

PROTOCOL

Project Title

Psychological Interventions for Postnatal Depression –
Randomised Controlled Trial and Economic Evaluation

Planned Investigation

The trial will specifically address the research question posed, “What is the cost-effectiveness of psychological treatment for postnatal depression?” The purpose of the study is to evaluate in a randomised controlled trial (RCT), the effectiveness and costs of two interventions for postnatal depression – one based on the principles of Person-Centred Counselling and one based on the principles of Cognitive Behavioural Counselling, delivered by health visitors (HVs) in their usual clinical setting. The unit of random allocation will be the GP practice with all the HVs who work there.

The aim is to establish whether there is any association between a Person-Centred Approach (PCA) or a Cognitive-Behavioural Approach (CBA) and improvements in clinical or cost outcomes, or both. The Edinburgh Postnatal Depression Scale (EPDS)¹ will be used and those women in the intervention practices found to be at risk of postnatal depression (PND) will be interviewed to assess symptom severity. The trial will therefore assess effectiveness according to severity, history and duration of depression. Women with mild depression who consent to participate in the trial will be offered an intervention by their HV according to the practice randomisation. For women with moderate to severe depression, the trial will also clarify treatment preferences. The design will reflect the practicalities of primary care service delivery and will ensure that a wide range of effects is identified. This will be the first study of a one-to-one HV intervention for PND based in routine primary care. The trial will identify any differences between interventions, in outcomes and costs for the mothers, their infants or partners. The study will compare the scores and costs of postal and face-to-face administration of the EPDS. The study will also evaluate the performance of the EPDS for routine use in primary care. The trial will address the issue of therapy allegiance by external quality assurance, monitor HVs’ treatment adherence and the therapeutic alliance between the HVs and the women in the trial. The trial will also assess women’s satisfaction and compliance with the intervention they are offered.

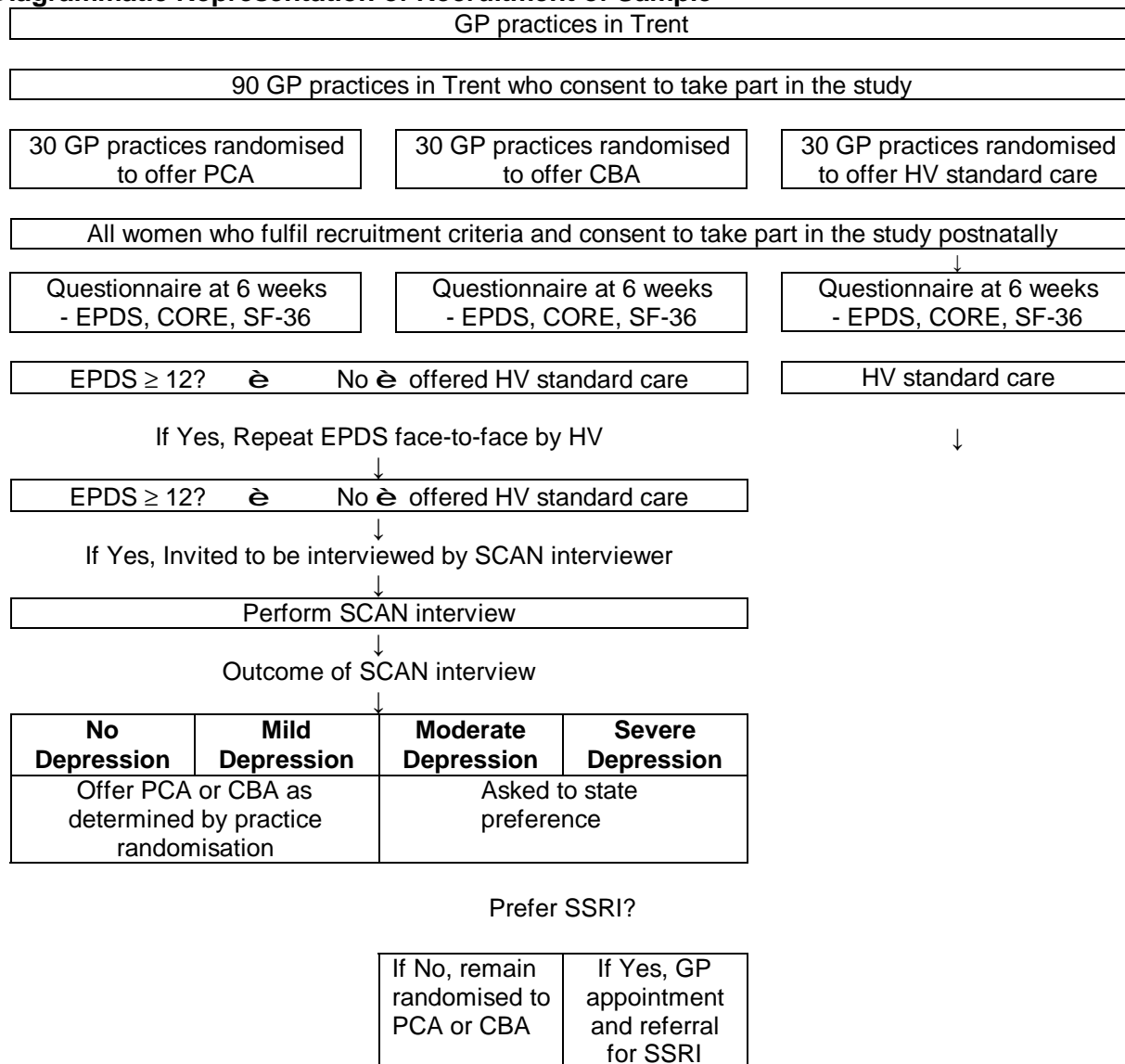
Research Objectives.

The aim of the study will be to reliably estimate any differences in outcomes for mother, child or family among women who receive the PCA or CBA or ‘HV standard care’.

The objectives for project monitoring purposes are to:

1. Prepare for the trial, gain MREC approval, recruit and randomise HVs and practices.
2. Recruit eligible women to the study and administer the EPDS to recruited women at 6 weeks post-natally.
3. Offer a pre-determined intervention to all ‘at risk women’ and assess satisfaction and continued compliance with the intervention.
4. Follow-up and measure outcomes for women, infants and families to 18 months.
5. Identify any differences in costs for use of services for women who receive PCA, CBA or ‘HV standard care’ and, if appropriate, calculate the cost-effectiveness of PCA or CBA from a NHS perspective, relative to ‘HV standard care’.
6. Test for interactions between the effectiveness of PCA or CBA and severity, history and duration of depression, and other cognitive mediators.
7. Assess any relationship between childhood injury and severity or resolution of depression.
8. Perform a planned subgroup analysis for women with different socio-demographic characteristics.
9. Produce a report and paper for publication.

Diagrammatic Representation of Recruitment of Sample



Existing research

Some PND resolves spontaneously, but it can be enduring with a detrimental effect on infants and older children.² There is a small, but significant risk of suicide and infanticide in some severely depressed women.³ Much PND is unidentified and some women are afraid to admit their true feelings to Health Visitors (HVs).⁴ Trained HVs are well placed to use their routine contacts with new mothers, to identify PND and offer interventions to support women with its milder forms,⁵ but approaches to screening, knowledge, skills and confidence among HVs vary widely.⁶ There are recommendations about the management of PND^{5,7} but no national policy on screening for PND,⁸ partly because there is weak evidence about the most effective intervention for treating women with PND.⁸ There have been no RCTs of one-to-one intervention for PND based in routine primary care, or single antidepressant treatment for PND.

There have been three systematic reviews covering: antidepressant drug treatment for PND;⁹ oestrogens and progestogens for preventing and treating PND;¹⁰ and caregiver support for PND.¹¹ The latter review concluded that professional and or social support might help in the treatment of PND but that it would be premature to make practice recommendations based upon two small trials.^{12,13} One of these was a RCT of one-hour 'listening' visits,¹² (based on Rogerian, NDC) each week for eight weeks, by one of 17 HVs who had received a brief

training in NDC, using videos, case discussion, role play, written information about counselling and PND, and an instruction manual. HVs were asked to visit postnatal women on their caseload that had been identified as depressed by a psychiatrist. The timing of the intervention is not clear. Of the 60 women who were found to be depressed, 26 and 24 women were allocated, by random numbers, to the intervention and control group, respectively. After 13 weeks, 69% of the counselled women had recovered, compared with 38% of the control group (95% C.I. 5-58; $P < 0.03$). It is difficult to generalise the results from such a small study to a wider population.

The other trial compared the effectiveness of 20mg fluoxetine and CBC for depressive illness in postnatal women.¹³ Women with PND prefer not to take antidepressants^{6,14} so compliance is not good. Because there is little information about the safety of antidepressants in breast-feeding women, physicians either prescribe a reduced, potentially non-therapeutic dose, advise women not to breast feed, or delay offering treatment until the woman has finished breast feeding.⁹ There were four treatment cells in the trial: 1) fluoxetine and 1 counselling session, 2) fluoxetine plus 6 counselling sessions, 3) placebo and 1 counselling session, 4) placebo plus 6 counselling sessions. Breast-feeding mothers were excluded. Of 188 eligible women, 87 agreed to participate and 61 completed 12 weeks of treatment. Reluctance to take medication was the commonest reason for refusal to take part. A psychologist, who had received brief training in counselling derived from the principles of cognitive-behavioural therapy, provided the intervention of either one or six counselling sessions for three months. This was to offer reassurance and practical advice, to address feelings of not coping, lack of enjoyable activities, or practical support, and caring for older children.¹³ The first session lasted one hour and subsequent ones lasted 30 minutes. There was improvement in all the treatment groups, but this varied according to the three psychiatric outcome measures, assessed by a psychiatrist, blinded to allocation. Those who received fluoxetine improved more than those who received placebo. Also, those who received six counselling sessions improved more than those who received one counselling session. The study looked at outcomes, equivalent to about 20 weeks postnatally. The authors concluded that women might decide which is the most appropriate treatment for themselves.

Two, as yet unpublished studies compare psychological-educational group or usual care women with PND¹⁵ and the prevention of PND.¹⁶ A new model of community postnatal care was associated with positive mental health outcomes at four months for women in 17 practices.¹⁷

Apart from the effects on cognitive and emotional development of children,² there is an association between depression in mothers and adverse effects on the health of their children. The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC)¹⁸ recently found that injuries were common amongst children of depressed mothers; 24% of infants experienced a fall or a burn in the first six months of life, and 26% of children aged 15 months experienced a fall, a burn or poisoning over a 9-month follow up period. The risk of injury was 30% greater amongst children whose mothers were categorised as depressed using the EPDS. The study also found a 40% increase in risk of multiple injuries amongst children of depressed mothers and higher rates of antibiotic use amongst children of depressed mothers.

Research Methods

Project Design. The design will be a pragmatic RCT and the administration of the EPDS and intervention will be organised to offer the best intervention for normal clinical practice. It will be designed to assess a combination of preference, therapeutic efficacy and practical effectiveness. Since preference may be an important prognostic variable in many RCTs, the trial will take account of elicited preferences in the final analysis.¹⁹ Acceptability of the programme to women will be monitored. To detect any systematic differences between the women who consent and those who decline to participate, HVs will obtain anonymised details

(age, parity, sex of baby, ethnic group, postcode) for all women who have a baby in the practices. The HVs will document reasons for ineligibility and for choosing not to participate.

The external validity of the trial outcomes will be maximised by ensuring that women recruited represent a primary care population with a range of PND severity; by monitoring by intention to treat; and by having an 18-month follow-up and outcome measurement to determine the degree of remission and relapse over time.

Setting. The setting will be 90 general practices in the (old) Trent region, which are highly appropriate for the trial, serving areas representing a diverse range of women in urban, suburban and rural localities and different levels of socio-economic need. The HVs will represent the variability in the approaches to screening, knowledge, skills and confidence among HVs. The participants, settings and providers will therefore be typical of the conditions in which a primary care service will be provided. Prior to recruitment to the trial all GPs and HVs in each practice must agree to take part; to the health visitor attending the complete training programme; and to the use of a referral protocol for the management of women with severe depression, tailored to specialist secondary mental health services provided locally.

Subjects. The study population will be all women registered with participating practices who have a baby and meet the inclusion criteria during the recruitment phase. The EPDS will be administered to women who consent to participate in the study at 6 weeks. The HVs in the intervention practices will re-administer the EPDS face-to-face for those women who score 12 or more on the EPDS two weeks later. Those women found to be 'at-risk women' (as defined by two scores of 12 or more on the EPDS) will be offered the intervention. In addition, the Health Visitor will offer the intervention to those women whom the Health Visitor feels may benefit from the intervention, irrespective of their EPDS score. The Health Visitors will document their reasons for offering the intervention to women who score 11 or less on the EPDS. There will be a sub-group analysis of the results for the women who scored 11 or less on the EPDS, but were regarded by their Health Visitor as a woman who might benefit from the intervention.

Planned Inclusion/ Exclusion Criteria. As a pragmatic trial, few women will be excluded. The study will include all women registered with participating practices who have a live baby within the recruitment interval and confirm that they are going to remain with their GP for four months. One problem with the EPDS is that it has not been validated in a non-English speaking community in the UK. Some of the practices will have a large number of women from different minorities. The HVs in these practices will be aware of the language spoken by each woman and will have access to appropriate translation and interpreting services. Rather than exclude all women unable to read or speak English, we will use a Punjabi Postnatal Depression Screening Questionnaire (PPDSQ) developed from several standard screening questionnaires to detect psychological distress, and an unvalidated Urdu version of the EPDS, for those who speak Punjabi and read Urdu respectively. Those unable to give informed consent will be excluded.

Randomisation. The unit of random allocation will be the GP practice including all the HVs who work there, not the individual woman. This will minimise the potential for contamination between treatments, if both were to be delivered by the same HV, or between HVs in the same practice. The method will be simple, random allocation, using random digits, in a ratio of 1:1:1 PCA practice to CBA practice to control group of HV standard care, encompassing all care currently given by HVs, stratified by practice size. The allocation schedule will be prepared in the research office by the statistician, who will be blind to the identity of the practices. Prior to randomisation, there will be an assessment of each HV's level of interest and motivation in counselling for PND, their counselling skills, qualifications, use of the EPDS and an assessment of their usual care when a woman is depressed postnatally.

Recruitment of Practices. Since one of the applicants (JM) is Research Co-ordinator for Trent Focus, the recruitment of participating practices will be principally via their well-established, quality controlled Collaborative Research Network (n=55). The PCTs in Nottingham have all been alerted to the trial (by EM) and additional recruitment will be through all PCTs in Trent, via Primary Health Care Teams. As a pragmatic trial, no practices will be excluded. There has been an impressive response from practices in Trent interested in participating, with some negative responses indicating HV workload, *“Our HV is over-stretched at present and I fear her regular work might suffer.”*

Recruitment of Women. To recruit women to the study, a research information leaflet with a covering letter from the practice, will be posted by the HV (to avoid disclosure of women’s details to the researchers) to all women registered with participating practices who are 32 weeks or more into their pregnancy and expected to give birth in the recruitment phase. This will allow women time to consider whether to take part in the study.²⁰ This letter will contain a sample research consent form and contact details of the research office so that women can express interest in taking part. The HVs will send an English and a translated version of the information appropriately to women whom they know to read Urdu. The HV will contact those women who express interest in participating, either when they attend an antenatal appointment or group at the practice, or at their home. The HV will confirm recruitment criteria, including that the woman is going to remain with their GP for four months. Once women have had enough information, including that they have the right to withdraw from the study at any time, the HV will obtain written, informed consent to participate in the study and confirmation of their postal address for six weeks post-natally. Women will complete a confidential antenatal questionnaire, coded for identity, to provide socio-economic details, and information about previous mental health problems. The HV will record anonymised details of women who choose not to take part, as well as those who are not eligible, to compare with the features of participants. As a safeguard to avoid sending a questionnaire to women who, for example, have had a stillbirth or perinatal mortality, the HV will let the local Project Co-ordinator know of all later reasons for women not being included in the study, e.g. after a stillbirth.

Identification of 'at-risk women'. The instrument to detect increased risk of PND will be the EPDS, administered at 6 weeks, as increasingly used by HVs in the UK. The studies to validate the use of the English version of the EPDS have used different recruitment methods, on different populations, at different times postnatally and the EPDS needs to be evaluated for routine use in primary care.²¹ However, we are not aware of any other tool which can confer advantages over the EPDS. The tool was developed because of the limitations in available tools for screening for depression.¹ and is a largely acceptable, simple, self-report scale. The self-administered scale eliminates observer bias.²² The tool was found to be sensitive to change over time and was evaluated in a community setting in 84 women.¹ On a 0-30 scale, a threshold score of 12 correctly included all women with definite, major depression but there were 5% false negatives (minor depression) and 17% false positives. At this threshold, the sensitivity for detecting true positives (n=35) was 86% and the specificity (n=35) was 78%. The positive predictive value was 73%. The authors emphasised that the EPDS is not a substitute for a clinical assessment and a score of 11 does not indicate the absence of depression.¹ The evaluation on a sample of 702 women²³ underlined the importance of the EPDS as a detection tool, but found a lower sensitivity of 67.7% at a threshold of 12. As a pragmatic trial, the study will use 12 as the threshold for intervention since this is widely used in practice and classifies at least 10% of women screened as 'at risk'.²⁴ The number of women with false-positive results will be reduced by the two-week repeat EPDS, which will identify 'at-risk women'. If any woman answers positively to item 10 (which indicates suicidal ideation), her HV or GP will be informed, provided she has consented to this. Within the trial we will compare the scores obtained and the costs of administering the

EPDS using a postal questionnaire with the scores obtained and costs of administering the EPDS face-to-face.

SCAN Interview. The diagnostic status of 'at-risk women' will be confirmed during an interview, using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN)²⁵ as the best validated and most comprehensive instrument used successfully in the general population to confirm self-reported depression.²⁶ Rather than be used as an inclusion criterion, this will be used for analysis by diagnosis and severity. The SCAN is designed for use by clinicians with adequate knowledge of psychopathology (e.g. RMN), to assess, measure and classify psychopathology and behaviour associated with major psychiatric disorders. The interview data are entered onto a laptop computer to produce an index of definitions and an ICD-10 diagnosis of no, mild, moderate or severe depressive illness. The results will be used to assess the performance of the EPDS.

Preference. For women with no depression or mild depression, the SCAN interviewer will explain that their practice had been randomised for the HV to offer the intervention to women with mild depression. For women with moderate to severe depression, the SCAN interviewer will give a verbal and written explanation of treatment choice, and discuss the implications of antidepressant treatment with the women, e.g. breastfeeding. These women will be asked to state their preference for treatment either by HV intervention or a Selective Serotonin Reuptake Inhibitor (SSRI) prescribed by their GP, and to state the strength of their belief about the effectiveness of HV interventions or SSRIs. The majority who are likely to prefer counselling over SSRI and the few who remain neutral will be offered either PCA or CBA from their HV as originally randomised. The few women with moderate to severe depression, who prefer SSRI, will be offered their preference of a GP appointment within a week and a referral letter. However, the aim of the trial will not be to investigate the efficacy of SSRIs. Rather, it is a study of two psychological interventions from HVs. The women who choose treatment with an SSRI will receive the standard support from their HV. Their GP consultation rate and prescription use will be monitored, and their outcomes will be measured to estimate the clinical effectiveness of preferred SSRI treatment from a GP.

Planned Interventions. Before administering the EPDS begins, HVs will have attended a training module to develop their skills in delivering *either* the PCA or the CBA, according to the random allocation, with the option of seeking 30 credit points to contribute towards their continuing professional development. The two forms of training will be well-balanced, and the two forms of intervention will be distinct and well-balanced. The intervention in *each* of the intervention arms will be offered for a maximum of eight, weekly sessions of up to one hour, focused on the needs of the mother. All HVs will use a referral protocol for the management of severely depressed women, endorsed by the GP practices, tailored to specialist secondary mental health services provided locally. This will include referral to GP or elsewhere for women with high risk of suicide or severe and enduring mental health problems. The local Project Co-ordinator (PC) will ask HVs not to discuss their intervention or the referral protocol with any other HVs to avoid leakage and contamination. A supervision system will be in place to provide support for HVs dealing with complex problems.

Therapy Allegiance. There is an established problem of researchers' own therapy allegiance tending to bias treatment outcomes in favour of their own preferred methods.²⁷ This is likely to be due to variations in the quality of treatment delivery. To ensure that each intervention is delivered as well as possible in the judgement of its respective professional constituency, a reference group of experienced trainers, chaired by Professor David Shapiro, will review the training programmes and comment on them, to provide external quality assurance.

Person-Centred Intervention. An intervention provided by HVs after a brief training, known as "listening visits" is currently being provided in parts of the UK. It involves up to 8 planned

weekly visits of 30 minutes or more from the HV. In the proposed trial, HVs in practices allocated to offer the PCA will receive training both in recognising PND, the use of the EPDS and the use of PCT skills. In PCT, conditions necessary for therapeutic change include; unconditional positive regard, empathy, and congruence. The focus of the training for the HVs will be upon their understanding of the theory of PCT and applying its principles to themselves, to develop their self-awareness, their ability to develop the attitudes or skills demanded in order to be truly accepting, empathic and congruent with the mother. The more the women feel accepted and understood, the more they will accept and trust themselves, and the more likely they will be to disclose difficult emotions. The HV will aim to adhere to what the client perceives and expresses as important experiences, not impose external views or goals.

Cognitive-Behavioural Intervention. The CBC intervention developed and piloted in Manchester was found to be effective in improving mood in women identified as having PND.¹³ One of the applicants (RW) ran and evaluated this pilot CBC treatment trial then developed and delivered the initial HV CBC training (1996). However, in the treatment pilot, a research psychologist provided the counselling intervention not the HVs. The counselling offered in the pilot included basic counselling skills (active listening, empathy, genuineness, warmth). It also included training in understanding the basics of cognitive behavioural therapy (connections between feelings, thoughts and behaviour). The CBC focused on identifying and dealing with negative automatic thoughts, advice about mood-elevating activities and practical solutions to problems (e.g. relationship with partner or other children, having time for oneself). Subsequently a training programme for HVs was developed. In the proposed trial, HVs in practices allocated to the use of this CBA will receive training in recognising PND, the use of the EPDS and the use of CBC principles and skills. Qualified cognitive-behavioural psychotherapists will deliver the teaching. There is continuing debate about the mechanism of change in CBC for depression,^{28, 29} with some evidence that behavioural activation alone is effective. The focus of the training for the HVs will be upon understanding therapeutic relationships, understanding CBT models and approaches and implementing CBC techniques. These strategies might include planning and reviewing tasks, together with identifying and dealing with negative automatic thoughts and problem-solving strategies. Small group supervision will use case discussion, reflection on learning, and skills rehearsal.

Treatment Adherence. An original training manual prepared by Elliott et al³⁰ is available for the original PCT ('Listening Visits') intervention. Two new manuals will be developed for use in the trial, one for the PCA and a second for the CBA, to minimise HV variation and to maximise reproducibility of the intervention. In addition, HV sessions will be audio-recorded to allow a randomly selected number to be independently assessed for treatment adherence. An external rater, with equal allegiance to both interventions will assess the HVs' competence in therapy and fidelity to both interventions, using measures appropriate to both interventions.

Therapeutic Alliance. Reviews of psychotherapy studies indicate that there is little evidence for the differential efficacy of therapies, partly because of the quality of the research evidence.³¹ Although different models have specific effects, all models of therapy contain non-specific effects or common factors, such as warmth and feeling supported. The quality of the therapeutic alliance, e.g. bond, between client and therapist, has a significant positive contribution to the outcome, although it is unclear how the process works.³¹ The Session Evaluation Questionnaire³² will be used to identify women's perspective about the relative importance of both the specific and the non-specific effects, including therapeutic alliance, associated with the two interventions.

South Asian Women. Women who score over the threshold for concern on the PPDSQ or Urdu version of the EPDS, will be offered up to eight weekly sessions of up to one hour, focused on the needs of the mother. The HVs in the intervention practices will do a joint visit with an interpreter, who may also be a link-worker. In some practices, a bi-lingual HV will offer

support to Punjabi-speaking 'at-risk women'. Alternatively, where projects exist to offer black and Asian women counselling, 'at-risk' women will be visited by an existing counsellor. Training will be provided for the linkworkers and interpreters specifically on understanding ethnic differences in mental illness, perception of depression after childbirth and the concept of counselling. The local Project Co-ordinator will work closely with the HVs for 'at-risk' women to arrange for collection of follow-up information either with an interpreter, or using appropriate translated versions of the follow-up questionnaires.

Compliance. Since the intervention will be offered by the women's usual care provider, there are likely to be few problems with compliance; compliance rates with HVs are usually high and are expected to be around 90%.² Good postal response rates to the EPDS of 88-97%^{33, 2} have been recorded and there is some evidence that women may complete a postal EPDS more honestly than one administered face-to-face by a HV.⁶ The rate of loss to follow-up was 21% at six months in a study of postnatal support, where HVs were not directly involved.³³

Proposed Outcome Measures. The outcomes for the mother, and the broader impact on the infant, and the mother's partner/infant's father will be monitored using established tools.

Maternal Outcomes. The outcome of most practical importance to the HV is the proportion of 'at-risk women' who still score 12 or more on the EPDS and require ongoing support. The EPDS¹ will therefore be used as a maternal mental health outcome measure at 6 months post-natally, along with the Clinical Outcomes in Routine Evaluation (CORE),³⁴ and the MHI-5³⁵ from the SF-36.³⁶ The CORE scores can be transformed to Beck Depression Inventory (BDI)¹ scores. There is accumulating evidence that postnatal emotional distress encompasses anxiety, as well as depressive symptoms. Because the psychological interventions could impact on both depression and anxiety, the state version of the State Trait Anxiety Inventory (STAI) will also be used.³⁷ To coincide with the end of the intervention; to capture short-term gains; and to monitor the process of natural remission, the EPDS and CORE will be used at 4 months. Jacobson's Clinical Significance (JCS) criteria³⁸ will be applied to identify the proportions of women who 'recover', 'improve', 'do not change', or 'deteriorate' on the CORE scale at 4 and 6 months. The most serious and rare outcome for women will be suicide and attempted suicide. Although not an outcome for the trial, these will be reported, along with the number of women with severe psychosis. Information will also be collected on breast feeding, use and acceptability of health services.

Longer-term outcomes. The trial will identify any sustained benefit and longer term or wide-ranging effects at 12 and 18 months, which were not apparent at 6 months. The CORE, MHI-5 from the SF-36 and the STAI will be repeated. The SCAN will incorporate a clinical history schedule to examine psychiatric history over the previous 18 months.

Family Outcomes. It is known to be exceptionally difficult to measure outcomes in children aged less than four, for whom reports from the mother or caregiver are usually used as a substitute measure. Whilst acknowledging that depressed mothers may have an altered perspective on the ability of their child, interactions with their infants will be reported by the mothers in the Short Form Parenting Stress Index (PSI)³⁹ at 6, 12 and 18 months. This will be used to derive an overall score of the level of parenting stress the mother is experiencing. To assess family dynamics, disharmony and concordance between the women and their partners, *both* will be asked to complete a Dyadic Adjustment Scale (DAS) at 6, 12 and 18 months.⁴⁰ Women's partners will also be asked to complete the SF-36 at 6, 12 and 18 months. In addition, at 6 months there will be 30 in-depth interviews by highly skilled interviewers to encourage women to talk freely about their experiences, attitudes and views in

¹ Beck, Steer, Garbin. Psychometric properties of the BDI: 25 yrs. *Clin Psychol Review* 1988;8:77-100.

relation to the support they received from their HV. The interview subjects will be identified pragmatically by the local research Co-ordinators, ten from each limb of the study. The women's partners will be asked to consent to be interviewed, to explore their experiences and elicit their views on living with a women who has depression postnatally.

Infant Outcomes. Effects on child development will be monitored and HVs will document whether the infant's immunisation programme was complete at six and 12 months of age.

Infant Injury Severity Scores. Data on parent-reported and medically-attended injury will be collected by questionnaire. Medically-attended injury will be validated from the primary and secondary care records, which will be used to derive injury severity scores (ISS) that will allow a severity adjusted comparison between therapeutic groups. Practice staff will photocopy the medical records of the children of mothers in the trial, when they have received the mother's consent form, then remove identifying features and send them to the study team. Accident and Emergency (A&E) department attendances will be ascertained by either the relevant A&E departments flagging the records of the infants of the mothers participating in the trial and producing a print out of the electronic records, or by the research team accessing the computerised or paper records for the infants. This method achieved 93% collection of injury outcome data from primary and secondary care records at two years.⁴¹

Summary of Timing and Administration of Outcome Measures

| Time | Mother | Father | Child |
|-----------|---|---|-------------------------------|
| 4 months | EPDS, CORE with JCS | | |
| 6 months | Postal questionnaire: EPDS, CORE with JCS STAI, SF-36, PSI, DAS. 30 Interviews | Postal Survey: SF-36, PSI, DAS. 30 Interviews. | Immunisation status Growth |
| 12 months | Postal questionnaire: CORE, STAI, SF-36, PSI, DAS. | Postal Survey: SF-36, PSI, DAS. | Immunisation status Growth |
| 18 months | SCAN interview. Postal questionnaire: CORE, STAI, SF-36, PSI, DAS. | Postal Survey: SF-36 PSI, DAS. | Immunisation status Growth |

Ethical Arrangements. After conditional approval, the trial will be submitted to the Trent MREC by November for the December meeting. The trial will include a control group because there is no national policy on screening for PND; there is weak evidence about the most effective intervention for treating women with PND;⁸ there have been no studies of one-to-one HV interventions for PND based in routine primary care; and a no treatment group is required for the economic evaluation. The HVs in the control group will represent the variability in the approaches to screening, knowledge, skills and confidence among health visitors. If a woman in the intervention group scores 12 or more on the EPDS or scores on item 10 on the EPDS to indicate suicidal ideation, on the six-week questionnaire, the information will be passed on to the woman's HV or GP, provided she signed a consent form to say she agrees with this disclosure. The six-week questionnaires from women in the control arm will not be opened until the end of the study period. We will inform women before they are asked to consent to take part in the study that we believe the risks to women of taking part in the study are negligible, and that they personally may not benefit from taking part in the study. We propose to retain coded trial information securely for ten years.

Sample Size Calculation. Cluster-based evaluations avoid major sources of bias and may reduce contamination between intervention groups, particularly when blinding is not possible.⁴² The GP practice will be the unit of randomisation, cluster, intervention and analysis, because that is where the intervention is aimed, even though the effect will be evaluated by individual woman.⁴³ To take account of between-cluster variation when estimating the sample size (or performing the analysis) the variance term in the standard sample size calculation needs to be increased by the design effect (variance inflation factor). This is the ratio of the

variance of the estimated outcome under the cluster sampling strategy to the expected variance in a study with the same number of individuals using simple random sampling.⁴² Estimates of intraclass correlation coefficient (ICC) (at GP level these may lie at less than 0.1)⁴² can be used to calculate the design effect (at GP level these may range from 1-4).⁴² The intra-cluster coefficient (ICC) (ρ) estimates derived from six-month EPDS scores by GP practice in a previous trial of 623 women³³ lies between 0.006 and zero, indicating little clustering by practice.⁴³ The within-cluster (σ_w^2) and between-cluster (σ_b^2) components of variance for the EPDS were 28.64 and 0.181 respectively. We have chosen to conservatively use the ICC of 0.006. Among the practices interested in participating, the annual rate of births ranges from 50-150 per practice, with an average of 78 births. Recruitment to PND studies is high at 94-98%.^{23,46} The proportion of 'at-risk' women detected per practice might range from 11-14, if the EPDS detects 14% to 17.5% of women. The cluster size might range from 6-7, or 8-11 women per practice assuming a conservative 50% or a 75% consent rate to take part in the trial, respectively.² A range of scenarios is presented below to estimate the number of clusters required and the numbers of women to be recruited per group to have 90% power at the 5% level of significance, to detect a 15% difference between the intervention and control group. Within the intervention group there will be 90% power to detect a 17% (0.05 significance) difference between the two types of intervention or 80% power to detect a 15% difference.

| Significance % | Power % | ICC | Average Cluster Size | Total Clusters (Practices) | Intervention arm | Control arm |
|----------------|---------|-------|----------------------|----------------------------|------------------|-------------|
| 5 | 90 | 0.006 | 6 | 87 | 346 | 173 |
| 5 | 90 | 0.006 | 7 | 75 | 348 | 174 |
| 5 | 90 | 0.006 | 8 | 66 | 350 | 175 |

We will therefore assume conservatively an average cluster size of 6 women will require 519 women recruited from 87 practices over one year. Assuming a 20%³³ loss to follow-up at six months, this will require 649 women in total and a recruitment phase of 15 months.

Statistical Analysis. The aim of the analysis will be to establish firstly whether there are benefits from either of the two forms of intervention compared with HV standard care, and then to identify whether there are any differences between the outcomes of the PCA and CBA. All analyses will be by intention to treat. The primary outcome will be the proportion of women at six months identified as an 'at-risk' woman by scoring 12 or more on the EPDS. The primary comparison will be between those women whose practices were randomised to intervention, versus those women whose practices were randomised to offer HV standard care. The secondary comparison will be between those practices randomised to administer PCA and CBA. Again the proportion of women at six months identified as an 'at-risk' woman by scoring 12 or more on the EPDS will be compared between these groups. At four months, the EPDS and CORE scores will be compared between the intervention and control groups, and then between the two intervention groups. At four and six months, Jacobson's Clinical Significance (JCS) criteria³⁸ will be applied to identify the proportions of women who 'recover', 'improve', 'do not change', or 'deteriorate' on the CORE scale, comparing the intervention and control groups then the two intervention groups. For the other maternal outcomes, that is, the CORE, STAI, SF-36, PSI and DAS, the average values will be compared between the intervention and control groups and between the two types of intervention (PCA v CBA), at 6, 12 and 18 months.

The family outcomes collected from the mother's partner/ baby's father at 6, 12 and 18 months (SF-36, PSI, DAS) will be compared between the intervention and control groups and between the two types of intervention (PCA v CBA). For the infants, Injury Severity Scores at 18 months will be compared between the intervention and control groups and between the two types (PCA v CBA) of intervention.

In all the analyses, multi-level modelling will be performed to allow for the clustered nature of the data and to adjust the outcome comparisons for individual level covariates, e.g. age (of mother), parity, and HV confounders e.g. age. The multi-level analysis will be conducted in STATA⁴⁵ or MLwiN.⁴⁶

The trial will examine the use of the EPDS, follow-up and outcomes by cultural background, as specified by the women themselves. Subgroup analyses will include parity, socio-economic characteristics, available support and severity of depression. Infant outcomes will be examined by gender.

Economic Evaluation. The objective of the economic evaluation is to establish the differences in costs associated with the two interventions, including the preparation and training of the HVs, and relate the cost to any health benefits found. The economic evaluation will be undertaken alongside the trial using widely accepted methods⁴⁷ and will take an NHS perspective. An evaluation from a wider societal perspective will not be undertaken however, because of the dangers of overloading women with requests for additional data and the problems of valuing production losses, which are exacerbated by the peculiarities of statutory maternity leave. The costing exercise will identify both the fixed costs (training, HV clinical support and administration) and the variable costs (NHS services used). The HV training costs will be apportioned over a number of years and discounted appropriately.

The economic evaluation has been designed as a cost-utility analysis, using the mother's SF-6D scores (which are based on a sub-set of SF-36 responses) as the main economic outcome measure.⁴⁸ However, the performance and sensitivity of the SF-6D in post-natal women is uncertain, so its appropriateness will be investigated by assessing its construct validity and sensitivity to change within the trial. If these analyses show the SF-6D to be deficient, the cost-utility analysis will be supplemented by a cost-consequences analysis using the EPDS as the measure of health benefit. Health benefits for the father and child will be assessed, but will not be incorporated into cost-utility or cost-effectiveness estimates. Their health benefits will be presented in disaggregated format, as a cost-consequences analysis, alongside the cost-utility estimates of the mothers.

Collection of Cost Data. Individual-level resource use data will be collected using woman's questionnaires, HV contact records and GP records. The resource use data will cover general practice, hospital services, secondary mental health services and prescription use.

Women who take part in the trial will be asked to keep a 'user-friendly' diary as an 'aide-memoire' when completing their postal questionnaires. In the diary, women will log NHS services use: the number and type of HV, GP and social services contacts (e.g. own home, clinic, practice, phone), prescription use, hospital and secondary mental health services use. A separate note will be made to distinguish contacts principally for herself or her baby. Similarly, health visitors will complete contact forms for all exchanges with women in the trial, separating those principally for the woman and those principally for her baby, to establish overall HV resource use. They will also record mother's prescription use (particularly antidepressants), duration of breast feeding and completion of immunisation programmes for the baby. The HV will keep details of acceptability (distinct from compliance) of the intervention offered. Major discrepancies between mother and HV records will be investigated.

Secondary care resource use will be estimated from primary care records which contain A&E departments' attendance slips and hospital discharge summaries by specialty. The practice staff will retrieve the woman's consent form from her notes and when requested at 18 months postnatally, they will photocopy the medical records of women in the trial and their children, remove identifying features and send the copy to the study team. A&E attendances will be ascertained by either the relevant A&E departments flagging the relevant records and

producing a print out of the electronic records, or by a member of the research team accessing the computerised or paper records. Unit costs for HV visits will be estimated through a bottom-up costing exercise to accurately account for length of visits and costs of training. The value of other services will be estimated from widely used sources, where possible⁴⁹ or local estimates.

Economic Analysis. Individual costs will be estimated by combining the resource use and unit cost data. Mean costs and outcomes will be compared between the study groups at 6 and 18 months, using appropriate methods.⁵⁰ The primary cost analysis will compare costs at 6 months post-natally. In the event of one treatment not dominating another, an incremental cost-per-QALY will be estimated using the SF-6D,⁴⁸ together with its associated acceptability curve.⁵¹

Sensitivity analysis will be undertaken to investigate the impact of any uncertainties in the methods and/or data used. This will include the re-estimation of costs based on different unit costs reflecting national variations. The longer-term resource consequences of any child morbidity will not be calculable within the study interval, so the feasibility of modelling possible longer-term effects will be assessed using published longitudinal data. If considered feasible, a simple model will be constructed to assess the magnitude of these costs and their impact on the within-trial results.

Potential Difficulties.

We are unable to predict the number of women who will consent to participate in the study or the trial. We have therefore conservatively estimated that only 50% will consent to participate in the trial, although the proportion may be much higher. To allow for possible under-recruitment, we have built in a 15-month recruitment phase, although if the required number of women is recruited within fewer months, we will halt recruitment at that point. A pilot study will take place whilst the HV training is in progress to test the practicalities and acceptability of the recruitment procedure, recruitment to the study, and to estimate levels of completion of the 'user-friendly diary' and how this might be improved.

Blinding. Blinding of the intervention will not be possible, but the identity of all the practices and the women will be coded. This will blind the statistician to the practices' identity for the initial random allocation. The statistician and the health economist will be blinded to the women's allocation to group for the data analysis. The SCAN interviewers and the psychologists who perform the infants' assessment will all be blinded to both the EPDS score of the women and practice allocation to intervention.

Independent Supervision of Trial.

The trial will follow the Good Clinical Practice in Clinical Trials guidelines drawn up by the MRC in consultation with the Department of Health. Prof. Jon Nicholl has been asked to chair the Trial Advisory Group that will be established. We will invite Prof. Lynn Murray, Prof. Ros Bryar (Chair of Community and Primary Care Nursing), Dr Denise Kendrick (expert on childhood accident data collection and analysis), and Prof. David Shapiro to be members. The group will also include two service users and two practising HVs. A Data Monitoring and Ethics Committee will be established and chaired by Prof. Mike Campbell.

Summary. The trial will have the following strengths for an economic evaluation of a HV intervention for PND²² by: using a RCT method in a multi-site study; conducting the trial using a naturalistic method in primary care, where it is relevant; measuring clinical outcomes as well as level of functioning; being powered to detect a clinically meaningful difference; assessing the acceptability of different interventions.

Project Timetable and Milestones

The project plan includes, mounting a new training programme and preparing the HVs to provide the intervention. The study will last for 36 months with a 17-months of recruitment phase and 18-months follow-up phase.

| Milestone | Detail | Start | End |
|----------------------------------|---|-------|-----|
| 1. Plan the trial | <ul style="list-style-type: none"> Recruit research personnel Finalise project plan Research Ethics Committee approval Convene Advisory group Enlist full support of PCTs, HVs and GP practices in Trent, randomise practices and train HVs Develop instruments | 1 | 6 |
| 2. Research Information | Post research information leaflets from to ante-natal women | 4 | 15 |
| 3. Pilot | Test recruitment method, questionnaire and postal administration of EPDS method in 1 site. | 5 | 6 |
| 4. Begin Full Recruitment | Identify women and obtain informed consent to participate in study in each site. | 7 | 22 |
| 5. 6-week administration of EPDS | <ul style="list-style-type: none"> Administration of EPDS SCAN interviews | 8 | 23 |
| 6. Intervention | GP practices referral protocol in operation for PCA and CBA intervention practices | 8 | 20 |
| 7. 6-month Follow-up | <ul style="list-style-type: none"> Postal questionnaire to women and partners. Qualitative interviews | 12 | 23 |
| 8. 12-month Follow-up | <ul style="list-style-type: none"> Postal questionnaire to women and partners. | 18 | 29 |
| 9. 18-month follow-up | <ul style="list-style-type: none"> SCAN interviews Postal questionnaire to women and partners. | 24 | 35 |
| 10. Analysis | Measure the outcomes and costs | 30 | 35 |
| 11. Reporting | Prepare final report | 35 | 36 |

Expertise.

The research will be based in a dedicated health services research unit, SchARR. The multi-disciplinary team of collaborators from several institutions represents a wide range of skills and experience, notably the design and management of multi-site RCTs in health services research, medical statistics, economic evaluations and government policy development. The team has experience in the management of PND (clinicians, psychologists, a GP, and a former HV), and in health visiting, and also includes Primary Care Trust Chief Executive. The experience of the NHS-based members of the project team typify the practicalities of primary care service delivery and the acknowledged genuine difficulties in performing research in the current NHS. The project team have previously successfully collaborated on cost-effectiveness trials in primary care, notably in this area on two HTA trials - a cluster RCT of Cognitive Behavioural Therapy in Primary Care (95/30/02), a RCT and economic evaluation of postnatal social support,³³ a comparison of SSRI and CBC in the treatment of postnatal depression,¹³ and a RCT to reduce psychosocial risk factors to prevent PND.²⁶ Some of the applicants are currently working on other studies of post-natal care, which include the use of the EPDS and SF-36. In addition, G Parry has experience in analysing infant development data.⁵²

Each member of the research team will contribute to the trial as follows:

J.M. - responsible for the preparation of proposal, research protocol and project plan; project and data management; management of local Project Co-ordinators; convening meetings of the Trial Steering Committee, Data Monitoring and Ethics Committee and Trainers Reference Group; monitoring achievement of project milestones; producing interim reports and final report.

R.W. - Experience from running and evaluating the Manchester pilot CBC treatment trial then developing and delivering the initial CBC training in Manchester (1996) and co-author of publication on CBC. ¹³ Preparation of research protocol, clinical advice and supervision.

NM - Practicing family physician with a long-standing interest in and a recent publication in PND, recruitment of participating practices, liaison/ co-ordination of GPs.

G.Parry - Additional advice on the statistical analysis and infant development data.

S.D. Methodological and Health Economics advice, data analysis, Trial Steering Committee

P.S. - (Consultant clinical psychologist) - Preparation of research protocol, Supervision of junior research psychologists.

E.M. - NHS Advice on practical aspects of the new service, co-ordination of practices in all PCTs in Nottingham.

G.Paley - Preparation of research proposal and project plan, monitoring of therapeutic alliance, advice on mental health nursing, Trial Steering Committee.

T.B. Preparation of proposal, clinical advice, Trial Steering Committee

Consumer Involvement. To ensure the outcome measures are relevant, primary care-based women who have recovered from PND (consumers/ service users) will be approached for consultation during the proposal preparation stage, to hear their views on the proposed trial, and to provide advice throughout the trial as members of the advisory group. ⁵³ Resources will be available to cover travel and child care costs if required. Trent Focus is developing a policy, resources and infrastructure to offer sustainable support to maximise consumer involvement at the highest appropriate level in Trent Focus research.

Justification of support required.

Staff requirements and training requirements are summarised in the table below. The HV training costs and service support costs comprise £104K and £60,600 respectively.

Summary of Staffing and Training requirements

| <i>Staff</i> | No. | % | For |
|--|-----|-----|-----------|
| Local Research Co-ordinators to recruit and Co-ordinate HVs | 3 | 100 | 18 months |
| Clerical support (questionnaire administration) | 1 | 100 | 18 months |
| HV support from psychologist | 3 | 5 | 18 months |
| Psychologists RA 1A to assess infants at 18 months | 2 | 100 | 12 months |
| Consultant clinical psychologist | 1 | 5 | 2 yr. |
| Statistician (statistical analysis) grade 2, point 2 | 1 | 5 | 3 yr. |
| Health Economist (economic modelling) | 1 | 5 | 3 yr. |
| Project Manager | 1 | 40 | 3 yr. |
| <i>Training Costs</i> | | | |
| 46 HVs for PCA training (15 per group, 8 days training) 120 journeys | | | |
| 46 HVs for CBA training (15 per group, 8 days training) 120 journeys | | | |

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