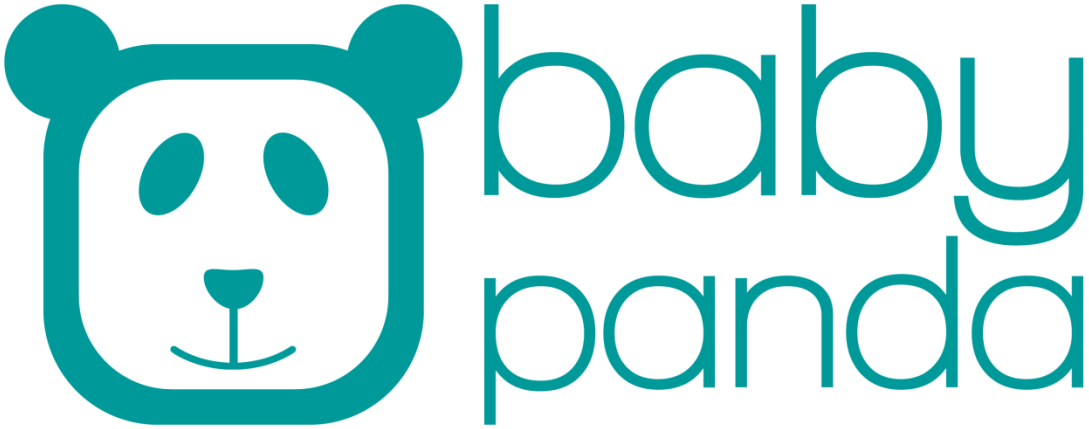

Born and Bred in Yorkshire: Perinatal Depression Diagnostic Accuracy Study

BABY PaNDA Study Protocol

Signature Page:

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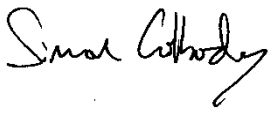

6th January 2016

Signature Date

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1 Study Identifiers

1.1 Full title of study

The detection and prognosis of perinatal depression: a prospective validation of the National Institute for Health and Clinical Excellence (NICE)-endorsed ultra-brief questions.

1.2 Acronym

BABY PaNDA Study: **B**orn **A**nd **B**red in **Y**orkshire: **P**eri**N**atal Depression **D**iagnostic **A**ccuracy Study

1.3 HS&DR Reference

11-2004-23

2 Background

Depression accounts for the greatest burden of disease among all mental health problems, and is expected to become the second-highest amongst all general health problems by 2020 (1). Depression during pregnancy and/or early motherhood (perinatal depression) is an important category of depression in its own right.

Perinatal depression affects up to 20% of women (2) and can lead to a variety of adverse outcomes. Depression during pregnancy (prenatal depression) has been shown to be associated with adverse neonatal outcomes, poor self-reported health, substance abuse and alcohol abuse, and poor usage of antenatal care services (3). There is now considerable evidence to show that postnatal depression (depression following the birth of a child) has a substantial impact on the mother and her partner (4), the family (5), mother-baby interactions (6) and on the longer-term emotional and cognitive development of the baby (7), especially when depression occurs in the first year of life (8). Unfortunately, despite such adverse consequences, less than

50% of cases of perinatal depression are detected by healthcare professionals in routine clinical practice (2).

The use of case-finding and screening strategies to detect perinatal depression has been advocated. The National Service Framework (NSF) made an explicit requirement that all areas should have local protocols for the management of postnatal depression (9). In practice, screening and case-finding strategies have tended to focus upon the routine or ad-hoc administration of the Edinburgh Postnatal Depression Scale (EPDS) in the postnatal period. Such NSF screening strategies have attracted substantial controversy (10). Criticisms of such a strategy are based upon the ethics of mass screening, the psychometric properties of available screening instruments (such as the EPDS), the acceptability (both to patients and healthcare professionals) of screening and case-finding strategies, and the absence of any evidence that screening, per se, leads to effective management and improved mother and infant outcomes (11).

It was in this context that the National Institute for Health and Clinical Excellence (NICE) produced recommendations on the psychological care of women around the time of childbirth (12). NICE recommended the use of ultra-brief screening (2-3 item) questions to aid the identification of depression (12) (see Box 1). These questions are often referred to as the Whooley questions (13). However, this recommendation was made despite the absence of definitive validation studies of the ultra-brief depression screening questions in a perinatal population. NICE also recommended that the ultra-brief screening questions be validated against a diagnostic gold standard, and against the EPDS (12).

NICE guidance therefore has been offered in the absence of research evidence and national screening policy (as issued by the National Screening Committee, NSC) (14) is not informed by sound research. The BABY PaNDA study will close this evidential gap in time for the next revisions of NICE guidance and NSC policy. We have conducted a systematic review, commissioned by the NIHR HTA programme, of existing perinatal mental

health research (15). We have since updated this review and there remain no published validation studies of the NICE ultra-brief depression screening questions (16). BABY PaNDA builds upon pilot work where we have tested the feasibility of longitudinal validation across the perinatal period in NHS services, and produced a preliminary estimate of diagnostic properties of the NICE ultra-brief questions (17). BABY PaNDA addresses the need to replicate these results in a larger sample of women with a different and wider geographical population.

1	"During the past month, have you often been bothered by feeling down, depressed or hopeless?"
2.	"During the past month, have you often been bothered by having little interest or pleasure in doing things?"
	A third question should be considered if the woman answers "yes" to either of the initial screening questions:
3.	"Is this something you feel you need or want help with?"

Box 1: Ultra-brief screening questions for identifying depression recommended by NICE (12).

The need for good prospective epidemiological estimates of perinatal depression and psychological co-morbidity has been identified in the most recent policy recommendation issued by the UK NSC (14). The natural history of depression during the perinatal period is under-researched with postnatal depression having received considerably more attention than prenatal depression. The finding that less than 50% of cases of perinatal depression are recognised is largely drawn from cross-sectional studies of postnatal depression. Consequently, we do not know the degree to which prenatal depression sufferers continue to be symptomatic in the postnatal period and what numbers of women with postnatal depression are 'new cases'. The BABY PaNDA study will allow us to examine the relationship between depression before and after birth.

Epidemiological research shows that depression commonly co-exists with other common mental health disorders such as general anxiety and

somatoform complaints. This is important since assessments of depression without the recognition of co-existing psychological symptoms will lead to suboptimal treatment strategies. There is an increasing need for psychosocial interventions that address the range of co-morbid symptoms that are present and the rational use of such interventions should be informed by epidemiological estimates of need. Recent NICE guidance (18) has highlighted the importance of psychological co-morbidity. However, the issue of co-morbidity is not well understood in perinatal mental health research. The BABY PaNDA study seeks to address this knowledge gap by using a structured gold standard diagnostic interview to capture the full range of common mental health disorders.

Our previous research has shown that there are limited studies into the acceptability of routine screening and case-finding for postnatal depression (15, 19). If depression screening questions are to be used in routine clinical practice, then they should be acceptable to both expectant and new mothers and to healthcare professionals. Our research will therefore inform the implementation of the NICE-endorsed screening strategy based on expectant and new mothers' and healthcare professionals' acceptability of the depression screening tools and assessment of potential implications for the care pathway for women diagnosed with perinatal depression.

There is concern that screening for perinatal depression is not an efficient way of improving the quality of healthcare for new mothers. The additional health benefit which accrues from screening programmes may be limited by a number of factors, including the uptake and the degree to which additional cases are well managed and respond to treatment. The enduring criticism of psychological screening programmes is that they identify less severe disorders, and that such disorders would have remitted anyway without the provision of intervention. We have previously addressed this issue in a state of the art decision model (15, 20) to help understand the important clinical and economic drivers of cost-effectiveness in relation to routine screening and case-finding for postnatal depression. Our model was limited by the availability of primary research on diagnostic utility; on estimates of the

temporal stability of screening scores and the natural history of screen-positive depression across the perinatal period. The BABY PaNDA study will help populate this existing decision model and will enable us to produce the best estimates of cost effectiveness in relation to routine screening and case finding for perinatal depression.

This prospective validation study will fill an important evidential gap and have an immediate impact on NHS patients and services by informing NICE guidance and UK NSC policy, which will enable the NHS to plan services and make informed decisions on the basis of screening results.

3 Research Objectives

This is an integrated health services research project which combines epidemiological, psychometric, qualitative and health economic methods to meet a series of objectives which emerge from a clinically-important topic.

The BABY PaNDA study will be a prospective validation of two depression screening tools (the ultra-brief NICE depression screening questions and the EPDS) against a diagnostic gold standard in a perinatal population. The study will include a concurrent economic and qualitative evaluation. The BABY PaNDA study research objectives are:

1. **Instrument Validation:** To validate the ultra-brief NICE-endorsed depression screening questions and the Edinburgh Postnatal Depression Scale (EPDS) against a diagnostic gold standard at 20 weeks pregnancy and at 3-4 months post-birth.

2. **Longitudinal Assessment:** To judge the temporal stability of positive and negative screens between pre- and post-birth, and to ascertain whether there is an optimum time to screen for perinatal depression.

3. **Standardised Diagnostic Assessment of Co-Morbidity:** To examine the co-existence of depressive symptoms alongside common mental health problems.

4. **Evaluation of Acceptability:** To determine the acceptability (to expectant and new mothers and healthcare professions) of the NICE ultra-brief depression screening questions and the EPDS during the perinatal period, and the potential implications for the care pathway.

5. **Estimation of Cost-Effectiveness:** To assess the cost-effectiveness of the NICE ultra-brief depression screening questions against the EPDS for routine screening for perinatal depression in maternity services.

4 Methods

4.1 Design

The BABY PaNDA study will be a prospective validation study. The study will be embedded within the framework of the existing BABY (Born and Bred in Yorkshire, www.bornbredyorks.org) cohort study (see appendices 1 & 2 for flow diagrams of the BABY and BABY PaNDA studies).

4.1.1 The BABY cohort

BABY is a population-based cohort of babies and their parents and is a collaborative project between the Hull York Medical School (HYMS, www.hyms.ac.uk); the Mental Health & Addictions Research Group (MHARG, www.mharg.york.ac.uk) and the Epidemiology & Cancer Statistics Group (ECSG, www.ecsg.york.ac.uk) within the Department of Health Sciences at the University of York; and colleagues within local NHS Trusts.

Established in 2011, BABY provides a comprehensive cohort of women recruited during pregnancy, their partners and babies. In the BABY cohort we collect data on maternal and infant health during the antenatal period, labour and the neonatal period, gathered primarily via routine systems from medical

records. Data are also collected on the psychological wellbeing of mothers and their partners during pregnancy and for one year after their baby's birth, gathered directly from parents via questionnaires. The BABY cohort has a target population of more than 10,000 births a year. Women (and their partners) are invited to take part in the BABY cohort at approximately 12-14 weeks of pregnancy (see BABY study protocol for detailed information).

A motivating design principle of the BABY cohort is therefore to measure the psychological wellbeing of all mothers taking part. Such information will allow us to establish population norms for the commonly used routine measures of psychological wellbeing, against which we can compare the outcomes of women taking part in BABY PaNDA. This is important since there are very little data in this area. In addition, all mothers participating in the BABY cohort will contribute to the BABY PaNDA study. Data collected from all BABY mothers, including self-report measures of psychological wellbeing at three time points – once during pregnancy and twice after birth – as well as obstetric and neonatal data collected from maternity records, will be used to interpret the BABY PaNDA outcomes. This will allow us to contextualise findings from BABY PaNDA against the larger BABY population cohort.

4.1.2 Instrument Validation, Longitudinal Assessment & Standardised Diagnostic Assessment of Co-Morbidity

The two depression screening tools - the NICE ultra-brief depression screening questions and the EPDS - will be validated against a WHO (World Health Organisation) diagnostic gold standard clinical assessment of depression (International Classification of Disease, ICD-10) at two stages - 20 weeks pregnancy and 3-4 months post-birth. By cross-validating the diagnostic gold standard against scores on the two depression screening tools at these two time points in the perinatal care pathway we will be able to assess the diagnostic accuracy of these tools in terms of false positives, false negatives and true negative results. This in turn will yield measures of sensitivity, specificity and positive and negative likelihood ratios (with 95% confidence intervals) and hence the diagnostic utility of the depression screening tools. This validation method will also permit us to judge the

temporal stability of positive and negative screens between pre- and post-birth and the natural history of screen-positive depression across the perinatal period. This will also enable us to ascertain the persistence of early screens in predicting longer-term problems. This will provide important information on the nature of the relationship between depression before and after birth.

A diagnostic assessment of co-morbidity will be made in two ways: by using previously validated questionnaires and by using the WHO diagnostic gold standard structured interview to ascertain the presence of common mental health problems, such as anxiety disorders and somatoform complaints (physical symptoms with a lower probability of physical pathology). An assessment of psychological co-morbidity will be made at three time points during pregnancy and early motherhood: 20 weeks pregnancy, 3-4 months post-birth and 1 year post-birth. This will allow us to examine the co-existence of depressive symptoms alongside other common mental health problems during the perinatal period. This will inform the delivery of psychosocial treatments by mental health practitioners to take account of other common mental health problems, such as anxiety and somatic complaints.

4.1.3 Evaluation of Acceptability

The aim of the qualitative evaluation is to investigate the acceptability and impact of the NICE ultra-brief depression screening questions and the EPDS and the extent to which they each capture appropriate information for effective screening of depression in perinatal care.

Objectives of the qualitative evaluation are:

1. To assess the acceptability of the NICE ultra-brief and EPDS depression screening questions for women and healthcare professionals.

2. To understand women's processes of answering the NICE ultra-brief and EPDS depression screening questions in terms of their understanding, confidence and recall methods.

3. To explore women's perceived effectiveness of the NICE ultra-brief and EPDS depression screening questions in relation to their current and historical symptoms.

4. To explore assessment of the impact of the NICE ultra-brief and EPDS depression screening questions in relation to their subsequent symptoms and experience on the care pathway.

Acceptability of the NICE ultra-brief depression screening questions and the EPDS will be evaluated among women and healthcare professionals using a mixed methods approach. This includes data collection using both a quantitative survey tool and in-depth interviews. Reported service-use data will be triangulated against medical records. Both the general acceptability of the depression screening tools and the individual questions will be interrogated.

All women who consent to take part in BABY PaNDA will complete the quantitative survey tool as part of the data collection procedure for the study (see sections 4.3 and 4.4). Additional consent for women to participate in the in-depth interviews will be sought at the point of consent to the study; women can choose not to provide consent to be approached to take part in the in-depth interviews whilst still participating in BABY PaNDA.

Quantitative survey

All women participating in BABY PaNDA will complete a brief self-report acceptability survey at two stages: 20 weeks of pregnancy and 3-4 months post-birth. The acceptability survey will be administered immediately following completion of the NICE ultra-brief depression screening questions and the EPDS. This brief survey was designed as a self-report tool to assess the acceptability of the EPDS (21) and was adapted by Mann and colleagues (17) to include an assessment of the acceptability of the NICE ultra-brief depression screening questions. For the purposes of this study, the Mann acceptability survey (17) has been further adapted to assess a range of concepts regarding the acceptability of the depression screening tools and the

processes for completing the questions. This quantitative data will provide an overview of acceptability and process related issues for each of the two depression screening tools from a large and diverse sample of women. These issues will be explored in more detail in a sub-sample of women participating in semi-structured in-depth interviews.

In-depth semi-structured interviews

A purposive sub-sample of 25-30 women will also participate in a maximum of three in-depth, face-to-face interviews; if women are unable to conduct the interview face-to-face, the option of a telephone interview will be provided. Subject to data saturation, women will participate in two or three in-depth interviews following completion of the BABY PaNDA outcome measures at 20 weeks pregnancy, 3-4 months post-birth and/or 1 year post-birth (see section 4.4) to discuss their views and experience of completing the NICE ultra-brief depression screening questions and the EPDS and/or their associated experience on the care pathway. This sample is expected to achieve data saturation (22) on the complex issues underpinning acceptability of the two depression screening tools for women from different socio-economic backgrounds, age, parity, positive/negative screens for depression (based on the NICE ultra-brief depression screening questions) and study sites.

A semi-structured topic guide based on the cognitive interviewing method attributable to Tourangeau (23) will elicit recognised concepts of questionnaire acceptability, understanding, confidence in ability to answer the questions, and recall methods for each of the depression screening tools and their individual questions. Additional open-ended probes will examine the case-history of, and experience on the care pathway for, individual women. In-depth, longitudinal interviews will be conducted by the same experienced qualitative researcher to improve the quality and depth of data collected (15).

In-depth single interviews will also be conducted among a purposive sample of 6 midwives and 6 health visitors, including diversity in age, location, professional grade and experience, to explore their experience of delivering the depression screening tools in routine clinical practice and their training

needs. Interviews will be conducted face-to-face or over the telephone depending on participant preference. This will be explored against descriptions of recommended and routine practice from health professionals in the respective site

Subject to consent, interviews among women and health professionals will be audio-recorded.

4.1.4 Estimation of Cost-Effectiveness

Design and theoretical/conceptual framework

The cost effectiveness analysis will be based on a decision analytic model comparing the NICE ultra-brief depression screening questions with the EPDS for screening perinatal depression. The analysis will make a clear link between the diagnostic accuracy of the screening strategy in the study, the impact on subsequent treatment decisions and the ultimate effect on health outcomes and costs. Hence, the costs and outcomes of each of the four diagnosis groups – true positive, false negative, true negative and false positive – will to be assessed. A previously published decision model for postnatal depression (20) will be adapted for this study.

Data collection

The main outcome will be cost per quality-adjusted life year (QALY). This is because it is necessary to assess the value of improved outcomes from more accurate identification strategies in units that can be compared with those of programmes and interventions in other specialties and disease areas that are competing for finite health-care resources (24). The performance indicators for the two perinatal depression screening questionnaires and data on health-related quality of life and resource utilisation will be obtained from the validation study, while other parameters in the model will be derived from literature sources and relevant databases. Cost data will include the cost of administering the screening methods, the cost of any subsequent treatment, and the cost associated with incorrect diagnosis. The administration cost will be based on the time involved in administering screening. The NHS resource use during the perinatal period will be evaluated based on primary data

collected from women participants using a bespoke resource utilisation questionnaire (see section 4.4). The questionnaire will be completed by women at three time points during pregnancy and early motherhood: 20 weeks pregnancy, 3-4 months post-birth and 1 year post-birth. Data will be collected on the use of community-based primary care services, hospital-based services and the use of antidepressant medication. Unit costs of health service utilisation will be based on national reference costs (25, 26). We will also review NICE clinical guidelines on management of perinatal mental health conditions to evaluate the expected resource use during the perinatal period; subsequently, the cost parameters will be populated in the decision model. Utility values will be based on primary data collected from the women participants using health-related quality of life questionnaires at 20 weeks pregnancy, 3-4 months post-birth and 1 year post-birth. QALYs will be estimated based on utility values associated with perinatal depression.

4.2 Inclusion and Exclusion Criteria

Eligible participants will be identified from the wider BABY cohort over a 12 month period. All women approached to participate in the BABY PaNDA study will have already consented to take part in the wider BABY cohort.

4.2.1 Inclusion criteria

Women will be approached to participate in BABY PaNDA if they have already consented to the BABY cohort *and* have consented to be contacted again *and* are less than 20 weeks pregnant; *and* are aged 16 years and above; *and* are currently living in one of the research areas (York, Hull, Harrogate, or Scunthorpe & Goole).

4.2.2 Exclusion criteria

Women will only be excluded if they are non-English speaking. Women with literacy difficulties will not be excluded; in these cases all study information and questionnaires will be read out to them. Women who return a completed consent form will not be eligible to take part in the study if they are over 24 weeks pregnant at the time the consent form is received.

We feel the option of providing translated versions of all study questionnaires to women participants with literacy difficulties is not appropriate within the context of this study. The English and translated versions could not be considered equivalent and therefore could not be combined in statistical analyses. We anticipate too few numbers of women participants who would require translated versions of the questionnaires to enable us to validate these.

4.3 Recruitment & Consent

Recruitment will take place over a 14 month period across four study sites – York, Hull, Harrogate, and Scunthorpe & Goole. Recruiting from these geographically and demographically distinct health economies will help us to ensure the results of epidemiological insights from this study are generalisable to the wider NHS.

Approximately 40% of eligible women are currently consenting to the BABY cohort in York. Of 800 women recruited to the cohort by the end of 2012, around 50% gave consent before 18 weeks of pregnancy. The recent pilot validation study (17) reported a consent rate of 58% from the Born in Bradford (BiBs) birth cohort. We feel a 14 month recruitment period is therefore realistic to achieve our recruitment target.

An information pack will be sent at approximately 15-18 weeks gestation to women who have consented to the BABY cohort by that stage of their pregnancy and who have also given their consent to be contacted again. The information pack will contain an invitation letter, a summary information sheet which describes the key aspects of the study, a participant information sheet which provides full details of the study, a consent form and a pre-paid stamped-addressed return envelope. The summary information sheet and the participant information sheet will provide contact details for the Project Manager in the event a woman requests further information about the study. Sending the information pack at 15 to 18 weeks gestation should provide

sufficient time for women to make an informed decision about whether they want to take part in BABY PaNDA (and to contact the research team if they have any questions) and for the researcher to organise the first interview at 20 weeks gestation following receipt of a completed consent form. The BaBY PaNDA summary information sheet will also be made available to women who may be interested in taking part in the BaBY cohort study either during visits to antenatal clinic and/or during contact with members of the BaBY study team.

Women who have not returned a completed consent form after two weeks of being sent the information pack may be contacted by a member of the BaBY study team to discuss the BaBY PaNDA study and to provide them with an opportunity to ask any questions they may have about the study. Women will be contacted by telephone, email or text, depending on the method(s) of contact they have provided during consent to the BaBY study. Interested women who are contacted following receipt of a BaBY PaNDA information pack will still need to complete the consent form and return this to the BaBY PaNDA research team.

All general practitioners (GPs) in the BABY cohort areas are sent information about the BABY cohort study before recruitment in their area begins. This material will additionally include information about the BABY PaNDA study. Information about the BaBY and BaBY PaNDA studies will also be visible in locations where pregnant women attend as part of their maternity care pathway (e.g. as posters and on ‘BaBY TV’ in antenatal clinics, as posters in Children’s Centres, GP surgeries) and will be provided online (www.bornbredyorks.org). Hospital and community midwives across each recruitment site may also discuss the BaBY and BaBY PaNDA studies with pregnant women under their care. Information about BaBY and BaBY PaNDA may also be promoted through press releases, local press activities and through appropriate local advertising avenues (e.g. online information and/or support groups, local magazines).

After consent has been received, women will be contacted by a member of the local research team to arrange the 20 week pregnancy assessment. At this point the researcher will confirm that women understand why the research is being conducted and what they will be asked to do during the study; this will provide a further opportunity for women to ask any questions they may have. The 20 week assessment will take place at a time and location of the woman's choice – expected locations include the local hospital maternity unit (for example, at the time of the woman's 20 week scan appointment), health and social care locations in the community, the woman's home, at the University of York or elsewhere.

After consent has been received, one copy of the woman's consent form will be sent to the women's GP along with a letter informing them that their patient has been included in the study, and one copy of the consent form will be kept by the woman. A BaBY PaNDA study sticker will also be placed in the woman's maternity records by a member of the maternity research team.

4.4 Outcome Measures & Data Collection

Data will be collected from all women at three time points during the course of the study:
Stage 1: Prenatal (20 weeks pregnancy)
Stage 2: Postnatal (3-4 months post-birth)
Stage 3: Follow-up (1 year post-birth)

The following outcomes measures will be collected:

Depression screening measures:

- NICE ultra-brief depression screening questions (13) and the additional help question (27) will be administered as a self-report questionnaire at stages 1, 2 & 3.

  A "yes" or "no" response is required for each of the two screening questions (see Box 1). A "yes" response to either of these screening

questions will be considered a ‘positive screen’ for perinatal depression and will require a “yes”, “yes, but not today”, or “no” response to the additional help question to enquire if help is needed (see Box 1). If any women respond “yes” to this help question they will be advised to speak with their GP and that information about perinatal depression can be found on the NHS website (www.nhs.uk). The two screening questions have been validated in primary care samples (13, 27) and other clinical populations (28-30). The two screening questions have since been validated in a limited perinatal population; this study reported 100% sensitivity at both the antenatal and the postnatal stage, and specificity of 68% at the antenatal stage and 65% at the postnatal stage. Additionally, they showed that for positive screens, the use of the additional help question improved the specificity and the ability to rule in depression (17).

- Edinburgh Postnatal Depression Scale (EPDS) (31) will be administered as a self-report questionnaire at stages 1, 2 & 3.

  The EPDS is a 10-item self-report questionnaire and is currently the most utilised self-report measure to detect postnatal depression in maternity and child services (32). Each item is scored on a 4-point scale (0-3) with a total score ranging from 0-30. Using a cut-off score of ≥13 to detect major depression in the postnatal period, the EPDS has been shown to have a sensitivity of 91% and a specificity of 91%.

Diagnostic gold standard:

- The Clinical Interview Schedule – Revised (CIS-R) will be administered as a self-report computer-based assessment at stages 1, 2 & 3.

  The CIS-R is a diagnostic gold standard, lay-administered computer-based interview schedule which assesses the presence or absence of depression and other common mental health disorders according to ICD-10 criteria (33, 34). It has been validated in primary care samples,

has been shown to have good reliability (33) and has been used in national psychiatric morbidity surveys (35). It has also been shown to have comparable validity when delivered over the telephone (36).

Secondary outcome measures

Minimal biographic and demographic information will be collected at stage 1 only.

The following outcomes measures will each by administered as self-report questionnaires:

- *PHQ-9* (Patient Health Questionnaire) (37) at stages 1, 2 & 3: a 9-item questionnaire which records the core symptoms of depression and has been validated in a primary care population (38). It is widely used in primary care for all cases of depression
- *GAD-7* at stages 1, 2 & 3: a 7-item questionnaire which assesses symptoms of anxiety (39)
- *PHQ-15* at stages 1, 2 & 3: a 15-item questionnaire which assesses somatoform complaints (40)
- *SF-12* at stages 1, 2 and 3: a 12-item questionnaire which assesses health-related quality of life (41)
- *EQ5D* at stages 1, 2 & 3: a 5-item questionnaire which assesses health-state utility (42)
- *Resource-use questionnaire* at stages 1, 2, & 3: a detailed questionnaire used to capture service-use data.
- *Acceptability Survey* at stages 1 & 2: a self-report tool designed to assess the acceptability of the EPDS (12). This has since been adapted to include an assessment of the acceptability of the NICE ultra-brief depression screening questions (17) and further adapted for the purposes of this study (see section 4.1.3).

In addition, the researcher administering the NICE ultra-brief depression screening questions and the EPDS at stages 1 and 2 will record the time it

takes for them to administer each screening questionnaire when completed face-to-face or over the telephone. These data will feed into the cost-effectiveness evaluation.

Method of data collection

Outcome measures will be obtained during face-to-face interviews at stages 1 & 2; if women are unable to attend a face-to-face interview the data will be collected by telephone, or by a combination of telephone (diagnostic gold standard – CIS-R) and post (self-report questionnaires). Outcome measures at stage 3 will be obtained by telephone, or by online completion (via a secure University of York website) or by a combination of telephone (diagnostic gold standard - CIS-R) and post (self-report questionnaires); face-to-face interviews will be arranged for those women who specifically request this method of data collection. Interviews at stages 1 to 3 will last no longer than 60 minutes.

Outcome measures will be administered within the same interview by one researcher. The depression screening questionnaires will be administered before the diagnostic gold standard (CIS-R). For instances where it is not possible to administer the depression screening questionnaires and the CIS-R within the same interview, the CIS-R will be administered within two weeks of women completing the depression screening questionnaires. Any issues which may arise during interviews will be documented in order to provide information about potential sources of bias. To ensure blinding of outcome results between stages, interviews will be conducted by different researchers, except where it is more appropriate / sensitive for the same researcher to conduct each interview.

Face-to-face interviews will take place at a time and location of the woman's choice (expected locations include local hospital maternity units, health and social care locations in the community, the woman's home, at the University of York or elsewhere). All data will be collected by a member of the study research team. All researchers will follow a lone worker policy when conducting face-to-face interviews.

Protocols will be in place for those women identified as at risk of depression and/or anxiety and/or self-harm/suicide, and for the identification and reporting of adverse events (see Appendices 3 and 4, and section 8).

4.6 Withdrawal

Withdrawal can occur at any stage during the study following consent at the request of the woman. Data will be retained for all women up to the date of withdrawal, unless they specifically request for their information to be removed. All personal information will be destroyed following the request to withdraw from the study.

Following consent to the study, any women who subsequently suffer a fetal loss (such as miscarriage, termination of pregnancy, stillbirth or neonatal death) will not automatically be withdrawn from the study. However, women will be contacted by letter by a member of the BaBY PaNDA study team to offer condolences , thank them for their interest in the study and to provide them with the opportunity to remain in the study should they wish to do so. Women who do not respond to this letter will not be contacted again by the BaBY PaNDA study team. Data will be retained for these women up to the date of the event, unless they specifically request for their information to be removed. Robust protocols will be in place via the BABY cohort (and in liaison with clinical teams using routine NHS systems at each study site) which will act to alert the BABY PaNDA study team of such events.

5 Statistical Considerations

5.1 Sample size calculation

We will aim to recruit 379 pregnant women. This sample size calculation is based on a previously developed method (43), for an expected sensitivity of 95% and a minimal acceptable lower 95% confidence interval (CI) of more than 0.80 with 0.95 probability, where estimated prevalence of prenatal and

postnatal depression is 20%. Attrition is estimated at 34% based on a previous pilot validation study of the NICE ultra-brief depression screening questions to identify perinatal depression in a limited perinatal population (17).

5.2 Data Analysis

5.2.1 Quantitative data analysis

The sensitivity, specificity and predictive values of the NICE ultra-brief depression screening questions and the EPDS will be calculated at 20 weeks of pregnancy and 3-4 months post-birth with two-by-two contingency tables against the ICD-10 diagnostic gold standard. Associated 95% confidence intervals will also be calculated for each estimate at each time point. Receiver Operating Characteristic (ROC) curves will also be constructed to determine performance characteristics for each depression measure. Based on the predictive properties of the depression screening measures, optimum times for screening will be identified. The numbers of women with indeterminate and/or missing results will be summarised, together with the reason for indeterminate or missing results (if available). The baseline characteristics of women with indeterminate and/or missing results will be compared to those who have complete data using descriptive statistics. A logistic regression model will also be used to identify predictors of non-response.

McNemars test will be used to explore the temporal stability of responses between 20 weeks of pregnancy and 3-4 months post-birth for each of the depression screening measures. The co-existence of depressive symptoms alongside other common mental health problems will be summarised descriptively (mean, standard deviation, median, minimum and maximum and frequency and percentages at established cut points) at each time-point.

5.2.2 Qualitative data analysis

Audio-recordings will be fully transcribed with all personal data anonymised to ensure confidentiality. Transfer of data to any external transcribers will be via the University based secure web-based data transfer system.

Quantitative data from the acceptability survey will be scored to produce population frequency descriptive data on core concepts of acceptability and user-preference. Thematic content analysis will be performed on the qualitative data from the acceptability survey including coding of data using techniques of constant comparison within the broader context of the existing literature.

Data from the in-depth interviews will be examined holistically on a case-by-case basis using phenomenological research methods to describe and examine the experience of women and health professionals in relation to their own situation and over time (44-46). The cognitive interviewing approach will assess the sources of response error for each of the screening tools.

The in-depth interview data will be used to further examine findings from the large-scale acceptability survey and integrated into the main study to validate clinical diagnostic data within the study. Health records of individual women sampled as having a positive screen of 'at risk' of depression at one of their study assessments at 20 weeks pregnancy or 3-4 months post-birth (based on the NICE ultra-brief depression screening questions) may also be checked to triangulate women's experience of the depression screening tools and their care pathway.

5.2.3 Economic Evaluation Analysis

The cost-effectiveness analysis will be conducted from the NHS and personal social services perspective. The decision analytic model will evaluate a hypothetical population of pregnant women managed in primary care setting. The model will consist of two parts including: (1) an identification model reflecting the diagnostic performance and administration costs of the alternative identification strategies; and (2) a treatment model that will evaluate the health-related costs and outcomes (expressed in QALYs) that may flow after administration of screening instruments. The model will be evaluated for each of the four diagnosis groups – true positive, false negative, true negative and false positive. Based on sensitivity and specificity of the

screening questionnaires, the impact of true and false identification and treatment of depression on costs and QALYs will be evaluated over the period of the study.

To evaluate uncertainty in mean parameter estimates (including clinical, cost and utility parameters) in the decision model, probabilistic sensitivity analysis (PSA) will be conducted using Monte Carlo simulation method (47). The simulation approach will propagate uncertainty in input parameters through the model to evaluate decision uncertainty. Finally, the joint distribution of incremental costs and QALYs will be presented using cost-effectiveness acceptability curve (CEAC). The CEAC will represent the probability that the use of NICE ultra-brief depression screening questions is the optimal choice over the EPDS, conditional on a range of willingness to pay thresholds that a decision maker may be willing to pay (48).

6 Ethical Issues

Whilst we do not anticipate any major ethical issues given that we are not providing any form of intervention, we are aware that some women may be vulnerable during pregnancy and may feel anxious about the possible identification of risk of depression. Such anxiety may arise following completion of study questionnaires or participation in qualitative interviews. Further ethical issues may relate to the identification of possible self-harm or suicide. Members of the research team are well placed to deal with such concerns and clinical members of the research team (Simon Gilbody and Dean McMillan) will be available to discuss such cases with the researchers and/or the participant, if deemed necessary. Protocols will be in place to deal with such instances (see Appendices 3 & 4).

6.1 Anticipated risks and benefits

This study does not involve any form of intervention and is therefore considered low risk for participants. All participants will continue to receive their usual maternity care and participation in the study will not affect the

standard of care participants receive from their GP, midwife or health visitor. No treatment will be withheld from participants by their participation in the study.

6.2 Informing participants of anticipated risks and benefits

The participant information sheet will provide potential participants with information about the possible benefits and any known risks of taking part in the study. The participant information sheet suggests potential participants may wish to discuss their participation in this study with their GP. The Study Coordinator will inform the participant if new information comes to light that may affect the participant's willingness to participate in the study.

6.3 Obtaining consent

Potential participants will receive an information pack about the study. The pack will contain an invitation letter, participant information sheet and a consent form. The participant information sheet provides contact details for the research team in the event a potential participant requests further information about the study before they provide their written consent. Written informed consent will be obtained prior to the participant being contacted by a member of the research team. The researcher will discuss the study and answer any questions during initial contact with the participant following receipt of written informed consent.

6.4 Retention of study documentation

All data will be stored for a minimum of 20 years after the end of the final analysis of the study and will be accessed by the Study Statistician. The storage of study data will be stored in accordance with the Department of Health Sciences Data Security Policy at the University of York. All paper records will be stored in secure storage facilities. Personal identifiable paper records will be stored separately from anonymised paper records. All electronic records will be stored on a password protected server within the Department of Health Sciences at the University of York. All personal information will be destroyed securely at the end of the study.

7 Patient & Public Involvement

Patient and public involvement (PPI) input into the design, conduct and dissemination of the study comes from Deborah Morgan, who is a named co-applicant. Deborah has lived experience of perinatal illness and is the founder and CEO of the registered charity Perinatal Illness UK (www.pni-uk.com), which is also a registered stakeholder with NICE. Perinatal Illness UK provides support and advice to women and their families affected by perinatal illness. Deborah will sit on the Study Management Group and the research team will follow good practice in terms of ensuring PPI representatives are able to contribute to our discussions.

We will also develop a small PPI group consisting of a variety of stakeholders from different backgrounds, including those with lived experience of perinatal depression and users of maternity services. Deborah, along with the PPI group, will be involved in the development of study materials and will play an instrumental role in developing and implementing a dissemination strategy which is inclusive, accessible and effectively delivered to a wide-range of patients and other interest groups.

8 Research Governance

The study will be conducted to protect the human rights and dignity of the participant as reflected in the 1996 version of the Helsinki Declaration. Participants will not receive any financial inducement to participate in the study. The explicit wishes of the participant will be respected including the right to withdraw from the study at any time. The interest of the participant will prevail over those of science and society. Provision will be made for indemnity by the investigator and sponsor.

8.1 Monitoring and reporting adverse events

This study does not meet the requirements stipulated for a CTIMP (Clinical Trial of Investigational Medicinal Product) or a non-CTIMP as no form of intervention or treatment will be given to participants. This study is therefore not subject to any additional restrictions. We will have no influence on the participants' maternity care or the usual care they receive from their GP. Decisions about participants' treatment or prescription of medications will be made by the participant in conjunction with their GP and/or midwife. If a participant asks a member of the research team for an opinion on medical issues, they will be strongly encouraged to seek advice from their GP.

This study will record details of any Serious Adverse Events (SAEs) that are required to be reported to the Research Ethics Committee (REC) under the terms of the Standard Operating Procedures for RECs . An SAE is defined as an untoward occurrence that:

(a) Results in death;
(b) Is life-threatening;
(c) Requires hospitalisation or prolongation of existing hospitalisation;
(d) Results in persistent or significant disability or incapacity;
(e) Consists of a congenital anomaly or birth defect; or
(f) Is otherwise considered medically significant by the investigator.

If a participant experiences an SAE we will report this to our main REC where in the opinion of the Chief Investigator or clinical members of the Study Management Group the event was:

- 'related': that is, resulting from the administration of any of the research procedures; and
- 'unexpected': that is, a type of event not listed in the protocol as an expected occurrence.

In the context of the current study, an occurrence of the type listed in (a) to (f)

above will be reported as an SAE if:

- It is suspected to be related to an aspect of the research procedures (e.g. completion of questionnaires, participation in qualitative interviews), or
- It is an unexpected occurrence

Hospitalisations are expected in the study population as women will give birth during the course of the study and most births in the UK take place in hospital; in addition, women may require overnight hospital monitoring during their pregnancy. Hospitalisations resulting from giving birth or from monitoring during pregnancy will therefore not be reported as an SAE. SAEs that result from physical health problems will not be subject to expedited reporting.

Any adverse event which is judged to be serious should be reported to the Study Manager within 48 hours. If possible the researcher reporting the SAE should complete a Serious Adverse Event form which should be faxed to the Study Manager; where this is not possible the researcher should report the SAE to the Study Manager by telephone and the Study Manager will complete an SAE form. A copy of the SAE form will be stored in the participant's records. The Study Manager will inform the Chief Investigator (CI) and at least two members of the Study Management Group who will jointly decide whether the event is related to the study and should be reported to the main REC as an SAE. All SAEs will be reported to the main REC within 15 days of the CI becoming aware of the event where the event is related to the administration of any of the research procedures and is unexpected.

The occurrence of adverse events during the study will be monitored by the Study Management Group (SMG). The Study Steering Committee (SSC) will immediately review all SAEs thought to be related to the study and they will review all SAEs not thought to be related to the study by the SMG at each scheduled meeting.

8.2 Suicide and self-harm

Although many participants taking part in this study may not be suffering from the condition under scrutiny (depression), there remains the risk of suicide and deliberate self-harm. All participants will be subject to their usual standard of care from their GP and maternity services. However, we will follow good clinical practice in monitoring suicide risk during researcher encounters with study participants. Where any risk to participants due to expressed thoughts of self-harm is encountered, we will follow the study suicide protocol (see appendix 4).

9 Study Management

9.1 Study Sponsorship

The University of York, who are the sponsor for the BABY cohort study, will also act as a sponsor for the BABY PaNDA study.

Sue Final
Intellectual Property Manager
University of York
Research Innovation Office
Innovation Centre
York Science Park
York
YO10 5DG

9.2 Indemnity

Normal NHS indemnity procedures will apply. The University of York will also provide relevant cover.

9.3 Funding

Research funding has been secured from the National Institute of Health Research - Health Services & Delivery Research Programme (NIHR HS&DR). Project Reference: 11-2004-23

9.4 Study Management & Applicant Responsibilities

The Study Management Group (SMG) will consist of the Chief Investigator, co-applicants, local study collaborators, lead research midwife/nurse, study statistician and data manager. The SMG will meet every quarter to monitor the study's progress and to ensure study milestones are being met as planned. The SMG will also review any serious adverse events. Regular telephone meetings will be held between the BABY PaNDA and BABY cohort researchers at each study site to ensure effective communication and provide reports on progress at each study site.

The Chief Investigator (Professor Simon Gilbody) will have overall responsibility for the management of the study. The York-based Study Manager (Liz Littlewood) will have responsibility for the day-to-day management of the study and for coordination of the study between sites. Pat Ansell and Dean McMillan are the lead researchers/coordinators for the BABY cohort and will provide the vital link between the BABY PaNDA and BABY study teams.

Recruitment will be overseen by the York site as the coordinating site for the study. Assessments will be undertaken by the study's research midwives/nurses and research support staff at each study site. Administrative support will be provided by research support staff. Pat Ansell and Liz Littlewood will provide supervision to the research midwives/nurses and other research support staff. All qualitative interviews will be undertaken by an experienced qualitative researcher (Lisa Dyson) who will lead the qualitative

component of the study. Lisa Dyson will act as facilitator to the PPI group along with one of the study's research midwives/nurses. Deborah Morgan will be the PPI organisation representative for the study and will provide advice on the development of study materials and effective dissemination of the study findings.

Catherine Hewitt will be the lead study statistician. Shehzad Ali will lead the economic analysis. Expertise in the conduct of diagnostic test accuracy studies will be provided by Dean McMillan and Rachel Mann, and Rachel Mann will provide methodological advice regarding recruitment and assessment methods. Simon Gilbody and Dean McMillan will act as the study's mental health specialists.

9.5 Study Steering Committee

The study does not require a Study Steering Committee (SSC) or a Data Monitoring and Ethics Committee (DMEC) as it does not involve any form of intervention or investigation of a medicinal product. However, a SSC will be convened to provide an independent overview of the study and to provide relevant expertise. The SSC will also review all serious adverse events. Membership of the SSC will include an independent chair and two other independent members, along with the chief investigator and other study investigators. The SCC will meet annually (see appendix 5 for members).

10 Dissemination

We will publish papers relating to this study that will include (as a minimum) the results of the validation study, and the results of both the cost effectiveness analysis and qualitative analysis. We will also publish in professional journals to ensure that clinicians have prompt access to our findings. We will also produce a short summary of the study findings that can be distributed to all study participants as well as relevant patient and other interest groups. We will present our findings at national conferences on

perinatal depression, providing an effective way of disseminating the study findings to a key audience of midwives, GPs, health visitors and mental health professionals. Finally, we will aim to ensure coverage of our findings in the wider media by issuing a press release. This will serve to bring the public and clinicians' attention to our findings.

11 Project Timetable & Milestones

December 2012 to March 2013	Prepare and submit applications for ethical approval, R&D approvals for all sites (as required) and for adoption onto NIHR portfolio
April 2013	Study officially starts
June/July 2013	Recruitment starts at York, Harrogate & Hull sites for a 14 month period Qualitative interviews begin
December 2013	Recruitment starts at Scunthorpe & Goole site for a 8 month period
July/August 2014	Recruitment ends – data collection completed for 20 week assessments
April/May 2105	Data collection completed for 3-4 month assessments.
May 2015 to August 2015	Data cleaning and statistical data analysis for 20 week and 3-4 month data.
January/February 2016	Data collection completed for 12 month follow-up assessments Qualitative interviews completed
February 2016 to June 2016	Data cleaning. Statistical data analysis for remaining data Economic analysis Study write-up

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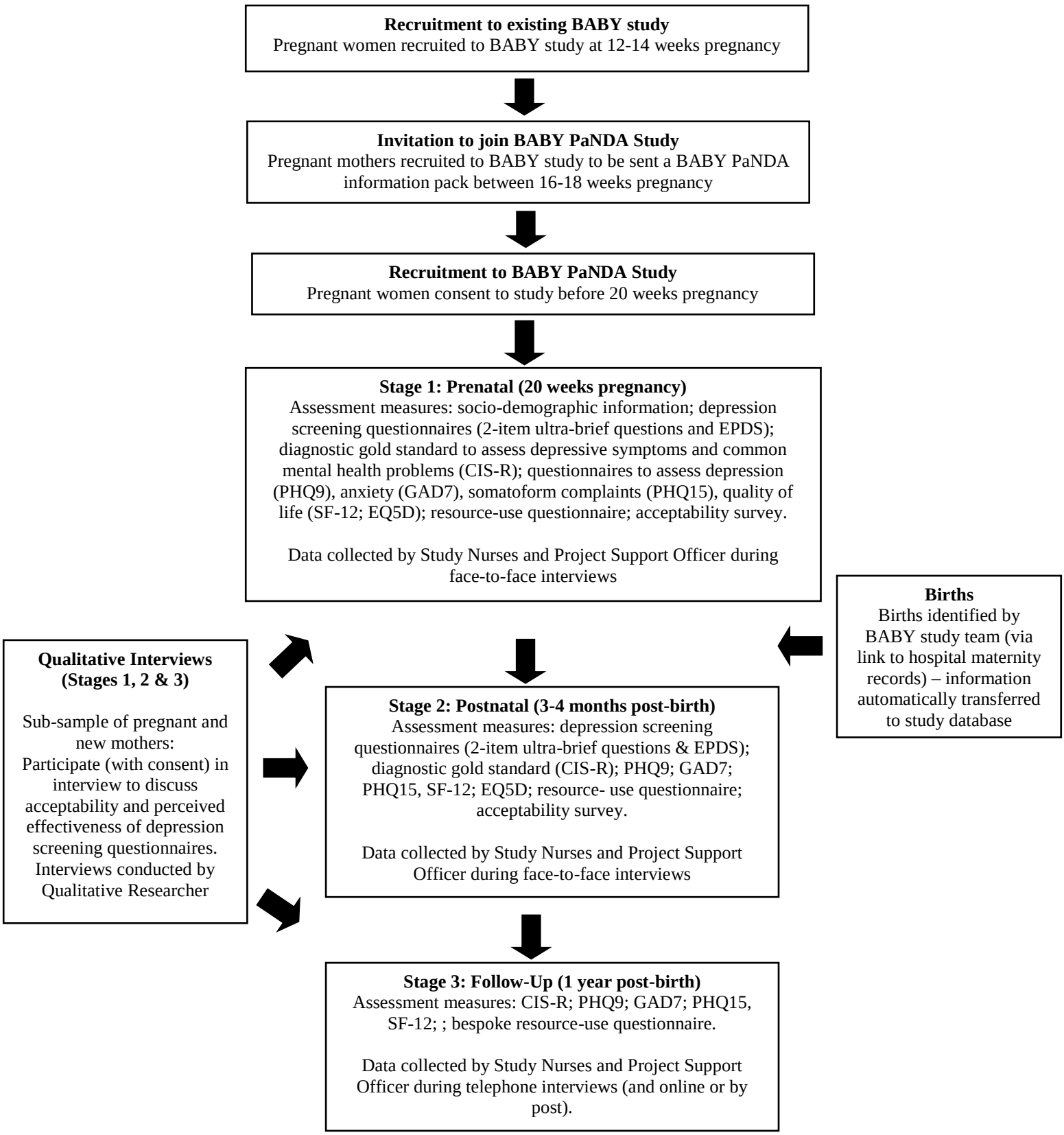
Appendix 1 – Flow Diagram: BABY PaNDA Study

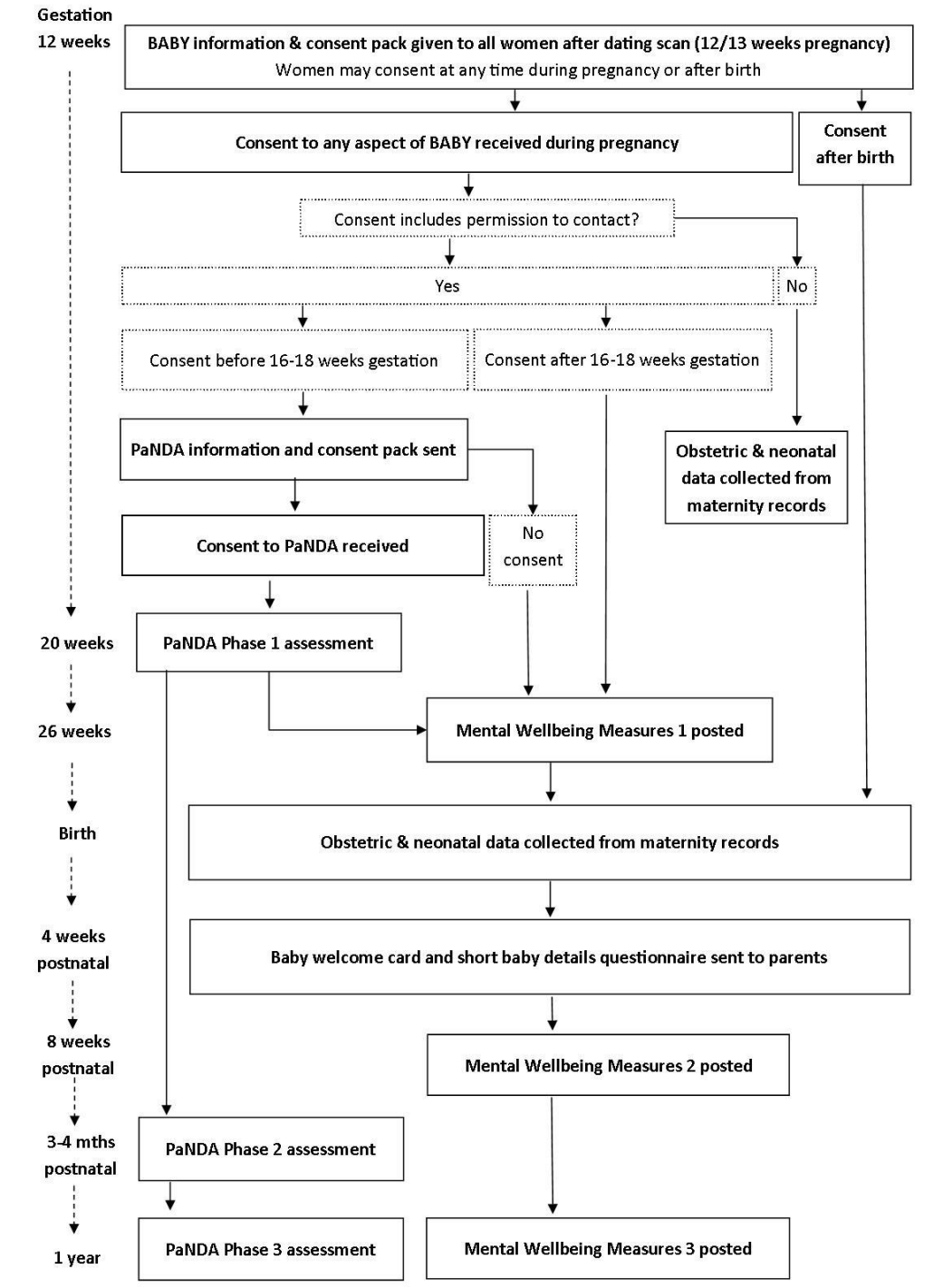


Additional Notes

Adverse Events will be reported throughout the study and recorded as per the study protocol (with information being shared between both BABY PaNDA and BABY studies).

Protocols will be in place for any women identified as at risk of depression and/or at risk of suicide and/or self-harm.

Appendix 2 – Flow Diagram: BABY Cohort & BABY PaNDA Studies



Appendix 3: BABY PaNDA Identification of Risk of Depression/Anxiety Protocol

Identification of Risk of Depression/Anxiety Protocol

This protocol provides the guiding principles for instances when the clinical diagnostic interview (as assessed by the Clinical Interview Schedule - Revised; CIS-R) identifies a participant as currently experiencing depression and/or anxiety.

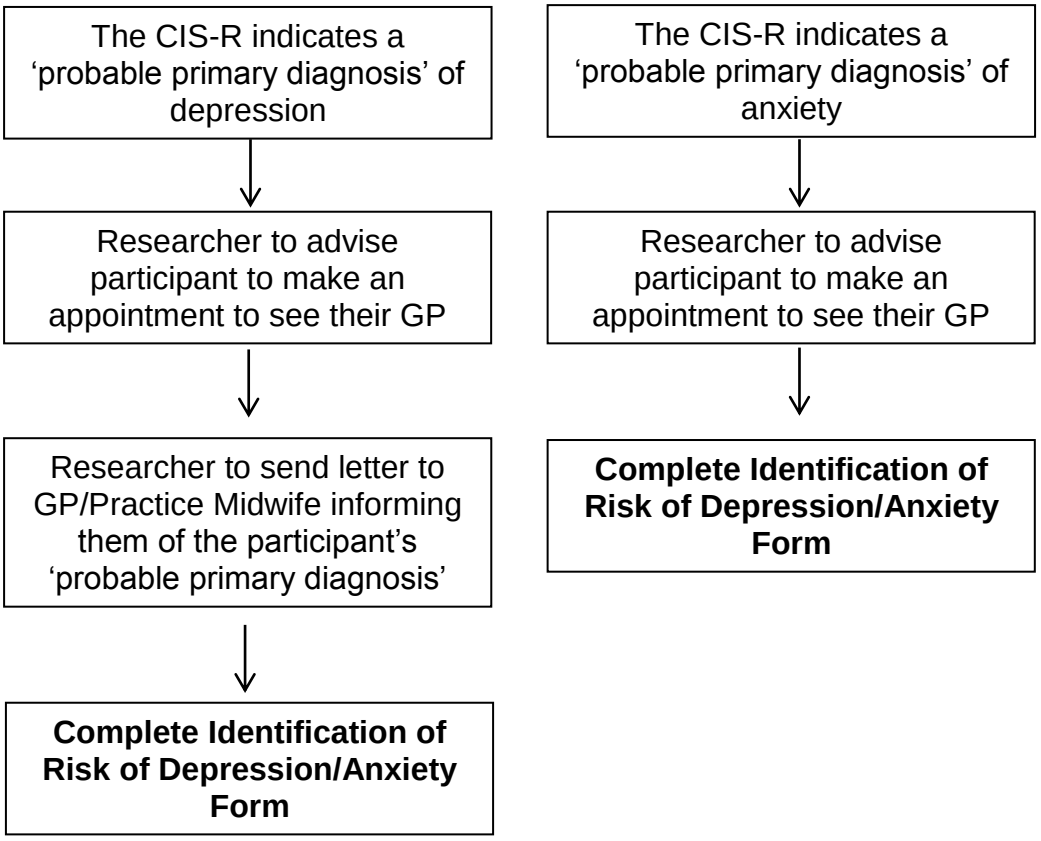
Participants will complete the CIS-R during face-to-face assessments and during telephone assessments. All BABY PaNDA researchers will have received training on how to interpret the CIS-R output. The Identification of Risk of Depression/Anxiety protocol will be implemented following a participant assessment.

The following documents provide an overview of the processes to be followed and associated documentation:

- Identification of Risk of Depression/Anxiety Flowchart – identified via face-to-face or telephone assessments
- Identification of Risk of Depression/Anxiety Form
- Clinical Contact Details

There may be instances where a different course of action needs to be implemented from those detailed here, where this is deemed clinically appropriate following consultation with a clinician. Any such instances will be documented appropriately on the Identification of Risk of Depression/Anxiety Form.

Identification of Risk of Depression/Anxiety Flowchart: Identified via face-to-face or telephone assessment



Identification of Risk of Depression/Anxiety Form

The patient below has received a 'probable primary diagnosis' of depression and/or anxiety on the CIS-R during a BABY PaNDA assessment.

Participant ID Code: ☐☐ / ☐☐☐☐☐

Date of Assessment: ☐☐ / ☐☐ / ☐☐☐☐

Assessment: 20 weeks pregnancy / 3-4 months post-birth / 1 year post-birth

Probably Primary Diagnosis on CIS-R:

Depressive Episode	☐
Anxiety Episode	☐

Has participant been advised to contact their GP?: Yes ☐ No ☐

Has the GP/Practice Midwife been sent the Notification of Identification of Risk of Depression letter?:

Yes ☐ No ☐ N/A ☐

Comments:

Researcher Name: ……..... Study Site: …….

Research Signature: …… Date: ……...

Name of Clinical Contact: ……..

Clinical Contact Signature: …… Date: ……..

Clinical Contact Details for all study sites

	Contact 1: **Dr Dean McMillan**	**Contact 2:** **Professor Simon Gilbody**
Role	Clinical Lead	Chief Investigator
Landline		
Mobile		
Email	dean.mcmillan@york.ac.uk	simon.gilbody@york.ac.uk

Appendix 4: BABY PaNDA Suicide Protocol

This protocol provides the guiding principles for instances where a participant gives cause for concern regarding their risk of suicide or self-harm.

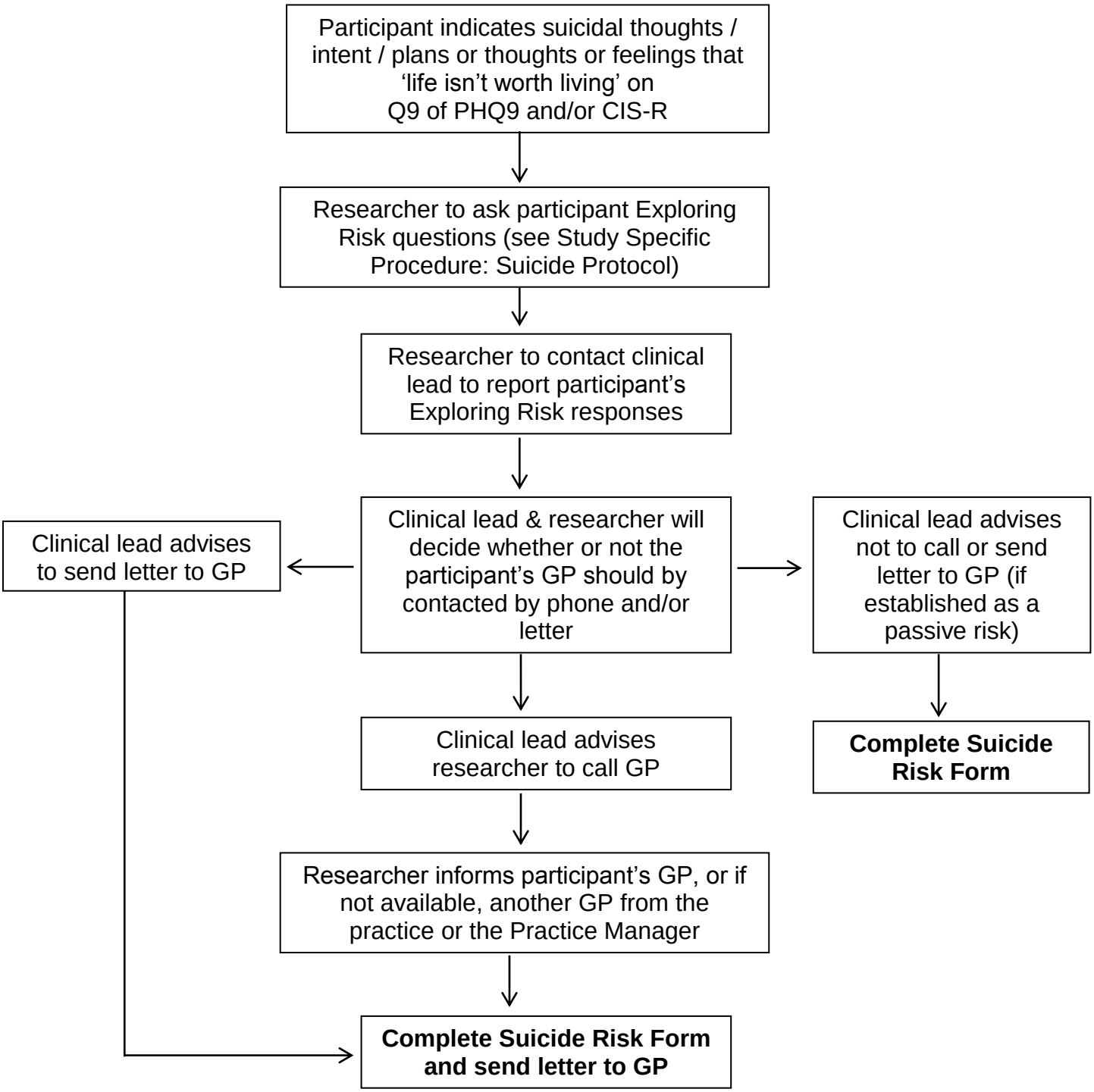
The suicide risk protocol will be implemented as soon as the BABY PaNDA study team are aware of any risk to participants due to expressed thoughts of suicide or self-harm. All BABY PaNDA researchers will have received risk training.

Researchers in the BABY PaNDA study team will respond appropriately if any potential risk is identified during face-to-face assessments, during telephone assessments, via data on returned postal questionnaires, via data on questionnaires completed online, and during in-depth qualitative interviews. The following documents provide an overview of the processes to be followed and associated documentation:

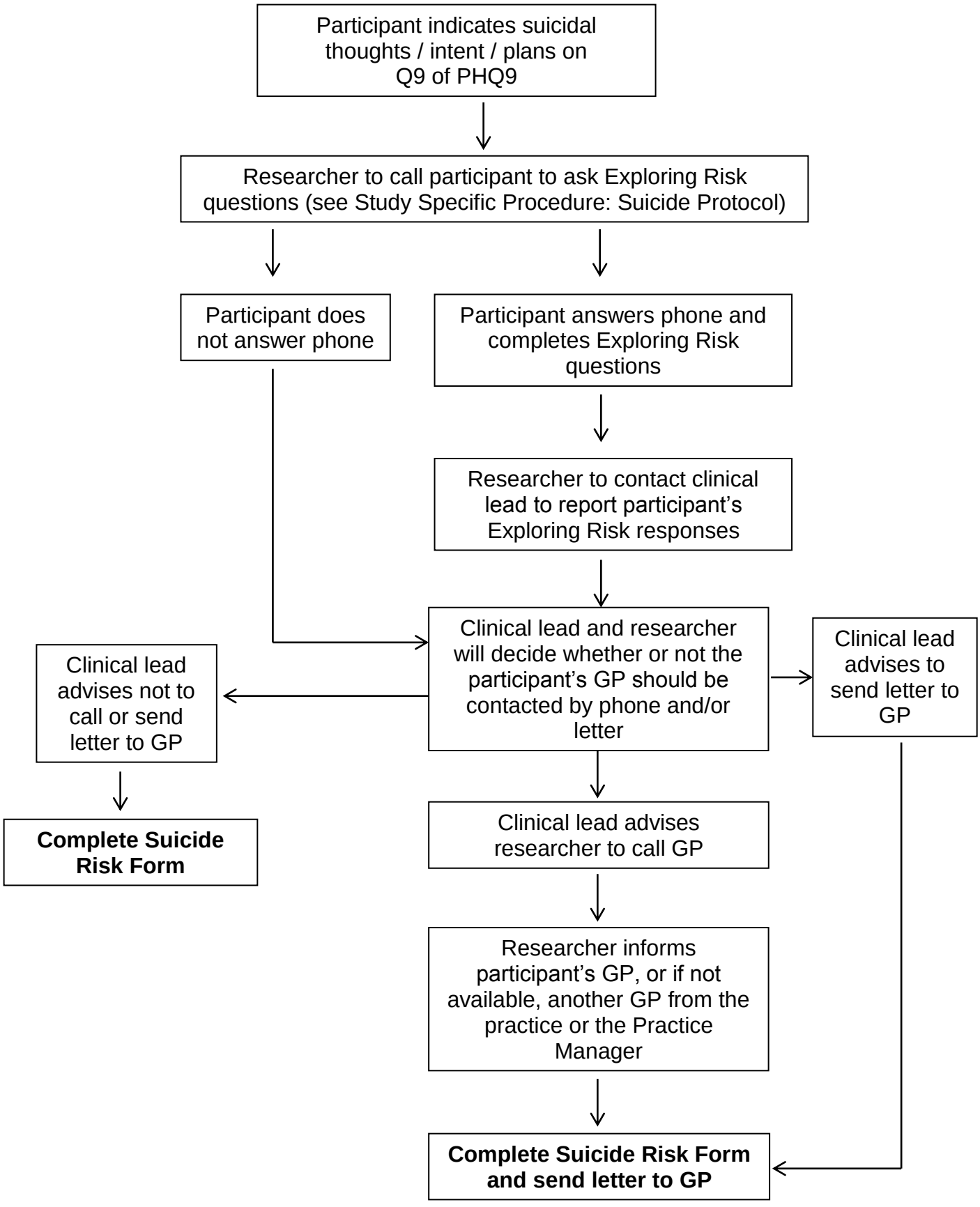
- Suicide Risk Flowchart 1 – identified via face-to-face or telephone assessments
- Suicide Risk Flowchart 2 – identified via postal or online questionnaires
- Suicide Risk Flowchart 3 – identified via qualitative interviews
- Exploring Risk Questions
- Contact Details
- Suicide Risk Form

There may be instances where a different course of action needs to be implemented from those detailed here, where this is deemed clinically appropriate following consultation with a clinician. Any such instances will be documented appropriately on the Suicide Risk Form.

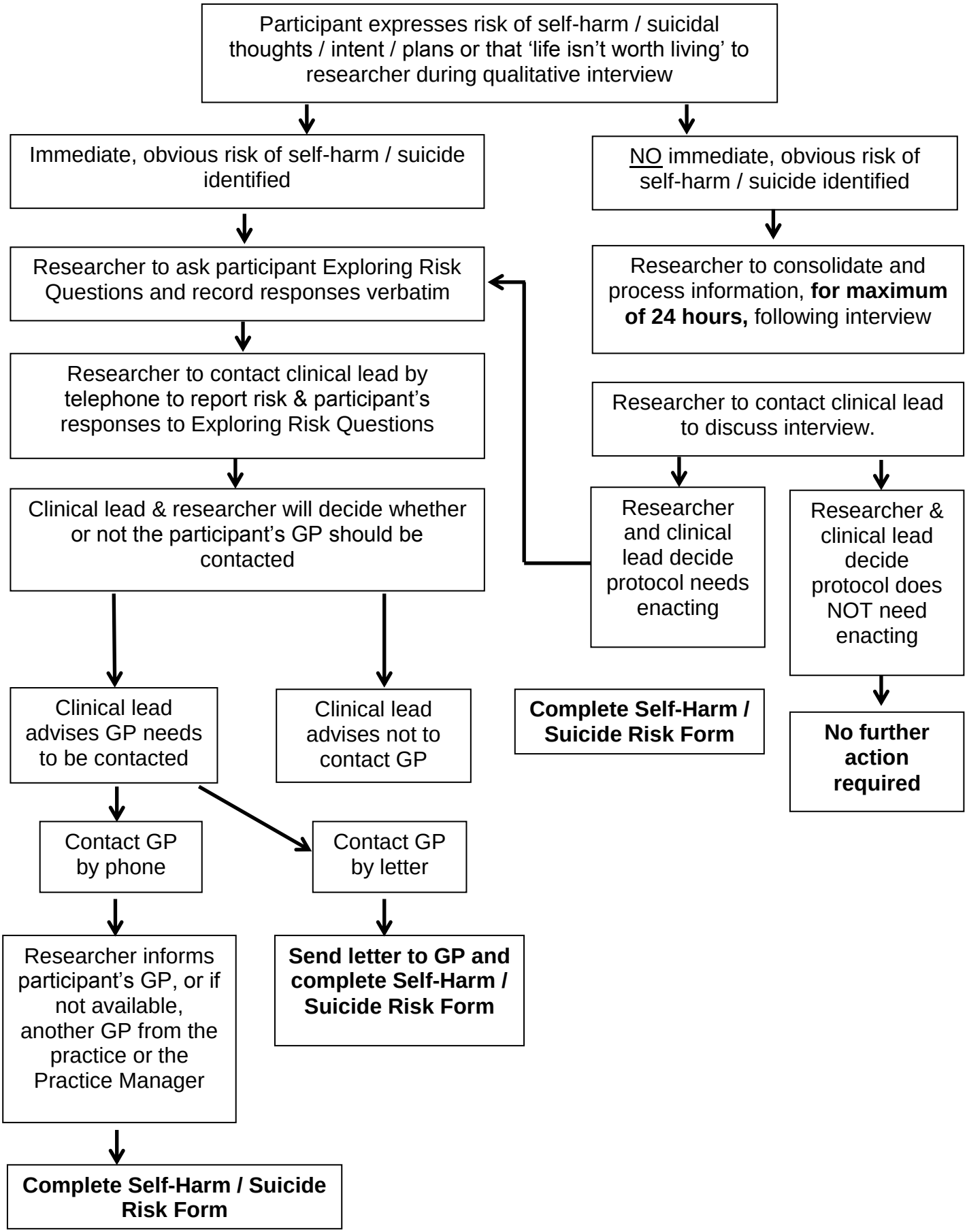
Suicide Risk Flowchart 1:
Identified via face-to-face or telephone assessment



Suicide Risk Flowchart 2:
Identified via postal or online questionnaires



Suicide Risk Flowchart 3:
Identified via qualitative interviews



Exploring Risk Questions

Plans	
1. Do you know how you would kill yourself? If **Yes** – details	Yes / No
2. Have you made any actual plans to end your life? If **Yes** – details	Yes / No
Actions	
3. Have you made any actual preparations to kill yourself? If **Yes** – details	Yes / No
4. Have you ever attempted suicide in the past? If **Yes** – details	Yes / No
Prevention	
5. Is there anything stopping you killing or harming yourself at the moment? If **Yes** – details	Yes / No
6. Do you feel that there is any immediate danger that you will harm or kill yourself? If **Yes** – details	Yes / No

Clinical Contact Details for all study sites

	Contact 1: **Dr Dean McMillan**	**Contact 2:** **Professor Simon Gilbody**
Role	Clinical Lead	Chief Investigator
Landline		
Mobile		
Email	dean.mcmillan@york.ac.uk	simon.gilbody@york.ac.uk

Suicide Risk Form

The patient below has expressed thoughts of suicidal intent / self-harm on the PHQ9 or CIS-R during a BABY PaNDA assessment or during a qualitative interview.

Participant ID Code: ☐☐ / ☐☐☐☐☐

Date of Assessment: ☐☐ / ☐☐ / ☐☐☐☐

Assessment: 20 weeks pregnancy / 3-4 months post-birth / 1 year post-birth

Risk of suicide / self-harm identified from:

Face-to-face or telephone assessment	PHQ9	☐
	CIS-R	☐
Postal Questionnaire	PHQ9	☐
Qualitative interview		☐

Summary of how suicide risk protocol was implemented:

(Which clinician gave advice, what advice was given, was risk judged as passive or active? If advised to contact GP – name of practice, name of GP spoken to, date of contact)

Researcher Name: ……..... Study Site: …….

Research Signature: …… Date: ……...

Name of Clinical Contact: …….....

Clinical Contact Signature: …… Date: ……..

Appendix 5: Study Steering Committee Membership

Professor Julie Jomeen	Director of Research & Scholarship & Midwifery Lecturer, University of Hull Email: J.Jomeenm@hull.ac.uk
Professor Sarah Byford	Professor of Health Economics & Co-Deputy Director, Centre for the Economics of Mental & Physical Health, Institute of Psychiatry at King's College London Email: s.byford@kcl.ac.uk
Dr Jeremy Dawson	Reader in Health Management, School of Health and Related Research, The University of Sheffield Email: j.f.dawson@sheffield.ac.uk
Mrs Alice North	PPI representative
Plus BABY PaNDA Co-Investigators	