NETSCC, HTA

15 March 2012

Project title: A pragmatic randomized controlled trial of physical activity as an aid to smoking cessation during pregnancy (LEAP Trial)

1. Research Objectives

The primary objective of the proposed study is:
1. To compare the efficacy of individual behavioural support plus a physical activity intervention relative to individual behavioural support alone among pregnant women on smoking cessation at the end of pregnancy.
Secondary objectives are:
2. To make comparisons as in 1., above: at four weeks after the quit date and six months following the birth.
3. To compare between groups in 1: changes in self-reported physical activity levels between baseline and end of treatment and end of pregnancy.
4. To compare between groups in 1: during the first week of smoking abstinence, self-reported tobacco withdrawal symptoms, urges to smoke, self-confidence for quitting smoking and for taking regular physical activity.
5. To investigate whether physical activity levels mediate the association with smoking abstinence at end of pregnancy and six months following the birth.
6. To compare groups in 1.: changes in depression scores between baseline and end of pregnancy and six months after the birth.
7. To collect qualitative data from women participating in the trial, from individuals declining participation and from researchers involved with the trial, relating to their views on the trial.

2. Background

Harm of smoking in pregnancy

Smoking during pregnancy is harmful for both the fetus and the mother, as well as for offspring. As up to 30% of pregnant women smoke it is a major public health problem.[1;2] Smoking is one of the few preventable factors associated with increased risk of miscarriage and stillbirth, causing 4000 deaths annually, as well as causing low birth weight with its associated risks.[3;4] Smoking also presents immediate risks for the mother, including abruptio placenta,[5;6] as well as the longer term risks reported for smokers in general. Children of mothers who smoke while pregnant are at increased risk of neo-natal mortality, sudden infant death syndrome, learning difficulties in childhood, problem behaviour, asthma and childhood obesity.[7;8;9;10;11]

Smoking cessation in pregnancy

Only around 25% of pregnant smokers stop for even part of their pregnancy and, of these, around two thirds re-start post-natally.[2] Those who continue to smoke are more likely to come from economically disadvantaged backgrounds.[12] The UK government has prioritised smoking cessation for pregnant women and has set a target to reduce smoking during pregnancy to 15% by the year 2010[13], so effective methods for promoting smoking cessation among pregnant women are needed. The most effective smoking cessation therapy in non-pregnant smokers is a combination of behavioural support and nicotine replacement therapy (NRT), bupropion or Varenicline.[14;15;16] However, neither Bupropion nor Varenicline are likely to be licensed for use during pregnancy and as the safety and efficacy of NRT use during pregnancy is not yet known,[1] many pregnant women are reluctant to use NRT.[17] Behavioural support through the NHS can increase smoking cessation rates in pregnancy by up to 7%.[1] Hence, treatments are needed that increase the effectiveness of behavioural support. It is likely that even improved behavioural support will attract only a minority of pregnant smokers,[18] but even so it will be extremely worthwhile and cost-effective as a way of preventing mortality and morbidity.

Arguments for physical activity as an aid to smoking cessation in pregnancy

Physical activity is proposed here as a potentially effective and popular adjunct to behavioural support for smoking cessation during pregnancy. Moderate intensity physical activity is recommended during

pregnancy[19] and smoking and non-smoking pregnant women are equally likely to be physically active during pregnancy[20]. Moreover, physical activity may represent an attractive aid to smoking cessation for those women who fear post-cessation weight gain and among those who are concerned about weight and tone issues during post-partum[21].

Reducing cigarette cravings is likely to help smokers to stop and NRT is believed to work in part because of reduced craving[16]. This provides a plausible mechanism for why exercise might aid smoking cessation. For example, among non-pregnant smokers, a number of studies have established that moderate intensity physical activity (e.g. brisk walking on a treadmill) significantly reduces cigarette cravings[22] and the results of our pilot study suggests that this is also the case in pregnancy, but there are no studies investigating exercise for smoking cessation in pregnancy, making this study highly innovative.

Trials of physical activity as an aid to smoking cessation in non-pregnant smokers

Among non-pregnant smokers, four adequately-powered RCTs, have assessed physical activity for smoking cessation[23]. A study by one of the investigators[24] showed that vigorous intensity exercise (e.g. stationary cycling) on three days a week over 15 weeks plus behavioural support produced higher cessation rates at 12 months of borderline significance, relative to controls, among female smokers (Odds Ratio=2.4, 95% CIs=1.0 to 5.6, P=0.05). However, during pregnancy moderate rather than vigorous activity is recommended, and three studies have investigated moderate intensity exercise. One study showed that four sessions of supervised exercise produced higher abstinence rates, versus controls, at end of 12 weeks of treatment (EOT) (OR=3.2, 95%,CIs=1.6 to 6.6), but not at 6 or 12 months[25]. Another study, led by the PI, found that, although there were some increases in activity levels, physical activity counselling alone (7 sessions) did not increase abstinence rates at EOT or 12 months. [26,27] A final study found that supervised weekly exercise for 8 weeks significantly increased abstinence rates at 3 months (OR=2.8, 95%,CIs=1.3 to 6.8), but not at 12 months, among women smokers. [28] However, women achieving at least 110 minutes/week of activity were significantly more likely to achieve cessation at 12 months. Across all three studies, although attendance at supervised exercise sessions was high, participants did not raise their 'unsupervised physical activity' levels sufficiently to achieve the overall activity levels thought necessary to achieve smoking cessation. As regards the proposed study, the current evidence suggests that if levels of moderate intensity physical activity can be raised to at least 110 minutes a week over 8 weeks this activity is likely to aid long-term abstinence among women and supervised exercise sessions, on two or more days a week, in combination with physical activity counselling is likely to be necessary to achieve this increase in activity levels.

Pilot studies of physical activity as an aid to smoking cessation in pregnancy

We have conducted two pilot studies to assess the feasibility of using physical activity for smoking cessation in pregnancy, at St. George's hospital which has 5000 booked pregnancies a year. In the first study, across a two month period in 2000, of 734 women who booked to St Georges for antenatal care, 89 (12%) were recorded as smokers on the patient administration system (PAS) following their first ante-natal appointment (at 12-14 weeks gestation). 10 women (11% of pregnant smokers on the PAS) were recruited by telephoning those listed as smokers on the PAS. These women attended 8 weekly sessions combining individual behavioural support for smoking cessation with 30 minutes of brisk walking and activity counselling. Five women (50%) achieved continuous abstinence (CO validated) to end of pregnancy. All the women requested a more extensive physical activity programme. In the second pilot, across a period of 22 weeks in 2007, 2430 pregnancies were recorded, of which 179 (7%) were listed on the PAS as current smokers. 12% (22/179) of pregnant smokers recorded on the PAS were recruited, through a combination of direct telephoning and midwife referral. Over a nine week period, the women received individual smoking cessation support (7 sessions) plus 14 sessions of supervised exercise (brisk treadmill walk or stationary cycling) and physical activity counselling. Three women (14%) maintained abstinence to end of pregnancy; attending, on average, 11 of the 14 exercise sessions. All the abstinent women achieved the target of 110 minutes of physical activity each week. Combining both pilots, 25% (8/32) of the women sustained continuous (CO validated) abstinence to end of pregnancy. Women were recruited at a rate of one per

week and 94% (30/32) of them said that they would be willing to enter a controlled study even if they had an equal chance of being allocated standard smoking cessation support rather than to the physical activity group.

Overall, our pilot work suggests that the proposed intervention could prove an effective addition to the usual behavioural treatment and provide a valuable blueprint for physical activity programmes to promote smoking cessation among NHS patients. The proposed trial is important since it is necessary to assess whether interventions for pregnant smokers are effective among those who accept them. The intervention is being trialled for evidence of effectiveness within the NHS (rather than in an exercise laboratory), and should it be found effective, then replicating the intervention in routine clinical practice would be straightforward.

3. Research Methods

3a Study Design and randomisation

We proposed conducting a pragmatic randomised controlled trial comparing efficacy of individual behavioural support plus a physical activity intervention relative to individual behavioural support alone among pregnant women on smoking cessation at the end of pregnancy. Potential participants will be informed that they will have an equal chance of being assigned to either group. As individual behavioural support is provided via NHS Stop Smoking Services to pregnant women as a standard treatment, we will be testing an intervention that could be readily introduced into current NHS practice and might be expected to cost less per patient than conventional treatments, such as NRT. Table 1 presents a flow diagram for the planned study.

Participants will be randomised to one of the two treatment arms based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham University Clinical Trials Unit (CTU) in accordance with their SOP and held on a secure server. We will use block randomisation, to maintain balance between the two groups over time, and stratify by centre, to ensure balance between centres. Access to the sequence will be confined to the CTU Data Manager. Allocation to treatment arms will be in the ratio 1:1 and investigators will access the treatment allocation for each subject by means of a remote, secure internet-based randomisation system developed and maintained by the Nottingham CTU. The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection, and laboratory analyses are complete.

3b Planned Interventions

(i) Standard treatment: Behavioural support for smoking cessation

Those in the control group will only receive individual behavioural support for smoking cessation; which is provided via NHS Stop Smoking Services to pregnant women as a standard treatment. The researchers (either a Research Midwife or a Research Assistant may be appointed) delivering this intervention will be trained to Health Development Agency Standards[29] and written therapist manuals will be followed. All the women will receive six weekly sessions of individual behavioural support for smoking cessation lasting for 15-20 minutes. This will commence before the target quit date and ending four weeks after the quit date. As is customary, the quit date will be set one week after the first appointment. The smoking cessation program will be pregnancy-specific.[30;31] Topics will include lapse-free abstinence, managing withdrawal symptoms and urges to smoke and enhancing self-confidence for quitting smoking. Additionally, relapse prevention strategies will be used which focus on identifying and resolving tempting situations.[32;33] If the women's partner smokes they will be encouraged to quit with the woman and to attend with her, but the intervention will not be aimed at helping partners quit, although the women will asked at follow-ups if her partner has quit. During the follow-up at end of pregnancy advice will be given about avoiding post-partum relapse. There is little evidence that NRT is effective or safe in pregnancy[1], many pregnant smokers prefer not to use NRT[17] and our pilot work shows that pregnant smokers are willing not to use NRT as part of a research study. Allowing women to use NRT might cause problems of confounding, therefore women who indicate that they wish to use NRT will not be eligible to be recruited to the study. Following their quit day, and on a weekly basis,

participants will be asked whether they have used NRT. Those indicating that they have used NRT will be retained in the trial and the extent of their use of NRT will be monitored.

During the intervention period the Researcher will arrange a system so that she is alerted if the woman develops any complications.

(ii) Physical activity intervention

Those in the physical activity group will receive a physical activity intervention in addition to individual behavioural support for smoking cessation. There will be 14 sessions of supervised exercise; twice a week during the first six weeks of the intervention, and then once a week for two weeks. Similar physical activity interventions are already used in the NHS (e.g. exercise on prescription for cardiovascular disease). During the first six weeks, when the smoking cessation support is provided, one of the exercise sessions will be combined with the smoking cessation support and the remaining exercise session will be 'stand-alone'. The women will use a treadmill in a private room on the hospital site or in a community health centre. Following a familiarisation session at the first visit, they will be advised to aim for 30 minutes of exercise during each session. They will have the option of completing this as a single bout of 30 minutes or in multiple bouts with short breaks (i.e. two bouts of 15 minutes or three bouts of 10 minutes). A moderate intensity of exercise will be prescribed according to age and current activity levels, following recent guidelines[34], and will be monitored using a polar heart-rate monitor. In addition, intensity of exercise will be guided by Rating of Perceived Exertion (RPE, 'fairly light' to 'somewhat hard')[35] and by the "Talk test", whereby, the intensity of activity is too high if the woman cannot carry on a conversation. Once a week, prior to the supervised exercise, the women will also receive 15-20 minutes of physical activity counselling to increase PA undertaken outside the supervised sessions (total 8 sessions). This will entail standard theory-based cognitive-behavioural techniques; including goal setting, self-monitoring (daily diary), decision balance sheets and relapse prevention plans.[36] This counselling protocol has been used successfully to increase physical activity levels in a previous trial of physical activity and smoking cessation[26] and has been successfully adapted to pregnancy in our pilot studies. The women will be given information about local physical activity opportunities which are appropriate during pregnancy (e.g. aqua-natal classes, walking schemes) and about the general benefits of a physically active pregnancy (e.g. improved birth outcomes, easier labour). The women will also be encouraged to view exercise as a self-control strategy for reducing cigarette cravings and withdrawal[22].The participants will be encouraged to increase their levels of moderate intensity physical activity (equivalent to a brisk walk) during and following their pregnancy and will receive a leaflet about using physical activity as an aid to smoking cessation. Overall, the women will be advised to be active for continuous periods of at least 10 minutes at a time, aiming to progress towards accumulating 30 minutes of activity on at least five days of the week, as consistent with current recommendations for pregnancy.[37] The emphasis will be on brisk walking, which is popular among pregnant smokers.[38;39] Swimming, will also be suggested as it is popular and recommended.[40] As a further option, a home-based antenatal exercise DVD (YMCA) and booklet will be provided.[40]

To further promote physical activity, the women will be given a pedometer (Digi-Walker SW-200) for monitoring the number of steps they take while walking, a device that has been shown to increase activity levels in women[41] and to be acceptable during pregnancy.[42] The women will asked to log their daily steps and to gradually progress towards achieving 10,000 steps each day.[43] The pedometers were popular with the women in our pilot studies. The researchers will be trained in physical activity counselling and written therapist manuals will be followed.

3c Planned inclusion/exclusion criteria

Previous exercise trials for smoking cessation have generally targeted those who report smoking five to 10 or more cigarettes a day. However, many pregnant smokers are likely to under-report the number of cigarettes that they are smoking;[45] therefore the eligibility criteria in terms of smoking levels will be less stringent than for non-pregnant smokers. Women will be eligible if they report that they are currently smoking at least one cigarette a day, report smoking at least five cigarettes daily before pregnancy, are 16 to 50 years of age, are 10-24 weeks pregnant (recruitment of those between 10 to

12 weeks pregnant will be subject to self-reports that they have had a scan to show a viable pregnancy), are motivated to quit smoking, are able to walk continuously for at least 15 minutes and are available to attend all the appointments. Women will be excluded if they report having any injury or illness that might be exacerbated by exercise. There are no documented contraindications to moderate intensity exercise, but if they have been advised by their doctor or midwife not to take exercise during pregnancy, if they have any complications during their pregnancy, or if they have any cautions for taking exercise (using the Physical Activity Readiness Questionnaire[19;46]) a consultant Obstetrician and Gynecologist at their hospital (the local PI) will be consulted to check that it is safe for them to take part in the trial. Women who wish to use NRT will also be excluded. We will also exclude those with chemical dependence/alcohol addiction problems and those who cannot give informed consent. Women who are not eligible for the study, or who seek help but do not wish to join the trial will be referred to their local Stop Smoking Service. All participants will provide written informed consent and GPs. Midwives and obstetricians will be informed of their patient's participation in the study.

3d Proposed sample size

A Cochrane review,[1] suggests that approximately 9% of women who are still smoking at the time of their first antenatal visit will stop smoking with usual care through to the end of their pregnancy, and a further 6% to 7% will stop as a result of a smoking cessation programme using individual behavioural support. This means that, in our control group (individual behavioural smoking cessation support), we can expect a smoking cessation rate of around 15% at the end of pregnancy. Combining both our pilot studies, 25% (8/32) of the women in the treatment group (physical activity programme plus individual behavioural support) sustained continuous (CO validated) abstinence to the end of pregnancy. Therefore in the trial we conservatively estimate an abstinence rate of 23% at end of pregnancy in the exercise group, which would be similar to the effect shown for NRT with non-pregnant smokers.[16] We will conduct a trial with 433 women recruited to each arm that would detect the above absolute difference (8%) in smoking cessation rates between the two groups at end of pregnancy (approximately five months of abstinence) with a two-sided significance level of 5% and a power of 83%. This power calculation is based on a chi-squared test with Yate's correction. This sample size is similar to that for the ongoing SNAP trial which is assessing the effects of NRT on smoking cessation in pregnancy.

We will use an 'intention-to-treat' approach in which data from all randomized smokers are included in the analysis. Following recommendations,[47] participants who are included in the analysis are counted as smokers if their smoking status cannot be determined. Our power calculations have taken account of this by using data from previous studies which have used a similar approach. At 4 weeks after the quit day and end of pregnancy an attempt will be made to validate smoking abstinence among all those who have entered the trial. Among those who have withdrawn from treatment, and report smoking abstinence, a home visit will be offered for follow-up at 4 weeks after the quit day. Midwives in the seven hospitals involved in the study all routinely collect smoking status data from women giving birth and record smoking status at the time of childbirth for 90% of women under their care. We believe that by using a dedicated research midwife at each hospital to collect this information we can follow-up around 90% of trial participants.

We anticipate that relatively few women will fail to complete the intervention due to perinatal complications because during screening all those with contraindications to exercise would have been excluded. In addition, women will be recruited to the trial after 10 weeks gestation, by which time the majority of sporadic miscarriages will have occurred. Using U.K. Department of Health Statistics, and data from the HTA SNAP trial, we estimate that up to 2.5% of women will fail to complete the intervention due to complications of pregnancy that include pre-eclampsia, preterm labour and other rarer events, and an attempt will be made to follow-up these women in order to record their smoking status.

3e Recruitment of pregnant smokers

Our pilot work shows that we will be able to randomise 50 trial participants annually from a hospital with 5000 births each year and with similar rates of smoking amongst women attending for their first

antenatal appointment (around 10%). To complete trial recruitment of 866 women within the study period we need a network of hospitals that have a total of 35,000 births annually. We have recruited the maternity units of seven collaborating NHS Hospital Trusts (St. George's, Epsom and St. Helier, Mayday, Kingston, Imperial College, Guy's and St Thomas', and Chelsea and Westminster) with a total of 36,500 births each year to allow for variation in centre recruitment rates. These hospitals serve socio-economically diverse populations. In all hospitals, smoking status for all pregnant women is recorded in the computerized patient administration system (PAS) at the first antenatal booking visit (at 10-14 weeks gestation). At four of the Trusts (Imperial, Epsom & St Helier, Chelsea & Westminster and Guys' and St Thomas') midwives currently telephone all women who are recorded as smokers at their first ante-natal booking visit and invite them to receive support towards stopping smoking. The women are not asked for permission to be telephoned as this is part of their routine antenatal care and the midwife is part of the woman's clinical care team. For the research, at the latter four trusts a research midwife will be employed who will also be employed by the hospital for routine midwifery work. Therefore, as consistent with current practice the midwives at these four sites will telephone all pregnant women recorded as smokers and invite them to join the study. At the other trusts a Research Assistant, rather than a Research Midwife, will be appointed and this person is not considered part of the Clinical Care Team. Therefore, at the first antenatal booking visit, the women will be asked to give consent to be contacted about help with stopping smoking. Women who are not interested in taking part or who are not eligible, but who would like help with quitting, will be referred to the NHS Stop Smoking Service.

In order to further advertise the study and to give women the opportunity to join the study as early as possible, the letters giving the first ante-natal appointment and the ultrasound appointment will both be accompanied by a flyer inviting women who smoke to join the study and indicating that women may be contacted by telephone about the study. The study will also be advertised through posters in the ante-natal clinics and on 'baby' TV. This advertising will provide a contact telephone number, giving the women the option of volunteering for the study before being contacted by the researcher. In all these cases, those women expressing interest in joining the study will be screened for eligibility via the telephone. Women agreeing to join the study, as well as those who are undecided, will be sent a patient information sheet about the study. Using a similar method of recruitment, findings from a U.K. trial of smoking cessation during pregnancy by one of the co-investigators suggests that around 14% of pregnant smokers per year are likely to be recruited for a trial involving face-to-face support.[49] While in our recent pilot studies of pregnant smokers we recruited 10% of pregnant smokers (50/500) per year in a hospital with 5000 pregnancies and on this basis it will take 2 years 6 months to recruit the 866 women.

The above methods of recruitment rely on women informing their midwife that they smoke; however, many women may not disclose this information.[50] Also, using the above approach most women are likely to join the study after 14 weeks of pregnancy. Our recent work with the HTA funded SNAP trial (testing the use of nicotine patches for pregnant smokers) has shown that the rate of recruitment can be increased by asking clerical staff in the ultrasound units (at 10-12 weeks gestation) to distribute and collect (via a box in the clinic) a questionnaire to all pregnant women about smoking status and interest in being contacted about the trial. We propose using this approach in the trial.

As a further aid to recruitment and to increase attendance rates, all the women who attend all the treatment sessions will be entered into a lottery for nine prizes of £100 Marks & Spencers' Vouchers. During the 2.5 years of recruitment, three prizes will be given every 10 months. This approach was popular among the women taking part in the pilot study.

In summary we will recruit women using the following approaches:

1. Send a flyer advertising the study with the appointment letters for the ultrasound screening visit (at 10-12 weeks gestation) and the ante-natal booking visit (10-14 weeks gestation).
2. At the ultra sound screening visit ask all pregnant women to complete a questionnaire about smoking status and interest in being contacted about the trial.

3. Posters and baby TV in the antenatal clinics.
4. At the ante-natal booking visit ask midwives to obtain contact details of women who would like help with quitting and the researcher will telephone them and invite them to join the trial.
5. Women who are recorded as smokers at their ante-natal booking visit but have not indicated whether or not they would like help with quitting will be telephoned and invited to join the trial

Combining all these approaches we aim to maximize the number of opportunities that the women have to join the trial.

3f Proposed outcome measures

Table 2. summarises the schedule of measures.

The primary outcome measure will be prolonged abstinence from smoking from the quit date through to the end of pregnancy. Following recommendations,[51] prolonged abstinence allows a total of 5 cigarettes after the quit day. Prolonged abstinence cannot be comprehensively validated, but if participants report prolonged abstinence at each assessment (validated by exhaled CO measurement), and this is also confirmed by cotinine assessment at 4 weeks after the quit day and end of pregnancy, then they will be considered to have a positive primary outcome.

As secondary outcomes, prolonged smoking abstinence will also be assessed at four weeks after quit day (to compare success rates with NHS standards) and six months after the birth. We will also assess continuous abstinence at 4 weeks after the quit date and at end of pregnancy, whereby no cigarettes are allowed after the quit day. Self-reports of smoking abstinence since the last visit[52] will be validated with an expired carbon monoxide (CO) concentration (Bedfont Smokerlyzer) of less than 8ppm. Self-reports of smoking status will not be validated at six months after the birth. At this time the NHS traceline service will be used to help us to track women (using NHS/hospital number) who have moved home. We will also register with the Office of National Statistics which will alert us if any of the women die.

Cotinine assay tends to be a more accurate biochemical validation of abstinence than expired CO;[53] therefore, salivary cotinine[54] will be measured at the key outcome points at four weeks after the quit day and at end of pregnancy. Self-reports of smoking abstinence will be confirmed with a cotinine level of less than 57 nmol/L (10ng/ml)[55]. If a woman's report of continuous abstinence is disconfirmed by either her CO reading or cotinine level she will be considered as having resumed smoking. If a woman fails to attend a smoking cessation session she will be contacted by telephone in an attempt to make another appointment within 48 hours. If the woman reports she is abstinent from smoking but is unwilling to attend she will be recorded as having resumed smoking. In order to increase compliance, for the post-treatment follow-up a home visit will be offered. For the follow-ups, hospital databases and clinics will be consulted to confirm the health of mother and baby. Where possible, this data will be imported from the hospital database into the research database, stored anonymously. In cases where the mother or baby are not in full health, or where a still-birth or neonatal death has occurred, the women will not be approached for a follow-up visit. If a woman cannot be contacted by telephone to confirm her smoking status and, if necessary, to arrange a follow-up visit, we will send her a pre-paid enveloped enclosing a smoking status questionnaire.

At end of term (36-38 weeks gestation) all those women who report to the researcher that they have remained abstinent from smoking (via telephone) will be followed-up and their smoking status will be validated. We estimate this will be no more than 10 women per year at each site. At this time the women will be due to have a routine ante-natal check and, if this is agreeable with the woman and her midwife, the research midwife will carry out this check. This will save the woman attending two appointments. If this option is not acceptable to the woman or midwife or if a Research Assistant, rather than a Research Midwife, is appointed then the smoking cessation follow-up will be arranged separately from the routine ante-natal check-up. For those women who we are unable to make an appointment at 38 weeks (e.g. premature births) we will aim to catch them at delivery or within two weeks of the birth. It will be acceptable to conduct this follow-up at any time between 36 weeks

gestation and ten weeks after the birth. We will ask a clerk at the delivery ward to inform the researcher when a woman arrives at the hospital. A note will placed in the women's hand-held file and in the antenatal database to remind the delivery staff that the woman is in the trial. In the HTA SNAP this procedure works well and often the women's partner will call the Research Midwife. In order to give the women an incentive to provide information for the follow-ups at end of pregnancy and six months after the birth, all women who complete these follow-ups will be given a £10 shopping voucher for each follow-up they complete.

Continuing support will be offered to those women who fail to stop smoking. Many women report that, rather than stopping smoking, they reduce their smoking intake during pregnancy; [56;57] and there is some evidence to suggest that a 50% or more smoking reduction is associated with increased infant birth weight.[58] Therefore, among those women who relapse (as measured by CO or cotinine), levels of smoking reduction will be measured as a secondary outcome.

Other secondary outcome measures will be changes in urges to smoke, tobacco withdrawal symptoms, self-confidence in stopping smoking and self-confidence for maintaining regular physical activity; all in the first week of abstinence (details given below), between the two groups. Although these variables will be measured beyond the first week of abstinence and changes recorded, different abstinence rates in the two groups after the first week from the quit date may confound differences in these other measures, and so they cannot be specified a priori as outcome variables. For the two groups we will also compare: changes in depression between baseline and end of pregnancy and six months after the birth; changes in maternal weight between baseline, 4 weeks after the quit date and end of pregnancy; and peri-natal outcomes. Once a week, up to four weeks after the quit date, participants will rate their desire to smoke[60;61] before after either a bout of supervised exercise (exercise group) or before and after the smoking cessation counselling (control group). We will examine the acute effects of exercise by comparing changes in reports of desire to smoke from pre to post-intervention, for the exercise group versus the control group.

At baseline demographic characteristics will be recorded; including age, marital status, number of children, highest education qualification, ethnicity/race, occupation, weeks of gestation and history of any previous premature births (>24 and <37 weeks). At this time smoking history will also be recorded; including partner's smoking status, social support for stopping smoking, cigarettes smoked per day (both now and before pregnancy), type of cigarette smoked, prior quit attempts, and Fagerström Test for Nicotine Dependence score.[59] Following the quit day, self-reports of smoking[52] and expired carbon monoxide (CO) concentration (< 8ppm) will be measured on a weekly basis up to four weeks after the quit. Further questionnaires will be administered in order to measure tobacco withdrawal symptoms,[60;61] weekly urges to smoke, and daily urges to smoke during the first week of quitting[60;61], desire to smoking before and after the interventions[60;61] and self-confidence for giving up smoking for good at this attempt.[62] Depression will be assessed with the 10-item Edinburgh Postnatal Depression Scale (EPDS) [63]. If any of the women reach the cut-off score for depression on the EPDS we will ask their permission to refer them to their GP. If a woman appears to be suicidal, the researcher will contact the designated responsible clinician for this element of the study (Dr Andy Kent, Perinatal Mental health Consultant at St George's), so as to formulate an emergency plan that ensures the woman's safety. Maternal gestational weight gain will be assessed through the women being weighed at their first antenatal booking visit, at the end of treatment and at end of pregnancy. Also, the reasons for withdrawing from the study or for missing exercise sessions will be collected during pregnancy and post-partum.

Self-confidence for taking up regular physical activity will be assessed[64]. Physical activity levels in the previous week will be assessed for both groups via interview of seven day recall[65] at baseline, one week after the quit date, four weeks after the quit date, end of physical activity treatment (6 weeks of abstinence, this will be assessed via telephone for the control group) and at both follow-ups. We will use the Actigraph motion monitor (formally CSA, Computer Science and Applications, Inc.) to objectively measure physical activity. The Actigraph records physical activity by using an internal accelerometer to measure movement. The Actigraph is small, lightweight, worn on the waist, is practicable during pregnancy[66] and has been widely validated. [67;68] Ten percent of participants in both the exercise group and the control group will wear the Actigraph monitor for seven continuous

days during the fourth week after the quit date. In our recent pilot study pregnant smokers reported that they found it acceptable to wear an Actigraph.

The following perinatal measures will be accessed through examining each women's record in the PAS: (i) antenatal complications, including any admissions and the reasons for the admissions; (ii) gestation at onset/induction of labour (and indication for induction where appropriate); (iii) duration of labour and mode of delivery; (iv) apgar scores of newborn, and where available acid-base status of newborn, and rates of transfer to the neonatal intensive care unit; (v) birthweight and placental weight. Monitoring of intervention: Numbers of appointments attended will be noted in each group and the time taken to deliver interventions at attended appointments will be logged.

3g Qualitative data

Qualitative data, collected via semi-structured interviews and focus groups, will compliment the quantitative data being collecting in the trial. Qualitative data, from trial participants, from those declining to take part in the trial and from researchers involved with the trial, will increase our depth of understanding of the effects the exercise intervention produces and of the challenges to implementing the intervention; for example, relating to recruitment, maintaining high attendance levels and coordinating with PCT and hospital services.

In-depth interviews with trial participants

At the time the women provide consent to participate in the RCT they will also be invited to give consent to be interviewed, after the birth of their child, about their experience of the trial. Women that have already been randomised, and are less than one month post-partum, will also be invited to be interviewed, and will complete the revised consent form prior to interview.

Each woman will be interviewed on a single occasion between one and two months after they have given birth. Interviews will not be held before this time in case the experience of being interviewed influences patients' views of the trial and any treatment received. Face-to-face interviews, lasting around 60 minutes, will be conducted by an experienced interviewer/researcher. The interviews will explore participants' experiences of the trial, and of the exercise intervention (e.g., of supervised exercise, exercise counselling and pedometer programme) and of the standard smoking cessation intervention. They will have the option of being interviewed at their home, at the location of where they received the intervention or at St George's University of London. Based on previous interviews we carried out with pregnant smokers in a pilot study of exercise, and due to the travel distance for many women, it is anticipated that most women will choose to be interviewed in their home. The women will be able to choose the time of the interview and will be offered £30 (shopping vouchers) financial compensation for their time and travel.

About 45 trial participants will be interviewed; with 30 from the exercise group and 15 from the control group, the final number depending on when data saturation is reached. Interviewees will be purposively sampled, within each treatment group, to ensure approximately equal numbers of women having high attendance at intervention sessions and having low attendance or having withdrawn from the intervention. Low attenders and 'withdrawers' will be invited to give reasons for their withdrawal or low attendance. We will select women who withdraw at different times (e.g., shortly after randomisation or later on in the trial). We will also purposively sample to aim for maximum variation in relation to smoking status at the end of pregnancy (primary outcome in the RCT), baseline depression score, age and social class. There will be the opportunity to select women from all 14 hospital trusts that are participating in the RCT.

Interviewing women who have declined to take part in the trial

It is important that we interview 'decliners', as these women may have specific views towards exercise as an aid for smoking cessation, particularly in terms of its acceptability and effectiveness. During the process of screening women for the RCT, women who decline to participate in the trial will be asked whether they are willing to be interviewed by telephone for 20 to 30 minutes about their reasons for not wishing to take part in the trial. It will be made clear that they will be able to choose the time of the

interview and that they will be financially compensated with £30 in shopping vouchers for their time. They will provide consent via the telephone. At the time of the screening, decliners agreeing to be interviewed will be asked to confirm some socio-demographic details (e.g., age, gestation) and to give their main reason for not wishing to participate. We will aim to interview 15 decliners. We will conduct interviews as soon as possible after the women have declined to participate.

Interviewing researchers delivering the trials interventions

It is anticipated that around 10 researchers involved with the trial will be available to take part in focus groups. For each of the two focus groups we will purposively select four to six researchers; some of whom recruited low numbers of participants and some who had high recruitment rates. We will aim for a mix of researcher midwives and research nurses within each focus group. The focus groups will investigate factors influencing recruitment to the trial and researchers' experiences of implementing the interventions and of generally running the trial. The interviews will also cover the researcher's perceptions of smokers' reactions to behavioural support and the exercise intervention.

Qualitative Data analysis

With participants' permission, the interviews will be audio-taped and transcribed verbatim. Transcripts will be read and interpreted in order to gain an understanding of each individual's views and experiences, and to develop a coding frame. Each transcript will be imported into a software package to allow electronic coding and retrieval of data. Transcripts will be coded by independent researchers in order to maintain reliability of coding. Analysis will rely upon "constant comparison" and will continue until no new themes emerge. Information on women's reasons for declining or not adhering to the intervention will be listed and quantified, providing information on the range of reasons given and their frequency.

3h Cost effectiveness

We will examine the cost effectiveness of smoking cessation support plus exercise relative to smoking cessation support alone, from a health service perspective. We will document resources consumed that are related to each intervention. Relevant resources include; cost of personnel, materials, space, equipment and administrative overheads. Data will be collected for: (i) staff time will be accounted for using time and effort reports, (ii) an accounting system for computer time, mailing and program costs will be created to facilitate real time aggregation of these costs, (iii) interviews with staff will be used to determine the amount of time they devote to tasks related to the programme. The benefits of smoking cessation in pregnancy will be modelled and not measured. Long-term cessation leads to long-term benefits to the mother, which must be discounted appropriately. In 'normal quitters' that sustain abstinence for about six months, meta-analyses show that half will relapse and half will become lifetime abstainers and enjoy these benefits.[69;70] Based on this, we might expect that most women who stop in pregnancy, usually for at least six months, would maintain lifetime abstinence. However, a much higher proportion of women who stop smoking return to it after pregnancy than would be expected in these models, diminishing the benefits to the woman herself from smoking cessation. However, the benefits of smoking cessation in pregnancy also extend to the fetus, which will be less likely to be born preterm. [1] This leads to NHS costs avoided on the one hand and a lower likelihood of complications such as cerebral palsy and similar health problems on the other. These latter health problems avoided lead to QALY gains for the baby that must also be included in the utility measure of the decision analytic model. Thus we will utilize an existing cost-effectiveness model that has been used for cost-effectiveness modeling for NICE, updating utility estimates to include the benefits to the fetus. The evidence for this model on the benefits to the fetus and child will be derived from a systematic review of the effects of smoking cessation in pregnancy on the consequences for the fetus and child that will be conducted by a team at the University of Nottingham, led by Dr. Tim Coleman (coinvestigator).

The analysis will allow us to calculate incremental cost-effectiveness ratios for the smoking cessation support plus exercise intervention compared with smoking cessation support alone in terms of cost of treatments per smoker quit. We will also be able to examine ratios for subgroups; for example, according to nicotine dependence or age at baseline.

3i Statistical Analysis

Primary analysis will be on an intention to treat basis, presuming that women lost-to-follow-up are continuing to smoke. Initially we will compare the two groups descriptively in terms of baseline characteristics. We will then compare the two groups in terms of our primary outcome, prolonged smoking abstinence, and other binary outcome measures, in unadjusted analysis, using the chi-squared test, with the estimate of effect given as the odds ratio. We will use multiple logistic regression to adjust for variables predicted to be related to the outcome (education, nicotine dependence, age, depression). We will also adjust for other variables where there is an imbalance at baseline between groups and the variable is found to be related to the outcome.

Multivariate regression analysis will also be used to examine the determinants of smoking abstinence and the determinants of physical activity adherence, with adjustment for, and looking for effect modification by, treatment group. We will look at the association between change in physical activity levels and smoking abstinence in the two groups, and, if the intervention is effective, use mediation analysis to examine whether there is evidence that the change in physical activity levels is the likely causal factor in determining smoking abstinence.

Between group differences in urges to smoke in the first week of abstinence will be assessed by t-test or Mann Whitney U test, according to the distribution of the data. After that time any between group differences in abstinence rates could bias the results. We will compare physical activity level, withdrawal symptoms and self-confidence between the two groups in the first week of abstinence, and changes in these variables, and in maternal gestational weight and depression, over subsequent time points using repeated measures analysis of variance, or the non-parametric equivalent. Analysis of covariance (ANCOVA) will be used to examine the effect of the treatment versus control on peri-natal outcomes; including infant birth weight and gestation at birth. ANCOVA will also be used to assess the acute effect of the interventions on desire to smoke. Continuous measures that cannot be transformed to normality will be analysed by equivalent non-parametric analyses.

4. Ethical issues

(i) Risks to the subjects

Moderate intensity physical activity (e.g. brisk walking) is safe and is recommended for the nearly all women during pregnancy and has no contraindications. For healthy women there are no risks associated with moderate intensity physical activity during pregnancy.

(ii) Adequacy of protection against risks

Prior to joining the study all volunteers will be sent a patient information sheet detailing the nature of the research and explaining that they will have an equal chance of being assigned to the physical activity condition or to standard treatment. The women will be informed that they can choose to drop out of the study at any time without prejudicing their subsequent antenatal or smoking cessation treatments. At the first visit any queries will be addressed concerning the nature of the study and the women will be asked to sign a consent form for participation in the study.

There are no documented contraindications to moderate intensity exercise, but during the screening process, if the woman has been advised by her doctor or midwife not to take exercise during pregnancy, if she has any complications during her pregnancy, or if she has any cautions for taking exercise (according to a standard screening questionnaire) a consultant Obstetrician and Gynecologist at her hospital (the local PI) will be consulted to check that it is safe for her to take part in the trial.

The women will be continuously monitored for cautions to exercise and for adverse events (see section (v) 'Data and safety monitoring plan' below). Prior to their entry into the study, the women's GPs will be informed that their patient has volunteered for a research study which may involve regular moderate intensity physical activity, such as brisk walking. The women will be advised to pursue moderate, rather than vigorous intensity activities. During the weekly supervised exercise sessions there will be guidance about exercise intensities and about safe exercise practices during pregnancy (e.g. the importance of keeping fully hydrated). Exercise booklets and videos will be used to aid appropriate exercise 'at home'.

If any of the women reach the cut-off score for depression on the Edinburgh Postnatal Depression Scale we will ask their permission to refer them to their GP. If a woman appears to be

suicidal, the researcher will immediately contact the designated responsible clinician for this element of the study (Dr Andy Kent, Perinatal Mental Health Consultant at St George's), so as to formulate an emergency plan that ensures the woman's safety.

(iii) Potential benefits of the proposed research to the participants and others

The women participating in the study have a significantly increased chance of stopping smoking and staying stopped, relative to those women who try to stop without behavioural support. It is hypothesised that those in the exercise condition will have a further enhanced opportunity of stopping smoking. Those who maintain regular exercise during and following the study will receive many general health benefits, including a reduced risk of developing cardiovascular disease and some cancers.

(iv) Importance of the knowledge to be gained

If the exercise intervention was shown to be effective for aiding smoking cessation during pregnancy it would reduce harm to the fetus and mother, and to the child following birth. Pregnancy also presents an opportunity to attempt to achieve sustained abstinence from smoking in these women. Long-term smoking cessation reduces cancer risk in the mother and reduces the risk of smoking uptake and cancer development in her children. If found to be successful, the knowledge gained from this study could provide a blueprint for disseminating physical activity programmes for pregnant smokers throughout the industrialised western world.

(v) Data and safety monitoring plan

It is anticipated that there will be few, if any, adverse events in response to the moderate intensity physical activity intervention. Any adverse events (AEs) will be monitored by the researchers. If necessary these events will be discussed with a Consultant Obstetrician at St. George's (Dr. Manyonda, coinvestigator), who will act as Medical Monitor. Where necessary Adverse Event Reports will be produced and will be forwarded to the Data Monitoring and Ethics Committee (DMEC), or to the TSC if a DMEC is not considered necessary for the trial (see **6** below). This will include, reviews of the research protocol and any recommendations for changes to the safety monitoring procedures. In addition, any adverse events which could possibly be related to the study will be followed up. At each treatment session and follow-up appointment all the women will be asked to complete a form declaring any change in their health status since the last visit, particularly regarding pregnancy complications. The women will also be asked to inform the research midwives if they experience any of the possible minor adverse events associated with exercise (specifically: nausea, extreme breathlessness, extreme pains in the chest, or extreme dizziness) either during or following the supervised treadmill walking.

5. Quality control plan

A quality control plan will be implemented as follows:

(i) Sampling and recruitment: Screening information will be entered into the online database and the system will only randomised the women if she satisfies all the criteria. If it is found at the first visit that a woman has failed to satisfy the inclusion and exclusion criteria she will be withdrawn, but will continue to be offered smoking cessation support from the local stop smoking service.

(ii) Intervention delivery: Audio recordings will be made of the intervention sessions and 10% of these will be checked for adherence to the protocol.

(iii) Data entry: All data will be entered directly into the online database.

(iv) Data collection: 20% of all online clinical record forms (CRFs) will be checked by the Trial Administrator or Trial Manager. If any baseline data on demographics or smoking characteristics are missing the women will be contacted and the data will be entered.

(v) Cotinine assays: Using the manufacturers' recommendations, the performance of the cotinine assay will be monitored and errors will be estimated in each analytical run. In addition, the laboratory carrying out the cotinine assay is routinely subjected to external quality control.

(vi) Data security and confidentiality: The data will be entered on to an online database by the researchers, and will be later transferred to STATA for analysis. The database will be held on a secure internet server at the Clinical Trials Unit at Nottingham University. The participants will be assigned a study number and will be identified on the database only by this number and will not be identified by name. Access to the database will be password protected and will be permitted only by the researchers, the CI, the trial statistician, the Trial Manager and the Trial Administrator. The researchers will only have access to the section of the database relating to their site. Only the researchers, the CI and trial statistician will have the information linking the study numbers to the participants' names. A copy of the database on CD will be stored in a locked filing cabinet in the Division of Community Health Sciences, St.George's, University of London. Only the Trial Manager and the CI will know the location of this CD and will have access to it. For the purpose of following up participants their contact details will be stored on a separate online database. This database will have restricted access (username and password), that can only be viewed by members of the coordinating site for the purpose of trial follow-ups. For additional security the fields in the database will be encrypted.

The saliva samples (for cotinine) will be labelled with the participants study number and will not be identifiable by name. Only the researchers, the CI and trial statistician will have the information linking the study numbers to the participants' names. These samples will be stored in a locked freezer at each site, only accessible by the researcher, until they are ready to be transported for analysis.

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Table 1. Planned flow of participants

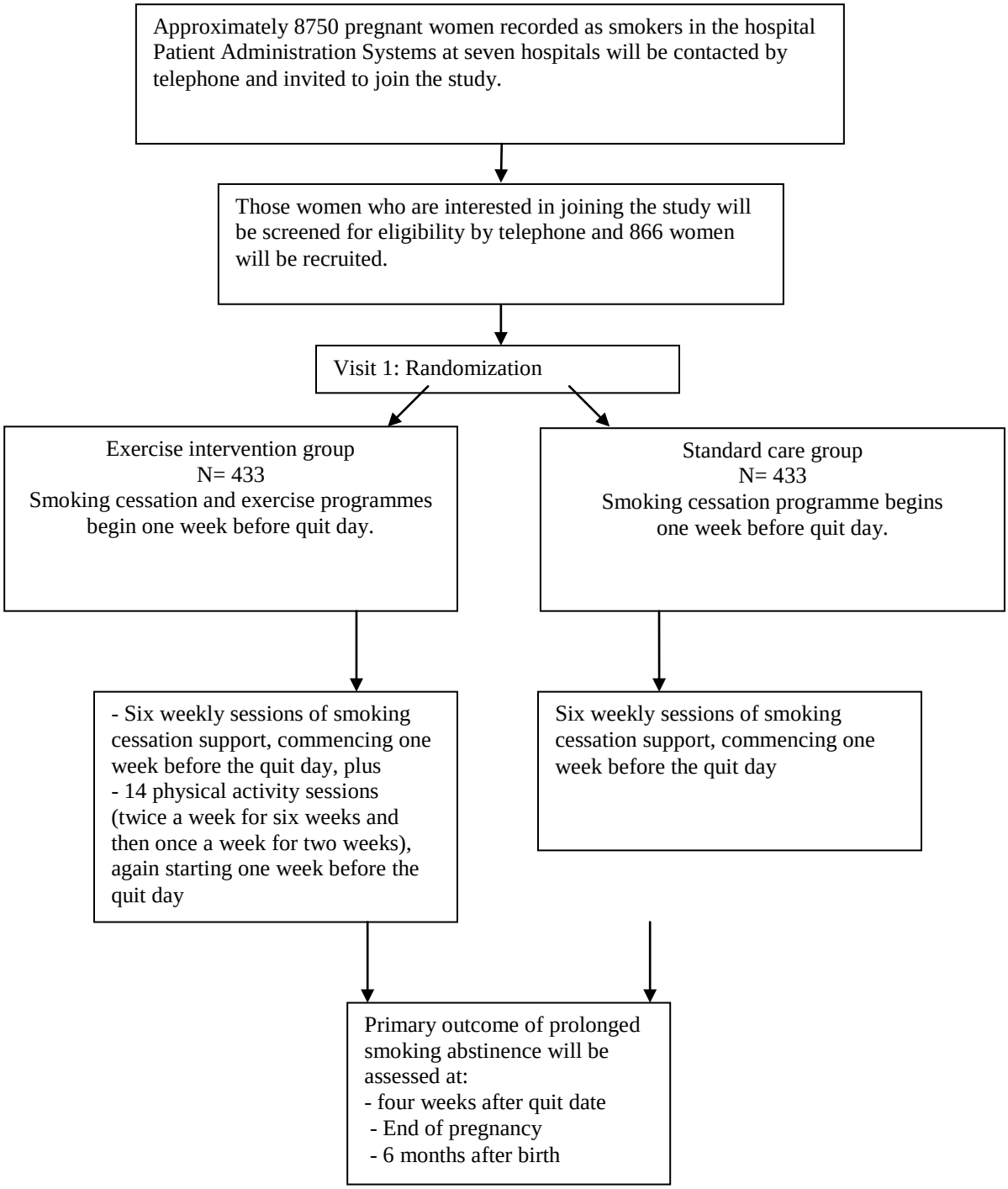

Table 2. Schedule of assessment for LEAP study

Measure	Baseline (visit 1)	V2	Quit day	1 wk after quit	Weekly throughout treatment up to 4 weeks quit	4 weeks after quit	6 weeks after quit	End of pregnancy	6 mths after birth
Demographics & smoking history	X								
Maternal gestational weight	X					X		X	
Self-report of smoking abstinence				X	X	X		X	X
Expired carbon monoxide reading	X			X	X	X		X	
Cotinine						X		X	
Partner's smoking status	X					X		X	X
Withdrawal symptoms	X			X		X			
Weekly urges to smoke	X			X	X	X			
Daily urges to smoke				X					
Desire to smoke before and after intervention	X	X	X	X	X	X			
Confidence for quitting	X			X		X		X	X
Depression	X							X	X
Duration of each bout of supervised exercise	X	X	X	X	X	X	X		
Reports of physical activity levels	X			X		X	X	X	X
Self-confidence for physical activity	X			X		X		X	X