**Title page**

**Title**

**Financial voucher incentives provided with UK Stop Smoking Services for pregnant women: a phase III Randomised Controlled Trial**

**Subtitle**

**Cessation in Pregnancy Incentives Trial phase III (CPIT III)**

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**for the Cessation in Pregnancy Incentives Trial phase III (CPIT III) local research teams**

**Title:** Financial voucher incentives provided with UK Stop Smoking Services (SSSs) for pregnant women: a phase III Randomised Controlled Trial

**Objective:** To examine effectiveness, cost-effectiveness, generalizability and acceptability of financial incentives for smoking cessation during pregnancy ‘bolted-on’ to variously organised UK SSSs. This paper reports effectiveness.

**Design:** A prospective pragmatic, multi-centre, parallel group, single-blinded, individually randomised controlled superiority trial with 1:1 allocation augmented by embedded cost-benefit and mixed methods studies of generalisability and acceptability**.**

**Setting:** Seven UKSSSs provided in primary and secondary care facilities in Scotland, Northern Ireland and England.

**Participants:** 944 pregnant self-reported smokers (at least 1 cigarette in the last week) when asked at first maternity visit, ≥16 years, <24 weeks gestation notified to the trial team by routine SSSs entered the study. 941 (471 intervention, 470 control) completed the study as 3 asked for their data to be removed.

**Interventions:** The offer of usual SSS support for control participants with the addition of up to £400 ($523, 583 euros) of LoveToShop financial voucher incentives for engaging with current SSSs and/or quitting smoking during pregnancy ‘bolted-on’ with intervention (bolted-on - current services changed as little as possible).

**Outcomes:** The primary outcome was self-reported smoking cessation in late pregnancy (random date between 34-38 weeks gestation) corroborated by saliva cotinine (and anabasine if using nicotine replacement products).Secondary outcomes included point and continuous abstinence 6 months after expected date of delivery, engagement with SSS, biochemically validated abstinence 4 weeks later, birth weight, cost-effectiveness, generalisability documenting SSS formats and acceptability to pregnant women and their carers.

**Results:**126/471(26.8%) quit from the intervention group and 58/470(12.3%) from the control group AOR 2.78 (1.94 to 3.97) p<0.001 - adjusted for age, smoking years, Index of Multiple Deprivation, Fagerström score, pre or post COVID, recruitment site. Serious Adverse Events (SAEs) were early miscarriages and other ‘expected’ pregnancy events requiring hospital admission and all SAEs were unrelated to the intervention. Most who quit from both groups relapsed after their baby was born.

**Conclusions:**The offer of up to £400 of financial voucher incentives to stop smoking during pregnancy ‘bolted-on’ to current heterogeneous UK Stop Smoking Services is highly effective. This bolt-on intervention will help implement new NICE guidance which includes the addition of financial incentives to support pregnant women to stop smoking. Continuing incentives to 12 months after birth are being examined to prevent relapse.

**Trial Registration:**International Standard Randomised Controlled Trial Number 15236311

400 words

Maternal smoking is responsible for significant ill health and death among women and their offspring including 7% of acute childhood admissions for respiratory infection, 20% of infant deaths and 30% of babies born small.1 Women who permanently quit during pregnancy will have a near normal lifespan whereas those who continue will lose up to 10 years of life.2 Eighty percent of women in the UK have at least one pregnancy, providing an opportunity to help most young women to stop smoking before their health is permanently compromised.3

In the UK midwives routinely lack time, appropriate training and perceive that detailed conversations about smoking cessation can instil guilt and undermine their relationship with pregnant women.4 As a result, pregnant smokers are offered counselling5 usually by a dedicated Stop Smoking Service (SSS) signposted by midwifery services in early pregnancy. Despite lack of evidence of effectiveness during pregnancy,6 in the UK7 (but not in many other countries including the US8), Nicotine Replacement Therapy (NRT) and E-cigarettes, are seen as risk reduction, providing nicotine only and not other dangerous chemicals from burning tobacco. The proportion of pregnant women who smoke has declined in both the US9 and the UK.10 Women in the US have been supported by Medicaid through changes to the Affordable Care Act targeting pregnant smokers.11 In Scotland, UK between 1995 and 2019 self-reported smoking among pregnant women declined from 30.5% to 14.6%,12 with associated declines in miscarriage (6.9% to 4.5%)13 and small births for gestational age (4.2% to 2.5%)14

Despite this progress, there is evidence that those who persist with smoking while pregnant may not engage with cessation services.15 Interventions using financial incentives, piloted in the US,16,17 led to service developments in the UK.18,19 The acceptability of financial incentives to change behaviour depends on: effectiveness - even a small improvement increases acceptability; the type of incentive – grocery vouchers are more acceptable than cash or vouchers for luxury items; the target behaviour - weight management is more acceptable than smoking cessation.20 However, large pragmatic trial evidence for effectiveness in the UK is missing.21 This paper reports a large phase III Randomised Controlled Trial to test the hypothesis that financial incentives increase smoking cessation during pregnancy when added to current UK Stop Smoking Services.

**Methods**

Study design is based upon a successful phase II feasibility trial undertaken in Glasgow, Scotland.22

POPULATION

Pregnant women were recruited from seven UK Stop Smoking Services (SSS) serving maternity hospitals in Scotland, Northern Ireland and England. Births at sites ranged from 1000-6000 per year. Eligible women were self-reported smokers (>1 cigarette in the last 7 days), 16+ years, <24 completed weeks gestation, English speakers for verbal telephone consent.

CHARACTERISTICS OF SSS

Examination of heterogeneity of SSSs at 5 of 7 trial sites was part of the process evaluation outlined in the trial protocol.23

COSTS AND BENEFITS TO THE NHS

The cost-effectiveness analysis for the NICE guideline24 was based on the feasibility trial CPIT II.25 Cost-effectiveness analysis from an NHS perspective from this trial26 generalisable to heterogeneous UK SSSs is presented in a sister paper pre-print – <https://medrxiv.org/cgi/content/short/2022.06.21.22276693v1>.

TRIAL DESIGN AND INTERVENTIONS

Appendix A the trial protocol is published in a readable format.23 In summary, CPIT III was a pragmatic, multi-centre, parallel group, single-blinded, individually randomised controlled superiority trial with 1:1 allocation. Posters and a shortened version of the Patient Information Sheet (PIS) were placed in antenatal clinic waiting rooms and information packs. Routinely collected self-report of current smoking prompted automatic referral to SSSs. Information about the trial was given during first SSS contact – ‘You may also be suitable to take part in a study that we are currently running. The study wants to find out if giving pregnant women an incentive will help them to stop smoking. You could potentially obtain up to £400 in high street shopping vouchers if you stop smoking with our service.’ Verbal permission was taken for personal details to be passed to the Trial Team who dispatched a PIS. Trained telephone call-centre staff within a database management company enrolled participants. Baseline and consent questions required database entry prior to automated randomised group allocation, ensuring concealment.Non-stratified randomisation used randomly-permuted blocks of varying size (four, six, eight). Randomisation sequence was computer-generated by York Trials Unit and stored in a specially designed secure online data collection program.22,23

In order to aid recruitment, a new region in England with 5 separate sites was added.

The trial enrolment period was extended to achieve the calculated primary outcome sample size resulting in 25% of participants not reaching the secondary outcome 6-month post-partum by database closure.

Control participants were offered usual SSS care based upon NICE guidelines21 which includes Withdrawal Orientated Therapy5 and the offer of Nicotine Replacement Therapy (NRT).6 Care varied by site in terms of general population or targeted, smoking only or more general health promotion, where care took place, who provided care, what was provided, who funded care – submitted (bmjopen-2022-066494) and summarised in Appendix B. The trial team liaised with SSS staff either directly or via SSS service notes to verify participant engagement including setting a quit date, quit after 4 weeks and carbon monoxide breath test (CO) result. Trial staff entered available CO results into the database. Trial staff did not contact control participants before the late pregnancy primary outcome point.

Intervention participants were offered the addition of up to £400($540, 480 euros) at 4 points. Incentive 1: A £50 voucher to engage with SSS and set a quit date (face to face prior to start of COVID 14/03/2020, then usually telephone); Incentive 2 (if a quit date was set): A £50 voucher if not smoking after 4 weeks confirmed by CO (after start of COVID self-report by telephone was accepted rather than CO which required face to face consultation and was stopped by UK SSSs); Incentive 3 (if CO verified quit at 4 weeks): £100 voucher if smoke-free after 12 weeks confirmed by CO; Incentive 4 (all intervention participants): £200 voucher if CO verified smokefree, when the call-centre phoned in late pregnancy – at a random date between 34 and 38 weeks gestation (calculated from start of last menstrual period). Incentives were LoveToShop shopping vouchers redeemable in many retail outlets. If CO results were not available for intervention participants who self-reported quit at 4 and 12 weeks from SSSs, trial staff arranged tests usually by home visit. Trial staff entered the CO result into the database, which triggered the incentives vouchers to be dispatched by registered post from a fulfilment house. This intervention was bolted-on to current services meaning current services were changed as little as possible.

Call centre staff made multiple attempts to contact *all* participants in late pregnancy to establish self-report of smoking. If unsuccessful, local trial teams took over collection of primary outcome information. Some participants had delivered their babies early or had miscarried much earlier.

Call centre staff attempted to contact *all* participants again 6 months after the expected date of delivery supported by local trial teams.

For *all* participants who self-reported as smokefree, in late pregnancy and 6 months after the expected date of delivery, trial staff arranged a CO test. If negative, a saliva sample was taken to biochemically verify self-report. To minimise loss to follow-up, women in both groups received shopping vouchers - £50($70, 60 euros) and £25($35, 30 euros) respectively for providing late pregnancy and six months post-partum outcome data including saliva for biochemical verification if abstinent.

OUTCOMES AND DATA COLLECTION

The primary outcome was cotinine/anabasine verified self-report of smoking abstinence for at least 8 weeks in late pregnancy. Self-report was usually obtained by the call centre. At the same contact, other data were collected including current use of NRT and/or E-cigarettes.

If the participant reported that they were still smoking or had smoked in the last 8 weeks then this outcome was accepted as true and documented on the trial database. For early participants who completed primary outcome follow-up prior to COVID, if the participant reported abstinence, call centre staff made appointments with research staff, using the online database, to verify abstinence initially by visiting the participant’s home to collect a CO breath test. If negative a saliva sample was collected at the same visit. If participants were persistently not available to provide a carbon monoxide breath test they were assumed to be smoking. The final arbiter for cessation was biochemical examination of the saliva sample. For later participants Appendix D describes the changes that were agreed by the ethics committee in order to cope with COVID-19 where CO tests and direct contact were stopped. Saliva samples for self-reported abstinence were taken by participants themselves with telephone support from trial staff. Receipt of saliva samples by trial staff prompted incentive voucher dispatch.

Cotinine is produced by the liver from nicotine from burning tobacco, nicotine patches or inhaled nicotine e.g. E-cigarette - UK guidelines.7 Anabasine is a metabolic by-product of burning tobacco and not produced from nicotine patches or e-cigarettes sold in the UK. Both can be measured in saliva. Women were defined as biochemically verified non-smokers if a) saliva cotinine was <10ng/ml27 OR b) where current NRT/e-cigarette use was reported and saliva cotinine was ≥10ng/ml, the saliva anabasine was ≤0.2ng/ml.28

Secondary outcomes:23

1. Proportion of women who engage with SSS (either arrived at a face-to-face appointment or were available for the appointment by telephone and set a quit date)

2. Proportion of women with biochemically validated (CO) self-reported abstinence from smoking for at least 14 days at 4 weeks after quit date

3. Proportion of women with cotinine/anabasine-verified (using same cotinine/anabasine cut-offs as the primary outcome) self-reported point abstinence from smoking for at least 8 weeks at 6 months post-partum

4. Proportion of women with cotinine/anabasine-verified (using same cotinine/anabasine cut-offs as the primary outcome) self-reported continuous abstinence from smoking from late pregnancy to 6 months post-partum

5. Mean difference in birth weight

6. Cost-effectiveness26 presented in a sister paper - <https://medrxiv.org/cgi/content/short/2022.06.21.22276693v1>.

7. Process evaluation23 which provided information for heterogeneity of service formats at 5 of the 7 sites summarised in Appendix B – ‘Usual care’ paper submitted for publication (bmjopen-2022-066494).

In addition, severity of prematurity (calculated from last menstrual period to date of birth) was collected as a proxy for length of neonatal stay, pre-specified in the Statistical Analysis Plan (SAP) -Appendix C.

A small number of residual blood samples routinely taken for other purposes in late pregnancy were assayed for cotinine to assess if those lost to follow-up were still smoking or using nicotine replacement products.

Appendix D describes changes made from March 2020 due to COVID-19.

TRIAL OVERSIGHT

The trial was conducted within Good Clinical Practice guidelines and ethical principles with the protocol23 (Appendix A) approved by West of Scotland Research Ethics Committee 4. Participants provided audio-recorded informed consent obtained by specially trained call centre operators blind to random allocation. Data was added to the trial database by trained researchers using a secure internet portal.

Data monitoring co-ordinated by York Trials Unit (appendix E) was undertaken by local researchers. From March 2020, light touch data monitoring focused on the primary outcome and key secondary outcomes, consistent with NIHR COVID guidance29 (see Study and Data Monitoring Plan, Appendix E). Serious Adverse Events (SAEs) were reviewed by the Chief Investigator overseen by the Trial Steering Committee.

STATISTICAL ANALYSIS

The planned sample size was 940 participants (470 per trial group). This gave 90% power at 5% significance with 15% attrition to detect a clinically significant doubling of smoking cessation from 7% with usual care.

Analyses were carried out in accordance with a prespecified SAP -Appendix C - using Stata (StataCorp, Stata Statistical Software: Release 17; College Station, TX, USA). Statistical hypothesis tests were two-sided, with a significance level of 5%. The intention-to-treat population was defined as being all participants randomised to the study who did not ask for all of their data to be removed (n=3) and includes those women who were no longer pregnant at the primary outcome data collection point.

Baseline data were summarised descriptively by treatment group for all randomised participants, and for participants with primary outcome data.30 For each outcome, the number of participants who provided data was presented. For analysis of primary and each of the secondary outcomes relating to smoking i.e. biochemically and CO-verified smoking status, participants were assumed to be smokers (as per the Russell Standard)31 where the outcome was missing. Primary outcome analysis used a mixed-effects logistic regression model including randomised treatment group, age, smoking years, Index of Multiple Deprivation (IMD) quintile,32 Fagerström score33 and whether outcome was obtained before 16th March 2020 (Covid-19) as fixed effects. Recruiting site was adjusted for as a random effect. The primary outcome for CPIT III was pooled with the identical outcome from CPIT II Glasgow feasibility trial22 using a random effects meta-analysis (appendix F) to obtain a pooled risk ratio.

To assess sparse data impact,34 the primary outcome was analysed using a Firth logistic regression model, adjusting for the same covariates as the primary analysis, with site as a fixed effect. The sensitivity to missing data was assessed using two methods, multiple imputation by chained equations and a pattern-mixture model to assess the sensitivity to deviations from ‘the missing at random’ assumption.

In order to respond to reviewers’ concerns with regards to anabasine testing, a post-hoc ‘extreme case’ sensitivity analysis was carried out. This repeated the primary analysis under the assumption that participants in the incentives group requiring anabasine testing were smokers, while assuming participants who required anabasine testing in the control group were non-smokers.

For each of the following subgroups, the primary analysis was repeated with addition of an interaction term between randomised treatment group and subgroup: maternal age (≤28 years vs >28 years), IMD quintile (1st vs 2nd vs 3rd vs 4th vs 5th), years of smoking (≤10 years vs >10 years) and Fagerstrom score (≤6 vs >6). Subgroup analyses were prespecified in the SAP.

Engagement with SSS, 4-week CO validated smoking status, and continuous and point abstinence at six months post-partum were analysed using a logistic regression model adjusting for the same fixed and random effects as the primary outcome. Birth weight analysis used mixed-effects linear regression, including treatment group, age, height and weight of the mother at booking, years of smoking, income status, Fagerström score and data collection before 16th March 2020 as fixed effects, and site as a random effect. A Complier Average Causal Effect (CACE)35 analysis used an instrumental variable approach (appendix F) to explore intervention effects on birth weight accounting for non-compliance. Severity of pre-term birth was summarised descriptively.

Covid-19 disrupted some trial processes. Primary and secondary outcomes were summarised descriptively by treatment group and pre- or post-Covid data collection timing for self-reported non-smokers, self-reported non-smokers with a biochemical sample, biochemically-verified non-smokers, and the number of returned biochemical samples (reported in Appendix D).

PATIENT AND PUBLIC INVOLVEMENT

Trial planning included two smokers from the Glasgow feasibility trial22 and the UK Centre for Tobacco and Alcohol Studies smokers’ panel with additional representation on the Trial Steering Committee.

**Results**

From 9th January 2018 to 4th April 2020, 4032 women (Figure 1) were screened, 3088(76.6%) were either not eligible or declined consent. 944 participants were recruited (Incentives 472; Control 472) from 7 sites (n=468, 267, 77, 43, 34, 28, 27). Median age at randomisation was 28.0 years and median gestational age at maternity booking was 11.3 weeks. 351(37.2%) and 171(18.1%) participants reported using NRT and E-cigarettes respectively – Appendix G. Baseline characteristics were similar between randomised groups (Table 1). In total, there were 22 participants who withdrew from the study (Incentives 12; Control 10). Twenty had withdrawn at or before the late pregnancy follow-up, while two withdrew at the postpartum follow-up. Seven withdrew due to a miscarriage or stillbirth (Incentives 5; Control 2), with one termination of pregnancy in the incentives group. Other reasons were: one participant not being allocated to intervention group, one participant in the control group not agreeing with using incentives to quit, one participant in the incentives group seeking support more locally, GP asked for withdrawal for one participant offered incentives and 10 did not wish to continue in the trial (Incentives 4; Control 6).

Three participants along with withdrawing, also asked for their data to be removed from the trial database (Incentives 1; Control 2). These participants were excluded from the analysis of the primary and secondary outcomes, along with the sensitivity analyses. Of the 690 participants who had or would have had their postpartum follow-up initiated at the planned time, 12 had withdrawn from the study (Incentives 6; Control 6).

**Figure 1. Consort Diagram**

Potential participants, enrolled and randomised participants, to end of study showing reasons for non-eligibility and any drop-outs.

**Primary Outcome**

Participants reached primary outcome between June 2018 and November 2020 at mean gestation 36.0 weeks (SD 1.2 weeks). 843 (89.3%) (Incentives 412 (87.3%); Control 431 (91.3%)) provided self-report and biochemical verification if not smoking. There was a significant difference in biochemically-verified non-smokers [126/471(26.8%) offered incentives versus 58/470(12.3%) control] AOR 2.78 (95% CI: 1.94 to 3.97; p<0.001). Table 2 gives information on the primary outcome analysis and the derivation of the primary outcome.

The findings were unaltered by Firth logistic regression (AOR 2.72; 95% CI: 1.91 to 3.88; p<0.001) and multiple imputation by chained equations (AOR 3.03; 95% CI: 2.10 to 4.36; p<0.001). Pattern mixture modelling showed interpretation was robust to large deviations from the missing at random assumption.

There were 31 participants who at the late pregnancy primary outcome had an anabasine result (Incentives 22; Control 9). Assuming that for the 22 participants in the incentives group, that these participants were smokers, while for the 9 in the control, that these participants were not smokers, there remained a large treatment effect favouring incentives (AOR 2.17; 95% CI: 1.51 to 3.12; p<0.001).

NRT and e-cigarette use is reported in appendix G.

There was no statistically significant interaction between treatment allocation and pre-specified subgroups.

Although Russell standard31 designated those missing as smokers, of 25 incentives participants lost to follow-up (table 2), six had an available residual late pregnancy blood sample and 5 were cotinine verified smokers or using NRT/e-cigarettes. Similarly, of 16 controls lost, 4 had samples and 3 were smokers or using NRT/e-cigarettes.

A random-effects meta-analysis of CPIT III with CPIT II found a pooled risk ratio of being a biochemically-verified non-smoker towards the end of pregnancy of 2.30 (95% CI: 1.82 to 2.91; p<0.001).

**Secondary outcomes**

Secondary and exploratory outcomes are summarised in Table 3. Smoking 6 months post-partum was collected between January 2019 and March 2021. Significantly more engagement with SSS and CO-verified non-smoking at 4-weeks post-quit date was seen with incentives. Data at 4 weeks post quit date was only obtained for 493 [52.2%] participants (Incentives 302 (64.0%); Control 191 (40.5%)), those who engaged with SSSs.

Trial recruitment went on longer than expected. This did not affect the primary outcome, but only 690/941 (73.3%) (Incentives 348/471 (73.9%), Control 342/470 (72.8%)) could be followed up to 6 months post-partum within the trial funding envelope. Data on biochemically-verified smoking status was obtained for 526/690 (76.2%) participants (Incentives 267 (76.7%); Control 259 (75.7%)) with no significant difference between groups in biochemically-verified non-smokers (table 3) (AOR 1.39; 95% CI: 0.69 to 2.79; p=0.36).

Birth weight of babies from 443/471(94%) intervention participants mean 3.18kg (SD 0.61) and 450/470(96%) control participants mean 3.13kg (SD 0.60) showed no significant difference between groups – mean difference 0.05kg (95%CI: -0.03 to 0.13, p=0.21). A CACE analysis found a clinically important non-statistically significant difference in the subset of participants who complied with their treatment allocation (AMD 0.31 kilograms (a 10% birthweight increase); 95% CI: -0.18 to 0.80 kilograms; p=0.22). Severity of preterm birth was similar between groups.

Fifty eight participants (Incentives 39; Control 19) had 61 Serious Adverse Events (SAEs) (Incentives 42; Control 19): 17 miscarriages (Incentives 12; Control 5), 4 Stillbirths (Incentives 2; Control 2), 5 Terminations Of Pregnancy (Incentives 4; Control 1) [two of which were for birth defects (both in incentives)], 3 neonatal deaths (Incentives 2; Control 1), 1 birth defect in the incentives group, 1 participant in the incentives group died from a drug overdose, 1 premature birth in the incentives group, 5 COVID admissions (Incentives 4; Control 1). There were 24 other events that required hospital admission – 17 reduced foetal movements (Incentives 11; Control 6), 1 hyperemesis (Incentives), 1 deep vein thrombosis (Incentives), 1 tooth abscess (Control), 1 for urine monitoring (Control), 1 abdominal pain (Incentives), 1 per vaginal bleeding (Control), 1 back pain and fever (Incentives). All SAEs were ‘unrelated’ to intervention. It is possible that there was detection bias in the collection of adverse event data, given that the nature of the intervention meant participants randomised to incentives had more contact with the trial team, meaning there were more opportunities to report adverse events.

**SSS formats**

Appendix B summarises heterogeneity of SSS formats at trial sites.

**Discussion**

**Principal findings**

Offering up to an additional £400 ($523, 483 euros) of financial incentives to engage with current UK SSS and/or stop smoking during pregnancy increased biochemically validated quit rates from 12% to 27% towards the end of pregnancy – OR 2.78 (95% CI: 1.94 to 3.97); p<0.001. Meta-analysis with the feasibility trial22 which used the same ‘bolt-on’ intervention in Glasgow, another Scottish Health Board area, provided a risk ratio of 2.30 (95% CI: 1.82 to 2.91; p<0.001).

**Strengths and limitations**

Design of this phase III trial was informed by a large feasibility trial in one UK centre Glasgow (CPIT II).22 CPIT II was reviewed within the BIBS study36 funded by the UK National Institute for Health Research (NIHR) to establish a platform for financial incentives trials. BIBS highlighted acceptability and feasibility of individually randomised trial design. Contamination was explored in the current trial process evaluation by asking control group participants, in interviews, how they felt about their allocation. Though some indicated disappointment, none said this had put them off stopping smoking, and this will be reported with supporting quotations in a future process evaluation paper. There was no evidence from interviews that control participants felt any resentment towards those in the incentive group. The pragmatic nature, ‘bolting-on’ financial incentives to heterogeneous SSSs formats from three UK countries, Scotland, England and Northern Ireland (appendix B), did not disrupt current services and supports generalisability.

Reliability of anabasine analysis, used to identify non-smokers using nicotine replacement products, has been questioned. A worst-case scenario sensitivity analysis indicates that a strong effect from incentives on smoking cessation remains - adjusted odds ratio 2.17 (95% CI: 1.51 to 3.12; p<0.001).

A potential trial weakness relates to enrolment of only 944/4032(23%) of self-reported smokers: participants needed to agree for their contact details to be passed by SSS to the trial team. ‘Screening’ by SSS (Figure 1) reduced the population of pregnant smokers for recruitment by 50% from over 4000 to less than 2000. Nearly 800 were lost through failed SSS contact (a common service difficulty) which may have resulted in bias towards smoking cessation, potentially raising quit rates in both groups but not relative quit rates. Quit rate among control participants was 12% compared with 7% used to calculate trial sample size. Of note the rate of recruitment of those screened (23%, 944/4032) was higher than two recent smoking cessation in pregnancy trials where only 10% of those screened were enrolled.37,38

**Comparisons with other studies**

Unlike other trials, acceptability of financial incentives to pregnant women and health professionals from recorded interviews23 was examined as was cost-effectiveness26 - <https://medrxiv.org/cgi/content/short/2022.06.21.22276693v1>. Two contemporary US trials39,40 demonstrated similar cessation improvements when financial incentives were added to ‘Best Practice’ defined by the Centres for Disease Control. The first also examined cost-effectiveness.41 A recent multicentre French study offered similar value incentives with improvement in quit rate from 7% to 16% with incentives (odds ratio 2.45, 95% CI 1.34 to 4.49).42 Although intervention took place in 18 maternity wards with different professionals providing support, the French incentives were closely integrated with a single cessation support design. This would make simple UK roll out difficult without significant changes to heterogeneous UK SSS formats. A phase IV ‘in real life’ study in Glasgow Scotland43 showed that the ‘bolt-on’ format of financial incentives in the current trial can be integrated into normal care and remain cost-effective even with reduced incentive value.

**Policy implications**

This study programme, including the current trial, the feasibility trial22 and the phase IV study in Glasgow43 have shown that financial incentives more than double the quit rate and can be integrated without substantially changing current UK SSS. The effectiveness should increase acceptability of using financial incentives.20 The variety of ‘usual care’ SSS formats included in this trial summarised in appendix B and submitted for publication (bmjopen-2022-066494), and cost-effectiveness – <https://medrxiv.org/cgi/content/short/2022.06.21.22276693v1> support UK-wide roll-out. This trial supports implementation advocated in recent NICE guidelines24 by demonstrating an effective, cost effective and generalisable pragmatic bolt-on UK format for incentive payments with ‘real life’ experience from the phase IV service development in Glasgow.43

**Unanswered questions and future research**

Many studies have shown a rapid return to smoking post-partum suggesting continued incentive payments post-partum to prevent relapse (subject of an ongoing trial https://doi.org/10.1186/ISRCTN55218215).19 The current trial demonstrates a clinically important44,45 increase in birthweight among compliers +0.31kg (10% of birthweight) (95% CI: -0.18 to 0.80kg), similar to the feasibility trial35 - +0.15kg (5% of birthweight) (95% CI: -0.62 to 0.80kg) and application of CACE analysis to the French trial42 - +0.52kg (15% of birthweight). Meta-analysis of these and other relevant data may allow a definitive answer to be reached regarding an important birth weight increase44,45 among compliers - who quit smoking with the offer of financial incentives but would not have quit without that offer. Additional research questions include: What format and incentive level at what frequency achieves the most effective and cost-effective outcome? Further trials, or well-planned (phase IV) service evaluations using routinely collected SSS data,18,43,46,47 can now refine incentive formats for maximum effect at least cost.

**SUMMARY BOX**

**Section 1: What is already known on this topic**

There has been a 50% reduction in the proportion of women who smoke during pregnancy over the last 20 years

Women who persist with smoking during pregnancy are more difficult to reach

It is known that the offer of financial incentives increases smoking cessation among pregnant women

**Section 2: What this study adds**

This study provides an effective bolt-on incentives framework that does not disrupt current heterogeneous UK Stop Smoking Services

This study confirms that adding financial incentives to current cessation support for pregnant women is cost saving to the NHS in the longer term

**Trial Database Management, Call Centre and Fulfilment House:**

ECHO Managed Services Ltd developed and managed the trial database, and their call centre staff provided an exemplary service which made this trial possible. Their links with the fulfilment house, Latchams, allowed vouchers to be triggered by the trial database and sent by registered post, largely eliminating difficulties of using monetary vouchers.

**Study Sponsor:**

The study was sponsored by NHS Greater Glasgow & Clyde Health Board.

**Independent Trial Steering Committee Members:**

Dr Felix Naughton – Chair; Dr Amy Whitehead – Statistician; Dr Tom Barlow – Funder Representative, Chief Scientist Office, Scottish Government; Dr Anbalakan Paramasivam - Funder Representative, Cancer Research UK; Geraldine Lucas – Stop Smoking Services Glasgow; Dr Allison Kurti – International Representative Stop Smoking Services Research; Margaret Ogden – Lay Representative

**Contributors:**

Professor Tappin DMT was the chief investigator who designed the study, wrote all the funding applications, wrote the original protocol and applied for ethics approval, oversaw and line managed Glasgow based research staff, managed all the funding, provided reports to grant funders, solved problems to do with COVID, adding 5 English sites, as well as difficulties with ECHO moving the call centre from Bristol to Walsall, wrote the current paper. DMT with LS, MM and LRS worked with ECHO Managed Services to design all aspects of the data collection programme and problem solved making adjustments via ECHO database builders as problems occurred.

Lesley Sinclair LS was the main Trial Manager who controlled all the day to day running of the trial, problem solved all aspects of trial delivery, at 7 sites including travelling to 6 sites with DT and MM to support local researchers, ran the 7th site with MM, wrote the protocol publication and reviewed the current paper drafts. Lesley managed the trial administrator based in Glasgow.

Professor Kee FK line managed research staff at one site, supported trial design, led application for funding at the site as well as additional funding for the process evaluation, provided support and advice to DMT whenever asked for, reviewed drafts of the current publication.

Margaret McFadden MM was the lead research nurse for the whole trial, who supported all the research nurses at the 6 research sites as well as running the trial at the 7th site. Margaret travelled to all sites with DMT and LS solved problems, and with DMT and LS travelled to ECHO in Bristol and Walsall to train call centre staff and monitor performance and provide further advice. Margaret reviewed the current manuscript.

Dr Lyn Robertson-Smith LRS took control of the ethics and NHS Research and Development approval including all protocol amendments. Lyn also supported LS with the running of the whole trial. Lyn organised the Steering Committee and Trial Management Group meetings providing all the paperwork and recorded minutes. Lyn organised for all the saliva samples to be packaged and transferred to the laboratory from all 7 sites. Lyn developed and put in place the Trial Data Monitoring Plan. Lyn reviewed this manuscript.

Alex Mitchell AM provided the main statistical support to the trial. Alex supported re-development of the trial database. Alex wrote the Statistical Analysis Plan. Alex developed the programmes to analyse the trial data. Alex provided all the results for this manuscript. Alex wrote the statistical analysis section of the manuscript and reviewed the manuscript multiple times.

Ada Keding supervised all the work of AM and gave frequent advice as required. Ada helped develop the Statistical Analysis Plan and guided the analysis and statistical aspects of responses to reviewers comments. Ada reviewed this manuscript.

Dr Judith Watson JW oversaw the clinical trial methodology of the study and supported LRS with all aspects of trial oversight. Judith reviewed this manuscript.

Sinead Watson SW and Alison Dick AD ran one site organising and implementing data collection and data entry into the trial database. Sinead also liaised locally with NHS R&D who provided approvals. Sinead and Alison supported the process evaluation aspects of the trial by creating an online questionnaire with Jennifer McKell JMK to augment face to face interviews in order to gather the opinions of health carers regarding the use of financial incentives to support smoking cessation during pregnancy. Alison and Sinead supported LRS with sample transport.

Professor Torgerson DT and Professor Hewitt CH provided clinical trial unit support for all aspects of CPIT III. They allocated time for AM, LRS, AK, JW to work on the trial, adjusted commitment and timelines to cope with two trial extensions allowing the statistical analysis and interpretation to be documented when needed. DT and CH both reviewed the manuscript and DT provided comments on drafts many times in a very timely way.

Jennifer McKell JM supervised by Pat Hoddinott PH and Fiona Harris FH undertook the process evaluation for the CPIT III trial. JM travelled to sites and observed interactions between the central trial team and local site research nursing staff. JM interviewed face to face local research nurses, local maternity care and Stop Smoking Service staff as well as trial participants and pregnant smokers who did not participate. JM developed with SW and AD the online questionnaire for local staff to augment face to face interviews which were curtailed by COVID 19. JM, PH and FH developed the analysis plan for the process evaluation and undertook the analysis. JM wrote the sister paper submitted to BMJ Open. McKell J, Harris FM, Sinclair L, Bauld L, Tappin D, Hoddinott P. Usual care in a multi-centre randomised controlled trial of financial incentives for smoking cessation in pregnancy: qualitative findings from a mixed methods process evaluation. bmjopen-2022-066494. This paper provides information on heterogeneity of Stop Smoking Services at sites in the trial summarised in Appendix B. JM, PH and FH have reviewed and provided changes to this manuscript.

Nicola McMeekin NM supervised by Kathleen Boyd KB provided the health economic assessment for the CPIT III trial. NM travelled to sites with the central trial team and developed the health economics data collection system with local site research staff. NM worked with AM and produced a health economics dataset. NM analysed the data and both NM and KB wrote a sister paper reporting the health economic outcomes of the CPIT III trial <https://medrxiv.org/cgi/content/short/2022.06.21.22276693v1> . NM and KB have read, and provided input to drafts of this manuscript.

Michael Ussher MU has provided advice and input to the trial from the beginning of grant applications in 2015 through until the present. MU has been an active member of the Trial Management Committee. Having run a trial of exercise to support pregnant smokers to quit, he has important insights into difficulties and provided solutions. He has read and reviewed many drafts of this manuscript and helped respond to reviewers comments.

Linda Bauld LB has worked with DMT on this programme of work since 2008. LB has guided grant application, removed or found a way around roadblocks and supported prolonged frustrating efforts to fund this important trial. LB has guided the trial team through difficult situations and provided support to DMT and line management to LS the trial manager. LB guided the team to gain approval for two extensions, one funded by CRUK and the Chief Scientist Office. LB has reviewed this manuscript.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Funding:**

Cancer Research UK C48006\_A20863; Chief Scientist Office, Scottish Government HIPS\_16\_1; HSC Public Health Agency Northern Ireland (NI) – SM/R/22; HSC R&D Division NI Opportunity-Led Research Award - COM/5352/17; Chest Heart and Stroke Northern Ireland 2017\_09; The Scottish Cot Death Trust; The Lullaby Trust 272. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

**Competing Interests:**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Patient consent:** Not applicable

**Ethical Approval:**

West of Scotland Research Ethics Committee 4 – 17/WS/0173, IRAS Project ID - 227489

**Data Sharing:**

Limited data will be made available on reasonable request to York Trials Unit alex.mitchell@york.ac.uk

**Transparency:**

The lead author (the manuscript’s guarantor) DMT affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Dissemination to participants and related patient and public communities:**

A lay summary has been created and sent to all participants who wished to receive it. A summary for the Chief Scientist Office, Scottish Government will be available after publication of this manuscript: <https://www.cso.scot.nhs.uk/outputs/focus-on-research-summaries/focus-on-research-reproductive-health-and-childbirth/>

**Provenance and peer review:** Not commissioned; externally peer reviewed.

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**Table 1:** Baseline characteristics presented by group for the ‘as randomised’ and ‘as analysed’ populations.

|  |  |  |
| --- | --- | --- |
|  | **All randomised1 Participants (n=944)** | **Participants who provided a smoking status at the primary outcome stage (n=843)** |
|  | **Incentives****(n=472)** | **Control****(n=472)** | **Incentives****(n=412)** | **Control****(n=431)** |
| **BMI, kg/m2** |  |  |  |  |
| n (%) | 434 (91.9) | 449 (94.5) | 381 (92.5) | 412 (95.6) |
| Mean (SD) | 27.44 (6.35) | 26.76 (6.18) | 27.44 (6.32) | 26.85 (6.23) |
| Median (IQR)  | 26.5 (22.5 to 31.4) | 25.8 (22.1 to, 30.5) | 26.5 (22.5 to 31.4) | 25.9 (22.2 to 30.7) |
| **Ethnicity, n (%)** |  |  |  |  |
| White | 466 (98.7) | 464 (98.3) | 407 (98.8) | 426 (98.8) |
| Mixed/multiple ethnicities | 3 (0.6) | 3 (0.6) | 3 (0.7) | 3 (0.7) |
| African/Caribbean/Black | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| Asian/Asian British | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 (0) |
| Missing | 1 (0.2) | 3 (0.6) | 0 (0) | 1 (0.2) |
| **Maternal age at randomisation, years** |  |  |  |  |
| n (%) | 471 (99.8) | 470 (99.6) | 412 (100) | 431 (100) |
|  Mean (SD) | 27.92 (5.71) | 27.89 (5.86) | 28.06 (5.60) | 28.00 (5.91) |
| Median (IQR)  | 27.8 (23.2 to 31.7) | 27.9 (23.2 to 32.2) | 28.0 (23.4 to 31.7) | 27.9 (23.2 to 32.3) |
| **Previous live births** |  |  |  |  |
| n (%) | 448 (94.9) | 454 (96.2) | 406 (98.5) | 426 (98.8) |
| Mean (SD) | 2.1 (1.3) | 2.2 (1.3) | 2.1 (1.3) | 2.2 (1.4) |
| Median (IQR) | 2 (1 to 3) | 2 (1 to 3) | 2 (1 to 3) | 2 (1 to 3) |
| **Gestational age at maternity booking** |  |  |  |  |
| n (%) | 446 (94.5) | 440 (93.2) | 393 (95.4) | 403 (93.5) |
| Mean (SD) | 11.3 (3.3) | 11.3 (3.2) | 11.3 (3.3) | 11.2 (3.3) |
| Median (IQR) | 11.1 (9.3 to 12.7) | 11.2 (9.1 to 13.0) | 11.1 (9.3 to 12.7) | 11.1 (9.0 to 12.9) |
| **Index of multiple** **deprivation, n (%)** |  |  |  |  |
| 1st quintile (most deprived) | 203 (43.0) | 199 (42.2) | 174 (42.2) | 181 (42.0) |
| 2nd quintile | 132 (28.0) | 131 (27.8) | 120 (29.1) | 125 (29.0) |
| 3rd quintile | 74 (15.7) | 71 (15.0) | 62 (15.0) | 64 (14.8) |
| 4th quintile | 33 (7.0) | 32 (6.8) | 30 (7.3) | 25 (5.8) |
| 5th quintile (least deprived) | 15 (3.2) | 19 (4.0) | 12 (2.9) | 19 (4.4) |
| Missing | 15 (3.2) | 20 (4.2) | 14 (3.4) | 17 (3.9) |
| **Carbon monoxide reading at maternity booking, ppm** |  |  |  |  |
| n (%) | 323 (68.4) | 291 (61.7) | 281 (68.2) | 257 (59.6) |
| Mean (SD) | 9.7 (7.3) | 9.6 (6.7) | 9.7 (7.2) | 9.6 (6.6) |
| Median (IQR) | 8 (4 to 13) | 8 (5 to 13) | 8 (4 to 13) | 8 (5 to 13) |
| **Fagerström scor**e |  |  |  |  |
| n (%) | 454 (96.2) | 446 (94.5) | 396 (96.1) | 409 (94.9) |
| Mean (SD) | 4.1 (2.1) | 4.0 (2.2) | 4.1 (2.1) | 4.0 (2.2) |
| Median (IQR)  | 4 (3 to 6) | 4 (2 to 6) | 4 (3 to 6) | 4 (2 to 6) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cigarettes smoked a day at enrolment, n (%)** |  |  |  |  |
| 10 or less | 282 (59.7) | 279 (59.1) | 241 (58.5) | 251 (58.2) |
| 11-20 | 165 (35.0) | 168 (35.6) | 149 (36.2) | 157 (36.4) |
| 21-30 | 22 (4.7) | 21 (4.4) | 20 (4.9) | 21 (4.9) |
| 31 or more | 2 (0.4) | 2 (0.4) | 2 (0.5) | 2 (0.5) |
| Missing | 1 (0.2) | 2 (0.4) | 0 (0) | 0 (0) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Partner smokes, n (%)** |  |  |  |  |
| Yes | 286 (60.6) | 271 (57.4) | 248 (60.2) | 249 (57.8) |
| No | 177 (37.5) | 190 (40.3) | 157 (38.1) | 173 (40.1) |
| Missing | 9 (2.1) | 11 (2.3) | 7 (1.7) | 9 (2.1) |
| **Age at which participant started smoking, years** |  |  |  |  |
| n (%) | 471 (99.8) | 470 (99.6) | 412 (100) | 431 (100) |
| Mean (SD) | 14.7 (3.0) | 14.8 (2.8) | 14.7 (3.0) | 14.8 (2.8) |
| Median (IQR) | 14 (13 to 16) | 15 (13 to 16) | 14 (13 to 16) | 15 (13 to 16) |
| **Uses NRT n (%)**  |  |  |  |  |
| Yes | 175 (37.1) | 176 (37.3) | 161 (39.1) | 164 (38.1) |
| No | 296 (62.7) | 294 (62.3) | 251 (60.9) | 267 (61.9) |
| Missing | 1 (0.2) | 2 (0.4) | 0 (0) | 0 (0) |
| **Uses e-cigarettes n (%)** |  |  |  |  |
| Yes | 88 (18.6) | 83 (17.6) | 79 (19.2) | 74 (17.2) |
| No | 383 (81.1) | 387 (82.0) | 333 (80.8) | 357 (82.8) |
| Missing | 1 (0.2) | 2 (0.4) | 0 (0) | 0 (0) |
| 1Note: The 3 participants who requested their data be removed from the trial database after withdrawing, are included in the denominator when reporting the percentage of non-missing data e.g. the missing data for ‘Cigarettes smoked a day at enrolment’, is due to the 3 participants who requested their data be removed after withdrawing. |

**Table 2:**Primary outcome derivation and primary analysis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Incentives**  | **Control** | **Residual blood cotinine estimation** | **Adjusted odds ratio (95% CI)** | **p-value** |
|  |  |  |  |  |  |
| **Self-reported smoking status, n (%)** |  |  |  |  |  |
|  Non-smoker | 169/472 (35.8) | 87/472 (18.4) | - | - | - |
|  Smoker | 267/472 (56.6) | 360/472 (76.3) | - | - | - |
|  Missing (assumed to be  smoking) | 36/472 (7.6) | 25/472 (5.3) | 3 smokers/1 non-smoker | - | - |
|  No contact |  25/36 (69.4) |  16 (64.0) |  | - | - |
|  Withdrew |  11/36 (30.6)1 |  9 (36.0)2 |  | - | - |
| **Saliva test changed outcome from non-smoker to smoker, n (% of self-reported non-smokers)** |  |  |  |  |  |
|  Yes | 19/169 (11.2) | 13/87 (14.9) | - | - | - |
|  No | 126/169 (74.6) | 58/87 (66.7) | - | - | - |
|  Multiple appointments  missed for saliva test  (assumed to be  smoking) | 24/169 (14.2) | 16/87 (18.4) |  |  |  |
| **Biochemically-verified smoking status incorporating Russell Standard (primary analysis)** |  |  |  |  |  |
|  Non-smoker | 126/471 (26.8) | 58/470 (12.3) |  | 2.78 (1.94 to 3.97) | <0.001 |
|  Smoker | 345/471 (73.2) | 412/470 (87.7) |  |  |  |

**Table 3:** Secondary outcome analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Incentives** | **Control** |  |  |
|  | **No. with data** | **No./Total****(% non-smokers)** | **No. with data** | **No/Total****(% non-smokers)** | **AOR** **(95% CI)** | **p-value** |
| **Secondary outcomes** |
|  Engaged with SSS  and set quit date | 469 | 335/469(71.4) | 470 | 301/470(64.0) | 1.42(1.06 to 1.92) | 0.02 |
|  Carbon monoxide- verified non-  smoker at 4-weeks  post-quit date | 302 | 162/471(34.4) | 191 | 62/470(13.2) | 4.11(2.85 to 5.92) | <0.001 |
| Biochemically- verified point non- smoker at 6- months post-partum | 267 | 21/348(6.0) | 259 | 15/342(4.4) | 1.39(0.69 to 2.79) | 0.36 |
| Biochemically- verified continuous  non-smoker at 6-  months post-partum | 267 | 20/348(5.7) | 259 | 15/342(4.4) | 1.32(0.65 to 2.67) | 0.44 |
| **Preterm birth (exploratory)** | 446 |  | 453 |  |  |
| Term |  | 406(91.0) |  | 423 (93.4) | Not calculated as Statistical Analysis Plan indicated a descriptive summary only. |
| Preterm <37, >32weeks |  | 33(7.4) |  | 26/453(5.7) |
| Very preterm <32, >28weeks |  | 5(1.1) |  | 3/453 (0.7) |
| extreme preterm <28weeks |  | 2(0.4) |  | 1/453(0.2) |