

STUDY PROTOCOL:



Optimising psychological treatment for Anxiety Disorders in Pregnancy: a feasibility study for a Trial of time-intensive CBT versus weekly CBT (ADEPT)

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Study Title:

Optimising psychological treatment for Anxiety Disorders in Pregnancy: a feasibility study for a Trial of time-intensive CBT versus weekly CBT (ADEPT)

Trial Registration:

ISRCTN:	ISRCTN81203286		
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Protocol Number:	Version 2	Date:	19.09.2019

Protocol version:

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Trial Management Group (TMG)

The TMG comprises:

Laura Potts – trial statistician

Dr Ben Carter – statistical and trials expertise

Dr Vanessa Lawrence – expertise in qualitative methodology

Dr Fiona Challacombe – chief investigator

The TMG have inputted into the protocol.

Data Monitoring Committee

Trial steering group

2x clinicians

1 statistician

1x expert by experience

Will meet prior to start of the trial and annually to check data and adverse events.

A patient advisory group (PAG) comprising 4-6 women with lived experience of perinatal mental health problems will be set up to advise on the study and will meet approximately annually.

Background and Rationale

The mental health of pregnant women and those with a baby up to one year (known as the perinatal period) is a priority and its importance has been recognised in the recent NHS Five-year Forward View for Mental Health (1). Anxiety disorders are common, affecting 11-16% of women in pregnancy and 8-17% of women in the postpartum period (2-5). They are by definition functionally impairing. Pregnancy can exacerbate or trigger anxiety disorders and can also elicit new fears related to pregnancy and parenting (6). For most women, the antenatal anxiety disorder persists into the postpartum period (4, 7) and also increases the risk of postpartum depression (8). Postpartum anxiety disorders have been associated with impaired maternal functioning (9-12), excessive infant crying and feeding problems including lower rates of breastfeeding. Elevated anxiety symptoms (a feature of all anxiety disorders) during pregnancy have been associated with child behavioural problems up to eighteen years, possibly due to elevated cortisol levels in utero (13, 14). Children of parents with anxiety disorders are at increased risk of developing an anxiety disorder themselves (15, 16). The potential negative effects of chronic anxiety disorders in parents are wide ranging.

It is therefore important to identify and treat antenatal anxiety disorders quickly to ameliorate or prevent these short and long term outcomes for both mother and child. Shorter exposure of the developing fetus to the elevated levels of maternal cortisol associated with anxiety may protect the child; successful antenatal treatment would improve quality of life for the mother and potentially reduce the impact on parenting. Clinical practice guidelines reflect the need to treat women quickly in the perinatal period to reduce the risk of harm to the infant (CG192; 2014).

Pregnant women prefer psychological treatments to pharmacotherapy, but practical factors are also paramount; in a survey of 428 pregnant women, concern regarding committing to a full course of treatment sessions during pregnancy for anxiety was reported (17). UK primary mental health care sites have reported dropout rates prior to treatment for perinatal women of up to 40% (18). Shorter, but more intensive, treatment could therefore be an innovative and welcome format that may improve engagement and optimise outcomes for both mother and baby. In England, pregnant women will be in regular contact with maternity services with many potential opportunities to detect and treat mental disorders. Psychological treatments for anxiety disorders, primarily cognitive behaviour

therapy, have a substantial evidence base (NICE guidelines CG159, CG113, CG31) and women are usually offered one-to-one disorder specific CBT, as supported by a recent systematic review of clinical evidence (19). However, NICE guidelines for perinatal mental health (CG192; 2014) highlight the need for more research on moderate to severe anxiety disorders, in particular OCD, panic, PTSD and social phobia (recommendation 7.7.2.4). Each of these disorders can be triggered or exacerbated in the context of pregnancy and can affect mother-infant interactions and parenting (20).

CBT is usually delivered in approximately 12 hour-long weekly sessions, depending on the presenting disorder. Individual CBT is 'semi-idiographic', that is, based on shared principles but tailored to the individual context and needs of the client (CORE, UCL). Modifications may be made according to the client's physical state, for example, not running upstairs in a panic exposure exercise if the person is unable, instead identifying other means to test relevant beliefs. Such modifications in pregnancy have been suggested and there is evidence supporting the use of exposure based CBT in pregnancy (19).

Time-intensive CBT treatments (IN-CBT) have been trialled in (non- perinatal) patients with OCD, PTSD, social phobia and panic disorder with equivalent outcomes to weekly treatments, but achieved in a much shorter time frame of one to two weeks (21-24). This format has been found acceptable to patients. IN-CBT for postpartum OCD has been found to be safe and effective in the reduction of maternal OCD symptoms and acceptable to mothers (25, 26). Given the clear aim of delivering fast and effective treatment ideally before the baby is born, IN-CBT is likely to be a helpful modification to traditional weekly CBT for pregnant women with anxiety disorders and may be more beneficial in terms of longer-term outcomes.

Specific evidence is therefore needed to establish whether IN-CBT approaches are acceptable, produce equivalent engagement and adherence with treatment during pregnancy, are efficacious during pregnancy and helpful for maternal symptoms and parenting in the postpartum.

Research Question (1) Is antenatal IN-CBT acceptable to women with anxiety disorders?

Research Question (2) Is it feasible to test the effectiveness of IN-CBT compared with standard CBT in a full-scale trial?

Trial Design and Objectives

Aims & Objectives

The primary aim of the research is to test the feasibility of a definitive trial of antenatal IN-CBT against standard weekly antenatal CBT for anxiety disorders with 30 women recruited into each arm.

- (i) This will establish:
- (ii) the best means of recruiting women (physical or mental health settings)
- (iii) if participants will be randomised
- (iv) if the intervention is delivered as intended
- (v) the acceptability of the interventions
- (vi) the properties of the primary outcome measure and other measures
- (vii) follow up rates for participation in a full trial.

Trial design

This will be a parallel group, 1:1 feasibility trial. Participants will be randomised to one of the two treatment arms (time-intensive or standard weekly CBT) and will complete measures at baseline and primary outcome point. An assessor blind to group allocation will collect data at this point.

Methods: Participants, interventions & Outcomes

Study Setting

Currently, perinatal women are being offered CBT within outpatient Improving Access to Psychological Therapies (IAPT) services by qualified CBT therapists delivering standard CBT. Each of the SLAM IAPT services (Lambeth, Lewisham, Southwark, Croydon) has a named perinatal lead, who are qualified experienced therapists and will provide standard and IN-CBT within the trial. Alternatively, an experienced therapist within the service will be nominated. The perinatal leads have agreed to participate and are supportive of the study. CBT therapists at the Centre for Anxiety Disorders and Trauma (part of Lambeth, Lewisham and Southwark IAPT services) will also provide both treatments.

Eligibility Criteria

Inclusion criteria:

- Women over the age of 18
- a current primary anxiety disorder according to DSM-V criteria OCD, PTSD, Social anxiety or panic disorder
- Pregnant (12 weeks – 25 weeks)
- Eligible to be seen under Lambeth, Lewisham, Southwark, Croydon IAPT services
- Available for either intensive or weekly treatment
- Either not on psychotropic medication or on a stable dose of medication for at least six weeks with no plans to change this during the intervention.

Exclusion:

- Women with a primary DSM-V depressive disorder, affective or psychotic disorder or current problems with substance abuse.
- Women with 'complex PTSD' (prolonged multiple traumas affecting a number of domains)
- Women who have high-risk conditions requiring significant additional management (e.g. Multiple Sclerosis, Lupus, Polycystic Ovary Syndrome)
- Women who are receiving psychological therapy elsewhere
- Unable to read English adequately to complete questionnaires

Interventions:

There are well developed specific protocols and techniques for CBT for anxiety disorders (27). In general CBT follows the course of establishing the participant's goals for therapy and developing a patient-specific formulation based on the relevant model (e.g. Salkovskis for OCD; Wells & Clark Social Phobia; Ehlers & Clark, PTSD; Clark Panic disorder). The formulation identifies relevant beliefs and behaviours that maintain the anxiety disorder. Cognitive and behavioural strategies are then used to help patients change the beliefs and behaviours that maintain their anxiety disorder. A standard modification to treatment in the perinatal context would be to include planning and support for the demands of the postpartum environment whilst the person is attending antenatal treatment. All participants and therapists tape-record sessions (as per standard clinical practice) to listen to between appointments and participants will be encouraged to apply new learning and strategies as homework. The content of treatment will be the same for both arms.

Standard CBT: This will comprise 8-10 hours (depending on the disorder) of one to one CBT on a one hour per week basis. This is termed 'high intensity' CBT in IAPT services and will be offered to all women who participate in the trial and are randomised to standard CBT. Two follow up sessions of one hour will then be offered by the treating therapist which will include one in late pregnancy, one at 1m postpartum.

Intensively delivered CBT (IN-CBT): This will deliver the disorder-specific treatment in 4-5 sessions over 1-2 weeks, delivered at the earliest convenient point between 5 and 8 months of pregnancy, and totalling 8-10 hours. Two follow up sessions of one hour will then be offered which will include one in late pregnancy, one at 1m postpartum.

Intensive and standard treatments for each disorder will therefore be matched according to the IAPT standard of 12 hours face to face contact.

Criteria for discontinuation or modifying intervention

Adverse events will be monitored and recorded including the mental and physical health of the mother and any pregnancy-related events. Should participants deteriorate clinically in terms of significantly increased symptoms of anxiety or depression, or an increase in risk to themselves or others, then the intervention will be stopped and a referral made to specialist perinatal services and/or other services as clinically appropriate.

Fidelity and adherence

Quality of treatment: Training on IN-CBT will be delivered prior to recruitment for trial therapists. All therapists will receive weekly in-service supervision on clinical cases as is standard practice. The amount of supervision on trial cases will be recorded.

Fidelity will be defined as delivering all key treatment components during treatment and will be established by a checklist of key components of treatment derived from core competencies for specific disorders using treatment notes (22). This will be completed by the therapist at the end of each session. Standardised therapy note sheets will be kept and checked to establish fidelity against the checklist. Therapists will also be required to submit

a random selection of therapy recordings to be rated for fidelity to CBT on an established scale, the Cognitive Therapy Rating Scale (CTS-R).

Client engagement and adherence to therapy will be rated by therapist at each session on a Likert scale, number of sessions attended will be recorded and the participants' perspective will be assessed in detail in a qualitative interview at 3 months.

Concomitant care and interventions

Participants will be asked about any contact with physical or mental healthcare services at each point of contact. Healthcare usage (eg. GP appointments) will also be recorded using the ADSUS (service use questionnaire). This will capture healthcare usage for mother and baby.

Outcomes

Feasibility & acceptability

The aim of the research is to test the feasibility of a definitive trial of IN-CBT against weekly antenatal CBT for antenatal anxiety disorders. The objectives are to establish:

- (i) if we can identify/recruit patients via (a) information provided in healthcare settings at booking visits/by midwives/self-referral (midwives are currently using the GAD-2 to screen for anxiety) and (b) approach by a primary care therapist. We would require a minimum of 30% potentially eligible participants from each recruitment method for each to be deemed feasible. An acceptable recruitment rate would be at least 3 participants/month.
- (ii) if participants are willing to be randomised. We would require a take-up of >70% of eligible participants to be deemed feasible.
- (iii) if the intervention is received as intended in both arms in terms of being the intended mode of treatment and treatment fidelity using a content checklist. A minimum of 80% of participants in the trial would need to complete >60% of each intervention in hours for each to be deemed feasible, ie. 7.5 hours out of 12 (28). For completers in the intensive arm, these treatment hours (8 out of 10 hours) will need to be completed in the two-week window for IN-CBT to be considered to be delivered as intended.
- (iv) acceptability of both interventions to participants; this will be determined by qualitative investigation, a brief rating scale asking if the treatment was useful at the end of treatment and numbers completing treatment
- (v) establishing the parameters needed in order to estimate the sample size for a full trial
- (vi) participation and data completion at 3m outcome assessment; a follow up rate of >80% is required to determine feasibility.
- (vii) the acceptability of assessment measures to participants; this will be determined by qualitative interview and brief rating scales asking if it was useful and clear

A qualitative interview will investigate treatment experiences in women undergoing IN-CBT and those undergoing standard CBT. This will enquire about experiences of having an

anxiety disorder in pregnancy, experiences of randomisation, experiences of treatment including perceived benefits, limitations and challenges during treatment and in postpartum adjustment. Experiences of recruitment and assessments will also be explored. Topics will be derived in collaboration with the project advisory group. Interviews will take place at the final outcome point 3 months postpartum. These will be recorded and transcribed. The number of participants will be guided by theoretical saturation.

Baseline and outcome measures

Please see table for timings.

Initial clinician interview

1. *Structured clinical interview for DSM-V (SCID-V; (29))*. This semi-structured interview is used by clinicians to establish DSM-V diagnoses, which will be part of initial screening for inclusion in the trial (30).

Routinely collected IAPT data

1. *Demographic* – maternal age, occupation and pregnancy stage will be recorded.
2. **GAD-7 (31)* is a well validated and widely used 7 item measure of anxiety and a key IAPT outcome measure used routinely. A change of 4 or more on the GAD has been found to be clinically significant across anxiety disorders (32). *This is the potential primary outcome measure.
3. *PHQ-9 (33)* is well validated 9 item questionnaire used to measure symptoms of depression. It is also a key IAPT outcome measure.
4. The *Work and Social Adjustment Scale (34)* is a 5-item patient self-report measure, which assesses the impact of a person's mental health difficulties on their ability to function in terms of work, home management, social leisure, private leisure and personal or family relationships.
5. Disorder specific measures: one of the following will be used depending on primary disorder.
 - a) *OCD: Obsessive Compulsive Inventory-Revised (OCI; (35))*. This is a 42-item self-report inventory concerning symptoms of OCD. The internal consistency for the full scale is high (0.86-0.95), The OCI also shows good discriminative validity and is reliable to measure change in symptoms over time [35].
 - b) *Panic: Mobility Inventory (alone) (36)*. This self-report scale requires respondents to rate avoidance of a range of specific situations over the last week on a scale of 0-4. The inventory has good reliability, validity and sensitivity to change.
 - c) *PTSD: Impact of Events Scale (IES (37))*. This is a 22 item self-report scale of symptoms of PTSD. The scale has excellent internal consistency (38).
 - d) *Social Phobia: The Social Phobia Inventory (SPIN (39))* has 17 items and a cut-off score of 19 or above. For each item, respondents rate from 0-4 how bothered they have been by the item during the past week. The total score provides a measure of the severity of social phobia and the item has good sensitivity to change.

Trial-specific measures

Working alliance inventory – Short Revised

6. Working Alliance Inventory – Short Revised. (Hatcher, This 12 item questionnaire will be completed by therapists and participants after the first 2 hours of treatment in both arms.

Pregnancy Anxiety

7. *Pregnancy related anxiety questionnaire (PRAQ; (40))*. This 10 item self-report questionnaire assesses anxiety related to childbirth and will be administered at baseline and the last antenatal appointment treatment session. The pregnancy related anxiety scale has acceptable internal reliability (Cronbach's $\alpha = .78$).

Infancy related measures:

8. *Postpartum bonding questionnaire (PBQ) (41)*. This self-report instrument consists of 25 items to be rated on a scale of 0 ("never") to 5 ("always") and assesses the maternal perception of her felt bonding with the infant.

9. Mother Infant Interactions

Mother-infant interactions at 3 months postpartum will be captured in a 3-minute video clips taken during play and nappy change at home and subsequently assessed by a trained rater using the CARE Index (42). This tool has been widely used in scientific research with mothers that have mental health difficulties as early as one to five months postpartum (43-45) and validated for use with families from different social classes and cultural backgrounds (46). Coding comprises seven aspects of adult and infant dyadic behaviour: four aspects concentrate on affect (facial expression, verbal expression, affection and body contact) and three focus on temporal contingencies (turn-taking, control and developmental appropriateness of chosen activity). Each aspect of adult and infant behaviour is evaluated individually and summed to make seven scale scores. For adults, these are sensitivity, unresponsiveness and controlling. Infants (birth to 15 months of age) are coded on cooperativeness, difficultness, compulsivity and passivity. Interactions receive a score on each aspect of adult and infant behaviour and scores are then summed to create the seven scale scores, each on a range from 0 to 14 (42). For example, a "sensitive dyad", the mother must achieve a score of 11 or higher on the sensitivity scale. A score of 7 or more is required to rate the interaction as "adequate". 5 to 6 points mark the "inept" range and suggest the need for parental education. 4 or fewer points are considered as in the "high risk" range, implying risk of abuse or neglect. Coding of the interaction takes between approximately 30-40 minutes. Video-taped interactions will be coded by trained, reliable coders, as recommended by Crittenden (42). To reduce measurement bias, the coders will be unaware of the hypotheses that are being tested in the study and blind to the mental health status of the women.

Measures 9-10 have been included to assess the potential impact on parenting and service use.

Health Economic Measures

10. Adult Service Use Measure (ADSUS, unpublished). The AD-SUS is a measure of resource use developed for use in mental health populations and a version adapted for use in prenatal populations as part of an NIHR PGfAR will be used (the ESMI study). This measure will be used to capture maternal and child utilization of all health and social care services (including health visitor, GP visits).

Table of measures and timings

Measure	Pre-treatment baseline assessment		Every treatment session	After first 2 hours of treatment	Late pregnancy follow up session	1m postnatal follow up session	3m outcome
1. SCID	X						
2. Demographics	X						
3. PHQ-9	X		X		X	X	X
4. GAD-7	X		X		X	X	X
5. WSAS	X		X		X	X	X
6. Disorder specific measure	X		X		X	X	X
7. WAI				X			
8. Pregnancy anxiety	X				X	X	
9. PBQ						X	X
10. Mother-infant interactions							X
11. ADSUS							X
12. Qualitative interview							X

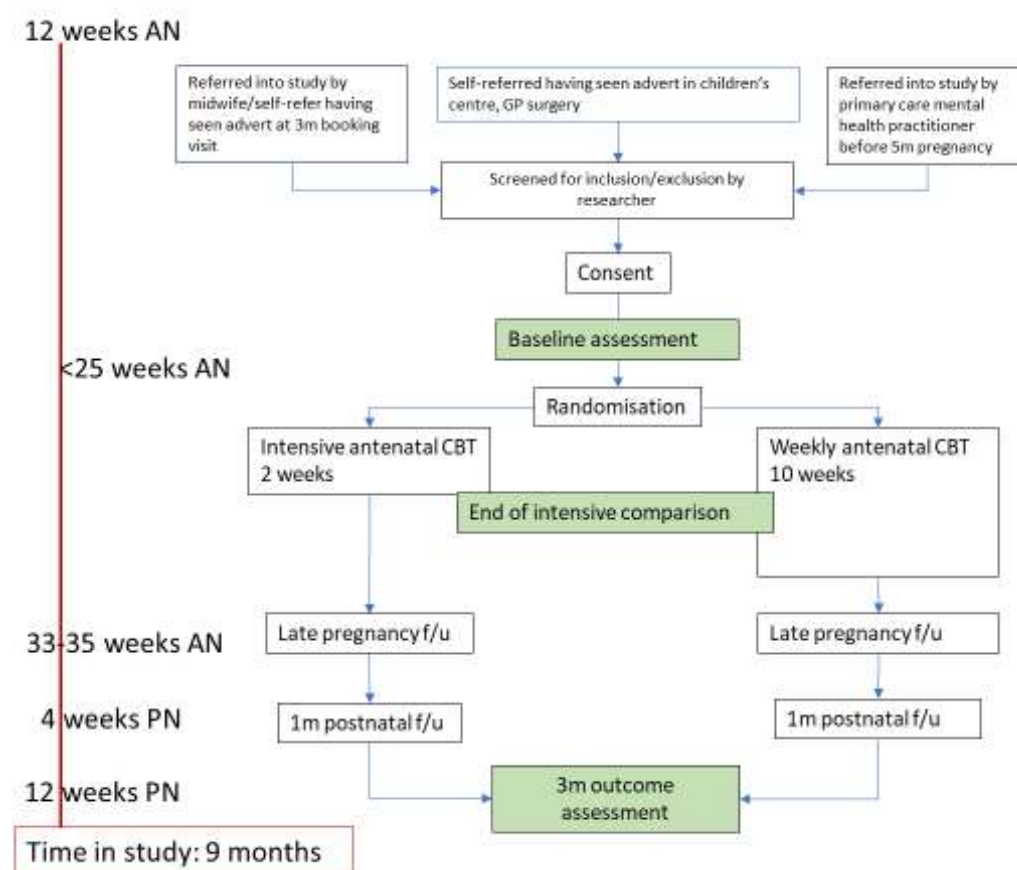
(For key, see above; numbers correspond to above list)

Therapist related measures

Therapist time, including participant contact and assessment of time spent in other indirect participant related activities (e.g. supervision, training, administration etc.), will be recorded by therapists using standardised clinical notes.

As is standard practice in CBT, therapy sessions will be audio-recorded by therapists (clients are also asked to audio record sessions in order to make the most of sessions). A random selection of therapy tapes from each therapist will be rated by assessors blind to the aims of the study using a standardised measure of cognitive therapy skills, the cognitive therapy rating scale (CTS-R; (47)).

Participant timeline



Sample Size

In line with guidance on feasibility studies no power calculation has been carried out (48). A sample size of 30 in each group has been recommended to answer questions relating to feasibility (49, 50).

This feasibility study will clarify recruitment rates, the practicality of delivering intervention in the proposed setting, acceptability of interventions to participants and standard deviation of the primary outcome measure in this sample.

Recruitment:

Midwives at local hospitals will be made aware of the study and colleagues working in specialist perinatal services as well as local IAPT services in Croydon, Southwark, Lambeth and Lewisham. In line with procedures for IAPT services, women can be referred into or will be able to self-refer into the project. All women will be registered for treatment as a client in IAPT. One recruitment method is that women with an anxiety disorder (OCD, social anxiety, PTSD and panic disorder) will be identified during routine antenatal booking appointments using standard GAD-2 questions asked by midwives.

Women may also be identified via self-referral (leaflets and advertising for the study will be placed in waiting areas prior to booking visits; leaflets for the study will also be placed in GP surgeries and children's centres). Once identified or self-identified, women who have read the information sheet and are interested in taking part will be referred to a research psychologist who will confirm a diagnosis of anxiety disorder and inclusion/exclusion criteria by telephone. Women will be registered as a patient under IAPT services and a therapist identified who can treat the woman. If suitable and if she consents to take part in the study, an initial assessment pack will be completed by the woman, and ideally a face to face meeting will be arranged in order to collect questionnaires, discuss any questions she has and find out the random allocation.

Participants will receive a small remuneration for their time in completing the assessments of £10 shopping voucher per assessment point (Pre-randomisation and 3m). This is also known to increase response rates [50].

Clinicians will be regularly reminded about the study and flyers and posters made available.

Assignment of interventions

Allocation:

Participants will be allocated to the intervention group (IN-CBT) or standard CBT (ratio 1:1) via an independent online system based at the King's Clinical Trials Unit (King's CTU) based at King's College London. Random allocation will be at the level of the individual participant, stratified by disorder (OCD, Panic, PTSD, Social Phobia). Any preference on allocation will be recorded prior to randomisation.

Allocation concealment

Participants will be stratified according to disorder. Simple randomisation, with no blocks, ensures allocation concealment is high. Allocation to treatment can only be guessed.

Implementation:

The CI will enrol participants and will assign participants to interventions.

Blinding:

The patient, therapist and CI will know of the allocation. The 3m outcome assessor will not be aware of allocation, and will conduct the qualitative interview last as it will likely lead to unblinding. The senior statistician will also be blind to allocation until the end of the trial.

Data Collection, Management and analysis

Data Collection Methods:

Questionnaire data will be collected via weblink using existing data collection methods in IAPT services and/or hard copies as preferred, completed in participants own time. Initial clinician interviews will be conducted over the phone at a suitable time for the mother, or in person if she prefers. IAPT measures are routinely collected at each contact so collecting this treatment data will not involve additional burden for women.

The primary outcome point is 3m postpartum; video and qualitative interview audio data will be collected during a visit to the participant's home at this point in addition to the IAPT measures.

As per standard practice in IAPT services, anxiety, depression and disorder specific measures will be taken at each point of contact. Participants will be asked to complete the additional measures at the baseline and outcome points (see table above).

All video recordings will be collected using password-protected iPads. The iPads will be brought back to the university site for secure storage directly after the interview. Video recordings will be immediately uploaded on to the secure university computer network, which is password-protected and which only the research team have access. Once the video recordings have been transferred onto the secure computer network they will be permanently deleted from the iPads. In order to verify the deletion of the files, we will empty the "trash" file of the iPads. The iPads will be linked to a cloud account in order to be able to wipe them remotely should they be stolen. The video data files will be saved on the secure university computer network using only participant ID and date as identifiers, and only researchers involved in the project will have access to the drive with the video recordings.

Promotion of participant retention – data collection from dropout

Participants will receive an incentive (£10) for the additional burden incurred from completing assessments at the final outcome point. They will be able to take part in this assessment regardless of treatment completion. They will also have received £10 for participating in the baseline assessment.

Data management

The trial statistician will assist with management of the trial data which will be split into 3 databases. The participant main database and therapy database will be stored in separate SPSS files on a network drive accessible by the CI and trial statistician. The AE (adverse events) database will be stored as an Excel file on a network drive accessible by the CI only. All databases will be backed up periodically (approx. every three months), by creating a date-stamped ZIP file storing all databases and storing in a subfolder titled "Archives". This should be carried out by both the trial statistician and the CI separately. Each database will

contain data validation and more information is provided in the database specification document.

All research data will be pseudonymised using unique identification numbers and stored without contact details (names or addresses). Associations between participants' contact details and identification numbers will be stored in a separate encrypted electronic password-protected database. Access to this document will be restricted to the Chief Investigator. All data will be held on a secure database on an encrypted, password-protected computer, and access to it will be restricted to the research team. Audio files of the qualitative interviews will be retained until they have been transcribed to written form. Transcriptions of qualitative interviews will be completed as soon as possible after collection, anonymised and uploaded to the computer software programme, Nvivo. Hardcopies of study consent forms held by the central research team will be kept in a locked cabinet at the Institute of Psychiatry, Psychology & Neuroscience and retained for 7 years post research data analysis.

Video data

Once uploaded from the Ipad which is then cleared. The video data files will be saved on the secure university computer network using only participant ID and date as identifiers, and only researchers involved in the project will have access to the drive with the video recordings.

Statistical methods

Quantitative

Quantitative data analysis will be primarily descriptive to aid the planning of a future RCT. Participant flow through the study will be presented following CONSORT guidelines. Descriptive data will be presented in the form of means and standard deviations; medians and ranges; or percentages with 95% confidence intervals, as appropriate depending on the data being described. The following will be calculated: (1) percentage of participants meeting eligibility criteria (by disorder), (2) percentage of individuals consenting to the study, (3) percentage entering the randomisation phase, (4) treatment completion in each arm (number of participants completing over 60% of treatment hours), (5) percentage completing the outcome measures at 1m follow up and 3m outcome point, (6) between group pre-post effect sizes and confidence intervals and variance on the potential primary outcome measure (7) descriptive data on acceptability of intervention and outcome measures.

Descriptive data on therapist competence and compliance will be calculated using standardised cognitive therapy scale ratings (CTS-R) and number of treatment elements completed from checklist.

Qualitative

Focussed thematic analysis will be utilised as in a previous study evaluating experiences of treatment (51, 52) which compared participants' experiences in a non-randomized trial of intensive and weekly CBT for OCD. Constant comparison method (Glaser, 1978) will be used to delineate themes and sub-themes relating to participants' experiences and attitudes towards treatment.

Multiple coding will be conducted on three transcripts to allow researchers to identify and discuss alternative interpretations of the data. An analytical framework will be constructed around the perceived value, acceptability and feasibility of the treatment, which will be applied to the remaining transcripts, with themes and subthemes refined as necessary. Ideas about themes and their relationships will be recorded in theoretical memos and discussed among our Project Service User Advisory Group. The computer programme QSR N-VIVO will be used to process the transcripts, enabling coding and retrieval of a large volume of narrative data.

Data Monitoring:

Data Monitoring Committee

A data monitoring committee will be established to examine the clinical progress of trial participants given they are a vulnerable population; this will meet prior to recruitment and then every 12 months to oversee the trial.

Adverse effects

Participants will be carefully monitored throughout treatment by asking them for relevant information at each contact. Data will be collected from participants on potential adverse effects including pregnancy outcomes and prematurity.

Ethics and Dissemination

Research Ethics Approval

Approval was given by London Surrey Borders REC Reference 19/LO/0622 .

Protocol amendments

Any protocol amendments will be communicated to all involved parties by email.

Consent

The CI will obtain informed consent from participants prior to randomisation.

Confidentiality

Participants will be registered as patients under secure local NHS clinical patient records systems (known as IAPTUS in Lambeth, Lewisham and Southwark) which will hold their personal data. Participants research data (questionnaires) will be pseudonymised and entered on password protected databases as described above, kept on university computers. Video and audio data will be identified by participants number only. Participants names would be kept in a separate password protected database.

Declaration of Interests

None

Ancillary and post-trial care

Women requiring and wishing for further intervention after the end of the trial will be referred or signposted to appropriate intervention. This may be for further therapy within IAPT or within more specialised perinatal mental health services.

Dissemination Policy

1. Results of the trial will be fed back to participants via a newsletter.
2. Findings from the study will be published in a series of high quality peer reviewed papers. These will include journals targeted at academics, CBT practitioners, perinatal specialists and health service managers.
3. Study results will be presented at academic and service user led conferences as well as conferences for managers. Examples would be the BABCP conference, Marce conference, Maternal Mental Health Alliance conference.
4. Findings from the study will be disseminated to service user groups in perinatal mental health and for anxiety disorders and umbrella organisations such as the maternal mental health alliance.
5. Clinical approaches developed from the study would be disseminated in clinical skills workshops and training for existing and new CBT therapists. These would take place in IAPT and specialist perinatal settings.

Public access to full protocol, participant-level dataset and code

The protocol will be published on the trials registry website.

The protocol will be published on a trial registry database.

References

1. England N. Five Year Forward View for Mental Health. <https://www.england.nhs.uk/ourwork/futurenhs/>; England.nhs.uk. ; 2016.
2. Goodman JH, Chenausky KL, Freeman MP. Anxiety disorders during pregnancy: A systematic review. *Journal of Clinical Psychiatry*. 2014;75(10):e1153-e84.
3. Andersson L, Sundström-Poromaa I, Wulff M, Åström M, Bixo M. Depression and anxiety during pregnancy and six months postpartum: a follow-up study. *Acta obstetrica et gynecologica Scandinavica*. 2006;85(8):937-44.
4. Fairbrother N, Janssen P, Antony MM, Tucker E, Young AH. Perinatal anxiety disorder prevalence and incidence. *Journal of Affective Disorders*. 2016;200:148-55.
5. Dennis C-L, Falah-Hassani K, Shiri R. Prevalence of antenatal and postnatal anxiety: systematic review and meta-analysis. *The British Journal of Psychiatry*. 2017.
6. Martini J, Asselmann E, Einsle F, Strehle J, Wittchen HU. A prospective-longitudinal study on the association of anxiety disorders prior to pregnancy and pregnancy- and child-related fears. *J Anxiety Disord*. 2016;40:58-66.
7. Ross LE, McLean LM. Anxiety Disorders During Pregnancy and the Postpartum Period: A Systematic Review. *Journal of Clinical Psychiatry*. 2006;67(8):1285-98.
8. Martini J, Petzoldt J, Einsle F, Beesdo-Baum K, Hofler M, Wittchen H-U. Risk factors and course patterns of anxiety and depressive disorders during pregnancy and after delivery: A prospective-longitudinal study. *Journal of Affective Disorders*. 2015;175:385-95.
9. Warren SL, Gunnar MR, Kagan J, Anders TF, Simmens SJ, Rones M, et al. Maternal panic disorder: Infant temperament, neurophysiology, and parenting behaviors. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2003;42(7):814-25.
10. Murray L, Lau PY, Artech A, Creswell C, Russ S, Zoppa LD, et al. Parenting by anxious mothers: Effects of disorder subtype, context and child characteristics. *Journal of Child Psychology and Psychiatry*. 2012;53(2):188-96.
11. Stein A, Craske MG, Lehtonen A, Harvey A, Savage-McGlynn E, Davies B, et al. Maternal Cognitions and Mother-Infant Interaction in Postnatal Depression and Generalized Anxiety Disorder. *Journal of Abnormal Psychology*. 2012;121(4):795-809.
12. Challacombe FL, Salkovskis PM, Woolgar M, Wilkinson EL, Read J, Acheson R. Parenting and mother-infant interactions in the context of maternal postpartum obsessive-compulsive disorder: Effects of obsessional symptoms and mood. *Infant Behavior and Development*. 2016;44:11-20.
13. O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry*. 2003;44(7):1025-36.
14. Glover V. Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done. *Best practice & research Clinical obstetrics & gynaecology*. 2014;28(1):25-35.
15. Martini J, Knappe S, Beesdo-Baum K, Lieb R, Wittchen H-U. Anxiety disorders before birth and self-perceived distress during pregnancy: Associations with maternal depression and obstetric, neonatal and early childhood outcomes. *Early Human Development*. 2010;86(5):305-10.

16. Merikangas KR, Avenevoli S, Dierker L, Grillon C. Vulnerability factors among children at risk for anxiety disorders. *Biological Psychiatry*. 1999;46(11):1523-35.
17. Arch JJ. Cognitive behavioral therapy and pharmacotherapy for anxiety: Treatment preferences and credibility among pregnant and non-pregnant women. *Behaviour Research and Therapy*. 2013(0).
18. Health Do. IAPT Perinatal Positive Practice Guide. In: Health Do, editor. 2013. p. 18.
19. Marchesi C, Ossola P, Amerio A, Daniel BD, Tonna M, De Panfilis C. Clinical management of perinatal anxiety disorders: A systematic review. *Journal of Affective Disorders*. 2016;190:543-50.
20. Tietz A, Zietlow A, Reck C. Maternal bonding in mothers with postpartum anxiety disorder: The crucial role of subclinical depressive symptoms and maternal avoidance behaviour. *Archives of Women's Mental Health*. 2014;17(5):433-42.
21. Jonsson H, Kristensen M, Arendt M. Intensive cognitive behavioural therapy for obsessive-compulsive disorder: A systematic review and meta-analysis. *Journal of Obsessive Compulsive and Related Disorders*. 2015;6:83-96.
22. Ehlers A, Hackmann A, Grey N, Wild J, Liness S, Albert I, et al. A randomized controlled trial of 7-day intensive and standard weekly cognitive therapy for PTSD and emotion-focused supportive therapy. *The American Journal of Psychiatry*. 2014;171(3):294-304.
23. Mortberg E, Clark DM, Bejerot S. Intensive group cognitive therapy and individual cognitive therapy for social phobia: Sustained improvement at 5-year follow-up. *Journal of Anxiety Disorders*. 2011;25(8):994-1000.
24. Oldfield VB, Salkovskis PM, Taylor T. Time-intensive cognitive behaviour therapy for obsessive-compulsive disorder: A case series and matched comparison group. *British Journal of Clinical Psychology*. 2011;50(1):7-18.
25. Challacombe FL, Salkovskis PM. Intensive cognitive-behavioural treatment for women with postnatal obsessive-compulsive disorder: A consecutive case series. *Behaviour Research and Therapy*. 2011;49(6-7):422-6.
26. Challacombe FL, Salkovskis PM, Woolgar M, Wilkinson EL, Read J, Acheson R. A pilot randomized controlled trial of time-intensive cognitive-behaviour therapy for postpartum obsessive-compulsive disorder: effects on maternal symptoms, mother-infant interactions and attachment. *Psychol Med*. 2017;1-11.
27. Roth ADP, S. . The Competences Required to Deliver Effective Cognitive and Behavioural Therapy for People with Depression and with Anxiety Disorders. London: Department of Health; 2007.
28. Glenn D, Golinelli D, Rose RD, Roy-Byrne P, Stein MB, Sullivan G, et al. Who Gets the Most Out of Cognitive-Behavioral Therapy for Anxiety Disorders?: The Role of Treatment Dose and Patient Engagement. *Journal of consulting and clinical psychology*. 2013;81(4):639-49.
29. RL; FMWJKRS. Structured Clinical Interview for DSM-5—Research Version. Arlington, VA: American Psychiatric Association; 2015.
30. Association AP. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.; 2013.
31. Spitzer RL, Kroenke K, Williams JW, Löwe B. A brief measure for assessing generalized anxiety disorder: The gad-7. *Archives of Internal Medicine*. 2006;166(10):1092-7.

32. Gyani A, Shafran R, Layard R, Clark DM. Enhancing recovery rates: Lessons from year one of IAPT. *Behaviour Research and Therapy*. 2013;51(9):597-606.
33. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a Brief Depression Severity Measure. *Journal of General Internal Medicine*. 2001;16(9):606-13.
34. Mundt JC, Marks IM, Shear M, Greist JM. The Work and Social Adjustment Scale: A simple measure of impairment in functioning. *The British Journal of Psychiatry*. 2002;180(5):461-4.
35. Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, et al. The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychological assessment*. 2002;14(4):485-95.
36. Chambless DL, Caputo GC, Jasin SE, Gracely EJ, Williams C. The Mobility Inventory for Agoraphobia. *Behaviour Research and Therapy*. 1985;23(1):35-44.
37. Weiss DSM, C.R. The Impact of Event Scale-Revised. In: J.P. Wilson TMKE, editor. *Assessing Psychological Trauma and PTSD: A Practitioner's Handbook*. New York: Guilford Press.; 1997. p. 399-411.
38. Creamer M, Bell R, Failla S. Psychometric properties of the Impact of Event Scale - Revised. *Behav Res Ther*. 2003;41(12):1489-96.
39. CONNOR KM, DAVIDSON JRT, CHURCHILL LE, SHERWOOD A, WEISLER RH, FOA E. Psychometric properties of the Social Phobia Inventory (SPIN). New self-rating scale. 2000;176(4):379-86.
40. Huizink AC, Delforterie MJ, Scheinin NM, Tolvanen M, Karlsson L, Karlsson H. Adaption of pregnancy anxiety questionnaire-revised for all pregnant women regardless of parity: PRAQ-R2. *Arch Womens Ment Health*. 2016;19(1):125-32.
41. Brockington IF, Fraser C, Wilson D. The Postpartum Bonding Questionnaire: a validation. *Archives of Women's Mental Health*. 2006;9(5):233-42.
42. Crittenden PM. CARE Index manual. Miami: Family Relations Institute; 2003.
43. Steadman J, Pawlby S, Mayers A, Bucks RS, Gregoire A, Miele-Norton M, et al. An exploratory study of the relationship between mother-infant interaction and maternal cognitive function in mothers with mental illness. *Journal of Reproductive and Infant Psychology*. 2007;25(4):255-69.
44. Kenny M, Conroy S, Pariante CM, Seneviratne G, Pawlby S. Mother-infant interaction in mother and baby unit patients: Before and after treatment. *Journal of Psychiatric Research*. 2013;47(9):1192-8.
45. Conroy S, Pariante CM, Marks MN, Davies HA, Farrelly S, Schacht R, et al. Maternal psychopathology and infant development at 18 months: the impact of maternal personality disorder and depression. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012;51(1):51-61.
46. Amy Leventhal, Teresa Jacobsen, Laura Miller, Elena Quintana. Caregiving Attitudes and At-Risk Maternal Behavior Among Mothers With Major Mental Illness. *Psychiatric Services*. 2004;55(12):1431-3.
47. Blackburn IJ, I.; Milne, D.; Baker, C.; Standart, S.; Garland, A.; Reichelt, F. THE REVISED COGNITIVE THERAPY SCALE (CTS-R): PSYCHOMETRIC PROPERTIES. *Behavioural and Cognitive Psychotherapy*. 2001;29(4):431-46.
48. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology*. 2010;10(1):67.

49. Browne RH. On the use of a pilot sample for sample size determination. *Statistics in medicine*. 1995;14(17):1933-40.
50. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 2004;10.
51. Bevan A, Oldfield VB, Salkovskis PM. A qualitative study of the acceptability of an intensive format for the delivery of cognitive-behavioural therapy for obsessive-compulsive disorder. *British Journal of Clinical Psychology*. 2010;49(2):173-91.
52. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology*. 2006;3(2):77-101.