**Effectiveness of offering tailored text message, self-help smoking cessation support to pregnant women who want information on stopping smoking: MiQuit3 randomised controlled trial (RCT) and meta-analysis**

Tim Coleman, Miranda Clark, Charlie Welch, Rachel Whitemore, Jo Leonardi-Bee, Sue Cooper, Catherine Hewitt, Matthew Jones, Stephen Sutton, Judith Watson, Karen Daykin, Michael Ussher, Steve Parrott, Felix Naughton

**Miranda Clark  
Tim Coleman  
Sue Cooper  
Karen Daykin  
Matthew Jones  
Rachel Whitemore**

Division of Primary Care,   
Tower Building,  
University of Nottingham,  
NG7 2RD

**Jo Leonardi-Bee**  
Division of Epidemiology and Public Health,   
Clinical Sciences Building,  
University of Nottingham,   
NG5 1PB  
  
**Stephen Sutton**  
Institute of Public Health   
University of Cambridge  
CB2 0SR  
  
**Felix Naughton**  
School of Health Sciences  
University of East Anglia  
NR4 7TJ

**Michael Ussher**  
Population Health Research Institute  
St. George’s, University of London SW17 0RE &

Institute for Social Marketing and Health  
University of Stirling  
FK9 4LA

**Catherine Hewitt**  
**Steve Parrott**  
**Judith Watson**  
**Charlie Welch**

York Trials Unit  
Department of Health Sciences  
University of York  
YO10 5DD

**Trial registration**

ClinicalTrials.gov Identifier: NCT03231553 (Trial closed)

**Abstract 301**

**Aims**To test efficacy of “MiQuit’, a tailored, self-help, text message stop smoking programme for pregnancy, as an adjunct to usual care (UC) for smoking cessation in pregnancy.

**Design**

Multicentre, open, two-arm, parallel-group, superiority randomised controlled trial (RCT) and a Trial Sequential Analysis (TSA) meta-analysis combining trial findings with two previous ones.

**Setting**

24 English hospital antenatal clinics.

**Participants**

1002 pregnant women who were ≥16 years old, were ≤ 25 weeks gestation, and smoked ≥ one daily cigarette and accepted information on cessation with no requirement to set quit dates.

**Interventions**

UC or UC plus ‘MiQuit’: 12 weeks of tailored, smoking cessation text messages focussed on inducing and aiding cessation.

**Measurements**

*Primary outcome*: biochemically-validated cessation between 4 weeks after randomisation and late pregnancy. *Secondary outcomes*: shorter and non-validated abstinence periods, pregnancy outcomes and incremental cost-effectiveness ratios.

**Findings**

*RCT*: cessation was 5.19% (26/501) and 4.59% (23/501) in MiQuit and UC groups [adjusted odds ratio (adj OR) for quitting with MiQuit versus UC, 95% confidence interval (CI), 1.15 (0.65 to 2.04)]; other abstinence findings were similar, with higher point estimates. Primary outcome ascertainment was 61.7% (309) and 67.3% (337) in MiQuit and UC groups with 71.1% (54/76) and 69.5% (41/59) abstinence validation rates, respectively. Pregnancy outcomes were similar and the incremental cost per Quality-Adjusted Life Year was -£1,118 (95% CI -£4,806 to £1,911). More MiQuit group women reported making at least one quit attempt (adj OR (95% CI) for making an attempt, 1.50 (1.07 to 2.09).   
  
*TSA Meta-analysis*: This found no significant difference in prolonged abstinence between MiQuit and UC (pooled OR 1.49, adjusted 95% CI 0.62 to 3.60).

**Conclusions**

Irrespective of whether they want to try quitting, when offered a tailored, self-help, text message stop smoking programme for pregnancy (MiQuit) as an adjunct to usual care, pregnant women are not more likely to stop smoking until childbirth but they report more attempts at stopping smoking.

**BACKGROUND**Smoking in pregnancy is strongly associated with increased risks of miscarriage, stillbirth, prematurity, low birthweight, perinatal morbidity and mortality, neo-natal and sudden infant death,1 poorer infant cognition and adverse infant behavioural outcomes.2 3 In high income countries 11% to 25% of pregnant women smoke4 and rates are increasing in developing ones.5 In England, the highest rates are seen amongst younger and socially disadvantaged women.6 Smoking-attributable annual UK maternal and infant health care costs were estimated as £87.5 million in 20107 and the extra healthcare cost, generated by each child born to women who smoked in pregnancy until age 5, is estimated as £222 (2015 prices).8 After conception, around half of women who smoke try quitting9 and many want help10 but few interventions can assist them. Behavioural support has a strong evidence base11 and many women use Nicotine Replacement Therapy (NRT)12-14, which may be less effective in pregnancy.15Financial incentives contingent on cessation are effective but infrequently provided.16

Self-help behavioural support for smoking cessation in pregnancy increases the odds of cessation (OR 1.83, 95% CI 1.23 to 2.73).17 Self-help consists of structured programmes that develop quitting skills without health professional involve

ment17, and can be delivered digitally, as text messages.18 Text message cessation support is effective for non-pregnant people motivated to make a quit attempt19-21 and, is likely to work in pregnancy. However, generic programmes for non-pregnant people are not likely to be effective for pregnant women because these effectively ignore women’s gestation and their desire to protect the fetus which are both key cessation motivations in pregnancy.9 Generic programmes also typically include recommendations on exercise and avoiding weight gain which are inappropriate in pregnancy. Behavioural support tailored to users’ contexts enhances the likelihood of this working22, therefore, text support which is relevant in pregnancy and builds on pregnant women’s motivations for quitting would be expected to engender enthusiastic engagement and be more likely to work.

We developed a tailored, self-help, text message stop smoking programme for pregnancy called MiQuit. In a feasibility RCT, in MiQuit and control groups, validated 7-day point prevalence abstinence at 12 weeks was 12.5% and 7.8% respectively (OR 1.68, 95% CI 0.90 to 3.16)23 and in a multi-centre pilot RCT, prolonged abstinence from smoking, validated in late pregnancy was 5.4% (MiQuit) and 2.0% (control) (OR 2.70, 95% CI 0.93-9.35).24 Here we report a comprehensive evaluation of MiQuit, including a third RCT with economic analysis and a Trial Sequential Analysis (TSA) 25 of all MiQuit trials.

**METHODS**

This was an individually randomised, multicentre, parallel group, outcome assessor-blind, superiority RCT, with participants recruited from 24 English National Health Service (NHS) hospital antenatal clinics between December 2017 and February 2019. Further details are in the published protocol.29 Participants were eligible if they were not already using text message support, smoked at least one daily cigarette (five before pregnancy), were 16 years or older, up to 25 weeks gestation and able to receive and understand English text messages. During antenatal visits, potential participants were identified, given participant information sheets and, where possible, consented. Alternatively, consent was obtained verbally later, by telephone.

Baseline data were collected and, participants were randomised in a 1:1 ratio using York Clinical Trials Unit’s online randomisation platform. Randomisation used computer generated blocks of randomly varying size (4, 6 and 8 allocations), stratified by gestation at baseline (<16 weeks or ≥16 weeks). Following randomisation, researchers posted information packs to participants which gave details of their study allocations; the unmasked researchers had no further study involvement.

**Interventions and procedures**

*Usual care (UC)*: Participants could use any smoking cessation information, advice or support available to them within usual NHS antenatal care and were given a the “Baby on the way, quit today” smoking cessation booklet (see Supplementary materials).

*Intervention*: UC plus the 12-week MiQuit programme starting 2 days after enrolment. Full details of MiQuit are published elsewhere.23 26 MiQuit was designed for any pregnant woman who smokes. In those who lack motivation and are not ready to try stopping, it aims to encourage quit attempts and to ‘induct’ women into quitting. Women who want to try stopping are encouraged to set a quit date. Messages are personalised using 14 recipient characteristics, such as name, week of gestation, partner’s smoking,23 26 nicotine dependence27 28 and, for those who set them, quit dates. Messages are more frequent early in the programme and the number sent varies between users; in the pilot study, the average number sent to each participant was 84. Messages include information on fetal development, motivation for and preparing to stop, managing cravings and withdrawal, combatting smoking ‘triggers’ and preventing lapses. Users can vary text frequency by texting MORE or LESS, or end messages with STOP. After texting HELP, they receive ‘on-demand’ support. Texting SLIP provides tips for combatting urges and QUIZ initiates a texted trivia game to distract from urges.

At baseline, we asked about education, ethnicity, gestation; pre-pregnancy and current daily cigarettes smoked; nicotine dependence;27 strength and frequency of smoking urges29; intention to quit; whether a quit date was set; number of pregnancies beyond 24 weeks, partner’s or significant other’s smoking, and health status (EQ-5D-5L).30

Four weeks after randomisation, masked to study allocation, a researcher phoned participants to ask about smoking in the previous week and repeated EQ-5D items; if no contact occurred, we texted and emailed weblinks to online questionnaires or mailed paper copies. At 36 weeks gestation, a researcher called again and initially, when still masked, asked about smoking in the past week and since the earlier call; quit attempts; use of cessation support and EQ-5D. If participants reported 7-day smoking abstinence, we arranged hospital or home visits to collect exhaled-breath carbon monoxide (CO) readings and/or saliva samples for validation. Alternatively, we posted ‘self-donation’ saliva collection packs with instructions. Before providing saliva, women were asked if they had smoked and / or used NRT or e-cigarettes in the previous week. We offered £5 shopping vouchers for provision of complete data at each contact and, if this was provided for all 3 contacts were, an additional £10 one was offered (£45 maximum). Additionally, we offered a £30 voucher following successful validation visits. We sought pregnancy outcome data from hospital records.

**Outcomes**

The primary outcome was self-reported prolonged abstinence between 4 weeks post-randomisation and late pregnancy, at around 36 weeks gestation, with biochemical validation of self-reported 7-day abstinence at the later time point. Biochemical validation was based on an exhaled CO reading with a cut-point of ≤9ppm, and/or saliva cotinine (cut-point ≤10 ng/mL) or anabasine (cut-point ≤0.2 ng/mL) readings. 31 Participants for whom there was no self-reported abstinence data at late pregnancy or whose abstinence reports remained unvalidated were assumed to be smoking (See Figure S1 in the supplementary material). There were six further abstinence outcomes (See Table S1 in the supplementary material). Other cessation outcomes collected at late pregnancy included the number of quit attempts lasting >24 hours, daily cigarette consumption and use of NHS stop smoking support. Pregnancy outcomes included miscarriage, stillbirth, birthweight, gestational age at birth, and maternal/infant hospital/ICU admissions. For economic analyses we monitored additional costs required to deliver MiQuit.

**Statistical analysis**

*Sample size*: We estimated the size of this RCT (called ‘*MiQuit3’*) such that, when combined in a Trial Sequential Analysis (TSA) with findings from MiQuit feasibility23 and pilot24 RCTs, the optimal information size would be reached. 25 The MiQuit pilot24 and MiQuit3 trials were very similar in design and the only major difference was that the pilot had a smaller sample size (n = 407). The MiQuit feasibility RCT23 was smaller still (n = 207) with a very similar design, but assessed the primary endpoint, validated cessation, at 12 weeks post randomisation, rather than the end of pregnancy, and only minor changes were made to MiQuit between the feasibility and other trials. We anticipated event rates, as in the MiQuit pilot RCT24, of prolonged abstinence from smoking at 4 weeks after enrolment until 36 weeks’ gestation as 5.4% in the MiQuit arm versus 2.0% for usual care (3.4% absolute difference). For 90% power in a two-sided test of size 5%, an optimal information size, unadjusted for diversity (D2=0%), of 1296 participants was required. As MiQuit feasibility23 and pilot24 RCTs had primary outcome data on 605 participants, MiQuit3 needed to recruit a further 692 (346 per group). Trial recruitment was very rapid so, three months after starting, we re-visited the information size estimate to investigate whether a larger MiQuit3 sample size would be sufficient to detect an overall smaller intervention effect in the TSA. With funders’ permission we increased the sample size of MiQuit3 to 1000 (500 per group); this sample size could detect a modestly smaller treatment effect and was consistent with available resources. We did not attempt to recruit an even larger sample because modelling of changes to the TSA-based sample size estimate showed that, with even quite large further increases in sample size (i.e. > 1000), the study would not have much more power to detect even smaller treatment effects. Further details of sample size estimation and how trials’ data were combined are published elsewhere.32

*Main RCT analysis*: All within-trial outcomes were analysed once at the trial’s conclusion following a TSC approved statistical analysis plan. Analyses were undertaken in Stata v16.0 following intention-to-treat principles, with participants being analysed as part of the group to which they were allocated, regardless of subsequent adherence to the allocated treatment.

Baseline data were summarised descriptively by group. The primary outcome and secondary abstinence outcomes were analysed using Firth logistic regression models, with allocation, weeks’ gestation at baseline (the stratification factor) and recruitment site included as fixed effects. Odds ratios (ORs) with 95% profile penalised likelihood confidence intervals and estimated risk differences with Wald 95% confidence intervals were obtained from the fitted models. The primary analysis was an intention to treat analysis with those lost to follow up assumed to be still smoking (i.e. outcome data were assumed to be missing not at random). It was anticipated that there could be differences in baseline “risk” of abstinence across sites (e.g. due to different support being available, different patient demographics etc.). To model this outcome heterogeneity, we used fixed effects for site (as opposed to fitting random intercepts for sites) for a couple of reasons; 1) to be consistent with the approach used in the previous MiQuit trials in order to facilitate synthesis 2) due to concerns about obtaining a reasonable estimate of the between-site variance with a relatively small number of sites. Several sensitivity analyses of the primary outcome were undertaken to investigate the possible influence of additional baseline covariates (partner’s smoking status, strength of nicotine dependence and educational attainment), missing data assumptions (via imputation methods) and the choice of analysis model. CACE analyses were undertaken using an instrumental variable approach to explore the impact of compliance (time they spent on the programme (>4 weeks vs <=4 weeks) and self-reported receipt of texts) on the primary outcome.

Binary pregnancy outcomes (infant mortality, hospital/ICU admissions, pre-term birth) were analysed using Firth logistic regression models adjusting for allocation, recruitment site, weeks’ gestation at baseline, strength of nicotine dependence and maternal education. Continuous pregnancy outcomes (birthweight and gestational age) were analysed using linear regression of the untransformed response on the same set of covariates outlined above. Birthweight and infant ICU admissions were analysed at the level of the participating mother (as opposed to the individual infant for multiple births).

*Trial sequential analysis meta-analysis:*  A prospective cumulative meta-analysis approach based on a random effects model was used to pool the trial results with those from the two previous trials. 23 24 To overcome issues related to multiple testing within the cumulative meta-analysis, a TSA was also conducted to assess whether the cumulative Z curve crosses the TSA monitoring boundary and to estimate an adjusted 95% confidence interval for the pooled odds ratio. An inner wedge was applied. Inferences concerning the effectiveness of MiQuit were based on the comparison of this pooled odds ratio and its associated cumulative Z score with pre-determined trial sequential monitoring boundaries. The analyses were conducted using the TSA program (developed by The Copenhagen Trial Unit, Center for Clinical Intervention Research, Denmark). The main TSA analysis investigated the confidence we could have in findings with respect to the anticipated 3.4% difference between MiQuit and usual care and, a sensitivity analysis investigated the likelihood that a smaller 2% difference might be present. However, it is worth noting that, due to the substantial health gains which accrue from stopping smoking, even smaller differences than this would be considered clinically effective if they could be robustly detected.33

*Economics:*   As both arms were eligible to receive the same cessation support from NHS SSS, the costs of providing this were assumed to be the same and were excluded from the analysis, therefore the only additional costs were those attributable to the MiQuit3 intervention. These included the cost per text message sent, and the monthly cost of providing a virtual reply number. The ‘per participant’ cost was estimated by dividing the total cost by the number of participants in the experimental arm. All costs were in 2018-2019 prices. The ‘per-participant’ cost and quit rates from MiQuit3 trial arms were inputted to the Economics of Smoking in Pregnancy (ESIP) model34 35, which performed a cost-utility analysis from a NHS perspective over both the maternal and infant lifetimes, estimating an incremental cost per additional Quality-Adjusted Life Year (QALY) ratio and return on investment (defined as savings in healthcare expenditure). ESIP includes costs and health outcomes associated with several long term health conditions as well as pregnancy morbidities which have been associated with smoking.34 35 Costs and outcomes were discounted at 3.5%, and a probabilistic sensitivity analysis was performed to indicate uncertainty.36 37   EQ-5D was collected because the ESIP was still in development alongside the trial. However, as the ESIP model was complete and validated before the trial analysis was undertaken ESIP was used in preference to the trial EQ-5D data.

**FINDINGS**

Between December 2017 and February 2019, 3,964 pregnant smokers at 25 English antenatal clinics were assessed for eligibility. Of these, 1,002 (25.3%) were recruited to the study, with 501 participants being randomised to each arm. 24 sites recruited at least one patient, with sites recruiting a median of 34 patients (IQR = 12.5 to 49).

Figure 1 shows participant flow through the study. Of the 1,002 participants, 739 (73.8%) were followed up at 4 weeks and 646 (64.5%) in late pregnancy. Pregnancy outcomes were available for 930 (92.8%) participants. Thirty-eight (3.8%) participants fully withdrew (withdrawal of consent n = 24, fetal death n = 14), 21 (4.2%) in the MiQuit group and 17 (3.4%) in the control group. Of the 38 participants who fully withdrew, 5 provided data at 4 weeks but none did in late pregnancy. 17 of the 21 withdrawals were prior to completion of the MiQuit programme. 28 participants who sent a STOP text were considered to have withdrawn from the MiQuit programme, but not from the trial. Therefore, 456 (91.0%) participants allocated to MiQuit remained on the programme for the full 87-day duration.

**Baseline data**

Participants’ characteristics were similar in both groups and are summarised in Table 1. Participants were predominantly white, had an average age of 27.3 years and average gestation of 15.0 weeks at enrolment. Self-reported daily cigarette consumption was generally lower at the time of the baseline visit than prior to pregnancy, with 856 (85.4%) participants reporting lower consumption at enrolment than before pregnancy. Strength of nicotine dependence was generally low to moderate, with 989 (98.7%) scoring less than or equal to four on the Heaviness of Smoking Index.27 The 646 participants who were followed up at late pregnancy had reasonably similar characteristics, with educational attainment being a possible exception (see supplementary material Table S2).

**Abstinence outcomes**

Of the 1,002 participants, 356 (35.5%) were lost to follow up in late pregnancy: 192 (38.3%) in the MiQuit group and 164 (32.7%) in the control group. Of the 646 (64.5%) participants followed up in late pregnancy, 135 (20.9%) reported 7-day abstinence and, of these 95 (70.4%) underwent biochemical validation; six had CO readings only, 59 had CO readings and saliva samples, and 30 had saliva only. Details of the biochemical validation are in Figure S2. 101 (15.6%) of the 135 women who reported 7-day abstinence also reported smoking no more than five cigarettes between 4 weeks post-randomisation and the later follow up point, 54 in the MiQuit group and 47 in the control group. 32 of these participants did not provide either an CO reading or a saliva sample. Hence 69 participants who reported both prolonged and 7-day abstinence underwent some form of validation: 66.7% (36/54) in the MiQuit group and 70.2% (33/47) in the control group. Figure 2 details primary outcome ascertainment.

Forty-nine (4.9%) participants had values below relevant validation test thresholds and were classed as abstinent, 26 (5.19%) were in the MiQuit and 23 (4.59%) in the control group. The adjusted odds ratio (OR) was 1.15 (95% CI 0.65 to 2.04) and, the adjusted difference in the proportions was 0.76% (-2.38% to 3.89%) (Table 2). Treatment effect estimates for abstinence outcomes 2 – 7 are broadly similar to the primary outcome estimate, however, those reflecting shorter abstinence periods (outcomes 3-7) were more favorable towards MiQuit, albeit with reasonably wide confidence intervals that easily included OR = 1 (Table 2).

Further adjustment for partner’s smoking status, nicotine dependence and educational attainment did not materially change the estimates, although there was some evidence that these adjustments led to slightly improved model fit (see Table S3). The proportion of participants who were validated as abstinent, out of those who self-reported abstinence (either prolonged or 7-day) was similar in both groups. Of the participants in the MiQuit group who reported prolonged abstinence, 48.1% were validated as abstinent, compared with 48.9% in the control group. Of the participants in the MiQuit group who reported 7-day abstinence, 50.0% were validated as abstinent, compared with 49.2% in the control group.

Missing outcome data (and missing values of variables included in the imputation model) were imputed using multiple imputation by chained equations, assuming these data were missing at random (MAR). The primary analysis model was fitted to each of the imputed datasets, with the point estimates being combined using Rubin’s rules and profile penalised likelihood confidence intervals being obtained following the approach described by Heinze.38 39 This gave an OR of 1.14 (95% CI 0.66 to 1.98) and similar inference to the primary analysis. Tables S4-9 and Figures S7-10 present findings from analyses exploring variation in the missing data assumptions, with full details of sensitivity analyses and alternative estimands, provided in the supplement. We also explored the sensitivity of the results to departures from MAR less extreme than missing = smoking and, allowed the missingness mechanism to vary by randomised group.40 Findings suggested that both primary and imputed data analyses were reasonably robust, as relatively implausible assumptions about the missing data mechanisms is required for the primary outcome conclusions to be altered (Table 3 and Figure S10).

**Trial sequential analysis (TSA)**

A meta-analysis of the three MiQuit trials found no significant difference in the effectiveness of MiQuit compared with usual care (pooled OR 1.49, 95% adjusted-confidence intervals 0.62 to 3.60, p=0.12), with low levels of heterogeneity (I2 = 10%) and diversity (D2 = 17%, 95% confidence intervals 0 to 64%). Due to the estimated diversity, the diversity-corrected optimal information size was increased from 1296 to 1555 participants. The TSA for this analysis demonstrates that the diversity-adjusted optimal information size was reached, but the monitoring boundary for superiority had not been crossed. However, the inner wedge had been crossed (Figure S3), thereby indicating evidence of futility, such that further trials of this intervention may not be required. In the sensitivity analysis, where a smaller absolute difference of 2% was anticipated between the intervention groups, the diversity-adjusted optimal information size was 3669. The cumulative Z-statistic did not reach the optimal information size and had not crossed the trial sequential monitoring boundary, thereby indicating that further trials are required before a firm conclusion regarding the effectiveness of the intervention can be concluded (Figure S4).

**Use of stop-smoking services and strategies**

Table 4 summarises participants’ use of stop smoking support as reported in late pregnancy. Of 646 participants followed up at late pregnancy, 509 (78.8%) indicated that they had either used a form of cessation support or talked to a health professional about stopping smoking (251 in the MiQuit group and 258 in the control group) and 99 (15.3%) indicated that they had not used any.

**Pregnancy outcomes**

Pregnancy outcomes were available for 930 (92.8%) participants (922 single births and 8 twin births). There were 911 live single births, 8 live twin births (hence 927 live infants born), 8 miscarriages and 3 stillbirths. Of the 72 participants for whom no pregnancy outcome data were available, 13 had fetal deaths; 24 withdrew consent, including for provision of pregnancy outcomes and for the remaining 35 these data were missing without explanation. The timing of the 13 fetal deaths were unknown, meaning these cannot be classed as either miscarriages or stillbirths. However, these fetal deaths are included as part of the fetal mortality outcome reported below. Pregnancy outcomes data are summarised in the supplementary material (Tables S10-12).

The adjusted ORs for the risk of miscarriage, stillbirth and fetal mortality in the MiQuit group compared with control were 0.32 (95% CI 0.06 to 1.20), 0.25 (95% CI 0.01 to 1.95) and 0.54 (95% CI 0.23 to 1.21) respectively (Table 5a). There is little evidence to support the hypothesis that the MiQuit programme influences the likelihood of maternal hospital admissions (adjusted OR 1.07 (95% CI 0.44 to 2.63)), infant ICU admissions (adjusted OR 1.10 (95% CI 0.70 to 1.73)), or pre-term births (adjusted OR 0.86 (95% CI 0.58 to 1.27)). Findings were similar when gestational age at birth was treated as a continuous outcome (adjusted difference 0.12 weeks (95% CI -0.16 to 0.40)). There was also little evidence to suggest MiQuit has any substantial effect on birthweight (adjusted difference 0.05kg (95% CI -0.03 to 0.12)) (Table 5b and 5c).

**Non–abstinence smoking outcomes**

Among participants who provided data at the late pregnancy follow up, those in the MiQuit group reported smoking slightly fewer daily cigarettes than those in the control group [mean (SD) 4.0 (3.9) and 4.9 (5.0) for MiQuit and control groups, respectively (Table S13). Additionally, MiQuit group women were more likely to report having made at least one quit attempt lasting more than 24 hours during the study; 239 (78.9%) of the MiQuit group who responded to this item reported at least one quit attempt, compared with 230 (71.0%) in the control group, adjusted OR = 1.50 (95% CI 1.07 to 2.09).

**Economics**

The incremental cost of the MiQuit intervention was £3.96 per participant; Table 4 shows that use of other cessation support was very similar in trial groups so, the assumption that costs of providing this to each group would also be similar appears reasonable. Using a lifetime horizon for ESIP analyses, for combined maternal and offspring outcomes, the incremental cost per QALY was -£1,118, (95% CI -£4,806 to £1,911) and, the estimated return on investment was £2.11 in healthcare savings for every pound spent on MiQuit by the NHS, (95% CI, - £7.92 to £14.98). Figures S5 and S6 show the cost effectiveness acceptability curve and the cost effectiveness plane.

**DISCUSSION**

This trial provides little evidence that ‘MiQuit’, a text message, self-help support programme offered to pregnant women who expressed interest in receiving information about stopping smoking, increases prolonged cessation rates in pregnancy compared with usual care. There is also little evidence that MiQuit affects pregnancy outcomes. However, women randomised to MiQuit, reported smoking fewer cigarettes and were more likely to report at least one quit attempt; additionally, modelling suggested that, if MiQuit demonstrated only minimal efficacy, the text message programme could prove highly cost-effective.

Rates of trial missing outcome data are a potential weakness. Despite repeated attempts, 26.5% of participants could not be contacted at first follow up, and 35.5% could not in late pregnancy; at both follow ups, 5-6% fewer intervention group participants responded. Researchers who contacted participants were masked to study allocations, so different response rates are more likely due to participant behaviour. The greater number of text message contacts made to intervention group women may have made some less likely to respond to follow up calls. However, we assumed those lost to follow up were smoking, a likely conservative assumption given that there was more missing outcome data in the MiQuit group. Furthermore, sensitivity analyses suggested reasonably implausible assumptions regarding the unobserved abstinence data would be required before the primary analysis reached substantively different conclusions, a phenomenon documented by others.41 Additionally, although we validated 70.4% of abstinence reports and, may have not identified some participants with positive outcomes, there was little evidence that trial groups had different rates of “failed” validation so, it seems unlikely that this issue invalidates the principal findings.

Study strengths include the robust assessment of unforeseen potential harms, potential generalisability of findings and study size. Pregnancy outcomes were obtained for 93% of participants and, to our knowledge, this is the largest and most comprehensive evaluation of a text message programme for smoking cessation in pregnancy. One would not expect MiQuit to impact adversely on pregnancy outcomes and, no such effect was found. As the trial recruited from routine antenatal care settings, MiQuit was delivered as an adjunct to usual care and around one-quarter of eligible women joined the trial, study findings are probably generalisable to women attending routine UK antenatal care. Additionally, the MiQuit3 RCT recruited 46% more participants than was originally envisaged in the study sample size calculation, and was the final component in an evaluation which included economic and trial sequential analyses so, a false negative finding is unlikely.

A Cochrane review found ‘moderate‐certainty evidence’ that automated text message interventions promote prolonged smoking abstinence.42 Only one study from this review enrolled pregnant women and this reported a relative risk (95% CI) for 30-day abstinence due to the ‘Quit4Baby’ text intervention of 1.34 (1.09 to 1.64).43 One simple explanation for MiQuit3 trial findings is that MiQuit is not effective or, at least, not as effective as the impact we sought to demonstrate. However, since this is a cheap and acceptable intervention44 and, it is difficult to see how it would cause harm, it it reasonable to consider why text messaging used for smoking cessation in other studies and, particularly by non-pregnant quitters, appears more effective. Almost all Cochrane review studies advertised for participants so, those enrolled are more likely to have been motivated for cessation42. Some study procedures may also have selected out motivated people as participants. For example, in the ‘txt2stop’ RCT, participants had to agree a quit date before enrolling45 and in the ‘Quit4Baby’ RCT, 508 participants were recruited from 35,957 US women signed up to an antenatal health text information service;43 so, one would expect more strongly cessation-motivated women to have joined that trial too. In contrast, 25.3% of eligible women participated in MiQuit3; they could join if they agreed to receive information about stopping and they were not required to set quit dates. Hence, it is plausible that, participants in this and earlier MiQuit trials would have less motivation to quit, an observation which may partially explain the smaller treatment effects found in the MiQuit3 trial compared with other RCTs of similar text interventions.

We found no evidence that MiQuit offered as an adjunct to usual care results in a 3.4% or more increase in prolonged cessation by pregnant women, and, our studies also do not rule out MiQuit having a smaller but, clinically-effective impact on cessation. As MiQuit is a very cheap intervention the low, albeit imprecise, incremental cost per QALY estimate suggests that, with only a slightly larger treatment effect than the 0.6% difference in quit rates found in the MiQuit3 RCT, MiQuit would very likely prove cost-effective and cost saving to healthcare providers. In all MiQuit studies, the text message programme was offered to women who simply agreed to receive information on stopping smoking and so, this was aimed at both encouraging quitting (‘cessation-induction’) and helping women succeed in quit attempts (‘aid-to-cessation’). Given the successful way text message systems have been used in trials which have reported since MiQuit was developed, it would be logical to test MiQuit as an ‘aid to cessation’, offered only to pregnant women who are motivated try stopping and who agree to set quit dates. MiQuit users reported positive changes in smoking behaviours, and the imprecise point estimates in treatment effects for causing shorter durations of abstinence than measured by the primary outcome, were overwhelmingly in a positive direction. Hence, it is plausible, that if MiQuit were to be used by only motivated quitters, as a cessation aid, it would have more pronounced effects. As most pregnant women try stopping soon after conception9, any effects could be maximised by offering MiQuit earlier in pregnancy than was possible in the MiQuit3. Also, as women's motivation to quit may fluctuate in pregnancy, the effect of text message support might be further increased by adapting messages to these fluctuations.

As it is implausible that text systems like MiQuit could harm pregnant women or babies, and these have such potential for cost effectiveness through minor impacts on smoking behaviours, further studies testing MiQuit or similar texted cessation programmes in ways suggested above are required. However, even RCTs testing intensive behavioural and pharmacological cessation interventions for pregnant women can have difficulty demonstrating prolonged abstinence periods. This is probably because such RCTs have generally recruited women after 12 weeks of pregnancy, and trials’ participants include women who have not managed, or perhaps not even tried to stop smoking by then15 46 and some participants might be less able or less motivated to stop smoking than pregnant women in general. To robustly detect very small differences in prolonged smoking cessation rates would require substantial resources; our TSA sensitivity analysis showed that, to detect 2% quit rate difference, 2062 more RCT participants’ data would need adding to the TSA meta-analysis. Perhaps future evaluations of texted cessation programmes should consider using outcomes which are proxies for prolonged cessation, but which are indicative of positive behavioural change? For example, shorter abstinence periods, or the proportion of participants making cessation attempts could be primary outcomes in RCTs of texted cessation programmes. Shorter abstinence periods have been demonstrated as important for fetal health47, and in both non-pregnant people48 49 and in pregnant women50, quit attempts prompted by health professionals lead to cessation. Despite the massive impact of smoking in pregnancy, there are few evidence-based treatment options for pregnant women, so it is imperative that all interventions which display positive signals of effect are thoroughly evaluated.

**Contributions of authors**

Tim Coleman is study guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish; as corresponding author he attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors were involved in writing this paper. TC, JLB, SC, SS, MU, SP, CH and FN were all involved in securing funding and planning the work. All authors were involved at different stages of study conduct and CW, CH, JLB and MJ undertook study analyses.

**Independent Steering Committee**

Prof Paul Aveyard (Chair), Prof Jayne Marshall, Dr Elinor Olander and Dr Amy Whitehead

**Declaration of Interests**

This project was co-funded by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research programme (RP-PG-0109-10020) and Cancer Research UK (CRUK) (C11232/A23434). The views expressed in this article are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care (DHSC). Professor Coleman is a National Institute for Health Research (NIHR) Senior Investigator. The funders had no role in design, analysis, or decision to publish. The study was sponsored by the University of Nottingham; the authors alone decided to publish the paper and this was not influenced by the Sponsor. All authors work or worked in institutions which received the two research grants above; there are no other competing interests to declare.

**Exclusive licence**

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence (<http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.doc> ) to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution and convert or allow conversion into any format including without limitation audio, iii) create any other derivative work(s) based in whole or part on the on the Contribution, iv) to exploit all subsidiary rights to exploit all subsidiary rights that currently exist or as may exist in the future in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above. All research articles will be made available on an Open Access basis (with authors being asked to pay an open access fee—see <http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse> ). The terms of such Open Access shall be governed by a Creative Commons licence—details as to which Creative Commons licence will apply to the research article are set out in our worldwide licence referred to above.

**Transparency declaration**

Tim Coleman affirms that this 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 have been explained.

**Data sharing**

Reasonable requests for patient level data should be made to the corresponding author. Consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low. To gain access, data requestors will need to sign a data access agreement with the study sponsor (University of Nottingham).

**Ethics approval**

The trial was approved by Nottingham 1 Research Ethics Committee study (Ref.:17/EM/0327).

**Dissemination**

The research team will disseminate findings to participants after publication of principal trial findings as outlined in this manuscript.

**Patient & Public involvement**The MiQuit text system was developed and modified with input from pregnant women who had experience of smoking as were bids made to research funders. All trial materials were co-produced with PPI experts who will also be involved in production of lay dissemination materials.

**Acknowledgments**

In addition to listed authors, the **MiQuit3 trial team** includes:

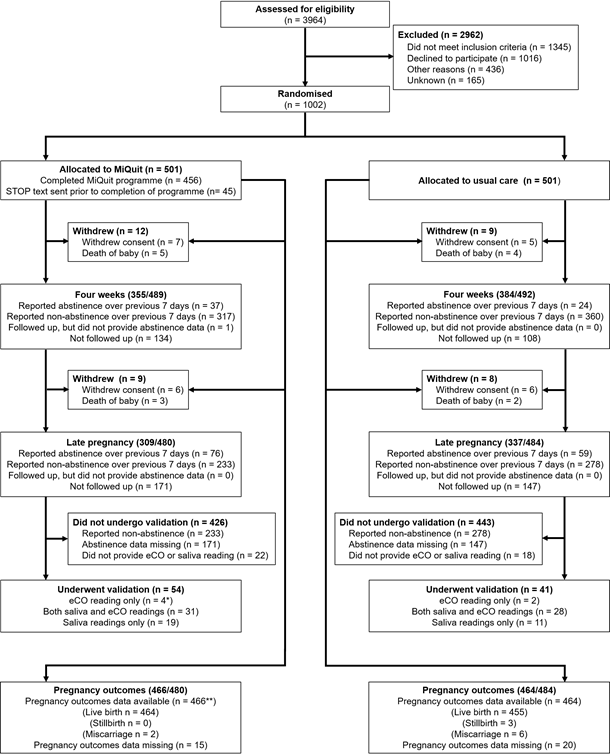
**University of Nottingham**   
*Research Administration*: Tom Coleman-Haynes, Sarah Connelly, Anne Dickinson, Emily Dickinson, Julia Howarth, Rebekah Howell, Darren Kinahan-Goodwin, Katarzyna Kowalewska, Lucy Phillips, Ross Thomson,

**University of Cambridge**James Brimicombe, Senior Data Manager.

**University of York Trials Unit**  
Matthew Bailey Software Development Team Lead; Tanya Pawson; Data Manager; Jonno Witts, Software Developer; Sarah Gardner, Data Manager

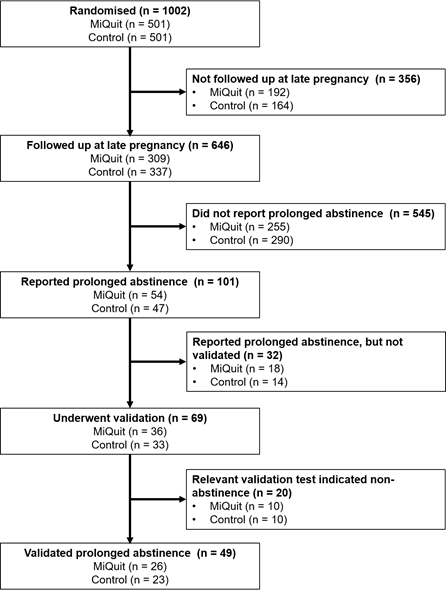
**Investigating sites\****Countess of Chester Hospital NHS Foundation Trust* - Kerry Barker-Williams and team   
*Mid Cheshire Hospitals NHS trust* -Janet Brown and team   
*Northumbria Healthcare NHS foundation Trust* - Helen Howlett and team  
*Newcastle Upon Tyne Hospitals NHS Foundation Trust* - Catherine McParlin and team  
*City Hospitals Sunderland NHS Foundation Trust* - Lesley Hewitt and team  
City Hospitals Sunderland NHS Foundation Trust - Laura Hipple and team  
*East Lancashire Hospitals NHS Trust* - Cathie Melvin and team  
*The Pennine Acute Hospitals NHS Trust* - Rachel Newport and team  
*United Lincolnshire Hospitals Trust* - Sunday Ikhena and team  
*United Lincolnshire Hospitals Trust* - Claire Hewitt and team  
*University Hospitals of Derby and Burton NHS Foundation Trust* - Elaine Coulborn and team, *Sherwood Forest Hospitals NHS Trust* - Jyothis Rajeswary and team  
*Birmingham Women’s NHS Foundation Trust* - Chloe O'Hara and team  
Heart of England NHS Foundation Trust - Mirriam Sangombe and team  
*University Hospitals of North Midlands NHS Tr*ust - Donna Brayford and team  
*Royal Berkshire NHS Foundation Trust* - Fidelma Lee and team  
*Plymouth Hospitals NHS Trust* - Heidi Hollands and team  
*Oxford University Hospitals NHS Foundation Trust* - Sarah Collins and team

\*Trusts with two teams had two hospital sites

**Figure 1:** **Flow diagram**\*Two participants also provided a saliva sample, but there was insufficient sample volume to obtain cotinine and anabasine readings

\*\*Pregnancy outcomes data available for one participant who fully withdrew

**Figure 2:** **Flow diagram showing ascertainment of primary abstinence outcome**



**Table 1:** **Key baseline characteristics by allocation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Randomised treatment group** | | |
| **MiQuit** (N = 501) | **Control** (N = 501) | **Total** (N = 1002) |
| **Age (years)** |  |  |  |
| Mean (SD) | 27.1 (5.6) | 27.5 (5.7) | 27.3 (5.6) |
| Median (Q1, Q3) | 26.4 (22.7, 31.0) | 26.9 (23.2, 31.5) | 26.7 (22.9, 31.2) |
| Min, Max | 16.7, 43.4 | 16.4, 43.2 | 16.4, 43.4 |
| **Ethnicity, n (%)** |  |  |  |
| White | 469 (93.6) | 476 (95.0) | 945 (94.3) |
| Indian | 2 (0.4) | 2 (0.4) | 4 (0.4) |
| Pakistani | 5 (1.0) | 2 (0.4) | 7 (0.7) |
| Black Caribbean | 3 (0.6) | 2 (0.4) | 5 (0.5) |
| Black African | 2 (0.4) | 0 (0.0) | 2 (0.2) |
| Other Asian (non-Chinese) | 0 (0.0) | 1 (0.2) | 1 (0.1) |
| Mixed race | 18 (3.6) | 16 (3.2) | 34 (3.4) |
| Missing | 2 (0.4) | 2 (0.4) | 4 (0.4) |
| **Gestation at baseline (weeks)** |  |  |  |
| Mean (SD) | 14.9 (4.0) | 15.0 (3.8) | 15.0 (3.9) |
| Median (Q1, Q3) | 13.1 (12.3, 19.3) | 13.4 (12.3, 19.3) | 13.3 (12.3, 19.3) |
| Min, Max | 6.0, 24.7 | 6.0, 24.9 | 6.0, 24.9 |
| **Previous pregnancies beyond 24 weeks** |  |  |  |
| Mean (SD) | 1.3 (1.4) | 1.4 (1.4) | 1.3 (1.4) |
| Median (Q1, Q3) | 1.0 (0.0, 2.0) | 1.0 (0.0, 2.0) | 1.0 (0.0, 2.0) |
| Min, Max | 0.0, 7.0 | 0.0, 7.0 | 0.0, 7.0 |
| **Previous pregnancies beyond 24 weeks, n (%)** |  |  |  |
| Zero | 177 (35.3) | 162 (32.3) | 339 (33.8) |
| One or more | 324 (64.7) | 339 (67.7) | 663 (66.2) |
| **Partner's smoking, n (%)** |  |  |  |
| Single | 85 (17.0) | 81 (16.2) | 166 (16.6) |
| Partner a non-smoker | 90 (18.0) | 103 (20.6) | 193 (19.3) |
| Partner a smoker | 326 (65.1) | 317 (63.3) | 643 (64.2) |
| **Cigarettes/day before pregnancy** |  |  |  |
| Mean (SD) | 17.2 (9.0) | 16.7 (6.6) | 16.9 (7.9) |
| Median (Q1, Q3) | 15.0 (10.0, 20.0) | 15.0 (10.0, 20.0) | 15.0 (10.0, 20.0) |
| Min, Max | 5.0, 100.0 | 5.0, 40.0 | 5.0, 100.0 |
| **Cigarettes/day now** |  |  |  |
| Mean (SD) | 8.6 (5.5) | 8.9 (5.5) | 8.8 (5.5) |
| Median (Q1, Q3) | 8.0 (5.0, 10.0) | 8.0 (5.0, 10.0) | 8.0 (5.0, 10.0) |
| Min, Max | 1.0, 40.0 | 1.0, 40.0 | 1.0, 40.0 |
| **Time from waking to first cigarette, n (%)** |  |  |  |
| Within 5 minutes | 149 (29.7) | 148 (29.5) | 297 (29.6) |
| 6 - 30 minutes | 160 (31.9) | 174 (34.7) | 334 (33.3) |
| 31 - 59 minutes | 75 (15.0) | 75 (15.0) | 150 (15.0) |
| 1 - 2 hours | 68 (13.6) | 71 (14.2) | 139 (13.9) |
| More than 2 hours | 49 (9.8) | 33 (6.6) | 82 (8.2) |
| **Heaviness of Smoking Index\*** |  |  |  |
| Mean (SD) | 1.9 (1.4) | 2.0 (1.4) | 2.0 (1.4) |
| Median (Q1, Q3) | 2.0 (1.0, 3.0) | 2.0 (1.0, 3.0) | 2.0 (1.0, 3.0) |
| Min, Max | 0.0, 6.0 | 0.0, 6.0 | 0.0, 6.0 |
| **Strength of addiction\*\*, n (%)** |  |  |  |
| Low addiction | 306 (61.1) | 319 (63.7) | 625 (62.4) |
| Moderate addiction | 188 (37.5) | 176 (35.1) | 364 (36.3) |
| High addiction | 7 (1.4) | 6 (1.2) | 13 (1.3) |
| **Education, n (%)** |  |  |  |
| No formal qualifications | 78 (15.6) | 76 (15.2) | 154 (15.4) |
| GCSEs (or equivalent) | 266 (53.1) | 265 (52.9) | 531 (53.0) |
| A Levels (or equivalent) | 116 (23.2) | 109 (21.8) | 225 (22.5) |
| Degree or higher | 37 (7.4) | 46 (9.2) | 83 (8.3) |
| Missing | 4 (0.8) | 5 (1.0) | 9 (0.9) |
| **Urges to smoke in past 24 hours, n (%)** |  |  |  |
| Not at all | 14 (2.8) | 10 (2.0) | 24 (2.4) |
| A little of the time | 116 (23.2) | 115 (23.0) | 231 (23.1) |
| Some of the time | 209 (41.7) | 222 (44.3) | 431 (43.0) |
| A lot of the time | 98 (19.6) | 99 (19.8) | 197 (19.7) |
| Almost all of the time | 38 (7.6) | 36 (7.2) | 74 (7.4) |
| All of the time | 26 (5.2) | 19 (3.8) | 45 (4.5) |
| **Strength of urges in past 24 hours, n (%)** |  |  |  |
| No urges | 7 (1.4) | 5 (1.0) | 12 (1.2) |
| Slight | 134 (26.7) | 117 (23.4) | 251 (25.0) |
| Moderate | 185 (36.9) | 222 (44.3) | 407 (40.6) |
| Strong | 107 (21.4) | 95 (19.0) | 202 (20.2) |
| Very strong | 35 (7.0) | 36 (7.2) | 71 (7.1) |
| Extremely strong | 10 (2.0) | 10 (2.0) | 20 (2.0) |
| Missing | 23 (4.6) | 16 (3.2) | 39 (3.9) |
| **Seriously planning to quit?, n (%)** |  |  |  |
| Within next 2 weeks | 126 (25.1) | 127 (25.3) | 253 (25.2) |
| Within next 30 days | 137 (27.3) | 121 (24.2) | 258 (25.7) |
| Within next 3 months | 190 (37.9) | 208 (41.5) | 398 (39.7) |
| No | 46 (9.2) | 44 (8.8) | 90 (9.0) |
| Missing | 2 (0.4) | 1 (0.2) | 3 (0.3) |
| **Longest previous quit attempt, n (%)** |  |  |  |
| Quit not attempted | 125 (25.0) | 112 (22.4) | 237 (23.7) |
| Less than 2 weeks | 97 (19.4) | 114 (22.8) | 211 (21.1) |
| 2 - 5 weeks | 77 (15.4) | 62 (12.4) | 139 (13.9) |
| 6 - 11 weeks | 29 (5.8) | 43 (8.6) | 72 (7.2) |
| 12 weeks or more | 173 (34.5) | 170 (33.9) | 343 (34.2) |
| **How important is it to you to stop smoking at least until your baby is born?, n (%)** |  |  |  |
| Not at all | 4 (0.8) | 3 (0.6) | 7 (0.7) |
| A little | 15 (3.0) | 17 (3.4) | 32 (3.2) |
| Moderately | 62 (12.4) | 64 (12.8) | 126 (12.6) |
| Very much | 174 (34.7) | 152 (30.3) | 326 (32.5) |
| Extremely | 246 (49.1) | 264 (52.7) | 510 (50.9) |
| Missing | 0 (0.0) | 1 (0.2) | 1 (0.1) |
| **How confident are you that you can stop smoking until your baby is born?, n (%)** |  |  |  |
| Not at all | 34 (6.8) | 30 (6.0) | 64 (6.4) |
| A little | 97 (19.4) | 90 (18.0) | 187 (18.7) |
| Moderately | 189 (37.7) | 198 (39.5) | 387 (38.6) |
| Very much | 119 (23.8) | 124 (24.8) | 243 (24.3) |
| Extremely | 62 (12.4) | 58 (11.6) | 120 (12.0) |
| Missing | 0 (0.0) | 1 (0.2) | 1 (0.1) |

\*Heaviness of Smoking Index (HSI) based on number of daily cigarettes at time of the baseline visit and time from waking to first cigarette

\*\*Based on HSI: low addiction if HSI = 0, 1 or 2, moderate addiction if HSI = 3 or 4, high addiction if HSI = 5 or 6

**Table 2:** **Analysis of abstinence outcomes 1 to 7**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome\*** | **MiQuit** N = 501 | **Control** N = 501 | **Unadjusted OR** (95% CI) | **Unadjusted difference** (95% CI) | **Adjusted OR** (95% CI)\***\*** | **Adjusted difference** (95% CI)\*\*\* |
| **Abstinence 1** Validated prolonged abstinence  (primary outcome) | 26  (5.19%) | 23  (4.59%) | 1.14  (0.64 to 2.02) | 0.60%  (-2.07% to 3.27%) | 1.15  (0.65 to 2.04) | 0.76%  (-2.38% to 3.89%) |
| **Abstinence 2**  Self-reported prolonged abstinence | 54  (10.78%) | 47  (9.38%) | 1.17  (0.77 to 1.76) | 1.40%  (-2.33% to 5.12%) | 1.19  (0.78 to 1.80) | 1.64%  (-2.34% to 5.61%) |
| **Abstinence 3**  Seven-day abstinence at both 4 weeks (self-report) and late pregnancy (validated) | 14  (2.79%) | 10  (2.00%) | 1.41  (0.62 to 3.21) | 0.80%  (-1.09% to 2.69%) | 1.43  (0.64 to 3.30) | 1.18%  (-1.47% to 3.83%) |
| **Abstinence 4**  Self-reported seven-day abstinence at both 4 weeks and late pregnancy | 27  (5.39%) | 16  (3.19%) | 1.73  (0.92 to 3.25) | 2.20%  (-0.31% to 4.70%) | 1.79  (0.96 to 3.42) | 2.86%  (-0.18% to 5.91%) |
| **Abstinence 5**  Validated seven-day abstinence at late pregnancy | 38  (7.58%) | 29  (5.79%) | 1.34  (0.81 to 2.20) | 1.80%  (-1.29% to 4.89%) | 1.34  (0.81 to 2.23) | 2.02%  (-1.43% to 5.47%) |
| **Abstinence 6**  Self-reported seven-day abstinence at late pregnancy | 76  (15.17%) | 59  (11.78%) | 1.34  (0.93 to 1.93) | 3.39%  (-0.83% to 7.62%) | 1.37  (0.95 to 1.99) | 3.73%  (-0.65% to 8.11%) |
| **Abstinence 7**  Self-reported seven-day abstinence at 4 weeks | 37  (7.39%) | 24  (4.79%) | 1.58  (0.93 to 2.69) | 2.59%  (-0.36% to 5.55%) | 1.62  (0.96 to 2.78) | 3.11%  (-0.26% to 6.49%) |

\*Detailed specifications of abstinence outcomes 1 - 7 are given in Table S1 of the supplementary material.

\*\*Adjusted OR for allocation from Firth logistic regression model adjusting for weeks gestation at baseline (mean-centred) and recruitment site (penalised profile likelihood confidence interval).

\*\*\*Adjusted difference in proportions from Firth logistic regression model adjusting for weeks gestation at baseline (mean-centred) and recruitment site (Wald confidence interval with standard errors obtained via delta method).

**Table 3: Sensitivity of the primary analysis to variation assumptions used to impute missing primary outcome data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Informative missingness odds ratio** | **Odds ratio for allocation (95% CI)** | | |
| **MiQuit arm only** | **Control arm only** | **Both arms** |
| **0.0** | 1.13 (0.70 to 1.83) | 1.13 (0.70 to 1.83) | 1.13 (0.70 to 1.83) |
| **0.2** | 1.32 (0.80 to 2.18) | 1.01 (0.63 to 1.60) | 1.17 (0.72 to 1.90) |
| **0.4** | 1.50 (0.89 to 2.52) | 0.91 (0.58 to 1.42) | 1.20 (0.74 to 1.95) |
| **0.6** | 1.68 (0.99 to 2.87) | 0.83 (0.53 to 1.28) | 1.23 (0.75 to 1.99) |
| **0.8** | 1.85 (1.07 to 3.20) | 0.76 (0.50 to 1.17) | 1.24 (0.77 to 2.02) |
| **1.0** | 2.03 (1.16 to 3.53) | 0.71 (0.46 to 1.07) | 1.26 (0.78 to 2.05) |

**Table 4:** Use of smoking cessation support

|  |  |  |  |
| --- | --- | --- | --- |
| **Service/technology** | **Randomised treatment group** | | |
| **MiQuit** (N = 309) | **Control** (N = 337) | **Total** (N = 646) |
| Talked to GP/nurse about quitting, n (%) | 58 (18.8) | 63 (18.7) | 121 (18.7) |
| Talked to midwife about quitting, n (%) | 177 (57.3) | 187 (55.5) | 364 (56.3) |
| Text message support in addition to MiQuit, n (%) | 27 (8.7) | 14 (4.2) | 41 (6.3) |
| Attended individual NHS stop smoking service session, n (%) | 37 (12.0) | 35 (10.4) | 72 (11.1) |
| Attended group NHS stop smoking service session n (%) | 3 (1.0) | 4 (1.2) | 7 (1.1) |
| Used nicotine replacement therapy, n (%) | 80 (25.9) | 70 (20.8) | 150 (23.2) |
| Called stop smoking telephone helpline, n (%) | 4 (1.3) | 4 (1.2) | 8 (1.2) |
| Used e-cigarettes, n (%) | 130 (42.1) | 125 (37.1) | 255 (39.5) |
| Visited stop smoking website (e.g. NHS smokefree), n (%) | 43 (13.9) | 35 (10.4) | 78 (12.1) |
| Used stop smoking mobile phone app, n (%) | 23 (7.4) | 12 (3.6) | 35 (5.4) |
| Missing stop smoking service/technology usage data, n (%) | 16 (5.2) | 22 (6.5) | 38 (5.9) |

**Table 5a:** **Fetal mortality outcomes**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **MiQuit** | **Control** | **Unadjusted OR** (95% CI) | **Unadjusted difference** (95% CI) | **Adjusted OR** (95% CI) | **Adjusted difference** (95% CI) |
| **Miscarriage**  (<24 weeks gestation) | 2/466  (0.43%) | 6/464  (1.29%) | 0.33  (0.07 to 1.64) | -0.86%  (-2.05% to 0.32%) | 0.32  (0.06 to 1.20) | -2.37%  (-5.04% to 0.30%) |
| **Stillbirth**  (≥24 weeks gestation) | 0/466  (0.00%) | 3/464  (0.65%) | -\* | -0.65%  (-1.38% to 0.08%) | 0.25  (0.01 to 1.95) | -2.04%  (-5.07% to 1.00%) |
| **Fetal death** | 9/473  (1.90%) | 15/470  (3.19%) | 0.59  (0.25 to 1.36) | -1.29%  (-3.30% to 0.72%) | 0.54  (0.23 to 1.21) | -2.17%  (-5.01% to 0.66%) |

\*Undefined due to the absence of recorded cases of stillbirth in the MiQuit group

**Table 5b:** **Binary pregnancy outcomes**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **MiQuit** | **Control** | **Unadjusted OR** (95% CI) | **Unadjusted difference** (95% CI) | **Adjusted OR** (95% CI) | **Adjusted difference** (95% CI) |
| **Maternal hospital admission** | 10/464  (2.16%) | 9/455  (1.98%) | 1.09  (0.44 to 2.71) | 0.18%  (-1.66% to 2.02%) | 1.07  (0.44 to 2.63) | 0.23%  (-2.71% to 3.17%) |
| **Infant ICU admission** | 44/464  (9.48%) | 43/455  (9.45%) | 1.00  (0.65 to 1.56) | 0.03%  (-3.75% to 3.82%) | 1.10  (0.70 to 1.73) | 0.85%  (-3.24% to 4.94%) |
| **Pre-term**  (<37 weeks gestation) | 54/464  (11.64) | 62/455  (13.63) | 0.83  (0.57 to 1.23) | -1.99%  (-6.28% to 2.31%) | 0.86  (0.58 to 1.27) | -1.78%  (-6.32% to 2.76%) |

**Table 5c:** **Continuous pregnancy outcomes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome** | **MiQuit** | **Control** | **Unadjusted**  (95% CI) | **Adjusted difference** (95% CI) |
| **Birth Weight (kg)** N | 464 | 455 | 0.06  (-0.02 to 0.13) | 0.05  (-0.03 to 0.12) |
| Mean (SD) | 3.1 (0.6) | 3.0 (0.6) |
| Median (Q1, Q3), Min, Max | 3.1 (2.7, 3.5), 0.6, 4.8 | 3.1 (2.7, 3.5), 0.7, 4.5 |
| **Gestational age at birth (weeks)** |  |  | 0.16  (-0.12 to 0.44) | 0.12  (-0.16 to 0.40) |
| N | 464 | 455 |
| Mean (SD) | 38.7 (2.0) | 38.5 (2.3) |
| Median (Q1, Q3) | 39.0 (37.8, 40.0) | 39.0 (37.7, 40.0) |
| Min, Max | 27.9, 42.1 | 26.1, 42.3 |

**REFERENCES**

1. Smoking and the young. A report of a working party of the Royal College of Physicians. London: RCP, 1992.

2. Batstra L, Hadders-Algra M, Neeleman J. Effect of antenatal exposure to maternal smoking on behavioural problems and academic achievement in childhood: prospective evidence from a Dutch birth cohort. *Early Human Development* 2003;75(1-2):21-33. doi: <https://doi.org/10.1016/j.earlhumdev.2003.09.001>

3. Thapar A, Fowler T, Rice F, et al. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *AmJ Psychiatry* 2003;160(11):1985-89.

4. Lange S, Probst C, Rehm J, et al. National, regional, and global prevalence of smoking during pregnancy in the general population: a systematic review and meta-analysis. *The Lancet Global Health* 2018;6(7):e769-e76. doi: 10.1016/S2214-109X(18)30223-7

5. Oncken CA, Dietz PM, Tong VT, et al. Prenatal tobacco prevention and cessation interventions for women in low- and middle-income countries. *Acta Obstet Gynecol Scand* 2010;89(4):442-53. doi: 10.3109/00016341003678450 [published Online First: 2010/03/20]

6. McAndrew F, Thompson J, Fellows L, et al. Infant Feeding Survey 2010: Health and Social Care Information Centre, 2012.

7. Godfrey C, Pickett KE, Parrott S, et al. Estimating the costs to the NHS of smoking in pregnancy for pregnant women and infants. University of York: Public Health Research Consortium, 2010.

8. Vaz LR, Jones MJ, Szatkowski L, et al. Estimating the health-care costs of children born to pregnant smokers in England: cohort study using primary and secondary health-care data. *Addiction* 2018;113(7):1305-16. doi: 10.1111/add.14183 [published Online First: 2018/02/06]

9. Cooper S, Orton S, Leonardi-Bee J, et al. Smoking and quit attempts during pregnancy and postpartum: a longitudinal UK cohort. *BMJ Open* 2017;7(11) doi: 10.1136/bmjopen-2017-018746

10. Naughton F, Vaz LR, Coleman T, et al. Interest in and use of smoking cessation support across pregnancy and postpartum. *Nicotine & Tobacco Research* 2019 doi: 10.1093/ntr/ntz151

11. Chamberlain C, O'Mara-Eves A, Oliver S, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database Syst Rev* 2013;10:CD001055. doi: 10.1002/14651858.CD001055.pub4

12. Fahy SJ, Cooper S, Coleman T, et al. Provision of smoking cessation support for pregnant women in England: results from an online survey of NHS stop smoking services for pregnant women. *BMC Health Services Research* 2014;14(1):107. doi: 10.1186/1472-6963-14-107

13. Dhalwani NN, Szatkowski L, Coleman T, et al. Prescribing of nicotine replacement therapy in and around pregnancy: a population-based study using primary care data. *Br J Gen Pract* 2014;64(626):e554-60. doi: 10.3399/bjgp14X681361 [published Online First: 2014/09/03]

14. Cooper S, Orton S, Campbell K, et al. Attitudes to E-Cigarettes and Cessation Support for Pregnant Women from English Stop Smoking Services: A Mixed Methods Study. *International Journal of Environmental Research and Public Health* 2019;16(1):110. doi: doi:10.3390/ijerph16010110

15. Claire R, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 2020(3) doi: 10.1002/14651858.CD010078.pub3

16. Tappin D, Bauld L, Purves D, et al. Financial incentives for smoking cessation in pregnancy: randomised controlled trial. *BMJ* 2015;350 doi: 10.1136/bmj.h134

17. Naughton F, Prevost AT, Sutton S, et al. Self-help smoking cessation interventions in pregnancy: a systematic review and meta-analysis. [Review] [52 refs]. *Addiction* 2008;103(4):566-79.

18. Griffiths SE, Parsons J, Naughton F, et al. Are digital interventions for smoking cessation in pregnancy effective? A systematic review and meta-analysis. *Health Psychology Review* 2018:1-24. doi: 10.1080/17437199.2018.1488602

19. Abroms LC, Ahuja M, Kodl Y, et al. Text2Quit: results from a pilot test of a personalized, interactive mobile health smoking cessation program. *Journal of health communication* 2012;17 Suppl 1:44-53. doi: 10.1080/10810730.2011.649159

20. Abroms LC, Boal AL, Simmens SJ, et al. A randomized trial of Text2Quit: a text messaging program for smoking cessation. *American journal of preventive medicine* 2014;47(3):242-50. doi: 10.1016/j.amepre.2014.04.010

21. Free C, Whittaker R, Knight R, et al. Txt2stop: a pilot randomised controlled trial of mobile phone-based smoking cessation support. *Tobacco control* 2009;18(2):88-91. doi: 10.1136/tc.2008.026146

22. Livingstone-Banks J, Ordonez-Mena JM, Hartmann-Boyce J. Print-based self-help interventions for smoking cessation. *Cochrane Database Syst Rev* 2019;1:CD001118. doi: 10.1002/14651858.CD001118.pub4 [published Online First: 2019/01/10]

23. Naughton F, Prevost AT, Gilbert H, et al. Randomized Controlled Trial Evaluation of a Tailored Leaflet and SMS Text Message Self-help Intervention for Pregnant Smokers (MiQuit). *Nicotine & Tobacco Research* 2012;14(5):569-77. doi: 10.1093/ntr/ntr254

24. Naughton F, Cooper S, Foster K, et al. Large multi-centre pilot randomized controlled trial testing a low-cost, tailored, self-help smoking cessation text message intervention for pregnant smokers (MiQuit). *Addiction* 2017;112(7):1238-49. doi: 10.1111/add.13802. [published Online First: 2nd May 2017]

25. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61(1):64-75. doi: 10.1016/j.jclinepi.2007.03.013

26. Naughton F, Cooper S, Bowker K, et al. Adaptation and uptake evaluation of an SMS text message smoking cessation programme (MiQuit) for use in antenatal care. *BMJ Open* 2015;5(10):e008871. doi: 10.1136/bmjopen-2015-008871

27. Heatherton TF, Kozlowski LT, Frecker RC, et al. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *British Journal of Addiction* 1989;84(7):791-99.

28. Riaz M, Lewis S, Coleman T, et al. Which measures of cigarette dependence are predictors of smoking cessation during pregnancy? Analysis of data from a randomised controlled trial. *Addiction* 2016:n/a-n/a. doi: 10.1111/add.13395

29. West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology (Berl)* 2004;177(1-2):195-9. doi: 10.1007/s00213-004-1923-6 [published Online First: 2004/06/05]

30. Latvala E, Janhonen S. Helping methods used by nurses in a psychiatric hospital environment. *International Journal of Nursing Studies* 1998;35(6):346-52.

31. Benowitz NL, Bernert JT, Foulds J, et al. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. *Nicotine & Tobacco Research* 2019 doi: 10.1093/ntr/ntz132

32. Claire R, Gluud C, Berlin I, et al. Using Trial Sequential Analysis for estimating the sample sizes of further trials: example using smoking cessation intervention. *BMC Med Res Methodol* 2020;20(1):284. doi: 10.1186/s12874-020-01169-7 [published Online First: 2020/12/02]

33. West R. The clinical significance of "small" effects of smoking cessation treatments. *Addiction* 2007;102(4):506-9. doi: 10.1111/j.1360-0443.2007.01750.x

34. Jones M, Smith M, Lewis S, et al. A dynamic, modifiable model for estimating cost-effectiveness of smoking cessation interventions in pregnancy: application to an RCT of self-help delivered by text message. *Addiction* 2018;0(0) doi: doi:10.1111/add.14476

35. Jones MJ. The development of the Economic impacts of Smoking In Pregnancy (ESIP) model for measuring the impacts of smoking and smoking cessation during pregnancy [PhD]. University of Nottingham, 2015.

36. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press 2006.

37. Glick HA, Doshi JA, Sonnad SS, et al. Economic evaluation in clinical trials. Oxford: Oxford University Press 2014.

38. Heinze G, Ploner M, Beyea J. Confidence intervals after multiple imputation: combining profile likelihood information from logistic regressions. *Stat Med* 2013;32(29):5062-76. doi: 10.1002/sim.5899 [published Online First: 2013/07/23]

39. logistf: Firth’s Bias-Reduced Logistic Regression [program]. Version 1.23 version.

40. rctmiss: Stata module to analyse a RCT allowing for informatively missing outcome data version 0.12.4 [program]. Boston College Department of Economics.

41. Tompsett D, Sutton S, Seaman SR, et al. A general method for elicitation, imputation, and sensitivity analysis for incomplete repeated binary data. *Stat Med* 2020;39(22):2921-35. doi: 10.1002/sim.8584 [published Online First: 2020/07/18]

42. Whittaker R, McRobbie H, Bullen C, et al. Mobile phone text messaging and app-based interventions for smoking cessation. *Cochrane Database Syst Rev* 2019;10:CD006611. doi: 10.1002/14651858.CD006611.pub5 [published Online First: 2019/10/23]

43. Abroms L, Johnson P, Leavitt L, et al. A Randomized Trial of Text Messaging for Smoking Cessation in Pregnant Women. *American Journal of Preventive Medicine* 2017;53(6):781-90. doi: 10.1016/j.amepre.2017.08.002

44. Sloan M, Hopewell S, Coleman T, et al. Smoking Cessation Support by Text Message During Pregnancy: A Qualitative Study of Views and Experiences of the MiQuit Intervention. *Nicotine & Tobacco Research* 2017;19(5):572-77. doi: 10.1093/ntr/ntw241

45. Free C, Knight R, Robertson S, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. *Lancet* 2011;378(9785):49-55. doi: 10.1016/S0140-6736(11)60701-0

46. Chamberlain C, O'Mara-Eves A, Porter J, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database of Systematic Reviews* 2017(2) doi: <https://doi.org/10.1002/14651858.CD001055.pub5>

47. Reynolds CME, Egan B, Kennedy RA, et al. The implications of high carbon monoxide levels in early pregnancy for neonatal outcomes. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2019;233:6-11. doi: <https://doi.org/10.1016/j.ejogrb.2018.11.020>

48. Murray RL, Lewis SA, Coleman T, et al. Unplanned attempts to quit smoking: missed opportunities for health promotion? *Addiction* 2009;104(11):1901-09.

49. Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. *Cochrane Database Syst Rev* 2013(5):CD000165. doi: 10.1002/14651858.CD000165.pub4

50. Campbell KA, Cooper S, Fahy SJ, et al. 'Opt-out' referrals after identifying pregnant smokers using exhaled air carbon monoxide: impact on engagement with smoking cessation support. *Tobacco Control* 2017;26:300-06. doi: <https://doi.org/10.1136/tobaccocontrol-2015-052662>