1. PROTOCOL FULL TITLE

Protocol Short Title/ Acronym:

Patient Decision Aid (PDA) for Antidepressant Use In Pregnancy: a pilot RCT

Trial Identifiers

ClinicalTrials.gov identifier	NCT02492009		
REC Number:	15/LO/0601		
UKCRN Number:	19051		
Protocol Version Number:	2	Date:	22/01/2016

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2. Study Synopsis

TITLE OF CLINICAL TRIAL:	**Patient Decision Aid (PDA) for Antidepressant Use In Pregnancy: a pilot randomised controlled trial**
Protocol Short Title/ Acronym:	PAUSE-P
Study Phase If Not Mentioned In Title:	
Sponsor Name:	King's College London and South London and Maudsley NHS Foundation Trust
Chief Investigator:	Professor Louise Howard
UKCRN Number:	19501
REC Number:	15/LO/0601
Medical Condition Or Disease Under Investigation:	Depression in pregnancy

Purpose Of Clinical Trial:	The proposed study is a pilot randomized controlled trial (RCT) of an electronic patient decision aid (PDA) for antidepressant use in pregnancy. The overall aim of this pilot RCT is to establish the feasibility of future large international RCT of the PDA's effectiveness.
Primary Objective:	The *primary objective* of this pilot is to assess the feasibility of the trial protocol; measured through three components: (1) feasibility (how well the trial protocol can be implemented), (2) acceptability (usability and tolerability of the intervention and of randomisation including patient and provider views) and (3) adherence (the degree to which the trial protocol is followed).
Secondary Objective(s):	The *secondary objective* is to inform sample size calculations for a future RCT by obtaining potential estimates of the PDA's efficacy (in terms of the primary outcome of decisional conflict, and the secondary outcomes of knowledge about treatment options, participant-provider interaction and depressive / anxiety symptoms at follow-up).
Trial Design:	Pilot parallel-group investigator-blinded RCT
Endpoints:	The primary outcome for this pilot study is the feasibility of conducting a large RCT to evaluate the efficacy of the PDA; assessed in terms of (a) feasibility of the trial protocol, (b) acceptability of the intervention and randomisation procedures to patients and clinicians and (c) adherence with the trial protocol. Secondary outcomes, which will generate preliminary effect sizes of the PDA and inform sample size calculations for the future RCT, include: Decisional Conflict Scale[1], Knowledge Questionnaire (adapted from Metcalfe et al)[2], Edinburgh Postnatal Depression Scale (EPDS)[3], Spielburg State-Trait Anxiety Inventory (STAI)[4] and the OPTION Scale measure of shared decision-making[5]. A brief topic guide will also be used to qualitatively analyse the audiotaped clinical follow-up appointment.[6]
Sample Size:	50 (25 per arm)
Summary Of Eligibility Criteria:	Women are eligible to participate if they meet all of the following *inclusion criteria*: (a) aged over 18, (b) are planning a pregnancy or are <30 weeks pregnant at enrolment, (c) have been offered to start or continue an antidepressant as treatment for depression by their clinician and (d) have moderate-to-high decisional conflict (score of >25 on the Decisional Conflict Scale). Women will be excluded from the study if they meet any of the following *exclusion criteria*: (a) have had alcohol or drug abuse or dependence in the previous 12 months, or (b) have active suicidal ideation or psychosis, or (c) are incapable of consenting to participation, or (d) have any major obstetric complications or foetal cardiac anomaly in the current or in a past pregnancy, or (e) are visually impaired) or (f) do not have sufficient English language proficiency to use the PDA.
Intervention (Description, frequency, details of delivery)	Women allocated to the intervention arm will log in to the study website and receive access to an electronic patient decision aid (PDA) on antidepressant use in pregnancy. They will have access to the website until their final follow-up or until the end of the main study period, during which time they can use the PDA as often as they would like at a time and place that suits them,

	alone or with others (e.g. family, friends). They can choose the amount of complex information that they want to access and read (by clicking on 'further information' links). They will also have access to a printable PDF containing references to standard published information and resources on antidepressant use in pregnancy (see Appendix).
Comparator Intervention:	Women allocated to the comparator intervention will log in to the study website and receive access to a printable PDF containing references to standard published information and resources on antidepressant use in pregnancy (see Appendix). They will have access to the website until their final follow-up or until the end of the main study period.
Maximum Duration Of Treatment Of A Subject:	All participants will have access to the study website until their final follow-up or until the end of the main study period. They will be asked to make a follow-up appointment with their clinician within 4 weeks of randomisation. They will have follow-up assessments at two time points: (1) 4 weeks post-randomization; and (2) either 12 weeks postpartum (if the participant enrolled while pregnant) or 6 months post-randomization (if the participant enrolled while planning a pregnancy). Therefore, the overall duration of participation in the study is up to one year.
Version And Date Of Final Protocol:	Version 1, date 9/2/2015
Version And Date Of Protocol Amendments:	Version 2, date 22/01/2016

3. Revision History

Document ID - (Document Title) revision X.Y	Description of changes from previous revision	Effective Date
UK_PDA_Protocol v1 9/2/2015	New Protocol	03/06/2015
UK_PDA_Protocol_v2 22/01/2016	Change to national recruitment via self-referral from online advertising and information provided to relevant clinicians	

4. Glossary of terms (Optional)

5. Protocol Contents

6. Background & Rationale

Recent reviews highlighted that depression complicates around 10% of pregnancies [7] and that untreated or incompletely treated depression is associated with adverse effects for mother and unborn child, including maternal suicide, prematurity and childhood emotional problems.[7,8] Antidepressants are indicated for the treatment of moderate to severe depression in pregnancy, when psychotherapy alone is unlikely to result in substantive improvements.[9] Unfortunately, antidepressants are associated with small increased risks of adverse neonatal and obstetric outcomes, including congenital cardiac abnormalities, poor neonatal adaptation and preterm birth.[7] The safety evidence is largely observational, and it is difficult to disentangle the effects of depression, medication and associated lifestyle factors.[7]

When considering antidepressant use in pregnancy, women and clinicians have to weigh up the possible risks of ongoing depression versus antidepressant use, in the face of great scientific uncertainty. These complex decisions are often finely balanced, and need to be guided not only by the rapidly changing scientific evidence, but also by the woman's values, preferences and the extent to which she wants to be involved in the treatment decision.[9] Women experience high rates of conflict and uncertainty in relation to antidepressant use in pregnancy, and this is not addressed by usual clinical care - including expert consultation and standard information resources.[10] Recent studies identified key barriers to decision making in this context- including lack of information, difficulty in weighing up risks and benefits and unhelpful external influences[10]- but also women's desire for greater involvement in the decision making process.[11]

Patient decision aids aim to improve shared decision-making for complex health decisions such as this one, which involve weighing up uncertain benefits and harms. [12] A 2014 Cochrane Systematic Review of 115 decision aids for a variety of screening and treatment decisions found that their use improved patients' knowledge and risk perception, helped patients to make informed value-based choices and improved patient-clinician communication,[12] but to our knowledge there are no evaluated PDAs for antidepressant use in pregnancy.

To address this gap, we have developed an electronic PDA for antidepressant use in pregnancy. The PDA was developed by leading international experts in Canada, with expertise in decision aids, perinatal psychiatry and psychopharmacology (Louise Howard, PI, was on the advisory group and Simone Vigod, co-investigator, led the development). The PDA's content and layout were informed by: (1) The International Patient Decision Aids Standard (IPDAS) collaboration guidelines [13]; (2) Published systematic reviews of evidence related to the benefits and harms of antidepressant treatment in pregnancy (several conducted by team members) [14-17]; and (3) Evidence related to the decisional needs of patients faced with this complex decision.[10,11] The prototype was developed by the healthcare technology company, QoC Health (http://qochealth.com/). It was revised on the basis of feedback from a multidisciplinary international steering committee, and the findings of an open-label acceptability trial in the target population. The PDA's content and format are described in section 8.1 below (see Appendix for further details).

The proposed study is a pilot RCT of this PDA based in London with nationwide recruitment, to be conducted in parallel with a pilot RCT in Toronto. The latter is already underway, following an open-label trial (N=13 patients); which found that the PDA was acceptable to patients and that its use was associated with a 52% reduction in the Decisional Conflict Scale score. The findings from the pilot RCTs in London and Toronto will inform a future international definitive RCT.

7. Trial Objectives and Design

7.1 Trial Objectives

The *primary objective* of **this pilot study** is the feasibility of conducting a large RCT to evaluate the efficacy of the PDA. This comprises 1) feasibility (how well the trial protocol can be implemented), (2) acceptability (usability and tolerability of the intervention and of randomisation including patient and provider views) and (3) adherence (the degree to which the trial protocol is followed). *Secondary outcomes* will include preliminary effect sizes of the PDA to inform sample size calculations for the future RCT.

Primary endpoints

(A) Feasibility: Measured in terms of (1) eligibility (e.g. proportion of patients eligible); (2) recruitment (e.g. rates overall and by recruitment strategy, non-participation reasons); and (3) timing (e.g. enrolment to first log-in to the PDA).

(B) Acceptability: This will measured by: (1) The Decision Support Tool Acceptability Questionnaire (for participants randomized to receive the PDA intervention only). (2) Sudy website usage (including number of women who complete the PDA; number of electronic logins & length of time required to complete the PDA; number of participants who use the PDA summary sheet with their provider); (3) The Provider Perspective Survey

(C) Adherence with trial protocol: This will be measured by: (1) number of participants who follow-up with their clinician within the intended active study phase (i.e. 4 weeks post-randomization); and (2) The rate of follow-up data collection at each time point.

Secondary endpoints

Secondary outcomes will inform the sample size required for a future RCT of the effectiveness of the tool. Decisional conflict will be the primary outcome for the future RCT, as has been the case in previous PDA studies, [18,19] measured using the Decisional Conflict Scale.[20] Secondary outcomes measures for the future RCT are listed below.

A. Decisional Conflict Scale (DCS)[20] The purpose of this scale is to measure a person's perception of difficulty in making a decision including: (1) uncertainty in choosing between options, (2) modifiable factors contributing to uncertainty such as feeling uninformed, unclear about personal values, and unsupported, and (3) quality of the choice selected, which is defined as informed and consistent with personal values, and with which a person expresses personal satisfaction[20]. The DCS consists of 16 items (ranging from 1 to 5, with 5 being high decisional conflict). Scores of 25 or greater are associated with those who delay decisions. Test-retest and internal consistency coefficients exceed 0.78.
B. Knowledge Questionnaire:[2] Knowledge of depression treatment options will be assessed using a knowledge questionnaire that includes items regarding the effectiveness of various treatment options, as well as known possible adverse effects. Effectiveness estimates will be presented in the form of a continuous scale from 0 to 100%. Content knowledge items will be presented as 'true' or false'. This tool is a modified version of a tool previously created and validated by a member of the Canadian team in other PDA evaluations.
C. Participant-Provider Clinical Interaction: We will audiotape the first patient-provider visit following the intervention if patient and clinician agree. Audiotapes will be transcribed verbatim and analyzed using (i) framework qualitative analysis[6] and (ii) the OPTIONS scale; a 12-item observer-rated validated and widely used scale for measuring shared decision-

making.[5,21] Clinicians will have the opportunity to review the PDA and the research protocol prior to the start of the study and can opt out of the audiotaping at any time.

D. Edinburgh Postnatal Depression Scale (EPDS):[3]. We will measure depressive symptoms using the EPDS, a self-report depression screening measure that has been validated for use in pregnancyEPDS scores > 12 are predictive of a diagnosis of major depressive disorder.
E. Spielburg State-Trait Anxiety Inventory (STAI):[22] We will measure anxious symptoms using the STAI, a self-report anxiety screening measure that has shown good discriminately validity in perinatal populations. STAI scores > 48 are predictive of having an anxiety disorder diagnosis,

7.2 Trial Design

A pilot parallel group, investigator-blind randomised controlled trial.

7.3 Trial Flowchart

Trial flowchart							
Study Variable	**Sample**	**Measure**	**Prior to enrolment**	**Baseline**	**Clinic Visit**	**4 weeks**	**LT F/U[5]**
Eligibility	All subjects	Eligibility assessment	X				
Participation rate		Written consent (obtained in person, online or by post).	X				
Demographics		Participant Characteristics[Co]		X			
Mental Health		MINI[Co, 1]		X			
		EPDS[E, 2] & STAI [E, 3]		X		X	X
Decisional Conflict		Decisional Conflict Scale[E]		X		X	
Knowledge		Knowledge Questionnaire[E]		X		X	
Adherence		Website Use & Chart Review[F]				X	X
Patient-Provider		Audiotaped Clinic Visit[E]; analysed using qualitative Framework Analysis and the OPTIONS scale[4]			X		
Decision		Health Service Questionnaire[Co]		X		X	X
Participant View	PDA only	Acceptability Questionnaire[F]				X	
Provider Views	Providers	Provider Perspective Survey[F]					X*

Legend: [F]Feasibility; [E]Efficacy; [Co]Covariate; [1]Mini Neuropsychiatric Interview; [2]Edinburgh Postnatal Depression Scale; [3]State-Trait Anxiety Inventory; [4]Observing Patient Involvement in Shared Decision-making; [5]LT f/u = Long Term Follow-Up: At 12 weeks postpartum (for women enrolled while pregnant) or 6 months after baseline assessment (for women enrolled while planning a pregnancy); *Collected only after all other subject data collection is complete

8. Trial Intervention

8.1 Therapy/Intervention Details

Experimental and control group interventions will be delivered online. Women randomized to the *intervention arm* will access the electronic PDA described below. Women randomized to the

control arm will login to the study website and receive a printable PDF containing references to standard published information on depression and antidepressant use in pregnancy (see Appendix for details). This ensures women have access to accurate information on the benefits and risks of antidepressant medication in pregnancy (even though they will not receive the PDA). Also, this will allow us to evaluate the efficacy of the PDA (plus clinical care) compared to available information and resources (plus clinical care) in the future RCT. All participants will receive close clinical monitoring, as per standard care.

The interactive, electronic PDA has 3 main sections: (1) Evidence-based information about depression in pregnancy and each treatment option and procedure; (2) evidence-based information on the risks and benefits of both untreated depression and antidepressant treatment, integrated with a series of exercises to help women determine which risks and benefits are most important to them. This section also includes exercises to help women consider how their relationships with others (e.g. partners, friends, and providers) affects the decision-making process; and (3) a summary section that outlines the information reviewed and which benefits and risks they deemed most important. Participants can choose the amount of complex information that want to access and read (by clicking on 'further information' links). At the end of the module, they will see a summary PDF which they can print and use in clinical follow-up. They will also receive a printable PDF containing references to standard published information and resources on depression and antidepressant use in pregnancy (see Appendix).

Women will have access to the study website until their final follow-up or until the end of the main study period (at least three months after the final woman is randomised).. They can access it multiple times at a time and place that suits them, alone or with others (e.g. family, friends). For those who cannot access the study website on a personal computer, we will provide access in a private area in a clinical setting.

8.2 Frequency and duration of intervention

Baseline data will be collected by the researcher after consent has been obtained.

Consent will be obtained in person where possible (and mainly for participants recruited in London). For participants who are not seen in person, a copy of the Patient Information Sheet and the consent form will be made available online (on the study website) and also by post / email (if potential participants request this). Women interested in participating will be asked to provide their contact details (by online submission, email or phone) - and a member of the study team will phone them to answer any queries about the study and go through the consent form. Following this, women who want to participate will be asked to complete the consent form, including their name and date, and send it to the research team (by online submission, email or post). For consent forms sent by participants to the study team online or by email, we will not require a signature and participants will be asked to give their initials to indicate their consent.

Baseline data will be collected in person or over the phone (or on skype, as per patient preference). After completion of baseline measures, participants will be asked to access the study website and review the website information (i.e. PDA or control condition) *prior* to the next encounter with their clinical provider, which should be scheduled as soon as possible (and within 4 weeks of randomisation) because of the urgency of deciding on treatment for depression in pregnancy. A 4-week time period in which to review the PDA and follow-up with the clinical provider was chosen to allow women adequate time to review the PDA (perhaps log-in multiple times if desired) and make treatment decisions with their clinical provider. Participants will have access to the PDA until their final follow-up or until the end of the main study period.

The researcher will arrange to audio-tape the first follow-up appointment after randomisation, to assess the impact of the PDA on participant-provider clinical interaction (if clinicians and patients

agree to this and if it is feasible for the researcher to travel to the clinical site with an audio-recorder).

The researcher will collect follow-up outcome measures at: (1) 4 weeks post-randomization; and (2) either 12 weeks postpartum (if the participant enrolled while pregnant) or 6 months post-randomization (if the participant enrolled while planning a pregnancy). This will be done in person or over the phone (or on skype, as per patient preference). Providers whose patients were enrolled in the study will complete a Provider Perspective Survey. The overall time spent in the study will be up to one year.

8.3 Intervention records

Access to the study website will be recorded using the web-system log. The first follow-up appointment after randomisation will be audiotaped (if feasible and if the doctor and patient agree to this) to assess the impact of the PDA on participant-provider clinical interaction.

8.4 Subject Compliance.

Participant compliance will be determined by measuring (a) access to the study's electronic website, using the web-system log; (b) proportion of patients who attend a follow-up appointment within 4 weeks of randomisation; (c) proportion of participants randomised to the PDA arm who bring the PDA's summary PDF to their follow-up appointment

8.5 Study adherence

We will use several post-recruitment retention strategies to retain participants in this study and optimize follow-up data collection rates. We will provide travel expenses as required and both baseline and follow-up data can be collected over the phone or on skype. Women will receive £20 following completion of the baseline interview and each of the follow-up interviews, in appreciation of their time. After completion of the first follow-up questionnaire and audio-taped clinic visit, women will be contacted by telephone and/or email to remind them about their second follow-up assessment. In addition, women without computer and/or internet access at home will be provided with access to a laptop which can be used at a clinical site to complete the online component of the study intervention, if this is feasible to arrange.

Adherence (i.e. access to the study website and rates of clinical follow-up within 4 weeks) will be measured as in section 8.4 above.

8.6 5.5 Concomitant Medication

This pilot will recruit women who are considering starting or continuing an antidepressant during pregnancy. Participants may be prescribed one or more medications during the trial period, including an antidepressant, and any such prescribing is permitted concurrently with the intervention. All medications prescribed will be recorded at baseline and each follow-up point.

9. Research environment

This pilot RCT will be based in London, recruiting from local services (see below) and nationally via self-referral (e.g. through online advertising), and will be conducted in parallel with a pilot RCT in Toronto, Canada.

The pilot will recruit women in London who are under the care of one or more of the following services: (a) GP practices in London; (b) mental health services in South London and Maudsley NHS Foundation Trust, including specialist perinatal psychiatric services in King's College Hospital,

St Thomas's Hospital and community clinics in Lewisham and Croydon and (c) maternity services in King's College Hospital, Guy's & St Thomas's hospital and Croydon University Hospital. National recruitment will occur via online advertising to potential participants and information sent to relevant clinicians. The clinicians outside London will not recruit women into the study but will be able to provide information about the study (e.g. details of the study website) to potentially eligible women who will then be able to self-refer into the study or find out more about the study using the contact sheet on the website. Please see Appendix for details.

10. Selection and Withdrawal of Subjects

10.1 Inclusion Criteria

Women are eligible to participate if they meet all of the following *inclusion criteria*:

- Aged 18 or over
- Are planning a pregnancy or are <30 weeks pregnant at enrolment
- Have been offered to start or continue an antidepressant as treatment for depression by their clinician
- Have moderate-to-high decisional conflict (score of ≥25 on the Decisional Conflict Scale).
- Have given written informed consent to participate.

10.2 Exclusion Criteria

Women will be excluded from the study if they meet any of the following *exclusion criteria*:

- Are aged <18
- Have had alcohol or drug abuse or dependence in the previous 12 months
- Have active suicidal ideation or psychosis
- Are incapable of consenting to participation
- Have any major obstetric complications or foetal cardiac anomaly in the current or in a past pregnancy
- Are visually impaired
- Do not have sufficient English language proficiency to use the PDA

When we discuss antidepressants in this decision aid, we are talking about all of the following antidepressant medications:

Generic name (US brand name)	**UK brand name**
• Citalopram (Celexa™)	**Cipramil**
• Escitalopram (Cipralex™)	**Cipralex**
• Fluoxetine (Prozac™)	**Prozac, Olena**
• Fluvoxamine (Luvox™)	**Faverin**
• Paroxetine (Paxil™)	**Seroxat**
• Sertraline (Zoloft™)	**Lustral**
• Venlafaxine (Effexor™)	**Efexor**
• Duloxetine (Cymbalta™)	**Cymbalta**

- Desvenlafaxine (Pristiq™) Not used in UK

Only women who are taking or have been recommended to start taking an antidepressant listed above are eligible to participate in this study. This decision aid does not focus on antidepressant medications such as Mirtazapine (RemeronTM) or Bupropion (Wellbutrin TM), nor other, less commonly prescribed medications for depression such as tricyclic antidepressants or monoamine oxidase inhibitors.

10.3 Selection of Participants

The study will aim to recruit 50 women over a one year period, and to establish the most effective recruitment strategies for use in a future definitive RCT. We will recruit in London from: (a) GP practices; (b) mental health services in South London and Maudsley NHS Foundation Trust, including specialist perinatal psychiatric services in King's College Hospital, St Thomas's Hospital and community clinics in Lewisham and Croydon and (c) maternity services in King's College Hospital, Guy's & St Thomas's hospital and Croydon University Hospital. We will identify potential participants using a variety of methods, including: (a) asking clinicians to identify and refer potentially eligible patients who are interested in taking part; (b) using the SLAM 'Consent for Contact' programme and (c) direct advertising to patients in clinical areas and via websites and social media. We will recruit nationally through online advertising to potential participants. For example, through the website NetMums, which offers support and information on pregnancy and parenting, including a section on perinatal depression, and has collaborated with research on antenatal depression in the recent past. Organisations which provide information and support about pregnancy (e.g. NCT, Tommy's Baby Charity and PANDAS [Pre and Postnatal Depression Advice and Support]) will also be approached to promote the study on social media (e.g. Twitter and Facebook). All online advertising will link to a webpage about the study (see Appendix) hosted on the King's College London website, which will provide women with more details about the study including the participant information sheet and consent form, contact details for the research team, and a form to enable women to provide the researchers with their contact details. In addition, we will send information about the study to relevant clinicians nationally. The clinicians outside London will not recruit women into the study but will provide information about the study (e.g. details of the study website) to potentially eligible women who will then be able to self-refer into the study and find out more about the study using the contact sheet on the website.

Multiple methods of recruitment are being used for this study because it is a pilot trial and aiming to assess the feasibility of a number of alternatives for recruitment that could be used in a larger trial of the Patient Decision Aid. In all cases, we will only enrol patients after their clinical team has been contacted, to establish eligibility and inform them of the woman's planned participation in the trial. We will obtain consent (written or verbal) from women to contact their clinical team.

10.4 Randomisation Procedure / Code Break

Participants will be randomized to the PDA or control group using a computer-generated random allocation sequence. After consent has been obtained and baseline assessments have been administered, the researcher will provide the participant with a card or email with the website address for the study and the participant's study ID number, which will serve as their website login. At login, the participant ID will be matched automatically within the program to the predetermined, concealed, allocation sequence and the participant will receive the allocated intervention. Participants will be randomized 1:1 ratio with stratification by whether they are recruited from primary care or psychiatric settings.

10.5 Withdrawal of Subjects

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAE's, protocol violations, administrative reasons or other reasons (see below for details). It is

understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients will be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from the study, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Safety will be assessed at all follow-up time points and be routinely reviewed by the PI. Adverse events will be recorded and serious adverse events immediately reported (within 24 hours by telephone or fax) to the CI (Louise Howard) for consideration of further action. Protocols will be developed regarding specific criteria for participant withdrawal during the active study phase that will include active suicidal ideation, psychosis and acute pregnancy complications that might change the considerations required for treatment decisions. If withdrawal criteria are met, the participant will be withdrawn from the study intervention and followed by her physician as per usual care. We will attempt to collect follow-up data, with the patient's permission. Participants who terminate early will be part of intention to treat analysis.

10.6 Expected Duration of Trial.

The study duration will be from the patient's first baseline assessment to the last follow-up assessment: either 12 weeks postpartum (if the participant enrolled while pregnant) or 6 months post-randomization (if the participant enrolled while planning a pregnancy). So overall, the expected duration is 6 to 12 months.

11. Trial Procedures

11.1 By Visit

- At pre-enrolment: the researcher will assess eligibility and obtain written informed consent from those willing to participate (using the procedure described in section 8.2).
- At the baseline assessment, the researcher will administer the relevant study questionnaires to the patient (see section 7.3); provide the participant with a card or email with the study website address and the participant's study ID number (which will serve as their website login) and ask the patient to book a follow-up appointment with their clinician within 4 weeks
- The first clinical follow-up appointment post randomization will be audiotaped if this is feasible and the patient and doctor agree to this
- At the 4-week and long-term research follow up appointments, the researcher will administer the relevant study questionnaire to the patient (see section 7.3)

11.2 Laboratory Tests

No laboratory measurements are required.

12. Assessment of Efficacy

12.1 Primary Efficacy Parameters

For this pilot RCT, the primary efficacy outcome is the feasibility of the study protocol, as detailed in section 7.1. This is because the primary aim of this pilot is to assess the feasibility of a future definitive RCT of the PDA's efficacy.

12.2 Secondary Efficacy Parameters

Secondary outcomes will inform the sample size required for a future RCT of the effectiveness of the tool: Decisional conflict will be the primary outcome for the future RCT, as has been the case in previous PDA studies[18,19]. Additional outcome measures will include knowledge comprehension, the impact of the PDA on the participant-provider clinical interaction and psychiatric symptoms at follow-up. See section 7.1 for details.

12.3 Procedures for Assessing Efficacy Parameters

Efficacy parameters will be measured using questionnaires and analysis of an audiotaped clinical follow-up appointment. See section 7.1 and 7.3 for details. The table detailing the relevant measures is copied here for ease of reference:

Trial flowchart							
Study Variable	**Sample**	**Measure**	**Prior to enrolment**	**Baseline**	**Clinic Visit**	**4 weeks**	**LT F/U[5]**
Eligibility	All subjects	Eligibility assessment	X				
Participation rate		Written consent (obtained in person, online or by post).	X				
Demographics		Participant Characteristics[Co]		X			
Mental Health		MINI[Co, 1]		X			
		EPDS[E, 2] & STAI [E, 3]		X		X	X
Decisional Conflict		Decisional Conflict Scale[E]		X		X	
Knowledge		Knowledge Questionnaire[E]		X		X	
Adherence		Website Use & Chart Review[F]				X	X
Patient-Provider		Audiotaped Clinic Visit[E]; analysed using qualitative Framework Analysis and the OPTIONS scale[4]			X		
Decision		Health Service Questionnaire[Co]		X		X	X
Participant View	PDA only	Acceptability Questionnaire[F]				X	
Provider Views	Providers	Provider Perspective Survey[F]					X*

Legend: [F]Feasibility; [E]Efficacy; [Co]Covariate; [1]Mini Neuropsychiatric Interview; [2]Edinburgh Postnatal Depression Scale; [3]State-Trait Anxiety Inventory; [4]Observing Patient Involvement in Shared Decision-making; [5]LT f/u = Long Term Follow-Up: At 12 weeks postpartum (for women enrolled while pregnant) or 6 months after baseline assessment (for women enrolled while planning a pregnancy); *Collected only after all other subject data collection is complete

13. Assessment of Safety

13.1 Specification, Timing and Recording of Safety Parameters.

The intervention in this pilot RCT (the use of an electronic patient decision aid) is a low risk procedure. A recent Cochrane review of 115 RCTs of PDAs for a range of clinical decisions did not identify any harms from the use of PDAs to the patient, the decision-making process or the patient-provider interaction.[12] Nonetheless, safety will be assessed by the researcher at each assessment point (baseline, 4-week follow-up, long-term follow-up). Safety will also be assessed by the clinician in the course of routine clinical care, which often involves intensive follow-up in this

population. Protocols will be developed regarding specific criteria for participant withdrawal during the active study phase that will include active suicidal ideation, psychosis and acute pregnancy complications that might change the considerations required for treatment decisions. If withdrawal criteria are met, the participant will be withdrawn from the study intervention and followed by her physician.

13.2 Procedures for Recording and Reporting Adverse Events

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a therapy has been administered including occurrences which are not necessarily caused by or related to that therapy.

Adverse Reaction (AR): Any untoward and unintended response in a subject to a therapy which is related to any duration of therapy administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information known about the therapy in question in the view of the investigator

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

Reporting Responsibilities

All SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator to the R&D office

13.2.1 Adverse events that do not require reporting

No potential related adverse events are expected in this pilot trial. As part of the study interventions, the woman will access information on depression and antidepressant use in pregnancy. This will be done in the context of a health professional having recommended an antidepressant in pregnancy, so any queries or concerns arising from accessing this information via the study intervention would be addressed in the course of usual clinical care. If there are any concerns about a woman's mental health or risk during the course of the study (e.g. emotional distress, suicidal ideas), the researcher will alert the CI (Louise Howard) and will arrange for the woman to have increased support from her clinical team.

13.3 Stopping Rules

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the regulatory authority or ethics committee concerned (for example if important new risk information emerges about antidepressant use in pregnancy during the study period which is not incorporated into the PDA).

The trial may also be prematurely discontinued due to lack of recruitment. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

14. Statistics

14.1 Sample Size

We estimated that a minimum sample size of 40 (20 per intervention arm) was required for this pilot RCT based on (a) a review by Hertzog, which suggested a range of 20-40 participants for assessing the acceptability of an intervention[23]; and (b) pilot data for the primary outcome that we intend to use in a future efficacy RCT- the Decisional Conflict Scale (DCS). Among women with mean DCS score=30 (moderate-high) and SD 14.8 (based on pilot data), a total sample size of 40 participants would allow the detection of a 13-point difference in DCS scores (clinically significant) between intervention & control groups with probability (power) 0.8 (alpha=0.05). We aim is to recruit at least 25 participants to each intervention group, allowing for 20% loss to follow-up for a minimum of 20 per group retained in the study.

In the hospitals affiliated with King's Health Partners (King's College Hospital and Guy's and St Thomas's Hospitals) there are approximately 12,000 deliveries per year. Based on UK national data and Toronto pilot work, we assume that (a) at least 3% of pregnant women would be considered for an antidepressant (based on national UK data),[24] and (b) 40% of these women would be eligible for this study,[10] and (c) 60% of those eligible would agree to participate[10]. Therefore, if all potentially eligible women were identified and referred to the study team, we could reach our recruitment target of 50 women over a 7-month period in our study setting. In practice, we have discovered that the rate of identification and referral of potentially eligible women into the study is extremely low (over a 5-month period seven potentially eligible women were referred to the study, of whom two were eligible and one participated in the study). We are therefore expanding to include national recruitment via online advertising and information sent to relevant clinicians.

14.2 Randomisation

Participants will be randomized 1:1 ratio with stratification by whether they are currently pregnant or planning pregnancy.

Researchers will be blind to group allocation at all data collection time points. PDA acceptability data will be collected by a different researcher in order to maintain blinding. Participants cannot be blinded as to which intervention they received, due to the nature of the intervention, but they will be blinded to study hypotheses. Providers may or may not become aware of the participant's allocation depending on whether or not participants discuss their use of the PDA with them. However, providers will not collect outcome data, minimizing risk for measurement bias due to lack of blinding.

14.3 Analysis

(1) Statistical analysis: Means will be calculated to determine feasibility and compliance estimates for recruitment rate for each strategy, rates of nonparticipation, completion rate of the PDA, follow-up rates at the various intervals, and so on. We will calculate the acceptability of the intervention using the Likert-type scale responses from the participant and provider questionnaires, and will collate additional comments made by participants or providers for consideration of modifications to

the content, layout or technical capacity of the PDA. To compare decisional conflict between women receiving the PDA to women receiving the comparison condition at 4 week follow-up we will use the intention-to-treat principle. Missing data points will be excluded from the analysis, and individuals with less than 2 DCS measurements will be treated as lost to follow-up. An on-treatment analysis will also be performed as a sensitivity analysis (for best possible performance of the PDA). Means of the DCS scores of the experimental and comparison groups at the primary endpoint will be compared using a one-way ANCOVA model, where the covariate will be baseline DCS score. Results will be stratified by centre. This effect size will be used to generate the sample size needed for the future RCT

(2) *Qualitative analysis*: after transcribing the audiotaped follow-up appointment, data will be analysed using framework analysis (which entails the 5 key steps of familiarisation, coding, developing an analytical framework, indexing and data interpretation).[6] The interview will also be analysed using the observer-rated OPTION Scale for shared decision-making.[5]

15. Trial Steering Committee

A Trial Steering Committee will not be used for this small, low-risk pilot RCT.

16. Data Monitoring Committee

Because of the low risk nature of this intervention, an independent Data Safety Monitoring Board will not be developed. Safety will be assessed at all follow-up time points and be routinely reviewed by the PI. Adverse events will be recorded and serious adverse events immediately reported (within 24 hours by telephone or fax) to the CI (Louise Howard) for consideration of further action.

17. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), and REC direct access to source data and other documents (eg patients' case sheets).

18. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005.

This protocol and related documents will be submitted for review to London - Queen Square Research Ethics Committee (REC)

The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor

19. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team. A committee consisting of the UK and Canadian PIs and study co-investigators and the research assistants will hold teleconferences as necessary (every 2 months) to discuss study progress, including participant recruitment, and unexpected issues. The lead sponsor, King's College London, will take primary responsibility for ensuring that the design of the trial meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.

20. Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Patient data will be anonymised
- All anonymised data will be stored on a password protected computer.
- All trial data will be stored in line with the Data Protection Act.
- and archived in line with Sponsor requirements

21. Data Management

Two electronic databases will be created using Excel spreadsheets (a) a database with identifying data (name, contact details), which will be password-protected and (b) a separate anonymised database, using study IDs only, which will contain study-specific outcomes (e.g. details on eligibility, consent, reasons for non-participation and findings from the baseline and follow-up assessmsents). Data will be handled in line with the Data Protection Act as detailed in section 20.

22. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

23. Insurance / Indemnity

King's College London provides cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research subject for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions).

24. Financial Aspects

Funding to conduct the trial is provided by an NIHR Research Professorship (£1,499,280 over a 5-year period from 2013-2018)

25. Signatures

_____ _____

Chief Investigator Date

Print name

_____ _____

Statistician (if applicable) Date

Print name

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27. Appendices

- Patient Information Sheet
- Sample Consent Form
- Study Measures
- Study webpage preview
- Clinician email (to ensure that the woman is suitable to participate)
- Login email (participant email with study log-in details)
- Summary for clinicians (summary of the study for clinicians)