Version no. 1.0

Date: 7th November 2012

Full trial title: A pragmatic randomised controlled trial of physical activity as an aid to smoking cessation during pregnancy

Acronym: London Exercise And Pregnant smokers (SNAP) trial

International Standardised Randomised Controlled trial Number: ISRCTN48600346

Trial sponsor: St George's University of London

Chief investigator: Professor Michael Ussher

Analysis Plan prepared by: Professor Michael Ussher, Professor Sarah Lewis,

Nominated statisticians for analysis: Professor Sarah Lewis, Professor Michael Ussher, Muhammad Riaz

Projected start date: 1st April 2009

Recruitment to be completed: end of Nov 2012

Expected completion date: July 2013 (primary endpoints)

Published Trial protocol: Ussher et al (2012) Physical activity as an aid to smoking cessation during pregnancy (LEAP) trial: study protocol for a randomized controlled trial. Trials, 13(1):186.

1. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

1.1 Objectives and aims

The LEAP trial will investigate whether or not a physical activity intervention plus behavioural support is more effective than behavioural support alone (control) in achieving smoking cessation at 'end of pregnancy' for women who are between 10 and 24 weeks pregnant, who currently smoke 1 or more cigarettes daily and who smoked 5 or more cigarettes daily before pregnancy. We will also determine the cost-effectiveness of the intervention.

1.2 Trial configuration: Multicentre, parallel group with 1:1 allocation between physical activity and control.

1.3 Randomisation procedures

1.3.1 Points of randomisation and the baseline visit

After confirming eligibility, informed consent for trial entry is sought. After consenting to trial entry, women are randomised. Randomisation is via the Nottingham Trials Unit web-based database and randomisation service. In each centre the recruiting research midwife (RM) has a username and password. She logs on to the trial website that hosts the trial database confirms that the patient eligibility criteria are all met and enters *registration* data about the participant and centre before randomisation is possible. The computer then issues a trial number, which is a unique identifier for the trial participant, and a treatment allocation code.

1.3.2 Specify block size, whether randomly varied

Random permuted blocks of randomly varying size.

1.3.3 Stratified allocation, or post-stratified analysis

Randomisation is stratified by trial centre only.

1.4 Allocation concealment:

As this is a behavioural intervention, there is no allocation concealment for participants or researchers.

1.5 Stopping rules determined as part of the protocol

Stopping rules have not been specified.

1.6 Outcomes

1.6.1 Primary outcome

The primary outcome is self-reported, continuous abstinence from smoking between the quit date and end of pregnancy, validated by exhaled carbon monoxide (CO) or salivary cotinine.

Continuous abstinence is defined as having smoked less than 5 cigarettes since the quit day.

Exhaled CO: The criteria for confirming abstinence is a reading of <8ppm.

Salivary cotinine: The criteria for confirming abstinence is a value of <10ng/ml.

End of pregnancy: It is acceptable for this measure to be taken at a follow-up up to 4 weeks before birth, at delivery, or within 10 weeks after the birth.

The primary outcome is dichotomous; i.e. abstinent or non-abstinent.

For a participant to be classed as abstinent from smoking at end of pregnancy (i.e. positive primary outcome)**:**

At 4 weeks post-quit (It is acceptable for this measure to be taken between 25 days to 6 weeks post-quit): [a]

Have you smoked at all since your quit day?= 'No not even a puff' or 'yes just a few puffs' or 'Yes, between 1 and five cigarettes' or 'missing' [a] (i.e. any response other than 'yes, more than 5 cigarettes')

AND CO is <8ppm

AND/OR cotinine is <10ng/ml

OR CO or cotinine is missing[b]

AND

At end of pregnancy:

Have you smoked at all since your quit day?= 'No not even a puff' or 'yes just a few puffs' or 'Yes, between 1 and five cigarettes' (i.e. any response other than '5 or more cigarettes')

AND CO is <8ppm[b]

AND cotinine is <10ng/ml[c]

For a participant to be classed as non-abstinent from smoking at end of pregnancy (i.e. negative primary outcome)**:**

At 4 weeks or end of pregnancy:

- Have you smoked at all since your quit day?= 'yes, more than 5 cigarettes'

- CO or salivary cotinine values do not confirm abstinence.

- Has withdrawn from the study (i.e. refuses follow-up).

- Fails to set a quit date which the follow-up assessment can be referenced against.

At end of pregnancy:

- Refuses to allow biochemical validation

- Refuses to self-report number of cigarettes smoked.

- Unable to contact in order to confirm smoking status (i.e. lost to follow-up).

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[a]Some women will not have data for self-report of smoking or biochemical validation at 4 weeks. If these women are confirmed as abstinent at end of pregnancy it will be considered as a positive primary outcome. All those classed as abstinent at end of pregnancy will automatically be classed as abstinent at 4 weeks post-quit.

[b]Some participants will only have CO or cotinine and, for these women, a reading in the stated range is defined as a positive primary outcome (even without the reading for the other biochemical measure). Most participants will have both CO and cotinine and, for these women, BOTH readings must fall within the defined ranges to count as a positive outcome.

[c]If a new normative value becomes available during the trial this will be used.

1.6.2 Secondary outcomes

Included in paper reporting primary outcomes:

a) Smoking abstinence

Self-reported, continuous abstinence from smoking (up to 5 cigarettes allowed) between quit date and 4 weeks, with biochemical validation (to compare success rates with NHS standards).

b) Physical activity

1. Self-reports of physical activity levels at 1, 4 and 6 weeks after the quit date and at end of pregnancy. Also, at each time point, the numbers reporting walking as the main physical activity.

2. Record of duration of time on treadmill, during supervised exercise.

3. Accelerometer record (Actigraph) of minutes of at least moderate intensity physical activity, during the first week after the quit date. This data is only for 10% of participants.

4. Among those in the exercise group, record of pedometer steps (among those choosing to wear a pedometer at 1, 2, 3, 4, 5 and 6 weeks after the quit date.

c) Aids to smoking cessation

1. Use of nicotine replacement

2. Use of behavioural support other than that provided in the trial

Included in other papers:

a) Smoking abstinence

1. Self-reported, continuous abstinence from smoking (up to 5 cigarettes allowed) between quit date and 6 months after delivery (no biochemical validation).

2. Among those women who relapse, levels of smoking reduction between baseline and end of pregnancy.

3. Lapse free smoking abstinence between quit date and 4 weeks and end of pregnancy (both biochemically validated) and between quit date and six months (without validation).

b) Physical activity

Self-reports of physical activity levels at six months after the birth

c) Psychological outcomes

1. Weekly urges to smoke at baseline and 1, 2, 3 and four weeks after the quit day.

2. Daily urges to smoke on each day in the first week following the quit day.

3. Desire to smoke before and after supervised exercise weekly up to 4 weeks after the quit day.

4. In control group only: Desire to smoke before and after smoking cessation counselling weekly up to 4 weeks after the quit day.

5. Tobacco withdrawal symptoms at baseline and 1 and 4 weeks after the quit day.

6. Self-confidence in stopping smoking at baseline, 1 and 4 weeks after the quit day, end of pregnancy and 6 months after the birth.

7. Self-confidence for maintaining regular physical activity at baseline, 1 and 4 weeks after the quit day, end of pregnancy and 6 months after the birth.

8. Self-reported depression at end of pregnancy and 6 months after the birth.

d) Maternal weight

Maternal gestational weight at baseline, 4 weeks after the quit day and end of pregnancy. (Some of the end of pregnancy measures may be up to 10 weeks after the birth).

e) Fetal loss and morbidity and other fetal and birth outcomes

The following perinatal measures are extracted from patient's hospital records: (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 infants, and where available acid-base status of infants, and rates of transfer to the neonatal intensive care unit, (v) birth weight and placental weight.

1. Miscarriage (non-live birth prior to 24 weeks gestation) and stillbirth (non-live birth at 24 weeks gestation or later)
2. Intrapartum death (i.e. at delivery)
3. Neonatal death (i.e. from live birth to 28 days)
4. Intrauterine growth restriction (IUGR)
5. At 20 week scan, abdominal circumference, head circumference, femur length
6. Oligohydramnios (deficiency of amniotic fluid)
7. Polyhydramnios (excess of amniotic fluid)
8. Congenital malformation (and type of malformation)
9. Individualized birth weight Z score (i.e. birth weight adjust for gestational age, maternal height, maternal weight at booking and ethnic group).
10. Unadjusted birth weight and birth weight as Z-score
11. Apgar score
12. Cord blood pH
13. Gestational age at birth
14. Intraventricular haemorrhage
15. Neonatal enterocolitis
16. Neonatal convulsions
17. Congenital abnormality
18. Neonatal intensive care unit (NICU) admission
19. Infant ventilated > 24 hrs
20. Elective termination
21. Elective termination undertaken for fetal morbidity judged incompatible with fetal / infant survival

f) Maternal morbidity and mortality and other maternal outcomes

1. Maternal mortality
2. Gestational hypertension/Pregnancy induced hypertension (PIH)
3. Pre-eclampsia (PET):
4. Antepartum haemorrhage (APH) requiring hospital admission
5. Urinary tract infection (UTI) in pregnancy (and number of infections)
6. Pre-labour rupture of membranes at pre-term (i.e. before 37 weeks) (PPROM)
7. Pre-labour rupture of membranes at term (i.e. 37 weeks onwards) (PROM)
8. Number of antenatal day unit (ADU) attendances
9. Hospital admissions overnight for women to antenatal ward:
10. Reason/s for antenatal attendance
11. Other antenatal complications
12. Onset of labour (e.g. induced)
13. Pain relief
14. Mode of delivery
15. If caesarean section, reason for CS
16. Duration of three stages of labour and total duration of labour
17. Duration of ruptured membranes
18. Blood loss at delivery
19. Proteinuria

g) Health economic data

1. Duration of maternal hospital admission for childbirth

2. Duration of any admission (of baby) to special care

1.7 Determination of Sample Size

A Cochrane review 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% will stop as a result of a smoking cessation programme using individual behavioural support. Thus, in our control group we expect a smoking cessation

rate of around 15% at the end of pregnancy. Combining our pilot studies 25% (8/32) of participants in the treatment group sustained continuous smoking abstinence to the end of pregnancy. Therefore in the trial we conservatively estimate an abstinence rate of 23% at end of pregnancy in the treatment group, which would be similar to the effect shown for NRT with non-pregnant smokers [14]. We aim to recruit 433 women to each arm to detect the above absolute difference (8%) in smoking cessation rates between the groups at end of pregnancy with a two-sided significance level of 5% and a power of 83%. This calculation is based on a chi-squared test with Yate's correction.

1.8 Protocol amendments that have statistical implications should be described.

For the follow-up at end of pregnancy the valid period for assessment was originally defined as 38 weeks gestation to two weeks after the birth. This was revised to 36 weeks gestation to 10 weeks after the birth.

2. ANALYSIS CONSIDERATIONS

2.1 Analysis for primary outcome

Initially, we will conduct a descriptive comparison of the baseline characteristics of the two treatment groups. Our primary outcome measure, continuous abstinence from smoking from quit date to end of pregnancy, will be compared between treatment groups using logistic regression, adjusted for recruitment centre only, with statistical significance determined by the likelihood-ratio test and with the estimate of effect given as the odds ratio and 95% confidence interval. Our primary analysis will not adjust for any further variables since effect estimates can be sensitive to decisions concerning what variables to adjust for and how these are specified. Nevertheless, the adjustment for baseline covariates is often advised. First, to correct for any chance imbalances in important prognostic variables following randomisation and secondly, because adjusting for highly important prognostic variables in an RCT can improve the precision of treatment effect estimates even when the outcome measure is binary (Robinson, 1991). Statistical testing for baseline imbalances is not advised and instead key covariates should be selected prior to analysis based on the likely magnitude of the association with the outcome measure. Therefore as a sensitivity analysis treatment effects will be reported adjusting for the following variables in addition to centre:

(i) Nicotine dependence score at baseline (Fagerstrom Test of Cigarette Dependence Score, FTCD)

(ii) Age of finishing full time education (in years), as a proxy for socioeconomic status. For a small number of women still in full time education at the time of enrolment the participant's current age will be used instead of age of finishing education.

(iii) maternal age at baseline

(iv) Depression score at baseline (Edinburgh Post-natal Depression Scale, EPDS)

(v) Partner's smoking status (This was not specified in the published protocol, see section 6, p.8 of this SAP).

If we observe differences between the two groups in use of NRT, or use of behavioural support outside of the intervention sessions, then we will conduct a sensitivity analysis to examine the effect of controlling for any differences between groups in these variables. We will analyse other binary smoking outcomes in a similar way.

2.2 Unit of analysis considerations

For outcome measures relating to smoking cessation the women randomised will represent the unit of analysis. All other outcomes will be related to these women, except those related to the offspring (e.g. birth weight), in which case the offspring will be the unit of analysis instead. A small number of children will be born as multiple births (e.g. twins) and data for these cases will be clustered rather than independent. The primary analysis will be of singleton births and we will carry out a sensitivity analysis, including multiple births allowing for the clustering of outcomes. More specifically:

Outcomes where the offspring is the unit of analysis will comprise singleton births only to allow for the fact that observations will be non-independent and that non-singleton births are likely to have very different birth outcomes in any case. In a subsidiary analysis multiple births will be included and clustering accounted for using an approach previously published (Gates S & Blocklehurst P, 2001). This adapts methodology previously created for use with cluster randomised RCTs, assuming that each women is regarded as the 'cluster' and her number of offspring the cluster size.

2.3 Effect modification and sub-group analyses

For our primary outcome, if the intervention is effective, we will look for effect modification by age at leaving full time education and baseline levels of physical activity. Our multiple logistic regression models will therefore be augmented with appropriate interaction terms. Initially, both age at leaving education and baseline physical activity will be fitted as continuous terms to maximise power when testing for an interaction. If evidence of an interaction is present (taken as a p-value of < 0.05) then further subgroup analyses will dichotomise these variables (at the median) for ease of interpretation. The purpose of these models is to establish whether women with low or high levels of education, or high or low baseline levels of physical activity, could benefit preferentially from a physical activity intervention. If there is evidence of interaction, we will perform subgroup analysis of the efficacy of PA compared with usual care in subgroups defined by levels of age at leaving full-time education and by levels of baseline physical activity.

2.4 Analysis for secondary outcomes (not in main paper)

We will compare secondary outcomes, including urges to smoke, withdrawal symptoms, self-confidence and PA, in the first week of abstinence, and the same variables and maternal gestation weight and depression, over subsequent time points, using mixed effects modelling to allow for repeated measures, with adjustment for centre. To deal with non-normally distributed variables we will use transformations to normality, residual bootstrapping, or dichotomising. Differences between groups in perinatal outcomes, including birth-weight and gestation, mode of delivery and complications, will be analysed by linear or logistic regression, with adjustment for centre.

2.5 Timing of analyses

Baseline data with be complete in November 2012 and the baseline characteristics of the sample will then be analysed using descriptive statistics and the results will be presented in tables.

There will be two further main phases of analyses. The first will be begin around July 2013, once the end of pregnancy follow-ups are complete. The second will be conducted for data at

six months after delivery and this analysis will commence around February 2014. Data collected for secondary outcomes will not be analysed until the trial has ended with respect to the primary outcome measure.

2.6 Analysis populations and missing data conventions

Analysis will be on an intention-to-treat (ITT), that is, including all those women randomised to physical activity or usual care. Participants who, for any reason, have missing outcome data on the primary outcome or any secondary smoking outcomes, will be assumed to have resumed smoking.

We will determine the quantity and distributions of missing data. We will carry out a complete case analysis, and we will compare this with an analysis using multiple imputation to deal with missing values, which assumes data is missing at random, describing any differences in terms of the likely biases in the data. The exception is smoking outcomes, where those with missing data will be assumed to have resumed smoking.

2.7 Protocol Deviations

Failure to attend treatment sessions will not constitute a protocol deviation. The only possible protocol deviation is: Women who choose to withdraw from the trial, and choose not to consent for the use of their data for primary or secondary outcomes.

2.8 Derived variables:

Low birth weight – births of <2500g

Preterm birth – births of < 37 weeks gestation

Post-randomisation fetal death - a composite measure of all fetal deaths after randomisation– ***defined as*** – all [miscarriages + stillbirths + neonatal deaths + elective terminations conducted for fetal abnormalities judged inconsistent with fetal / infant life].

Perinatal deaths (a composite measure of all infant deaths following live births) – ***defined as*** – all [stillbirths + neonatal deaths]

2.9 Treatment Compliance and mediation analysis

We will compare compliance between the PA and control groups in terms of the percentage of treatment sessions attended. If the intervention is effective, we will use mediation analysis to examine whether there is evidence that the change in PA levels is the likely causal factor in determining smoking abstinence. We will examine the association between treatment group and change in PA levels, and the association between level of PA and abstinence. Finally, we will include level of PA in a logistic regression model of the association between treatment group and abstinence, with mediation assessed using MacKinnon's causal steps criteria.

2.10 Software used

We will use STATA version 11.

2.11 Levels of significance

All tests will be two-tailed, using a p value of < 0.05 to indicate statistical significance, and 95% confidence intervals will be calculated.

2.13 Format of electronic files for archiving

Excel and SPSS

3. ANALYSIS OF PARTICIPANT CHARACTERISTICS

3.1. Describe methods used to summarise data.

Continuous data that are approximately normally distributed will be summarised in terms of the mean, standard deviation, median, minimum, maximum and number of observations. Skewed data will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages.

3.2. Disposition

We will summarise the number of patients screened for entry, excluded prior to randomisation by major reason and overall, the number of patients randomised and the number entering and completing each phase of the study by treatment group and overall. We will use a CONSORT flow chart for this.

3.3. Baseline

We will summarise demographic variables (e.g. age, daily number of cigarettes prior to delivery and currently, gestational age at randomisation, exhaled CO, ethnic group, education, parity, etc) by treatment group.

4. ANALYSIS OF ADVERSE EVENTS

The number of adverse events and serious adverse events will be compared between the two groups. There is unlikely to be sufficient adverse events to warrant these being reported in a table.

5. LIST OF PROPOSED SUMMARY TABLES

The proposed tables to be included in the main publication are presented below. We will also produce a CONSORT flow diagram showing exclusions, enrollment and evaluable participants.

6. Changes to statistical analysis plan relative to published protocol

After further statistical review, we request that the TSC approve the following amendment:

1. 'Partners smoking status' has been consistently related to success at quitting smoking in pregnant women and we proposed adjusting for this variable (see section 2.1 above).

2. Section 2.3 'Effect modification and sub-group analyses' was not specified in the protocol and, if the intervention is effective, we propose including this analysis.

Demographic and smoking characteristics

(give ranges for all variables)	Exercise group n= Mean (SD)	Control group n= Mean (SD)
Age (years) (range)		
Age at leaving full-time education		
BMI (kg/m^2)		
Weight (kg)		
Gestational age (weeks)		
Cigarettes smoked daily before pregnancy		
Cigarettes smoked daily at randomization		
FTCD score		
Expired carbon monoxide (ppm)		
EPDS score		
Weekly minutes of PA of at least moderate intensity		
	n/%	n/%
Married or living with partner		
Caucasian†		
Professional/managerial occupation		
Smoked in a previous pregnancy		
Parity§ 0-1 2-3 ≥4		
Previous preterm birth††		
Women with partner who smokes		
High confidence for quitting smoking (rated as very or extremely high)		
Takes alcohol ≥ twice a week		

Consumes ≥3 alcoholic drinks on a drinking day		
EPDS score ≥12		
High confidence for PA (rated as very or extremely confident)		
Positive expectation for benefits of PA for quitting (rated as moderate or large positive effect)		

FTND=Fagerstrom Test of Cigarette Dependence EPDS=Edinburgh Post-natal Depression Scale; PA=Physical Activity; BMI=Body Mass Index

† Race or ethnic group was self-reported. Race was categorized according to standard U.K. Census categories.

§ Parity was defined as the number of previous pregnancies that had progressed beyond 24 weeks.

¶ Data exclude XX women in the PA group and XX in the conytrol group who had no partner.

†† Previous preterm birth was defined as any previous pregnancy that lasted from 24 to 37 weeks.

Compliance

	Exercise group n= Mean (SD)	Control group n= Mean (SD)
Time walked on treadmill during supervised exercise Baseline one week post-quit 4 weeks post-quit 6 weeks post-quit		NA
Self-reported weekly minutes of physical activity of at least moderate intensity Baseline one week post-quit 4 weeks post-quit 6 weeks post-quit end of pregnancy		
	n/n %	n/n %
Treatment sessions attended		

Primary and secondary abstinence outcomes

Outcome	**Exercise group (N=)** Number (percent)	**Control (N=)** Number (percent)	**Odds Ratio (95% CI) †**	**Adjusted Odds Ratio (95% CI)**
Primary Self-reported continuous abstinence[a] at end of pregnancy[b] with biochemical validation[c]§				
Secondary Self-reported continuous abstinence for 4 weeks after quit day with validation†				

† Odds ratios were adjusted for recruitment center only (as a stratification factor).

‡ Odds ratios were adjusted for center, Fagerstrom Test of Cigarette Dependence score at baseline, partner's smoking status and age at leaving full-time education.

[a]Continuous abstinence is defined as having smoked less than five cigarettes since the quit day.

[b]End of pregnancy is defined as between 36 weeks gestation and 10 weeks after the birth.

[c]Validated by either exhaled carbon monoxide or salivary cotinine.

§The biochemical tests did not validate the report of not smoking (i.e., probable false reporting of cessation) in X of X women (X%) in the physical activity group and in X of X (X%) receiving usual care alone.

†§The biochemical tests did not validate the report of not smoking (i.e., probable false reporting of cessation) in X of X women (X%) in the physical activity group and in X of X (X%) receiving usual care alone.