merged dataset will only be accessible to authorised members of the

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study team at University of Exeter. This data transfer workflow will be reviewed and approved prior to study launch by the UCLA Health Information Technology Security team.

The study Project Director is responsible for ensuring that the infrastructure to support data collection and storage follows policies of the UCLA OHRPP regarding protection of privacy, confidentiality, and data security; and for ensuring transfer of de-identified data only to the Exeter team. The study Project Manager is responsible for managing the IRB application and ensuring all study personnel are compliant with trainings, and are listed on the IRB. The UCLA Depression Grand Challenge (DGC) research team is responsible for overseeing long-term data storage.

17.8. Financial and other competing interests

The chief investigator and other collaborating investigators do not have any competing interests. Members of the TSC and DMEC will complete conflict of interest forms declaring any competing interests. Copies of all completed forms will be filed in the TMF.

17.9. Indemnity

The University of Exeter as Sponsor of the study has insurance in place to cover legal liabilities arising from the management, conduct, and design of the research. The University of Exeter holds clinical trial insurance to provide for the payment of compensation to research participants arising from injury or illness arising from the clinical trial where there is no legal liability. If an injury arises as a result of how the study has been set up, insurance cover is provided by the University of Exeter's clinical trials policy on a non-negligence basis.

USA-specific detail

Participants from Imperial Valley will be informed via the informed consent process that they should notify the UCLA study team if they believe they have been injured because of taking part in the study, as UCLA will provide the necessary medical treatment. The cost of treatment may be covered by the University of California, or billed to the participant's insurance, depending on a number of factors. UCLA do not normally provide any other form of compensation for injury. Contact information for the UCLA OHRPP will be provided in the US version of the consent form.

17.10. Amendments

Amendments to the study protocol and/or study documents will be made as required throughout the study. ExeCTU will be responsible for preparing, submitting and distributing amendments upon request of the Chief Investigator. All substantial amendments and relevant non-substantial amendments will be discussed by the TMG and with the LEAP if appropriate. The Chief Investigator will be responsible for the final decision on making an amendment to the protocol. The approval of the TSC will be sought for substantial amendments to the protocol in advance of submitting to the REC and/or HRA, and if necessary, a meeting of the TSC will be convened to discuss the amendment. The funder representative will be notified of relevant substantial amendments in advance of submission, and a full list of all substantial and non-substantial amendments will be provided as part of routine funder reports.

The Sponsor will decide if an amendment is substantial or non-substantial following HRA guidance.

All amendments will be submitted to the NHS REC that issued a favourable opinion (if appropriate) and/or the HRA following the appropriate HRA amendment process in place at the time of submission.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

Amendments will be reviewed by the relevant approval bodies as determined by the HRA Amendment Tool. This may include the HRA, NHS REC and the Confidentiality Advisory Group (CAG), depending on the nature of the amendment. An amendment will not be implemented until all necessary approvals are in place.

As the study will not involve individual participating sites, amendments will be implemented upon receipt of all relevant approvals.

The Chief Investigator or delegate will inform the study registry of changes to the study.

An amendment log will be maintained by ExeCTU and filed in the TMF. The protocol version history will be recorded in the protocol. A document version control list will be maintained throughout the study.

If any updates are required to the MyDataHelps platform these will all be documented with a log of changes and the reason for the changes. Beyond this, any changes will be categorised and handled in the following ways:

1) Bug fixes (e.g. changes to manage operating system updates or technical problems that do not change interface or functionality) require no action other than documentation.
2) Changes to manage usability problems will be reported to oversight committees via routine reports.
3) Changes that may potentially impact the content of the intervention itself/framing of psychological strategies will be reported to the TMG and TSC for review prior to implementation.

USA-specific detail

University of Exeter will provide all amended documents to the research team at UCLA (USA) to submit for local UCLA IRB approval. Copies of all amendment approvals from UCLA will be sent to the University of Exeter and filed in the TMF.

17.11. Post trial care

Participants will not receive medical treatment (e.g., medicine, surgery, radiotherapy) as part of this study. There are no plans for post-study care. Participants will be signposted to relevant resources where they can continue to seek support, but no further support will be provided by the research team once a participant has exited the study.

17.12. Access to the final study dataset

Prior to publication, only researchers at the University of Exeter will have access to the full dataset. Once published, we will store anonymised research data and outputs in the University of Exeter Open Research Exeter repository (https://ore.exeter.ac.uk/repository/) or another approved public repository (e.g. Datamind) to facilitate open access to, and increase the impact of, our research. Each dataset will be issued a unique and persistent DOI to link with associated publications. Anonymised data will be made available under a Creative Commons CC0 licence, ensuring appropriate future use.

Docusign Envelope ID: 5EECCA47-2E4B-4731-B470-822D237434DC

18. DISSEMINATION POLICY

18.1. Dissemination policy

University of Exeter will be the data controller for the study and will hold the final dataset. The results of the study will be disseminated regardless of outcome. We aim to publish the findings in peer reviewed journals and via presentations at local, national and international meetings. We aim to publish the primary results in an open access journal within 24 months of study completion. Outcome papers will adhere to the relevant CONSORT guidelines. We will work with our LEAP to provide a lay-accessible summary of the results to all study participants who opt to receive them. Participants will not be provided with copies of their individual data or results.

Once published, the study results will also be available on the study website and be promoted via our social media channels.

The results will be posted on the publicly available registry (ISRCTN). A summary of the results will be submitted to the REC within 12 months of the end of the study in line with HRA guidelines.

The study protocol will be published in a peer-reviewed journal before the end of the recruitment stage and will be made publicly available through the ISRCTN registry.

18.2. Authorship eligibility guidelines and any intended use of professional writers

Authorship on relevant publications will be offered in line with The International Committee of Medical Journal Editors guidance. This will include contributors to study development (e.g. grant funding, protocol development, managing the LEAP), running the study (e.g. recruiting and supporting participants, being a lead investigator, collecting data) and other aspects of study design/analysis (e.g. statistical and methodological work).

The study team do not plan to engage the use of professional writers for this study.

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