NETSCC, HTA

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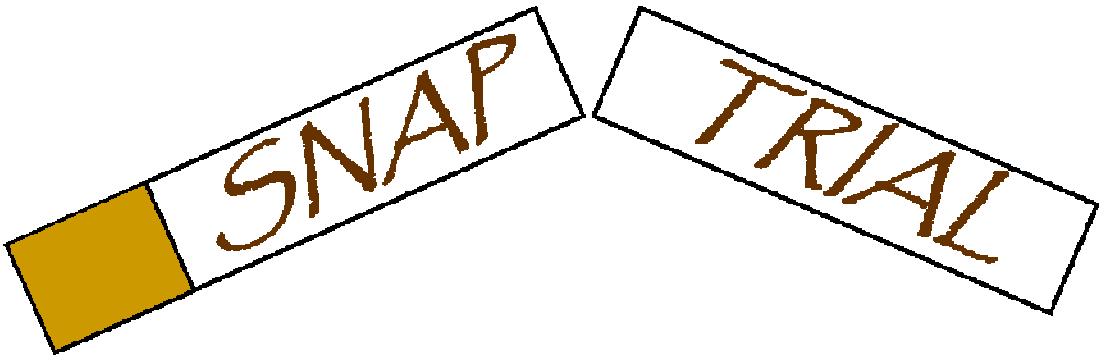

Protocol for the SNAP (Smoking Nicotine And Pregnancy) Trial

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Trial title:	**Double-blind, randomised, placebo-controlled trial of nicotine replacement therapy in pregnancy**
Acronym:	***S*moking, *N*icotine *a*nd *P*regnancy (SNAP) trial**
International Standardised RCT Number (ISRCTN):	**ISRCTN07249128**
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Summary

The HTA-funded smoking, nicotine and pregnancy (SNAP) trial will investigate whether or not nicotine replacement therapy (NRT) is effective, cost-effective and safe when used for smoking cessation by pregnant women. Over two years, in 5 trial centres, we will randomise 1050 pregnant women who are between 12 and 24 weeks pregnant as they attend hospital for ante-natal ultrasound scans. Women will receive either nicotine or placebo transdermal patches with behavioural support. The primary outcome measure is biochemically-validated, self-reported, prolonged and total abstinence from smoking between a quit date (defined before randomisation and set within two weeks of this) and delivery. At six months after childbirth self-reported maternal smoking status will be ascertained and two years after childbirth, self-reported maternal smoking status and the behaviour, cognitive development and respiratory symptoms of children born in the trial will be compared in both groups.

Contents

1. Background

Maternal smoking during pregnancy harms unborn children and, as up to 30% of pregnant women smoke[1], it is a significant public health problem. The adverse effects of smoking during pregnancy include an increased risk of miscarriage and stillbirth, accounting for 4000 deaths annually, and of pre-term birth and low birth weight leading to increased perinatal morbidity[2;3]. Children of mothers who smoke whilst pregnant are at increased risk of neo-natal mortality, sudden infant death syndrome and asthma[2]. Maternal smoking whilst pregnant is also associated with an increased risk of attention deficit and learning problems in childhood.[3;4] Currently only around 25% of pregnant smokers stop for even part of their pregnancy and, of these, around two thirds re-start post-natally[1].

Effective methods for promoting smoking cessation by pregnant women are required. The most effective smoking cessation therapy in non-pregnant smokers is a combination of behavioural support and pharmacotherapy with either nicotine replacement therapy (NRT)[5] or bupropion.[6] Behavioural support alone can increase smoking cessation rates by up to 7%[7] and the addition of pharmacotherapy increases this further by 1.5 to 2-fold. Behavioural support is usually provided without pharmacotherapy, however, because of concerns that drug therapy may harm the fetus.[8] This is understandable for bupropion, but is far less logical for nicotine.

Pregnant women who smoke will already expose their unborn children to nicotine. Nicotine has well documented potential adverse effects in pregnancy, since it is a vasoconstrictor and nicotine from cigarettes causes dose-related increases in maternal blood pressure and heart rate and has lesser effects on the fetal heart rate.[9] In rats chronic nicotine exposure is associated with dose-dependant alterations in behavioural and cognitive responses, CNS toxicity and a diminished adrenal response to hypoxia that, in humans, could pre-dispose to sudden infant death syndrome.[9] Consequently, nicotine may also be responsible for the attention deficit and learning problems that are described above.[4] Cigarette smoke, however, contains numerous other toxins in addition to nicotine and it is not known which of these actually cause harm, though the fetal effects of nicotine have been most widely studied. The cardiovascular effects of nicotine from NRT are less than those observed from smoking and regular NRT use generates lower plasma nicotine concentrations (when body weight is accounted for) than those in the animal experiments described above.[9] There is also no evidence that NRT use in pregnancy results in higher plasma nicotine concentrations than smoking[9]. For these reasons, and because using NRT in pregnancy results in exposure to only nicotine and no other toxins, there is expert consensus that NRT use is safer than smoking in pregnancy as long as pregnant women using NRT do not receive more nicotine from NRT than they would have done by smoking[10; 11]. It is difficult, though, for health professionals to give clear guidance to pregnant women on using NRT when the safety of NRT in pregnancy is justified primarily on theoretical grounds and its efficacy has not been established.

To date, evidence on the effectiveness of NRT in pregnancy comes from 3 studies and is inconclusive.[12-14] Two of these studies were trials investigating NRT as transdermal patches[12;13] but one[13] was stopped after only 40 patients had been randomised. The other[12], however, randomised 250 women but produced no clear evidence that NRT was effective, since the odds ratio for smoking cessation using NRT versus placebo was 1.1 with a 95% CI of 0.7 to 1.8. This odds ratio is much lower than that obtained from meta-analysis of trials of NRT patches in non-pregnant subjects (OR, 1.74) [5] and raises questions about whether using

NRT in pregnancy is effective for smoking cessation. The third study was not placebo controlled and randomised women to intensive behavioural support with an additional option to use NRT patches and / or gum[14] or a 'normal care' group which received only very minimal smoking cessation advice. Although, 75 women in this trial opted to use NRT, this design makes it difficult to disentangle any effect of NRT from that of intensive behavioural support. Where reported, no harmful effects of NRT were demonstrated in these 3 studies. In the larger patch trial[12], babies born in the NRT group were significantly heavier than others [mean birth weight (adjusted for prematurity) difference = 186g (95%CI 35,336g)], suggesting that pure nicotine as NRT has less impact on fetal growth in utero than smoking. Additionally, in the trial which allowed a group of women to use either NRT patches or gum or a combination of these, mean birth weights in fetuses born after 37 weeks were not statistically different between the 2 trial groups [non-significantly lighter (by 32g) in NRT group]. In both trials that reported the distribution of low birth weight infants between groups[12;14], no significant differences were noted.

It has recently become apparent that conventional doses of nicotine contained in NRT may be insufficient for pregnant women and this may explain the negative findings from the one trial of NRT in pregnancy. In pregnancy, the metabolic clearances of nicotine and cotinine (the principal metabolite of nicotine) are increased by 60% and 140% respectively[15]. Accordingly, even when pregnant women take standard doses of NRT for adequate periods, these may still be ineffective because they may require higher doses of NRT to replace the nicotine they would have received via smoking. Higher doses of NRT might, therefore, be needed in pregnancy, but because there is very little human-subject research into the effects of nicotine on the developing fetus, it is not known whether these might increase the risk of fetal damage. Until the effectiveness of the current conventional dose of NRT is established, it is hard to justify trials of higher ones.

In summary, although consensus opinion suggests that taking NRT during pregnancy is likely to be safer than smoking[10; 8;11;16], there is little direct trial evidence to support this and we do not know if NRT is actually *effective* in promoting smoking cessation amongst pregnant smokers. The *SNAP* trial will produce direct evidence on these important questions.

2. Hypothesis

The *SNAP* trial will investigate whether or not NRT is more effective than placebo in achieving smoking cessation for women who and are between 12 and 24 weeks pregnant, who currently smoke 5 or more cigarettes daily and who smoked 10 or more cigarettes daily before pregnancy.

3. Interventions

Treatment group: Pregnant women will receive an eight week course of 15mg / 16hr NRT transdermal patches. Although many studies have used longer courses, there is no evidence that these are more effective.[5] Patches will be issued in conjunction with individual behavioural support (*Section 10*) which is an effective smoking cessation intervention in pregnancy.[7] Four weeks after their quit dates, women who are not smoking will be issued with a second four week supply of patches if required.

Control group: Women in the control arm of the trial will receive an identical placebo NRT patch and the same behavioural support as those in the treatment group. In both control and intervention groups, participants will be blind to their group allocation.

4. Randomisation procedure

After collecting pre-randomisation baseline data (*section 9*), exhaled carbon monoxide readings will be taken from women and assuming that readings indicate that women do smoke [cut off 8 ppm[17]], informed consent for trial entry will be sought. After consenting to trial entry, women will receive an initial behavioural support session (*section 10*) before being randomised.

Randomisation will be via the Nottingham Trials Unit web-based database and randomisation service. In each centre the recruiting research midwife (RM) will have a username and password. (S)he will log on to the trial website that hosts the trial database (https://ctsu.nottingham.ac.uk/snap/login.asp), confirm that the patient eligibility criteria are all met and enter an agreed minimum amount of *registration* data about the participant and centre before randomisation is possible. Data to be entered at this stage are found in *section 9*. The computer will then issue a trial number which will be the unique identifier for the trial participant and a trial pack number which will reflect the treatment allocated. Randomisation will be stratified by trial centre only.

Numbered packs of active and placebo patches will be distributed by Queen's Medical Centre pharmacy and stored in either the local pharmacy or the participating ante-natal/ultrasound clinics, depending on local agreements or arrangements. After randomisation, a prescription with a container number will be generated by the database. The local pharmacy or research midwife will select the patch pack with the appropriate container number and issue this to the participant. The research midwife and the trial participant will both be blind to group allocation. When research midwives visit women at home to enrol them into the trial, immediate internet randomisation will not be possible. In this circumstance the research midwife will return to her / his hospital base to randomise the enrolled woman and the appropriate trial pack will be posted to the trial participant.

5. Outcome measures

Primary end point: Self-reported, prolonged and total abstinence[19] from smoking or the use of any non-pharmacological nicotine containing substances between a quit date set within two weeks of randomisation and immediately prior to childbirth **and** validation of abstinence from smoking at this point by both exhaled CO measurement[a] and salivary cotinine estimation[a].

Permitted timing and rules of data collection:

Self reported smoking data will be used if this is collected within i) eight weeks of the one month follow up point and ii) within one month of delivery.

Biochemical validation data will be used if this is collected within one month of any data collection point. Biochemical validation of self reported, prolonged smoking cessation will use exhaled CO measurement (at one month) and, additionally, salivary cotinine estimation[a] at delivery.

Prolonged abstinence from smoking will be considered to have occurred when no smoking is reported between the quit date and delivery (or other follow up point). For the purposes of attributing positive or negative primary outcomes, very occasional, minor lapses during reported abstinence will not be counted as a return to smoking unless women report smoking more than 5 cigarettes in total between their quit date and delivery.

Secondary end points:

a) Smoking

1. Self reported, prolonged abstinence from smoking between quit date and one month.
2. Self reported, prolonged abstinence from smoking between quit date and delivery.
3. Self reported, prolonged abstinence from smoking between quit date and delivery, with biochemical validation of this at both one month follow up and delivery.
4. Self reported smoking cessation for previous 24hr period at delivery validated by exhaled CO and saliva cotinine estimation.
5. Self reported, prolonged abstinence from smoking between quit date and 6 months after delivery.
6. Self reported smoking cessation for previous 7 day period at 6 months after delivery.
7. Self reported, prolonged abstinence from smoking between quit date and 2 years after delivery.
8. Self reported smoking cessation for previous 7 day period at 2 years after delivery.

b) Fetal loss and morbidity

1. Miscarriage (less than 24 weeks gestation) and stillbirth (24 weeks gestation and over)
2. Neonatal death (i.e. from birth to 28 days)
3. Post-neonatal death (29 days to 2 years)
4. Individualized birth weight Z score (i.e. birth weight adjust for gestational age, maternal height, maternal weight at booking and ethnic group).
5. Apgar score
6. Cord blood ph
7. Gestational age at birth
8. Intraventricular haemorrhage
9. Neonatal enterocolitis
10. Neonatal convulsions
11. Congenital abnormality

c) Maternal morbidity and mortality

[a] cut offs are 8 ppm for exhaled CO and 10ng/ml for salivary cotinine[17]

1. Maternal mortality
2. Mode of delivery
3. Proteinuria
4. Hypertension in pregnancy

d) Early childhood outcomes

1. Behaviour and development at 2 years
2. Disability at 2 years
3. Respiratory symptoms at 2 years

e) Health economic data

1. Duration of maternal hospital admission for childbirth
2. Duration of any admission (of baby) to special care
3. Health status at 6 months (EQ5D)20

6. Number of patients required

Sample size: We need to recruit 525 women into each arm of the study. A trial with 500 women in each arm would detect an absolute difference of 9% in smoking cessation rates between the two groups immediately before childbirth with a two-sided significance level of 5% and a power of 93%. We anticipate that up to 5% of women will be lost to follow up and inflate our sample size (of 500) by a factor of 1.05 to allow for this. This size of study would allow us to detect smaller treatment effects with lower power. For example, we would have 80% power to detect an absolute difference in cessation rates of 7%.

Justification: A Cochrane review has shown that approximately 10% of women who are still smoking at the time of their first antenatal visit will stop smoking with usual care and a further 6% to 7% will stop as a result of a formal smoking cessation program using intensive behavioural counselling[15]. This means that in our control group (*placebo plus intensive behavioural counselling)* we can expect a smoking cessation rate of around 16%. The most recent Cochrane review of NRT, reports a treatment effect (odds ratio) for transdermal patches of 1.74 95%CI (1.57-1.93)[5]. Consequently, if we were to find NRT as effective in pregnancy as it is generally, we could expect a smoking cessation rate of approximately 25% in our treatment group (*NRT plus intensive behavioural counselling*).

7. Eligibility criteria

Inclusion criteria: Eligible women are aged 16 to 50, between 12 and 24 weeks pregnant, who report smoking at least ten cigarettes daily *before* pregnancy and who *still currently* smoke at least five cigarettes daily. They also must have an exhaled CO reading at least 8 ppm. Women may only enrol into the trial once and may participate in other non-conflicting research projects.

Exclusion criteria: Women with the following contraindications to the use of NRT will be excluded: severe cardiovascular disease, unstable angina, cardiac arrhythmias, recent cerebrovascular accident or TIA, chronic generalized skin disorders or known sensitivity to nicotine patches, chemical dependence / alcohol

addiction problems. Also, women who cannot give informed consent and those with known major fetal anomalies will be excluded. IUGR is not an exclusion criterion.

8. Trial process

Diagrams in Appendix A summarise the trial process.
All trial materials (e.g. PIS and questionnaires) appear in Appendix B.

Recruitment: All pregnant women between 12 and 24 weeks into pregnancy who smoke and are interested in stopping smoking are potentially recruits to the study. Three methods of recruitment will be used:

a) It is usual practice in most areas for the community midwives to routinely ask women at their booking appointment about smoking status and whether they would like help to stop smoking. This information is then passed to the local smoking cessation service. These referred women will be sent a patient information sheet by the smoking cessation service and a letter asking whether they would be interested in participating in the trial. Women who were eligible and interested would be seen by the research midwife for consent and data collection as below. If they were not interested or eligible they would be seen by the smoking cessation service as per normal practice.
b) Brief information about the trial and patient information sheets (PIS) will be posted to all women who attend trial site hospitals for ante natal care with their routine antenatal ultrasound scan appointment letters (scans are usually performed at between 12 and 20 weeks gestation). In each trial hospital, a research midwife (RM) working with a clerical assistant will use a systematic method to identify smokers who are interested in participating from all women attending for ultrasound examinations. During piloting a questionnaire was used for this (example in Appendix B) and a similar instrument could be used in any or all of the trial centres. The final method of identifying eligible patients will be agreed with the Chief Investigator. Research midwives will also agree a method for monitoring the numbers of women identified as potentially eligible to join the trial and the proportion of these that eventually enrol.
c) As an alternative to b) above, a leaflet advertising the trial and/or a questionnaire which identifies women who are interested in participating in the trial will be posted to all women who attend trial site hospitals for antenatal care with their routine antenatal ultrasound scan appointment letters or given to women by their community midwife at an antenatal appointment. Women who are interested in joining the trial will be invited to contact the research midwife directly or when they attend hospital for their ultrasound scans. These women will be sent / given a PIS to consider and will be contacted again after 24 hours to ascertain whether or not they want join the trial. After this, consent and other trial procedures will be followed as described below.

Consent: Women who are interested in participation will be asked to discuss this with the research midwife. The research midwife will ascertain if women are eligible to join the study and have read the PIS at least 24 hours earlier. If they have read the PIS, the research midwife will answer any questions that women have about trial enrolment and seek informed consent to:

i) trial participation
ii) collection of follow up data on materno-fetal outcomes from medical

records
iii) participants' registration with the Office for National Statistics
iv) collection of a blood sample for cotinine estimation and DNA extraction & storage
v) collection of saliva samples for cotinine estimation
vi) potential future contact for follow up studies by University of Nottingham based investigators

If women have not read the PIS, but express an interest in the study, they will be given a copy. These women will be contacted after 24 hrs and if they are still interested in enrolling in the study, informed consent will be sought.

Once consent is recorded, baseline data, saliva, blood samples and exhaled CO readings are obtained. Next the research midwife delivers the first session of behavioural support to the participant during which a quit date which is within 2 weeks when they will start using transdermal patches is agreed.

Registration & randomisation: Immediately after the behavioural support session, the research midwife uses a PIN to log on to the University of Nottingham internet randomisation service and enters the ***mandatory enrolment data*** (*section 9*), without which randomisation will not be permitted. The participant is automatically allocated a trial number (i.e. unique ID) and a trial treatment pack number which identifies the treatment required and the RM issues the corresponding trial treatment pack.

Many trial participants will need a home visit for consenting, intensive behavioral counseling and subsequent randomization. In this situation, the research midwife (RM) will ensure that all base line data including the ***mandatory enrolment data*** is collected whilst visiting the participant. The RM will return to base and randomise the participant via the internet before posting an appropriate treatment pack to the study participant.

The research midwife then sends letters to the participant's general practitioner and hospital obstetrician to inform them that she is enrolled in the trial. One copy of the consent form is placed in the hospital medical records, another accompanies the letter to the GP and the third is sent to the Trial Office.

Further behavioural support: The research midwife will contact the participant on their quit day and three days afterwards. The research midwife will give the participant contact details for the local NHS stop smoking service and also pass the participants' details to this service. Participants will receive further behavioural support sessions from the NHS stop smoking service according to an agreed format, or from the research midwife if other local support is not available or not wanted by the participant.

Data handling: RMs will enter the data which they collect on to a secure database hosted by the University of Nottingham via an internet connection and will also make paper copies of data collection to allow audit. Once data collection at any one time point (e.g. baseline or one month) is complete, the research midwife will post a copy of the data collection sheet to the Trial Office. Infant records within the database will be created from within maternal ones and will automatically be linked to maternal and sibling trial records.

Biological samples
i) For DNA extraction, 2x5ml EDTA blood samples are required. These can be refrigerated or frozen (if later than 24 hrs elapses between collection and dispatch). If frozen, this needs to be to -20° centigrade. Samples will be

dispatched to Professor Ian Hall at the University of Nottingham for long term archiving. Frozen samples require non-glass tubes.

ii) Blood for serum cotinine estimation (5ml sample minimum) need to be placed in BD Gold top tubes (or equivalent). These need to be frozen as per i) above before transport to the Nottingham Trial Coordination Team prior to dispatch to Professor Michael Coughtrie at the University of Dundee.

iii) Saliva for salivary cotinine estimation is also transported to Dundee after collection.

All frozen samples need to be transported on ice in non-glass containers labelled with:

- Trial number
- Hospital number
- Subject's initials

Withdrawal from patch treatment: If for any reason, a participant terminates patch treatment, every effort must still be made to collect follow up data.

Follow-up at one month after agreed quit date: If required, participants will be seen by the research midwife (RM) for further supplies of patches. To allow some flexibility this follow up will occur between 3 and 6 weeks after randomisation. The RM will contact participants to ascertain women's smoking status and those who report not smoking regularly (confirmed by exhaled CO measurement) and who wish to receive a further supply of patches will be issued with a new trial treatment pack number (obtained by the RM from the online database) and will receive a corresponding treatment pack (containing 4 weeks' patches). A saliva sample to measure cotinine levels on treatment will be taken if women are not smoking and are still wearing the patches at one month. The Trial Office will send one postal questionnaire asking about smoking status to women whom the research midwife has been unable to contact at one month. When women report continued smoking cessation but do not wish to receive further NRT, the research midwife will arrange CO validation of this, visiting them at home, if necessary.

Follow-up immediately before childbirth: When participants are admitted to hospital whilst in established labour *prior to childbirth*, Delivery Suite staff will be asked to contact the research midwife who will visit participants to ascertain their self-reported smoking status and use of transdermal patches. Women who report abstinence from smoking in the previous 24 hours will be asked by the research midwife to perform exhaled CO testing and provide a saliva sample for cotinine estimation. The RM will have overall responsibility for data collection and will arrange with Delivery Suite staff for this to be obtained in her / his absence. The RM will telephone those missed whilst in hospital as soon as possible afterwards (within 4 weeks maximum) to collect smoking behaviour data. Where participants report smoking cessation, the research midwife will measure their exhaled CO readings and obtain a saliva sample for cotinine estimation, visiting women at home if necessary.

Further infant, fetal and maternal data will be obtained from medical records (*section 9c*)

Data monitoring by RM between data collection points: These data are required to ensure that the Data Monitoring and Ethics Committee is provided with adequate information to form an opinion concerning trial safety:

Development of major fetal abnormality between randomisation and labour onset
Miscarriage and stillbirth between randomisation and labour onset
Maternal death between randomisation and labour onset
Hospital admission

Each month the Trial Office will provide RMs in the centres with a list of trial numbers for participants who are still pregnant. The RM will use these to access subjects' computer records to obtain the information listed above. In the event of a hospital admission the RM will assess whether or not a serious adverse event has occurred and act accordingly (*Section 12*). If the RM enters a miscarriage or stillbirth into the database, this will automatically prevent further infant follow up and the RM will liaise with the mothers' obstetrician to determine whether or not asking for follow up information concerning smoking behaviour around the anticipated time of delivery is acceptable. Major fetal abnormalities will also be reported to the trial office who will review these individually before deciding whether or not the participant should be allowed to continue within the trial.

Registration with Office for National Statistics: The Trial Office will "flag" participants (women and babies) with the Office for National Statistics (ONS) [now called the NHS Information Centre] at birth to facilitate follow up. Each week during the 2 year follow up period, the ONS will inform the trial team of any post-neonatal (i.e. between 29 days and 2 years) or maternal deaths.

Procedure for administering postal follow up questionnaires: Appendix A summarises the procedure for follow postal up after delivery. After infant deaths, questionnaires will not be sent and, where maternal deaths are reported, infants' general practitioners will be consulted about the appropriateness of continued follow up. The Trial Office will send questionnaires directly to study participants using contact details provided at study recruitment. For non-respondents or where questionnaires are returned labelled "*not at this address*", the office will check participants' addresses by contacting infants' grandparents and, if necessary, the ONS / NHS Information Centre (NHSIC). ONS / NHSIC will trace the infant or mother and provide details of the Primary Care Trust (PCT) which provides their NHS health services and the Trial Office will then contact the infant's general practitioner so that a questionnaire can be sent. To maintain contact between researchers and participants, study infants will be sent Christmas cards and birthday cards.

Immediately following childbirth: When appropriate, mothers will be sent or given a simple "Congratulations on the birth of their baby" card.

Follow-up 6 months after childbirth: A postal questionnaire, with one postal and one telephone reminder, will be used to collect the data items specified in *Section 9d,* below.

Follow-up 1 year after childbirth: Before infants' 1st birthdays, *parents* will be sent a 1st birthday card and a questionnaire to collect the data items specified in *Section 9e*, below. Non-respondents will be sent a questionnaire reminder and then followed up by telephone.

Follow-up 2 years after childbirth

i) *Parent questionnaire*: Four weeks before infants' 2nd birthdays, we will dispatch to *parents* a questionnaire and two weeks later, all participating infants will be sent a 2nd birthday card, with questionnaire non-respondents being sent a reminder . Parents who do not respond after two questionnaires will be followed

up by telephone. The questionnaire will measure child behaviour, development, hospital admissions, respiratory symptoms and maternal smoking behaviour and will use standard questions to record parents' reports of infants' respiratory symptoms[21] and behaviour[22], the appropriate 'Ages and Stages' questionnaire[35], with reference to the evidence base for questionnaire design[24]. It will also include simple questions designed to measure children's disability according to a standard definition.[25] Three methods that have been demonstrated to improve postal returns of questionnaires will be used.[36] Before the questionnaire is sent a card will be sent to the parent reminding them that they will be receiving a questionnaire shortly, and asking them to inform us of any change of address. When the questionnaire is sent, a £5 voucher will be enclosed along with a colouring competition for the child. The colouring competition will have a £50 voucher prize, with a winner chosen 3 times per year.

ii) *Health professional questionnaire*: When parents do not respond to the 2 year follow up questionnaire described above, we will attempt to obtain responses to items measuring children's disability from health professionals. To do this, we will post to participants' general practitioners (GPs) a very short questionnaire containing only items to measure children's disability which correspond to those that were on the questionnaire sent to parents. These items are designed to be easily completed using medical or health visitors' records. Health professionals completing these questionnaires require relatively little knowledge of the patient and GPs will be asked to complete them. If GPs cannot complete questionnaire, they will be asked to forward these to children's' health visitors (HV). We will use an initial postal and subsequent telephone reminder to GPs to obtain the required information. Items used will be based on those included in a previously-used questionnaire which has been validated and used with GPs and HVs [26;27'].

Expected start date:	1st April	2006
Expected completion date:	31th March	2013

9. Data collection

This section specifies the items of data collect at different points during the trial.

a) Baseline (i.e. pre-randomisation) data collection

Although online forms will allow data to be inputted to an online database, a paper copy of data will be kept for audit purposes.

***i) Mandatory enrolment data (i.e. required for randomisation)*:** The RM will collect the following data from participants immediately after obtaining informed consent. The RM **must** enter the following data items about participants to the online database **before** randomisation is permitted:

DoB (valid range equiv to age 16-50)
participant's initials
hospital number
daily number of cigarettes smoked before pregnancy[28]
daily number of cigarettes smoked currently[28]
agreed gestational age at time of randomisation (valid range 12^0-24^6) [estimated delivery date will be calculated automatically within database]
time elapsed since last cigarette
exhaled CO reading of at last 8ppm
blood sample requested (for cotinine assay, DNA extraction & storage)
indication that patient has signed consent form

indication that participant's contact details have been recorded on paper (see below)
agreed quit date

***ii) Remaining baseline data for online entry*:** The following data will be collected with above data and the RM will also enter this on to the online database but entering these variables will **not** be mandatory before online randomisation is permitted.

NHS number (for ONS registration)
ethnic group
age left full time education
number of previous births beyond 24 weeks (valid range 0-12)
time to first cigarette of day[29]
partner's smoking status
maternal height
maternal weight at booking appointment
saliva sample

***iii) Baseline data stored on paper and secure database*:**
Participant name and contact details (including landline / mobile telephone number & postcode)
previous surname(s) – for ONS registration
Participant's general practitioner and / or name of practice plus practice address
grandparents' contact details, including phone numbers

b) One month after quit date*:* RM collects data from those who return. Postal questionnaires sent from NTCT to those who do not. The following data are collected:

RM notes *whether or not follow up occurs* and the *date of any follow up*. RM also inspects participants' supply of patches to calculate the number used.

Smoked at all in the previous 24 hrs
Smoked since quit date (further details on outcomes form 1)
Exhaled CO reading
On how many days have patches been used?
On how many days (if any) have non-trial patches been used?
How many behavioural support sessions with NHS stop smoking services used (telephone & face to face)?
Saliva sample for cotinine estimation taken if not smoking and patches still used

c) Upon admission for childbirth or as soon as possible afterwards:
The following data are recorded by the RM or delivery suite staff:

Date of follow up / exhaled CO reading or saliva sample
Smoked at all in the 24 hrs prior to delivery
Smoked between quit date and delivery
Both of, *i) exhaled CO reading & ascertainment date ii) saliva sample* (for cotinine) if not smoking at delivery
On how many days have patches been used?
On how many days (if any) have non-trial patches been used?
How many behavioural support sessions with NHS stop smoking services used (telephone & face to face)?

i) These data obtained by RM from ***maternal*** or ***infant medical records****:*

maternal
hypertension (>140/90) on 2 occasions (excluding labour)
miscarriage (between randomisation and 24 weeks)
labour onset (spontaneous, induced, no labour)
mode of delivery (SVD, instrumental, caesarean)
ante natal or post natal maternal hospital admission
infant
baby initials
D.O.B
Gender
Baby NHS number
Prompt for RM to confirm full name and address and contact details of baby and to record these on paper (see below)
Prompt for RM to make a new record of contact details if these have differed from previous (i.e. maternal) ones
baby hospital number
birth weight
Number of births
if multiple birth, indicate number and birth order
live or stillbirth?
cord ph < 7.0
Apgar <7 at 5min
Gestational age at birth - to be calculated within database from gestation at recruitment

These infant personal details will be recorded on paper and secure database:

baby name
baby address (inc postcode)

ii) These data obtained by research midwife from ***infant medical records after*** discharge*:*

If live birth ? live on leaving hospital
ventilation > 24 hrs
necrotising enterocolitis
neonatal convulsions
admitted to special care
intraventricular haemorrhage (4 categories)
congenital abnormality present (y/n). If y then free text to describe this.

See Appendix A for diagram explaining follow up procedure after birth.

d) Six months after delivery: The following data will be requested:

Smoking status
Length of maternal inpatient stay for delivery of > 24 hours duration (if any)
Any infant neonatal admission to special care
Length of any infant inpatient stay on special care
Maternal use of NRT / NHS stop smoking services since childbirth,
Infant feeding method
EQ5D questionnaire[20]

e) At 1 year after delivery: The following data will be requested:
smoking status, respiratory symptoms, infant hospital admissions for respiratory illness and other causes, and infant feeding method

e) At 2 years after delivery: The following data will be requested:

Parent questionnaire *- Smoking status, infant behaviour, development, respiratory symptoms and hospital admissions.*
Health professional questionnaire *- Child's disability*

10. Interventions

Details of NRT patches are given in *section 3.* Details of behavioural support follow. The *first behavioural support session* will be provided at recruitment by a research midwife who has been trained in smoking cessation methods in accordance with national standards[30] and who has dedicated time for this task. Models of behavioural support that are effective in pregnancy vary greatly[7] and in non-pregnant subjects, behavioural support following very different psychological models are all equally effective[31]. We will, therefore, standardise the first support session to include information on:

i) the harmful effects of smoking in pregnancy
ii) the role of nicotine addiction in sustaining smoking
iii) how to use NRT (including safety concerns)
iv) coping with withdrawal symptoms.

Support will be specific to the needs of pregnant women and may involve:
i) enlisting partner support
ii) a partner quit attempt
iii) ensuring that the partner has information about smoking cessation services

Study midwives will use brief cognitive - behavioural counselling, combining components from effective counselling strategies that are effective[31], such as:
i) providing structure to quit attempts
ii) agreeing a "contract" for any attempt

A quit date which is within 2 weeks will be agreed and participants will be instructed to start using patches on this date.

Local NHS stop smoking services will provide *subsequent behavioural support sessions*. These follow up sessions will reinforce women's reasons for quitting and strategies for success. A standardised approach to follow up support sessions is important and NHS stop smoking service staff will be orientated towards this. If no local support is available or if the woman declines it, then the research midwife will provide further support as required.

11. Statistical analysis plan

General
a) Primary outcome measure: The proportion of women who report prolonged and total abstinence from smoking immediately before child birth will be compared between treatment groups by Chi-squared test, on an intention to treat basis (all those randomised) with smokers lost to follow up considered to have

continued smoking. For this analysis, we will assume that women in each group use their allocated treatments as directed and no randomised participants will be excluded from analyses. Baseline data on smoking behaviour and demographic information will be compared between groups, and adjustment made for any differences, using logistic regression.

b) Child behaviour and development scores at 2 years: We will compare in children born to women in the control and intervention groups, using t-test (via log transformation) or the Mann-Whitney U statistic. Again this will be done on an intention to treat basis. A small number of children will be born as multiple births (e.g. twins) and data for these cases will be clustered rather than independent. Robust standard errors, or a similar appropriate statistical method will be used in analysis of child data to allow for this.

There will be two analyses. The first will be conducted upon data obtained around delivery. The second will be conducted at 2 years after delivery, using data obtained between delivery and this time point. Data collected for secondary outcomes will not be analysed until the trial has ended with respect to the primary outcome measure.

c) Other outcomes

i) *Fetal birth outcomes* (section 5b) and ii) *Maternal birth outcomes* (section 5c) will also be compared on an intention to treat basis between the 2 groups in the first analysis at delivery (as *a* & *b* above)

As these outcomes relate to the safety of NRT in pregnancy we will also conduct an analysis of these outcomes comparing participants in each group who report using any patches with those in each group who report using none.

d) Sub group analyses

These will be conducted to investigate the relationship between i) baseline cotinine levels and cessation and ii) maternal educational level (proxy for socio-economic status) and cessation. We will model the relationship between smoking cessation, pre-treatment plasma cotinine levels and treatment group in a logistic regression, to establish whether there is effect modification by pre-treatment plasma cotinine and whether efficacy at given levels of plasma cotinine varies. The model will also establish whether or not smoking cessation is constant across all levels of pre-treatment plasma cotinine in the NRT group, or reduces with increasing pre-treatment plasma cotinine, which could be indicative of inadequate replacement of nicotine. We will use similar methods to investigate ii) above.

Health economics

Economic analysis will be undertaken to investigate short term and longer term potential cost-effectiveness of NRT in pregnancy. The cost-effectiveness of NRT use by the general population has been established[32] and a small number of studies have investigated the potential cost saving of smoking cessation interventions in pregnancy[33], but few have used empirical data on costs of interventions. Analyses for this study will be primarily undertaken from an NHS perspective. Uptake of behavioural support and NRT will be monitored and costs of both estimated with both locally-specific and national average values. The differential consequences in terms of length of maternal stay and post natal delivery to special care between the two arms of the trial will be used with the estimated costs of delivering interventions with and without NRT patches and differential smoking cessation rates to estimate the incremental cost-effectiveness ratio. Sensitivity analyses exploring assumptions made in

estimating the control state (no NRT) will be undertaken. The primary health outcome will be maternal smoking cessation immediately before delivery and differences in health status at 6 months (from EQ5D data) will be converted into QALYs to allow cost-utility modelling. Additionally, a range of modelling techniques will be used to estimate longer-term cost-utility from two year follow-up data. Epidemiological and economic models will be used to estimate lifetime gains in QALYs from smoking cessation and savings in health care expenditures[32;34]. A full literature review will be undertaken to explore the potential for providing monetary estimates of the long term impacts on the child of their differential birth outcomes.

Safety
To minimise the likelihood of women or infants being harmed by unexpected effect(s) of nicotine that could not predicted from previous research, the Data Monitoring & Ethics Committee will have access to birth outcome data. These data will be available for the DMEC to analyse as is considered appropriate to investigate whether or not significant or clinically-important differences arise between study groups (e.g. in birth weight).

12. Safety reporting

Nicotine has very low toxicity when used in NRT outside of pregnancy, but the impact of nicotine in pregnancy is not clearly defined. Safety reporting, therefore, necessarily involves monitoring a range of adverse pregnancy outcomes, such that any previously-unknown adverse effect of NRT in pregnancy can be detected.

a) The following will be considered ***adverse events*** **(AEs)**:

i) Withdrawal from patch treatment due to skin reaction or other symptom(s) which are potentially caused by NRT (listed in section 4.10 BNF)

ii) Events requiring hospital admission which are related to the underlying pregnancy (see footnote)

AEs will be reported in an annual safety report to the MHRA, REC and Sponsor.

DMEC meetings will consider unblinded AE data and, if data indicates it appropriate, will recommend that individual AEs should be re-classified as SAEs, so that in-trial monitoring of such events is more rigorous.

b) The following will be considered ***Serious Adverse Events*** (SAEs):

Baby:	miscarriage, stillbirth, neonatal and post-neonatal death
Maternal:	maternal death
	Other events requiring hospital admission apart from those related to the underlying pregnancy or a pregnancy related condition (see footnote for excluded hospital admissions)[a]

[a] The following pregnancy-related hospital admissions are **not** SAEs but will be treated as AEs: delivery (not AE or SAE), recognised pregnancy or postnatal complications, including pre-term delivery before 32 weeks, low birth weight (< 2,500g), birth injury, infection, thrombosis, haemorrhage, hypertensive disease, instrumental delivery (not AE or SAE), caesarean section (not AE or SAE), and antenatal admissions for pregnancy related diseases such as false labour, infection, thrombosis, haemorrhage, hypertensive disease, suspected or confirmed fetal compromise, vaginal bleeding fetal congenital abnormalities, and infant hospital admissions. Incidental hospital

Any other serious unexpected event.

All SAEs will be reported on a standard form and assessed by Professor Jim Thornton or a named deputy to determine whether or not they should be considered as being **Suspected Unexpected Serious Adverse Reactions (SUSARs)** which are potentially-related to trial treatments.

Life threatening or fatal SUSARs will be reported to the MHRA and REC within 7 days (follow up report within 15 days) and also to relevant NHS trust R&D office according to local policies.

Non life threatening SUSARs will be reported to the MHRA and REC within 15 days and also to R&D offices, as appropriate.

SUSARs will also be reported to the DMEC chair along with the treatment allocation group of the trial subject and a cumulative count of SAE and SUSAR frequency in each trial arm.

SAEs which are not considered SUSARs will be reported in an unblinded manner to each DMEC meeting and in the annual report to MHRA, REC and Sponsor with AEs.

13.Publication policy

The success of *SNAP* is dependant upon participating doctors, midwives and NHS stop smoking service staff who successfully recruit and treat patients within the trial. For this reason, credit will be assigned to them in reports from the study and they will be named in the trial report. The principal trial report will be authored by "The SNAP Trial Team".

14. Trial steering committee

Mr Peter Brocklehurst (Chair)	Director, National Perinatal Epidemiology Unit, University of Oxford
Professor Peter Hajek	Professor of Clinical Psychology, Tobacco Dependence Research Centre, Barts and The London, Queen Mary's School of Medicine and Dentistry
Dr Carol Coupland	Senior Lecturer in Medical Statistics, Division of Primary Care, University of Nottingham
Mrs Sue Maguire	Lay member
Dr Michael Murphy	Director, Childhood Cancer Research Group, University of Oxford

admissions for minor, gastrointestinal diseases, respiratory, cardiac, renal skin, psychiatric and neurological problems.

15. Data monitoring and ethics committee

Professor Janet Peacock (Chair)	Professor of Health Statistics, Brunel University
Professor Khalid Khan (till Oct 2008)	Professor of Obstetrics, Gynaecology and Clinical Epidemiology, University of Birmingham
Professor David Field	Professor of Neonatal Medicine, University of Leicester
Professor Christopher Butler (from Jan 2009)	Professor of Primary Care, Cardiff University

16.Centres

In each hospital recruiting centre there is a PI and a midwife lead (hospital based) and a NHS stop smoking service lead.

Hospital recruiting centre	**NHS stop smoking service**
Derby City General Hospital	**Fresh Start**
Jonathon Allsop (PI), Julia Savage	Mary Styles
Kings Mill Centre, Mansfield	**New Leaf, Notts County tPCT**
Karen Glass (PI), Alison Witham	Barbara Brady
North Staffordshire University Hospitals	**North Staffordshire Quit Smoking Service**
Khaled Ismail (PI), Christine Kettle	Deborah Richardson
Nottingham City Hospital	**New Leaf, Nottingham**
Jim Thornton (PI), Amanda Lindley	Indu Hari
Queens University Medical Centre, Nottingham	**New Leaf, Nottingham**
Margaret Ramsey (PI), Amanda Lindley	Indu Hari
Leighton Hospital, Crewe	**Central Cheshire Stop Smoking Service**
Simon Cunningham (PI), Sandra Smith	Paul Jackson
Macclesfield District General Hospital	**Central Cheshire Stop Smoking Service**
Vince Hall (PI), Grace Hopps	Paul Jackson

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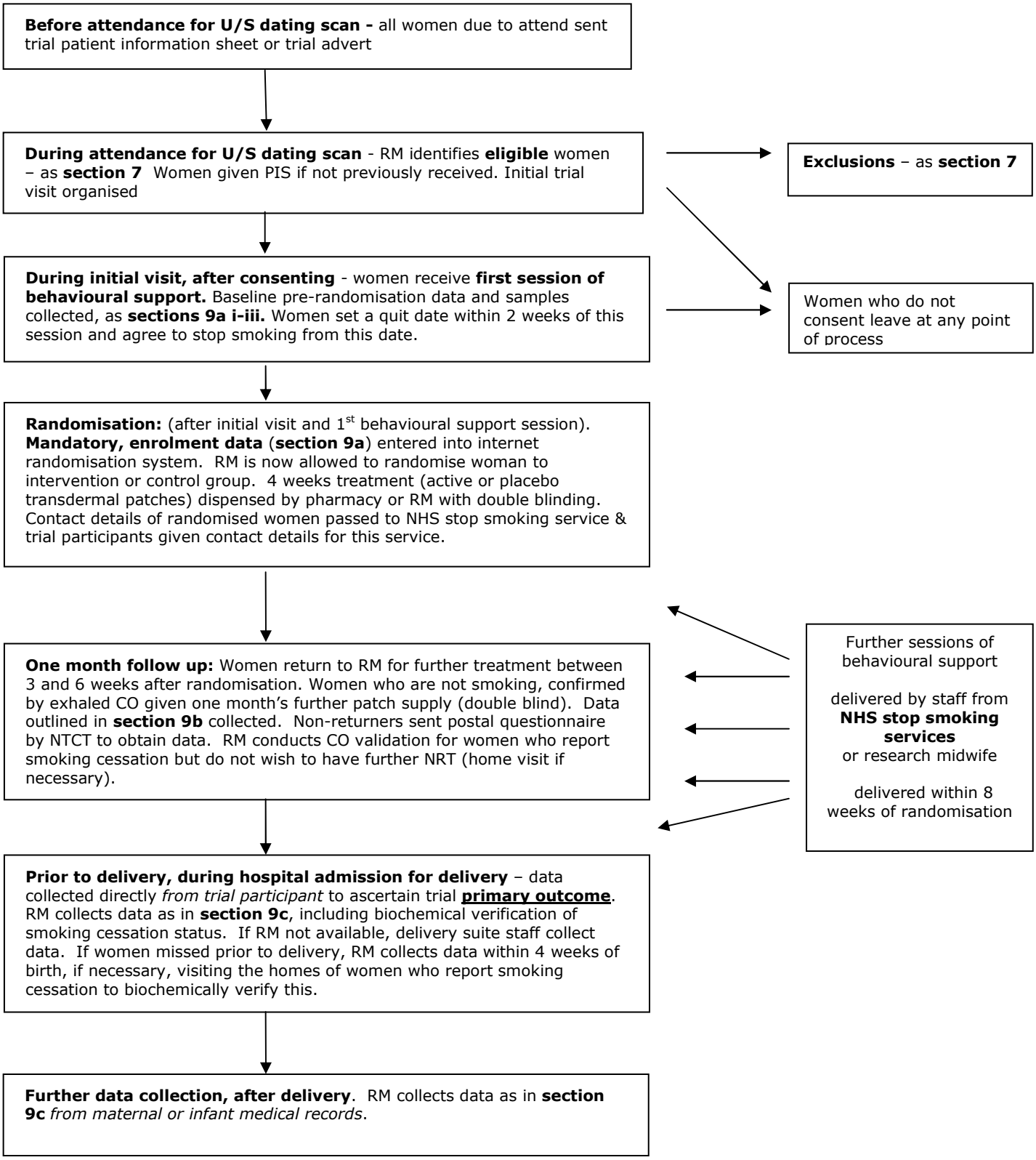
19. Data Collection Forms

3 data collection forms will be designed for RMs to use as a paper record of data collected at i) baseline ii) one month after quit date and iii) delivery and immediately afterwards. These will be finalised once the online database is completed (and if possible generated from this). NB: These forms will record data obtained by RMs and will not be completed by trial participants.

Appendix A: Trial Process

1 Trial flow from recruitment to delivery *(primary outcome ascertainment)*



Research midwives in each centre are responsible for accurate data entry to internet hosted database, for sending blood samples to appropriate university departments and accurate paper copies of data collection sheets from i) baseline (pre-randomisation) ii) one month follow up and iii) delivery to the Nottingham Trial Co-ordinating Team.

2 Trial follow- up: delivery to infants' 2nd birthdays

All questionnaires & cards sent by Nottingham Trial Coordinating Team (NCTC)

Mailings to infants / parents

6 months (infant age): Postal questionnaire measuring self reported smoking status and health economic data. One postal / one telephone reminder.

Congratulations card sent, as appropriate, to mother after baby is born

Christmas cards sent, as appropriate, to children born within trial

2 weeks before 1st birthday: postal questionnaire to mother

1 year : All infants sent 1st birthday card

*Non-respondents to questionnaire above***:** One postal reminder sent, followed by one telephone reminder.

Not known at this address – use maternal grandparent contact details or ONS.

2 weeks before 2nd birthday: (infant age): Postal questionnaire to ***parents***.

Two years: All infants sent 2nd birthday card

*Non-respondents to questionnaire above***:** One postal reminder sent, followed by one telephone reminder.

Not known at this address – use maternal grandparent contact details or ONS.

Mailings to health professionals

Two years: (infant age): Postal questionnaire to ***GP / health visitor***.

Non-respondents at two years: One postal followed by one telephone reminder.

Appendix B: Trial materials

1 Patient information sheet

2 Letter to patient, accompanying patient information sheet

3 Sample questionnaire for use in subject identification

4 Patient consent form

5 Letter to GPs / consultants about enrolled patients

6 Postal questionnaire for women who do not return for treatment at one month post quit date

7 Letter to accompany postal questionnaire sent at one month after quit date

8 Postal questionnaire sent out at six months after childbirth

9 Letter to accompany questionnaire sent out six months after child birth

10 Maternal questionnaire sent out at 1 year after childbirth

11 Letter to accompany parental questionnaire sent out at 1 year after child birth

12 Questionnaire to participant sent out at 2 years after childbirth

13 Letter to accompany parental questionnaire sent out at 2 years after child birth, plus advance notification card, and reminder letter

14 Health professional questionnaire sent at 2 years after childbirth

15 GP Letter to accompany health professional questionnaire sent at 2 years after childbirth

16 Trial advert and information leaflet

17 Colouring competition sheet sent at 2 years after childbirth