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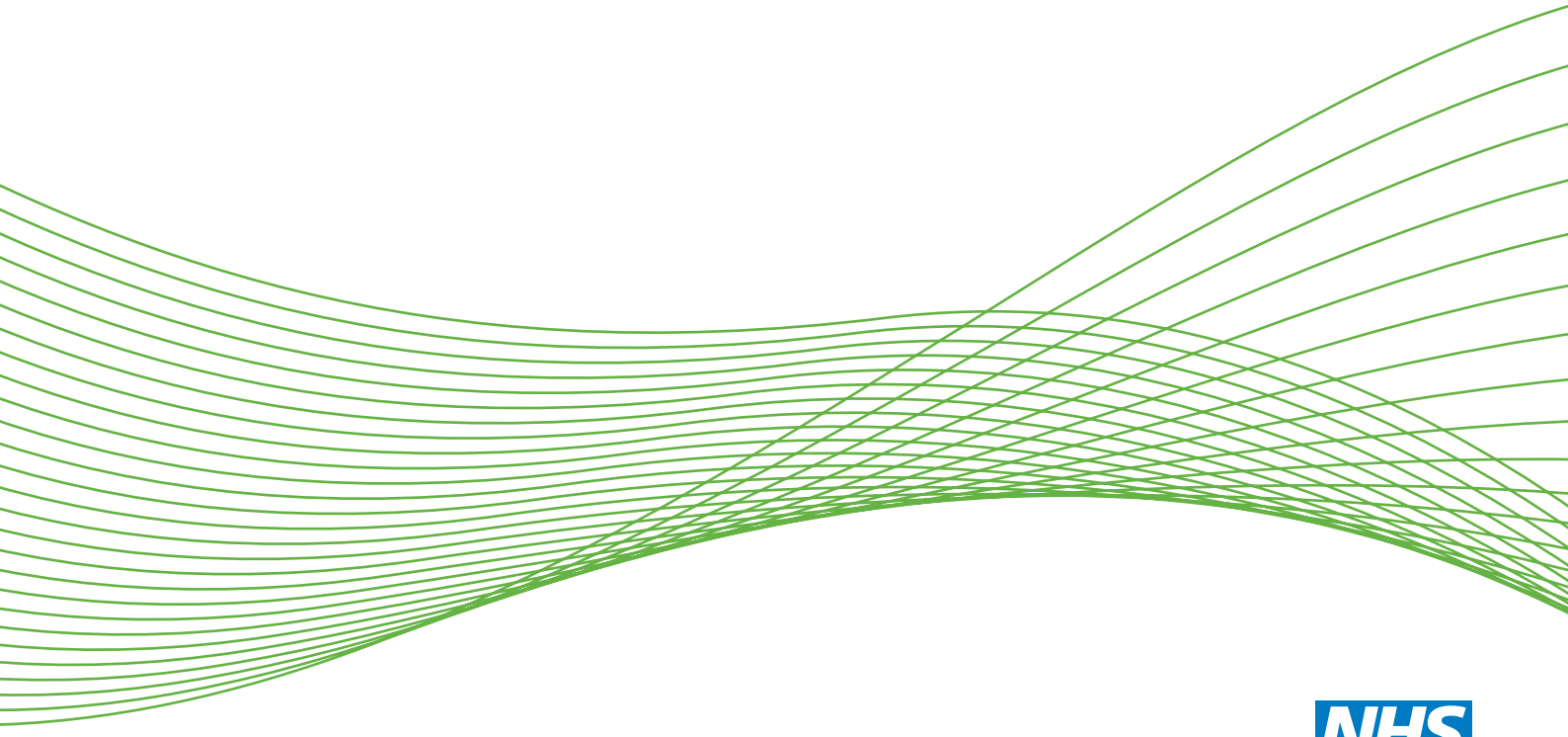

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Abstract

The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy – clinical effectiveness and safety until 2 years after delivery, with economic evaluation

Sue Cooper,[1*] Sarah Lewis,[2] James G Thornton,[3,4] Neil Marlow,[5] Kim Watts,[6] John Britton,[2] Matthew J Grainge,[2] Jaspal Taggar,[1] Holly Essex,[7] Steve Parrott,[7] Anne Dickinson,[1] Rachel Whitemore[1] and Tim Coleman[1] for the Smoking, Nicotine And Pregnancy (SNAP) Trial Team[†]

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Background: Smoking during pregnancy causes many adverse pregnancy and birth outcomes. Nicotine replacement therapy (NRT) is effective for cessation outside pregnancy but efficacy and safety in pregnancy are unknown. We hypothesised that NRT would increase smoking cessation in pregnancy without adversely affecting infants.

Objectives: To compare (1) at delivery, the clinical effectiveness and cost-effectiveness for achieving biochemically validated smoking cessation of NRT patches with placebo patches in pregnancy and (2) in infants at 2 years of age, the effects of maternal NRT patch use with placebo patch use in pregnancy on behaviour, development and disability.

Design: Randomised, placebo-controlled, parallel-group trial and economic evaluation with follow-up at 4 weeks after randomisation, delivery and until infants were 2 years old. Randomisation was stratified by centre and a computer-generated sequence was used to allocate participants using a 1 : 1 ratio. Participants, site pharmacies and all study staff were blind to treatment allocation.

Setting: Seven antenatal hospitals in the Midlands and north-west England.

Participants: Women between 12 and 24 weeks' gestation who smoked ≥ 10 cigarettes a day before and ≥ 5 during pregnancy, with an exhaled carbon monoxide (CO) reading of ≥ 8 parts per million (p.p.m.).

Interventions: NRT patches (15 mg per 16 hours) or matched placebo as an 8-week course issued in two equal batches. A second batch was dispensed at 4 weeks to those abstinent from smoking.

Main outcome measures: Participants: self-reported, prolonged abstinence from smoking between a quit date and childbirth, validated at delivery by CO measurement and/or salivary cotinine (COT) (primary outcome). Infants, at 2 years: absence of impairment, defined as no disability or problems with behaviour and development. Economic: cost per 'quitter'.

Results: One thousand and fifty women enrolled (521 NRT, 529 placebo). There were 1010 live singleton births and 12 participants had live twins, while there were 14 fetal deaths and no birth data for 14 participants. Numbers of adverse pregnancy and birth outcomes were similar in trial groups, except for a greater number of caesarean deliveries in the NRT group. Smoking: all participants were included in the intention-to-treat (ITT) analyses; those lost to follow-up (7% for primary outcome) were assumed to be smoking. At 1 month after randomisation, the validated cessation rate was higher in the NRT group {21.3% vs. 11.7%, odds ratio [OR], [95% confidence interval (CI)] for cessation with NRT, 2.05 [1.46 to 2.88]}. At delivery, there was no difference between groups' smoking cessation rates: 9.4% in the NRT and 7.6% in the placebo group [OR (95% CI), 1.26 (0.82 to 1.96)]. Infants: at 2 years, analyses were based on data from 888 out of 1010 (87.9%) singleton infants (including four postnatal infant deaths) [445/503 (88.5%) NRT, 443/507 (87.4%) placebo] and used multiple imputation. In the NRT group, 72.6% (323/445) had no impairment compared with 65.5% (290/443) in placebo (OR 1.40, 95% CI 1.05 to 1.86). The incremental cost-effectiveness ratio for NRT use was £4156 per quitter (£4926 including twins), but there was substantial uncertainty around these estimates.

Conclusions: Nicotine replacement therapy patches had no enduring, significant effect on smoking in pregnancy; however, 2-year-olds born to women who used NRT were more likely to have survived without any developmental impairment. Further studies should investigate the clinical effectiveness and safety of higher doses of NRT.

Trial registration: Current Controlled Trials ISRCTN07249128.

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List of abbreviations

AE	adverse event
ASQ-3™	Ages and Stages Questionnaire®, third edition
CI	confidence interval
CO	carbon monoxide
CONSORT	Consolidated Standards of Reporting Trials
COT	salivary cotinine
CRF	case report form
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EQ-5D	European Quality of Life-5 Dimensions
GCP	good clinical practice
GP	general practitioner
HPQ	health professional questionnaire
ICER	incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMOR	informatively missing odds ratio
ITT	intention to treat
LBW	low birthweight
MedDRA®	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Nottingham Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
NIHR	National Institute for Health Research
NRT	nicotine replacement therapy
OR	odds ratio
p.p.m.	parts per million
PCT	primary care trust
PIS	participant information sheet
PQ2	2-year participant questionnaire
QALY	quality-adjusted life-year
QMC	Queen's Medical Centre
RCT	randomised controlled trial
RM	research midwife
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SNAP	Smoking, Nicotine And Pregnancy trial
SSS	Stop Smoking Service
TSC	Trial Steering Committee

Plain English summary

Smoking in pregnancy harms developing babies, but stopping smoking before childbirth improves infants' health. Nicotine replacement therapy (NRT) helps non-pregnant smokers quit but, in pregnancy, women's bodies process nicotine faster. Therefore, we cannot assume that NRT will help pregnant smokers and previous research studies have not shown that it does. We tested whether or not NRT patches help pregnant women stop smoking and looked at effects on their newborn babies and when they reached 2 years of age.

A total of 1050 smokers joined the study and were randomly allocated to a 2-month supply of either NRT or identical dummy patches. Women's smoking was monitored 1 month after joining the study, at childbirth and at 6, 12 and 24 months afterwards. Babies' health was monitored at birth and their development and breathing problems were assessed when they were 2 years old.

Effects on smoking were modest. Those using NRT were twice as likely to stop smoking for 4 weeks immediately after joining the study; however, at childbirth and until 24 months, although there were slightly fewer smokers in the NRT group, this small difference would not usually be considered important. Babies' health at birth was very similar no matter which patches mothers had been allocated. However, 2-year-old children born to women in the NRT group were more likely to have no development problems and there was no difference in the frequency of breathing problems between groups.

We need further research to find out if higher doses of NRT could help pregnant women to stop smoking.

Scientific summary

Background

Maternal smoking in pregnancy causes substantial morbidity and mortality and remains a public health problem internationally. Although in many developed countries the rates of smoking in pregnancy are falling, increases in populous middle- and low-income jurisdictions are expected to transfer a rising health burden to these nations in future years. In addition to improving women's health, stopping smoking in pregnancy improves fetal and infant health outcomes; cessation has, for example, been shown to reduce the incidence of low-birthweight (LBW) infants. Unfortunately, there is a limited evidence base to guide the delivery of cessation support in pregnancy. Only behavioural support from a health professional and 'self-help' support, are of proven efficacy.

Pregnant women generally avoid medications and the only drug treatment for cessation that is widely used during gestation is nicotine replacement therapy (NRT). The consensus view is that NRT should be safer than smoking because it contains medicinal nicotine alone, whereas inhaled tobacco smoke contains nicotine and many additional toxins. However, there are strong, biological reasons to suspect that standard doses of NRT, which have only been demonstrated to work in non-pregnant smokers, may be less effective for smoking cessation in pregnancy. Nicotine metabolism is much quicker in pregnancy, therefore, nicotine substitution will be less complete when pregnant women use this and successful amelioration of nicotine withdrawal symptoms is less likely. Prior to this trial, only 695 women had been enrolled in studies investigating the efficacy and safety of NRT in pregnancy and, together, these provided insufficient evidence to say whether or not NRT could be effective or safe when used for smoking cessation in pregnancy. The **S**moking, **N**icotine **A**nd **P**regnancy (SNAP) trial was designed to provide much needed evidence for both issues.

Objectives

The overall aim of the study was to investigate whether NRT is more effective than placebo in achieving smoking cessation for women between 12 and 24 weeks pregnant, who currently smoke five or more cigarettes per day and who smoked at least 10 cigarettes per day before pregnancy.

The specific study objectives were to compare:

i. the clinical effectiveness and cost-effectiveness for achieving biochemically validated smoking cessation of 15 mg per 16 hours transdermal nicotine patches with placebo patches in women at delivery
ii. the effects of maternal NRT patch use with placebo patch use during pregnancy on (1) disability, behaviour and development and (2) respiratory symptoms in infants at 2 years of age.

Methods

The SNAP trial was a double-blind, randomised, placebo-controlled trial with an accompanying health economic evaluation. Potentially interested pregnant smokers with the above characteristics (see *Objectives*) were identified as they attended ultrasonography appointments at seven hospital antenatal clinics in the Midlands and north-west England. Research midwives (RMs), who worked in each centre, discussed the study with potential participants and enrolled them and gained consent, as appropriate. Participants set quit dates and RMs provided behavioural support lasting up to 1 hour before randomising women to receiving either a 4-week supply of 15 mg per 16 hours transdermal nicotine patches or visually

identical placebos. One month later, women who remained abstinent were issued another 4-week patch supply. RMs provided three more telephone behavioural support sessions on participants' quit dates, 3 days afterwards and at 1 month. Those women who collected a second month's supply of NRT also received face-to-face support at 1 month. Women were offered further support from the RM and from local NHS Stop Smoking Services (SSS), and delivery of behavioural support was guided by a shared manual.

Research midwives followed up participants at 1 month after their quit dates and when women were admitted to hospital in established labour, or as soon as possible afterwards. Following delivery, RMs retrieved birth outcome data from medical records. After childbirth, follow-up was conducted from a central trial office and postal questionnaires were sent to women at 6, 12 and 24 months after childbirth with a variety of methods used to maintain contact with participants and maximise response rates. If responses were not received at 24 months, follow-up questionnaires enquiring about infants' health was sent to participants' general practitioners (GPs).

The primary outcome was self-reported prolonged abstinence from smoking between the quit date and childbirth, validated at delivery by exhaled carbon monoxide (CO) and/or salivary cotinine (COT) estimation. Temporary, brief smoking lapses of up to five cigarettes in total (on up to five occasions) were permitted. Further outcomes were collected 2 years after birth and the primary outcome at this time point was infant survival 'without impairment', defined as no disability or problems with behaviour and development having been detected using standard parental or health professional questionnaires (HPQs).

Smoking status and smoking behaviour were ascertained at all follow-up points. The following outcomes were also ascertained: at delivery, maternal and fetal birth outcomes and pregnancy morbidity; at 6 months, health status [using the European Quality of Life-5 Dimensions (EQ-5D) scale] and health service use; at 1 year, respiratory symptoms and, at 2 years, child development outcomes, including 'survival without impairment' and respiratory symptoms.

We aimed to recruit 1050 participants providing 93% power at a 5% significance level to detect a 9% absolute difference between groups. We anticipated a 16% cessation rate in the placebo group, based on the observations that 10% of smokers stop with usual care after their first antenatal visit and behavioural support results in cessation by another 6–7%. We sought to detect the same treatment effect that NRT patches have outside of pregnancy [odds ratio (OR) 1.74, 95% confidence interval (CI) 1.57 to 1.93], giving a projected 25% NRT group cessation rate.

At delivery, participants who, for any reason, had missing smoking outcome data were assumed to be smoking. For fetal outcomes, the primary analysis was of singleton births and for all outcomes, analysis was on an intention-to-treat (ITT) basis and logistic regression, adjusted for centre, was used to compare treatment groups. At 2 years, impairment of infants (i.e. disability or behaviour and development problems) was assessed using parent-completed items from the Ages and Stages Questionnaire®, third edition (ASQ-3™) (Squires J and Bricker D. *Ages and Stages Questionnaire: A Parent-Completed Child-Monitoring System*. 3rd edn. Baltimore, MD: Paul H Brookes Publishing Co.; 2009) and questionnaires returned by health professionals. The proportions of singleton infants without impairments were compared and multiple imputation methods investigated the impact of missing data. Singleton 'complete case' analyses using data from both questionnaires and an analysis including twin births with allowance for clustering were also conducted.

Economic analyses aimed to determine costs of delivering the intervention, to conduct a cost-effectiveness analysis using 'cost-per quitter' as an outcome and, also, to undertake a cost–utility analysis using EQ-5D data collected at 6 months after delivery, combined with modelling of the impacts of any variation in birth outcomes.

Results

A total of 1050 women were enrolled in the trial (521 NRT, 529 placebo). From 1050 pregnancies, there were 1034 live births (1010 singletons, 24 twins), five miscarriages, seven stillbirths, one elective termination, one missed abortion (documented as having occurred before randomisation) and 14 for which birth outcomes were unknown. Completeness of follow-up rates were similar in both groups at all time-points and ascertainment rates based on participants' responses were at 1 month, 82%; at delivery, 93%; at 6 months, 66%; at 1 year, 58% and at 2 years, 90%. Ascertainment rates for birth outcomes were even higher. Rates of biochemical validation of smoking status at delivery were 89% in NRT and 92% in placebo groups, respectively, and, at one month, corresponding rates were 89% and 85%. Adverse event (AE) rates were similar in both groups. All 1034 (1010 singleton) infants were included in the follow-up and, of singletons, among whom principal analyses were conducted, information on 88.2% (891; 445 NRT and 446 placebo group) was returned at 2 years.

Smoking outcomes: at delivery, the validated, prolonged smoking cessation rate was 9.4% in the NRT and 7.6% in the placebo group (OR for cessation with NRT 1.26, 95% CI 0.82 to 1.96). At 1 month, the validated cessation rate was significantly higher in the NRT group (21.3% vs. 11.7%, OR for cessation with NRT 2.05, 95% CI 1.46 to 2.88). After delivery, there were no statistically significant differences in cessation. Self-reported prolonged abstinence since the quit date was: at 6 months, 5.4% in the NRT group and 3.2% in the placebo group; at 1 year, 3.7% and 2.1%; and, at 2 years, 2.9% and 1.7%, respectively.

Adherence: relatively few participants reported using a full 8-week course of NRT. Of the 981 participants followed up at delivery, only 7.2% (35/485) of women randomised to NRT and 2.8% (14/496) randomised to placebo reported using trial medications for over 1 month. Additionally, of the 205 women who reported abstinence at 1 month (173 had validated abstinence), only 101 accepted the offer of a further 4-week supply of patches.

Birth outcomes: these were generally similar between treatment groups. The only significant difference was that more caesarean births occurred in the NRT group than in the placebo group (20.7% vs. 15.3%).

Infant outcomes at 2 years: 72.6% (323/445) of NRT group infants survived with 'no impairment', compared with 65.5% (290/443) born to participants in the placebo group (OR 1.40, 95% CI 1.05 to 1.86). Sensitivity analyses including twins or using only questionnaires returned by parents gave similar findings. There was no significant difference between groups in infants' reported respiratory problems; these occurred in 132 out of 444 (29.7%) of NRT and 111 out of 444 (25%) of placebo group infants, respectively (OR for symptoms in NRT vs. placebo 1.30, 95% CI 0.97 to 1.74).

Economic analyses: total mean costs (costs of delivering the intervention and resource-use costs) were approximately £91 higher in the NRT group and the incremental cost-effectiveness ratio (ICER) associated with NRT use was £4926 per additional quitter (bootstrapped 95% CI –£114,128 to £126,747), or £4156 (bootstrapped 95% CI –£65,994 to £82,059) in analyses restricted to singleton infants; however, CIs show there was substantial uncertainty around these estimates. It was not possible to model cost–utility of NRT owing to very similar adverse birth outcomes rates and EQ-5D scores in both trial groups and the likely amplification in uncertainty of estimates that such analyses would have caused.

Conclusions

The SNAP trial demonstrates that at 12–24 weeks' gestation, supplementing behavioural support with a 15 mg per 16 hours nicotine patch was no more effective than placebo in promoting sustained smoking cessation throughout pregnancy. Despite significantly higher cessation rates occurring at 1 month in the NRT group, this effect did not persist until delivery. The quit rate was slightly, but not statistically

significantly, higher in the NRT group at delivery and this (still non-significant) difference remained at 6, 12 and 24 months. We do not know why NRT had a large, clinically and statistically significant effect early in pregnancy, which disappeared as gestation progressed. There was no evidence for NRT having either a beneficial or a harmful effect on birth outcomes, apart from slightly higher caesarean rates in the NRT group. However, as adherence was poor, birth outcome findings are difficult to interpret and could have been different had greater adherence with trial treatments occurred.

At 2 years, infants born to participants randomised to NRT were more likely to have survived without any impairment, but there were no significant differences in infants' respiratory problems. The most likely reason for better NRT group infant outcomes are the lower, albeit largely non-significant, smoking rates in NRT group mothers.

Total mean costs were approximately £91 higher in the NRT group, representing a small (3%) difference in costs between trial groups and these higher costs were mainly attributable to the cost of the NRT patches (mean = £46). According to the incremental cost-effectiveness estimates, NRT would be the preferred option if decision-makers are willing to pay more than £4926 for an additional quitter. However, there was substantial uncertainty around the estimates and there is no accepted threshold for funding health-care interventions based on this kind of outcome.

Recommendations for research (in priority order)

1. Randomised controlled trials (RCTs) investigating the efficacy and safety of NRT when used for smoking cessation in pregnancy should test a higher than standard dose NRT such as (1) patches delivering more than 15 mg nicotine in 16 hours (21 mg in 24 hours), (2) 4-mg gum used as required or, (3) NRT patch combined with any 'on demand' short acting NRT (e.g. gum or nasal spray).
2. To investigate whether or not apparent differences in infants' outcomes persist into childhood. RCTs investigating NRT for smoking cessation in pregnancy should assess infants' clinical and economic outcomes after 2 years of age.
3. Randomised controlled trials investigating the efficacy of NRT or other interventions for smoking cessation used in pregnancy should include an assessment of impacts on infants using outcomes similar to those employed in SNAP.
4. Reasons for pregnant women's low levels of adherence with NRT should be investigated; findings could be used in future trials to enhance participants' adherence with NRT.
5. Increases in nicotine metabolism, occurring as pregnancy progresses could explain the reduced efficacy that NRT has in later pregnancy. Further research should investigate this hypothesis.

Implications for health care

In the UK and some other health-care systems, NRT has become an established component of cessation support for pregnant women. Although the SNAP trial found no evidence that standard dose NRT is effective for smoking cessation, there was also no evidence that this is less safe than smoking; indeed, the study suggests that NRT use in pregnancy is safe in terms of infant outcomes assessed at 2 years and may have a protective effect on infant development. Although this is the first time that a smoking cessation intervention has been observed to have a beneficial effect on pregnant smokers' offspring, this finding provides support for interventions involving NRT in pregnancy. Overall, our findings provide no evidence that NRT should not be used in pregnancy, rather that NRT might be beneficial in this setting.

Effects of NRT on infant development are likely to be mediated through the small, observed changes in maternal smoking. There are good reasons to believe that NRT used at higher doses might affect both maternal smoking and infant development more substantially and trials of higher-dose NRT are indicated. Other cessation interventions delivered in pregnancy might have similar impacts on infants, but this

requires confirmation. Choosing between interventions for use with pregnant smokers is, therefore, difficult; both 'self-help' and behavioural smoking cessation support promote maternal smoking cessation and improve birth outcomes. However, while there is no evidence that NRT has these effects, NRT does appear to have a potentially important protective effect on infant development. Therefore, this study supports the offering of NRT to pregnant women who smoke; however, any such offer should take account of the rather stronger research evidence from other studies indicating that behavioural and 'self-help' support both have beneficial effects on smoking behaviour in pregnancy.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN07249128.

Funding

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Chapter 1 Introduction

The problem

Maternal smoking during pregnancy is the most important, and preventable, cause of adverse pregnancy outcomes including placental abruption, miscarriage, birth before 37 weeks' gestation (pre-term birth) and low birthweight (LBW).[1] Pre-term birth is the principal cause of neonatal death and morbidity, with up to 50% of infants' neurodevelopmental problems being attributable to this.[2] Similarly, LBW births are a marker of ill health and are associated with the future development of coronary heart disease, type 2 diabetes and obesity.[3]

Tobacco smoking in pregnancy is a worldwide public health problem. The UK's estimated rate of pre-natal smoking is 12%[4] and rates are similar in most developed countries, including Australia (17%),[5] Denmark (16%),[6] the USA (11%)[7] and Germany (13%).[8] Some other European countries, such as Spain[9] and Poland,[10] have considerably higher rates of maternal smoking in pregnancy, reaching around 30%. Although the prevalence of smoking in pregnancy appears generally to be reducing in high-income countries, in low- and middle-income countries, rates of maternal smoking in pregnancy are believed to be increasing.[11] It is predicted that in the future, higher rates of maternal smoking in low- and middle-income countries will substantially transfer the health burden from smoking during pregnancy to these nations.[12] Additionally, in high-income countries, rates of smoking in pregnancy remain highest among younger women and those who are more socially disadvantaged.[4] As the children of mothers who smoke are twice as likely to become smokers,[13] smoking in pregnancy perpetuates cycles of deprivation and health inequalities across generations that permanent smoking cessation initiated in pregnancy could reduce.

Treatments for smoking cessation in pregnancy

Stopping smoking in pregnancy not only benefits maternal health but has positive impacts on infant outcomes and effective cessation interventions which are used by pregnant women reduce numbers of LBW and pre-term births.[14] Presumably, because the harms of smoking and the benefits of stopping are widely known, many smokers stop when they are planning a pregnancy or soon after conceiving; for example, in England and Wales, around 50% of smokers manage to stop smoking during at least part of their pregnancy.[4] For pregnant women who are unable to stop smoking without assistance, there are only two proven cessation interventions which could help them with this: behavioural[14] and self-help[15] smoking cessation support. Intensive behavioural support, which is delivered outside women's routine antenatal care, can reduce smoking in later pregnancy[14] [pooled risk ratio (RR) for reduction in smoking prevalence after behavioural support 0.94, 95% confidence interval (CI) 0.93 to 0.96], as can self-help cessation interventions[15] [odds ratio (OR) for cessation following self-help intervention 1.83, 95% CI 1.23 to 2.73]. Behavioural support usually involves psychologically orientated counselling that can broadly be described as 'cognitive–behavioural therapy'. However, for this intervention to have an effect, women must attend appointments with health professionals in addition to their routine antenatal care; however, in countries such as England, where such support has been freely available for some time, relatively few pregnant smokers have made use of this. Using the NHS Stop Smoking Service (SSS)[16] and maternity statistics[17] combined with national survey data,[4] one can estimate that, in 2011, only 14% of English pregnant smokers set quit dates using such support and as few as 6% subsequently managed to stop smoking for at least 4 weeks. Self-help support, including books, manuals, text messaging and DVDs, involves structured interventions that may be introduced briefly to smokers by health professionals, but are primarily designed for motivated quitters to work through on their own. Self-help interventions are not likely to appeal to all smokers and do require a certain level of cognitive ability for successful use.

Outside of pregnancy there are more cessation interventions of proven efficacy available to assist smokers, including nicotine replacement therapy (NRT),[18] bupropion (Zyban®, GSK)[19] and varenicline (Champix®, Pfizer).[20] NRT works by substituting the nicotine inhaled in tobacco smoke, which is accompanied by many other toxins, for 'clean' medicinal nicotine (e.g. transdermal patches or lozenges). Using NRT after becoming abstinent permits the smoker to lessen or avoid withdrawal symptoms and, eventually, as the amount or dose of NRT reduces, these are eliminated. Bupropion is an antidepressant with an uncertain mechanism of action, but is thought to promote smoking cessation by antagonising nicotinic acetylcholine receptors. Varenicline is an alpha-4 beta-2 nicotinic acetylcholine receptor partial agonist; it binds to nicotinic receptors and is thought to act by preventing the pleasurable sensations that smokers experience after smoking, making them less likely to do so and, hence, more likely to achieve cessation. Unfortunately, neither varenicline nor bupropion is approved for use in pregnancy. Also, possibly owing to fears that either drug might cause fetal harm, there are insufficient studies in pregnancy to draw any conclusions about the efficacy of safety of either drug for use by pregnant smokers.

Nicotine is the active ingredient of NRT and its impacts in pregnancy have been much more thoroughly researched.[21] Nicotine is a known neurotoxin and may be expected to affect developing fetal nerve tissues. This may explain observed associations between behavioural problems and attention deficit disorder among smokers' children.[22,23] However, while tobacco combustion creates and releases many potential fatal toxins in addition to nicotine, NRT delivers nicotine alone. Consequently, there is an international, expert consensus that maternal use of NRT in pregnancy should be safer for the fetus than continued smoking.[24] It should be noted that this consensus, while logical, is theoretically based and is not underpinned by research evidence. Nevertheless, this consensus has had an impact internationally on the use of NRT in pregnancy and has contributed to a relaxation in indications for NRT prescribing during pregnancy in some countries. For example, since 2003 in the UK, the *British National Formulary*[25] (the manual used to guide prescribing in the UK NHS) has listed pregnancy as a 'caution' rather than a 'contraindication' to using NRT. Additionally, in 2005, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued guidance that specifically stated that pregnant women who had not managed to stop smoking using other means could be prescribed NRT. Many other countries take similar approaches; the authoritative website, www.treatobacco.net, hosts all nations' smoking cessation guidelines and the vast majority of those written in English recommend cautious use of NRT for smoking cessation in pregnancy.[26]

Current evidence for nicotine-replacement therapy use in pregnancy

Health policy recommendations for NRT use in pregnancy have developed in the absence of scientific evidence. In 2004, when the study described in this report [the Smoking Nicotine And Pregnancy (SNAP) trial] was commissioned, only three trials had investigated NRT for smoking cessation in pregnancy[27–29] and the largest of these[29] was excluded from a later meta-analysis[30] and Cochrane review[31] because its design made it impossible to attribute treatment effects to NRT. Pooling of data from these three studies, including the trial which was not included in later reviews, suggested that NRT used in pregnancy had borderline effectiveness for reducing smoking in later pregnancy (pooled RR 0.94, 95% CI 0.89 to 1.00).[32] In addition, one of these studies had found that slightly heavier and, therefore, potentially healthier, infants were born to women who had been randomised to NRT.[27] While the SNAP trial was running, three further trials investigating the efficacy and safety of NRT for smoking cessation in pregnancy were published.[33–35] However, a systematic review and meta-analysis that included these three more recent trials and also the two previous relevant studies[27,28] found no evidence that that NRT was effective for smoking cessation in pregnancy (pooled RR for cessation after NRT 1.63, 95% CI 0.85 to 3.14).[30] This lack of evidence for the use of NRT in pregnancy comes from trials conducted in Canada, the USA, Denmark and Australia, which randomised a total of 695 women.[27,28,33–35]

Unfortunately, despite the knowledge that nicotine is potentially fetotoxic, there is little evidence available to assess whether or not using NRT in pregnancy is safe. Of the five trials above that reported before the SNAP trial concluded, only three monitored maternal or infant birth outcomes[27,34,35] and none collected data on infants' outcomes after delivery. Given this paucity of empirical data, meta-analyses investigating the impact of NRT on infants' birth outcomes have been inconclusive[30] and more data are required. In addition, as nicotine could be one of the tobacco smoke constituents responsible for the cognitive and behavioural problems seen in infants born to smokers,[22] studies that assess the impact of NRT used for cessation in pregnancy on early infant outcomes are also needed. It remains likely that nicotine is not solely responsible for these adverse effects; indeed, it may have no such impacts, and other toxins in tobacco smoke could be partially, or perhaps even completely responsible for them. However, this should not be assumed.

In summary, smoking in pregnancy is an extremely harmful behaviour and an increasing public health problem internationally. There are only two cessation interventions of proven efficacy for use in pregnancy and no licensed drug cessation treatments have been shown to be safe or effective in pregnancy. There is a consensus in favour of using NRT in pregnancy, but NRT remains of unproven efficacy and its impacts on infants born to mothers who use it in pregnancy require determining. Consequently, the SNAP trial, a double-blind, randomised placebo-controlled trial of NRT used for smoking cessation in pregnancy, was planned and is described within this report.

Objectives

The overall aim of the study was to investigate whether or not NRT is more effective than placebo in achieving smoking cessation for women between 12 and 24 weeks pregnant, who currently smoke five or more cigarettes per day and who smoked at least 10 cigarettes per day before pregnancy.

The specific study objectives were to compare:

i. the clinical effectiveness and cost-effectiveness for achieving biochemically validated smoking cessation of 15 mg per 16 hours transdermal nicotine patches with placebo patches in women at delivery
ii. the effects of maternal NRT patch use with placebo patch use during pregnancy on (1) disability, behaviour and development and (2) respiratory symptoms in infants at 2 years of age.

Chapter 2 Methods

Trial design

This was a phase IV, multicentre, double-blind, randomised (1 : 1 allocation and stratified by site), placebo-controlled, parallel-group trial of standard-dose (15 mg per 16 hours) NRT patches. Participants were monitored from their recruitment at between 12 and 24 weeks' gestation until the delivery of their babies and then followed up by questionnaire for a further 2 years.

Participants and recruitment

Eligibility criteria

Eligible women were aged 16–50 years, between 12 and 24 weeks' pregnant, smoked at least 10 cigarettes per day before pregnancy and continued to smoke at least five cigarettes per day. The eligible women also had an exhaled carbon monoxide (CO) concentration of at least 8 parts per million (p.p.m.). They were excluded if they had contraindications to the use of NRT including severe cardiovascular disease, unstable angina, cardiac arrhythmias, recent cardiovascular accident or transient ischaemic attack, chronic generalised skin disorders or known sensitivity to nicotine patches, chemical or alcohol dependence, known major fetal abnormalities, or were unable to give informed consent. Women could enrol in the trial only once but could participate in other non-conflicting research projects.

Recruiting centres

Participants were recruited from seven hospital antenatal clinics in the Midlands and north-west England. Initially, these were at Nottingham University Hospitals NHS Trust City Hospital campus, Nottingham University Hospitals NHS Trust Queen's Medical Centre (QMC) campus, Sherwood Forest Hospitals NHS Foundation Trust (King's Mill Hospital) and University Hospital of North Staffordshire NHS Trust (City General Site). Three further sites were added later to improve recruitment rates: Mid Cheshire Hospitals NHS Foundation Trust (Leighton Hospital), East Cheshire NHS Trust (Macclesfield District General Hospital) and Derby Hospitals NHS Foundation Trust (Derby City General, later to become Royal Derby Hospital).

Research midwives

In each centre, research midwives (RMs) undertook all trial-related procedures. RMs were trained in research procedures by the trial manager with input from the chief investigator and attended monthly staff update meetings. In addition, Clare Mannion, one of the trial co-investigators and a UK expert trainer of smoking cessation professionals, provided the RMs with training, to English national standards, in delivery of behavioural support to pregnant women.[36]

Recruitment and consent

We used three methods of identifying and recruiting eligible women who were interested in stopping smoking.

1. Community midwives usually ask women about smoking status at their booking appointment and then refer those who would like help to stop smoking to their local NHS SSS. In some recruiting areas, women referred to NHS SSS were asked if they would be interested in finding out about the trial and the RM contacted any who expressed interest. Those who were not interested or eligible for enrolment, but who wanted to stop smoking, were seen by the NHS SSS as per normal practice.
2. Leaflets containing brief information about the trial were sent to women before their antenatal clinic or routine ultrasonography scan appointments. Women attending these clinics were then asked to complete a screening questionnaire to identify those who were eligible and interested (see *Appendix 1*).

3. Some women who had seen information leaflets or posters advertising the study in hospitals contacted the RMs directly.

Potentially eligible women who expressed interest in the trial were given a participant information sheet (PIS) and, after having chance to consider this for at least 24 hours and discuss with a RM, gave their written informed consent before trial data were collected. In addition to trial participation, women were asked to give consent for researchers to have access to their and their child's medical records, for information held by the NHS to be used to keep in touch with them and to follow their health status, and also for storage of blood samples for possible use in future research. For most trial participants, consent and baseline data collection took place in their homes.

Interventions

The only difference in interventions delivered to trial groups was in the type of transdermal patches allocated to women. In the intervention group, these were active nicotine patches (15 mg per 16 hours NRT transdermal patches), whereas women in the control group received visually identical placebo patches.

At enrolment, RMs delivered behavioural support lasting up to 1 hour. During counselling, RMs applied techniques to encourage cognitive and behavioural changes among smokers such that smoking cessation could be successfully achieved. The initial session focused on behavioural advice and tips for smokers, including preparation for quitting and how to avoid smoking lapses once a quit attempt had begun in addition to instruction and advice on how to use patches (which could be either placebo or nicotine). During the session, participants were required to set a quit date within 2 weeks from which follow-up was timed. A manual used by RMs to guide the support sessions ('The SNAP trial's guide to stopping smoking during pregnancy': see *Appendix 2*) was written by Clare Mannion and included some techniques from the US 'Smoking Cessation and Reduction in Pregnancy Treatment' trials[37] that were believed to be relevant to UK smokers. As is consistent with good smoking cessation practice, this manual, which contained tips and suggestions for becoming smoke-free, was left with women so that they could refer to it after their support session. Subsequently, participants were randomised to equal-sized groups receiving either a 4-week supply of 15 mg per 16 hours NRT transdermal patches or visually identical placebos (United Pharmaceuticals, Amman, Jordan), which women were instructed to start on their quit dates. One month after quitting, those not smoking, validated by CO measurement of < 8 p.p.m.,[38] were issued with another 4-week patch supply if they wanted it. In addition to behavioural support delivered at enrolment, RMs provided three further behavioural support sessions to all participants. Telephone behavioural support was delivered on participants' quit dates, at 3 days afterwards and at 1 month afterwards; those women who collected a second month's supply of NRT also received face-to-face support from the RM at the time this was delivered to them. These sessions involved reinforcement of earlier behavioural sessions, with an added focus on ways of avoiding relapse now that quit attempts had begun.

Provision of additional behavioural support and nicotine-replacement therapy to trial participants and availability of nicotine-replacement therapy to non-participants

Prior to starting the trial, we visited local NHS SSSs in the recruiting areas and discussed their service provision, as it was intended that these would provide behavioural support to women enrolled onto the trial. Primary care trusts (PCTs) in all of the trial's recruiting areas had NHS SSSs for pregnant women, but several PCTs had recently undergone local reorganisations and there was considerable variation in the delivery of cessation services. Some services were already issuing NRT to pregnant women, despite the absence of evidence for its effectiveness. We hoped to get agreement from PCTs that, for the duration of the trial, NRT would be issued only to pregnant women within the trial, thereby ensuring that local availability did not jeopardise recruitment and/or retention of participants or interpretation of trial findings. The outcome of these visits meant that, in most trial areas (all except Derby), women's contact details were shared with their local NHS SSS, which agreed to contact participants and offer them additional

behavioural support. They also agreed that they would not normally offer participants any non-trial NRT products. Women were encouraged to ask for further behavioural support as necessary, and RMs or NHS SSS staff, guided by the manual, delivered any additional support that participants required. In Derby, where participants' contact details were not shared with the NHS SSS, RMs provided additional support. The provision of additional behavioural support to participants and the availability of NRT to participants and non-participants who contacted the NHS SSS are shown in *Table 1*, which illustrates the context in which trial recruitment occurred.

TABLE 1 Provision of additional behavioural support to participants and availability of NRT to participants and non-participants by trial centre

Trial centre	PCTs hosting NHS SSS within the area of each trial centre	Provision of additional behavioural support	NRT availability within PCT	
			Trial participants	Non-participants
Nottingham University Hospitals NHS Trust (City Hospital and QMC campuses)	Nottingham City PCT (Nottingham City New Leaf)	Nottingham City New Leaf (Stop Smoking) Service	Not offered or prescribed NRT; if any enquired about NRT, referred back to a trial researcher for further discussion	NRT still offered as judged appropriate to non-trial pregnant women
	Nottinghamshire County PCT (Nottinghamshire County New Leaf)	Nottinghamshire County New Leaf (Stop Smoking) Service	NRT not prescribed to any pregnant women through the service for the duration of the trial	NRT not prescribed to any pregnant women through the service for the duration of the trial
	Derbyshire County PCT (few participants only from the Nottingham University Hospitals NHS Trust centres)	By RMs	No agreements made; NRT available via local NHS SSS	No changes to NRT provision; available via local NHS SSS
Sherwood Forest Hospitals NHS Foundation Trust (King's Mill Hospital)	Nottinghamshire County PCT (Nottinghamshire County New Leaf)	Nottinghamshire County New Leaf (Stop Smoking) Service	NRT not prescribed to any pregnant women through the service for the duration of the trial	NRT not prescribed to any pregnant women through the service for the duration of the trial
University Hospital of North Staffordshire NHS Trust (City General site)	Stoke PCT (North Staffordshire NHS SSS)	RMs until 1 month, then passed to North Staffordshire NHS SSS for further support if required	No NRT prescribed to women enrolled onto the trial	NRT prescribed only to pregnant women not eligible or not interested in participating in the trial
Mid Cheshire Hospitals NHS Foundation Trust (Leighton Hospital)	Central and Eastern Cheshire PCT (Central and Eastern Cheshire NHS SSS)	Central and Eastern Cheshire NHS SSS	All eligible women informed and referred to trial. NRT not offered or prescribed to any pregnant women enrolled in the trial	NRT initially not prescribed to any pregnant women; later changed so available to women not eligible or interested in participating in the trial
East Cheshire NHS Trust (Macclesfield District General Hospital)	Central and Eastern Cheshire PCT (Central and Eastern Cheshire NHS SSS)	Central and Eastern Cheshire NHS SSS	All eligible women informed and referred to trial. NRT not offered or prescribed to any pregnant women enrolled in the trial	NRT initially not available to any pregnant women; later changed so available to women not eligible or interested in participating in the trial
Derby Hospitals NHS Foundation Trust (Derby City General Hospital)	Derby City and Derbyshire County PCTs (Fresh Start)	By RMs	No agreements made; trial participants not referred to NHS SSS	No changes to NRT provision; available via local NHS SSS

Randomisation and blinding

Eligibility criteria were entered into a secure online database before internet-based randomisation that was stratified by recruiting site and used a computer-generated, pseudorandom code using random permuted blocks of randomly varying size, with a 1 : 1 allocation ratio, which was created by the Nottingham Clinical Trials Unit (NCTU) and held on a secure server in accordance with their standard operating procedures. Following randomisation, the database issued participants with a unique identifier and allocated a trial treatment-pack number to them. Identically packaged treatments, previously prepared by one central pharmacy (QMC pharmacy, Nottingham University Hospitals NHS Trust), were dispensed by local pharmacies. All pharmacists, research staff and trial participants were blinded to treatment allocations.

In addition, during the follow-up period in the 2 years after ascertainment of the primary outcome at delivery, participants and anyone involved in following them up and entering data remained blind to the treatment allocation.

Data collection to delivery

Baseline

At baseline, RMs collected women's demographic and contact details: 'Heaviness of Smoking Index',[39] a measure of nicotine addiction recorded on a scale of 0 (lower) to 6 (higher nicotine addiction); number of daily cigarettes smoked before pregnancy; partner's smoking status; gestation; ethnicity; age completed full-time education; parity; use of NRT in current pregnancy; height and weight. Women were also asked to provide an exhaled CO measurement, blood and saliva samples for cotinine estimation and a blood sample for future deoxyribonucleic acid (DNA) extraction (any studies using the DNA samples would require further funding and relevant ethical approvals).

One month

One month after the quit date, RMs telephoned participants and asked for details about their smoking status. This included whether or not they had smoked since their agreed quit date and, if so, how often this had occured and whether or not they had smoked in the previous 24 hours. RMs also asked about the number of times they had received additional behavioural support and whether this had been face to face, by telephone or by mobile telephone text message; the number of trial patches they had used (i.e. adherence); and whether or not they had obtained and used any additional NRT outside of the trial. Those who reported not smoking were visited for CO validation and a saliva sample (for cotinine measurement) was obtained from any women who were still using trial patches and not smoking. Non-contactable women were sent a postal questionnaire.

Delivery

When participants were admitted to hospital in established labour prior to childbirth, or as soon as possible afterwards, as at the 1-month contact, RMs or delivery suite staff ascertained smoking status, use of trial and 'non-trial' NRT, including reported numbers of patches used and additional behavioural support received. Exhaled CO measurements and saliva cotinine samples were obtained from women who reported not smoking for at least 24 hours before delivery. RMs telephoned those missed while in hospital, and any who reported abstinence were visited at home for biochemical validation within a maximum of 4 weeks after delivery. Maternal and infant birth outcomes were obtained from medical records. Maternal outcomes included hypertension (> 140/90 mmHg) measured on two or more occasions during pregnancy, miscarriage or stillbirth, labour onset (spontaneous, induced or no labour), mode of delivery (spontaneous vaginal, assisted vaginal or caesarean section) and antenatal or postnatal hospital admissions. Infant data and outcomes collected at delivery or after discharge included date of birth, name, hospital and NHS numbers, sex, birthweight, gestational age at birth, number of births (with number and birth order if multiple birth), live birth or stillbirth, arterial cord-blood pH (either ≥ 7 or < 7), Apgar score (either ≥ 7 or < 7),

intraventricular haemorrhage, neonatal convulsions, admissions to neonatal intensive care units (NICUs) and any congenital abnormalities.

Adverse event monitoring

During each contact with participants, RMs enquired about adverse events (AEs) or symptoms the participant had experienced. RMs also obtained this information from monthly examination of medical records. They then summarised the descriptions in the case report forms and on the study database. Descriptions were used to code the AEs according to standard terms in the Medical Dictionary for Regulatory Activities (MedDRA®) version 13.1 [www.meddra.org/; MedDRA is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA trademark is owned by International Federation of Pharmaceutical Manufacturers and Associations on behalf of ICH]. The incidence of events was analysed according to the MedDRA System Organ Class categorisation and preferred terms. Information about deaths after delivery was obtained from the NHS Health and Social Care Information Centre's Data Linkage Service (previously Office for National Statistics) with whom all trial participants and their infants had been flagged. After starting the trial, it was realised that many relatively common pregnancy-related events were being reported as serious adverse events (SAEs), including pregnancy-related hospital admissions, premature birth and LBW and, on clinical review, none of these had been considered to be related to the study drug. The Trial Steering Committee (TSC) and the sponsor, therefore, advised that it would be appropriate to amend the protocol so that only maternal and fetal/infant deaths and hospital admissions unrelated to the underlying pregnancy would be reported as SAEs, and ethical approval was received for this. We continued to collect and monitor these along with other AEs, and the Data Monitoring Committee (DMC) reviewed data showing the distribution of all AEs and SAEs within trial groups at their meetings.

Figure 1 is a flow chart showing the data collection process from recruitment until delivery.

Data collection and follow-up after delivery

After primary outcome data were collected, participants were followed up by postal questionnaire at 6 months, 1 year and 2 years after delivery of their infants. Questionnaires were not sent after maternal or infant deaths, if no birth details were available, if the participant had withdrawn consent for follow-up, or if no contact details could be obtained for the participant and if they were not registered with a general practitioner (GP). The NHS Health and Social Care Information Centre sent the trial office a report including information on any participant and infant deaths every 3 months. However, because of a delay in receiving the death report, a questionnaire was sent inadvertently to a participant whose infant had died; we subsequently sent the NHS Health and Social Care Information Centre a list of participants and infants who were due to be sent questionnaires for them to check every month. For non-respondents, or if questionnaires had been returned undelivered, the trial office contacted alternative family members using contact details that the participant had provided when they enrolled onto the trial and, if necessary, the participant's GP or PCT were contacted to obtain their current contact details. During the follow-up period in the 2 years after ascertainment of the primary outcome at delivery, all those involved in following-up participants and in entering data remained blind to the treatment allocation.

A flow chart outlining the follow-up process from delivery until the infants' second birthdays is shown in *Figure 2*.

The evidence base for questionnaire design was taken into account when composing instruments[40] and the following evidence-based methods to improve postal returns of questionnaires were used to maximise response rates.[41] At each follow-up point, participants were sent a postal questionnaire followed by one postal reminder after 2 weeks. After a further 2 weeks, participants were telephoned and asked to complete the questionnaire over the telephone with an appointment made to call them back when necessary.

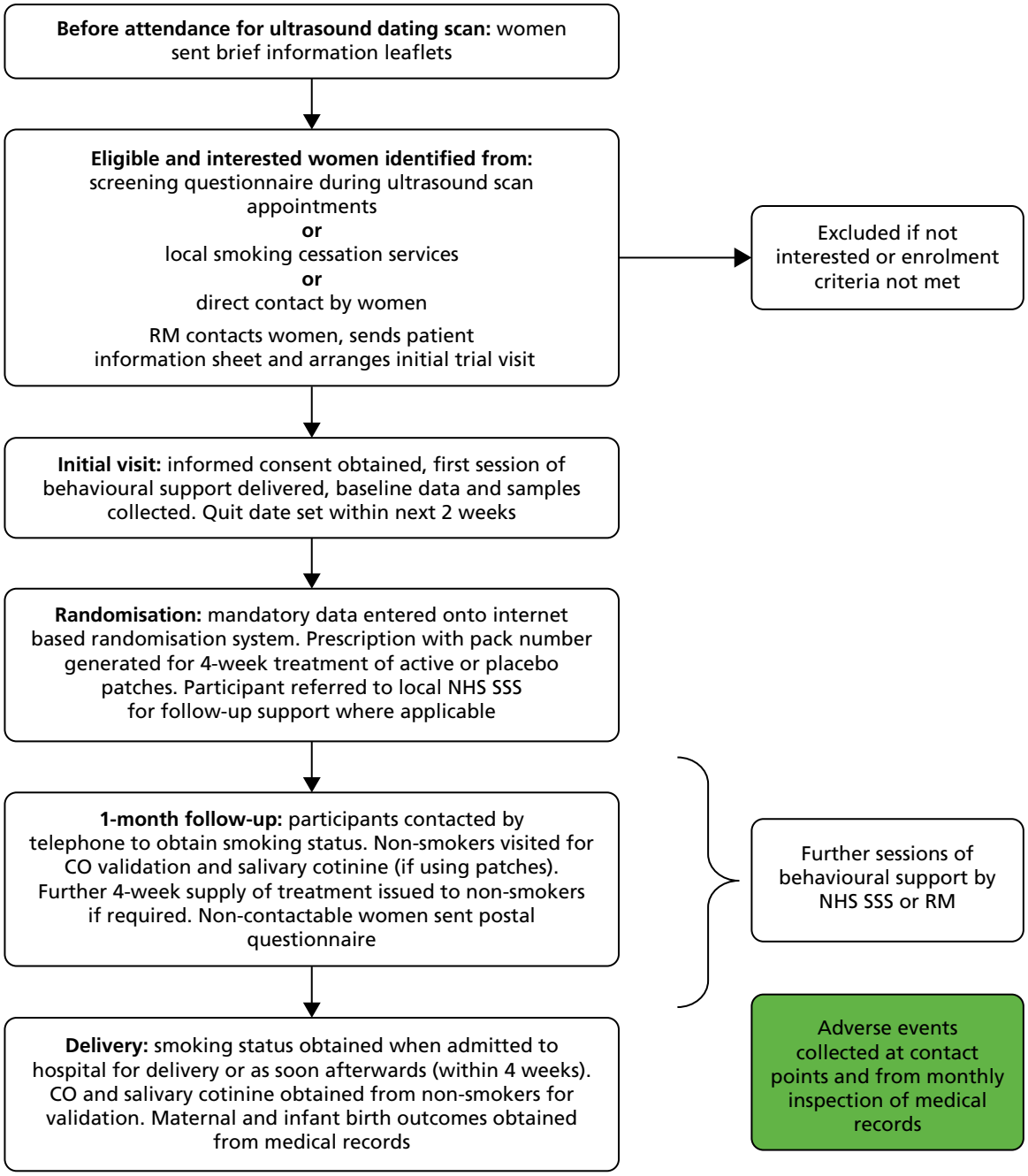

FIGURE 1 Trial flow from recruitment to delivery.

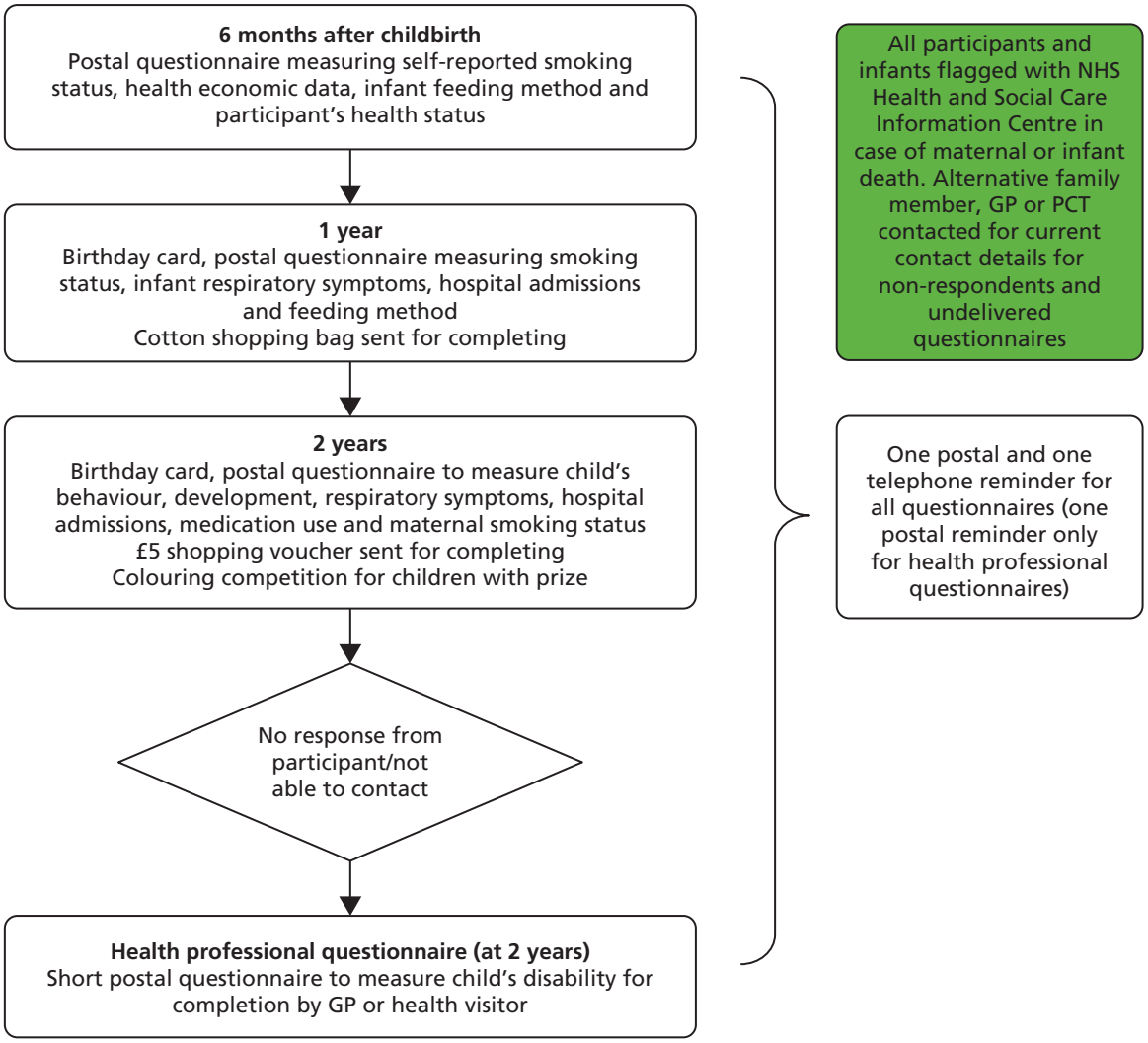

FIGURE 2 Trial follow-up from delivery to infants' second birthdays.

To maintain contact between researchers and participants, the trial office sent greetings cards following childbirth, at Christmas and on the child's first and second birthdays and participants were sent cards reminding them to inform the team of any address changes. At 1 year, a cotton shopping bag was sent to participants on completion of the questionnaire; at 2 years, participants were given a £5 shopping voucher for questionnaire completion and there was a colouring competition that children of respondents could enter. The colouring competition had a £50 shopping voucher prize, with a winner chosen three times per year.

Six months after childbirth

The following information was collected from participants 6 months after delivery: current smoking status, smoking status since childbirth, maternal use of NRT and NHS SSSs since childbirth, length of any maternal hospital inpatient stay after delivery lasting > 24 hours, length of any infant inpatient stay in special care after birth, numbers of additional infant hospital admissions for respiratory illness or other causes, infant feeding method and a health status measure – the European Quality of Life-5 Dimensions (EQ-5D).[42]

One year after childbirth

A shorter questionnaire was sent at 1 year, primarily to maintain contact with the participant, but also to collect the following information: current smoking status, smoking status since birth of infant, infant's respiratory symptoms, infant hospital admissions for respiratory illness and other causes, and infant feeding method.

Two years after childbirth

At 2 years, a questionnaire sent to participants, the 2-year 'participant questionnaire' (PQ2) asked about maternal smoking behaviour and infant development. The PQ2 used items from the Ages and Stages Questionnaire®, Third Edition (ASQ-3™),[43,44] which has been developed for assessing child development at 2 years and is valid for use from 23 months until 25 months and 15 days. It was designed to be completed by parents and to distinguish between children with suspected developmental delay and those for whom development is within the normal range. In a US population, the ASQ-3 has been reported to have a sensitivity of 92.2% and a specificity of 71.9% for detecting developmental delay at 24-months.[45] With permission from the authors and publishers, the wording of some questions was slightly adapted for our UK population. Items 1–30 on the PQ2 consisted of all 30 ASQ-3 items on child development covering five domains: communication, gross motor, fine motor, problem solving and personal–social development. Seven additional PQ2 items (i.e. PQ2 items 31–36 and 44), also taken from the ASQ-3, were mixed 'yes' or 'no'/free text questions investigating both general and specific parental concerns relating to infant health and development. The PQ2 also contained items that were not from the ASQ-3 asking about infant hospital admissions, parental reports of infants' respiratory symptoms and any medication taken for these.

Health professional questionnaire

If, at 2 years, participants did not respond to the PQ2 questionnaire, the health professional questionnaire (HPQ) was posted to their GPs. This shorter questionnaire was designed to be easily completed using medical or health visitors' records and health professionals completing HPQs required little knowledge of the infants. If GPs could not complete HPQs, they were asked to forward these to health visitors. The HPQ contained items that corresponded to those on the PQ2 and were also intended to measure children's disability and general health in a manner consistent with the ASQ-3.[46–48] This included open-response questions that corresponded to 'non-domain' ASQ-3 items included on the PQ2.

For any participants for whom we received both the completed PQ2 and HPQ, only responses from PQ2 were used in analyses.

The system we used to map the question responses to outcomes is outlined in the *Derivation of composite 'impairment' outcome for infants* section and in the statistical analysis plan (SAP) (this can be accessed at http://eprints.nottingham.ac.uk/3283/).

Outcome measures and definitions

Primary outcome to delivery

The primary outcome was self-reported, prolonged and total abstinence from smoking between the quit date and delivery, validated by exhaled CO and salivary cotinine (COT) at childbirth. Occasional minor lapses (no more than five cigarettes in total between the quit date and delivery) were not counted as a return to smoking; this is consistent with standard criteria for assessing outcome in cessation studies.[49] CO readings of ≤ 8 p.p.m. and COT of < 10 ng/ml indicated not smoking.[38] The method used for deriving the primary outcome from responses at 1 month and delivery is detailed in *Box 1*.

Secondary outcomes

(a) Smoking outcomes monitored *until* delivery

i. self-reported, prolonged abstinence from smoking between the quit date and 1 month
ii. self-reported, prolonged abstinence from smoking between the quit date and 1 month with biochemical validation (exhaled CO) (this outcome was not listed in the trial protocol).
iii. self-reported, prolonged abstinence from smoking between the quit date and delivery

BOX 1 Derivation of primary outcome from responses at 1 month and delivery

For a positive response (i.e. abstinent from smoking), the following were required:

at 1 month: 'smoked since quit date' = 'no' or 'missing' **or** 'how often have you smoked' = 'five times or less' **or** 'at least weekly but less than daily' **or** 'missing' (i.e. any response *other than* 'on most days or frequently')

and

at delivery: 'smoked in last 24 hours' = 'no' **and** 'smoked since quit date' = 'no' **and** CO result is between 0 and 8 **and/or** COT[a,b] < 10 ng/ml **or** 'how often have you smoked' = 'five times or less' **and** CO result is between 0 and 8 **and/or** COT < 10 ng/ml.

a Some participants will only have CO measurements and, for these women, readings in the stated reference range are defined as a positive primary outcome (even without COT). Most trial participants will have both CO and COT measurements and, for these women, BOTH readings must fall within defined ranges to count as having a positive outcome.

b At the outset of the trial, CO only was used to validate abstinence from smoking at delivery, but at DMC/TSC request this was changed and COT was added. Consequently, for most participants, both CO and COT were available at delivery. Therefore, either CO or COT could be used individually for validation, but if both were available then they both needed to indicate abstinence for a positive outcome.

iv. self-reported, prolonged abstinence from smoking between the quit date and delivery, with biochemical validation of this at both 1-month follow-up and delivery
v. self-reported smoking cessation for the previous 24-hour period at delivery validated by exhaled CO and saliva cotinine estimation.

(b) Smoking outcomes monitored *after* delivery

i. self-reported, prolonged abstinence from smoking between the quit date and 6 months after delivery
ii. self-reported smoking cessation for the previous 7-day period at 6 months after delivery.

(c) Birth and maternal outcomes

i. miscarriage (non-live birth prior to 24 weeks' gestation) and stillbirth (non-live birth at 24 weeks' gestation or later)
ii. neonatal death (i.e. from live birth to 28 days)
iii. post-neonatal death (29 days to 2 years)
iv. individualised birthweight *z*-score (i.e. birthweight adjust for gestational age, maternal height, maternal weight at booking and ethnic group)
v. unadjusted birthweight and birthweight as *z*-score
vi. Apgar score
vii. cord blood pH
viii. gestational age at birth
ix. intraventricular haemorrhage
x. neonatal enterocolitis
xi. neonatal convulsions
xii. congenital abnormality
xiii. NICU admission
xiv. infant ventilated > 24 hours

xv. elective termination
xvi. elective termination undertaken for fetal morbidity judged incompatible with fetal/infant survival
xvii. maternal mortality
xviii. mode of delivery
xix. hypertension in pregnancy (> 140/90 mmHg at least twice).

Outcomes 2 years after delivery

(a) Infant impairment

Defined as presence of disability and/or behaviour and development problem(s) and categorised as:

i. survival with no impairment: two of the outcomes in the protocol at 2 years were (1) behaviour and development and (2) disability. These outcomes were combined for analysis and reporting purposes and the mapping of protocol outcomes on to those listed above is fully described in the next section (see *Derivation of composite 'impairment' outcome for infants*) and the SAP (http://eprints.nottingham.ac.uk/3283/)
ii. survival with definite impairment (this outcome was not listed in the trial protocol)
iii. survival with suspected impairment (this outcome was not listed in the trial protocol).

Survival with 'no impairment' was the *primary outcome* at 2 years.

(b) Infant respiratory symptoms
(c) Smoking outcomes

i. self-reported, prolonged abstinence from smoking between quit date and 2 years after delivery
ii. self-reported smoking cessation for previous 7-day period at 2 years after delivery.

Derivation of composite 'impairment' outcome for infants

Overview

Full details of how these outcomes were derived from questionnaire responses can be found in the SAP (http://eprints.nottingham.ac.uk/3283/), but a summary follows. This process was discussed with the TSC and the independent TSC statistician approved the SAP before analyses began.

Rationale

At the outset of the trial, we proposed two discrete infant outcomes at 2 years and these were (1) behaviour and development and (2) disability. However, there was no expectation that infants born within the trial would have particularly high rates of disability or developmental problems; therefore, when preparing the SAP for the follow-up analyses, the decision was taken to amalgamate data on both outcomes into one composite outcome. The rationale was that this would permit the trial to demonstrate with greater confidence whether or not NRT is safe for use in pregnancy, as judged in terms of infant development at 2 years.

Impairments were categorised in a mutually exclusive way so that all infants for whom questionnaires had been returned were allocated to just one of the following categories: 'survival with no impairment', 'definite developmental impairment' or 'suspected developmental impairment'. This categorisation was based on responses to selected PQ2 and HPQ items, including the ASQ-3 domains. The scoring of the domains is explained in the following section [*Scoring of Ages and Stages Questionnaire (2-year participant questionnaire) domain scores*], followed by an explanation of how these domain scores and other PQ2/HPQ responses were collated to form outcomes. In some cases, one or more members of the research team inspected hard copies of questionnaires to allocate outcomes after making judgements about free-text responses and, in all such cases, assessors were blind to participants' treatment allocations.

Scoring of Ages and Stages Questionnaire (2-year participant questionnaire) domain scores

Ages and Stages Questionnaire items from the PQ2 that are components of ASQ-3 domains were scored and these individual item scores were summed to give overall 'domain' scores, as described in the ASQ-3 User Guide.[45] Overall 'domain' scores were then compared with standard thresholds/cut-off points to determine whether domain scores should be categorised as 'normal', 'abnormal' or 'borderline'. In clinical practice, any infants with 'abnormal' scores for any ASQ-3 domain would be considered to have 'failed' the ASQ-3 and would be recommended to undergo a more detailed assessment for development delay and those with borderline scores would be closely monitored.

Primary outcome: survival with no impairment

We classified infants as having 'survived with no impairment' if scores were normal for all ASQ-3 domains included on the PQ2 AND *no* problems were reported in PQ2 items 31–35 (i.e. free-text response questions also taken from the ASQ-3). If the PQ2 was not completed but a HPQ had been returned, this was used instead and 'survival with no impairment' was considered to have occurred when *no* HPQ responses indicated potential developmental problems.

Definite and suspected impairment

1. *'Definite' developmental impairment*: we classified infants as having developmental impairment if scores were *at or below* the cut-point in any ASQ-3 domain(s) **or**, if no participant questionnaire had been completed, if the HPQ indicated severe problems for any of questions 1–4 *and/or* severe disability was indicated by the response to question 9 *and/or* severe development delay was indicated in response to question 10.
2. *'Suspected' developmental impairment*: we classified infants as having suspected developmental impairment if *all* ASQ-3 scores were *above* the cut-point, *but* one or more domains scores fell within the borderline range **and/or** this classification was used if responses to either the PQ2 or HPQ reported concerns about developmental impairment that were judged to represent *potential* impairment. 'Yes' responses to PQ2 items questions 31–37 or HPQ questions 1–6 were examined by the research team; if these were judged to potentially reflect valid developmental impairments, infants were placed in the 'suspected impairment' category **and/or** any response stating that a child had mild or moderate disability on HPQ question 9 and/or mild or moderate development delay on HPQ question 10 was classed as suspected developmental impairment.

It should be noted that HPQ/PQ2 items dealing with feeding and behaviour problems were not used in derivation of these early child outcomes; these kinds of problems are frequently reported and have a variety of causes. A priori, we decided not to consider reports of these problems as indicative of impairment. In addition, as questions 1–4 were yes/no responses with free text, the severity of problems could be difficult to establish. Therefore, we used caution and if there were doubts about the severity of problems we classified them as 'suspected' impairment.

Derivation of infant respiratory problems

Infants were judged to have a respiratory problem if, at 2 years, any of questions 38–42 of the PQ2 *and/or* question 7 of the HPQ indicated this. On the PQ2, these questions included hospital admissions for respiratory problems, problems with chest or breathing (yes/no, free text), wheeze or whistling in chest (yes/no, frequency), doctor diagnosed asthma (yes/no), asthma medications taken (yes/no, inhaler description free text). The HPQ asked whether or not the child has problems with their chest or breathing (yes/no, free text).

Maternal smoking outcomes after delivery

We assessed these in a manner consistent with Russell Criteria[49] and with smoking outcomes reported at delivery. The derivation of smoking outcomes is described below:

1. *Positive outcome for 'Self-reported, prolonged abstinence from smoking between quit date and 2 years after delivery'*: the participant must have met the criteria for prolonged abstinence at delivery (i.e. positive primary outcome), plus one of the following responses

   'smoked since 2-year-old was born' = 'No'
   or
   'how often have you smoked' = 'five times or less'
   If any participant questionnaires were completed at 6 and/or 12 months, these should all have had the same responses as above for a positive outcome.

2. Smoked in last week (self-reported smoking cessation for previous 7-day period at 2 years after delivery):

   'smoked since two year old was born' = 'No'
   or 'smoked in last week' = 'No'

3. Smoked in last 2 years (self-reported prolonged abstinence from smoking between delivery and 2 years) (this outcome was not listed in the trial protocol)

   'smoked since two year old was born' = 'No'
   or
   'how often have you smoked' = '5 times or less'
   If any participant questionnaires had been completed at 6 and/or 12 months, these should all have had the same responses as above for a positive outcome.

Outcomes collected on 6-month and 1-year questionnaires

Smoking status and respiratory outcome items were included on 6-month and 1-year questionnaires. These were not listed in the study protocol and only smoking outcomes are reported later. In addition, at 6 months, the EQ-5D questionnaire items were also used and questionnaire items asked about length of stay in hospital and/or special care unit after delivery, infant hospital admissions and medications taken; these data were intended for the Health economics analysis (see *Chapter 4*).

The 6-month and 1-year questionnaires included questions about breast and bottle-feeding and, again, these items were not included in the original study protocol and data are not presented in this report.

Sample size

We planned 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%. It was anticipated that up to 5% of women would be lost to follow-up, and the sample size (of 500) was inflated by a factor of 1.05 to allow for this. This size of study allowed smaller treatment effects to be detected with lower power. For example, there would be 80% power to detect an absolute difference in cessation rates of 7%.

A Cochrane review showed that approximately 10% of women who are still smoking at the time of their first antenatal visit stop smoking with usual care, and a further 6–7% will stop as a result of a formal smoking cessation programme using intensive behavioural counselling.[32] Therefore, in our control group (placebo plus intensive behavioural counselling), a smoking cessation rate of around 16% was anticipated.

The most recent Cochrane review of the efficacy of NRT outside of pregnancy had reported a treatment effect (OR) for transdermal patches of 1.74 (95% CI 1.57 to 1.93).[50] Consequently, if NRT were similarly effective in pregnancy, one could expect a smoking cessation rate of approximately 25% in the treatment group (NRT plus intensive behavioural counselling).

Tables in the SAP show the consequences to study power if the treatment effects in the trial were smaller or overall quit rate was lower than expected (http://eprints.nottingham.ac.uk/3283/).

Statistical methods

The SAP for the primary analysis was finalised before any analyses started. For analyses to be conducted on follow-up data, the analysis plan was added to and finalised during the follow-up period, before any follow-up analyses commenced. (The SAP containing both primary and follow-up analyses can be found at http://eprints.nottingham.ac.uk/3283/). Data cleaning and preparatory work were performed blind to study arm allocation and all analyses of outcomes recorded at delivery were performed blind to study arm allocation, with treatment codes revealed after these were completed. However, it was not possible to perform all follow-up analyses blind. Statistical analyses were performed using SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA) and Stata/SE version 11.2 (StataCorp LP, College Station, TX, USA).

Analysis to primary outcome point (delivery)

Analysis was on an intention-to-treat (ITT) basis and participants who, for any reason, had missing outcome data were assumed to be smoking. The proportion of women who reported prolonged abstinence from smoking immediately before childbirth was compared between treatment groups by logistic regression and adjusted for recruitment centre as a stratification variable. Statistical significance was assessed using the likelihood ratio test. The primary analysis adjusted for no further variables as multivariate analysis results, and therefore overall conclusions, can be sensitive to decisions concerning which variables to adjust for and how these are specified. Nevertheless, we planned a secondary analysis adjusting for baseline COT (continuous variable), maternal education (in years) and partners' smoking status (binary variable), as adjusting for potentially important prognostic factors can improve the precision of treatment effect estimates.[51] Other smoking cessation outcomes were analysed similarly.

Fetal and maternal birth outcomes were compared on an ITT basis. For binary outcomes, ORs were obtained using logistic regression adjusted for recruitment centre and also using the likelihood ratio test (with Fisher's exact test used and stratification by centre ignored when numbers of events were small). For continuous outcomes, we compared means between groups with adjustment for recruitment centre using multiple linear regression.

For fetal outcomes, primary analysis was of singleton births only to allow for the fact that observations will be non-independent and that non-singleton births are likely to have different birth outcomes. However, we undertook a sensitivity analysis including multiple births, with clustering of outcomes accounted for using an approach previously published. This adapts the methodology previously created for use with cluster randomised controlled trials (RCTs), assuming that each woman is regarded as the 'cluster' and her number of offspring the cluster size.[52]

In all analyses, a p-value of < 0.05 was taken to indicate statistical significance and 95% CIs were calculated.

Analysis at the 2-year follow-up point

The ASQ-3 does not require adjustment of an infant's age to allow for prematurity once he or she reaches 24 months of age; therefore, as the questionnaire was sent shortly before the child's second birthday, no adjustment to infant ages was made in analyses.

Maternal characteristics at baseline and delivery and infant birth outcomes at delivery were compared between those participants and infants who did and did not have outcomes ascertained at 2 years after delivery. We also compared maternal and infant characteristics according to whether follow-up at 2 years was by PQ2, HPQ or neither.

Analysis of early childhood outcomes was on an ITT basis with participants analysed in the treatment groups to which they were randomised. Participants with no live birth (i.e. miscarriage, stillbirth or elective termination) or those where the pregnancy outcome was unknown were excluded from the ITT analysis, but postnatal infant deaths were included in the denominator for developmental outcomes. The primary analysis was restricted to singleton births to allow for the fact that observations will be non-independent and that multiple births may have very different outcomes. For the primary outcome, survival with no impairment, a complete case analysis was compared with an analysis using multiple imputation to deal with missing values. Multiple imputation was carried out using the 'mi' commands in Stata and in our multiple imputation we included all of the complete baseline and the treatment code, and used 20 imputations. Using this approach, multiple imputation was also used for the other developmental outcomes: suspected and definite developmental impairment. The infant impairment and respiratory outcomes at 2 years were analysed as binary indicators of presence or absence of the outcome. The ORs for the effect of treatment group were obtained by logistic regression adjusting for centre as the stratification factor. In a subsidiary analysis, multiple births were included and clustering accounted for by the same method as in analysis at delivery. We also conducted sensitivity analyses comparing the results of analyses based on parental responses only and those based on a combination of parental and health professional responses.

Smoking outcomes were also analysed on an ITT basis, with all women analysed in the treatment groups to which they were randomised and all non-respondents assumed to be smoking. ORs for the effect of treatment group on smoking cessation outcomes were also obtained by logistic regression. As at delivery, the primary analysis adjusted only for centre, but we carried out sensitivity analysis that also adjusted for baseline COT, partner's smoking status and age at finishing education.

We tested the assumption that those missing at follow-up were smokers by exploring alternative associations for the relationship between smoking status and 'missingness'.[53] In this analysis, we defined the OR for the association between quitting and being missing as the informatively missing odds ratio (IMOR) and we looked at the effect on the size of the treatment effect on smoking abstinence outcome by varying the size of this OR between 0 and 1. In the main analysis, the assumption that those missing at follow-up are smokers is equivalent to assuming that IMOR equals 0 (i.e. that all those who are missing are smokers). We altered this OR up to IMOR equals 1, which is equivalent to assuming that there is no association between being missing data and smoking status. We carried out this analysis using the mean score method to estimate the treatment effect under the pattern mixture model, $\text{logit}[E(y|r,m_y)] = \alpha_1 + \beta_1 r + m_y\delta$, where m_y is an indicator of whether the outcome is missing or otherwise, r is the treatment effect, and exponential (δ) [the OR between outcome y and m_y (IMOR)] is varied in the range 0–1.[54] α_1 and β_1 are estimated using the subgroup with outcome data, missing values of y (the outcome) are replaced by $\text{invlogit}(\alpha_1 + \beta_1 r + \delta)$, the mean of this new y variable is calculated for the intervention and control arms (say a1 and a0), and ORs calculated from these mean values accordingly $[a1/(1-a1)]/[a0/1-a0)]$.

Secondary analysis

A priori, we planned to investigate whether or not there was any relationship between self-reported nicotine patch use in pregnancy and the presence or absence of developmental impairment in infants at 2 years. For this, we conducted an exploratory regression analysis with absence of impairment at 2 years as the dependent variable and the number of nicotine patches women reported having used when asked at delivery as an explanatory variable. 'Suspected' and 'definite' impairment categories were combined into one group representing infants who did not have impairment-free survival at 2 years. We investigated the possibility that baseline maternal characteristics may have a confounding effect on any relationship and adjusted for confounders as appropriate. For those in the placebo group, we set adherence with nicotine patches as zero. Additionally, if data on adherence were not reported at delivery, we imputed 0 days use of nicotine patches.

Trial management and conduct

The trial was co-ordinated from a central trial office located within the University of Nottingham, with the day-to-day running supervised and organised by a local trial management group and trial manager. The trial was sponsored by the University of Nottingham and conducted in accordance with good clinical practice (GCP) guidelines. All research staff received GCP and research governance training in addition to the study-specific training. Monthly research staff meetings were held in Nottingham, which all RMs were encouraged to attend; the aim was to keep them motivated, updated and trained, as well as to give them the opportunity to network with each other.

In addition to GCP and research governance training, all RMs were trained to English national standards in delivering smoking cessation advice, with particular emphasis on the issues faced by pregnant smokers. RMs completed the 2-day training before they started recruiting, with additional refresher training during the trial. The general aim of training was to provide RMs with an understanding of the basic epidemiology of smoking behaviour, the motivations behind this, harm caused by smoking and environmental tobacco smoke exposure, why people smoke and key barriers to quitting experienced by those smokers who attempt cessation. Skills-focused sessions also aimed to equip RMs with the counselling skills required to help smokers to begin thinking differently about their habit (cognitive change) and to apply recognised techniques to overcoming their addiction (behavioural change). RMs were trained to put emphasis on the value of behavioural approaches for cessation in pregnancy, on the uncertainty regarding the efficacy of NRT and the inappropriateness of using either bupropion or varenicline in pregnancy. In addition, they were trained to counsel participants in the appropriate use of patches (i.e. as if all were issued with active patches) and to instruct them not to smoke or use non-trial NRT preparations in addition to trial medications.

The NCTU provided a web-based database and randomisation system, data management reports and MedDRA coding of AEs. The system was held on a secure server in the NCTU, had a full electronic audit trail and full back-ups of the database were made every 24 hours. Baseline and follow-up data were collected on paper case report forms (CRFs) or questionnaires and then inputted onto the database by the RM or trial administrator. The database included validation checks on data fields, whereby responses not meeting expected criteria would be flagged so that data entry errors were minimised. The trial administrator or trial manager checked all database entries contributing to the outcomes at delivery against the CRF and clarified any queries with RMs. In addition, 10% of follow-up questionnaires were checked against database entries.

The independent TSC and the DMC met once or twice per year to monitor and supervise the progress and conduct of the trial and to review any safety or data issues. The DMC received blinded outcome data each time it met. Stopping rules were established such that if quit rates in the whole sample fell below 4%, or if recruitment rates fell below 25% of the target, then they would consider recommending that the trial be stopped.

Oxfordshire Research Committee A granted national research ethical approval, with additional local approvals for each recruitment centre and Clinical Trial Authorisation (CTA) approval from the MHRA (CTA number: 03057/0002/001-0001). The protocol was published,[55] with several approved amendments made to the original protocol after the start of recruitment; details of these amendments are given below (see *Protocol amendments*) and the final protocol can be found in *Appendix 3*. The trial was registered on the ISRCRN database (ISRCTN07249128) and was assigned a EudraCT number (2004-002621-46). The NHS National Institute for Health Research (NIHR) Primary Care Research Network adopted the study.

Bulk supplies of the NRT and placebo patches were manufactured by United Pharmaceuticals, purchased at market rates and imported into the EU via Almac Ltd, Clinical Trial Services, Craigavon, Northern Ireland. QMC Clinical Trials Pharmacy at Nottingham University Hospitals NHS Trust managed quality control testing, packaging and labelling of participant packs. To ensure stability for the whole study period, the

patches needed to be stored refrigerated at 2–8 °C before being dispensed to participants. However, as the drug was stable at temperatures of < 25 °C for 3 months, and only 1 month's supply of patches was issued at a time, it was not necessary for participants to store them in a refrigerator.

Baseline and 1-month saliva samples were analysed at laboratories within the Centre for Oncology and Molecular Medicine, Division of Medical Sciences at the University of Dundee, UK, under the overall supervision of Professor Michael Coughtrie (a co-investigator). Baseline blood samples were analysed by ABS Laboratories Ltd, Welwyn Garden City, Hertfordshire, UK, and saliva samples taken at delivery were analysed by Salimetrics Europe Ltd, Newmarket, Suffolk, UK.

Protocol amendments

Brief details of protocol amendments made after the start of recruitment, but prior to breaking treatment allocation codes, are listed below.

1. We originally anticipated that women would be sent the PIS before their clinic appointments so that they could then be recruited and consented when they attended for their antenatal scan appointment. However, it was soon realised that, overall, this was not a practical option and that most women were being enrolled on home visits. Therefore, rather than posting the PIS to all women, we added the option of just sending leaflets containing brief information about the trial, with the full PIS later posted to women who had been identified and contacted using the screening questionnaire.
2. Small changes were made to the protocol to clarify trial processes and allow for minor variations in practice in the different centres due to different local arrangements in, for example, prescribing and dispensing practices, local clinic arrangements, follow-up cessation support and time spent in hospital after delivery.
3. Ambiguities in the primary outcome measure were addressed and clarified in the protocol, including the time window in which data collected could be used for analysis, how self-report and biochemical validation data of smoking cessation contributed to a positive primary outcome and what constitutes 'prolonged abstinence from smoking'. Secondary outcomes were clarified to distinguish and define fetal death at different gestations, i.e. miscarriage and stillbirth.
4. We obtained ethical approval to send a 'congratulations on the birth of your baby' card to women after delivery.
5. The content of the questionnaires sent at 6 months, 1 year and 2 years after delivery was finalised and approved, along with a questionnaire to be sent to participants when they could not be contacted 1 month after their quit date. We also decided to include incentives of shopping vouchers and a colouring competition to help improve response rates for the 2-year questionnaires.[41]
6. Once the trial started, we realised that as many pregnancy-related conditions required hospital admissions this was resulting in a large number of SAE reports, none of which were felt to be related to the study drug. Therefore, the sponsor and TSC recommended that we should extend the list of conditions in the protocol that did not need to be reported as a SAE (any deaths of the mother or fetus/infant were still reported). All these AEs were still collected and reviewed by the DMC so that unforeseen impacts of NRT could be monitored.
7. Following further stability data from the manufacturer of the nicotine and placebo patches used in the study, the shelf life was extended from 24 to 42 months.

Trial extensions

The HTA granted two time extensions to the application, adding a total of 12 months to the original length of the trial. This was necessary as the start of recruitment was slightly delayed and the overall recruitment period took 10 months longer than the original estimate of 24 months. Careful budgeting of trial resources funded the majority of this extension, but a small addition to the budget was also awarded.

Chapter 3 Results

Recruitment and follow-up of outcomes at delivery

Recruitment and flow of participants through the trial

Participants were recruited between May 2007 and February 2010 (*Figure 3* and *Table 2*). We initially estimated that recruitment would take 24 months, but after the first 6 months, target figures were revised in line with actual recruitment figures and the recruitment period extended by 10 months.

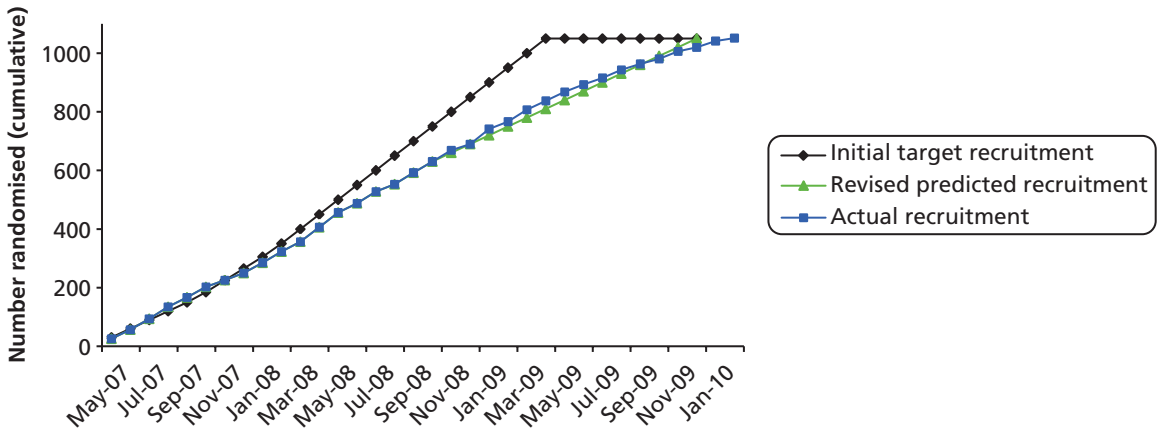

FIGURE 3 Cumulative trial recruitment.

TABLE 2 Recruitment numbers by study centre

Centre	NRT (*n*)	Placebo (*n*)	Total (*N* = 1050), *n* (%)
Nottingham University Hospitals NHS Trust (QMC campus)	61	62	123 (11.7)
Nottingham University Hospitals NHS Trust (City Hospital campus)	62	66	128 (12.2)
Sherwood Forest Hospitals NHS Foundation Trust (King's Mill Hospital)	108	108	216 (20.6)
University Hospital of North Staffordshire (City General Site)	127	130	257 (24.5)
Mid Cheshire Hospitals NHS Foundation Trust (Leighton Hospital)	83	84	167 (15.9)
East Cheshire NHS Trust (Macclesfield District General Hospital)	40	40	80 (7.6)
Derby Hospitals NHS Foundation Trust (Derby City General – later to become Royal Derby Hospital)	40	39	79 (7.5)

The Consolidated Standards of Reporting Trials (CONSORT) diagram (*Figure 4*) summarises the process of recruitment and flow of participants through the study to the primary follow-up point. Approximately 21,000 women were informed of the trial by questionnaires that were distributed and completed in antenatal clinics. The majority of these (around 18,590) were excluded without further contact either because the screening questionnaire showed that they were not eligible (usually because they were not smokers), or because they had no interest in joining the trial.

Of the 2410 women who expressed interest in the trial and were assessed for eligibility, 1051 (43.6%) were randomised: 521 were assigned to receive NRT and 530 were assigned to receive placebo patches (see *Figure 4*). One woman was mistakenly enrolled for a second time in a subsequent pregnancy; her second enrolment in the placebo group was removed from all analyses, giving a final sample size of 1050 (529 in the placebo group).

Protocol breaches were discovered for 13 other participants, but after consideration of violation details it was decided that these were not serious and would have no significant impact on trial participants or the scientific integrity of the trial. These participants, therefore, remained in the trial and their data were used in analyses; details of these protocol breaches are given in *Appendix 4*.

Two additional problems affecting 27 participants occurred within one site pharmacy, but, again, these were judged to have no significant impact on participants or trial integrity, and details are given in *Appendix 4*.

Of 1050 pregnancies, 1038 were singleton and 12 were twin.

At 1 month after their quit date, 866 women (82.5%) provided outcome data and, of these, 573 (66.2%) responded by telephone, 19 (2.2%) responded by questionnaire and 274 (31.6%) attended face-to-face consultations with RMs.

At delivery, 981 (93.4%) participants provided smoking outcome data, but 46 (4.4%) who could not be contacted within the necessary time frame, 10 (1.0%) who withdrew consent and 13 (1.2%) who experienced fetal or infant death (including one elective termination) were not asked for their smoking status.

For most participants who reported that they were non-smokers, biochemical validation was obtained. The validation rates at 1 month were 89% (116/131) in the NRT group and 85% (63/74) in the placebo group. At delivery, validation rates were 89% (58/65 women) in the NRT group and 92% (45/49) in the placebo group.

The ascertainment rate for birth outcomes was more complete than smoking outcomes as these were obtained from participants' hospital notes. *Figure 5* summarises numbers of births within participants and completeness of birth outcome ascertainment.

Further details on the numbers of participants who were followed up and for whom outcome data were obtained at 1 month and at delivery are presented by study centre in *Table 3*.

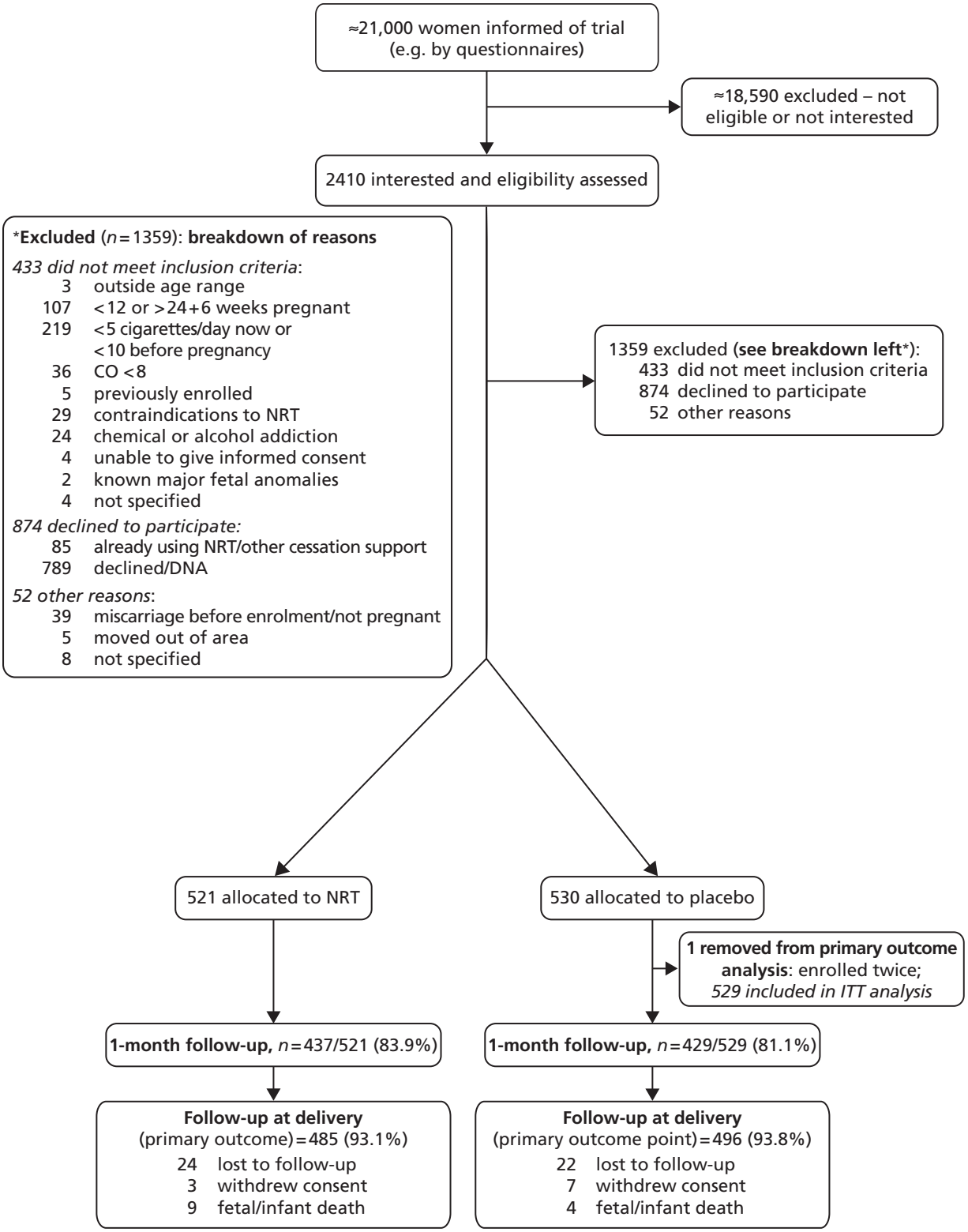

FIGURE 4 The CONSORT diagram showing flow of participants to delivery. From Coleman *et al.*[56] Copyright © 2012 Massachusetts Medical Society. Reprinted with permission. DNA, did not attend.

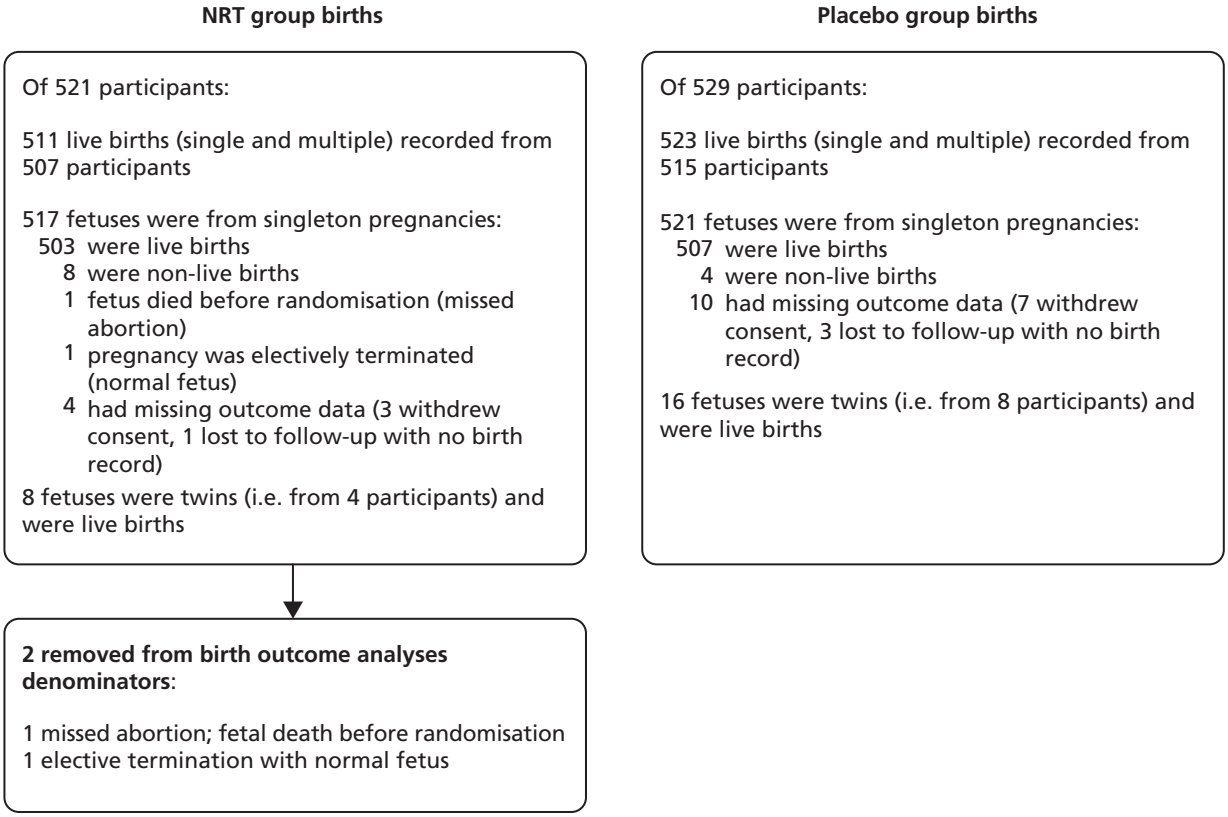

FIGURE 5 Completeness of birth outcome data. From Coleman *et al.*[56] Copyright © 2012 Massachusetts Medical Society. Reprinted with permission.

TABLE 3 Details of outcome ascertainment at 1 month and delivery by study centre ($N = 1050$)

Outcome ascertainment	Nottingham – QMC	Nottingham – City	King's Mill	North Staffs	Leighton	Macclesfield	Derby	Total
1-month visit,* n *(%)								
In person	36 (29.3)	33 (25.8)	41 (19.0)	52 (20.2)	75 (44.9)	20 (25.0)	17 (21.5)	274 (26.1)
Telephone or returned questionnaire	71 (57.7)	80 (62.5)	123 (56.9)	156 (60.7)	68 (40.7)	41 (51.3)	53 (67.1)	592 (56.4)
No contact at 1 month	16 (13.0)	15 (11.7)	52 (24.1)	49 (19.1)	24 (14.4)	19 (23.8)	9 (11.4)	184 (17.5)
Total	123	128	216	257	167	80	79	1050 (100)
Final trial status,* n *(%)								
Outcome data obtained	115 (93.5)	118 (92.2)	210 (97.2)	232 (90.3)	158 (94.6)	72 (90.0)	76 (96.2)	981 (93.4)
Fetal/infant death[a]	2 (1.6)	2 (1.6)	1 (0.5)	3 (1.2)	3 (1.8)	1 (1.3)	1 (1.3)	13 (1.2)
Lost to follow-up or withdrew consent	6 (4.9)	8 (6.3)	5 (2.3)	22 (8.6)	6 (3.6)	7 (8.8)	2 (2.5)	56 (5.3)
Total	123	128	216	257	167	80	79	1050 (100)

a Fetal/infant deaths occurring before trial smoking outcome data were obtained from participants at delivery.

Baseline characteristics

Sociodemographic characteristics, smoking behaviour, obstetric history and participants' prior use of NRT were similar in both trial groups (*Table 4*). Women had a mean age of 26 years and joined the trial at a mean gestational age of 16 weeks. Participants were heavy smokers and around one-third smoked within 5 minutes of waking and the median number of cigarettes smoked per day at randomisation was 14.

TABLE 4 Baseline characteristics by treatment group.[a] From Coleman *et al.*[56] Copyright © 2012 Massachusetts Medical Society. Reprinted with permission

Characteristic		NRT ($N = 521$)	Placebo ($N = 529$)
Mean age (years), (SD)		26.4 (6.2)	26.2 (6.1)
Median number of cigarettes smoked daily before pregnancy (IQR)		20 (15–20)	20 (15–20)
Median number of cigarettes smoked daily at randomisation (IQR)		13 (10–20)	15 (10–20)
Mean gestational age at baseline (weeks) (SD)		16.2 (3.6)	16.3 (3.5)
Ethnic group, *n* (%)	White British	503 (96.5)	515 (97.4)
	Other	18 (3.5)	14 (2.6)
Mean age left full-time education[b] (years) (SD)		16.2 (1.4)	16.3 (1.7)
Parity,[c] *n* (%)	0–1	356 (68.3)	363 (68.6)
	2–3	129 (24.8)	142 (26.9)
	≥ 4	36 (6.9)	24 (4.5)
Median baseline cotinine levels (ng/ml) (IQR)		123.1 (80.1–179.8)	121.2 (77.2–175.9)
Time to first cigarette (minutes), *n* (%)	0–15	281 (54.0)	285 (53.9)
	> 15–60	199 (38.2)	198 (37.4)
	> 60	41 (7.9)	46 (8.7)
Women with partner who smokes,[d] *n*/women with a partner, *n* (%)		356/481 (74.0)	360/482 (74.7)
Mean height (cm)[e] (SD)		163.2 (6.8)	163.0 (6.5)
Mean weight (kg)[f] (SD)		71.7 (18.2)	71.6 (17.2)
Previous preterm birth,[g] *n* (%)		42 (8.1)	50 (9.5)
Length of first behavioural support session (minutes), *n* (%)	≤ 30	84 (16.1)	81 (15.3)
	31–60	428 (82.1)	433 (81.9)
	> 60	9 (1.7)	15 (2.8)
Use of NRT within pregnancy and prior to enrolment,[h] *n* (%)		23 (4.4)	24 (4.5)

SD, standard deviation.
a All baseline differences between groups were non-significant ($p > 0.05$).
b Excludes 14 women still in full-time education at the time of recruitment.
c Defined as number of previous pregnancies that have progressed beyond 24 weeks.
d Excludes 40 in NRT group and 47 women in placebo group with no partner.
e Height was not recorded for 15 participants in the NRT group and 23 in the placebo group.
f Weight was not recorded for 12 participants in the NRT group and 11 in the placebo group.
g Defined as any previous pregnancy which lasted from 24 to 37 weeks.
h The median number of days before recruitment that women last used NRT among the 47 women who reported current or past use was 31 days for the NRT group (IQR 15 to 38 days) and 30 for the placebo group (IQR 14 to 68 days).

Primary outcome measure at delivery

The rate of prolonged abstinence at delivery with validation was 9.4% in the NRT group and 7.6% in the placebo group (OR for abstinence with NRT 1.26, 95% CI 0.82 to 1.96) (*Table 5*).

Secondary outcome measures at delivery

Smoking outcomes at delivery

For self-reported (i.e. non-validated) abstinence, there was a slightly larger but still non-significant difference in quit rates: 12.5% with NRT compared with 9.3% with placebo (OR 1.40, 95% CI 0.94 to 2.07) (see *Table 5*). At 1 month, the validated abstinence rate was significantly higher in the NRT group than in the placebo group (21.3% vs. 11.7%, respectively; OR 2.05, 95% CI 1.46 to 2.88). Similar findings were found for adjusted analyses with all smoking outcomes.

TABLE 5 Primary and secondary smoking cessation outcomes. From Coleman *et al.*[56] Copyright © 2012 Massachusetts Medical Society. Reprinted with permission

Outcome	*n* (%)		OR (95% CI)[a]	Adjusted OR (95% CI)[b]
	NRT (*N* = 521)	Placebo (*N* = 529)		
Primary				
Prolonged self-reported abstinence from smoking between quit date and delivery with COT and/or CO validation[c,d]	49 (9.4)	40 (7.6)	1.26 (0.82 to 1.96)	1.27 (0.82 to 1.98)
Secondary				
Prolonged abstinence from quit date to delivery without validation	65 (12.5)	49 (9.3)	1.40 (0.94 to 2.07)	1.41 (0.95 to 2.09)
Abstinence to 1 month after quit date without validation	131 (25.1)	74 (14.0)	2.07 (1.51 to 2.85)	2.13 (1.54 to 2.95)
Abstinence to 1 month after quit date with CO validation[e]	111 (21.3)	62 (11.7)	2.05 (1.46 to 2.88)	2.10 (1.49 to 2.97)
Prolonged abstinence to delivery with validation at 1 month after quit date and delivery	42 (8.1)	32 (6.0)	1.36 (0.84 to 2.19)	1.37 (0.84 to 2.22)
Point prevalence cessation (> 24-hour quit) at delivery with CO validation	63 (12.1)	53 (10.0)	1.23 (0.84 to 1.82)	1.24 (0.84 to 1.85)
Point prevalence cessation (> 24-hour quit) at delivery without validation	104 (20.0)	89 (16.8)	1.24 (0.90 to 1.70)	1.25 (0.90 to 1.72)

a Adjusted for centre only (as a stratification factor).
b Adjusted for centre, COT at baseline, partner's smoking status (partner smokes vs. partner does not smoke/no partner) and age at leaving full-time education.
c Either cotinine or CO values could be used for validation, but, if both were available, both were required to reflect abstinence.
d The biochemical samples did not validate the report of not smoking (i.e. probable false reporting of cessation) in 9 out of 58 women (16%) in the NRT group and 5 out of 45 women (11%) in the placebo group.
e This outcome measure was not included in the original protocol. The biochemical samples did not validate report of not smoking (i.e. probable false reporting of cessation) in 5 out of 116 women (4%) in the NRT group and 1 out of 63 women (2%) in the placebo group.

Birth outcomes at delivery

Table 6 shows outcomes for singleton births including deaths, mean birthweight and rates of preterm birth, LBW and congenital abnormalities, and these were mainly similar in the two study groups. However, there were significantly more deliveries by caesarean section in the NRT group than in the placebo group (20.7% vs. 15.3%). Analyses that included twin births gave very similar findings.

TABLE 6 Birth outcomes by treatment group.[a] From Coleman *et al.*[56] Copyright © 2012 Massachusetts Medical Society. Reprinted with permission

Fetal outcomes (singleton births only)	NRT ($N = 515$) *n/N* (%)	Placebo ($N = 521$) *n/N* (%)	OR (95% CI)[b]
Miscarriage[c]	3/515 (0.6)	2/521 (0.4)	1.52 (0.25 to 9.13)
Stillbirth[c]	5/512 (1.0)	2/519 (0.4)	2.59 (0.50 to 13.4)
Neonatal death[c]	0/507 (0)	2/517 (0.4)	Not calculated
Post-neonatal death[c,d]	1/507 (0.2)	0/517 (0)	Not calculated
	Mean (SD)	**Mean (SD)**	**Mean difference (95% CI)**
Birthweight, unadjusted (kg)	3.18 (0.61)	3.20 (0.59)	–0.02 (–0.10 to 0.05)
Birthweight (*z*-score)	–0.36 (0.99)	–0.31 (1.02)	–0.05 (–0.17 to 0.08)
Gestational age (weeks)	39.5 (2.1)	39.5 (2.1)	0.0 (–0.2 to 0.3)
	***n/N* (%)**	***n/N* (%)**	**OR (95% CI)[b]**
Preterm birth (< 37 weeks' gestation)	40/507 (7.9)	45/517 (8.7)	0.90 (0.58 to 1.41)
LBW (< 2.5 kg)	56/507 (11.0)	43/517 (8.3)	1.38 (0.90 to 2.09)
NICU admission	33/507 (6.5)	35/517 (6.8)	0.96 (0.58 to 1.57)
Apgar score at 5 minutes < 7	16/507 (3.2)	18/517 (3.5)	0.91 (0.45 to 1.80)
Cord-blood arterial pH < 7	4/507 (0.8)	7/517 (1.4)	0.57 (0.17 to 1.97)
Intraventricular haemorrhage	2/507 (0.4)	3/517 (0.6)	0.67 (0.11 to 4.05)
Neonatal convulsions	5/507 (1.0)	5/517 (1.0)	1.02 (0.29 to 3.54)
Congenital abnormalities[e]	9/507 (1.8)	13/517 (2.5)	0.70 (0.30 to 1.66)
Necrotising enterocolitis	3/507 (0.6)	6/517 (1.2)	0.50 (0.12 to 2.03)
Infant ventilated > 24 hours	10/507 (2.0)	11/517 (2.1)	0.93 (0.39 to 2.22)
Assisted vaginal delivery	38/507 (7.5)	43/517 (8.3)	0.95 (0.59 to 1.50)
Caesarean delivery	105/507 (20.7)	79/517 (15.3)	1.45 (1.05 to 2.01)

SD, standard deviation.

a Using an ITT analysis, we calculated an overall total of 1036 women after the exclusion of 12 women with multiple pregnancies and two from the NRT group [one missed abortion (i.e. the retention in the uterus of a dead fetus) before randomisation and one with elective termination of a normal fetus].

b Odds ratios were adjusted for recruitment centre (as a stratification factor).

c These outcomes were defined a priori as SAEs. There were no maternal deaths and no SAEs were judged to be related to NRT. The denominators for individual fetal outcomes are as follows: miscarriage – number randomised minus number of elective terminations; stillbirth – number randomised minus number of elective terminations and miscarriages. For all other outcomes, the denominator is the number of singleton live births, including those births for which outcome data were missing (507 in NRT group and 517 in placebo group).

d Post-neonatal deaths known about when birth outcomes were analysed.

e Congenital abnormalities in NRT group: congenital cystic kidney disease, congenital heart disease, multiple congenital abnormalities, tetralogy of Fallot, cleft lip and palate, congenital musculoskeletal anomaly, syndactyly, congenital deafness, talipes (all $n = 1$). Congenital abnormalities in placebo group: atrial septal defect ($n = 2$), talipes ($n = 2$), gastroschisis, neural tube defect, cardiac septal defect, congenital acrochordon, hypoplastic left heart syndrome, congenital cystic lung, hip dysplasia, kidney malformation, cleft palate (all $n = 1$).

Adverse events

Other AEs are shown in *Table 7* and, apart from skin reactions at the patch site (97 participants in NRT group reported skin reactions compared with 28 in placebo group), rates were similar in the two groups. In total, 46 participants in the NRT group and 32 in the placebo group stopped using the patches permanently owing to AEs. Further information on the distribution and nature of AEs is in *Appendix 5*.

Adherence with patches and use of smoking cessation support

Adherence with trial patches was low in both groups and rates are shown in *Table 8*. Only 7.2% of women (35/485) assigned to receive NRT and 2.8% (14/496) assigned to placebo reported using trial medications for more than 28 days. Additionally, although 111 NRT group participants were abstinent at 1 month and had this validated by a RM (see *Table 5*), only 72 of these (65%) accepted a second month's supply of patches. The corresponding figure for the placebo group was 47% (29/62). Only 2.5% of NRT group participants (12/485) and 2.2% (11/496) of placebo group participants reported using 'non-study' NRT for $\geq$ 20 days.

As per protocol, RMs attempted to contact participants and provide behavioural support on the quit date, 3 days after their quit date and 1 month after their quit date. In the NRT group, 368 (70.6%) were successfully contacted via a telephone call from a RM on their quit date and 386 (74.1%) 3 days after their quit date. A total of 69 (13.2%) were not successfully contacted on either day, while 302 (58.0%) had a call on both days. In the placebo group, 378 (71.5%) were successfully contacted on their quit date and 381 (72.0%) 3 days after their quit date. A total of 67 women (12.7%) were not successfully contacted on either day, while 297 (56.1%) received a call on both days. At 1 month, 428 (82.1%) participants in the NRT group received support from a RM either face to face [164 (31.5%)] or by telephone [264 (50.7%)]. In the placebo group, 419 (79.2%) participants received RM support [110 (20.8%) face to face, 309 (58.4%) telephone only]. The lower rate of face-to-face support delivered to the placebo group at 1 month reflects the fact that this was delivered at consultations arranged to validate abstinence from smoking. Support was received by participants on all three occasions (i.e. quit date, 3 days after their quit date and 1 month after their quit date) for 268 participants (51.4%) in the NRT group and 250 participants (47.3%) in the placebo group (see *Table 8*). Support was not received on any of these occasions for 27 participants (5.2%) in the NRT group and 28 participants (5.3%) in the placebo group.

Participants also reported little additional face-to-face or text message contact with, or support from, smoking cessation advisors who worked for local NHS SSS (see *Table 8*). Support by telephone was more common and both groups reported receiving a median of two telephone contacts from advisors.

TABLE 7 Adverse events[a] by treatment group. From Coleman *et al.*[56] Copyright © 2012 Massachusetts Medical Society. Reprinted with permission

AE	NRT (*N* = 521)	Placebo (*N* = 529)
SAEs, *n* (%)		
Maternal mortality	0	0
Other SAEs[b]	9 (1.7)	6 (1.1)
Maternal AEs potentially related to treatment, *n* (%)		
Patch stopped permanently owing to AE[c]	46 (8.8)	32 (6.0)
Skin reactions at patch site (but no treatment discontinuation)[d]	97 (18.6)	28 (5.3)
Maternal AEs as probable complications of pregnancy, *n* (%)		
Blood pressure > 140/90 mmHg on at least two occasions	24 (4.6)	25 (4.7)
Nausea or vomiting	16 (3.1)	19 (3.6)
Headache	25 (4.8)	16 (3.0)
Abdominal pain	54 (10.4)	50 (9.5)
Vaginal bleeding or haemorrhage	35 (6.7)	38 (7.2)
Premature rupture of membranes[e]	6 (1.2)	10 (1.9)
Uterine contractions during pregnancy[e]	24 (4.6)	30 (5.7)
Gestational diabetes	3 (0.6)	3 (0.6)
Pre-eclampsia or eclampsia	3 (0.6)	5 (0.9)
Hospital admission for other pregnancy complication[f]	44 (8.4)	41 (7.8)
Other less frequent maternal AEs[g]	63 (12.1)	73 (13.8)
Fetal AEs as probable complications of pregnancy, *n* (%)		
Decreased fetal movements (fetal hypokinesia)[e]	58 (11.1)	46 (8.7)
Other AEs affecting fetus[g]	5 (1.0)	5 (0.9)
Neonatal AEs[g]	32 (6.1)	29 (5.5)
Total AEs, *n*[h]	**535**	**450**

a AEs were coded using the MedDRA, version 13.1. For each treatment group, percentages were calculated as the number of women who experienced the specified AE at least once, divided by the number of women who were randomised. Column totals may add up to over 100% as participants may have experienced AEs in more than one category (row).
b Other SAEs included miscarriage, stillbirth, neonatal and post-neonatal deaths reported as pre-specified trial outcomes.
c Reasons for patch discontinuation are summarised in *Appendix 5*.
d AEs included pruritus, swelling, erythema, rash, blistering or vesicles, pain and other local reactions.
e Symptoms required hospital admission or assessment.
f Overnight admission for less frequent events (< 3% of participants); full breakdown available in *Appendix 5*.
g Events occurring in < 3% of women or infants; full breakdown available in *Appendix 5*.
h The total numbers of women or their infants who had at least one SAE or AE were 316 (61%) in the NRT group and 269 (51%) in the placebo group.

TABLE 8 Cessation support and adherence with NRT by treatment group. From Coleman *et al.*[56] Copyright © 2012 Massachusetts Medical Society. Reprinted with permission

Adherence and support		NRT, *n* (%)	Placebo, *n* (%)	*p*-value (by chi-squared test for trend)
Measures reported at 1 month		**N = *437*[a]**	**N = *429*[a]**	
Reported days trial patch use in first month	0–7	180 (41.3)	220 (51.5)	$p < 0.001$
	8–14	82 (18.8)	108 (25.3)	
	15–21	74 (17.0)	58 (13.6)	
	> 21	100 (22.9)	41 (9.6)	
Days of non-trial NRT use	0	425 (97.3)	406 (94.6)	$p < 0.05$
	1–4	8 (1.8)	11 (2.6)	
	5–9	1 (0.2)	5 (1.2)	
	≥ 10	3 (0.7)	7 (1.6)	
Additional face-to-face contacts with NHS SSS advisor[b] (*n*)	0	409 (93.6)	407 (94.9)	NS
	1	22 (5.0)	17 (4.0)	
	≥ 2	6 (1.4)	5 (1.2)	
Additional telephone contacts with NHS SSS advisor[b] (*n*)	0	146 (33.4)	139 (32.4)	NS
	1	122 (27.9)	114 (26.6)	
	2	95 (21.7)	94 (21.9)	
	3	41 (9.4)	43 (10.0)	
	≥ 4	33 (7.6)	39 (9.1)	
Additional SMS 'text' contacts with NHS SSS advisor[c] (*n*)	0	332 (76.0)	329 (76.7)	NS
	1	50 (11.4)	53 (12.4)	
	2	30 (6.9)	31 (7.2)	
	3	10 (2.3)	8 (1.9)	
	≥ 4	15 (3.4)	8 (1.9)	
Measures reported at delivery		**N = *485*[c]**	**N = *496*[c]**	
Days of non-trial NRT use	0	459 (94.6)	449 (90.5)	$p < 0.05$
	1–4	7 (1.4)	16 (3.2)	
	5–19	7 (1.4)	20 (4.0)	
	≥ 20	12 (2.5)	11 (2.2)	
Additional face-to-face contacts with NHS SSS advisor[b] (*n*)	0	429 (88.5)	448 (90.3)	NS
	1	36 (7.4)	32 (6.5)	
	2	15 (3.1)	11 (2.2)	
	≥ 3	5 (1.0)	5 (1.0)	
Additional telephone contacts with NHS SSS advisor[b] (*n*)	0	141 (29.1)	156 (31.5)	NS
	1–2	186 (38.4)	203 (40.9)	
	3–4	93 (19.2)	86 (17.3)	
	5–9	57 (11.8)	49 (9.9)	
	≥ 10	8 (1.7)	2 (0.4)	
Additional SMS 'text' contacts with NHS SSS advisor[b] (*n*)	0	347 (71.6)	365 (73.6)	NS
	1–2	87 (17.9)	85 (17.1)	
	3–4	24 (5.0)	27 (5.4)	
	5–9	24 (5.0)	17 (3.4)	
	≥ 10	3 (0.6)	2 (0.4)	

TABLE 8 Cessation support and adherence with NRT by treatment group. From Coleman *et al.*[56] Copyright © 2012 Massachusetts Medical Society. Reprinted with permission (*continued*)

Adherence and support		NRT, *n* (%)	Placebo, *n* (%)	*p*-value (by chi-squared test for trend)
Participants issued with a second month's supply of patches[d] (*n*)		72	29	
Reported days of trial patch use by participants issued with 2 months' worth of patches[d]	0–7	3 (4.3)	1 (3.6)	NS
	8–14	12 (17.1)	8 (28.6)	
	15–28	20 (28.6)	5 (17.9)	
	≥ 29	35 (50.0)	14 (50.0)	
Behavioural support from RMs		**N = *521***	**N = *529***	
Successful contacts with RMs (*n*)[e]	0	27 (5.2)	28 (5.3)	
	1	74 (14.2)	74 (14.0)	
	2	152 (29.2)	177 (33.5)	
	3	268 (51.4)	250 (47.3)	

NS, not significant; SMS, short message service.
a On occasions, at the 1-month visit, when responses to individual questions were missing (always $n \leq 12$), women were assumed to have had no contact with cessation advisors, to have never used non-trial NRT and to be in the lowest compliance category.
b These were contacts for additional behavioural support provided by local NHS SSS advisors.
c There were no missing responses to individual questions at delivery.
d A total of 101 women (29 placebo and 72 NRT) were issued with a further 28 days' supply of NRT. Out of these, 98 women provided data on compliance at the time of delivery and were included in the analysis of trial patch use at the time of delivery.
e Contact attempts were made with participants for behavioural support on their quit dates, 3 days after quit date and at 1 month after quit date.

Follow-up after delivery

Follow-up of participants and infants after delivery

Follow-up of participants and infants began after the first birth in July 2007 and continued until December 2012.

Two CONSORT diagrams are presented for the follow-up period from delivery until infants were 2 years old; participants indicated as withdrawn in either diagram were not sent further questionnaires after their withdrawal.

Participants' follow-up

The first diagram (*Figure 6*) is for all participants and summarises questionnaire distribution and response rates at the three follow-up time points, plus reasons for withdrawal. This provides denominators and follow-up data that are relevant to participant outcomes (e.g. smoking behaviour). By the final follow-up point, 150 participants [14.3% of the original study population: 73 out of 521 (14.0%) NRT, 77 out of 529 (14.6%) placebo] had withdrawn from the study, or a completed 2-year questionnaires had not been received from either the participant or their GP. This includes the 122 participants whose reasons for withdrawal are shown in *Figure 6*, plus 28 participants with fetal deaths or for whom no birth details were obtained. These are described in *Infants' follow-up*.

Infants' follow-up

The second diagram (*Figure 7*) provides similar details for the 1010 live infants that were known to be born from singleton pregnancies and provides information on follow-up that is relevant to the assessment of infant outcomes at 2 years. This shows the 14 fetal deaths recorded when birth outcome data were analysed (also described in *Figure 5*), plus 14 participants for whom no infant birth details were obtained.

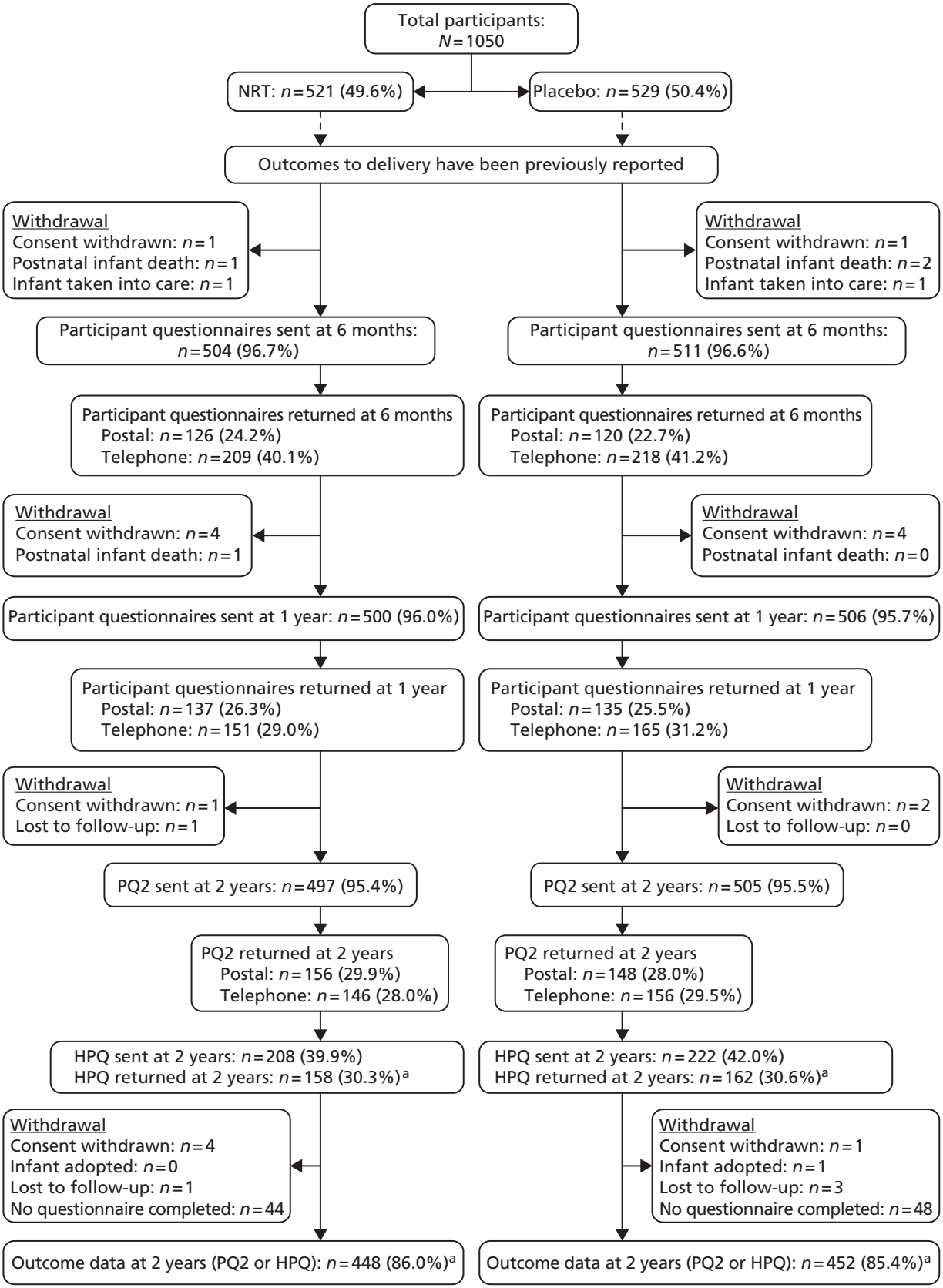

FIGURE 6 The CONSORT diagram showing flow of all trial participants during the 2-year follow-up period. a, 26 HPQs were returned in participants who had already returned a PQ2 ($n = 12$ NRT, $n = 14$ placebo) and these were not included in subsequent analyses. Reproduced with permission. Cooper S, Taggar J, Lewis S, Marlow N, Dickinson A, Whitemore R, *et al.* Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial [published online ahead of print 11 August 2014]. *Lancet Respir Med* 2014. doi:10.1016/S2213-2600(14)70157-2.

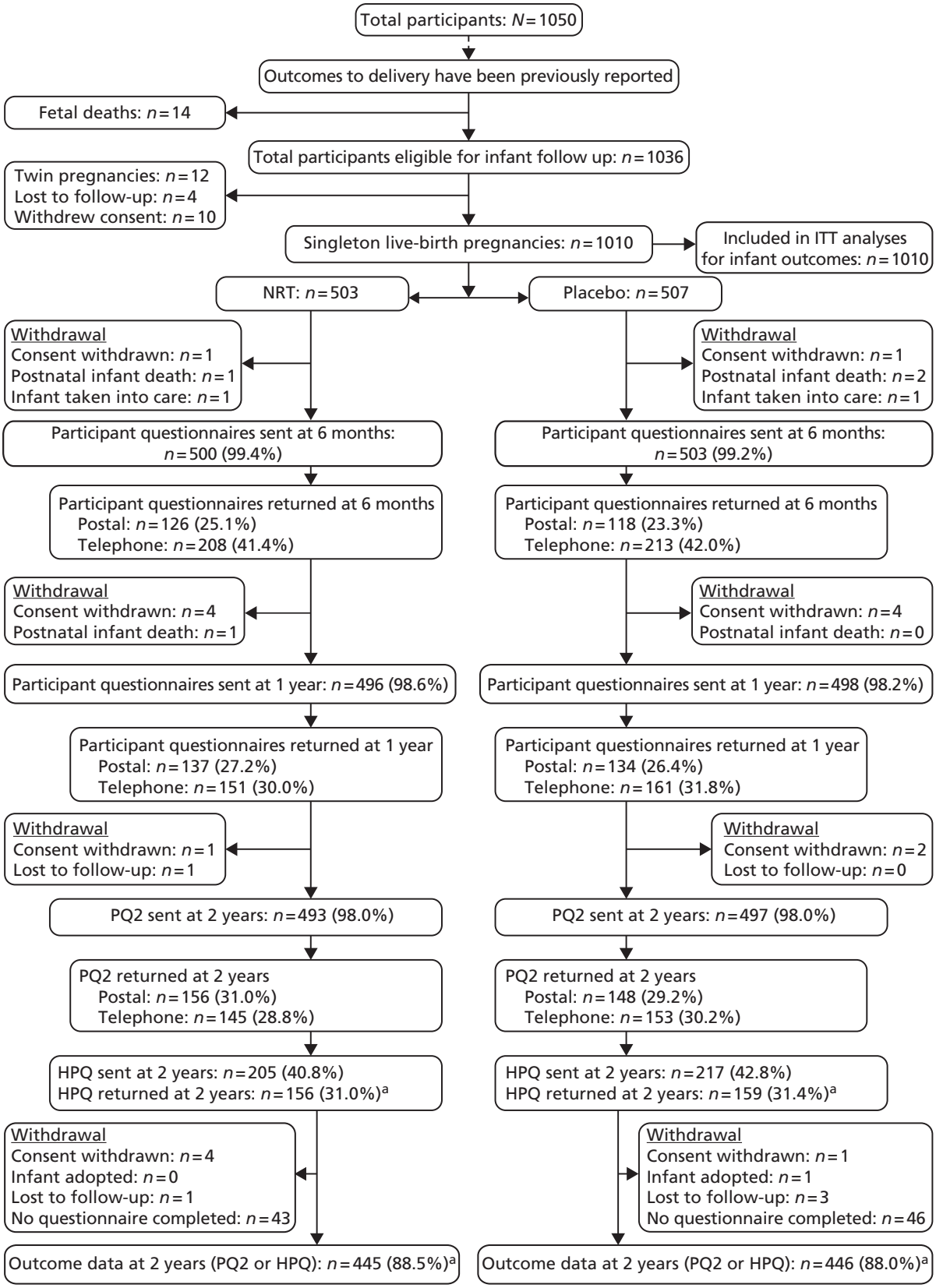

FIGURE 7 The CONSORT diagram showing flow of participants with live singleton births. These data were used for birth outcome analyses during the 2-year follow-up period. a, 26 HPQs were returned in participants who had already returned a PQ2 ($n = 12$ NRT, $n = 14$ placebo) and these were not included in subsequent analyses. Reproduced with permission. Cooper S, Taggar J, Lewis S, Marlow N, Dickinson A, Whitemore R, *et al.* Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial [published online ahead of print 11 August 2014]. *Lancet Respir Med* 2014. doi:10.1016/S2213-2600(14)70157-2.

Of those with no birth details, 10 withdrew consent before delivery (three NRT, seven placebo) and four were lost to follow-up (one NRT, three placebo); for ITT analyses of infant outcomes, it has been assumed that 14 live singleton infants were born to these participants. Four singleton infant deaths occurred between birth and the 2-year follow-up (two NRT, two placebo), of which one was known about and recorded when outcomes at delivery were analysed (see *Table 6*). For simplicity, and as primary analyses for infant outcomes did not include infants carried in multiple birth pregnancies, twin infants are excluded from *Figure 5*. However, sensitivity analyses included twins and either PQ2 or HPQ responses for 18 twin infants (6 NRT, 12 placebo) from nine of the 12 twin pregnancies were obtained and used in these.

Discrepancies in questionnaire follow-up

One participant in the placebo group was sent neither the 6-month nor the 1-year questionnaire as her birth details were not obtained until 18 months after delivery (i.e. it was not known that a live birth had occurred). Two participants were inadvertently sent questionnaires: one in the placebo group was sent a 6-month questionnaire as the trial team had not been informed that the child had been taken into care at delivery, and one participant in the NRT group whose infant had died was sent a 1-year questionnaire due to a delay in receiving the death report from the NHS Information Centre. There were 26 participants (12 NRT, 14 placebo), all with singleton births, for whom both PQ2 and HPQs were completed and returned, and for these respondents PQ2 responses were used.

Completeness of follow-up for early childhood outcomes

For the 1010 known singleton live births, there were 891 (445 NRT, 446 placebo) (88.2%) responses to either the PQ2 or the HPQ, which could be used in analyses contributing to the primary outcome at the 2-year follow-up (see *Figure 7*).

Completeness of follow-up for participants' smoking outcomes

From the full trial cohort of 1050 participants, 606 (302 NRT, 304 placebo) (57.7%) responded to the PQ2 questionnaire providing data that could be used in the analysis of participants' smoking outcomes at the 2-year follow-up (see *Figure 6*).

Overall follow-up rates were similar in both groups; the response rates for all follow-up time points can be seen in *Figure 6* and *Table 9*, and in chart form in *Figure 8*. Most participants required a reminder questionnaire and approximately half of those who provided data did so by completing the questionnaire over the telephone. Around three-quarters of health professionals returned the questionnaire by post,

TABLE 9 Response rates to questionnaires sent during the follow-up period

Questionnaire	Questionnaire sent (*N*)	Reminder sent *n* (% of questionnaires sent)	Returned by post *n* (% of questionnaires sent)	Completed by telephone *n* (% of questionnaires sent)	Total response *n* (% of questionnaire sent)
Participant 6-month	1015	886 (87.3)	246 (24.2)	427 (42.1)	673 (66.3)
Participant 1-year	1006	875 (87.0)	272 (27.0)	316 (31.4)	588 (58.4)
PQ2	1002	864 (86.2)	304 (30.3)	302 (30.1)	606 (60.5)
HPQ	430	306 (71.2)	320 (74.4)	NA	320[a] (74.4)
Combined 2-year response (i.e. PQ2 *or* HPQ returned)	1002	NA	NA	NA	900 (89.8)

NA, not applicable.
a This includes 26 HPQs that were returned for participants who had already returned a PQ2.

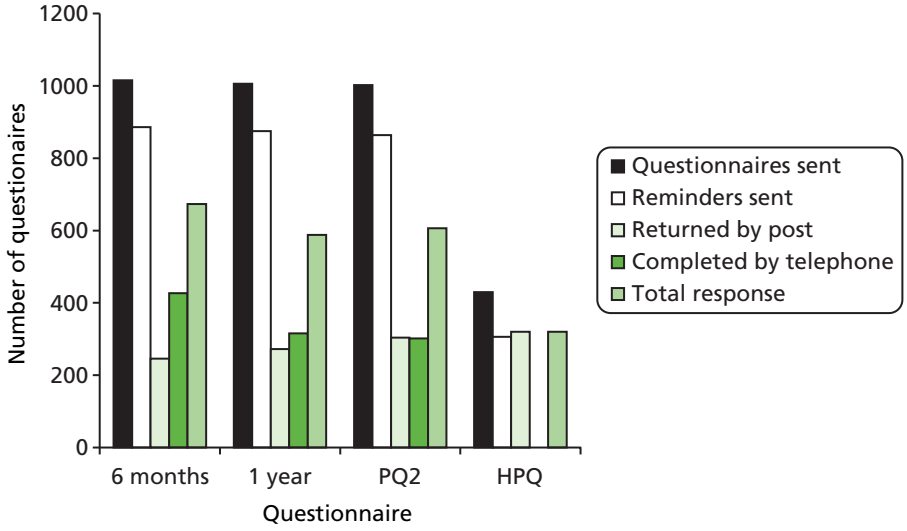

FIGURE 8 Numbers of questionnaires sent and returned during the follow-up period.

although most needed a postal reminder. The total combined response for participant or HPQs at 2 years was 900 (89.8% of those sent questionnaires at 2 years; 85.7% of all randomised participants). This figure excludes the 26 HPQs that were received for participants who subsequently returned their PQ2.

Characteristics of participants and infants who were followed up after delivery

Table 10 shows the maternal baseline characteristics and singleton birth outcomes for the 900 participants who had 2-year outcome data in the NRT and placebo groups. As with the whole trial cohort, these two groups had similar demographic characteristics at enrolment. Singleton infant birth outcomes were also similar in the two groups, apart from delivery by caesarean section, which, as found in the full cohort at primary outcome, was similarly slightly higher in the NRT group than in the placebo group (20.2% compared with 15.5%). The proportion of the participants providing data at 2 years who had prolonged, validated abstinence from smoking at delivery was 10.3% in the NRT group and 8.2% in the placebo group (see *Table 10*), which compares with 9.4% and 7.6% for NRT and placebo groups, respectively, for the full cohort (see *Table 5*).

Table 11 shows the same characteristics within those participants who provided 2-year follow-up data on the PQ2, those for whom a HPQ was completed instead and those for whom no data was obtained. Most of the demographic data are similar in these three groups; however, those with no follow-up data at 2 years had a slightly higher mean index of multiple deprivation (IMD) score (36.8, compared with 32.3 in those with PQ2 data and 32.2 in those with HPQ data). Their first behavioural support session may also have been slightly shorter (21.3% of this group had a behavioural support session of < 30 minutes, compared with 14.4% and 15.7% of those with PQ2 and HPQ data, respectively). Median COT levels at enrolment appear to be slightly higher in those who were followed up by HPQ (131.6 ng/ml, compared with 119.1 ng/ml in the other two groups).

Participants who completed a PQ2 were more likely to have validated abstinence between quit date and delivery (10.9%, compared with 5.8% of those with HPQ data and 4.0% of those with no 2-year data) (see *Table 11*).

TABLE 10 Comparison of maternal characteristics and birth outcomes for participants who provided data at 2 years

	NRT ($N = 448$)[a]	Placebo ($N = 452$)[a]
Maternal characteristics at study enrolment		
Mean age (years) (SD)	26.5 (6.2)	26.3 (6.1)
Median number of cigarettes smoked daily before pregnancy (IQR)	20 (15–20)	20 (15–20)
Median number of cigarettes smoked daily at baseline (IQR)	13 (10–20)	15 (10–20)
Mean gestational age at baseline (weeks) (SD)	16.2 (3.5)	16.3 (3.5)
Ethnic group, *n* (%)		
White British	434 (96.9)	442 (97.8)
Other	14 (3.1)	10 (2.2)
Age left full-time education (years)		
Mean (SD)	16.2 (1.4)	16.3 (1.7)
Missing data (*n*)	5	8
Index of multiple deprivation		
Mean (SD)	32.1 (16.7)	32.4 (16.9)
Missing data (*n*)	13	9
Parity, *n* (%)		
0–1	306 (68.3)	311 (68.8)
2–3	111 (24.8)	121 (26.8)
≥ 4	31 (6.9)	20 (4.4)
COT at baseline (ng/ml)		
Median (IQR)	123.7 (80.2–185.4)	120.9 (75.6–175.9)
Missing data (*n*)	35	33
Time to first cigarette, *n* (%)		
0–15 minutes	245 (54.7)	243 (53.8)
16–60 minutes	169 (37.7)	168 (37.2)
> 60 minutes	34 (7.6)	41 (9.1)
Women with partner who smokes		
n (%)	306 (68.3)	306 (67.7)
Missing data (*n*, %)	34 (7.6)	38 (8.4)
Height (cm)		
Mean (SD)	162.9 (6.8)	163.1 (6.4)
Missing data (*n*)	12	13
Weight (kg)		
Mean (SD)	71.2 (17.8)	72.3 (17.1)
Missing data (*n*)	8	8
Previous preterm birth, *n* (%)	38 (8.5)	42 (9.3)

TABLE 10 Comparison of maternal characteristics and birth outcomes for participants who provided data at 2 years (*continued*)

	NRT (*N* = 448)[a]	Placebo (*N* = 452)[a]
Length of first behavioural support session, *n* (%)		
< 30 minutes	66 (14.7)	67 (14.8)
31–60 minutes	376 (83.9)	371 (82.1)
> 60 minutes	6 (1.3)	14 (3.1)
Use of NRT earlier in pregnancy, *n* (%)	19 (4.2)	23 (5.1)
Maternal smoking outcomes at delivery		
Met primary smoking cessation outcome, *n* (%)	46 (10.3)	37 (8.2)
Infant birth outcomes at delivery (singleton pregnancies)	***NRT (n = 445)[b]***	***Placebo (n = 446)[b]***
Mean birthweight, unadjusted (kg) (SD)	3.2 (0.6)	3.2 (0.6)
Mean gestational age (weeks) (SD)	39.5 (2.1)	39.5 (2.2)
Preterm birth, *n* (%)	36 (8.1)	40 (9.0)
LBW (< 2.5 kg), *n* (%)	49 (11.0)	37 (8.3)
NICU admission, *n* (%)	29 (6.5)	32 (7.2)
Apgar score at 5 minutes < 7, *n* (%)	12 (2.7)	13 (2.9)
Congenital abnormalities, *n* (%)	7 (1.6)	12 (2.7)
Infant on ventilator > 24 hours, *n* (%)	8 (1.8)	10 (2.2)
Assisted vaginal delivery, *n* (%)	33 (7.4)	37 (8.3)
Delivery by caesarean section, *n* (%)	90 (20.2)	69 (15.5)

SD, standard deviation.
a All pregnancies (i.e. includes twins).
b Singleton pregnancies only.
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TABLE 11 Maternal and infant characteristics: comparison of participants and singleton infants for whom outcome data were and were not available at 2 years

All participants at randomisation (*N* = 1050)	Followed up: PQ2 (*N* = 606)	Followed up: HPQ (*N* = 294)[a]	Not followed up (*N* = 150)[b]
Maternal characteristics at enrolment/randomisation (all pregnancies)			
Mean age (years) (SD)	26.9 (6.3)	25.5 (5.6)	25.7 (6.3)
Median number of cigarettes smoked daily before pregnancy (IQR)	20 (15–20)	20 (15–20)	20 (15–20)
Median number of cigarettes smoked daily at baseline (IQR)	15 (10–20)	15 (10–18)	12 (10–15)
Mean gestational age at baseline (weeks) (SD)	16.2 (3.5)	16.4 (3.5)	16.2 (3.6)
Ethnic group, *n* (%)			
White British	588 (97.0)	288 (98.0)	142 (94.7)
Other	18 (3.0)	6 (2.0)	8 (5.3)
Mean age left full-time education (years) (SD)	16.3 (1.7)	16.2 (1.3)	16.3 (1.5)

continued

TABLE 11 Maternal and infant characteristics: comparison of participants and singleton infants for whom outcome data were and were not available at 2 years (*continued*)

All participants at randomisation (*N* = 1050)	Followed up: PQ2 (*N* = 606)	Followed up: HPQ (*N* = 294)[a]	Not followed up (*N* = 150)[b]
Mean index of multiple deprivation (SD)	32.3 (17.1)	32.2 (16.2)	36.8 (16.0)
Parity, *n* (%)			
0–1	424 (70.0)	193 (65.7)	102 (68.0)
2–3	144 (23.8)	88 (29.9)	39 (26.0)
≥ 4	38 (6.3)	13 (4.4)	9 (6.0)
Median COT level at baseline (ng/ml) (IQR)	119.1 (72.1–179.5)	131.6 (88.7–184.7)	119.1 (80.0–161.3)
Time to first cigarette, *n* (%)			
0–15 minutes	329 (54.3)	159 (54.1)	78 (52.0)
16–60 minutes	231 (38.1)	106 (36.1)	60 (40.0)
> 60 minutes	46 (7.6)	29 (9.9)	12 (8.0)
Women with partner who smokes, *n* (%)	408 (67.3)	204 (69.4)	104 (69.3)
Mean height (cm) (SD)	162.9 (6.8)	163.2 (6.3)	163.7 (7.0)
Mean weight (kg) (SD)	72.4 (16.6)	70.5 (19.1)	71.0 (18.9)
Previous preterm birth, *n* (%)	47 (7.8)	33 (11.2)	12 (8.0)
Length of first behavioural support session, n (%)			
< 30 minutes	87 (14.4)	46 (15.7)	32 (21.3)
31–60 minutes	505 (83.3)	242 (82.3)	114 (76.0)
> 60 minutes	14 (2.3)	6 (2.0)	4 (2.7)
Use of NRT earlier in pregnancy, *n* (%)	33 (5.5)	9 (3.1)	5 (3.3)
Maternal smoking at delivery (all pregnancies)			
Met primary smoking cessation outcome, *n* (%)	66 (10.9)	17 (5.8)	6 (4.0)
Infant birth outcomes (singleton pregnancies,* N = *1010)	***(N = 602)***	***(N = 289)***[a]	***(N = 119)***
Mean birthweight, unadjusted (kg) (SD)	3.2 (0.58)	3.1 (0.62)	3.2 (0.60)
Mean gestational age (weeks) (SD)	39.5 (2.1)	39.4 (2.3)	39.6 (2.1)
Preterm birth, *n* (%)	46 (7.6)	30 (10.4)	9 (7.6)
LBW (< 2.5 kg), *n* (%)	46 (7.6)	40 (13.8)	13 (10.9)
NICU admission, *n* (%)	39 (6.5)	22 (7.6)	7 (5.9)
Apgar score at 5 minutes < 7, *n* (%)	13 (2.2)	12 (4.2)	9 (7.6)
Congenital abnormalities, *n* (%)	8 (1.3)	11 (3.8)	3 (2.5)
Infant on ventilator > 24 hours, *n* (%)	11 (1.8)	7 (2.4)	3 (2.5)
Assisted vaginal delivery, *n* (%)	51 (8.5)	19 (6.6)	11 (9.2)
Delivery by caesarean section, *n* (%)	118 (19.6)	41 (14.2)	25 (21.0)

SD, standard deviation.

a Twenty-six participants who provided both HPQ and PQ2 data were excluded from this analysis (*n* = 12 NRT, *n* = 14 placebo, all singleton pregnancies).

b Includes participants who were lost to follow-up and those who did not return questionnaires at 24 months.

Outcome measurements after delivery

Infant outcomes at 2 years

Infants' developmental outcomes and any reports of respiratory problems at 2 years after delivery are shown in *Table 12*, separated by treatment group for all those with known outcomes, including four postnatal deaths. In *Table 13*, these results are broken down further to show outcomes by questionnaire and, for comparison purposes, postnatal deaths are not included in the denominators in this table.

Of the 1010 singleton infants, 891 (445 NRT, 446 placebo) had information about them returned on either the PQ2 or the HPQ questionnaire; however, owing to missing data, it was not possible to allocate developmental outcomes on one PQ2 (from placebo group) and six returned HPQs (two NRT, four placebo). Within these 891, infants born to women who had been allocated to the NRT group in pregnancy were significantly more likely to have survived with no impairment than those born to women allocated to placebo [323/445 (72.6%) of NRT group infants and 290/443 (65.5%) in the placebo group]. The OR for 'survival with no impairment' in the NRT compared with the placebo group obtained in the primary analysis (ITT with multiple imputation analysis) was 1.40 (95% CI 1.05 to 1.86, $p = 0.023$). Similar statistically significant differences in survival without impairment were also found for other analyses including the clustered analysis with twin births (OR 1.43, 95% CI 1.08 to 1.91, $p = 0.013$) (see *Table 12*) and the analysis of singleton infants using just the PQ2 responses (OR 1.52, 95% CI 1.09 to 2.11, $p = 0.012$) (see *Table 13*).

There were no significant differences between groups for any of the other infant outcomes (see *Tables 12* and *13*). Using definitions of developmental impairment described in the methods, 'definite' impairment was identified in 48 (10.8%) of the NRT and 64 (14.5%) of the placebo groups, and 'suspected' impairment in 72 (16.2%) of NRT and 87 (19.6%) of placebo groups. A greater number of questionnaires that were returned by participants reported potential child development problems than the health professional ones; 253 (42.0%) of the 602 returned PQ2s were categorised with definite or suspected impairment, compared with only 18 (6.2%) of the 289 HPQ responses.

A detailed breakdown of infant developmental outcomes from the PQ2 and HPQs, including ASQ-3 domain scores and problems reported in the supplementary questions, is shown in *Table 14*. Overall, participants were most likely to report problems with their infant's talking (23.1%), followed by behaviour (10.3%), but these showed no differences between groups. However, there were significant differences in the number of infants for whom all five ASQ-3 domain scores were normal: 190 (63.1%) in the NRT group compared with 163 (54.2%) in placebo (OR 1.47, 95% CI 1.06 to 2.05, $p = 0.02$) (see *Table 14*). For specific items that contributed to 'survival with no impairment', the only significant difference between groups was in the ASQ-3 'personal-social' domain; 254 (84.4%) had normal scores in the NRT group compared with 231 (76.7%) in the placebo group. However, although not significantly different, for infants in the NRT group, both the mean scores and the number of infants with normal scores were consistently higher in every ASQ-3 domain. The only other difference was with feeding problems (see *Table 14*), for which fewer participants allocated to NRT reported problems with their infants' feeding [18 (6.0%) NRT, 36 (12%) placebo (OR 0.47, 95% CI 0.26 to 0.85, $p = 0.011$)]. This outcome is not one used by the ASQ-3 questionnaire and did not contribute to 'survival with no impairment'.

TABLE 12 Infants born from singleton pregnancies: development and respiratory symptoms at 2 years

Infant development and respiratory outcomes within treatment groups						
	NRT, *n* (%)		Placebo, *n* (%)			
Number of respondents[a]	445		446			
Number with development outcomes allocated[b]	443		441			
Number of infant deaths (after delivery)	2		2			
Number with known developmental outcomes[c]	445		443			
Survival with no impairment[d]	323 (72.6)		290 (65.5)			
Definite developmental impairment[e]	48 (10.8)		64 (14.5)			
Suspected development impairment[f]	72 (16.2)		87 (19.6)			
Number with respiratory outcomes allocated[b]	444		444			
Respiratory problems[g]	132 (29.7)		111 (25.0)			
Findings from analyses investigating effects of treatment allocation on infant development and respiratory outcomes						
	Complete case analysis (singleton pregnancies)[h]		Complete case analyses (adjusted for clustering by twin pregnancies)[i,j]		Multiple imputation ITT analyses (singleton births) ($n = 1010$)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Survival with no impairment[d]	1.41 (1.05 to 1.87)	0.020	1.43 (1.08 to 1.91)	0.013	1.40 (1.05 to 1.86)	0.023
Definite developmental impairment[e]	0.71 (0.48 to 1.06)	0.093	0.73 (0.49 to 1.09)	0.13	0.71 (0.47 to 1.09)	0.12
Respiratory problems[g]	1.28 (0.95 to 1.73)	0.105	1.32 (0.98 to 1.77)	0.071	1.30 (0.97 to 1.74)	0.083

a Participants with singleton live births with a response to either questionnaire (PQ2 or HPQ) at 2-year follow-up.
b Owing to missing data, allocation of developmental outcomes was not possible for seven participants [NRT $n = 2$: HPQ (2); placebo $n = 5$: PQ2 (1), HPQ (4)]. Owing to missing data, there were three participants for whom an outcome of respiratory problems could not be attributed [NRT $n = 1$: HPQ (1); placebo $n = 2$: (PQ2 (1), HPQ (1)].
c Number with known development outcomes = number with development outcomes allocated + number of infant deaths after delivery. This is the denominator for the following three rows (survival without impairment, definite impairment and suspected impairment).
d Score above borderline score in ASQ-3 for all domains and no problems reported in additional sections of ASQ-3 (i.e. any hearing, talking, understanding, neuromotor or vision problems).
e That is, ASQ-3 score equal to or below the cut-point in ≥ 1 domain, HPQ indicates severe disability and/or severe developmental delay.
f That is, ASQ-3 borderline score in ≥ 1 domain, but no scores equal to or below the cut-point, and/or judged to have mild/moderate or possible impairment, disability or development delay from the additional questions on the PQ2 and/or HPQ including problems with hearing, speech, neuromotor, vision, behaviour or feeding problems.
g Any report of respiratory symptoms, asthma diagnosis, asthma medications or hospitalisation for respiratory problems at 2-year follow-up. Note: this denominator does not include post neonatal infant deaths as is not possible to attribute these infants with a respiratory outcome.
h Owing to missing data, denominators were different for each outcome: total infants with known developmental outcomes (including postnatal infant deaths) = 888 (445 + 443); total infants with known respiratory outcomes (excluding postnatal infant deaths) = 888 (444 + 444).
i There were 18 infants from nine twin pregnancies that had a PQ2 or HPQ returned ($n = 6$ NRT, $n = 12$ placebo).
j Owing to missing data, denominators were different for each outcome: total infants (including twins) with known developmental outcomes (including postnatal deaths) = 906 (451 + 455); total infants (including twins) with known respiratory outcomes (excluding postnatal infant deaths) = 906 (450 + 456).

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TABLE 13 Infants born from singleton pregnancies, broken down by questionnaire: development and respiratory symptoms at 2 years

Infant development and respiratory outcomes according to source of data and treatment group						
	NRT			Placebo		
	PQ2, *n* (%)	HPQ,[a] *n* (%)	PQ2 or HPQ,[a] *n* (%)	PQ2,[a] *n* (%)	HPQ,[a] *n* (%)	PQ2 or HPQ,[a] *n* (%)
Number of respondents[b]	301	144	445	301	145	446
Number with development outcomes allocated[a]	301	142	443	300	141	441
Survival with no impairment[c]	189 (62.8)	134 (94.4)	323 (72.9)	159 (53.0)	131 (92.9)	290 (65.8)
Definite developmental impairment[d]	47 (15.6)	1 (0.7)	48 (10.8)	64 (21.3)	0 (0)	64 (14.5)
Suspected development impairment[e]	65 (21.6)	7 (4.9)	72 (16.3)	77 (25.7)	10 (7.1)	87 (19.7)
Number with respiratory outcomes allocated[a]	301	143	444	300	144	444
Respiratory problems[f]	106 (35.2)	26 (18.2)	132 (29.7)	88 (29.3)	23 (16.0)	111 (25.0)
Findings from analyses investigating effects of treatment allocation on infant development and respiratory outcomes						
	Complete case analysis (singleton pregnancies)[g]		Complete case analyses (adjusted for clustering by twin pregnancies)[h,i]		Multiple imputation ITT analyses (singleton births) ($n = 1010$)	
	PQ2 OR (95% CI)[j]	PQ2 or HPQ OR (95% CI)[j]	PQ2 OR (95% CI)[k]	PQ2 or HPQ OR (95% CI)[k]	PQ2 or HPQ OR (95% CI)[l]	
Survival with no impairment[c]	1.52 (1.09 to 2.11)	1.41 (1.06 to 1.88)	1.58 (1.14 to 2.19)	1.44 (1.08 to 1.91)	1.36 (1.02 to 1.82)	
Definite developmental impairment[d]	0.67 (0.44 to 1.01)	0.71 (0.47 to 1.06)	0.66 (0.43 to 1.00)	0.73 (0.49 to 1.09)	0.72 (0.48 to 1.07)	
Respiratory problems[f]	1.38 (0.97 to 1.95)	1.28 (0.95 to 1.73)	1.40 (0.99 to 1.98)	1.32 (0.98 to 1.77)	1.30 (0.97 to 1.74)	

Note: unlike *Table 12*, for comparison purposes postnatal infant deaths are not included in the denominators in this table. In addition, if no questionnaire was returned, it was not possible to decide for these cases whether or not the death should be included in the denominator for PQ2 or HPQ analyses.

a Owing to missing data, allocation of developmental outcomes was not possible for seven participants [NRT $n = 2$: HPQ (2); placebo $n = 5$: PQ2 (1), HPQ (4)]. Owing to missing data, there were three participants for whom an outcome of respiratory problems could not be attributed [NRT $n = 1$: HPQ (1); placebo $n = 2$: PQ2 (1), HPQ (1)].

b Participants with singleton live births who responded to the questionnaire at 2-year follow-up.

c Score above the borderline score in ASQ-3 for all domains and no problems reported in additional sections of ASQ-3 (i.e. any hearing, talking, understanding, neuromotor or vision problems).

d That is, ASQ-3 score equal to or below the cut-point in ≥ 1 domain, HPQ indicates severe disability and/or severe developmental delay.

e That is, ASQ-3 borderline score in ≥ 1 domain, but no scores equal to or below the cut-point, and/or judged to have mild/moderate or possible impairment, disability or development delay from the additional questions on the PQ2 and/or HPQ including problems with hearing, speech, neuromotor, vision, behaviour or feeding problems.

f Any report of respiratory symptoms, asthma diagnosis, asthma medications or hospitalisation for respiratory problems at 2-year follow-up

g Owing to missing data, denominators were different for each outcome: total infants with known developmental outcomes = 884 (443 + 441); total infants with known respiratory outcomes = 888 (444 + 444).

h There were 18 infants from nine twin pregnancies that had a PQ2 or HPQ returned ($n = 6$ NRT, $n = 12$ placebo).

i Owing to missing data, denominators were different for each outcome: total infants (including twins) with known developmental outcomes = 902 (449 + 453); total infants with known respiratory outcomes = 906 (450 + 456).
Likelihood ratio test *p*-values for developmental outcomes from PQ2 only and combined PQ2 and HPQ responses, respectively.

j $p = 0.012$ and $p = 0.0120$ for survival with no impairment; $p = 0.057$ and $p = 0.092$ for definite developmental impairment; and $p = 0.073$ and $p = 0.10$ for respiratory problems.
Wald test *p*-values for developmental outcomes from PQ2 only and combined PQ2 and HPQ responses, respectively:

k $p = 0.006$ and $p = 0.013$ for survival with no impairment; $p = 0.051$ and $p = 0.13$ for definite developmental impairment; and $p = 0.060$ and $p = 0.071$ for respiratory problems.
Wald test *p*-values for multiple imputation analyses:

l $p = 0.035$ for survival with no impairment; $p = 0.11$ for definite developmental impairment; and $p = 0.083$ for respiratory problems.

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TABLE 14 Comparison of ASQ-3 domain scores and supplementary questions in PQ2 and HPQ at 2 years by trial group

	NRT	Placebo	OR (95% CI)[a]	*p*-value
***ASQ-3 domain scores*[b]**				
Number providing data	301	301		
Number (%) of mothers providing data for at least one domain	301 (100)	301 (100)		
Fine motor skills (mean, SD)	51.3 (8.0)	50.5 (7.5)		
Fine motor skills normal, *n* (%)	264 (87.7)	255 (84.7)	1.30 (0.82 to 2.08)	0.2668
Gross motor skills (mean, SD)	55.1 (8.9)	53.4 (11.1)		
Gross motor skills normal, *n* (%)	263 (87.4)	251 (83.4)	1.40 (0.87 to 2.22)	0.1469
Communication (mean, SD)	52.3 (13.2)	51.0 (14.4)		
Communication normal, *n* (%)	265 (88.0)	259 (86.1)	1.21 (0.75 to 1.96)	0.4273
Problem solving (mean, SD)[a]	45.6 (10.6)	44.3 (11.1)		
Problem solving normal, *n* (%)	247 (82.1)	231 (76.7)	1.34 (0.90 to 2.01)	0.1479
Personal-social (mean, SD)[a]	51.3 (9.7)	49.1 (10.4)		
Personal-social normal, *n* (%)	254 (84.4)	231 (76.7)	1.64 (1.08 to 2.48)	0.0184
All ASQ-3 domains normal	190 (63.1)	163 (54.2)	1.47 (1.06 to 2.05)	0.0201
Below normal cut-off score in ≥ 1 domains, *n* (%)	47 (15.6)	64 (21.3)	0.67 (0.44 to 1.02)	0.0588
Below normal cut-off score in ≥ 2 domains, *n* (%)	19 (6.3)	30 (10.0)	0.59 (0.32 to 1.08)	0.0811
ASQ-3 supplementary questions [n (%) reporting problem]				
Hearing				
n (%)	6 (2.0)	11 (3.7)	0.54 (0.20 to 1.51)	0.2326
Missing data	1 (0.3)	1 (0.3)		
Speech (talking)				
n (%)	72 (23.9)	67 (22.3)	1.11 (0.76 to 1.63)	0.5789
Missing data	1 (0.3)	1 (0.3)		
Speech (understanding)				
n (%)	21 (7.0)	22 (7.3)	0.93 (0.50 to 1.73)	0.8119
Missing data	1 (0.3)	1 (0.3)		
Neuromotor (walking, running, climbing)				
n (%)	10 (3.3)	17 (5.7)	0.59 (0.27 to 1.33)	0.1990
Missing data	1 (0.3)	1 (0.3)		
Vision				
n (%)	11 (3.7)	18 (6.0)	0.59 (0.27 to 1.28)	0.1784
Missing data	1 (0.3)	1 (0.3)		

TABLE 14 Comparison of ASQ-3 domain scores and supplementary questions in PQ2 and HPQ at 2 years by trial group (*continued*)

	NRT	Placebo	OR (95% CI)[a]	*p*-value
Behaviour[c]				
n (%)	30 (10.0)	32 (10.6)	0.91 (0.54 to 1.55)	0.7362
Missing data	2 (0.7)	1 (0.3)		
Feeding[c,d]				
n (%)	18 (6.0)	36 (12.0)	0.47 (0.26 to 0.85)	0.0107
Missing data	1 (0.3)	1 (0.3)		
HPQ				
Number of health professionals providing data	144	145		
n *(%) reporting problems*				
Hearing	3 (2.1)	2 (1.4)	1.52 (0.25 to 9.24)	0.649[e]
Speech				
n (%)	6 (4.2)	9 (6.2)	0.57 (0.19 to 1.70)	0.3110
Missing data	0 (0)	5 (3.5)		
Neuromotor				
n (%)	3 (2.1)	5 (3.5)	0.54 (0.12 to 2.44)	0.4167
Missing data	1 (0.7)	0 (0)		
Vision	7 (4.9)	4 (2.8)	1.93 (0.54 to 6.86)	0.2988
Behaviour[c]				
n (%)	8 (5.6)	4 (2.8)	2.12 (0.62 to 7.21)	0.229[e]
Missing data	3 (2.1)	0 (0)		
Feeding[c]				
n (%)	6 (4.2)	4 (2.8)	1.52 (0.42 to 5.51)	0.523[e]
Missing data	0 (0)	1 (0.7)		
Current health status, *n* (%)				
No disability	136 (94.4)	137 (94.5)		
Mild disability	3 (2.1)	5 (3.5)		
Moderate disability	2 (1.4)	0 (0)		
Severe disability	1 (0.7)	0 (0)		
Missing data	2 (1.4)	3 (2.1)		
Concerns about development				
n (%)	2 (1.4)	5 (3.5)		
Missing data	1 (0.7)	1 (0.7)		
Formal development assessment carried out *(if yes)*				
n (%)	1 (50.0)	4 (80.0)		
Missing data	1 (50.0)	1 (20.0)		

continued

TABLE 14 Comparison of ASQ-3 domain scores and supplementary questions in PQ2 and HPQ at 2 years by trial group (*continued*)

	NRT	Placebo	OR (95% CI)[a]	*p*-value
Overall development delay *(if yes)*, *n* (%)				
Mild	0 (0)	3 (75.0)		
Moderate	1 (50.0)	0 (0)		
Severe	0 (0)	0 (0)		
Missing data	1 (50.0)	1 (25.0)		

SD, standard deviation.
a Missing data for problem-solving (placebo $n = 2$), personal-social (placebo $n = 1$).
b ASQ-3 domain cut-off scores: fine motor skills = 35.16, gross motor skills = 38.07, communication = 25.17, problem solving = 29.78, personal-social = 31.54.
c Responses from these questions were not used for primary outcome 'survival with no impairment', but did contribute to the 'suspected developmental impairment'.
d Item not from ASQ-3, but added to PQ2.
e Unadjusted analyses and Wald test *p*-value used owing to small cell sizes (all other multivariate analyses adjusted for site and likelihood ratio test used).
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Respiratory problems at 2 years were reported in 132 (29.7%) and 111 (25.0%) of infants born in the NRT and placebo groups, respectively (OR 1.30, 95% CI 0.97 to 1.74, $p = 0.083$) (see *Table 12*). As with the development questions, more respiratory problems were reported on participant-completed questionnaires [194 (32.2%) of returned PQ2s compared with 49 (17.0%) of HPQs included reports of respiratory symptoms]. A more detailed breakdown of singleton infants' respiratory problems is given in *Table 15*, including outcomes that were collected 1 year after delivery. The only significant difference was in the number of participants reporting at 2 years that their child had ever experienced any wheeze or whistling in their chest [74 (24.6%) NRT, 49 (16.3%) placebo (OR 1.72, 95% CI 1.14 to 2.59, $p = 0.0099$)].

Maternal smoking outcomes after delivery

After delivery, both point prevalence and prolonged abstinence from smoking was low and relapse to smoking gradually increased (*Table 16*). During the 2-year follow-up, the numbers of participants in the NRT and placebo groups reporting abstinence from smoking since their quit dates were 28 (5.4%) and 17 (3.2%), respectively, at 6 months, and 19 (3.7%) and 11 (2.1%), respectively, at 1 year. By 2 years after delivery, 15 (2.9%) allocated to NRT and nine (1.7%) allocated to placebo remained abstinent (OR 1.71, 95% CI 0.74 to 3.94, $p = 0.20$). *Table 17* shows that participants who did not provide any smoking data at the three postnatal follow-up time points were more likely to have been smokers at delivery, which is consistent with the assumption used in analyses of smoking behaviour, i.e. that participants who were lost to follow-up should be counted as smokers.

Additionally, the sensitivity analysis that further investigated this assumption found that varying the relationship between missingness and smoking status had almost no impact on ORs that compared smoking cessation rates between trial groups at 2 years. Varying the IMOR between 0 and 1 (in an unadjusted analysis) altered the OR for the effect of treatment group on self-reported prolonged abstinence since delivery from 1.117 (IMOR = 0) to 1.107 (IMOR = 1), the OR for self-reported 7-day cessation from 1.068 to 1.059, and the OR for prolonged abstinence from smoking between quit date and 2 years after delivery from 1.713 to 1.707. This provides added reassurance that treating those with missing outcome data as smokers had no substantial impact on the study findings for smoking outcomes.

TABLE 15 Infant respiratory outcomes between 6 months and 2 years after delivery

Infant respiratory outcomes (singleton pregnancies)[a]	NRT ($n = 503$)	Placebo ($n = 507$)	OR (95% CI)[b]	*p*-value	Adjusted OR (95% CI)[c]	*p*-value
1 year after delivery[d]						
Number (%) of respondents	288 (57.3)	295 (58.2)				
Wheeze or whistling						
n (%)	62 (21.5)	57 (19.3)	1.18 (0.78 to 1.77)	0.4356	1.00 (0.65 to 1.55)	0.9820
Missing data	0 (0)	1 (0.3)				
If yes, how many attacks in last year? *n* (%)						
0	6 (9.7)	8 (14.0)				
1–3	41 (66.1)	33 (57.9)				
4–12	12 (19.4)	10 (17.5)				
> 12	1 (1.6)	4 (7.0)				
Missing data	2 (3.2)	2 (3.5)				
How often has sleep been disturbed due to wheezing? *n* (%)						
Never	38 (61.3)	38 (66.7)				
< 1 night/week	14 (22.6)	12 (21.1)				
≥ 1 night/week	7 (11.3)	5 (8.8)				
Missing data	3 (4.8)	2 (3.5)				
Doctor diagnosed asthma, *n* (%)[e]	13 (4.5)	15 (5.1)	0.95 (0.44 to 2.06)	0.9005	0.97 (0.42 to 2.24)	0.9421
Dry cough at night						
n (%)	27 (9.4)	20 (6.8)	1.46 (0.79 to 2.69)	0.2219	1.26 (0.65 to 2.42)	0.4906
Missing data	1 (0.4)	1 (0.3)				
Seen by paediatrician or chest specialist about chest or breathing problems						
n (%)	28 (9.7)	28 (9.5)	1.06 (0.61 to 1.86)	0.8263	0.99 (0.55 to 1.78)	0.9680
Missing data	1 (0.4)	1 (0.3)				
2 years after delivery (maternal questionnaire: PQ2)						
Number (%) of respondents	301 (59.8)	301 (59.4)				
Respiratory related hospital admissions						
n (%)	39 (13.0)	34 (11.3)	1.22 (0.74 to 2.01)	0.4340	1.47 (0.85 to 2.53)	0.1615
Missing data	0 (0)	1 (0.3)				
Problems with chest or breathing						
n (%)	53 (17.6)	48 (16.0)	1.21 (0.78 to 1.88)	0.3881	1.22 (0.76 to 1.95)	0.4079
Missing data	1 (0.3)	1 (0.3)				
Wheeze or whistling						
n (%)	74 (24.6)	49 (16.3)	1.72 (1.14 to 2.59)	0.0087	1.79 (1.14 to 2.79)	0.0099
Missing data	0 (0)	2 (0.7)				

continued

TABLE 15 Infant respiratory outcomes between 6 months and 2 years after delivery (*continued*)

Infant respiratory outcomes (singleton pregnancies)[a]	NRT ($n = 503$)	Placebo ($n = 507$)	OR (95% CI)[b]	*p*-value	Adjusted OR (95% CI)[c]	*p*-value
If yes, how frequently? *n* (%)						
Every day	5 (6.8)	3 (6.1)				
Every week	10 (13.5)	3 (6.1)				
≤ once/month	58 (78.4)	42 (85.7)				
Missing data	1 (1.4)	1 (2.0)				
Doctor diagnosed asthma[e]						
n (%)	31 (10.3)	19 (6.3)	1.79 (0.98 to 3.28)	0.0547	1.74 (0.91 to 3.32)	0.0889
Missing data	0 (0)	1 (0.3)				
Medicines taken for cough/wheeze/chest problems						
n (%)	51 (16.9)	39 (13.0)	1.43 (0.90 to 2.27)	0.1231	1.42 (0.86 to 2.32)	0.1653
Missing data	0 (0)	2 (0.7)				
2 years after delivery (HPQ)[f]						
Number (%) of respondents	144 (28.6)	145 (28.6)				
Problems with chest or breathing						
n (%)	26 (18.1)	23 (15.9)	1.04 (0.57 to 1.89)	0.8953	1.05 (0.56 to 1.98)	0.8730
Missing data	1 (0.7)	1 (0.7)				

a The denominators for respiratory outcomes are based on participants with singleton births who responded at each follow-up time point (i.e. the outcomes for twin pregnancies have been excluded).
b Adjusted for centre only (as a stratification factor).
c Adjusted for centre, COT at baseline, partner's smoking status and age at leaving full-time education.
d Respiratory symptoms were collected at 1 year but were not listed as outcomes in the protocol.
e Diagnosed defined as a doctor ever having said your child has asthma.
f Twenty-six participants have been excluded who responded to the HPQ, as they had already provided PQ2 data ($n = 12$ NRT, $n = 14$ placebo).

TABLE 16 Maternal smoking outcomes between 6 months and 2 years after delivery

Maternal smoking outcomes[a]	NRT ($n = 521$)[a]	Placebo ($n = 529$)[a]	OR (95% CI)[b]	*p*-value	Adjusted OR (95% CI)[c]	*p*-value
6 months after delivery						
Number (%) of respondents	335 (64.3)	338 (63.9)				
Self-reported prolonged abstinence since delivery, *n* (%)[d]	57 (10.9)	50 (9.5)	1.18 (0.79 to 1.76)	0.4254	1.23 (0.81 to 1.87)	0.3251
Self-reported 7-day cessation, *n* (%)	56 (10.8)	52 (9.8)	1.11 (0.74 to 1.65)	0.6228	1.15 (0.76 to 1.74)	0.5032
Prolonged abstinence from smoking between quit date and 6 months after delivery, *n* (%)[e]	28 (5.4)	17 (3.2)	1.71 (0.92 to 3.17)	0.0836	1.84 (0.98 to 3.46)	0.0547
1 year after delivery						
Number (%) of respondents	288 (55.3)	300 (56.7)				
Self-reported prolonged abstinence since delivery, *n* (%)[d,f]	33 (6.3)	29 (5.5)	1.16 (0.70 to 1.95)	0.5640	1.18 (0.69 to 2.04)	0.5437
Self-reported 7-day cessation, *n* (%)[f]	55 (10.6)	37 (7.0)	1.57 (1.01 to 2.43)	0.0413	1.55 (0.98 to 2.46)	0.0574
Prolonged abstinence from smoking between quit date and 1 year after delivery, *n* (%)[e,f]	19 (3.7)	11 (2.1)	1.78 (0.84 to 3.78)	0.1273	2.20 (0.98 to 4.92)	0.0475
2 years after delivery						
Number (%) of respondents (PQ2 only)[g]	302 (58.0)	304 (57.5)				
Self-reported prolonged abstinence since delivery, *n* (%)[d]	23 (4.4)	21 (4.0)	1.11 (0.61 to 2.04)	0.7274	1.03 (0.53 to 1.98)	0.9409
Self-reported 7-day cessation, *n* (%)	45 (8.6)	43 (8.1)	1.06 (0.69 to 1.65)	0.7789	0.98 (0.62 to 1.56)	0.9483
Prolonged abstinence from smoking between quit date and 2 years after delivery, *n* (%)[e]	15 (2.9)	9 (1.7)	1.71 (0.74 to 3.94)	0.2036	1.96 (0.82 to 4.70)	0.1204

a For the smoking outcomes, participants who did not provide data or were lost to follow-up are assumed to be smokers and included in the denominator.
b Adjusted for centre only (as a stratification factor).
c Adjusted for centre, COT at baseline, partner's smoking status and age at leaving full time education.
d Self-reported prolonged abstinence since delivery defined as having smoked ≤ 5 times since the baby was born.
e Participant met criteria for prolonged abstinence at delivery (i.e. positive primary outcome) plus self-reported smoking ≤ 5 times since the baby was born.
f Cessation information was collected at 1 year but was not listed as an outcome in the protocol.
g Smoking status was only ascertained in the PQ2.

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TABLE 17 Sensitivity analyses of smoking outcomes: association between smoking status at delivery and smoking outcomes reported by participants at the three follow-up time points

Smoking status at delivery	Smoking data reported[a]	No smoking data reported[b]	*p*-value[c]
6-month follow-up	**N = *656***	**N = *325***	
Smoking at delivery, *n* (%)	579 (88.3)	313 (96.3)	< 0.001
Abstinent at delivery, *n* (%)	77 (11.7)	12 (3.7)	
1-year follow-up	**N = *571***	**N = *410***	
Smoking at delivery, *n* (%)	511 (89.5)	381 (92.9)	0.065
Abstinent at delivery, *n* (%)	60 (10.5)	29 (7.1)	
2-year follow-up	**N = *589***	**N = *392***	
Smoking at delivery, *n* (%)	523 (88.8)	369 (94.1)	0.004
Abstinent at delivery, *n* (%)	66 (11.2)	23 (5.9)	

This table is based on the 981 participants who provided primary outcome data at delivery.
a Smoking data reported: any smoking question with a response (smoked in the last week, smoked since delivery and smoking frequency).
b No smoking data reported: missing data for all three smoking questions.
c Chi-squared test *p*-value.

Secondary analysis: adherence with nicotine patches and impairment

Data on the presence or absence of impairment at 2 years of age were available for 884 singleton infants and this was the sample size for analysis. Reported adherence with nicotine patches was heavily skewed and skewness was increased by coding placebo group participants' adherence with nicotine patches as zero. We analysed adherence with nicotine-containing patches in three categories: 0 days' use and, for participants reporting at least use of one patch (1 day's use), we used a median split within these participants (median = 10 days' use) to create two categories of 'up to median use' (1–10 days) and 'above median use' (11–56 days). *Table 18* shows the numbers in each adherence category, the distribution of survival with no impairment within these categories and crude and adjusted OR for the association between adherence categories and survival with no impairment, using 0 days' adherence as a reference category. Adjustment was made for partner's smoking status, which was found to be associated with outcome in the multivariable model. Results in *Table 18* suggest that participants in the highest category of adherence with nicotine-containing patches were more likely to have infants who had survived without impairments (adjusted OR 1.72, 95% CI 1.22 to 2.57).

TABLE 18 Secondary analyses of smoking outcomes: associations between maternal adherence with nicotine-containing patches and infants' survival with no impairment

Reported number of days on which nicotine patches used (adherence category)	Number (%) participants in adherence category (*N* = 884[a])	Number (%) infants from each adherence category that survived with no impairment (*N* = 613)	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
0	474 (53.6)	313 (66.0)	1.00 (not estimable)	1.00 (not estimable)
1–10 (≤ median)	197 (22.3)	136 (69.0)	1.15 (0.80 to 1.64)	1.12 (0.78 to 1.60)
11–56 (> median)	213 (24.1)	164 (77.0)	1.72 (1.19 to 2.50)	1.77 (1.22 to 2.57)

a Excludes four infants who died before follow-up and for whom there were no outcome data.
b Adjusted for partner smoking status.
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Chapter 4 Health economics analysis report

Introduction

The cost-effectiveness of NRT use by the general population has been established[57,58] and a number of studies have investigated the potential cost saving of smoking cessation interventions in pregnancy,[59] but few have used empirical data on costs to calculate the incremental cost-effectiveness of smoking interventions.[60]

This chapter reports on an economic evaluation conducted alongside the SNAP trial, addressing the value for money and cost-effectiveness of NRT patches and behavioural support compared with behavioural support alone.

The objectives were:

i. to compare the costs associated with the control and intervention strategies
ii. to estimate the consequences of these alternatives
iii. to assess cost-effectiveness of NRT patches used in addition to behavioural support on smoking cessation at delivery
iv. to use EQ-5D data collected at 6 months after delivery to model longer-term cost–utility of NRT used for smoking cessation in pregnancy
v. to explore the potential for providing monetary estimates of the long-term impacts on the child of their differential birth outcomes.

Methods

Overview

A cost-effectiveness analysis was undertaken to compare NRT patches and behavioural support to behavioural support only, for women who were smoking during pregnancy. The main outcome for the economic evaluation was biochemically validated abstinence from smoking between a quit date and delivery. As recommended by the National Institute for Health and Care Excellence (NICE),[61] analyses were conducted from a NHS and personal-social services viewpoint, including direct health effects (maternal smoking cessation) and costs (or cost savings) to the NHS. Mothers were eligible for inclusion in the SNAP trial if they were between 12 and 24 weeks' gestation and outcomes were collected at delivery (up to 42 weeks' gestation); therefore, the time horizon of the trial was up to 7 months.

Cost estimation

There were two main components to the costing of the control and intervention strategies: first, the costs of the inputs required for the interventions and second, the resources used to care for each woman and her infant during the period between randomisation and delivery.

Intervention costs

The cost inputs for the interventions included training and staff time to deliver the behavioural support (band 7 midwives), CO monitors (breath testing equipment), consumables (NRT patches and consumables associated with CO breath testing) and overheads for premises.

Training costs were calculated for 2 days of training for 10 midwives (salary costs at a mid-point of band 7), provided by an NHS SSS advisor (salary costs an average of band 5 and 6) at an NHS SSS, including

overheads[62] and the cost of 1060 15-page manuals that were used both to guide intervention delivery and as information for participants.

At baseline, participants were given a 4-week supply of NRT patches at a dose of 15 mg per 16 hours. Participants in the placebo arm were given identical patches, without the active ingredients; however, these placebo patches represent a research cost and were therefore excluded from the costing. The placebo group will therefore be referred to as the control group throughout *Chapter 4*. At the baseline hospital antenatal visit, midwives also provided up to 1 hour of behavioural support. The time midwives spent providing face-to-face behavioural support was recorded and multiplied by salary and overhead costs to calculate a cost per session. All women provided a CO reading at baseline.

Three sessions of behavioural support were provided over the telephone on the quit date and at 3 days and 1 month after this. For each woman, successful calls were logged and these varied in length and although call times were not recorded, call lengths were estimated by a trial midwife to be the following: 2 minutes for the quit date call, 3.5 minutes for the call 3 days after the quit date, 4 minutes for the call 1 month after the quit date to self-reported smokers and 2 minutes for 1 month calls to self-reported non-smokers. The call for self-reported non-smokers was shorter as, during this, midwives would arrange a home visit to validate smoking cessation and provide face-to-face behavioural support. Midwives would try to contact participants several times if they did not get through; therefore, the cost of failed call attempts was also estimated. Failed calls were assumed to be 30 seconds per call attempt, with three call attempts per woman who did not speak to the midwife on the appropriate day, and for each successful call we also assumed a 30 second failed call attempt.

Women who self-reported not smoking at 1 month after the quit date were visited at home to have a session of behavioural support and for CO validation. Women biochemically verified as abstinent at 1 month were offered a second 4-week supply of patches. At delivery, midwives used CO monitors to verify smoking status, which took approximately 10 minutes of midwife time.

To calculate the costs of CO monitoring per use at baseline, 1 month and delivery, the costs of the equipment and associated consumables were totalled and divided by the total number of uses. The cost of four CO monitors was not depreciated as the life expectancy was estimated to be around 5 years (the length of the trial). One calibration kit was required for every two monitors. Based on usage evidence from the trial we assumed semidisposable mouthpiece adaptors were changed after 60 uses, batteries were changed every 240 uses and one disposable mouth piece and alcohol-free wipe was required for each use.

Resource-use costs

Resource-use data were collected from trial participants and from medical records. We collected data from participants on their use of NHS SSS (either face to face or by telephone). Information about antenatal hospital admissions and mode of delivery was collected from maternal medical records and data on admissions to neonatal special care came from infant medical records.

Valuation of costs

All data were valued in monetary terms and unit costs were reported in pounds sterling for the financial year 2009–10 (representing the mid-point of the trial). Any costs occurring in prior or later price years were inflated or deflated using the Hospital and Community Health Services pay and prices index.[63] As for the economic evaluation, we considered trial follow-up until to 7 months post randomisation only and no discounting was required. For standard NHS health care, UK unit costs were applied from national sources, increasing the generalisability of the results. *Table 19* presents a summary of resource use and unit costs, with the calculation of the costs detailed in *Calculating costs*.

TABLE 19 Unit costs (2009–10 prices)

	Unit cost (£)	Unit	Source of unit cost
Interventions			
15 mg per 16 hours NRT patches	1.28	Patch	The Health and Social Care Information Centre[64]
Dispensing cost	2.14	Prescription	www.psnc.org.uk/pages/archive.html[65]
Band 7 midwife time (including overheads)	35.28	Per hour	The NHS Staff Council,[66] Curtis[63]
Antenatal midwife home visit	45.00	Visit	Department of Health[67]
CO monitors and consumables	0.47	Per use	Estimated from the SNAP trial
Printing	0.96	15-page manual	Estimated from the SNAP trial
Resource use			
NHS SSS			
Face to face (individual or group session)	11.69	Session	NICE[62]
Telephone call (4-minute call)	1.27	Call	NICE[62]
Text message	0.16	Message	NHS Connecting for Health[68]
Maternal antenatal admission	1180.48	Admission	Department of Health[67]
Mode of delivery			
Unassisted vaginal delivery	1454.28	Obstetric delivery	Department of Health[67]
Assisted vaginal delivery	2095.06		
Caesarean section	3028.66		
Baby admission to neonatal unit	7532.31	Admission	Department of Health,[67] The Health and Social Care Information Centre[69]

Calculating costs

In order to calculate the costs of face-to-face NHS SSS sessions, a weighted average cost of individual and group sessions was calculated based on information from a NICE costing report.[62] Salary and overheads information from the same report were used to calculate the cost per minute of a phone call (assumed to be the same length as the calls reported for providing behavioural support).

The cost of mode of delivery was established by calculating a weighted average of unit costs of the different modes of delivery activities recorded in NHS reference costs. A similar method was used to calculate an average cost of a maternal antenatal admission, based on antenatal observations and investigations.

To calculate the cost of the admission of a baby to neonatal care, a weighted average of bed-day costs for neonatal critical care from NHS reference costs (£618) was multiplied by a weighted average length of stay for neonates with major diagnoses (12.2 days) according to Hospital Episode Statistics for 2009–10.[69]

Quantities of services used were multiplied by the relevant unit costs to estimate overall cost profiles for women in the trial.

Outcome measures

The measure of health benefit for the economic evaluation was the same as the primary measure of clinical effectiveness in the SNAP trial: self-reported and biochemically validated maternal smoking

cessation from quit date to immediately before delivery. Temporary smoking lapses of up to a total of five cigarettes (on up to five occasions) were permitted.

The National Institute of Health and Care Excellence (2008)[61] recommend that health outcomes should be measured in quality-adjusted life-years (QALYs) to facilitate comparisons between different health-care programmes. However, QALYs, commonly calculated from the generic health-related quality-of-life tool the EQ-5D,[70] may be inappropriate in a study including pregnant women. Generic quality of life studies have shown poorer quality-of-life in early pregnancy compared with population norms for women of child-bearing age[71] and substantial changes in quality of life, particularly declining physical functioning and vitality, occur over the course of pregnancy.[72] These dramatic changes in quality of life between pregnancy and the post-partum period would likely mask any potential short-term quality-of-life gains from smoking cessation. Nevertheless, EQ-5D data were collected at 6 months after delivery, within the postal questionnaire sent to participants, which is described in *Chapter 2*, *Methods*.

Analysis

An incremental cost-effectiveness analysis was undertaken, following the NICE guidance for health-care evaluations,[61] comparing the additional costs of NRT patches with behavioural support alone, as well as the additional benefits, to give a cost per additional quitter.

The incremental cost-effectiveness ratio (ICER) calculates the mean cost of the intervention group over and above the control and divides by the mean difference in health benefits. The following formula is for ICER, for which Δ represents change, C represents the costs, E represents the effects and subscript I and C refer to the intervention and control, respectively.

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{\bar{C}_I - \bar{C}_C}{\bar{E}_I - \bar{E}_C} \quad (1)$$

All analyses were conducted on an ITT basis in which all randomised participants were included and analysed in the groups to which they were randomised. Analyses were conducted in Microsoft Excel, 2010, version 14.0.7113.5005 (32-bit) (Microsoft Corporation, Redmond, WA, USA).

There were no missing data on the effectiveness outcome (validated smoking cessation from quit date to delivery), as any women without validated cessation were assumed to be smokers. Missing data for cost items were imputed using average costs for the appropriate arm of the trial, allowing the base-case analysis to be completed for all women in the trial and, therefore, with the same quit rate as the main effectiveness analyses in *Chapter 3*.

Cost data were bootstrapped to account for skewness, sampling with replacement observations 1000 times to generate a new population of sample means with an approximate normal distribution. Bootstrap results were presented graphically using a cost-effectiveness plane[73] to show the uncertainty around the mean estimates of incremental costs and effects.

The EQ-5D data collected at 6 months after delivery were converted into a single index summary score after applying UK population values.[74] Descriptive statistics for EQ-5D data are presented by trial group. We planned to use 6-month EQ-5D data in conjunction with smoking status utility values based on quit rates at 2 years after delivery to calculate the longer-term costs and benefits of differential quit rates between the intervention and the control arms.

Results

A total of 1050 women were recruited to the SNAP trial: 521 and 529 in the NRT and placebo arms, respectively.

Costs

The breakdown of intervention costs for the trial arms are presented in *Table 20*. Costs for providing behavioural support and CO monitoring were relatively equal in both arms, although costs of the 4-week home visits were slightly higher in the NRT group than the control group (£14.31 compared with £9.46, respectively) because rates of self-reported smoking cessation were higher in the NRT group at 4 weeks (25.1% compared with 14.0%). The mean total intervention cost in the control group was £47.75. The comparative cost of providing behavioural support and CO monitoring was £52.24 in the NRT group, and the total mean cost including NRT patches was £98.31.

Table 21 reports the resources utilised in the two arms of the trial. Use of NHS SSS, maternal antenatal hospital admissions and admissions to neonatal care were similar in the two groups, although more women had a caesarean section in the NRT group than in the control group: 20.9% and 16.1%, respectively.

Quantities of services used were multiplied by the relevant unit costs in *Table 19* to calculate the cost of resources used for each woman and total costs were calculated by adding resource-use costs to intervention costs. *Table 22* summarises total mean costs for the trial groups. Mean intervention costs were significantly higher in the NRT group, at a mean difference of £50.56. Total mean resource-use costs were £40.26 higher in the NRT group and overall costs were, therefore, £90.81 higher for this group; however, these differences were not statistically significant.

TABLE 20 Intervention costs by allocated group (prices in £ 2009–10)

Intervention	NRT group, *n* = 521, mean (SD)	Control, *n* = 529, mean (SD)
Training cost (per face-to-face session)		
Training costs for midwives (per hospital behavioural support session)	4.18	4.18
Treatment cost (per participant)		
NRT patches	46.07 (15.57)	0.00
Behavioural support session at hospital (including CO monitoring)	21.72 (4.18)	22.00 (4.62)
Telephone calls[a]		
Calls on quit date	1.30 (0.27)	1.30 (0.27)
Calls on quit date + 3 days	1.97 (0.64)	1.94 (0.66)
Calls on quit date + 1 month (self-reported smokers)	1.78 (0.88)	1.91 (0.87)
Calls on quit date + 1 month (self-reported non-smokers)	1.07 (0.27)	1.00 (0.24)
Home visit at 4 weeks for behavioural support for self-reported non-smokers (including CO monitoring)	14.31 (21.14)	9.46 (18.47)
10 minutes to monitor CO levels at delivery	5.92 (1.61)	5.96 (1.54)
Average intervention costs (per participant)	98.31 (35.21)	47.75 (19.03)

SD, standard deviation.
a Calls include the cost of failed attempts.

TABLE 21 Health-care service utilisation

	NRT, *N* = 521	Placebo, *N* = 529
NHS SSS		
Missing data, mean *n* (%)	36 (6.9)	33 (6.2)
Face-to-face session, mean *n* (SD)	0.18 (0.6)	0.16 (0.6)
Telephone call, mean *n* (SD)	2.06 (2.3)	1.84 (2.0)
Text message, mean *n* (SD)	0.80 (1.8)	0.71 (1.7)
Maternal antenatal hospital admission		
Missing data, mean *n* (%)	10 (1.9)	12 (2.3)
Admissions, mean *n* (%)	79 (15.2)	82 (15.5)
Mode of birth		
Missing data, mean *n* (%)	10 (1.9)	14 (2.7)
Unassisted vaginal birth, mean *n* (%)	362 (69.5)	386 (73.0)
Assisted vaginal birth, mean *n* (%)	40 (7.7)	44 (8.3)
Caesarean section, mean *n* (%)	109 (20.9)	85 (16.1)
Baby admitted to neonatal unit		
Missing data, mean *n* (%)	10 (1.9)	14 (2.7)
Admissions,[a] mean *n* (%)	37 (7.1)	39 (7.3)

SD, standard deviation.
a Including multiple births (four twin births in the NRT group and eight in the control group. *N* = 1062 babies).

TABLE 22 Total costs (prices in £ 2009–10)

Type of cost	NRT group, *n* = 521, mean (SD)	Control group, *n* = 529, mean (SD)	Difference[a] (95% CI)
Intervention costs	£98.31 (35.21)	£47.75 (19.03)	£50.56 (47.13 to 53.99)
Resource-use costs	£2571.56 (2393.63)	£2531.31 (2384.34)	£40.26 (–248.76 to 329.27)
Total costs	£2669.87 (2394.09)	£2579.06 (2385.68)	£90.81 (–198.31 to 379.94)

SD, standard deviation.
a Difference = cost in the intervention group minus cost in the control group.

Outcomes

Any women without biochemical validation of quitting were assumed to be smokers. In the NRT group, 49 out of 521 women (9.4%) were abstinent with biochemical validation from quit date to delivery and in the control group this was true for 40 out of the 529 women (7.6%), a non-significant difference of 1.8% (see *Chapter 3*).

Cost-effectiveness analysis and uncertainty

Table 23 presents the ICER, combining the differential costs of the treatment groups, with the differential quit rates. NRT plus behavioural support was found to be somewhat more costly than behavioural support alone, but with a slightly higher quit rate. This generates an ICER of £4926 per quitter. If decision-makers are willing to pay > £4926 for an additional quitter, then NRT would be the preferred option; otherwise, behavioural support alone should be adopted.

TABLE 23 Results of the incremental cost-effectiveness analysis (prices in £ 2009–10)

	NRT group, $n = 521$	Control group, $n = 529$
Cost (SD)	£2669.87 (£2394.09)	£2579.06 (£2385.68)
Quit rate	9.4%	7.6%
ICER	£4926 per quitter	
Bootstrapped 95% CI of ICER	–£114,128 to £126,747	

SD, standard deviation.

A cost-effectiveness scatter plot was produced based on the bootstrapping, including 1000 resamples of the costs and effects data. The bootstrapped results were plotted on a cost-effectiveness plane, visually displaying the uncertainty around the mean differences in costs and benefits between the trial arms (*Figure 9*). The majority of the plots in the scatter plot fall in the north-east quadrant, indicating that NRT is likely to be more effective but more costly than behavioural support alone. However, the scatter plot also shows the uncertainty around the cost estimates.

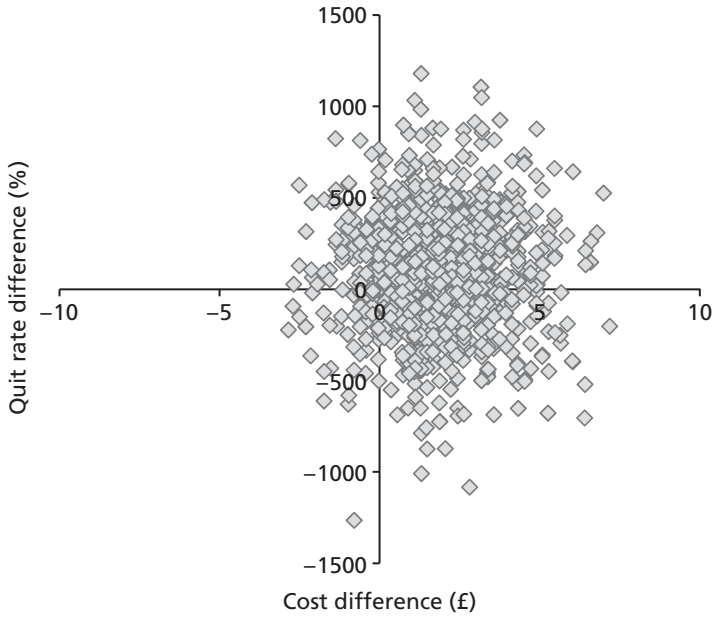

FIGURE 9 Cost-effectiveness plane.

Sensitivity analyses

To allow for uncertainty in our estimates of costs and consequences, we conducted a sensitivity analysis excluding 12 women who had multiple births (four twin births in the NRT group and eight in the control group) who are more likely to have complicated pregnancies and deliveries. *Table 24* shows the total costs and quit rates in the singleton-only analysis. Quit rates were very similar (+ 0.08% in the NRT group and –0.46% in the control group); total costs were lower in the singleton-only analysis, but by a similar amount in both groups (–£64.37 in the NRT group and –£72.32 in the control group). The corresponding ICER generated for singleton births was £4156 per quitter.

Projecting longer-term costs and benefits (objectives 4 and 5)

We had planned to use EQ-5D data collected 6 months after delivery in conjunction with smoking status utility values based on quit rates at 2 years to calculate the longer-term costs and benefits of differential quit rates between the intervention and control arms. These longer-term analyses were impeded for a number of reasons. First, there was only a small, non-significant difference in quit rates between groups. Second, there was no difference in EQ-5D scores between the groups at 6 months (*Table 25*). Third, there was great uncertainty in cost estimates in the alongside trial economic analysis, which would be amplified in any longer-term projections, generating non-robust estimates. Fourth, there were no significant differences in birth outcomes, precluding monetary estimates of the long-term impacts on the child.

TABLE 24 Results of the incremental cost-effectiveness analysis (singleton births only) (prices in £ 2009–10)

	NRT group, $n = 517$	Control group, $n = 521$
Cost (SD)	£2604.73 (£2198.98)	£2505.97 (£2184.43)
Quit rate	9.48%	7.10%
ICER	£4156	
Bootstrapped 95% CI of ICER	(–£65,994 to £82,059)	

SD, standard deviation.

TABLE 25 Mean EQ-5D index scores at 6 months

	NRT group, $n = 335$	Control group, $n = 338$
Missing data	3	11
Mean (95% CI)	0.896 (0.875 to 0.917)	0.894 (0.873 to 0.916)

Summary

- Total mean costs were £90.81 higher in the NRT group, representing around a 3% difference in costs between trial groups. The higher costs in the NRT group were mainly attributable to the cost of the NRT patches (mean = £46.07).
- The ICER associated with NRT patch use was estimated at £4926 per quitter. Sensitivity analyses including only singleton births resulted in an ICER of £4156 per quitter; however, there were very wide CIs around these estimates, indicating a high level of uncertainty. This uncertainty occurred because there were only small differences in total costs between the groups, but the total cost for each group was affected by high within-group variability, which was particularly influenced by costs attributable to antenatal or neonatal admissions. For example, in both groups, approximately 7% of babies were admitted to neonatal care and each had an admission cost of £7532, compared with an average between-group difference in costs of only £91. Therefore, as between-group cost differences are small, if women with these high resource-use costs happen to fall in one arm by chance, this could change the result of the ICER.
- If decision-makers are willing to pay > £4156 for an additional quitter, then NRT should be adopted; otherwise, behavioural support alone should be adopted.

Chapter 5 Discussion

Principal findings

Smoking outcomes

This trial demonstrates that, at 12–24 weeks' gestation, supplementing behavioural support with a 15 mg per 16 hours nicotine patch was no more effective than a placebo in promoting sustained smoking cessation throughout pregnancy. Clinically and statistically significant higher biochemically validated cessation rates were obtained with NRT at 1 month, but this effect did not persist into later pregnancy. After childbirth, self-reported, prolonged cessation since quit dates agreed in pregnancy were between 1% and 2% higher in women who had been randomised to NRT, but these small differences were not statistically significant.

Maternal and fetal birth outcomes

Maternal and fetal birth outcomes were generally very similar with almost no statistically significant differences between groups. Caesarean section births were more frequent in the NRT group and this difference was statistically significant (OR 1.45, 95% CI 1.05 to 2.01).

Infant outcomes at 2 years

At 2 years of age, singleton infants born to trial participants who had been allocated NRT were significantly more likely to have no developmental impairment than those born to participants in the placebo group. Very similar findings occurred whether using data obtained from only participant-completed questionnaires (PQ2) or data from both PQ2 and HPQ questionnaires combined. Additionally, very similar findings were noted in pre-specified analyses, which (1) included twin births and adjusted for clustering of outcomes and (2) applied multiple imputation methods to investigate the assumption that data missing were missing at random (i.e. that missingness was associated with baseline characteristics but not with the outcome itself). No significant difference in reported rates of infants' respiratory problems was noted.

Economic outcomes

Total mean costs were £90.81 higher in the NRT group, with the excess largely attributable to the cost of NRT patches (mean cost of patches = £46.07). For singleton births only, an ICER of £4156 per quitter was derived; therefore, if decision-makers are willing to pay this amount for each additional quitter, then NRT, used in addition to behavioural support, would be the preferred option. The results showed no differences between groups in birth outcomes or health status as measured by EQ-5D at 6 months postnatal. Therefore, it was not possible to estimate a cost per QALY or model long-term QALYs.

There has been little research investigating the cost-effectiveness of smoking cessation interventions in pregnancy. Although a number of studies have investigated the potential cost saving of smoking interventions for pregnant women,[59] these studies have mainly been conducted in the USA with restricted perspectives, particularly omitting data relating to infant outcomes. Only two studies have thus far reported QALYs: one being a simple model based on an American trial[60] and another a hypothetical model constructed for NICE guidance.[75] Although these studies suggest that smoking cessation in pregnancy may be cost-effective, they are mainly poor quality and the settings and methods used preclude comparison with our results. Furthermore, with the exception of the NICE model,[75] none of the studies has explored the cost-effectiveness of NRT.

Adherence

Adherence to both types of patch was low. Although adherence was not a trial outcome, the pattern of adherence may be related to, and at least partially explain, smoking cessation and birth outcomes and, consequently, requires discussion.

Limitations and strengths

Overall comments

This study is by far the largest of its type. Prior to the SNAP trial being completed, in the five previous RCTs of NRT for smoking cessation in pregnancy, only 695 women had been randomised.[30] We believe that this is the first trial to test whether or not a smoking cessation intervention delivered in pregnancy can affect infant outcomes. The study is also original in that in previous trials of NRT in pregnancy, maternal smoking behaviour has been investigated for only up to 3 months after childbirth,[34,35] whereas we followed up participants and infants until 2 years after birth. We can find only one trial testing any smoking cessation intervention (i.e. a non-NRT intervention) for pregnant women that attempted to monitor smoking behaviour up to and beyond 2 years after childbirth.[76] However, in this study, smoking data were not sought from all trial participants at predetermined time points, but was obtained opportunistically at multiple, different times between 8 and 54 months after childbirth, rendering smoking behaviour data difficult to interpret.

Outcomes recorded at and before delivery

By carefully implementing a double-blind, placebo-RCT design, most of the biases that could have influenced outcomes at these time points have been minimised. However, we did not ask women which treatment they perceived they had been allocated to and hence have no data to confirm whether participants remained blinded to their treatment allocations or, indeed, guessed their allocation. Consequently, it is possible that some participants may have correctly determined their treatment allocation and, if this had occurred, we would be unable to quantify its extent. However, unblinded trials of NRT in pregnancy tend to overestimate the treatment effect from NRT[30] and we found no effect at delivery. Additionally, loss of blinding among trial participants would not explain the very different pattern of findings with respect to efficacy at 1 month and delivery.

The strengths of the study appear to outweigh its weaknesses and overall findings reported are likely to be valid. Target sample size was achieved; therefore, the study was adequately powered to detect the anticipated 9% difference in cessation rates between trial arms. However, it remains possible that NRT could work for smoking cessation in pregnancy, but with a lesser impact because smaller treatment effects (i.e. $< 9\%$ absolute difference) would not necessarily have been detected by a trial of this size. At baseline, groups were well balanced for all variables recorded, including those with potential to influence findings; therefore, chance differences between groups are unlikely to explain these. Additionally, the high outcome ascertainment rates, which were very similar in both groups, reduce the likelihood that ascertainment bias influenced study outcomes. Birth outcome ascertainment rates were particularly high and, as RMs who extracted data on birth outcomes and AEs from medical records were blinded to patch allocation, these data are particularly likely to be free from bias. Similarly, when participants reported abstinence from smoking, equally high biochemical verification rates were obtained from participants in both trial groups, minimising any bias in the reporting of outcomes that may have occurred.

The validity of trial findings could have been affected by unintentional variation in treatments provided for participants, or in any support or treatment sought by them that was additional to trial interventions. For example, differences between NRT and placebo group outcomes would have been minimised if trial participants had also been prescribed NRT from their GPs, issued with it by local NHS SSSs or had bought it from pharmacies. However, only 2.2% in the placebo group (and 2.5% allocated NRT) reported using NRT obtained outside of the trial for more than 20 days and it seems unlikely that this level of usage, which was very similar in both trial arms, would have unduly affected findings. Finally, if participants were

inadequately prepared for, or inadequately instructed about using, NRT, then this could have affected their ability to use NRT sufficiently well for any impacts of this treatment to become apparent. However, the trial RMs, trained to English national cessation standards, provided accompanying behavioural support and, in both trial groups, participants' rates of accessing subsequent additional support were similarly low. This low level of additional support may have affected overall quit rates. However, the level of behavioural support was comparable with that used in 'low intensity support' nicotine patch trials conducted among non-pregnant subjects in which NRT has been found effective (RR 1.78, 95% CI 1.49 to 2.12),[18] for which NRT caused a near doubling of cessation at the 1-month follow-up point. Taken together, these points suggest that the behavioural support delivered in the trial probably gave women appropriate instruction in using NRT and, as no differences were seen between groups in additional support received by trial participants, this is unlikely to explain trial findings.

Infant outcomes at 2 years

Key strengths are that no previous trials have tested the impact of a smoking cessation intervention in pregnancy on infant outcomes and we achieved high (around 88%) outcome ascertainment rates combined with low withdrawal and missing data rates at 2 years. Follow-up rates were very similar in both trial groups, reflecting the fact that staff conducting follow-up were blind to participants' treatment allocations. Additionally, we used caution when classifying questionnaires reporting infants' development and respiratory symptoms and manually checked individual questionnaire responses, when necessary. We were cautious when categorising open-response questionnaire items, generally allocating infants as experiencing 'suspected', rather than 'definite' impairment, based on responses to these. A similar approach was also taken with open response items on respiratory problems. Consequently, it is unlikely that infants classed as having 'no impairment' were actually impaired or that infants categorised as experiencing 'respiratory problems' had not had these. Finally, with respect to the primary outcome monitored at 2 years, 'survival with no impairment', we obtained the same pattern of findings in all pre-planned analyses, irrespective of whether or not parental or health professional reports of infant health were used, or whether or not twins were included. This consistency of findings suggests that the overall finding, that NRT used in pregnancy has a beneficial effect on child development as measured by ASQ-3, is likely to be valid and unlikely to have occurred by chance.

A limitation is that the ASQ-3 is generally used as a screening tool to identify potential impairments that are subsequently confirmed or refuted by detailed face-to-face assessment.[43] We cannot, therefore, be certain that the parent-reported 'snapshot' of child development obtained via completed ASQ-3 questionnaires is perfectly valid for allocating infants as experiencing 'definite' or 'no impairment'. However, a previous UK obstetric trial used 30-item ASQ questionnaires to detect neurosensory disability and, in a subgroup of infants, compared a range of failed and non-failed ASQ scores with outcomes from 'gold standard' face-to-face developmental assessments.[77] This found that, when used for detecting neurodevelopmental problems in a cohort of participants and infants that was similar to those in this study, the 30-item ASQ compared well with standard face-to-face assessments and had a negative predictive value of 99.5% (95% CI 98.3% to 99.9%).[77] If, in our study, the ASQ-3 performed similarly and if we had employed gold standard face-to-face assessments, one would expect very few infants categorised by ASQ-3 as having no impairment to then be diagnosed with developmental problems in face-to-face assessments. Our use of a self-report questionnaire completed by health professionals to help decide whether or not infants had developmental impairments could also be criticised. Using this method of data collection, we do not know whether or not those completing questionnaires did so with reference to medical records or other knowledge of infants. However, very similar questionnaires have been used in previous authoritative cohort studies[78] and incorporation of such health professional data into analyses in this trial did not affect outcomes.

Smoking outcomes at 2 years

This was the first trial of a smoking cessation intervention to monitor longitudinal smoking rates within pregnant trial participants for as long as 2 years after delivery; therefore, the data are novel. Although data were self-reported and we obtained no information on smoking behaviour for around 40% of participants,

sensitivity analysis suggested that our assumption that non-respondents at 2 years were smokers was appropriate.

Economic analyses

We present a within trial incremental cost-effectiveness analysis, calculating the cost per additional quitter associated with NRT patch use. Owing to the issues around measuring the EQ-5D in a population of pregnant women, we did not propose to calculate QALYs, which reduces the comparability of our cost-effectiveness outcome with different health-care programmes. The trial did not find a difference in outcomes that would have enabled the projection of longer-term costs and benefits of NRT use, thus precluding conclusions about the long-term cost-effectiveness of NRT patch use in pregnancy.

Interpretation and generalisability

Smoking outcomes

In contrast to the negative primary outcome recorded at delivery, the increased cessation until 1 month after randomisation was of a similar magnitude to that seen following NRT use by non-pregnant smokers.[18] The lack of a statistically significant longer-term effect from NRT may be explained by the low adherence rates in the trial. One reason for the apparently low adherence is that many participants were specifically instructed to not use NRT when smoking and many failed to quit and restarted smoking. However, this does not explain why only 58% (101/173) of participants who were abstinent at 1 month accepted a second month's supply of NRT. Other NRT trials in pregnancy have reported similarly low rates of adherence: two studies of NRT patches found median durations of NRT use of 2 weeks[34] and 3 weeks,[27] and, in a trial that tested 2-mg nicotine gum, this was used for just over 5 weeks.[35] Outside pregnancy, most smokers who attempt to quit with NRT discontinue this within 1 month because they either start smoking again or they believe it is not working.[79] Nevertheless, despite such reports of adherence with NRT being lower than recommended,[79] trials[18] and cohort data from routine clinical care[80] both demonstrate that NRT used by non-pregnant smokers is effective for smoking cessation. Adherence with NRT is potentially an important influence on the efficacy of this treatment in pregnancy; NRT cannot have an effect if it is not used and reduced adherence with NRT in later pregnancy could explain the lack of effect shown at delivery. Therefore, potential influences on adherence in the trial require further exploration.

Trial participants often discontinue treatments after experiencing AEs or side effects; however, only 8.8% of women in the NRT group reported stopping patches after AEs. In previous similar trials, the discontinuation rate was 12% for nicotine gum[35] and 4.4% for nicotine patches or placebos.[27] These AE rates are much lower than participants' rates of early treatment discontinuation and hence can only partially explain this. Treatment discontinuation could be explained by increases in maternal nicotine and cotinine clearance in pregnancy; increases of 60% and 140%, respectively, have been reported to occur by 25 weeks' gestation.[81] Such increases would be expected to reduce NRT-generated nicotine levels and increase users' withdrawal symptoms. It is possible that, for NRT to consistently ameliorate women's nicotine withdrawal symptoms and be effective throughout pregnancy, a higher dose is required.[82] However, this trial did not include assessment of nicotine metabolism and did not assess withdrawal symptoms. In addition, factors other than increases in metabolism may explain low NRT adherence rates in this and previous trials.

In summary, this trial provides no evidence that NRT, as the 15 mg per 16 hours transdermal patch, is effective for smoking cessation in pregnancy. Women used the patches for shorter periods than recommended and this could explain negative trial findings. It is possible that, even with the low adherence displayed by trial participants, NRT actually does have a positive effect and, with a larger sample size, the 1.8% absolute difference in favour of treatment with NRT would have become statistically significant. However, a recent meta-analysis of this trial's findings with all previous similar studies ($n = 1745$) does not suggest this. In this analysis, the RR for cessation in later pregnancy after using NRT

compared with control was 1.33 (95% CI 0.93 to 1.91).[31] Even if the small difference between groups in this trial does represent a real effect of NRT that has not been statistically proven, it seems unlikely that, based solely on this small effect on maternal smoking behaviour, NRT used in pregnancy would be considered clinically useful. The number needed to treat (calculated using trial data) is 54, which means that if the magnitude of effect observed in this trial were to be found statistically significant (e.g. in a future meta-analysis), 54 women would require treatment with NRT to produce one successful quitter. This success rate would be unlikely to impress clinicians who would probably be inclined to use other methods of cessation support for pregnant smokers.

Other outcomes measured at delivery

Rates of adverse outcomes were similar between groups with the exception of caesarean deliveries, which were unexpectedly more frequent in the NRT group. This is difficult to explain and is likely to be a chance occurrence. However, caution is warranted when interpreting the overall similarity in birth outcomes between trial groups. Because many adverse birth outcomes are quite rare, some comparisons may have limited power and the low rate of treatment adherence makes it difficult to attribute the presence or absence of differences in birth outcomes to NRT.

Outcomes measured after delivery

This study has provided the first evidence that a smoking cessation intervention delivered to pregnant women can influence the development of their offspring. We found that NRT, used in pregnancy for smoking cessation, without having any statistically significant, long-term effect on maternal smoking in pregnancy, had a positive impact on subsequent child development. The most likely explanation for this impact lies in the altered smoking behaviour of women who were randomised to NRT. For example, the transient doubling of quit rates in the first month after trial enrolment and until around 20 weeks' gestation could have occurred at a crucial time for infants' brain maturation, resulting in the greater survival to 2 years of age with no developmental impairment. The slightly higher, but non-significant, quit rates observed from delivery until 2 years and the reduced accompanying exposure of infants to domestic environmental tobacco smoke may also have had additional positive effects. If the impact of NRT on infants is mediated through increased maternal smoking cessation, any effective smoking cessation intervention used by pregnant women would be expected to have similar effects. However, it remains possible that any protective impact of NRT on infants' development arises directly from the impact of nicotine itself and is not mediated by reduced fetal or infant exposure to tobacco smoke toxins. Irrespective of whether the impact of NRT on infants is direct or mediated (indirect), this trial is reassuring about NRT use in pregnancy. Although in controlled laboratory studies, nicotine has been shown to cause fetal tachycardia, albeit to a lesser extent than smoking,[21,83,84] this trial provides no evidence that NRT is harmful. Similarly, as nicotine is a neurotoxin and can cause behavioural problems in young rodents,[21,83] there has previously been concern that NRT might harm infants' developing nervous systems and that it could cause behavioural problems and poorer academic achievement in smokers' children.[22] However, study findings clearly suggest that nicotine is unlikely to be responsible for these problems.

As mentioned above, findings from this trial require confirmation; future studies of NRT and other smoking cessation interventions in pregnancy should follow-up infants and trial participants for at least 2 years after delivery to facilitate this. Additionally, the cohort of trial infants from this trial should be followed after 2 years, to determine whether or not impacts on child development attributable to NRT persist into childhood. If further studies can replicate findings or confirm that these benefits persist later into childhood, then this would provide reassurance that these findings did not occur by chance, which is important both scientifically and economically. Intervention costs were relatively low (< £100 per participant) and, should the impacts on infants identified in this study be confirmed, it is likely that NRT used in pregnancy for smoking cessation would be viewed as cost-effective, potentially generating cost savings for the NHS.

The trial had a relatively pragmatic design, with reasonably broad inclusion and few exclusion criteria, therefore, results are likely to be generalisable to most pregnant smokers. However, women recruited to the trial were between 12 and 24 weeks' gestation and, therefore, our results may be less applicable to

those trying to quit using NRT earlier or later in their pregnancy. For example, at earlier gestations, nicotine metabolism may not yet have increased and so the dose of NRT used in this trial may be sufficient to help such women to quit successfully. Our 1-month findings suggest that this could be likely and as we found no safety issues, future studies could consider including women earlier in pregnancy. Similarly, as we only included women who smoked at least 5 cigarettes a day, the results cannot necessarily be extrapolated to those who are very light smokers and less addicted to nicotine and they may also be more likely to be able to successfully quit with the dose of NRT used in this trial.

Conclusions

The NRT transdermal nicotine patches (15 mg per 16 hours) used in pregnancy for smoking cessation caused a transient, doubling of cessation that disappeared by delivery. Infants born to women in the NRT group were more likely to survive without impairment to 2 years of age, but there were no differences in the experience of respiratory symptoms between groups.

Recommendations for research (in priority order)

1. Randomised controlled trials investigating the efficacy and safety of NRT when used for smoking cessation in pregnancy should test higher than standard dose NRT such as:

    i. patches delivering more than 15 mg nicotine in 16 hours (e.g. 21 mg in 24 hours)
    ii. 4-mg gum used as required or
    iii. a NRT patch combined with any 'on demand' short-acting NRT (e.g. gum or nasal spray).

2. To investigate whether or not apparent differences in infants' outcomes persist into childhood. RCTs investigating NRT for smoking cessation in pregnancy should assess infants' clinical and economic outcomes after 2 years of age.
3. RCTs investigating the efficacy of NRT or other interventions for smoking cessation used in pregnancy should include an assessment of impacts on infants using outcomes similar to those employed in SNAP.
4. Reasons for pregnant women's low levels of adherence with NRT should be investigated; findings could be used in future trials to enhance participants' adherence with NRT.
5. Increases in nicotine metabolism, occurring as pregnancy progresses, could explain the reduced efficacy that NRT has in later pregnancy. Further research should investigate this hypothesis.

Implications for health care

In the UK and some other health-care systems, NRT has become an established component of cessation support for pregnant women. Although the SNAP trial found no evidence that standard dose NRT is effective for smoking cessation, there was also no evidence that this is less safe than smoking; indeed, the study suggests that NRT use in pregnancy is safe in terms of infant outcomes assessed at 2 years and may have a protective effect on infant development. Although this is the first time that a smoking cessation intervention has been observed to have a beneficial effect on pregnant smokers' offspring, this finding provides support for interventions involving NRT in pregnancy. Overall, our findings provide no evidence that NRT should not be used in pregnancy and instead suggest that NRT might be beneficial in this setting.

Effects of NRT on infant development are likely to be mediated through the small, observed changes in maternal smoking. There are good reasons to believe that NRT used at higher doses might affect both maternal smoking and infant development more substantially and trials of higher-dose NRT are indicated. Other cessation interventions delivered in pregnancy may have similar impacts on infants, but this requires confirmation. Choosing between interventions for use with pregnant smokers is, therefore, difficult; both

'self-help' and behavioural smoking cessation support promote maternal smoking cessation and improve birth outcomes. However, while there is no evidence that NRT has these effects, NRT does appear to have a potentially important protective effect on infant development. Therefore, this study supports offering NRT to pregnant women who smoke; however, any such offer should take account of the somewhat stronger research evidence from other studies indicating that behavioural or 'self-help' support both have beneficial effects on smoking behaviour in pregnancy.

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Contributions of authors

All authors made substantial contributions to conception and design and/or to acquisition of data and/or to analysis and interpretation of data as listed below.

All authors were involved in drafting the manuscript or revising it critically for important intellectual content.

All authors approved the final version.

Sue Cooper (SNAP Trial Manager, Senior Research Fellow) was involved in design, conduct, acquisition of data, analysis and report writing phases.

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Neil Marlow (Professor of Neonatology) was involved in design, conduct, analysis and report writing phases, in particular the follow-up of infants after delivery.

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Jaspal Taggar (Clinical Lecturer, statistics) was involved in the analysis and interpretation of follow-up data and in the report writing phase.

Holly Essex (Research Fellow, health economics) was involved in the conduct, analysis, interpretation and report writing for the health economics chapter.

Steve Parrott (Senior Research Fellow, health economics) was involved in the conduct, analysis, interpretation and report writing for the health economics chapter.

Anne Dickinson (Clinical Trial Research Assistant) was involved in the design, conduct and acquisition of data and in the report writing phase.

Rachel Whitemore (Administrative Assistant) was involved in the design, conduct and acquisition of data during the follow-up phase and in the report writing phase.

Tim Coleman (SNAP Trial Chief Investigator and Professor of Primary Care) was involved in design, conduct, analysis and report writing phases.

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University of Nottingham: Dan Simpkins (Clinical Trials Unit – database), Luis Vaz (assisting with secondary adherence analyses), Yvanna Kurlak, Clare Randall and John Taylor (assisted with trial administration).

University of Dundee: Sheila Sharp (sample analysis – baseline and 1-month COT).

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Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, Lewis S. A randomized trial of nicotine-replacement therapy patches in pregnancy. *N Engl J Med* 2012;**366**:808–18.

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Appendix 1 Antenatal screening questionnaire

Ante-natal Questionnaire

Dear Madam

We are looking at ways to improve the lifestyle and health of pregnant women and babies in the womb. As one part of this study we are asking all women attending for routine ultrasound examinations to fill in a 5-minute questionnaire.

We would like to invite you to participate in this study. If you are happy to fill in this 6-question questionnaire then tick the box marked 'YES' and then complete the form, following the instructions on it. If you do not wish to complete the questionnaire then just tick the box marked 'NO'.

YOUR ANSWERS WILL BE TOTALLY CONFIDENTIAL AND SEEN ONLY BY THE RESEARCH MIDWIFE AND RESEARCHERS AT THE UNIVERSITY OF NOTTINGHAM.

Many thanks for your help.
Best wishes

Dr Tim Coleman
Division of Primary Care, University of Nottingham, QMC Medical School, Nottingham. NG7 2RD.

For most questions, just tick the relevant box, like this ☑

CONSENT FORM

I am happy to fill in the antenatal questionnaire. I understand that I am under no obligation to take part and can withdraw at any stage.

Yes ☐ No ☐

Signed: ……..… Date: ……

Ante-natal Questionnaire

☐☐☐☐ ID

Centre number: ☐☐☐

Date ...../...../200.....

(tick one box)

1. Have you smoked any cigarettes or tobacco in the last week?
   - *Yes* ☐ 1
   - *No* ☐ 2

2. Are you between 12 and 25 weeks into your pregnancy?
   - *Yes* ☐ 1
   - *No* ☐ 2
   - *Don't know* ☐ 3

*If you answered '**No**' to either of the two questions above**,** you have finished and can hand back the questionnaire. If you answered '**Yes**' or '**Don't know**', continue below.*

(tick one box)

3. How often do you usually smoke cigarettes or tobacco?
   - *Every day* ☐ 1
   - *On most days* ☐ 2
   - *Less than most days* ☐ 3

*If you answered: '**less than most days**' to question 3 above you have finished and may hand the questionnaire back. If not, please continue.*

(tick one box)

4. **Before you became pregnant**, how often did you usually smoke cigarettes or tobacco?
   - *Every day* ☐ 1
   - *On most days* ☐ 2
   - *Less than most days* ☐ 3

*If you answered: '**less than most days**' to question 4 above you have finished and may hand the questionnaire back. If not, please continue.*

(tick one box)

5. Are you interested in stopping smoking during this pregnancy?

Yes ☐ 1

No ☐ 2

Not sure ☐ 3

*If you answered '**No**' to question 5 above, you have finished and can hand back the questionnaire. If you answered '**Yes**' or '**Not sure**', please read on and continue.*

Nicotine patches help smokers to stop smoking and smokers who use patches are twice as likely to manage to stop for good. Experts recommend that pregnant women who smoke should use patches to try to stop smoking because they believe that these are safer for expectant mothers and their babies than continuing to smoke.

Researchers from your hospital have teamed up with Nottingham University and are running a research project to find out if nicotine patches help pregnant women to stop smoking.

6. Are you interested in taking part in this project?

Yes ☐ 1

No ☐ 2

***IF YOU ARE INTERESTED** and answered '**Yes**' to question 6 above, please COMPLETE YOUR CONTACT DETAILS BELOW AND TELL THE PERSON WHO IS COLLECTING THIS QUESTIONNAIRE.*

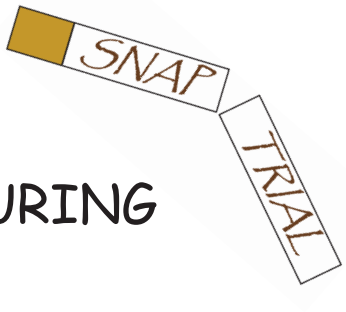
Name		
Address		
Telephone	Day	
	Evening	
	Mobile	
Best time to contact		

You have now finished.

THANK YOU FOR YOUR HELP

Appendix 2 Smoking cessation manual

THE SNAP TRIAL'S GUIDE TO STOPPING SMOKING DURING PREGNANCY



Written by

Clare Mannion
Stop Smoking Service Manager/ Co investigator
March 2007

Introduction

Stopping smoking at any stage during your pregnancy will help your baby to have the best start in life and the benefits for you and your baby will start the day you stop. So congratulations on taking the first step to stopping for good. We will be supporting you through the whole process and we hope this guide will help support you in your stop attempt.

So what are the benefits?

Benefits of Quitting Smoking for Mum and Baby
For Mum

- Less likely to feel sick during pregnancy
- Less likely to be admitted to hospital
- More likely to have a successful pregnancy
- Less likely to miscarry the baby
- Reduce the risk of bleeding
- Reduce the risk of still birth
- Reduce the risk of a complicated delivery

For Baby

- More likely to grow and develop normally
- Have a better chance of surviving the first year of life
- Less likely to be delivered too early
- Less likely to have complications at delivery
- Less likely to develop chest infections, asthma and ear problems including glue ear and possible hearing loss
- Less likely to have behavioural problems
- Less likely to become a smoker later on in life

Breathing in secondhand smoke will

- Double the risk of cot death
- Double the risk of breathing problems
- Double the chance of your child being admitted to hospital

So, what kind of smoker are you?

Is smoking "just a habit" or are you addicted? To quit successfully you will need to understand your addiction, the more you understand the easier it will be for you.

Please complete the following with your advisor and it will help you to understand your level of addiction to nicotine.

Fagerstrom Test for Nicotine Dependence

1. How soon after you wake up do you smoke your first cigarette?
- After 60 minutes (0)
- 31-60 minutes (1)
- 6-30 minutes (2)
- Within 5 minutes (3)

2. Do you find it difficult to refrain from smoking in places where it is forbidden?
- No (0)
- Yes (1)

3. Which cigarette would you hate most to give up?
- The first in the morning (1)
- Any other (0)

4. How many cigarettes per day do you smoke?
- 10 or less (0)
- 11-20 (1)
- 21-30 (2)
- 31 or more (3)

5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?
- No (0)
- Yes (1)

6. Do you smoke even if you are so ill that you are in bed most of the day?
- No (0)
- Yes (1)

Your score was: _____

Your level of dependence on nicotine is: _____

0-2	Very low dependence
3-4	Low dependence
5	Medium dependence
6-7	High dependence
8-10	Very high dependence

Scores under 5: "Your level of nicotine dependence is still low. You should act now and stop smoking before your level of dependence increases. "

Score of 5: "Your level of nicotine dependence is moderate. If you don't quit soon, your level of dependence on nicotine will increase until you become seriously addicted. Act now to end your dependence on nicotine."

Score over 7: "Your level of dependence is high. You aren't in control of your smoking – it is in control of you! When you start to quit, the skin patches that you are issued with could help you to break your addiction."

Understand what triggers *your* smoking: control your habit

Every smoker has a regular pattern of smoking and many have smoked this way for years. You probably smoke at particular times in situations which give you strong urges for cigarettes. For example, some smokers always light up after a meal.

Your 'Smoking Diary' can help you to find out **when** you are most likely to want a cigarette and what **triggers** your urges to smoke.

Fill in the first couple of diary days **now with your stop smoking advisor** and see if any of the tips provided in this manual can help you fight your urges to smoke.

Fill in more diary days **before you stop smoking**. Find out all of your triggers to smoking and think carefully about how you can avoid these and resist your urges to smoke.

How to fill in your diary

- Time – When did you have the need to smoke?
- Place – Where were you? What were you doing?
- With – Who were you with at the time?
- Mood – How did you feel just before you smoked - bored, angry, tired?
- Need – Was your need to smoke strong? Yes or No?
- Number of Cigarettes – How many did you smoke?

Your smoking diary - Day 1

Time	Place	With	Mood	Need	No of Cigs

Your Smoking Diary – Day 2

Time	Place	With	Mood	Need	No of Cigs

Your smoking diary

Time	Place	With	Mood	Need	No of Cigs

Your smoking diary

Time	Place	With	Mood	Need	No of Cigs

My 'triggers'

1.....

2.....

3.....

4.....

How to deal with my triggers

1.....

2.....

3.....

4.....

Before you quit, remember to look at your diary. Think about the difficult or tempting situations in which you find it difficult not to smoke (your '***triggers***') and try to work out how you are going to deal with these situations / triggers. We've listed some tips below, but you may want to go through your diary with your advisor to get more ideas for avoiding smoking at these times.

TIPS

Tip 1. Think about when you enjoy a cigarette and when you need one and then think again about how you are going to cope and not smoke at these times.

Example: If you always have a cigarette in the morning with a coffee, then stop having coffee – if you have fruit juice or water instead, you should not want to smoke as much.

Tip 2. If you feel the need to eat something instead of having a cigarette why not try a healthy food like sugar free gum or fruit. Research shows that taking dextrose (sugar) tablets regularly throughout the day (one pack per day) for the first 2 weeks after quitting reduces your urge to smoke. NB Please do not use these if you are a diabetic or have pregnancy related diabetes!

Tip 3. Identify diversions or distractions that can replace your desire to smoke.

Examples: Physical exercise (e.g. fast walking or swimming), texting a friend or even brushing your teeth can all take your mind off smoking.

Tip 4. Remember cravings increase in intensity for up to 3 minutes and then subside. Plan how you will distract yourself – ask your advisor about relaxation techniques.

Pro's and Con's

To help you prepare to stop smoking here's another exercise you may like to do. List what you think the benefits are to continuing to smoke and give them a score out of 10, with 10 being very important to you. Next list the reasons why you want to stop smoking and again give them a score out of 10. Then add up each column, if the column on the right has a higher score then you are ready to stop smoking.

Benefits of Smoking	Score	Reasons why I want to stop smoking	Score

If you score the benefits of smoking score more highly than your reasons for stopping, then you can talk about this with your advisor.

What is the cost of smoking to me and how much will I save?

Fill in the chart below and you might be surprised at how much you are spending on cigarettes. Work out the amount that you spend on smoking each week and, more importantly, how much you could save.

Time Quit	Amount Saved	What could I buy
1 week		
2 weeks		
1 month		
3 months		
1 year		

Are you ready to quit yet???

You've spent some time now planning and preparing for your quit attempt and this is really important. The more ready you are the more likely you are to succeed. Keep focused on your reasons for stopping and plan changes to your routine to help you through some of the difficult situations you may come across.

So all you need to do now is to set a date!!! Talk this through with your advisor and pick a day which suits you best. Pick a day that is no longer than 2 weeks away so that you don't lose your motivation.

MY QUIT DATE IS

Complete the list below ***the day before you quit***

- Set up your house and car as a smoke free zone
- Get rid of all your ashtrays, lighters, matches, and cigarettes
- Put up smoke free signs around the house to remind friends and family
- Buy some sugar free gum and dextrose tablets
- Keep your advisor's number nearby
- Plan some treats for yourself with the money that you will save

Ongoing support: Regular contacts with your stop smoking advisor in the early stages of your stop attempt have been proven to increase your chances of quitting forever. Please make sure we have the right contact details for you so that your advisor can ring/email/text you to offer you the support and advice you need to quit and to answer any questions you may have.

Secondhand Smoke (breathing in other peoples smoke!)

Did you know that?

- Non smokers who are exposed to secondhand smoke in the home, have a 25% increased risk of heart disease and lung cancer and is a cause of respiratory disease, cot death, middle ear disease and asthmatic attacks in children.

- More than 17,000 children under 5 are admitted to hospital every year because of secondhand smoke.

- Breathing in other peoples smoke will also increase your risk of relapsing back to smoking

What can you do?

- It will help you to stop smoking if your friends and family help you.

- If they smoke, one way that friends and family can help is by stopping too or ***at least*** not smoking in front of you.

- If no one smokes in your company, then you and your baby will not be exposed to any cigarette or tobacco smoke poisons and you will find it easier to stop for good.

- ***Tell*** friends and family that you are stopping smoking and ***ask*** them to help ***you and your baby*** by stopping themselves or not lighting up in front of you.

More Top Tips

- Make sure you have your patches ready by the bedside so that you can put one on as soon as you wake up. We would suggest you have some scissors nearby too, so that you can get your patch out the pack without any trouble or panic!

- Don't use any moisturisers or shower gels with added moisturiser on the area where you put your patches. You need to keep your skin here dry to make sure that the patches will stick. Choose a non hairy site too!

- Change the site where you stick your patch every day. The skin here may be irritable for the first 20 minutes after putting on the patch, but this should settle. If skin irritation continues for longer than 20 minutes, remove it and contact your stop smoking advisor

- Take your patch off each night and replace with a fresh patch each morning

- Take each day at a time, don't think too far ahead, short term goals will be more achievable

- Stay away from those triggers and keep yourself busy

- Count the number of cigarettes you have not had since stopping, it soon mounts up!!

- Start planning treats for yourself – 20 cigarettes per day can cost £1,820 per year. What could you do with all that cash?

- Think about yourself as a non smoker

- Do a crossword

- Send an email or text to a friend to tell them how well you're doing

- Drink juice instead of tea or coffee

- Brush your teeth and remind yourself how horrible cigarettes tasted

- If you are stressed, write down what's stressing you out, and then tear the piece of paper up into tiny pieces
- Compile a list of things that you have been meaning to do for ages and do them!
- Go to the cinema or watch a DVD
- Ring your stop smoking advisors and tell them how well you're doing
- Remind yourself of why you wanted to stop smoking

And Finally……

The Snap Trial team would like to thank you for participating in this very important study and wish you a great success in stopping smoking.

Thank You!!!

Useful Contact Details

NHS Pregnancy Smoking Helpline
0800 169 9 169

Textphone
0800 169 0 171

For Online Support and Information
gosmokefree.co.uk

NHS Asian Tobacco Helplines
0800 169 0 881 URDU
0800 169 0 882 PUNJABI
0800 169 0 883 HINDI
0800 169 0 884 GUJARATI
0800 169 0 885 BENGALI

For general information visit
www.ash.org.uk

If you change your contact details or have any questions about the SNAP Trial please contact us – thank you

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Appendix 3 Smoking, Nicotine and Pregnancy Trial protocol

Protocol for the SNAP (Smoking Nicotine And Pregnancy) Trial

Final Version 7.0, 11 June 2009

EudraCT No: 2004-002621-46
REC number: 04/Q1604/85
CTA number: 03057/0002/001-0001

Please ensure that you are using the most recent version of the protocol

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**
Trial sponsor: Contact name	**University of Nottingham** Mr Paul Cartledge Head of Research Grants and Contracts Research Innovation Services King's Meadow Campus Lenton Lane Nottingham NG7 2NR
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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.

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

1. Maternal mortality
2. Mode of delivery

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

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

15. Data monitoring and ethics committee

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

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

17. Funding

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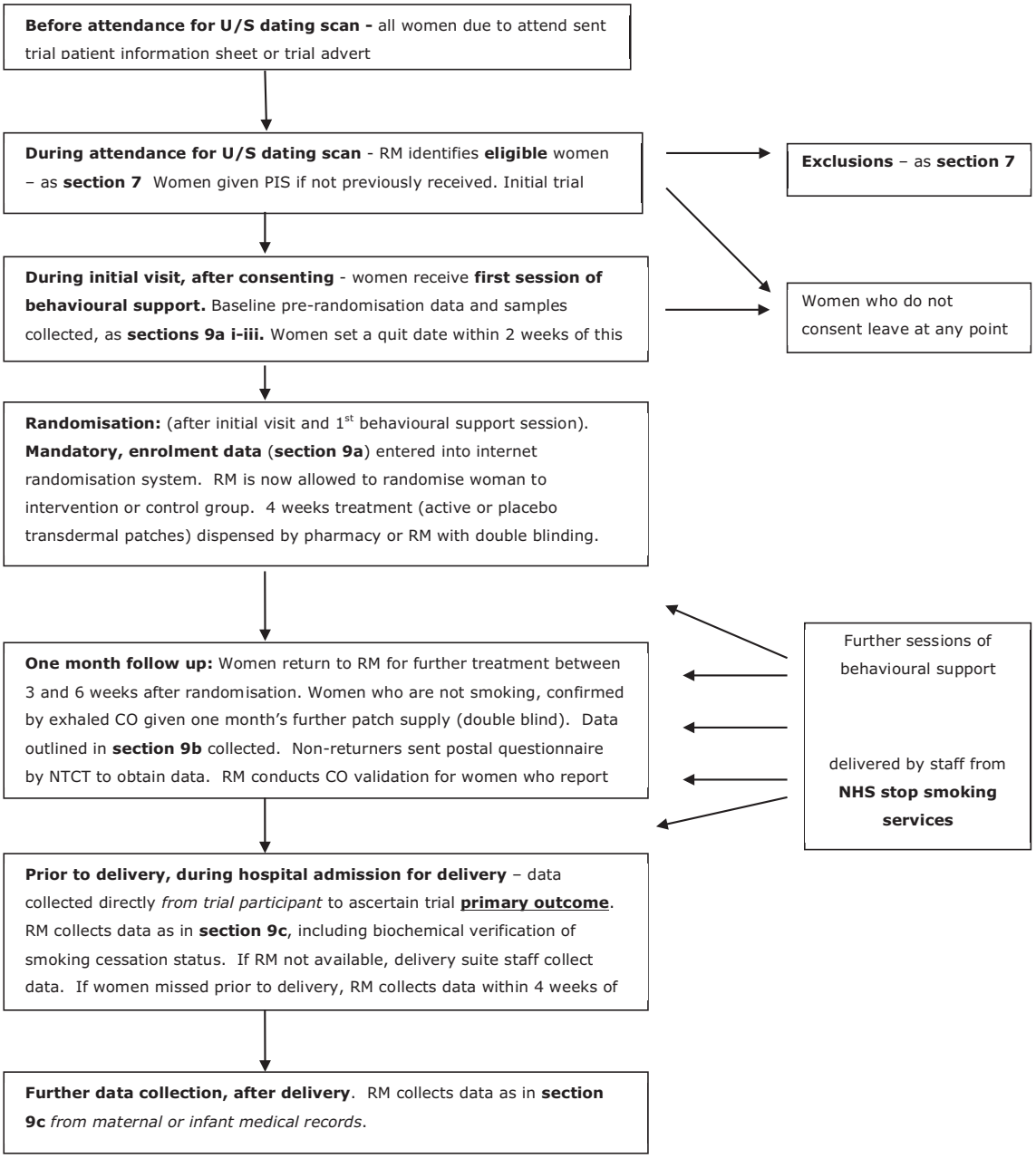
19. Data Collection Forms

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

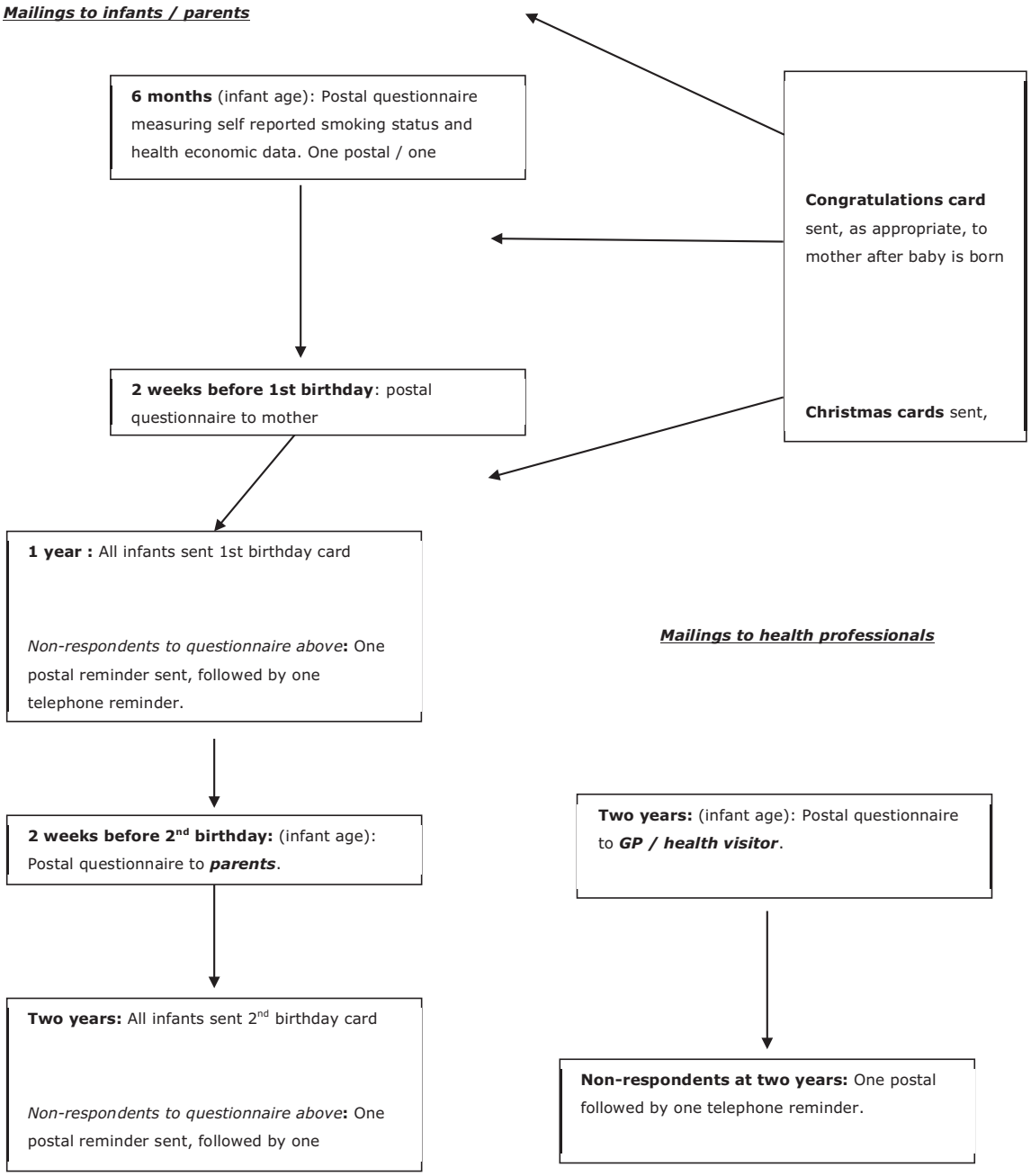
1 Trial flow from recruitment to delivery
(primary outcome ascertainment)



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)



Appendix 4 Protocol breaches

Of 2410 women who expressed an interest in the trial and were assessed for eligibility, 1051 (43.6%) were randomised: 521 were assigned to receive NRT and 530 to receive placebo patches (see *Figure 2*). One woman was mistakenly enrolled for a second time in a subsequent pregnancy; thus, her second enrolment in the placebo group was removed from all analyses, giving a final sample size of 1050 (529 in the placebo group).

Protocol breaches were discovered for 13 other participants, but after consideration of violation details it was decided that these were not serious and would have no significant impact on trial participants or the scientific integrity of the trial. Therefore, these participants remained in the trial and their data were used in analyses. Two participants had minor chemical dependence problems and three participants were enrolled 4–5 days before they reached 12 weeks' gestation; however, they were not randomised until 12 weeks. Seven participants did not receive their investigational medicinal product by their quit date owing to pharmacy problems, meaning that they needed to set a new quit date that was then > 2 weeks after their baseline visit. One participant received and used a second supply of patches after the first set appeared to have been lost in the post, however, as she was still smoking at 1 month she would not have been eligible to receive a second set.

Two additional problems affecting 27 participants occurred within one site pharmacy, but again these were judged to have no significant impact on participants or trial integrity. The temperature recorded in the pharmacy fridge at one site was in excess of 8 °C (this was the maximum temperature specified for patch storage before dispensing) for 12 days in a 1-month period and, during this time, 25 subjects had been assigned patches from the pharmacy. On discovery of the problem, unallocated packs were withdrawn, but as patches could be stored for 3 months at ambient temperature without the potency being reduced, and there were no safety issues, it was felt that other than informing participants that patches should not be used for longer than 1 month after issue, no further action needed to be taken with those packs that had been issued. In another incident, due to a mix-up by the site pharmacy, two participants were posted each others treatment pack for the first treatment period and had started to use the patches before the mistake was discovered. The treatment code was not broken, but the trial manager was informed that the participants had received the same treatment allocation and no further action was taken.

Appendix 5 Supplementary data on adverse events

See *Table 7* for information on AEs by treatment group.

Adverse events resulting in women permanently discontinuing treatment

Nicotine replacement therapy: 50 adverse events in 46 women

Application site reactions ($n = 33$), nausea ($n = 7$), headache ($n = 3$), dizziness ($n = 2$), palpitations ($n = 2$), dyspnoea, oropharyngeal pain, sensory disturbance (all $n = 1$)

Placebo: 38 adverse events in 32 women

Application site reactions ($n = 15$), nausea ($n = 7$), dizziness ($n = 5$), headache ($n = 3$), irritability ($n = 3$), dyspepsia ($n = 2$), fetal hypokinesia, influenza like illness, palpitations (all $n = 1$)

Overnight hospital admissions for other pregnancy complications

In total there were 143 events with hospital admissions in 95 women (NRT group) and 146 events with hospital admissions in 94 women (placebo group) (admission for any reason, not only pregnancy related).

Hospital admission for less frequent pregnancy-related events

Nicotine replacement therapy: 44 events

Miscellaneous hospitalisation for pregnancy-related events for which the outcome was no abnormality detected ($n = 7$), urinary tract infection ($n = 7$), maternal condition affecting fetus ($n = 3$), postpartum haemorrhage ($n = 3$), proteinuria ($n = 3$), antepartum haemorrhage ($n = 2$), dizziness ($n = 2$), polyhydramnios ($n = 2$), premature separation of placenta ($n = 2$), chest pain, constipation, disseminated intravascular coagulation, hepatic failure, pruritus generalised, pyelonephritis, renal failure, syncope, tachycardia, ultrasound Doppler abnormal, vision blurred, visual impairment, vulvovaginal candidiasis (all $n = 1$).

Placebo: 41 events

Miscellaneous hospitalisation for pregnancy-related events for which the outcome was no abnormality detected ($n = 5$), urinary tract infection ($n = 4$), maternal condition affecting fetus ($n = 4$), premature labour ($n = 2$), premature separation of placenta ($n = 2$), anaemia, anaphylactic reaction after iron infusion, antepartum haemorrhage, back pain, body temperature increased, cervix cerclage procedure, chest pain, cholestasis of pregnancy, deep-vein thrombosis, diarrhoea, dizziness, dyspnoea, haemoglobin decreased, migraine, musculoskeletal pain, oedema, placenta praevia, proteinuria, pyelonephritis, scar pain, threatened labour, abnormal ultrasound Doppler, urinary retention, visual impairment (all $n = 1$).

Other, less frequent, adverse events that occurred in < 3% of women or infants and are not logically grouped together

Nicotine replacement therapy

Maternal adverse events (63 events)

Dizziness ($n = 6$), fall ($n = 4$), abnormal dreams ($n = 3$), back pain ($n = 3$), dyspnoea ($n = 3$), urinary tract infection ($n = 3$), diarrhoea ($n = 2$), hypoaesthesia ($n = 2$), oedema ($n = 2$), oropharyngeal pain ($n = 1$), pruritus ($n = 2$), chest pain, antepartum haemorrhage, blindness transient, blood pressure decreased, cholelithiasis, hypothyroidism, influenza like illness, intervertebral disc protrusion, kidney infection, malaise, migraine, oligohydramnios, overdose, pain in extremity, palpitations, parvovirus infection, photopsia, pleural effusion, pollakiuria, polyhydramnios, premature separation of placenta, proteinuria, road traffic accident, sensory disturbance, skin disorder, symphysiolysis, type 1 diabetes mellitus, vaginal discharge, vaginal infection, vasodilatation, vision blurred, visual impairment (all $n = 1$).

Fetal adverse events (total 5 events)

Growth restriction ($n = 2$), heart rate deceleration, large for dates baby, hospital admission for fetal growth restriction (all $n = 1$).

Neonatal adverse events (total 32 events)

Jaundice ($n = 4$), feeding disorder ($n = 3$), hypoglycaemia ($n = 3$), hypothermia ($n = 2$), maternal condition affecting fetus ($n = 2$), tachypnoea ($n = 2$), sepsis ($n = 2$), shoulder dystocia ($n = 2$), arrhythmia, C-reactive protein increased, clavicle fracture, dehydration, Erb's palsy, infantile apnoeic attack, lower respiratory tract infection, aspiration, respiratory distress syndrome, pyelocaliectasis, temperature regulation disorder, unresponsive to stimuli (all $n = 1$).

Placebo

Maternal adverse events (total 73 events)

Fall ($n = 8$), dizziness ($n = 7$), abnormal dreams ($n = 4$), lower respiratory tract infection ($n = 3$), palpitations ($n = 3$), proteinuria ($n = 3$), visual impairment ($n = 3$), back pain ($n = 2$), malaise ($n = 2$), musculoskeletal pain ($n = 2$), oedema ($n = 2$), physical assault ($n = 2$), pruritus ($n = 2$), syncope ($n = 2$), vaginal discharge ($n = 2$), cholestasis of pregnancy, diarrhoea, influenza like illness, maternal condition affecting fetus, Bartholin's cyst, chlamydia test positive, cholestasis, dysgeusia, dysuria, emotional disorder, feeling abnormal, generalised oedema, ocular hyperaemia, pain in extremity, restless legs syndrome, road traffic accident, hyperhidrosis, injury, intentional self-injury, lethargy, meningitis, thrombophlebitis, toothache, umbilical hernia, unstable fetal lie, vulvovaginal discomfort (all $n = 1$).

Fetal adverse events (total 5 events)

Tachycardia ($n = 2$), heart rate decreased, small for dates baby, admission for fetal growth restriction (all $n = 1$).

Neonatal adverse events (total 29 events)

Jaundice ($n = 5$), hypoglycaemia ($n = 5$), feeding disorder ($n = 3$), grunting ($n = 3$), anaemia ($n = 1$), convulsion neonatal ($n = 2$), infantile apnoeic attack ($n = 2$), respiratory disorder ($n = 2$), Erb's palsy, fever, hypoxia, aspiration, respiratory distress syndrome, shoulder dystocia (all $n = 1$).

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