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RESEARCH REPORT

ADDICTION SSA

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

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Abstract

Aims: To test the 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: Twenty-four English hospital antenatal clinics.

Participants: A total of 1002 pregnant women who were ≥16 years old, were ≤25 weeks gestation and smoked ≥1 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% CI = 1.15 [0.65–2.04]); 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 −£1118 (95% CI = −£4806–£1911). More MiQuit group women reported making at least one quit attempt (adj OR [95% CI]) for making an attempt, 1.50 (1.07–2.09). TSA meta-

analysis: this found no significant difference in prolonged abstinence between MiQuit and UC (pooled OR = 1.49, adjusted 95% CI = 0.62–3.60).

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.

KEYWORDS
pregnancy, self-help, smoking cessation, text messaging

INTRODUCTION

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 smoke [4] and rates are increasing in developing ones [5]. In England, the highest rates are seen among younger and socially disadvantaged women [6]. Smoking-attributable annual United Kingdom (UK) maternal and infant health care costs were estimated as £87.5 million in 2010 [7] 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 quitting [9] and many want help [10], but few interventions can assist them. Behavioural support has a strong evidence base [11] and many women use nicotine replacement therapy (NRT) [12–14], which may be less effective in pregnancy [15]. Financial 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 = 1.23–2.73) [17]. Self-help consists of structured programmes that develop quitting skills without health professional involvement [17] and can be delivered digitally, as text messages [18]. Text message cessation support is effective for non-pregnant people motivated to make a quit attempt [19–21] 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 foetus, 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 working [22], therefore, text support that 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 randomised controlled trial (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 = 0.90–3.16) [23] and in a multicentre 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 [26]. 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 the 'Baby on the way, quit today' smoking cessation booklet (see Supporting Information).

Intervention

This started 2 days after enrolment and consisted of UC plus the 12-week MiQuit programme. Full details of MiQuit are published elsewhere [23,27]. 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 [23,27], nicotine dependence [28,29] 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 [28]; strength and frequency of smoking urges [26]; intention to quit; whether a quit date was set; number of pregnancies beyond 24 weeks; and 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 web links 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 ≤9 p.p.m, 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 (Supporting information Figure S1). There were six further abstinence outcomes (Supporting information Table S1). 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/intensive care unit (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 TSA with findings from MiQuit feasibility [23] and pilot [24] RCTs, the optimal information size would be reached [25]. The MiQuit pilot [24] 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 RCT [23] 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 RCT [24], 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 UC (3.4% absolute difference). For 90% power in a two-sided test of size 5%, an optimal information size, unadjusted for diversity (D^2 = 0%), of 1296 participants was required. Because MiQuit feasibility [23] and pilot [24] RCTs had primary outcome data on 605 participants, MiQuit3 needed to recruit a further 692 (346 per group). Trial recruitment was very rapid, therefore, 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. ORs with 95% profile penalised likelihood CIs and estimated risk differences with Wald 95% CIs 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. because of 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; (i) to be consistent with the approach used in the previous MiQuit trials to facilitate synthesis; (ii) because of 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. Complier Average Causal Effect (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 and 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).

TSA 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% CI for the pooled OR. An inner wedge was applied. Inferences concerning the effectiveness of MiQuit were based on the comparison of this pooled OR 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 UC, and a sensitivity analysis investigated the likelihood that a smaller 2% difference might be present. However, it is worth noting that, because of the substantial health gains that accrue from stopping smoking, even smaller differences than this would be considered clinically effective if they could be robustly detected [33].

Economics

Because 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 to 2019 prices. The 'per-participant' cost and quit rates from MiQuit3 trial arms were inputted to the Economics of Smoking in Pregnancy (ESIP) model [34,35], 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 that 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, because 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, 3964 pregnant smokers at 25 English antenatal clinics were assessed for eligibility. Of these, 1002 (25.3%) were recruited to the study, with 501 participants being randomised to each arm. Twenty-four sites recruited at least one patient, with sites recruiting a median of 34 patients (IQR = 12.5–49).

Figure 1 shows participant flow through the study. Of the 1002 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. A total of 17 of 21 withdrawals were before

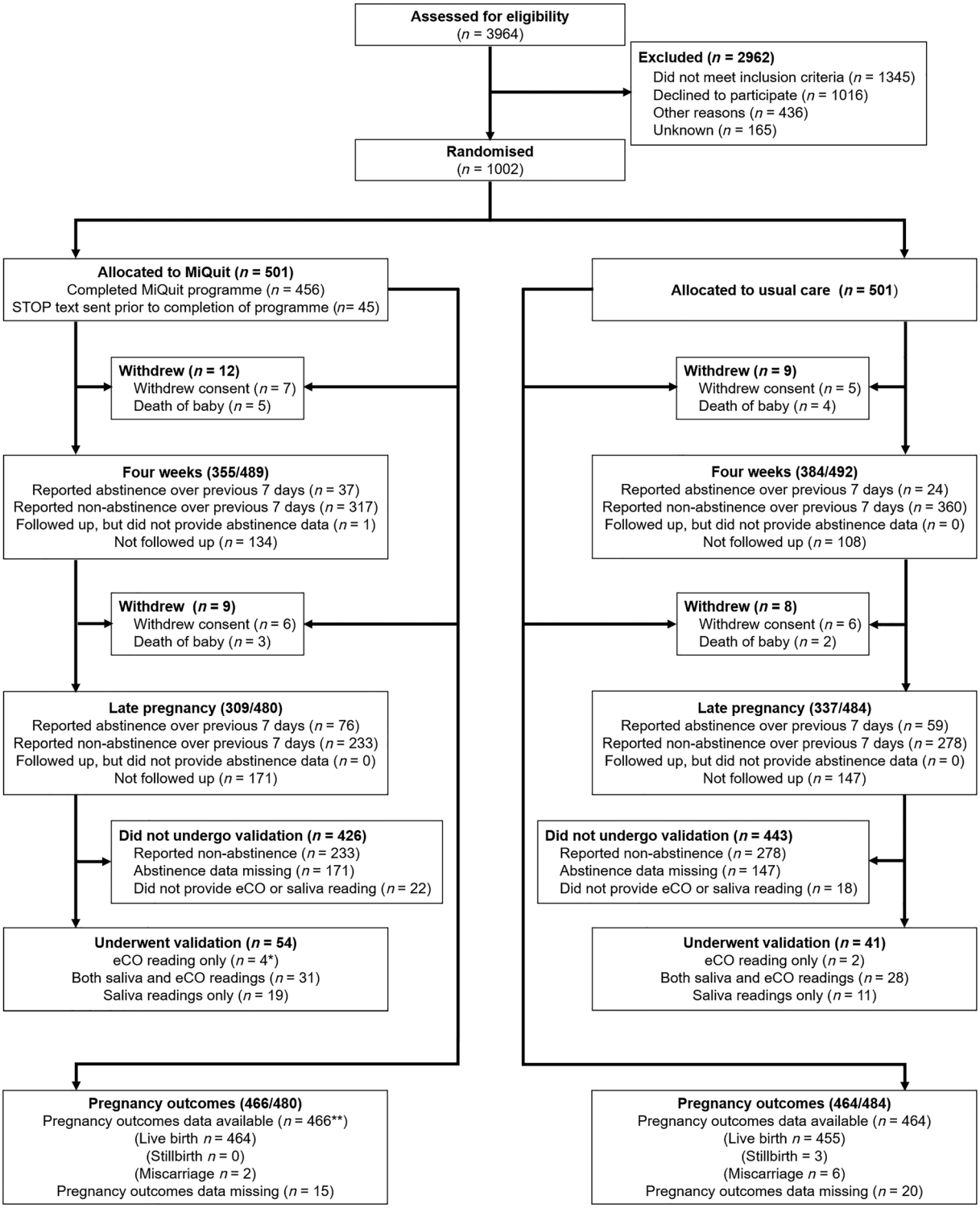

FIGURE 1 Flow diagram. *Two participants also provided a saliva sample, but there was insufficient sample volume to obtain cotinine and anabasine readings. **Pregnancy outcomes data available for one participant who fully withdrew

completion of the MiQuit programme. Twenty-eight 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

TABLE 1 Key baseline characteristics by allocation

	Randomised treatment group		
Characteristic	***MiQuit (n = 501)***	***Control (n = 501)***	***Total (n = 1002)***
Age (y)			
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 min	149 (29.7)	148 (29.5)	297 (29.6)
6–30 min	160 (31.9)	174 (34.7)	334 (33.3)
31–59 min	75 (15.0)	75 (15.0)	150 (15.0)
1–2 h	68 (13.6)	71 (14.2)	139 (13.9)
More than 2 h	49 (9.8)	33 (6.6)	82 (8.2)
Heaviness of Smoking Index[a]			
Mean (SD)	1.9 (1.4)	2.0 (1.4)	2.0 (1.4)

(Continues)

TABLE 1 (Continued)

Characteristic	Randomised treatment group		
	MiQuit (n = 501)	*Control (n = 501)*	*Total (n = 1002)*
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[b], *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)

(Continues)

TABLE 1 (Continued)

Characteristic	Randomised treatment group: MiQuit (n = 501)	Control (n = 501)	Total (n = 1002)
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)

[a]Heaviness of Smoking Index (HSI) based on number of daily cigarettes at time of the baseline visit and time from waking to first cigarette.
[b]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.
GCSE = General Certificate of Secondary Education; A Levels = Advanced Levels.

enrolment. Self-reported daily cigarette consumption was generally lower at the time of the baseline visit than before 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 ≤4 on the Heaviness of Smoking Index [28]. The 646 participants who were followed up at late pregnancy had reasonably similar characteristics, with educational attainment being a possible exception (see Supporting information Table S2).

Abstinence outcomes

Of the 1002 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 Supporting information Figure S2. A total of 101 (15.6%) of 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. Thirty-two of these participants did not provide either a 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 OR (adj OR) was 1.15 (95% CI = 0.65–2.04) and, the adjusted difference in the proportions was 0.76% (−2.38%–3.89%) (Table 2). Treatment effect estimates for abstinence outcomes 2 to 7 are broadly similar to the primary outcome estimate, however, those reflecting shorter abstinence periods (outcomes 3–7) were more favourable toward MiQuit, albeit with reasonably wide CIs 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 (Supporting information 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 imputations 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 CIs being obtained following the approach described by Heinze *et al.* [38,39]. This gave an OR of 1.14 (95% CI = 0.66–1.98) and similar inference to the primary analysis. Supporting information Tables S4–S9 and Supporting information Figures S7–S10 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 Supporting information Figure S10).

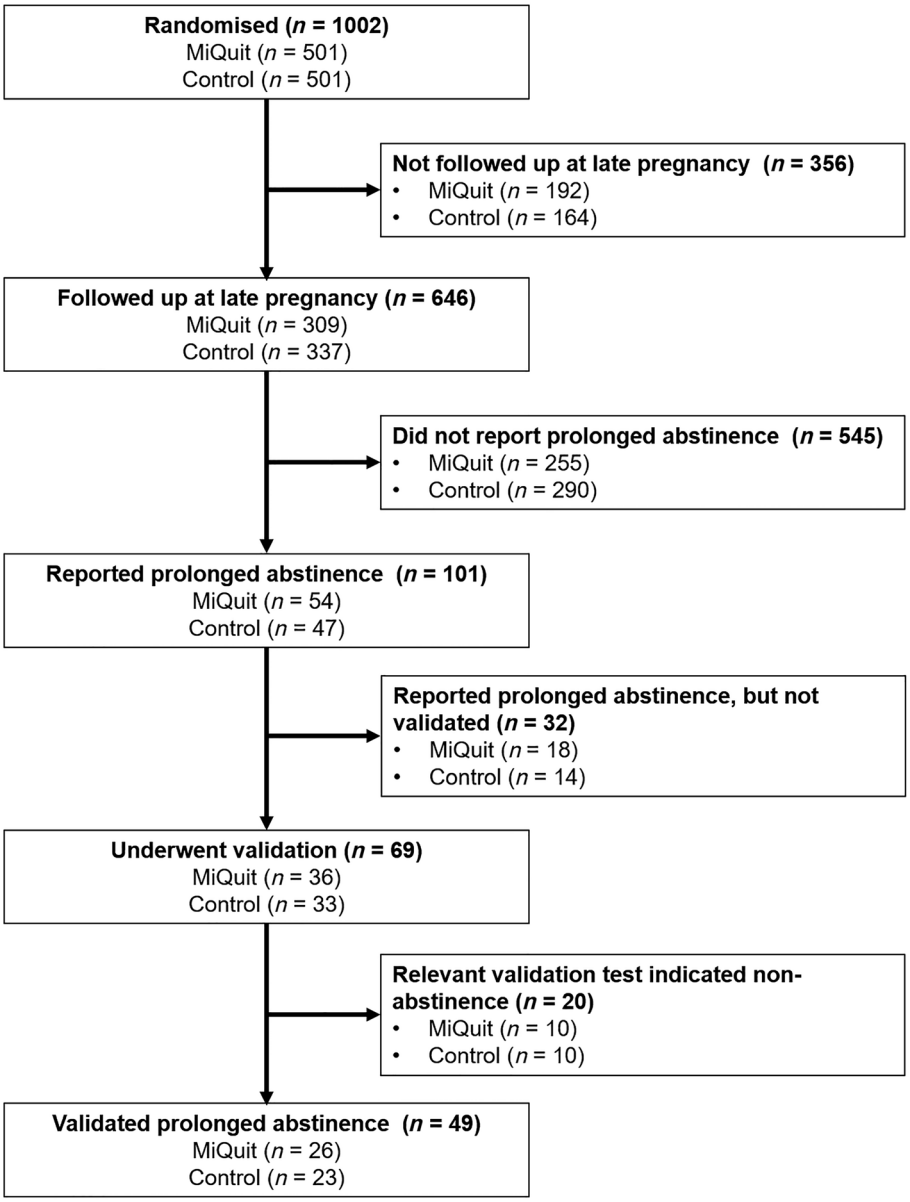

FIGURE 2 Flow diagram showing ascertainment of primary abstinence outcome

TSA

A meta-analysis of the three MiQuit trials found no significant difference in the effectiveness of MiQuit compared with UC (pooled OR = 1.49, 95% adjusted-CI = 0.62–3.60, $P = 0.12$), with low levels of heterogeneity ($I^2 = 10\%$) and diversity ($D^2 = 17\%$, 95% CI = 0%–64%). Because of 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 (Supporting information 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 (Supporting information 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.

TABLE 2 Analysis of abstinence outcomes 1 to 7

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

[a]Detailed specifications of abstinence outcomes 1–7 are given in Supporting information Table S1.
[b]Adjusted OR for allocation from Firth logistic regression model adjusting for weeks gestation at baseline (mean-centred) and recruitment site (penalised profile likelihood CI).
[c]Adjusted difference in proportions from Firth logistic regression model adjusting for weeks gestation at baseline (mean-centred) and recruitment site (Wald CI with standard errors obtained via delta method).

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 Supporting information (Supporting information Tables S10–S12).

The adj ORs for the risk of miscarriage, stillbirth and fetal mortality in the MiQuit group compared with control were 0.32 (95% CI = 0.06–1.20), 0.25 (95% CI = 0.01–1.95) and 0.54 (95% CI = 0.23–1.21) respectively (Table 5). There is little evidence to support the hypothesis that the MiQuit programme influences the likelihood of maternal hospital admissions (adj OR = 1.07, 95% CI = 0.44–2.63), infant ICU admissions (adjusted OR 1.10, 95% CI = 0.70–1.73), or pre-term births (adjusted OR 0.86, 95% CI = 0.58–1.27). Findings were similar when gestational age at birth was treated as a continuous outcome (adjusted difference 0.12 weeks, 95% CI = −0.16–0.40). There was also little evidence to suggest MiQuit has any substantial effect on birthweight (adjusted difference 0.05 kg, 95% CI = −0.03–0.12) (Tables 6 and 7).

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 (Supporting information 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, adj OR = 1.50 (95% CI = 1.07–2.09).

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, therefore, 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 −£1118, (95% CI = −£4806–£1911) and the estimated return

TABLE 3 Sensitivity of the primary analysis to variation assumptions used to impute missing primary outcome data

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

TABLE 4 Use of smoking cessation support

	Randomised treatment group		
Service/technology	*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 5 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 (0.07–1.64)	−0.86% (−2.05%–0.32%)	0.32 (0.06–1.20)	−2.37% (−5.04%–0.30%)
Stillbirth (≥24 weeks gestation)	0/466 (0.00%)	3/464 (0.65%)	–[a]	−0.65% (−1.38%–0.08%)	0.25 (0.01–1.95)	−2.04% (−5.07%–1.00%)
Fetal death	9/473 (1.90%)	15/470 (3.19%)	0.59 (0.25–1.36)	−1.29% (−3.30%–0.72%)	0.54 (0.23–1.21)	−2.17% (−5.01%–0.66%)

[a]Undefined because of' the absence of recorded cases of stillbirth in the MiQuit group.

On investment was £2.11 in healthcare savings for every pound spent on MiQuit by the NHS, (95% CI = −£7.92–£14.98). Supporting information 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

TABLE 6 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 (0.44–2.71)	0.18% (−1.66%–2.02%)	1.07 (0.44–2.63)	0.23% (−2.71%–3.17%)
Infant ICU admission	44/464 (9.48%)	43/455 (9.45%)	1.00 (0.65–1.56)	0.03% (−3.75%–3.82%)	1.10 (0.70–1.73)	0.85% (−3.24%–4.94%)
Pre-term (<37 weeks gestation)	54/464 (11.64)	62/455 (13.63)	0.83 (0.57–1.23)	−1.99% (−6.28%–2.31%)	0.86 (0.58–1.27)	−1.78% (−6.32%–2.76%)

TABLE 7 Continuous pregnancy outcomes

Outcome	*MiQuit*	*Control*	*Unadjusted (95% CI)*	*Adjusted difference (95% CI)*
Birth Weight (kg) *n*	464	455	0.06 (−0.02–0.13)	0.05 (−0.03–0.12)
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 (−0.12–0.44)	0.12 (−0.16–0.40)
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		

interest in receiving information about stopping smoking, increases prolonged cessation rates in pregnancy compared with UC. 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% to 6% fewer intervention group participants responded. Researchers who contacted participants were masked to study allocations, therefore, different response rates are more likely because of 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 therefore, 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. Because the trial recruited from routine antenatal care settings, MiQuit was delivered as an adjunct to UC and around one-quarter of eligible women joined the trial, study findings are probably generalizable 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 that included economic and trial sequential analyses therefore, 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 because of the 'Quit4Baby' text intervention of 1.34 (1.09–1.64) [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, because this is a cheap and acceptable intervention [44] and it is difficult to see how it would cause

harm, it is 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, therefore, those enrolled are more likely to have been motivated for cessation [42]. Some study procedures may also have selected out motivated people as participants. For example, in the 'txt2stop' RCT, participants had to agree to a quit date before enrolling [45] and in the 'Quit4Baby' RCT, 508 participants were recruited from 35 957 United States (US) women signed up to an antenatal health text information service [43]; 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 that 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 UC 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. Because 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 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 to 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. Because most pregnant women try stopping soon after conception [9], any effects could be maximised by offering MiQuit earlier in pregnancy than was possible in the MiQuit3. Because 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.

Because 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 then [15,46] 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 that 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 health [47], and in both non-pregnant people [48,49] and in pregnant women [50], 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; therefore, it is imperative that all interventions that display positive signals of effect are thoroughly evaluated.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov Identifier: NCT03231553 (Trial closed).

DECLARATION OF INTERESTS

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AUTHOR CONTRIBUTIONS

Tim Coleman: Conceptualization; funding acquisition; investigation; methodology; project administration. **Miranda Clark:** Investigation; methodology; project administration; supervision; validation. **Charlie Welch:** Data curation; formal analysis; methodology. **Rachel Whitemore:** Funding acquisition; investigation; project administration. **Jo Leonardi-Bee:** Conceptualization; formal analysis; funding acquisition; investigation; methodology. **Sue Cooper:** Conceptualization; funding acquisition; investigation; methodology; project administration. **Catherine Hewitt:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; supervision. **Matthew Jones:** Formal analysis; funding acquisition; investigation; methodology. **Stephen Sutton:** Conceptualization; funding acquisition; investigation; methodology; software. **Judith Watson:** Investigation; methodology; project administration. **Karen Daykin:** Investigation; methodology; project administration. **Michael Ussher:** Conceptualization; funding acquisition; investigation; methodology. **Steve Parrott:** Conceptualization; funding acquisition; investigation; methodology; project administration. **Felix Naughton:** Conceptualization; funding acquisition; investigation; methodology; project administration; software.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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