Clinical Investigation Plan (CIP)

Clinical investigation title:	RELAX – REducing Levels of AnXiety - in pregnancy and after birth. A study to see if a new online training (RELAX) can reduce anxiety in pregnant women and new mothers
Reference no.:	307468
CIP version no.:	1.8

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Revision History

Date	Revision Description
11.11.2022	Release of Initial document as Version 1.0
20.01.2023	Release of updated document as Version 1.1
02.02.2023	Release of updated document as Version 1.2 1. Updates to 8.1.4, primary and secondary endpoints added detail 2. Section added regarding missing data
09.02.2023	Release of updated document as Version 1.3

	1. Updates to standards of compliance listed in section 13 2. Updates to Figure 4 (section 16.4), timeframes added for each stage in figure
17.02.2023	Release of updated document as Version 1.4 1. Updates to section 16.1, added definition for device deficiency 2. Updates to reporting timeframes in sections 16.4 (including figure 4) and 16.8
05.04.2023	Release of updated document as Version 1.5 1. Updates to section 2 to reflect up-to-date titles, job roles and contact details of co-investigators 2. Correction of typographical error in exclusion criterion regarding multiple miscarriages in sections 3 and 8.3.2 3. Updates to section 8.2, minor wording changes have been made to the definition of usual care. Figure 1 (section 3.1) has also been updated to reflect these changes 4. Addition of internal pilot section (section 8.4.9) 5. Updates to section 9.2 to include information about sensitivity analyses and correct typographical errors under "missing data" section 6. Updates to Figure 3 (section 10) to reflect change in preferred transcription service supplier 7. Further updates to reporting timeframes in section 16.4 (including Figure 4)
23.05.2023	Release of updated document as Version 1.6 1. Updates to sections 8.4.5, 8.4.7 and 8.4.8 to include more details about the questions asked at follow-up assessments
22.08.2023	Release of updated document as Version 1.7 1. Updates to sponsor details and insertion of REC reference number in section 3 2. Updates to section 3.1, yellow highlights in flowchart showing tracked changes from previous versions removed 3. Updates to section 6.3 to clarify when risks will be escalated to adverse events status. Clarified that in situations of high risk, the GP/midwifery team will be contacted and GPs will be urged to refer women to perinatal mental health services for urgent assessment if necessary 4. Updates to section 8.4.1 to indicate that posters and leaflets may be placed in additional NHS sites and GP practices located across the United Kingdom 5. Updates to section 8.4.6 to indicate that we will aim to conduct semi-structured intervention follow-up interviews within two weeks of completion of T1
28.09.2023	Release of updated document as Version 1.8: 1. Updates to sections 3 and 8.3.1 to reflect change in inclusion criteria in terms of the cut-off score for inclusion based on the RTQ-10 (trait) 2. Updates to section 8.4.1 to clarify that verbal consent to be contacted by the research team (i.e., members outside of the direct care team) will be obtained when approaching women about the study following screening of electronic health records. This section has also been updated to include the addition of a

	Participant Identification Centre (GP surgeries in South London) as a recruitment strategy 3. Updates to wording in section 8.4.2 to allow for more flexibility in terms of the methods of contact used when following-up on invitations to the study outline call at the screening stage 4. Updates to section 8.4.6 to remove specification of the number of post-intervention semi-structured follow-up interviews that will be conducted 5. Section 19 has been updated to include references for the new RTQ-10 cut-off score for inclusion into the study at screening.

Table of Contents

1 Sponsor Details

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2 Investigators, Trial Statistician and Sites

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3 Investigation Synopsis

Short title:	RELAX – REducing Levels of AnXiety - in pregnancy and after birth. A study to see if a new online training (RELAX) can reduce anxiety in pregnant women and new mothers

Full Title:	A randomised controlled trial of a web-based early intervention (RELAX) targeting repetitive negative thinking (RNT) in pregnant women: an evaluation of its impact on perinatal anxiety and the mechanism of change
IRAS ID:	307468
REC Reference:	22/WM/0273
Device:	REducing Levels of AnXiety (RELAX)
Phase of trial:	Phase 2b
Primary Objective(s):	1. The primary clinical objective is to assess whether at-risk pregnant women who complete RELAX alongside receiving usual care (UC) experience less anxiety **before** birth than at-risk pregnant women who only receive usual care. 2. The primary mechanistic objective is to determine whether interpretation bias is the mechanism of action of the RNT targeted intervention.
Secondary objective (s):	To investigate whether, in comparison to pregnant women who only receive usual care, those who complete RELAX alongside receiving usual care have i) less anxiety **after** birth ii) lower levels of repetitive negative thinking, less general depression, lower levels of trait worry, less perinatal specific anxiety and depression, and better work and social functioning **before and after** birth. Further secondary objectives are to investigate whether there is any difference in RELAX versus usual care effects on anxiety at T2 by baseline anxiety levels, pregnancy complications and pre-existing health conditions.
Type of trial:	A phase 2b, two-arm, parallel group, multi-site randomised controlled trial in pregnant women (16-28 weeks gestation).
Trial design and methods:	Pregnant women (16-28 weeks gestation) with high levels of RNT and up to a moderate level of anxiety will be randomly allocated to complete RELAX (which consists of 12 web-based Cognitive Bias Modification for Interpretation (CBM-I) training sessions that are completed over a period of 4 weeks) alongside

	receiving usual care or only receive usual care. Randomisation will be stratified by recruitment site, parity, and pregnancy complications. There are 4 assessments yoked to randomisation: baseline pre-randomisation (T0; 16-28 weeks gestation); 4 weeks post-randomisation (T1; end of intervention for active arm; 20-32 weeks gestation); 8 weeks post-randomisation (T2; 24-36 weeks gestation), and 36 weeks post-randomisation (T3; 12-24 weeks post-birth).
Follow-ups:	There are 3 follow-ups: T1 (4 weeks post-randomisation; 20-32 weeks gestation); T2 (8 weeks post-randomisation; 24-36 weeks gestation); and T3 (36 weeks post-randomisation; 12-24 weeks post-birth)
Endpoints:	Primary clinical endpoint: T2 anxiety (measured by the Generalised Anxiety Disorder Questionnaire (GAD-7)). Primary mechanistic endpoint: interpretation bias measured by the Recognition Test (RT) at T1. Secondary clinical endpoints: T3 anxiety (measured by the GAD-7), T2 and T3 depression, RNT, perinatal depression, perinatal anxiety, trait worry, and work and social functioning (measured by the Patient Health Questionnaire (PHQ-9), Repetitive Thinking Questionnaire (RTQ-10 (trait)), Edinburgh Postnatal Depression Scale (EPDS), Perinatal Anxiety Screening Scale (PASS), Penn State Worry Questionnaire (PSWQ), and Work and Social Adjustment Scale (WSAS) respectively).
Trial duration per participant:	9 months
Estimated total trial duration:	February 2022 -July 2025
Planned trial sites:	Multi-site trial with 3 sites - 2 NHS sites (Guy's and St Thomas' (GSTT) and King's College Hospital (KCH)) + King's College London (KCL; where participants will be recruited via non-NHS routes)
Total number of participants planned:	268 participants (134 participants per arm)

Main inclusion/exclusion criteria:	Main inclusion criteria: ● Pregnant women between 16-28 weeks gestation ● Aged 18 years or older ● Based in the United Kingdom ● High levels of RNT (RTQ-10 (trait) ≥ 28) ● Up to only a moderate level of anxiety (GAD-7<15) ● Able to understand oral and written English ● Normal or corrected-to-normal hearing and vision ● Ability to access the internet on a PC, laptop, or tablet ● Provision of an email address and phone number for contact with the team Main Exclusion criteria: ● Current psychiatric disorder ● Past diagnosis of a psychotic disorder, bipolar disorder, an eating disorder, a substance use disorder and/or a personality disorder ● Current or recent history of risk: current suicidal intent, suicide attempt <2 years and/or self-harm <1 year ● History of stillbirth, neonatal-death, or multiple miscarriages (i.e., ≥3) ● Current participation in another study that is investigating a treatment for a mental health problem ● Not registered with a GP in the UK
Statistical methodology and analysis:	The primary analysis will investigate the effect of the intervention on the primary outcome of T2 anxiety (measured by GAD-7 at 8 weeks post-randomisation; 24-36 weeks gestation). This effect will be estimated according to intention-to-treat (ITT) principles using linear mixed effects models. The most important secondary analysis will be a complier average causal effect estimate (CACE) of the effect of the intervention in the population of compliers as compared to those who would have complied in the control intervention. The remaining continuous secondary outcomes will use similar methods to the primary outcome analysis. Three additional non-powered subgroup analyses will be conducted. One will investigate moderation of the treatment effect by baseline T0 anxiety levels on GAD-7 scores at T2 (8 weeks post-randomisation). We will also conduct subgroup analyses by pregnancy complications (yes/no) and pre-existing conditions (yes/no). Subgroup analyses will be done by adding intervention by time by subgroup variable of interest interactions terms to the main analysis models for the primary anxiety outcome at T2. If these

	interaction terms are statistically significant with respect to the subgroup variable, we will present RELAX versus UC estimates by subgroup levels. Furthermore, we will assess the effect of the intervention on interpretation bias (hypothesised mechanism) and mediation of the intervention effect on anxiety (GAD-7) via interpretation bias (RT) using structural equation modelling (SEM) and full information maximum likelihood estimation. We will also assess intervention acceptability (experimental arm) by analysing semi-structured telephone interviews (20 people at T2 selected by age (<30 vs >30), site (KCH vs GSTT vs KCL) and rates of adherence to RELAX sessions (0 sessions vs 1-9 sessions vs $\geq$ 10 sessions). Transcribed interviews will be analysed using Thematic Analysis (Maguire & Delahunt, 2017).

3.1 Flowchart

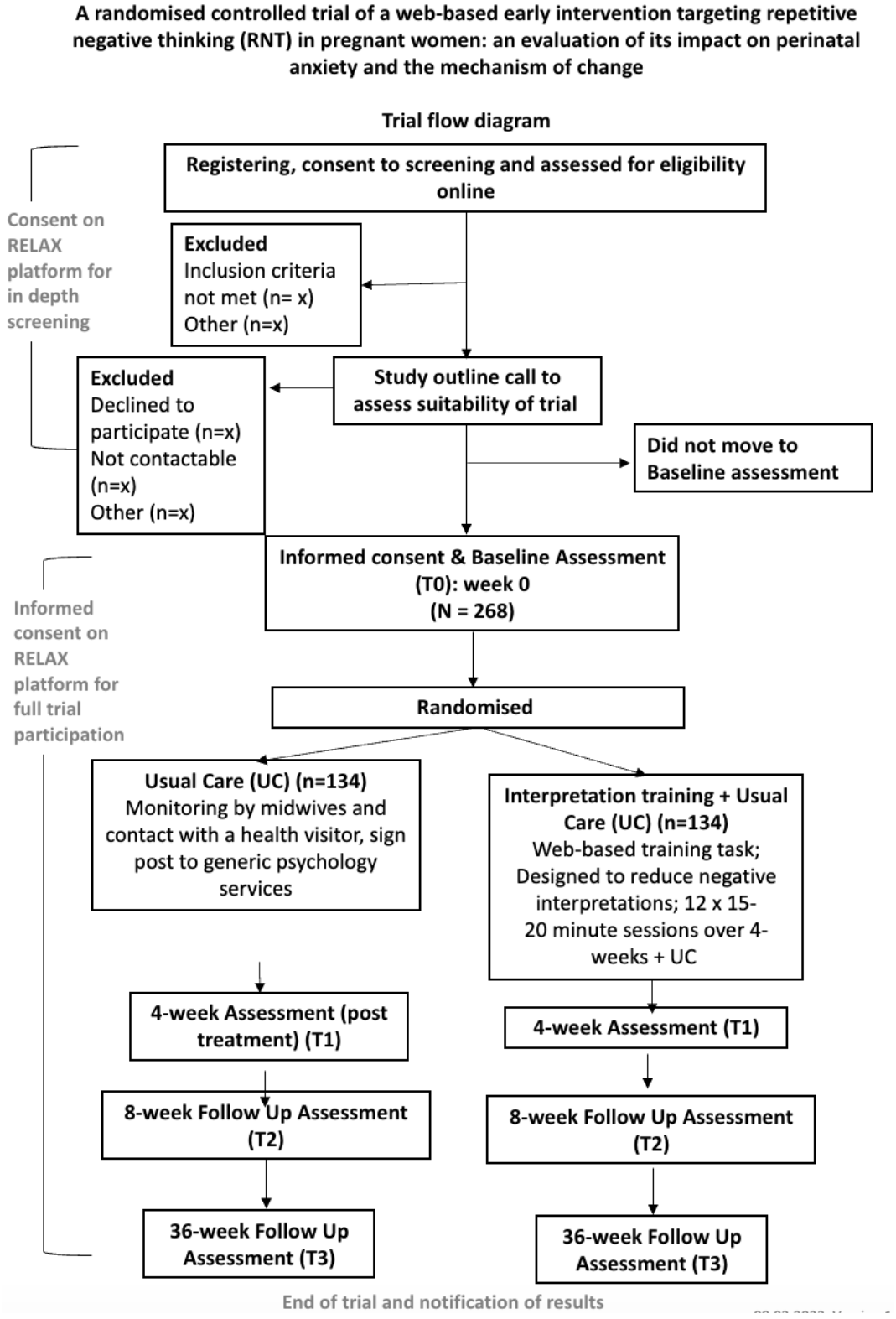

Figure 1. Trial flow diagram

4 Investigational Device

4.1 Summary description

The investigational device is a software medical device (a non-invasive digital therapeutic) that can be accessed online via the REducing Levels of AnXiety (RELAX) platform. The platform hosts a web-based early intervention for perinatal anxiety, RELAX.

RELAX is a Cognitive Bias Modification for Interpretation (CBM-I) intervention. Its purpose is to enable pregnant women with high levels of repetitive negative thinking (RNT), and low to moderate anxiety, to interpret uncertain/ambiguous information in realistic and more positive ways. This should lead to lower levels of anxiety during the perinatal period, compared to women not using RELAX.

RELAX comprises 12 web-based CBM-I training sessions (of 15-20 minutes duration) that are completed over a period of 4 weeks. In each session, users listen to short, ambiguous scenarios (30 per session) that can be interpreted in both negative and positive ways. Some of the scenarios are resolved in a positive way by the platform and the user is required to resolve some of them in a positive manner themselves. Users then imagine themselves in the positive outcome for each scenario.

4.2 Manufacturer

Name:	Avegen Limited
Address:	HQ King's Cross 344 - 354 Grays Inn Rd London, WC1X 8BP United Kingdom

4.3 Model details

Name:	RELAX - REducing Levels of AnXiety
Number:	1.0
Software version:	1.0

4.4 Traceability

The version of the RELAX web platform being used in the clinical investigation is V1.0. The device is prescription-use only, and its warnings, cautions and contraindications are as mentioned in the RELAX Device Label. A step-by-step guide on how to use the RELAX platform is provided in the Instructions for Use accessible through the platform itself.

4.5 Intended purpose

The purpose of RELAX is to provide Cognitive Bias Modification for Interpretation (CBM-I) to people at-risk of anxiety due to high levels of RNT. RELAX can be used to prevent escalating anxiety.

4.6 Detailed description

The investigational device is a software that can be accessed online via the RELAX platform. The platform will host a web-based psychological intervention for perinatal anxiety, RELAX. Users can access the online platform and RELAX sessions via a browser on their computer, laptop, or tablet. Users are also able to visit the RELAX platform and view the different webpages on their mobile phone, though they will be unable to complete any sessions using this device.

The RELAX intervention consists of 12 x 15-20 minute online CBM-I training sessions which are completed over a period of 4 weeks. Users can complete the online sessions at home at a time and day of their choice within the 4-week period, although the platform will encourage them to complete 3 to 4 sessions per week, and in most circumstances they will not be able to complete more than one session per day (see section 8.4.4 for more details).The sessions involve listening to 30 descriptions of ambiguous everyday situations (scenarios) that are pertinent to the daily lives of pregnant women. Some of the scenarios are resolved in realistic, positive ways (e.g., 'Your midwife is performing an ultrasound scan to check your baby's wellbeing. As she takes time to locate the baby's heartbeat, she turns to tell you that it is very strong') whilst some of them remain ambiguous (e.g., 'You are at a pregnancy exercise class. During a break there is a chance to talk to other women attending, who all seem to know each other. As you approach them you can tell whether it will be easy to join their conversation'), and users are required to resolve them positively themselves (e.g., 'it is easy to join in with the conversation'). In all the sessions, users imagine themselves in each positively resolved situation and complete comprehension questions that are designed to reinforce the positive interpretation (e.g., 'Does the midwife tell you the heartbeat is strong?' Correct answer: yes). Users will also be asked to rate how positive the ending they imagined was for 50 percent of trials, and how vividly they were able to imagine the ending for the remaining 50 percent of trials, which serves to reinforce the generation of positive interpretation and vivid imagery.

4.7 User training required

The web-based intervention is accessed via an online platform on a computer, laptop, or tablet and users are provided with clear instructions for the tasks they are required to complete in each session. Therefore, they do not need any training or experience to complete the RELAX sessions and effectively use the online platform.

4.8 Associated procedures

No medical or surgical procedures are involved in the use of the investigational device as it is an online psychological intervention.

4.9 References

Document Type	Title	Version
Investigator's brochure	307468-Investigator's Brochure-12092022	1.0
Instructions for use	307468-Instructions For Use-13022023	1.2

5 Clinical Investigation Design Justification

5.1 Background

Why is this research needed now?

Anxiety is common in the perinatal period. Up to 40% of pregnant women and new mothers experience high levels of anxiety (Fairbrother et al., 2017) with multiple significant adverse consequences for these women, their unborn child, children, and partners, including reduced responsivity to babies (Stein et al., 2012), impairments in childhood development, and a twofold increase in risk of a child developing psychological disorders (O'Donnell et al., 2014). We urgently need to develop and evaluate interventions for perinatal anxiety. To maximise the likelihood of efficacy, such interventions should directly target established, modifiable risk factors which predict and maintain anxiety (Moulds, Black, Newby, & Hirsch, 2018).

Whilst targeted approaches have proven effective in other anxious populations, there are currently no targeted early interventions for perinatal anxiety, despite its prevalence and recognition of this need in the NHS Long Term Plan. It is well-established that interventions that target individuals who are identified as being at-risk of psychological problems are more effective than non-targeted universal approaches (Werner-Seidler et al., 2017). Accordingly, the development of a low-intensity (self-help), highly accessible, cost-efficient intervention to address perinatal anxiety is an exciting prospect. Not only could completing such an intervention lead to fewer anxiety symptoms in pregnant women, it also has the potential to reduce the need to later access specialist, costly, high intensity mental health support in the postnatal period (e.g., individual cognitive behavioural therapy).

5.2 Rationale

The knowledge gap this research will address

Approach to the literature: We identified all directly relevant research in an extensive literature review. Specifically, we searched the following databases: Psychinfo, Medline,

Embase, and WHO trials database using variations on the following combinations of search terms: 'anxiety,' 'perinatal,' 'pregnancy,' 'early-intervention,' 'prevention,' 'treatment,' 'intervention.' We also consulted relevant recently published systematic reviews and meta-analyses (e.g., Bayrampour et al., 2019; Loughnan et al., 2018, 2019; Madhi et al., 2019). Overall, our review established that perinatal anxiety has received minimal research attention. This is startling given the documented prevalence (e.g., Fairbrother et al., 2017) and consequences (O'Donnell et al., 2014) of anxiety in the perinatal period. This gap in the literature is particularly evident for psychological interventions for perinatal anxiety.

Established perinatal anxiety treatments

To date, a limited number of treatment trials have evaluated psychological interventions for perinatal anxiety. Such trials have included women with high levels of anxiety or diagnosed anxiety disorders in the antenatal (e.g., Goodman et al., 2014; Green et al., 2015; Heller et al., 2020; Lilliecreutz et al., 2010) and postnatal (e.g., Green et al., 2015; Misri et al., 2004) periods. Whilst it is no doubt clinically important to treat perinatal anxiety once it has emerged, these designs leave untested the possibility that early interventions for pregnant women targeting an established risk factor which maintains and worsens anxiety may result in fewer anxiety symptoms later in the perinatal period.

Of studies that have taken such an approach and targeted at-risk samples, a key shortcoming is that the interventions tested are typically generic (e.g., a standardised cognitive behavioural therapy (CBT) package; Austin et al., 2008) and target cognitive and behavioural processes that play a role in psychopathology generally, rather than directly target identified, modifiable risk factors which predict and maintain perinatal anxiety specifically. As such, it is not possible to determine the specific treatment component/s that are most effective and deliver the most clinical benefit. There is a clear need for efficacious, evidence-based early-intervention protocols which are focused and target identified and modifiable psychological risk factors which confer vulnerability to perinatal anxiety.

Need for online interventions

Online interventions have the potential to increase access to psychological therapy for women in the perinatal period, for whom there are likely to be multiple practical barriers to attending therapy in a clinical setting. Despite multiple advantages of an online format, a recent review and meta-analysis (Bayrampour et al., 2019) identified only five e-health interventions to reduce perinatal anxiety symptoms (i.e., not restricted to studies with clinically anxious samples) and demonstrated that online interventions are effective in reducing anxiety relative to control conditions (see also Heller et al., 2020). Another recent systematic review (Loughnan et al., 2019) identified only one online study that evaluated a treatment for pregnant women with clinically diagnosed anxiety (i.e., women with a fear of childbirth specifically, rather than general anxiety).

Whilst such findings are encouraging, the current status of the field is such that there are **no randomised controlled trials in the published literature which have evaluated the efficacy of an online early intervention for perinatal anxiety.** Furthermore, no interventions currently exist which target an identified and modifiable psychological mechanism which increases the risk of pregnant women developing later anxiety.

Critically, our Patient and Public Involvement (PPI) work has established that interventions for perinatal anxiety delivered online would be the most feasible way to engage at-risk pregnant women. This population typically has multiple responsibilities, rendering a home-based intervention that can be completed at a time convenient for them as having greatest appeal.

Online interventions have the added practical advantages of being readily accessible and cost-efficient, and thus can be easily delivered at scale. In addition, online interventions are self-contained such that they do not necessitate clients disclosing extensive personal information or details, do not require travel to attend appointments and can be completed at times convenient for them. The online format similarly has benefits for midwives in the context of a busy clinical setting since they do not need to complete lengthy referral forms.

We urgently need simple, accessible, online, early interventions to **reduce perinatal anxiety by targeting modifiable psychological risk factors** which precede, predict, and maintain it.

<u>RNT as a modifiable mechanism to target to reduce perinatal anxiety</u>

The tendency to engage in RNT (worry about the future, ruminate about the past) is an established risk factor for anxiety. Levels of RNT about a stressful life-event predict subsequent anxiety symptoms (Nolen-Hoeksema & Morrow, 1991). Pregnancy, birth, and adjustment to motherhood are stressful and full of uncertainty that can trigger RNT, particularly now in the context of COVID-19 when this additional worry is leading to increased anxiety more generally. Our pilot work prior to COVID with pregnant (n = 133) and postnatal (n = 236) samples already established the link between perinatal RNT and anxiety (Hirsch, Meeten, Gordon, Newby, Bick & Moulds, 2020; Newby, Werner-Seidler, Black, Hirsch & Moulds, 2021).

No study to date has tested the possibility that an early intervention targeting RNT in pregnancy could result in lower anxiety later in the perinatal period relative to usual care. This is surprising given that we have effective interventions which target RNT in the general population and prevent the onset of later psychopathology. For example, Topper et al. (2017) found that an intervention targeting RNT in young adults who reported high levels of RNT resulted in less anxiety 12 months later. Since RNT is a modifiable risk factor that predicts psychological distress, this raises the possibility that similarly targeting RNT early in the

perinatal period may result in lower levels of anxiety developing over time. Interventions that target RNT during pregnancy need to be tailored to the unique experiences and challenges that pregnant women face.

Interpretation bias as mechanism that maintains RNT

Interpretation bias, the tendency to draw negative conclusions from unclear or ambiguous information, is evident across different types of anxiety problems as well as depression (Hirsch et al., 2016). Our cognitive model of RNT (Hirsch & Mathews, 2012) proposes that interpretation bias maintains RNT. We demonstrated that RNT is associated with interpretation bias in non-pregnant clinical and non-clinical populations (Krahe et al., 2019) and replicated this in pregnant women (Hirsch, Meeten, Gordon, Newby, Bick, & Moulds, 2020). Given the ambiguous nature of stressful situations during pregnancy (e.g., 'will the scan show baby is ok?'), there is frequent opportunity to make negative interpretations (e.g., 'the scan will find something wrong') that fuel RNT, in turn escalating anxiety. In contrast, individuals without RNT tend to generate more positive interpretations (e.g., 'the scan will be fine') and have lower levels of anxiety.

Proof-of-Concept that targeting RNT could help pregnant women at risk of high anxiety

We established that the tendency to generate negative interpretations is associated with increased RNT, anxiety and depression (Krahe et al., 2019). We developed an online intervention - Learning Effective New Strategies (LENS) - an effective web-based 'brain-training' (Cognitive Bias Modification for Interpretation; CBM-I) intervention targeting RNT in non-pregnant people with clinical anxiety and/or depression (Hirsch et al., 2018). LENS reduces negative interpretations, anxiety, worry, and depression in individuals with clinically high anxiety and/or depression (Hirsch et al., 2018), as well as those with high levels of RNT (Hirsch et al., 2020). Our latest large-scale study (Hirsch et al., 2021) replicated and extended these findings and established that LENS can be delivered with no face-to-face contact with the researcher (enabling national recruitment), paving the way for LENS to form a low-intensity self-help intervention that would not require the input of specialist mental health professionals. Encouragingly, as well as sustained effects at 4-month follow-up, there was high compliance with the intervention and excellent retention rates for follow-up assessments. We also demonstrated that the purported mechanism of change - interpretation bias - was effectively targeted by the intervention and that reducing interpretation bias mediated effects on anxiety, worry and depression in a non-pregnant population.

Our non-pregnancy studies discussed above were randomised controlled experiments (not RCTs). They included a control condition which matched the intervention for time on the platform and engagement with an almost identical task (listening to ambiguous scenarios and answering questions) that was not designed to change interpretations (i.e., scenarios remained

ambiguous and did not have to be resolved by the participant), and thus controlled for potential placebo effects. Participants in these studies were only followed-up to 4-months.

In our recent proof-of-principle study (Hirsch, Meeten, Newby, O'Halloran, Gordon, Krzyzanowski, & Moulds, 2020), we used one session of LENS to effectively modify interpretation bias in pregnant women with high levels of worry (i.e., a score of ≥56 on the Penn State Worry Questionnaire). LENS led to a significant reduction in negative interpretations, as assessed by the most commonly used interpretation bias measure, the Recognition Test (RT; Mathews & Mackintosh, 2000). Furthermore, LENS also reduced worry on a behavioural measure - the number of negative thought intrusions reported in the short-term – used in other single session studies (e.g., Hirsch et al., 2009). It is important to now establish the efficacy of an online CBM-I intervention which is tailored to women in the perinatal period, in order to maximise engagement. In addition, for longer-term clinical impact, the intervention needs to be multi-session (Hirsch et al., 2016; and in keeping with Hirsch et al., 2018, 2020, 2021). We will determine the efficacy of the intervention in reducing anxiety in pregnant and postnatal women compared to usual care alone.

How will our intervention improve the care of pregnant women and new mothers?

Given the long-standing consequences of perinatal mental health problems, our trial has the potential for significant clinical impact - in both the short and long term - and at multiple levels. For women, reducing perinatal anxiety via a low-intensity intervention in pregnancy has the capacity to improve mental health in the short-term, and thus enhance their ability to cope with and navigate the challenges of pregnancy and caring for a new baby. It also has the potential to reduce the likelihood of developing chronic psychological problems, and the need to access specialist mental health services postpartum. For the unborn child, intervening early with the mother-to-be to reduce the likelihood of later postnatal mental health problems will result in higher quality care-giving and maternal responsiveness. Moreover, in the long-term, such an approach may in turn reduce the likelihood of offspring developing later mental health problems (and therefore the need to seek psychological support) and mitigate the potential effects of postnatal mental health problems on an array of outcomes (cognitive, behavioural, academic).

What critical gap will our research address

We will work closely with women with lived experience of anxiety to tailor the scenarios used in our effective web-based intervention (LENS) - developed for non-pregnant people - to address the concerns relevant to pregnant women (RELAX). We will then conduct an RCT of the pregnancy-tailored LENS (RELAX) in at-risk pregnant women to compare perinatal anxiety outcomes for RELAX + usual care vs usual care alone, and thus evaluate whether LENS results in lower levels of anxiety in pregnancy and during the postnatal period. Furthermore, we will determine whether the purported mechanism of action of the RNT

intervention (change in interpretation bias) found in non-pregnant clinically anxious populations is also the mechanism for reducing anxiety in a perinatal sample. Should this be the case, such a finding will inform approaches to address interpretation bias in face-to-face psychological interventions, such as CBT. Further, the outcomes will inform theories of perinatal anxiety and the further development of perinatal mental health interventions, including e-health and face-to-face interventions for pregnant women seen by perinatal mental health services.

To our knowledge, RELAX is the only online intervention specifically aimed at targeting a key modifiable mechanism which puts women at risk of high anxiety in the perinatal period, and is adapted from an evidence-based intervention (tested in a non-pregnant population). It could form a stand-alone early-intervention, or if proven to be effective, could potentially be used as an adjunct to other treatments (e.g., to supplement therapy in those already experiencing high levels of perinatal anxiety). RELAX's online delivery format is a key feature which brings added value. The intervention will be widely accessible, delivered via technology participants already possess (Statista, 2020a) at no extra cost, and can be completed at home at a convenient time. It is simple to complete and not cognitively demanding (Van Bockstaele et al., 2020), even during stressful periods. In contrast, implementing other effortful therapeutic techniques (e.g., thought challenging component of CBT) can be difficult, given that clients' cognitive resources are already heavily taxed by RNT (Stefanopoulou et al., 2014).

6 Benefits and Risks

6.1 Anticipated clinical benefits

Given the long-standing consequences of perinatal mental health problems, our trial has the potential for significant clinical impact - in both the short and long term - and at multiple levels. For women, reducing perinatal anxiety via a low-intensity intervention in pregnancy has the capacity to improve mental health in the short-term, and thus enhance their ability to cope with and navigate the challenges of pregnancy and caring for a new baby. It also has the potential to reduce chronic psychological problems, and the need to access specialist mental health services postpartum. For the unborn child, intervening early to reduce the likelihood of later postnatal mental health problems will result in higher quality care-giving and maternal responsiveness. Moreover, in the long-term, such an approach may in turn reduce the likelihood of offspring developing later mental health problems (and therefore the need to seek psychological support) and mitigate the potential effects of postnatal mental health problems on an array of outcomes (cognitive, behavioural, academic).

6.2 Anticipated adverse device effects/risks associated with participation in the clinical investigation

As part of the clinical assessments, participants will complete the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) and the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987). This gives rise to a risk that participants will disclose that they are a potential threat to themselves. Participants could score highly on item 9 of the PHQ-9 and item 10 of the EPDS in any of the assessments they complete. These items ask participants to rate the frequency at which they have had thoughts of being better off dead or harming themselves in recent weeks. Please refer to section 6.3 which indicates how we will deal with responses to these questionnaires that indicate potential risk.

During the material development stage, we will conduct individual PPI interviews and PPI focus groups with women with lived experience of anxiety during the perinatal period to help us develop materials for the intervention that are pertinent to the day-to-day concerns that trigger anxiety in pregnant women. During these interviews/focus groups, individuals will be asked questions about their daily lives and their experiences of RNT during the perinatal period which could lead to transient anxiety. However, this increase in anxious mood is expected to dissipate quickly after the interview/focus group and individuals can stop the interview or leave the group discussion at any time. Section 6.3 outlines how we will minimise distress during the interviews/focus groups and respond if anything concerning arises during them.

In the RELAX sessions, participants will be presented with ambiguous scenarios that will either remain unresolved or be resolved in a positive manner. The presentation of unresolved ambiguous scenarios related to pregnancy and day-to-day concerns may lead to temporary increases in anxious and/or depressed mood. However, our past research with LENS has demonstrated that this rarely, if ever, happens. Additionally, if such increases do occur, they are expected to dissipate quickly as participants will be moving onto the next scenario relatively soon after hearing the previous one.

There is a possibility that participants in either arm of the trial will show increases in self-reported anxiety and/or depressive symptoms at any of the follow-up assessments. Since anxiety and depression levels commonly fluctuate over pregnancy and post-birth, such increases would be expected events and not trigger an adverse event assessment.

6.3 Steps that will be taken to control or mitigate the risks

Our established protocols have been adapted to pregnant and postnatal women to carefully monitor (at each assessment) and manage any risk/adverse events (distress caused by the platform/intervention, significant increases in self-reported depressive symptoms, self-harm, suicide attempt, suicide – none recorded in prior research with LENS). Any potential risks or adverse events will be flagged by the online system after a participant has submitted a given assessment, or when having contact with participants (including responding to participants

who have contacted us about adverse events or emails that mention information deemed as potential risk such as suicidal ideation).

In order to minimise distress during the PPI interviews/focus groups, it will be emphasised that participants may choose not to answer certain questions and should only disclose information they feel comfortable sharing. When participating in the intervention, if participants report distress thinking about ambiguous scenarios, they can discontinue and will be encouraged to discuss any concerns with their midwife or GP. They will also be provided with the contact details for organisations that offer mental health support (e.g., Samaritans) and will be encouraged to contact them if they feel they may be a risk to themselves at any point. If anything concerning arises during the PPI interviews/focus groups, at any assessment (e.g., significant increases in self-reported depressive symptoms), or suicide risk/risk to self is reported at any time, participants will be reminded of their right to discontinue with their sessions or withdraw from the trial and a member of the research team (i.e., trial coordinator, research assistant, research midwife, students/volunteers working on the project) will also carry out a risk assessment. The trial team member will attempt to contact the participant via email or telephone, ideally as soon as possible within working hours, to gather further information about the risk and document this information on the study risk assessment report form, and if pertinent also complete an adverse events form (i.e., if the risk meets the definition of an adverse event as summarised in Section 16). It may take longer to contact the participant during holiday periods (i.e., Christmas), but the study team will aim to reach out to the participant within two weeks in such periods. If a participant is deemed to be high risk, the GP/midwifery team will be contacted (with prior consent) and the participant will be put in contact with Chief Investigator, CH (Clinical Psychologist) or another clinician. All participants experiencing distress will be provided with the contact details for organisations that offer mental health support (e.g., Samaritans) and will be encouraged to make immediate contact with one of these organisations or their midwife, GP, or community mental health team (e.g., IAPT) if their mental health deteriorates. If current risk or significant deterioration in mental health occurs (pre-defined by Trial Steering Committee (TSC)), women will be referred to the perinatal mental health services for urgent assessment or GPs will be urged to do this on women's behalf.

6.4 Possible interactions with concomitant medical treatments as considered under risk analysis

There will be no possible interactions with concomitant medical treatments as the trial investigates a psychological intervention.

6.5 Rationale for benefit-risk ratio

Any increases in anxiety and depression that occur whilst completing the RELAX sessions are expected to be temporary and dissipate quickly. Furthermore, the scenarios used in the

RELAX sessions are designed to reflect the day-to-day concerns of pregnant women. Thus, any negative thoughts experienced by participants whilst completing the online sessions will be similar to those experienced in their daily lives. Finally, whilst we cannot completely rule out the possibility, it is unlikely that any significant increases in self-reported anxiety and/or depression at the follow-up assessments will be caused by the intervention as this has not occurred in any prior research with LENS. Additionally, the current trial is focusing on pregnant women with high levels of repetitive negative thinking because we know they are at risk of escalating anxiety (and depression) and consequently increases in anxiety (and depression) are to be expected in this population over the perinatal period. Therefore, given that the intervention has the potential to not only reduce perinatal anxiety to a degree of significant clinical impact, but also prevent unfavourable outcomes for the unborn child, we conclude that the anticipated benefits of the intervention are greater than the potential risks.

7 Aims

7.1 Clinical investigation purpose

The purpose of this RCT is to determine whether pregnant women with high levels of RNT who complete an early intervention, RELAX, alongside receiving usual care, experience significantly lower levels of anxiety later in the perinatal period, compared to those who receive usual care alone.

7.2 Objectives

This is a superiority trial where the primary clinical objective is to assess whether at-risk pregnant women who complete RELAX alongside receiving usual care experience less perinatal anxiety **before** birth than at-risk pregnant women who only receive usual care.

The primary mechanistic objective is to determine whether interpretation bias, measured using the RT, is the mechanism of action of the RNT targeted intervention.

Please refer to the sample size calculation in section 9.1 for information on effect size justification.

The secondary objectives are:

1. To investigate whether at-risk pregnant women who complete RELAX alongside receiving usual care experience less anxiety **after** birth than at-risk pregnant women who only receive usual care.
2. To investigate whether at-risk pregnant women who complete RELAX alongside receiving usual care experience lower levels of repetitive negative thinking, less general depression, lower levels of trait worry, and less perinatal specific anxiety and

depression **before and after** birth than at-risk pregnant women who only receive usual care.

3. To investigate whether at-risk pregnant women who complete RELAX alongside receiving usual care have better work and social functioning **before and after** birth than at-risk pregnant women who only receive usual care.
4. To investigate whether there is significant moderation of the intervention versus control arm effect on anxiety at T2.

7.3 Hypotheses

Relative to usual care (UC), participants in the intervention arm plus UC arm will report:

1. lower anxiety (Generalised Anxiety Disorder Questionnaire; GAD-7; Spitzer et al., 2006) at T2 (8 weeks post-randomisation; primary outcome) and at T3 (36 weeks post-randomisation)
2. lower depression (PHQ-9), less RNT (Repetitive Thinking Questionnaire (trait version); RTQ-10 (trait); McEvoy et al., 2014), lower perinatal anxiety (Perinatal Anxiety Screening Scale; PASS; Somerville et al., 2014), lower trait worry (Penn State Worry Questionnaire; PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990), lower perinatal depression (EPDS), and better work and social functioning (Work and Social Adjustment Scale; WSAS; Mundt et al., 2002) at T2 and T3
3. reduced negative interpretation bias at T1 (4 weeks post-randomisation; mechanism)

In relation to the therapeutic mechanism of action, we predict that:

4. effects on anxiety at T2 and T3 will be mediated by change in interpretation bias from T0 to T1.

We also predict that, at T2:

5. participants in the intervention plus UC arm with moderate levels of anxiety at T0 will experience a greater reduction in anxiety than those in the control arm who also had moderate levels of anxiety at T0.
6. participants in the intervention plus UC arm with pregnancy complications (current and/or past) or pre-existing health conditions will experience a greater reduction in anxiety than those in the control arm who have also experienced pregnancy complications (current and/or past) or pre-existing health conditions.

7.4 Risks and adverse device effects

As mentioned in section 6.2, individuals in the study are selected because their levels of repetitive negative thinking put them at risk for escalating levels of anxiety and depression. At each assessment, participants will be required to complete the PHQ-9 and GAD-7, which

will allow us to monitor changes in these scores, but they are likely to be a consequence of the normal trajectory in pregnancy (which will be potentially demonstrated by the control group). We can determine if an unexpected deterioration is greater in the active group compared to the control group by comparing levels of anxiety and depression in the two groups. If the active group have significantly higher levels of anxiety or depression at follow up, the Data Monitoring and Ethics Committee (DMEC) will determine this from their regular reports and inform the TSC as appropriate.

8 Clinical Investigation Design

8.1 General

8.1.1 Trial design

A multi-session online intervention using CBM-I, LENS, will be adapted from Hirsch et al. (2018, 2020, 2021) and tailored to be pertinent to the day-to-day lives of pregnant women (RELAX), in order to maximise engagement with the intervention.

A two-arm, parallel-group, multicentre, superiority, RCT in which randomisation will be stratified by recruitment site, parity and pregnancy complications will be conducted. The RCT will evaluate whether adding RELAX to usual care (UC) results in lower perinatal anxiety levels in women who are at-risk owing to their tendency to engage in high levels of RNT. Pregnant women with high levels of self-reported RNT, but only low to moderate levels of anxiety, will be recruited and randomised to either complete RELAX alongside receiving UC or receive UC alone. As this is an efficacy trial, treatment as usual is the most appropriate comparator for determining whether RELAX would be effective as an additive intervention for pregnant women who are at-risk of developing perinatal anxiety.

8.1.2 Randomisation

Randomisation will take place via Avegen's randomisation system. Participants will be randomised individually with equal allocation to the two arms, stratified by site (GSTT vs KCH vs KCL), parity (0 vs not 0) and pregnancy complications (no pregnancy complications vs pregnancy complications (current and/or past)), using a random permuted block design. Participants will be allocated to the intervention arm (receive usual care + RELAX) or control arm (usual care) at a ratio 1:1 via an online system independently developed and hosted by Avegen. Please see section 8.3.5 for more information on randomisation.

8.1.3 Blinding

For detail on individual and group level blinding for individuals involved in the conduct of the trial, please see Table 1.

Concealment of allocation will be used whereby members of the research team will only become aware of the condition that a participant is in at the point of randomisation (i.e., after the baseline assessment has been completed).

The senior statistician will not have access to the randomisation list or directly to the database platform at any point in the trial to remain fully blinded until review of the first draft of the statistical reports for checking, when they will become fully unblinded. The Chief Investigator, Co-Investigators and Principal Investigators at each investigation site will remain unblinded at the individual level and fully blinded at the group level until they review the finalised statistical report, when they will become fully unblinded. The trial statistician will be fully blinded until sign off of the statistical analysis plans, after which they will be fully unblinded so they can inspect and utilise platform usage/intervention-related data. The trial coordinator, research assistant, research midwife and any other members of the study team (e.g., students/volunteers working on the study) will be unblinded at the individual level only. The only individuals that will be able to summarise/see data by arm prior to the review of the statistical report are the trial statistician and the members of the DMEC. We will presume that the DMEC will remain partially blinded and will prepare the closed report accordingly.

Table 1. Overview of individual and group level blinding

Roles	**Individual Level**	**Group Level**	**Method of blinding OR justification for unblinding**
Trial Coordinator	U	B	No access to randomisation list or data summarised at group-level
Research Assistant	U	B	No access to randomisation list or data summarised at group-level
Research Midwife	U	B	No access to randomisation list or data summarised at group-level
Other members of study team	U	B	No access to randomisation list or data summarised at group-level

Study participants	U	B	No access to randomisation list or data summarised at group-level
Trial Statistician	B	U	Access to full randomisation list required for data monitoring & analysis. NB only unblinded after an initial draft of the SAP has been signed.
Senior Statistician	B	B	No access to full randomisation list *
Chief / Co / Principal Investigators	U	B	No access to randomisation list or data summarised at group-level
(Independent members of) DMEC	B	U/P	The level of DMEC blinding will be at their discretion but will likely see data split by group at least at a partially blinded level
Trial Steering Committee (TSC)	B	B	No access to randomisation list or data summarised at group-level

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

There will be 4 assessments yoked to randomisation: baseline pre-randomisation (T0; 16-28 weeks gestation); 4 weeks post-randomisation (T1; end of intervention for active arm; 20-32 weeks gestation); 8 weeks post-randomisation (T2; 24-36 weeks gestation), and 36 weeks post-randomisation (T3; 12-24 weeks post-birth). This will allow us to test the impact of RELAX on the primary and secondary clinical outcomes (indexed using the GAD-7; PHQ-9; RTQ-10 (trait), PASS, EPDS, PSWQ, and WSAS) and whether interpretation bias change is the mechanism of action at T1 (assessed via the most commonly used interpretation bias measure, the RT).

8.1.4 Primary and secondary endpoints

Please see Table 2 for overview of endpoint measures and the times of their assessment.

Primary clinical endpoint

(i) Anxiety (GAD-7) at 8-weeks post-randomisation (T2). We will present the mean difference in GAD-7 at 8 weeks between the intervention (RELAX + usual care) and control (usual care) arms adjusted for baseline GAD-7.

Primary mechanistic endpoint

(i) Interpretation bias (Recognition Test, the primary mechanistic endpoint) at 4-weeks post-randomisation (T1). We will present the mean difference in Recognition Test scores at 4 weeks between the intervention (RELAX + usual care) and control (usual care) arms adjusted for baseline Recognition Test. This variable will also be evaluated as a potential mediator of the effect of the RELAX intervention as outlined in Section 9.

Secondary clinical endpoints

Secondary clinical endpoints will all be presented as mean differences in outcomes between the intervention (RELAX + usual care) and control (usual care) arms adjusting for baseline. These endpoints are:

- Anxiety (GAD-7) at 36-weeks post-randomisation (T3)
- Depression (PHQ-9) at 8-weeks post-randomisation (T2)
- Depression (PHQ-9) at 36-weeks post-randomisation (T3)
- RNT (RTQ-10 (trait)) at 8-weeks post-randomisation (T2)
- RNT (RTQ-10 (trait)) at 36-weeks post-randomisation (T3)
- Trait worry (PSWQ) at 8-weeks post-randomisation (T2)
- Trait worry (PSWQ) at 36-weeks post-randomisation (T3)
- Perinatal depression (EPDS) at 8-weeks post-randomisation (T2)
- Perinatal depression (EPDS) at 36-weeks post-randomisation (T3)
- Perinatal anxiety (PASS) at 8-weeks post-randomisation (T2)
- Perinatal anxiety (PASS) at 36-weeks post-randomisation (T3)
- Work and social functioning (WSAS) at 8-weeks post-randomisation (T2)
- Work and social functioning (WSAS) at 36-weeks post-randomisation (T3)

Table 2. Overview of Endpoint Measures and Times of Assessment

Endpoint	Measure	Time Points	Rationale for Selection
Anxiety	GAD-7	T0, T1, T2, T3	The GAD-7 is a well-validated and widely used 7-item measure of anxiety. A change of 4 or more on the GAD-7 has been found to be clinically significant across anxiety disorders (Spitzer et al., 2006).

Interpretation bias	RT	T0, T1	The RT is the most commonly used interpretation bias measure. It has been used widely in the anxiety and depression literature and has also been used in our previous work with pregnant women (Hirsch, Meeten, Newby et al., 2021).
Depression	PHQ-9	T0, T1, T2, T3	The PHQ-9 is the 9-item depression module from the full PHQ. There is strong evidence for the validity of the PHQ-9 as a brief measure of depression severity (Kroenke et al., 2001).
Repetitive negative thinking (RNT)	RTQ-10 (trait)	T0, T1, T2, T3	RTQ-10 (trait) is an established transdiagnostic measure of RNT.
Trait worry	PSWQ	T0, T1, T2, T3	The PSWQ is an established measure of trait worry (i.e., general tendency to worry). This measure is included because worry is the primary form of RNT in relation to anxiety.
Perinatal depression	EPDS	T0, T1, T2, T3	EPDS is the most common measure for perinatal depression. Depression is known to be highly associated with anxiety, so this measure has been included as it is related to the target population.

Perinatal anxiety	PASS	T0, T1, T2, T3	The PASS measures perinatal specific anxiety. As it is not used in IAPT or the NHS, with less validation and no clinically meaningful change data, this is a secondary measure and the GAD-7 is the primary clinical measure.
Work and social functioning	WSAS	T0, T1, T2, T3	WSAS is a 5-item work and social adjustment scale that is commonly used in the NHS and IAPT. The WSAS exhibits good internal consistency and test-retest reliability as a measure of disorder- related functional impairment in adults with anxiety disorders (Mundt et al., 2002; Mataix-Cols et al., 2005)

8.1.5 Investigation sites

The trial will involve two NHS investigation sites: Guy's and St Thomas' NHS Foundation Trust (GSTT) and King's College Hospital NHS Foundation Trust (KCH). The research team at King's College London (KCL) will also share information about the study with non-NHS organisations and via social media so some participants will be recruited via these methods.

8.1.6 Completion of clinical investigation

The clinical investigation will end when the recruitment target has been met and when the final T3 follow-up assessment has been completed.

8.2 Investigational device and comparator

Participants in the intervention arm will complete RELAX, which consists of 12 web-based CBM-I training sessions (of 15-20 minutes duration), over a period of 4 weeks alongside receiving usual care. The RELAX sessions involve listening to short, ambiguous scenarios (30 per session) that can be interpreted in both negative and positive ways. Participants in the intervention arm complete RELAX alongside receiving usual care. Some of the scenarios are resolved in a positive way by the platform, and the user is required to resolve some of them in a positive manner themselves. Users then imagine themselves in the positive outcome for each scenario.

Those in the control arm will only receive usual care and if accessing the RELAX platform, a message will appear indicating the date on which their next assessment is due. Usual care typically involves monitoring by maternity services , and contact with a health visitor. Women may also be offered information on self-referral to local psychology services where they will be put on a wait list or be offered generic interventions (e.g., group treatment, computerised CBT).

As usual care sometimes involves being offered psychological treatment, individuals who are currently receiving or have recently received psychological treatment will not be excluded from the trial. We will monitor engagement in current psychological interventions throughout the trial as part of our monitoring of usual care.

Participants will not be required to use any other medical device or medication during the clinical investigation. RELAX is the only investigational device that will be used in this clinical investigation.

8.3 Subjects

8.3.1 Subject inclusion criteria

- Pregnant women between 16-28 weeks gestation
- Aged 18 years or older
- Based in the United Kingdom
- High levels of RNT (RTQ-10 (trait) ≥ 28; Joubert et al., 2021, 2023)
- Anxiety up to only a moderate level (GAD-7 < 15)
- Ability to understand oral and written English
- Normal or corrected-to-normal hearing and vision
- Ability to access the internet on a PC, laptop, or tablet (rather than mobile phone)
- Provision of an email address and phone number for contact with the team

8.3.2 Subject exclusion criteria

- Current psychiatric diagnosis (this will be assessed via the clinical interview schedule revised (CIS-R; Lewis & Pelosi, 1992) which participants will complete as part of the screening questionnaire as well as via general questions about a current diagnosis of a psychotic disorder, eating disorder, substance use disorder or personality disorder)
- Past diagnosis of a psychotic disorder (e.g., schizophrenia), bipolar disorder, an eating disorder, a substance use disorder (e.g., alcohol dependence) and/or a personality disorder (e.g., borderline personality disorder)
- Current or recent history of risk: current suicidal intent (PHQ-9 item 9 >1), suicide attempt < 2 years and/or self-harm < 1 year
- History of stillbirth, neonatal death, or multiple (i.e., ≥3) miscarriages
- Current participation in another study that is investigating a treatment for a mental health problem
- Not registered with a GP in the UK

8.3.3 Criteria and procedures for subject withdrawal or lost to follow-up

Participants will be informed that they are free to withdraw from the trial completely or discontinue with their RELAX sessions at any time. Participants will be verbally reminded of this, and it is also stated on the information sheet and consent form. Discontinuation of sessions refers to when participants in the intervention arm state that they no longer wish to complete their sessions but would still be willing to complete their follow-up assessments. In such cases, participants will no longer be contacted about completing any remaining sessions, but they will be invited to complete the semi-structured intervention follow-up interview (see section 8.4.6) on one occasion, which they are free to decline, and will also be contacted about their follow-up assessments. The research team will record the date of and reason for discontinuation of sessions. Withdrawal from the trial refers to when participants in the intervention arm state that they no longer want to complete their remaining sessions and follow-up assessments and those in the control arm state that they do not want to complete their follow-up assessments. In such cases, the research team will record the date of and the reason for withdrawal from the trial if known. All participants who withdraw from the trial will be asked on one occasion if they would be willing to complete a telephone interview about why they decided to withdraw, which they are free to decline. After this, they will no longer be contacted by the study team.

Women who experience pregnancy loss (e.g., miscarry), terminate pregnancy or need inpatient care will be sensitively approached about completing assessments. Given that some of the questions in the assessments relate to pregnancy or giving birth, they will be reminded that they are under no obligation to complete the assessments and will also be offered support as appropriate (e.g., through support organisations such as Tommy's Charity). Moreover, those in the intervention arm will not be required to continue with their sessions.

If participants report distress thinking about ambiguous scenarios, disclose anything concerning or encounter a difficult/stressful life event (e.g., family death/illness, divorce etc.) at any point during their participation in the study, we will remind them that they can discontinue with their RELAX sessions or withdraw from the trial.

Individuals in the intervention arm who fall behind on their sessions will be reminded to complete any remaining ones by the research team via email, text, and phone call. For example, if it has been more than three days since a participant completed their last session, they will be sent a reminder email. If they make no progress within the next two days, they will receive a reminder text message. If they still do not manage to complete their latest session, a member of the study team will attempt to give them a call and if there is no answer, the call will be followed up with another email or text message reminding them to complete their sessions. However, this is just an example, the number and frequency of reminders a participant receives will depend on how many sessions they have remaining and how long

they have to complete all their sessions before their T1 assessment is activated by the online platform.

During the study outline call, participants will be informed that they must complete their baseline assessment (T0) within 10 days of completing the screening questionnaire. Participants will then be asked to indicate the date on which they would like to start participating in the trial and their baseline assessment will be activated by the Avegen online system on this particular date (provided that the date falls within the 10-day timeframe). If participants do not complete their baseline assessment on the date that it is activated, they will receive a phone call, email or text message from the research team reminding them to complete it. Participants will receive up to three reminders to complete their baseline assessment. Individuals who do not complete their baseline assessment after the third reminder or who miss the deadline for completing their baseline assessment will not be further contacted by the research team and we will assume that they are no longer interested in participating in the trial. The team will record this information on the database.

An email will be sent a week before each follow-up assessment to let participants know that they will be emailed in relation to completing the assessment in 7 days' time. Individuals who do not submit their follow-up assessments on time (within 7 days of being sent the email link to the assessment) will be sent a reminder email. If they do not manage to complete it within three days after this, a member of the study team will try to contact them via telephone to remind them to complete it, and if there is no answer, the call will be followed up with an email or text message reminder. If participants have still not completed the assessment two weeks after it was due, they will be contacted by the study team again reminding them to complete it. For the T1 and T2 assessments, participants who have still not completed their assessment following the third reminder will receive a final reminder 20 days after its due date as the link will only remain active for 3 weeks. As the T3 assessment is the last assessment, it will remain active for 8 weeks following its due date. Therefore, participants who have still not completed their T3 assessment after the third reminder will be followed-up to complete it within this timeframe. When calling participants to remind them of late assessments, we will also attempt to troubleshoot any issues they are facing with regards to this and may need to escalate technical difficulties to the platform developers, Avegen, and will also offer, in necessary circumstances, participants the chance to complete their assessments over the phone with the researcher and enter this data into the back-end side of the Avegen built online portal.

Subjects who withdraw or are lost to follow-up will not be replaced. However, we might recruit more people than originally specified if the attrition rate is higher than the one used in the sample size calculation (see section 9.1) and the TSC or DMEC recommended this course of action.

8.3.4 Point of enrolment

Participants will be enrolled into the study once they have completed the baseline assessment (T0) as this is the point at which we will have obtained informed consent to them being randomised and participating in the clinical trial on the online platform.

8.3.5 Point of randomisation

Once the participant is enrolled in the study (i.e., after eligibility criteria are confirmed, informed consent has been obtained and the baseline assessment has been completed), they will be randomised to either the RELAX intervention alongside UC or receive UC alone. Stratified randomisation will be carried out via the RELAX platform by Avegen in a 1:1 ratio using randomly permuted blocks with varying block sizes. Stratification is by recruitment site (GSTT vs KCH vs KCL), parity (0 vs not 0), and pregnancy complications (no pregnancy complications vs pregnancy complications). The information needed to classify participants based on the stratification variables will be gathered via the screening questionnaire (and verified on the study outline call). Two extra recruitment sites will be allowed for in the randomisation list that we will designate as "site 4" and "site 5" in case we find we need to add in further sites to meet randomisation targets. The participant will be automatically assigned to a trial arm depending on their strata and the block sequence, and the platform will display the assigned arm to the participant. The researchers will also be able to see the arm that a participant is allocated to when accessing the clinical interface of the platform. The complete randomisation list sequence will be concealed from the investigators including the Chief Investigator and statisticians.

8.3.6 Total expected duration of the clinical investigation

The clinical investigation is expected to last from January 2023 to March 2025. It will commence when the first participant is enrolled in the study and terminate when the last participant completes the final follow-up assessment (T3).

8.3.7 Expected duration of each subject's participation

Participants will be enrolled in the study for around 9 months.

8.3.8 Number of subjects required to be included in the clinical investigation, and anticipated distribution of enrolment among the participating investigation sites

268 participants will need to be included in the study (please see the sample size calculation in section 9.1). We anticipate that distribution of enrolment amongst the two participating NHS investigation sites will be roughly equal with three-quarters of the participants being recruited via these and one-quarter being recruited on behalf of KCL via non-NHS routes.

8.3.9 Estimated time needed to select this number (i.e., enrolment period)

The enrolment period will last around 18 months.

8.3.10 Relationship of investigation population to target population

The investigation population will be recruited from the target population via NHS sites in London that service a diverse population locally and at national level. Participants will also be recruited via antenatal support organisations nationally. Therefore, we do not anticipate that there will be any difference between the investigation population and the target population.

8.3.11 Information on vulnerable, pregnant, and breastfeeding population, if applicable

Pregnant women who are between 16-28 weeks gestation will be recruited for this trial. They will be followed for the remainder of their pregnancy and post-birth for between 12-24 weeks depending on when they are randomised. Therefore, the sample will include both breastfeeding and non-breastfeeding individuals.

8.4 Procedures

8.4.1 Recruitment

Pregnant women's mental health is routinely screened by midwives at the first antenatal 'booking' appointment (7-10 weeks gestation). Maternity services at our partner NHS trusts see around 6000 (Guy's and St Thomas'; GSTT) and 4500 (King's College Hospital; KCH) pregnant women each year. Pregnant women who receive care via these maternity services are routinely invited to be involved in clinical trials (e.g., through research bulletins (which outline information about all open trials), direct recruitment, and posters). Details of the RELAX study will feature in bulletins, using approved wording from the Participant Information Sheet. We will also apply for adoption by the NIHR Clinical Research Network (CRN). The NIHR CRN research delivery midwives at both NHS sites will also help promote efficient recruitment.

Identification of potential participants via maternity health record systems:

Potential participants will be identified via site held records located on NHS electronic health record systems. Identification of elevated worry/anxiety (assessed on Generalised Anxiety Disorder Questionnaire-2 (GAD-2), estimated at 12% i.e., 1260 women per year on current data) may be recorded on online maternity health record systems. A member of the research team who is part of potential participants' direct care team will screen records of women booked to receive antenatal care at each participating site to identify pregnant women who are between 16-28 weeks pregnant who might be suitable for the study (e.g., due to reporting high levels of worry on the GAD-2 or having a history of anxiety). Potential participants' details (name, telephone number and email address (if available)) will be retrieved from the electronic health record systems and will be saved on a password-protected Excel spreadsheet maintained on NHS servers. Members of the research team who are involved in screening records will then approach the women identified to inform them about the study in-person when they attend their antenatal appointments, or via email/ telephone if required. If the potential participant is interested in the study, the team member will refer them to the

RELAX website to register and complete the screening questionnaires (see section 8.4.2 for more details). The team member will also obtain verbal consent from the potential participant to be contacted by members of the research team who are not part of the individual's direct care team. Initial contact with potential participants that is made via email will always be carried out using a secure NHS.net email address. Once a potential participant has registered on the RELAX platform, contact with them will be made via the platform or using the study KCL email address as written consent to being contacted by the broader researcher team will have been obtained thorough the consent to screening form.

Potential participants will freely decide whether or not they register for the study and complete the screening questionnaire on the RELAX website, either at the time of being informed about the study or at a later timepoint.

Introduction to study in clinic:

Potential participants will also be identified via antenatal clinics at participating NHS sites. Women will be informed about the study in person (or online if trust policies for in-person attendance to routine appointments change due to an increase in COVID-19 cases) when attending routine midwife appointments (e.g., 16-week midwife appointment, appointments at community antenatal hub clinics), unless they have previously opted out of being notified about research.

NHS trust midwives will introduce the study to women reporting worry during their antenatal appointments. Midwives will provide potential participants with the study team's phone number and email address, informing them to reach out to the study team if they would like to find out more about the study. Midwives will also collect the contact details (name, phone number and email address (if available)) of the potential participant to pass on to the research team. They will use an NHS.net secure email to pass on potential participants' contact details as well as providing further information as to why the individual might be suitable for the study. Midwives would assent on behalf of an individual and will obtain verbal consent for passing on their contact details and being approached by the research team regarding the study. They will then make a note of this referral in the patient's clinical notes and the involvement of all participants will be recorded in clinical notes, at the request of the study sites following standard practice. On receiving potential participants' details from clinic midwives, a member of the research team will initiate contact with the individual via email or telephone. This member will inform the individual about the study and provide them with an open invitation to register for the study if they are interested. Any initial email contact prior to a participant being registered on the platform will be made using a NHS.net email. Once an individual has registered on the RELAX platform, contact will be made via the platform and the study KCL email address.

Furthermore, other members of the clinical team (e.g., obstetricians, maternity support workers) may also inform women about the study if they report experiencing worry during pregnancy. These clinicians may obtain verbal consent from women for passing on their contact details to the research team and being approached by the research team regarding the study, making a note of this in women's clinical notes.

Additionally, members of the research team who belong to potential participants' direct care team will approach women in antenatal clinic waiting areas to inform them about the study. The research team member will provide women with the study information sheet and answer their questions about the study. NIHR CRN research delivery midwives may also help with recruiting participants from antenatal clinic waiting areas.

Members of the research team who are not part of potential participants' direct care team will obtain a research passport, providing them with permission to be on site to facilitate recruitment. Thus, once potential participants provide verbal consent to a member of their direct care team (e.g., midwife or obstetrician) to being approached about the study, these research team members will be available on some occasions in antenatal clinic waiting areas to discuss the study further with them.

Identification of potential participants via posters, leaflets and business cards:

The study will also be advertised via posters, QR codes linked to the study website, leaflets, business cards and other methods in antenatal clinics, toilets and other suitable areas in the hospitals. A 'permission to contact' box will be placed securely in the same clinics as the posters and leaflets for interested individuals to submit their contact details on a business card. Prize draws will be run for women who complete the screening questionnaire and for midwives/site staff who forward the team the most referrals for screening. Furthermore, posters and leaflets may be placed in antenatal or waiting areas in additional NHS sites and GP practices located across the United Kingdom (upon receiving ethical approval to do so and local site permission).

Identification of potential participants via maternity service apps:

Pregnant women belonging to some Trusts use apps to access their maternity records (for GSTT and KCH maternity services, this is currently called Badger Notes). All pregnant women using such apps at participating sites who are between 16-28 weeks pregnant will receive push notifications about the RELAX study. Through this, they will be able to read some information about the study as well as being provided with the link to the study website and contact details of the study team (email address and phone number). This will allow for interested women to either contact the study team for more information or register their interest and complete the screening questionnaire via the RELAX website.

Identification via South London GP surgeries:

South London GP surgeries will be a Participant Identification Centre. The NIHR CRN primary care team will screen patient records from GP surgeries in South London to identify individuals who are potentially eligible for the study. Potential participants will receive information about the RELAX study via a mailshot. Patients who do not want to be notified about the study will be able to opt out of receiving any information about it. The NIHR CRN primary care team will pass on the contact details (e.g., name, email address, phone number) of potential participants to the research team via an NHS.net email. As with all our NHS recruitment strategies, the research team will save the contact details of potential participants identified via GP surgeries on a password-protected Excel spreadsheet maintained on NHS servers. On receiving potential participants' details from the NIHR CRN primary care team, a

member of the research team will initiate contact with the individuals via email or telephone. This member will inform the individual about the study and provide them with an open invitation to register for the study if they are interested. Any initial email contact prior to a participant being registered on the platform will be made using a NHS.net email. Once an individual has registered on the RELAX platform, contact will be made via the platform and the study KCL email address.

Identification of potential participants via non-NHS sites:

PPI requested recruitment via non-NHS pregnancy support groups, community organisations and charities, so we will approach such organisations to advertise the study and subject to authorisation may attend events held by these organisations to promote the study, being available to discuss it in person with interested individuals. All advertisements made by the non-NHS organisations will contain the study email address and phone number as well as the link to the study website. Thus, if an individual would like to find out more about the study, they can access the information sheet on the study website and can also contact the study team via email or telephone if they have any further questions about the research.

Our recruitment pathways (Figure 2), which draw upon both NHS and non-NHS organisations, aim to cater to include a diverse range of participants, thus we have proposed a range of methods to encourage inclusivity. For all recruitment pathways, the process of recruitment will be free from any undue influence or pressure and no therapeutic promises will be made. After receiving information about the study or being invited to register, women can voluntarily decide to visit the RELAX website, with the website address and QR code to access the website being printed on participant recruitment materials (including the poster). On visiting the website, women will be able to read more details about the study and register their interest should they wish to. Upon registering, they will be asked to provide consent to screening and being contacted by the research team, after which they will be sent a link to complete the screening questionnaire (see section 8.4.2 for more details).

We estimate that 44 women will be approached per week via the multiple NHS recruitment pathways. We estimate that half of the women approached using these methods will complete online screening (i.e., 22 per week). We expect that recruitment via social media/non-NHS organisations will result in at least 4 additional women being screened on the platform every week.

Recruitment rates: Based on Hirsch, Meeten, Newby et al.'s (2021) sample, 40% of the 26 women who complete online screening per week (i.e., 10-11 participants) will meet criteria for high RNT (RTQ-10 (trait) $\geq$ 32) without current high anxiety (GAD-7>14). Based on Hirsch et al. (2020), we conservatively estimate that half of them will be eligible on other criteria (e.g., no current psychological disorder), resulting in 5-6 potential participants being identified as suitable per week. The team will call these women to discuss the study and obtain their agreement to being sent the link to fill out the baseline assessment. If two thirds choose to participate, we will randomise 3-4 women per week (a conservative estimate) at between 16 to 28 weeks gestation (depending on timing of screening).

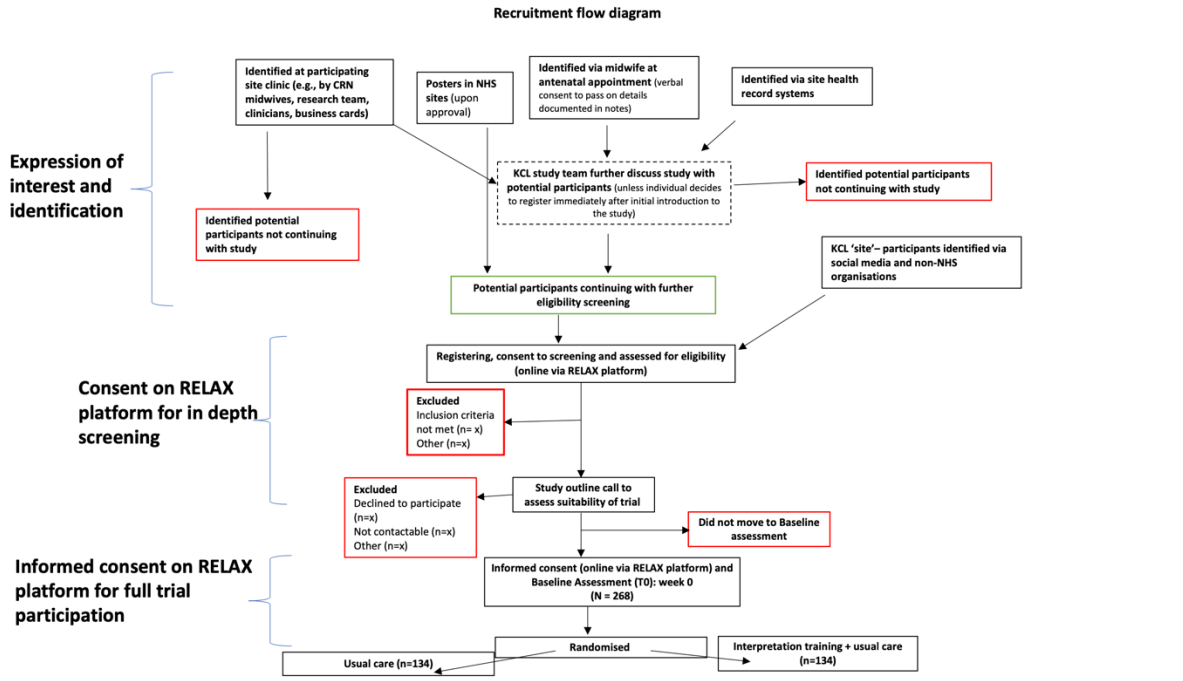

Figure 2. Recruitment flow diagram

8.4.2 Screening

If interested in participating, pregnant women will register on the online platform. Participants will be able to read the study information sheet on the RELAX platform. When registering, they will initially provide consent for us to process and use their screening data. They will then receive a link to the screening questionnaire, which contains a battery of questionnaires and some eligibility questions (e.g., English language fluency, ability to access and engage with the internet etc.). The battery of questionnaires will include measures of RNT (RTQ-10 (trait)), anxiety (GAD-7), depression (PHQ-9), and psychiatric diagnosis (CIS-R). Participants will also be asked to provide their full name, age, sex at birth, email address, phone number, and general practitioner, midwife and maternity service details. Furthermore, they will be asked to indicate how many weeks pregnant they are and will be asked some questions regarding their pathway of care, current/past pregnancy complications, and parity. Moreover, participants will be asked to indicate how they heard about the study. Participants will be able to use a computer, laptop, tablet, or mobile phone to register and complete the screening questionnaire.

Potential participants who are deemed to be ineligible for the study due their scores on the GAD-7 being too high, having a probable psychiatric diagnosis as assessed by the CIS-R, or indicating suicidal thoughts or self-harm behaviour on item 9 of the PHQ-9, will be signposted to the most appropriate mental health support resources and services. Their GP and midwife/maternity service may be contacted if an individual is identified as being at risk or very distressed at any point in the study or at screening.

Individuals who indicate that they are less than 15 weeks pregnant when filling out the screening questionnaire will be notified that they are currently ineligible for the study but will be informed that the research team will contact them when they are 15 weeks pregnant to invite them to complete the screening questionnaire again. Individuals who state that they are 15 weeks pregnant when completing the screening questionnaire will be able to proceed with filling out the questionnaire, and if they are eligible at the end of the questionnaire, they will be invited to the next stage of the screening process but will not be allowed to complete their baseline assessment until they are 16 weeks pregnant. Furthermore, individuals who indicate that they would prefer not to state their sex at birth when completing the screening questionnaire will be contacted by the research team to clarify whether they are eligible for the study or not.

If eligible after completing the screening questionnaire, participants will be emailed by the team and a telephone call will be scheduled at a convenient time for the participant to be further assessed for eligibility. The research team will also use this opportunity to provide more information about the study (including time commitments and randomisation), verify details provided in the screening questionnaire (e.g., GP, midwife and maternity service details, and information regarding their pathway of care and pregnancy complications), and answer any questions. If at the end of this call, the participant is eligible and happy to continue, they will be given information about completing the first assessment on the platform verbally, whilst on the telephone, and the information will also be provided via email. Those who are not eligible for the study will be thanked for their interest and time but will be informed that they cannot continue with the study as they do not meet the criteria for inclusion. Additionally, if after hearing about the study in more detail, an individual feels that they are unable to commit to the study and/or complete the RELAX sessions in the manner that is expected (e.g., completing around three sessions a week, generating positive mental images, completing the sessions in a quiet room with minimal distractions etc.), they will be offered the option to refrain from taking part and if they decide to do so, they will be classified as being unsuitable for the study by the research team.

If, after completion of the screening questionnaire on the study platform, participants do not respond to the email invitation to arrange a telephone call to discuss the study further, they will receive a further invite via email, text message or phone call. If there is still no response, a final attempt will be made to contact the individual to invite them to a telephone call with a member of the research team. The final attempt to contact the individual will be made via email, text message or phone call. If there is still no response following this final attempt of contact, it will be assumed that the individual no longer wants to participate in the research.

8.4.3 Baseline T0 assessment (16-28 weeks gestation)

Participants will complete this assessment online via the RELAX platform using a computer, laptop, tablet, or mobile phone. At the beginning of this assessment, participants will provide informed consent to being randomised and taking part in the clinical trial. The measures that participants will complete during this assessment can be found in Table 2.

Participants will also answer some additional questions to provide demographic and descriptive information about the sample. These questions will include their date of birth, ethnicity, religion, relationship status, social support, education level, employment status and due date. Participants will also be asked to provide information about pre-existing health conditions and to state the number of children they currently have (excluding those to be born). Furthermore, they will be asked to indicate whether they have ever been in contact with a health professional regarding their mental health, if they have ever had a diagnosis of a mental health condition, if they are currently receiving psychological treatment, and if they are taking any medication for a mental health problem. The assessment will take participants approximately 40 minutes to complete. The platform will not allow participants to submit their responses if they have not completed all parts of the assessment. Additionally, participants will not be randomised to the active or control arm by the online platform until their T0 assessment is fully completed.

Participants must complete their baseline assessment within 10 days of the date that they filled out the screening questionnaire. If they do not complete it within this timeframe and would still like to participate in the study, we will have to reassess their eligibility for the trial so they will be asked to fill out the screening questionnaire again.

Once the baseline assessment has been fully completed, the platform will register this and the participant will be randomly allocated to the intervention or control arm by Avegen's randomisation system (see section 8.3.5 for more details on randomisation). A letter detailing the study and the participant's involvement will be sent to their GP and midwife/maternity service. Participants joining the study via the KCL (i.e., social media/non-NHS organisations) route will be sent an email of the letter to forward to their midwife/maternity service.

8.4.4 Planned interventions

Active Arm – RELAX + Usual Care (UC):

Participants in the active arm will complete 12 sessions (of 15-20 minutes duration) of the RELAX intervention via the online platform at home using a computer, laptop, or tablet over the 4 weeks post-randomisation. Participants will be asked to complete their first session within 24 hours of completing the baseline assessment. They can then choose when to complete the remaining sessions, although the platform will encourage them to complete 3 to 4 sessions per week. Videos to support participants with understanding the rationale for training, how to complete training sessions and how to schedule their sessions will be

presented in the first session. If participants start a session but do not manage to complete it, they will be able to resume the session from the point at which they stopped up until the end of the next calendar day. In such cases, participants will receive an automatic alert from the platform reminding them to complete their session. If they do not complete the session by the end of the next calendar day, the session will reset and they will have to start it from the beginning. Participants will usually not be able to complete more than one session per day. However, in cases where a participant has an incomplete session from the previous day, the platform will allow the participant to complete the incomplete session as well as their next full session on the same day. A detailed description of what each session entails can be found in section 4.6.

In addition, at the start of the first session, participants will complete a one-off imagery training to facilitate positive imagery generation during the remaining sessions. This will involve watching a short video about imagery and completing imagery exercises used by Hirsch et al. (2020, 2021). They will then complete the training task which involves listening to scenarios, imagining positive outcomes to the scenarios, and answering comprehension questions (see section 4.6). Furthermore, at the end of the first session, participants will rate how logical the intervention seems and how useful they expect it to be. As a result of the imagery training, the first session will be longer than the subsequent sessions, lasting 30 minutes as opposed to 15-20 minutes.

Moreover, to help facilitate generalisation of the training to day-to-day life, after completing the third, sixth and ninth session, participants will be sent a text/email which encourages them to try to identify positive outcomes should they notice themselves worrying or thinking negatively about a situation. Participants will also receive UC (see section 8.2 for more details).

Comparison Arm – Usual Care:

Participants in this arm will only receive UC (see section 8.2 for a detailed explanation) and will not need to log onto the platform until the T1 assessment.

8.4.5 Post-intervention T1 (4 weeks post randomisation; 20-32 weeks gestation)

Participants will complete this assessment on the online platform using a computer, laptop, tablet, or mobile phone. Table 2 shows the battery of measures that participants will complete during this assessment. When the T1 assessment is activated on the platform, participants in the active arm will no longer have access to the sessions. Participants will also report any adverse events and pregnancy complications that they have experienced since the last assessment. Moreover, they will be asked to indicate if they are currently receiving psychological treatment and if they are taking any medication for a mental health problem.

Furthermore, those in the active arm will rate how logical and useful the intervention was and how confident they would be in terms of recommending it to a friend. This will be done at the end of the assessment. They will also be asked to indicate whether they encountered any issues when completing the RELAX sessions (which will aid in identifying any adverse device effects).

At this assessment, it is possible that a participant may report that they have given birth prematurely, or that they experienced a miscarriage, stillbirth, or neonatal death. In such cases, the participant's questionnaire journey would be the same as it would have been if they had indicated that this had occurred at T3. Specifically, if the participant indicates that they have experienced a miscarriage, stillbirth or neonatal death, the assessment will end and they will not be asked to complete the PASS, EPDS, RT, any online questions about current psychological treatment and medication or adverse events, or the intervention acceptability ratings (see above). If at this assessment a participant experienced a live birth, they will complete the pregnancy and birth complications form that is routinely done at T3. Thus, they will be asked about any pregnancy or birth complications and non-routine health professional contact in relation to the baby or the mother. Furthermore, participants who experienced a live birth will be asked to provide their date of delivery. Participants who reported that they gave birth prematurely at T1 will not be asked questions about their birth again at T2 or T3.

Participants must complete their T1 assessment within 3 weeks of its due date. If they do not complete it within this timeframe, they will no longer be able to access it but will still be allowed to complete their T2 assessment when it becomes available.

8.4.6 Semi-structured intervention follow-up interview

For the intervention arm only, follow-up interviews will be conducted via telephone with women who completed the intervention to gain an understanding of any barriers to the intervention to help guide potential amendments to the intervention prior to roll-out. We will review whether we are reaching saturation of themes as the trial progresses, and thus determine if it is necessary to invite all women to the interview. We will also interview women who discontinue with their RELAX sessions to determine why they did not want to continue with the intervention. We will aim for the interviews to take place within 2 weeks of a participant completing their T1 assessment. Participants will be emailed by the research team to arrange a convenient time to conduct the semi-structured interview over the phone. Separate protocols will be developed for those who complete the intervention and those who discontinue with the sessions. These interviews will be audio recorded for later analysis and participants will be asked to provide verbal consent to this at the beginning of the recording.

8.4.7 Follow-up T2 (8 weeks post-randomisation; 24-36 weeks gestation)

Participants will complete this assessment on the online platform using a computer, laptop, tablet, or mobile phone. Table 2 shows the battery of measures that participants will complete during this assessment. Participants will also report any adverse events and pregnancy complications that they have experienced since the last assessment. Moreover, they will be asked to indicate if they are currently receiving psychological treatment and if they are taking any medication for a mental health problem.

At this assessment, it is possible that a participant may report that they have given birth prematurely, or that they experienced a miscarriage, stillbirth, or neonatal death. In such cases, the participant's questionnaire journey would be the same as it would have been if they had indicated that this had occurred at T3. Specifically, if the participant indicates that they have experienced a miscarriage, stillbirth or neonatal death, the assessment will end and they will not be asked to complete the PASS, EPDS, or any online questions about current psychological treatment and medication or adverse events. If at this assessment a participant experienced a live birth, they will complete the pregnancy and birth complications form that is routinely done at T3. Thus, they will be asked about any pregnancy or birth complications and non-routine health professional contact in relation to the baby or the mother. Furthermore, participants who experienced a live birth will be asked to provide their date of delivery. Participants who reported that they gave birth prematurely at T2 will not be asked questions about their birth again at T3.

As with the T1 assessment, participants must complete their T2 assessment within 3 weeks of its due date. If they do not complete it within this timeframe, they will no longer be able to access it but will still be allowed to complete their T3 assessment when it becomes available.

8.4.8 Follow-up T3 (36 weeks post-randomisation; 12-24 weeks post-birth)

Participants will complete this assessment on the online platform using a computer, laptop, tablet, or mobile phone. Table 2 shows the battery of measures that participants will complete during this assessment. Participants will also report any adverse events and pregnancy complications that they have experienced since the last assessment. Moreover, they will be asked to indicate if they are currently receiving psychological treatment and if they are taking any medication for a mental health problem. In addition, participants who have not reported having their baby prematurely or experiencing a miscarriage, stillbirth, or neonatal death at a previous timepoint will be asked to indicate whether they had a live birth, stillbirth, or experienced neonatal death. Individuals who report that they had a live birth will be asked about any pregnancy or birth complications and non-routine health professional contact in relation to the baby or the mother. They will also be asked to provide their date of delivery. If a participant indicates that they experienced a stillbirth or neonatal death, the assessment will end and they will not be asked to complete the PASS, EPDS, or any online questions about current psychological treatment and medication or adverse events. After completing the 36-week follow-up, participants will be thanked for their contribution to the study and debriefed via email.

As T3 is the final follow-up assessment, participants must complete this assessment within 8 weeks of its due date. If they do not complete it within this timeframe, they will no longer be able to access it.

8.4.9 Internal Pilot

An internal pilot will assess recruitment rates and T2 & T3 assessment completion rates to ensure completion of the trial is feasible. The pilot is purely a term used to describe TSC/DMEC milestone review points of recruitment and completion rates to establish ongoing viability. No additional data will be collected for this purpose, no separate variables will be compiled, and the data will only be used for this purpose alongside the main aims described in this Clinical Investigation Plan.

The internal pilot decision point is 16 months after the start of the trial (i.e., after 6 full months of T3 assessments with one month leeway for late returns), when progression criteria will be assessed. Progression to the full trial will be justified if recruitment is on average at least 12 per month and assessment completion rates for T2 and T3 are at least 65% (sample size accounts for 35% attrition). If progression is not justified, we will consult the TSC for their recommendations and consult with NIHR and co-sponsors regarding further steps potentially including stopping all further recruitment and assessments.

8.5 Monitoring plan

A separate data management and monitoring plan will be drafted by the team and reviewed by the TSC.

9 Statistical Design and Analysis

A detailed statistical analysis plan will be drafted, reviewed by the DMEC and TSC, and signed off by the chair of the latter. The sample size calculation and a brief description of the analysis plan are below.

9.1 Sample size calculation

Clinical efficacy sample size

For a two-sided independent samples *t*-test, alpha = 0.05, assuming one baseline and three post-randomisation measures with correlation rho = 0.5 (conservative based on baseline – T2 estimate from Hirsch, Krahe et al., 2021 of rho = 0.42), deflation factor of 0.5 (Machin et al., 2009), and accounting for 35% attrition (based on online CBT: Van Ballegooijen et al., 2014), we will need 268 participants in total (134 per arm) to have 90% power to detect a GAD-7 effect size of 0.35. This is powered slightly conservatively, since natural anxiety trajectories in the perinatal period may be more variable, leading to greater standard deviations compared to non-pregnant populations included in our prior research - in which

the T2 effect size for GAD-7 was 0.40 (adjusted mean difference of 2/pooled SD of 5 at T2, Hirsch, Krahe et al., 2021). The previous study utilised a task matched control which also led to reductions in anxiety. The current study with a usual care comparator (appropriate for an efficacy trial) may well yield greater differences. This may be particularly pertinent for the current population, for whom RNT is likely to lead to escalating anxiety for those individuals not offered the active intervention during this highly stressful time in their lives. We consider a four point between-condition difference to be clinically meaningful, because, for example, four points within person change on the GAD-7 was defined as clinically meaningful (Toussaint et al., 2020).

Mechanistic analysis sample size

Using estimates of the mediation parameters from Hirsch, Krahe et al. (2021) to assume standardised estimates of the *a* (effect of intervention on mediator), *b* (effect of mediator on outcome) and *c'* (direct effect of intervention on outcome) paths in a mediation model of approximately 0.5, 0.2 and 0.15, and the methods of Thoemmes et al. (2010) to calculate appropriate parameters for Monte Carlo simulations with 10K repetitions to calculate power in Mplus (Thoemmes et al., 2010), a total sample size of 268 would give > 99% power to detect the mechanistic action of the intervention on interpretation bias (*a* path), and 83% power to detect the mediated effect of the intervention on GAD-7 via interpretation bias.

9.2 Analysis of data

Data cleaning will be completed prior to statistical analysis by the trial statistician, overseen by co-applicant KG.

Population under investigation

Intention to Treat (ITT):

The primary population for analysis will be the ITT population. This will be defined as all participants for whom any post-randomisation data are collected analysed in the arm in which they are randomised to.

CACE Analysis Population:

The population for the complier average causal estimate (CACE) of the effect of the intervention on the primary GAD-7 endpoint at 8 weeks post randomisation will be the population of compliers as compared to those who would have complied in the control intervention. A complier is defined as a participant who has completed all 30 trials within a session for at least 10 out of the 12 RELAX sessions.

Clinical Efficacy

The effect of the intervention on the primary GAD-7 outcome at 8 weeks post-randomisation will be estimated according to intention-to-treat principles using linear mixed effects models

with all post-randomisation measures as dependent variables. The models will include a dummy intervention variable and adjust for the baseline (T0) perinatal anxiety, stratification variables, a covariate (weeks of gestation at baseline), and include time, and time by intervention interaction terms to extract the effect at T2. Intervention effects will be presented as mean differences and 95% CI between intervention and control arms. Model assumptions will be assessed that the residuals are identically, independently, and normally distributed with a zero mean and constant variance. Bootstrapping will be considered where data may not be normally distributed.

As this is an efficacy trial, the most important secondary analysis will be a complier average causal effect estimate (CACE) of the effect of the intervention in the population of compliers as compared to those who would have complied in the control intervention. A complier is defined as a participant who has completed all of the trials in a session for at least 10 out of the 12 RELAX sessions. Therefore, to obtain the CACE, the platform will collect data regarding the time spent on each session and the number of trials completed in each session. The CACE will be obtained using instrumental variable methods, with GAD-7 at T2 as the dependent variable and adjusting for similar variables to those described for the primary ITT analysis. Analyses similar to that described for obtaining the ITT estimate of the effect of the intervention on GAD-7 will be undertaken for other secondary outcomes.

Furthermore, despite our study not being powered for sub-group analysis, our pre-registered analysis plan will indicate an additional analysis by levels of baseline T0 GAD-7 anxiety (low = 0 to 9, moderate = 10 to 14) to investigate whether there are different treatment effects by baseline anxiety on GAD-7 at T2. We will also conduct two other subgroup analyses, by pregnancy complications (yes/no) and pre-existing conditions (yes/no) for the continuous primary GAD-7 anxiety outcome at T2. Subgroup analyses will be done by adding intervention by time by subgroup variable of interest interactions terms to the main analysis model for this primary anxiety outcome. If these interaction terms are statistically significant with respect to the subgroup variable of interest, we will present RELAX versus UC estimates by pregnancy complications and pre-existing conditions levels.

Mechanistic analysis

We will assess the effect of the intervention on interpretation bias (hypothesised mechanism) and mediation of the intervention effect on anxiety (GAD-7) via interpretation bias (recognition test) using structural equation modelling (SEM) and full information maximum likelihood estimation, with T1 measure of interpretation bias as the mediator and the T2 and T3 measures of anxiety as outcomes. Under certain assumptions and with continuous mediator and outcome measures as we have here, SEM will give the same estimates as other methods available for parametric causal inference.

Process evaluation

We will assess intervention acceptability (experimental arm). The platform routinely records intervention adherence (median number of completed sessions), proportion receiving no intervention (0 sessions), partial adherers (1-9 sessions), full adherers (≥ 10 sessions). Intervention engagement will be assessed via accuracy rates of comprehension questions

completed during sessions. Semi-structured telephone interviews (20 people at T2 selected by age (<30 vs >30), site (KCH vs GSTT vs KCL) and adherence to RELAX sessions (0 sessions vs 1-9 sessions vs ≥ 10 sessions) will explore acceptability of the intervention. Transcribed interviews will be analysed using Thematic Analysis (Maguire & Delahunt, 2017).

Missing data

Loss to follow-up and other missing data:

The number and proportion of participants missing each primary and secondary outcome variable will be presented by intervention arm and overall, at each time point.

Missing items in scales and sub-scales:

Where available we will use missing value guidance provided for scales. Where this is not available, we will prorate missing items only when there are no more than 20% missing items (i.e., for a ten-item questionnaire, prorate only where one or two items are missing) by replacing the missing item values with the mean value of the complete items for each individual.

Missing baseline data:

All efforts will be made to avoid missing baseline data (i.e., requiring completion of baseline data before randomisation). However, we will summarise and report the number of participants with complete baseline measures and if this occurs, we will take an appropriate approach recommended by the literature, e.g., mean imputation as per the recommendations of White and Thompson (2005).

Missing outcome data:

Missing outcome data will be dealt with by using maximum likelihood methods to fit the mixed models. We will assess whether baseline variables predict missing outcome values so they can be included in models. We will employ the same methodology for identifying baseline predictors of missing outcome data to identify whether post-randomisation adherence to the intervention predicts missing outcome data. If this is the case and the proportion of participants with missing values for any of the primary or secondary outcome variables is equal or greater to 10%, we will consider using multiple imputation by chained equations.

Method for handling multiple comparisons

We will make no adjustments for multiple comparisons. We will make this explicit to the reader in the final publication.

Sensitivity analyses

We will perform sensitivity analysis of the missing not at random assumption for the primary GAD-7 outcome at 8 weeks post-randomisation and secondary GAD-7 outcome at 36 weeks post-randomisation only. We will create indicator variables 1 = missing 0 = not missing at each time point, and then perform multiple imputation of missing data under the missing at random assumption, separately by arm (Sullivan et al., 2018). The imputation models will be similar to or the same as the main analysis models, including all relevant variables. We will then test alternate assumptions by adding or subtracting an amount equal to 0.2 standard deviations (SD) of the baseline GAD-7 measure to imputed data that was initially missing (White et al., 2011). We will entertain the following scenarios: participants missing data worsening by 0.2 SD in both arms, improving by that amount in both arms, missing in the intervention arm worsening by this amount (leaving the control arm data imputed under the missing at random assumption), and missing in the control arm improving by this amount (leaving the intervention arm data imputed under the missing at random assumption).

10 Data Management

Data handling and storage

The Chief Investigator will act as custodian for the trial data. All trial data will be stored in line with the Data Protection Act (2018). Please refer to Figure 3 which outlines the data flow for the trial.

Clinicians (e.g., midwives and obstetricians) at participating sites will share personal information with the study team. They will send the study team the contact details (name, telephone number, email address (if available)) of potential participants via a secure NHS.net email. If stipulated, following routine trust practices, the study team will update the midwife/maternity care team of an individual's trial involvement status, for the electronic health records systems to be appropriately updated, in order to document that the person is taking part in this research trial or escalate reasons for non-participation.

During the trial, all personal data (such as the recruitment Excel logs of potential participants' contact details) will be stored as password-protected files on NHS secure servers or on Avegen's secure database. Only researchers directly involved in the study will have access to this data. Any personal data that is in paper form, such as the business cards, which potential participants voluntarily enter their contact details onto, will be stored in lockable filing cabinets in the Henry Wellcome Building at KCL during the trial. Personal data of participants will be retained for up to a year following the end of the clinical trial. Personal data of potential participants will be retained till the end of the recruitment period.

During the trial, all data will be pseudonymised using unique identification numbers (participants will be assigned a unique participant ID number for the duration of the clinical trial) and stored without identifying information (names, email addresses, phone numbers) on the Avegen database and KCL secure servers: KCL OneDrive and shared R drive.

After the trial, all data will be kept in anonymised form. Any anonymised data that is in electronic form will be stored in a password-protected file on the KCL One Drive for 12 years following the end of the study. Anonymised data that is in paper form will be stored in lockable filing cabinets in the Henry Wellcome Building at KCL for 12 years following the end of the clinical trial.

Study database

Online responses will be collected using the RELAX platform which will be hosted by Avegen. Avegen is committed to privacy and the need for data protection and management. Avegen is compliant to GDPR. All data through RELAX will be hosted on Amazon Web Services (AWS) based in Ireland.

Throughout the trial, Avegen will regularly send the data to the research team (including statisticians) in pseudonymised format via 'data dumps.' This data will be stored in one or more of the following KCL secure server locations: KCL OneDrive and shared R drive. Personal data that participants enter onto the RELAX platform will be visible to researchers with access credentials via the platform's clinical interface but will not be transmitted to KCL in the form of data dumps. Thus, pseudonymised data will be stored separately from personal data to prevent the identification of participants from their data. Data will be retained within the Avegen database after the database lock. At the end of the trial, all data will be returned to the sponsor and will be stored within KCL secure server locations. The data on the RELAX platform will then be deleted. Any interactions with Avegen will be logged and audited by a designated researcher.

Data extracts for DMEC reports will be used by the trial statistician for data monitoring purposes. No data analysis will be undertaken until databases are locked.

Audio recordings and transcription

Any interviews conducted throughout the research (e.g., to collect views on the trial and the RELAX intervention post-completion) will be recorded using a portable audio recorder. Interviews will only be recorded with participants' consent. Audio recordings and transcriptions will be pseudonymised and stored without contact details (names, email addresses, phone numbers) using unique participant IDs. These data will be stored in an electronic format on KCL servers and the audio recorder secured in a lockable drawer with the researcher. A KCL or GSTT preferred supplier will be used to transcribe the qualitative interviews. The GSTT current approved transcription supplier is Accuro (http://www.accuro.co.uk/contact-us/). The transcription service will be experienced in dealing with confidential data. Any transcribed data will be redacted for any personally identifiable information and will be entirely anonymous. A data sharing agreement will be in place and the files will be transferred using King's College London's secure server and will be encrypted.

Any identifying information (e.g., specific details that could serve to identify individuals - which is unlikely as the questions are not of personal nature) will be removed from any files or transcriptions made available to anyone beyond the research team (e.g., if reproducing excerpts of interviews in journal articles).

Paper study documents

Any data that is in paper form will be stored in lockable filing cabinets in the Henry Wellcome Building at KCL for the duration of the trial and will be retained for 12 years following the end of the clinical trial.

Direct Access to Source Data and Documents

The investigators and the institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other relevant documents.

Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996) and the principles of Good Clinical Practice (GCP). This protocol and related documents will be submitted for review to the Health Research Authority (HRA), Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA).

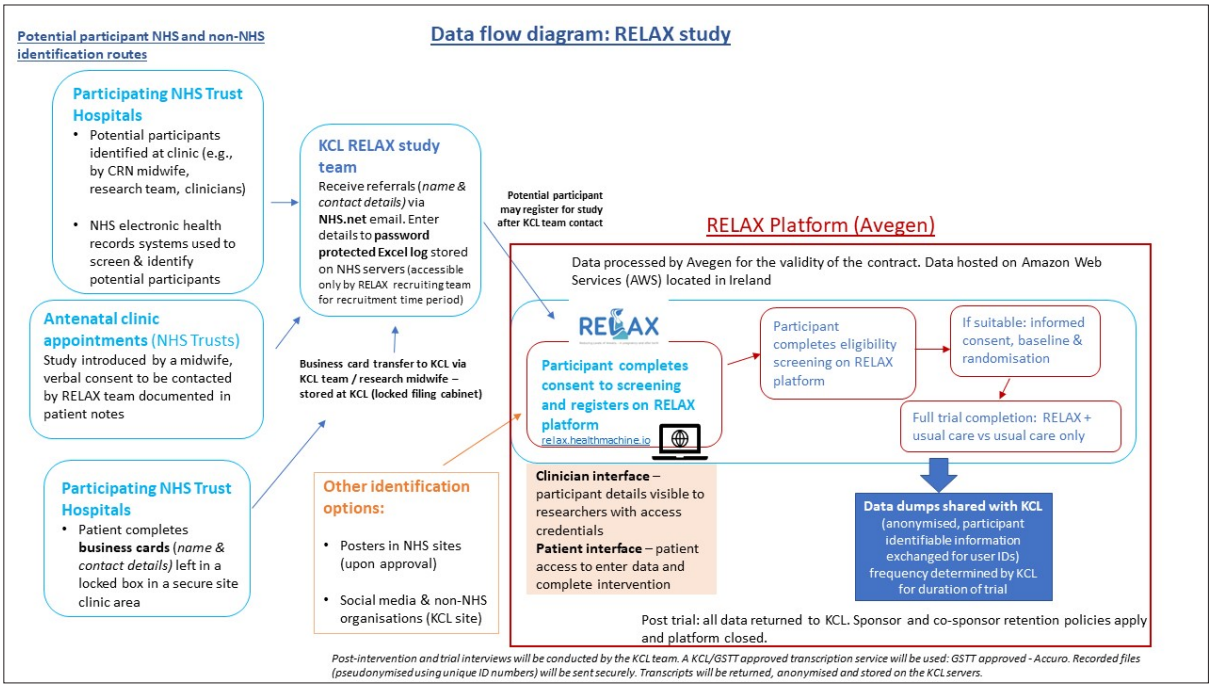

Figure 3. Data flow diagram for the trial

11 Amendments to the CIP

If any amendments need to be made to the CIP during the clinical investigation, they will be prepared by the Chief Investigator in consultation with the Co-Investigators (including the statistician) and will be approved by all investigators. We will inform R&D, to confirm whether an amendment is substantial or non-substantial. If appropriate, we will also consult the TSC and DMEC about any amendments. Any amendments will be made in accordance with written procedures for the control of documents and document changes. We will include a description of and justification for any amendments. If necessary, non-substantial amendments will be notified to the REC and, where appropriate, regulatory authorities. Substantial amendments will be notified to the REC and regulatory authorities (MHRA devices, HRA) and we will wait for their approval before implementing them. In order to keep track of the amendments, the version number of the CIP will be updated, and the date of amendments will be documented.

12 Deviations from the Clinical Investigation Plan

The investigator is not allowed to deviate from this CIP, except when required in emergency circumstances where deviations from the CIP to protect the well-being of human subjects may proceed without prior approval of the sponsor, REC and MHRA.

If any deviations from the protocol occur, we will have a procedure in place for recording and reporting at subsequent TSC (and DMEC) meetings if appropriate. Implications for analysis will be discussed with the DMEC. Any deviations will be documented and reported to the sponsor, REC and MHRA as soon as possible.

13 Device Accountability

This section is not applicable to this clinical investigation as there are no physical devices being distributed, however, Avegen's Quality Management System (QMS) does have procedures for Software Release Management and each software release shall be accompanied by instructions for use. Avegen operates a Quality Management System and an Information Security Management System that comply with the requirements of ISO 13485 and IEC/ISO 27001 respectively. The standards complied with during the development of RELAX are ISO 13485, ISO 27001, ISO 14971, ISO 15223, and ISO 20417. Standards compliant from a Software Safety Class A during the development of RELAX are IEC 62366-1 and ISO 62304.

14 Statements of Compliance

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

This clinical investigation will comply to BS EN ISO 14155:2020 (Clinical investigation of medical devices for human subjects - Good clinical practice) and any regional or national regulations.

This clinical investigation shall not begin until the required approval/favourable opinion from the REC and regulatory authorities have been obtained. Any additional requirements imposed by the REC or regulatory authorities shall be followed.

The study is co-sponsored by KCL and GSTT. The sponsors will, at all times, maintain adequate insurance in relation to the study. KCL through its own professional indemnity (Clinical Trials) and no fault compensation, and the GSTT having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of negligence by its employees, brought by or on behalf of a study participant.

15 Informed Consent Process

In situations where an individual is informed about the study by NHS midwives or other clinicians (e.g., obstetricians) when attending their antenatal appointment, the clinician will ask them to verbally consent to their details being passed on to the research team and to being approached by the research team regarding the study. The clinician will make a note of this in the potential participant's clinic notes.

The information sheet will be available on the RELAX platform. During screening, potential participants will be asked to indicate that they have read the study information sheet and then be asked to provide consent to screening and being contacted by the research team. Individuals who are eligible for the study following the screening questionnaire will be invited to complete a call with the study team. On the call, individuals will verbally receive information about the study and they will also verbally agree to be sent the link to the baseline assessment. The date and outcome of this call will be recorded on the database by the experimenter. When participants log on to the platform to complete the baseline assessment, they will need to provide full consent to being randomised and taking part in the trial on the online platform. They will have to check a list of boxes to agree to each point of the consent form and they will ‘sign’ the consent form by typing their name in a section at the bottom of the form. The date of ‘signature’ will be automatically populated by the online platform. Participants will be unable to continue to the next page unless they agree to all points on the consent form and they enter their name at the bottom of it.

E-health platforms that provide ongoing contact with patients e.g., via phone, text and or email, have better adherence to the intervention and less discontinuation. During the baseline assessment, participants will be asked to consent to being contacted by the research team via email, text, and phone throughout their participation in the study. This will allow us to contact participants should we need to for various reasons (e.g., to troubleshoot any technical

issues, arrange post-intervention follow-up interviews (intervention arm only), arrange interviews with participants who want to withdraw from the trial (both arms), remind participants of assessments that are due and to ask them to complete their sessions if they are behind schedule with them (intervention arm only)). Furthermore, it will allow us to contact participants if any new information becomes available during the course of the research that may be relevant to their continued participation. We will also contact them if risk or adverse events assessments need to be completed.

Participants will be reimbursed with £25 online vouchers for each assessment they complete (routine practice in mental health trials) to compensate for their time and to maximise data collection rate. Those not found to be eligible on the study outline call will be reimbursed via a £5 online voucher for their time. Furthermore, there will be a prize draw for anyone who completes the screening questionnaire in which individuals will have the chance to win a £50 voucher. Members of our PPI advisory group have favoured the idea of running a prize draw, which will occur every three months throughout the recruitment period.

16 Recording and Reporting of Adverse Events and Incidents

No serious adverse events related to the device (RELAX) are anticipated in this study. Participants will be managed according to usual care during the course of this study with the addition of RELAX training sessions to those allocated to the active condition.

16.1 Definitions of adverse events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event (SAE)	Any adverse event that: • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect
Device Deficiency	Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.
Adverse Device Effect (ADE)	An adverse device effect (ADE) is defined as an adverse event that is related to the use of the investigational medical device.
Serious Adverse Device Effect (SADE)	A serious adverse device effect (SADE) is any ADE that results in any of the consequences characteristic of a SAE.

*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

16.2 Assessments of adverse events

Each adverse event will be assessed for severity, causality, seriousness, and expectedness as described below.

16.2.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

16.2.2 Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study

	procedure). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g., the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

16.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the procedure **clearly defined in this protocol.**
Unexpected	An adverse event which is not consistent with the information about the procedure **clearly defined in this protocol.** *An unanticipated serious adverse device effect (USADE) is a SADE which by its nature, incidence, severity, or outcome is not identified in the risk analysis report.*

This includes listed events that are more frequently reported or more severe than previously reported.

16.3 Recording adverse events

All adverse events will be recorded on the RELAX platform. Clinical symptoms will be documented and accompanied with a simple, brief description of the event, including dates as appropriate. If it is in the best interest of the participant or clinical teams managing care for the participant, the study team will inform clinical teams of AEs that participants experience.

All AEs/ADEs will be recorded and any that escalate in a SAE/SADE will be reported to the sponsor and relevant regulatory authorities (excluding those which do not require reporting as outlined in section 16.5 below).

16.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and on the RELAX platform (Adverse events CRF), and the sponsor's AE log (see Figure 4 for flow diagram).

All SAEs and SADEs (except those specified in section 16.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The PI will complete a SAE form immediately (and always within 24 hours) of becoming aware of the event. The form will be preferably emailed to the CI and the Sponsor immediately, but not later than 3 calendar days after the investigational site study personnel's awareness of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible. The SAE/SADE will be reported to the MHRA immediately and within 2 calendar days after awareness by the sponsor. The REC/HRA will be notified of the SAE/SADE immediately (and always within 15 days of the CI becoming aware of the event).

The date, type, description, and severity of all AEs will be recorded on our RELAX database on the RELAX platform. We will also record whether the AEs were directly related to the use of RELAX or not and record AEs that may typically occur in pregnancy, such as severe headaches, severe nausea and vomiting, fatigue, high blood pressure etc., which will be captured and recorded as "expected AEs". We will endeavour to file reports of SAEs (and SADEs) in participants' medical records by being sent via e-mail to participants (recruited via social media) to pass on to their GP and midwife, unless having direct contact with the participant's midwifery team to forward the report. For KCH and GSTT, reports can be forwarded to local site contacts for filing.

If potential SAEs are identified, the TSC and DMEC will be informed. Adverse events will be recorded and summaries of the number of adverse events and number of people who experience such events will be collated for DMEC reports. We will estimate the event rates and 95% CI in each arm and compare rates between arms.

Completed forms for unexpected SAEs / SADEs must be sent within 24 hours of becoming aware of the event to the Sponsor
Email forms to: r&d@gstt.nhs.uk

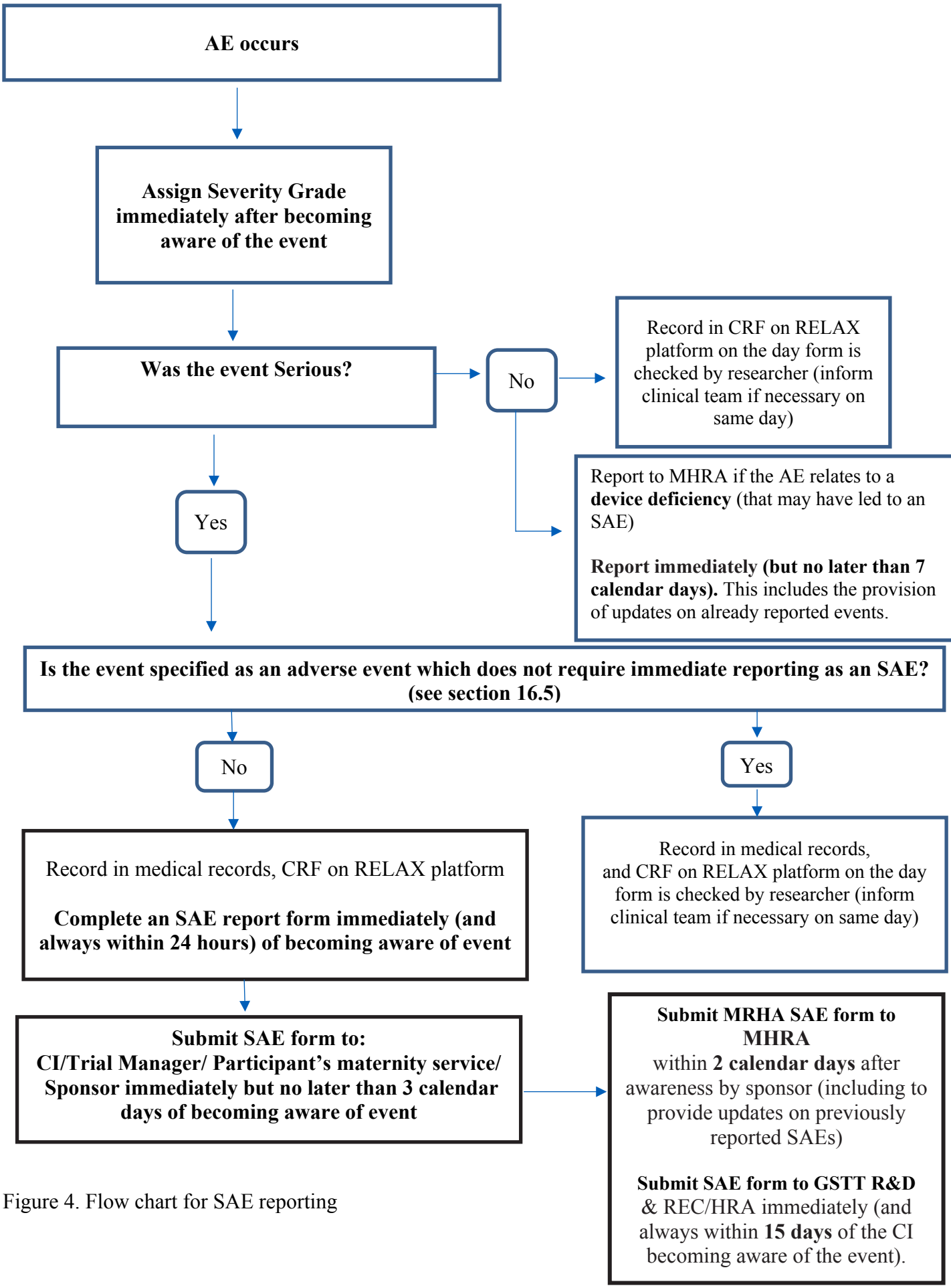

Figure 4. Flow chart for SAE reporting

16.5 Serious Adverse Events that do not require reporting

The following are considered to be expected in this population of pregnant women (and their babies) or a result of the routine care/treatment of a participant and as such do not need to be reported:

Maternal

- Hospitalisations for treatment planned prior to recruitment, and hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. This includes pregnancy. However, complications occurring during such hospitalisation will be AEs/SAEs.
- Admission in active labour
- Admission for cervical ripening or induction of labour
- Admission for social reasons
- Admission for unstable lie or external cephalic version
- Miscarriage
- Preterm delivery in maternal interest
- Preterm delivery in fetal interest
- Hospitalisation for pregnancy induced hypertension
- Hospitalisation for "rest"
- Hospitalisation for "observation" or "monitoring" for which the women is admitted for a period of less than 12 hours
- Delivery complications such as caesarean section or post-partum haemorrhage
- Admission for antepartum haemorrhage
- Admission for suspected preterm labour or preterm labour
- Admission for premature rupture of membranes
- Admission for other reasons for monitoring

The following outcomes are pre-specified and as such will be recorded on the RELAX platform CRFs but not expeditiously reported:

- Diagnosis of anxiety
- Diagnosis of depression
- Diagnosis of postpartum psychosis

16.6 Reporting urgent safety measures

If any urgent safety measures are taken, the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

16.7 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor, e.g., missed RELAX sessions or assessments. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the study

(b) the scientific value of the study.

The CI and R&D Office should be notified immediately of any case where the above definition applies during the study conduct phase.

16.8 Reporting incidents involving a medical device(s) (if applicable)

This has been summarised in the above sections, 16.1 and 16.4 specifically. In addition, in adherence to Medical Devices Serious Adverse Event Reporting guidelines (MEDDEV 2.7/3 revision 3), any SAE or device deficiency that may have led to an SAE if: a) suitable action had not been taken or; b) intervention had not been made; or c) if circumstances had been less fortunate, will be reported by the sponsor or authorised representative immediately (but not later than 7 calendar days for device deficiencies or 2 calendar days for SAEs). New findings and updates in relation to already reported events will also be reported within 7 calendar days (device deficiencies) or 2 calendar days (SAEs).

16.9 Trust incidents and near misses

The following is the policy of GSTT, we intend to adhere to this and apply this understanding across all participating sites, unless informed otherwise:

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to the specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors, or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with the potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX (or other Trust online incident reporting system) as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standards of patient care or service.
c) It places patients, staff members, visitors, contractors, or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with the potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

17 Suspension or Premature Termination of Investigation

Although there is no formal interim analysis, the DMEC will monitor the trial, and will communicate any issues with recruitment, data collection and/or data quality of concern to the TSC. If the TSC deem any issues to be a major threat to participant safety or the integrity of the trial, they may decide to terminate it prematurely.

The sponsors (KCL and GSTT) will be informed of any major issues concerning the trial as well as of any decisions about trial suspension or termination.

18 Publication Policy

This clinical investigation will be registered in a publicly accessible database and the results of the clinical investigation will be made publicly available.

The results of the clinical investigation will be offered for publication within 12 months of the end of the grant for this clinical investigation. Potential publications and media appearances will be brought to the attention of the Sponsor's office.

According to the NIHR, criteria for authorship includes:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- Drafting the work or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

All of these conditions must be met to qualify for authorship.

19 Bibliography

1. Austin, M. P., Frilingos, M., Lumley, J., Hadzi-Pavlovic, D., Roncolato, W., Acland, S., Saint, K., Segal, N. & Parker, G. (2008). Brief antenatal cognitive behaviour therapy group intervention for the prevention of postnatal depression and anxiety: a randomised controlled trial. Journal of affective disorders, 105(1-3), 35-44.

2. Bayrampour, H., Trieu, J., & Tharmaratnam, T. (2019). Effectiveness of eHealth Interventions to Reduce Perinatal Anxiety: A Systematic Review and Meta-Analysis. The Journal of Clinical Psychiatry, 80(1).

3. Cox, J. L., Holden, J. M., & Sagovsky, R. (1987). Edinburgh postnatal depression scale (EPDS). Br J psychiatry, 150, 782-786.

4. Fairbrother, N., Young, A. H., Zhang, A., Janssen, P., & Antony, M. M. (2017). The prevalence and incidence of perinatal anxiety disorders among women experiencing a medically complicated pregnancy. Archives of women's mental health, 20(2), 311-319.

5. Goodman, J. H., Guarino, A., Chenausky, K., Klein, L., Prager, J., Petersen, R., Forget, A. & Freeman, M. (2014). CALM Pregnancy: results of a pilot study of mindfulnessbased cognitive therapy for perinatal anxiety. Archives of women's mental health, 17(5), 373-387.

6. Green, S. M., Haber, E., Frey, B. N., & McCabe, R. E. (2015). Cognitive-behavioral group treatment for perinatal anxiety: a pilot study. Archives of women's mental health, 18(4), 631-638.

7. Heller, H. M., Hoogendoorn, A. W., Honig, A., Broekman, B. F., & van Straten, A. (2020). The Effectiveness of a Guided Internet-Based Tool for the Treatment of Depression and Anxiety in Pregnancy (MamaKits Online): Randomized Controlled Trial. Journal of medical Internet research, 22(3), e15172.

8. Hirsch, C. R., & Mathews, A. (2012). A cognitive model of pathological worry. Behaviour research and therapy, 50(10), 636-646.

9. Hirsch, C. R., Hayes, S., & Mathews, A. (2009). Looking on the bright side: accessing benign meanings reduces worry. Journal of abnormal psychology, 118(1), 44.

10. Hirsch, C. R., Krahé, C., Whyte, J., Bridge, L., Loizou, S., Norton, S., & Mathews, A. (2020). Effects of modifying interpretation bias on transdiagnostic repetitive negative thinking. Journal of consulting and clinical psychology, 88(3), 226.

11. Hirsch, C. R., Krahé, C., Whyte, J., Krzyzanowski, H., Meeten, F., Norton, S., & Mathews, A. (2021). Internet-delivered interpretation training reduces worry and anxiety in individuals with generalized anxiety disorder: A randomized controlled experiment. Journal of consulting and clinical psychology, 89(7), 575–589.

12. Hirsch, C. R., Krahé, C., Whyte, J., Loizou, S., Bridge, L., Norton, S., & Mathews, A. (2018). Interpretation training to target repetitive negative thinking in generalized anxiety disorder and depression. Journal of Consulting and Clinical Psychology, 86(12), 1017.

13. Hirsch, C. R., Meeten, F., Gordon, C., Newby, J. M., Bick, D., & Moulds, M. L. (2020). Repetitive Negative Thinking and Interpretation Bias in Pregnancy. Clinical Psychology in Europe, 2(4), 1-17.

14. Hirsch, C. R., Meeten, F., Krahé, C., & Reeder, C. (2016). Resolving ambiguity in emotional disorders: The nature and role of interpretation biases. Annual Review of Clinical Psychology, 12, 281-305.

15. Hirsch, C. R., Meeten, F., Newby, J. M., O'Halloran, S., Gordon, C., Krzyzanowski, H., & Moulds, M. L. (2021). Looking on the Bright Side Reduces Worry in Pregnancy: Training Interpretations in Pregnant Women. Clinical Psychology in Europe, 3(2), 1-17.

16. Joubert, A. E., Grierson, A. B., Chen, A. Z., Moulds, M. L., Werner-Seidler, A., Mahoney, A. E. J., & Newby, J. M. (2021). Managing rumination and worry: A pilot study of an internet intervention targeting repetitive negative thinking in Australian adults. *Journal of affective disorders*, *294*, 483–490.

17. Joubert, A. E., Grierson, A. B., Li, I., Sharrock, M. J., Moulds, M. L., Werner-Seidler, A., Stech, E. P., Mahoney, A. E. J., & Newby, J. M. (2023). Managing Rumination and worry: A randomised controlled trial of an internet intervention targeting repetitive negative thinking delivered with and without clinician guidance. *Behaviour research and therapy*, *168*, 104378.

18. Krahé, C., Whyte, J., Bridge, L., Loizou, S., & Hirsch, C. R. (2019). Are different forms of repetitive negative thinking associated with interpretation bias in generalized anxiety disorder and depression?. Clinical Psychological Science, 7(5), 969-981.

19. Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ□9: validity of a brief depression severity measure. Journal of general internal medicine, 16(9), 606-613.

20. Lewis, G., & Pelosi, A. J. (1992). The manual of CIS-R. London: Institute of Psychiatry.

21. Loughnan, S. A., Joubert, A. E., Grierson, A., Andrews, G., & Newby, J. M. (2019). Internet-delivered psychological interventions for clinical anxiety and depression in perinatal women: a systematic review and meta-analysis. Archives of women's mental health, 22(6), 737–750.

22. Loughnan, S. A., Wallace, M., Joubert, A. E., Haskelberg, H., Andrews, G., & Newby, J. M. (2018). A systematic review of psychological treatments for clinical anxiety during the perinatal period. Archives of women's mental health, 21(5), 481-490.

23. Machin, D., Campbell, M.J., Tan, S.B., & Tan, S.H. (2009). Sample Size Tables for Clinical Studies (3rd ed.). Blackwell Publishing, ISBN: 978-1-4051-4650-0.

24. Maguire, M., & Delahunt, B. (2017). Doing a thematic analysis: A practical, step-by-step guide for learning and teaching scholars. All Ireland Journal of Higher Education, 9(3).

25. Mahdi A, Dembinsky M, Bristow K, Slade P. Approaches to the prevention of postnatal depression and anxiety–a review of the literature. Journal of Psychosomatic Obstetrics & Gynecology. 2019 Oct 2;40(4):250-63.

26. Mataix-Cols, D., Rosario-Campos, M. C., & Leckman, J. F. (2005). A multidimensional model of obsessive-compulsive disorder. The American journal of psychiatry, 162(2), 228–238.

27. Mathews, A., & Mackintosh, B. (2000). Induced emotional interpretation bias and anxiety. Journal of abnormal psychology, 109(4), 602.

28. McEvoy, P. M., Thibodeau, M. A., & Asmundson, G. J. G. (2014). Trait Repetitive Negative Thinking: A Brief Transdiagnostic Assessment. Journal of Experimental Psychopathology, 1–17.

29. Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the Penn State Worry Questionnaire. Behaviour research and therapy, 28(6), 487–495.

30. Misri, S., Reebye, P., Corral, M., & Mills, L. (2004). The use of paroxetine and cognitivebehavioral therapy in postpartum depression and anxiety: a randomized controlled trial. The Journal of clinical psychiatry.

31. Moulds, M. L., Black, M. J., Newby, J. M., & Hirsch, C. R. (2018). Repetitive negative thinking and its role in perinatal mental health. Psychopathology, 51, 161-166.

32. Mumsnet | The UK's most popular website for parents - Mumsnet [Internet]. Mumsnet.com. 2022 [cited 13 September 2022]. Available from: https://www.mumsnet.com/

33. Mundt, J. C., Marks, I. M., Shear, M. K., & Greist, J. M. (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. The British Journal of Psychiatry, 180(5), 461-464.

34. Netmums: The UK's Most Inclusive Parenting Community [Internet]. Netmums. 2022 [cited 13 September 2022]. Available from: https://www.netmums.com/

35. Newby, J. M., Werner-Seidler, A., Black, M. J., Hirsch, C. R., & Moulds, M. L. (2021). Content and Themes of Repetitive Thinking in Postnatal First-Time Mothers. Frontiers in psychology, 12, 586538.

36. Nolen-Hoeksema, S., & Morrow, J. (1993). Effects of rumination and distraction on naturally occurring depressed mood. Cognition & Emotion, 7(6), 561-570.

37. O'Donnell, K. J., Glover, V., Barker, E. D., & O'Connor, T. G. (2014). The persisting effect of maternal mood in pregnancy on childhood psychopathology. Development and psychopathology, 26(2), 393-403.

38. Somerville, S., Dedman, K., Hagan, R., Oxnam, E., Wettinger, M., Byrne, S., ... & Page, A. C. (2014). The perinatal anxiety screening scale: development and preliminary validation. Archives of women's mental health, 17(5), 443-454.

39. Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine, 166(10), 1092-1097.

40. Statista 2020a. Percentage of households with home computers in the United Kingdom (UK) from 1985 to 2018. Available from: https://www.statista.com/statistics/289191/household-penetration- of-home-computers-in-the-uk/ [Accessed August 25 2020].

41. Stefanopoulou, E., Hirsch, C. R., Hayes, S., Adlam, A., & Coker, S. (2014). Are attentional control resources reduced by worry in generalized anxiety disorder?. Journal of abnormal psychology, 123(2), 330.

42. Stein, A., Craske, M. G., Lehtonen, A., Harvey, A., Savage-McGlynn, E., Davies, B., Goodwin, J., Murray, L., Cortina-Borja, M. & Counsell, N. (2012). Maternal cognitions and mother–infant interaction in postnatal depression and generalized anxiety disorder. Journal of abnormal psychology, 121(4), 795.

43. Sullivan, T. R., White, I. R., Salter, A. B., Ryan, P., & Lee, K. J. (2018). Should multiple imputation be the method of choice for handling missing data in randomized trials?. *Statistical methods in medical research*, *27*(9), 2610–2626.

44. Thoemmes, F., MacKinnon, D. P., & Reiser, M. R. (2010). Power analysis for complex mediational designs using Monte Carlo methods. Structural Equation Modeling, 17(3), 510-534.

45. Topper, M., Emmelkamp, P. M., Watkins, E., & Ehring, T. (2017). Prevention of anxiety disorders and depression by targeting excessive worry and rumination in adolescents and young adults: A randomized controlled trial. Behaviour research and therapy, 90, 123-136.

46. Toussaint, A., Hüsing, P., Gumz, A., Wingenfeld, K., Härter, M., Schramm, E., & Löwe, B. (2020). Sensitivity to change and minimal clinically important difference of the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7). Journal of affective disorders, 265, 395-401.

47. Van Bockstaele, B., Clarke, P. J., Notebaert, L., MacLeod, C., & Salemink, E. (2020). Effects of cognitive load during interpretation bias modification on interpretation bias and stress reactivity. Journal of Behavior Therapy and Experimental Psychiatry, 68, 101561.45.

48. Werner-Seidler, A., Perry, Y., Calear, A. L., Newby, J. M., & Christensen, H. (2017). School-based depression and anxiety prevention programs for young people: A systematic review and meta-analysis. Clinical psychology review, 51, 30-47.

49. White, I. R., & Thompson, S. G. (2005). Adjusting for partially missing baseline measurements in randomized trials. *Statistics in medicine*, *24*(7), 993–1007.

50. White, I. R., Horton, N. J., Carpenter, J., & Pocock, S. J. (2011). Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ (Clinical research ed.)*, *342*, d40.