STATISTICAL ANALYSIS PLAN

AFFIRM

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality - a stepped wedge cluster randomised trial?

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Christopher T. Weir — 5th October 2017

Professor Christopher Weir (University of Edinburgh) — Date

5th October 2017

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2.0	Amendments following Trial Steering Committee December 2016	Christopher Weir, Jane Norman	30 March 2017
3.0	Updates to account for missing data patterns in covariates, based on review of data blinded to randomised allocations	Christopher Weir	03 October 2017

1 Table of Contents

2 List of Abbreviations

AE	Adverse event
CEMACH	Confidential Enquiries into Maternal and Child Health
CI	Confidence interval
CONSORT	CONsolidated Standards of Reporting Trials
ECTU	Edinburgh Clinical Trials Unit
eDRIS	electronic Data Research and Innovation Service
ISA	International Stillbirth Alliance
ITT	Intention-to-treat
Max	Maximum
Min	Minimum
n	Number of patients with an observation
N	Number of patients in the dataset
PP	Per -protocol
Q1 , Q3	Inter quartile points at 25% and 75%
SAP	Statistical Analysis Plan
SD	standard deviation
SFTP	Secure File Transfer Protocol
SOP	Standard Operating Procedure
WHO	World Health Organisation

3 Introduction

This document details the criteria to be used for the definition of the analysis populations and the statistical methodology for analysis of the AFFIRM study. This document has been compiled according to Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) "Statistical and Analysis Plans". This document has been written based on information contained in the study protocol dated 27 February 2017 version 6.

3.1 Responsibilities

The trial statistician will be responsible for the production of the following items using ECTU SOPs: summary tables, formal statistical analysis and the statistical report.

Economics analysis is an out of scope activity for this SAP.

The nested qualitative study examining the acceptability of the intervention to patients and health care providers and identify process issues (barriers to implementation) is also an out of scope activity for this SAP.

3.2 Definitions

Throughout the reporting of the study, the studied interventions will be reported as "Active Phase" and "Control Phase", and will be collectively referred to as the Intervention groups.

Study time periods in this step wedge design will be defined as period 1 (1 to 4 months), period 2 (5 to 8 months), etc., until period 9 (33 to 36 months)

Two calendar months will be manually determined once the date for "Active Phase" and "Control Phase" are provided by the study team (i.e. for the 28 February 2015, two calendar months later will be 28 April 2015).

For all data, where applicable clinical visits/observations will be referred to as: delivery, 7 days post-delivery, between 7 days and 28 post-delivery and between 28 days and 1 year post-delivery.

4 Study Design

4.1 Brief Description

AFFIRM is a pragmatic, multi-centre, stepped wedge cluster design trial, in which participating hospitals in the UK will be randomized to the timing of introduction of a care package. The tested intervention is a package of care consisting of a management plan for identification and delivery of the 'at risk' fetus, together with strategies for increasing pregnant women's awareness of the need to report decreased fetal movements early.

Data in the 'Active Phase' after introduction of the intervention will be compared to data in the 'Control Phase'. There will be a washout period of two calendar months after the introduction of the intervention commences during which data will not be included in either group for analysis. Outcomes will be measured from routinely collected data.

5 Research Outcomes:

5.1 Primary:

The study Primary Endpoint is:

- Stillbirth (antepartum and intrapartum). We will use the Confidential Enquiries into Maternal and Child Health (CEMACH) definition of stillbirth which is "a baby

delivered without signs of life after 23+6 weeks". Where gestation is uncertain we will include all babies with a birth weight of 500g or more.

5.2 Secondary:

The study secondary endpoints are:

- Stillbirth at 28 weeks gestation and above (World Health Organisation (WHO) definition of stillbirth: "a baby born with no signs of life at or after 28 weeks' gestation")
- Stillbirth at 22 weeks gestation and above: Delivery of dead fetus at or more than 22 weeks gestational age determined by weeks of pregnancy at delivery or gestational age at diagnosis of fetal death, if known; or birth weight of 500 grams or more, if fetal gestational age is not known.
- Stillbirth at 37 weeks gestation and above
- Stillbirth amongst normally formed infants of 22 weeks gestation and above, 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks gestation and above (a normally formed infant is identified by the variable Fetal abnormality marker =No in the study dataset)
- Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and deaths in the first seven days of life)
- Rates of caesarean section
- Rates of induction of labour (overall)
- Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) overall
- Rates of induction of labour at 39 weeks 0 days gestation or later
- Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) in women delivered at 39 weeks 0 days gestation or later
- Mean gestation at delivery for women having induction of labour
- Rates of admission to the neonatal unit (and their reasons)
- Rates of admission to the neonatal unit for more than 48 hours
- Rates of admission to the neonatal unit for term babies (those born at 37 weeks 0 days or greater)
- Birthweight centile (according to the Intergrowth birthweight centile calculator at https://intergrowth21.tghn.org)
- Proportion of babies with fetal growth restriction (defined as "being less than the 10th centile (customised for gender) and remaining undelivered at or after 40+0 weeks gestation)
- Rates of spontaneous vaginal delivery

Other secondary outcomes are the baby parameters:

- Gestation at delivery
- Proportion of babies born preterm (≤ 37 weeks and 0 days gestation)
- Sex baby
- Birthweight of baby
- Birthweight centile (according to the Intergrowth birthweight centile calculator at https://intergrowth21.tghn.org)
- Apgar score at 5 minutes
- Proportion of babies with 5 minute Apgar score < 4
- Proportion of babies with 5 minute Apgar score < 7
- Resuscitation required at birth

5.3 Process outcomes:

These will be recorded in a subset of sites and women via clinical audit.

- Number of women presenting with decreased fetal movements
- Interval between perceiving decreased fetal movements and presenting to hospital

6 Statistical Methods Section from the Protocol

" 8.2 Proposed Analysis

For the binary outcomes being addressed in research questions Q1-Q4, data will be analysed by generalized linear mixed model with a random effect for hospital group and fixed effects for the intervention implementation and study time period. Data will be analysed on an intention to treat basis (the design of the trial means it is not possible to determine individual patient /caregiver compliance with the intervention). There will be no imputations for missing data. Subgroup analyses will include those with and without congenital anomalies. No interim analyses will be performed other than those requested by the trial steering committee, who will be the only group to view the interim analyses. A full statistical analysis plan will be developed and signed off prior to locking of the study database.

For research question Q5, the qualitative data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers' perspectives and experiences. NVivo will be utilised to support the analysis. The RA and SCB will work together to ensure rigour and validity.

The process outcomes being assessed in Q6 (rates of induction of labour, number of women presenting with decreased fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for Q1-Q4, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed in a normal linear mixed model".

7 Overall Statistical Principles

7.1 Data collection

As per section 7 of the study protocol data will be collected from four different regions of the study.

Data will then be sent to the electronic Data Research and Innovation Service (eDRIS) National Safe Haven (NHS National Services Scotland) by Secure File Transfer Protocol (SFTP) (or other similar) for storage and subsequent analysis within a secure project area (the AFFIRM study database).

7.2 Data analysis

The statistician at ECTU will perform the statistical programming and analysis to produce all summary tables and figures using the statistical packages SAS (v9.2 or a more recent version), IBM SPSS (version 19 or later) or R, whichever is the most appropriate to use in the National Safe Haven.

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, standard deviation (SD), minimum, maximum, inter quartile points at 25% and 75% (Q1 and Q3) and number of patients with an observation (n) in the statistical output,

All statistical tests will be 2-sided and will be performed using a 5% significance level, leading to 95% (2-sided) confidence intervals (CIs) and corresponding p-values, unless otherwise specified.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots. If the distributional assumptions for the parametric approach are not satisfied, further data transformation (for achieving Normality), or other suitable methods will be considered. This will be documented in the statistical results report together with the reasoning supporting the action taken, if applicable.

The Intent-to-treat (ITT) population will be used to summarise all data and all analyses unless otherwise specified.

For the main clinical paper, appropriate MS Word tables will be compiled using the statistical output generated at the National Safe Haven (Examples in Appendix 1)

7.3 Handling of missing data

There will be no imputation for the data with regard to missing values or withdrawals in the statistical summaries and statistical analysis unless otherwise specified (see sensitivity analysis).

Where smoking status during pregnancy is missing, data will be imputed using the woman's smoking history at booking. Age at delivery (years) [1] will also be considered as a possible variable to inform the imputation.

7.4 Quality Control (QC) of Summary Tables and Statistical Analysis

Suspected data errors identified in the database will be listed.

7.4.1 QC/Validation - Summary Tables

A random selection of summary output table items will be QC'd using alternative methods (i.e. comparison of items in the table to results calculated by an alternative method).

7.4.2 QC/Validation - Statistical Analysis

QC/Validation of statistical analyses will be performed by peer review of selected program codes, logs and outputs. Additionally, the primary outcomes analysis will be replicated independently by a second statistician.

7.5 Unblinding procedures

The randomisation list is held at ECTU. This will be made available to the statistician performing the analysis within the National Safe Haven once all imported data have been received and a finalised copy of the statistical analysis plan has been signed off.

8 Population for Analysis

8.1 Intent to treat population

The intention-to-treat (ITT) population will include all babies of women delivering at one of the AFFIRM study maternity units for the duration of the study.

9 List of Analyses

9.1 Recruitment and retention

No formal statistical testing will be performed for recruitment and retention. A flow chart following the CONSORT [2] extension for cluster trials, adapted for stepped wedge designs will be provided. The statistical report will tabulate the number of centres recruited, randomised, completed and discontinued by intervention and overall. The number of women and babies included by study centre and geographical region will be presented.

9.2 Demographics, Clinical Characteristics

No formal statistical testing will be performed for demographics and clinical characteristics. The following will be presented and summarised by intervention and overall:

Maternal parameters:

- Mother's age at delivery (years)
- Mother's height (cm)
- Mother's weight at booking (kg)
- Maternal BMI
- Ethnic group
- Smoker during pregnancy
- Smoking history at booking
- Deciles of deprivation (Scotland Only)
- Parity

- Number of births this pregnancy
- Mode of Delivery

9.3 Protocol deviations/violations

No formal statistical testing will be performed. All known protocol deviations/violations at centre level will be listed.

9.4 Compliance with allocated intervention by centre

This will measure how sites engaged with the intervention and will summarise whether the intervention was implemented; the timing of implementation versus the time point determined by the study randomisation; and the number of major protocol deviations by centre. The proportion of patients that fall within a compliant intervention period will be calculated by centre. Additionally, an "on treatment" variable will be calculated for which patients (women) will be grouped as active / control according to when the intervention was actually implemented in a site, instead of when it was randomised to have been implemented in that site. This variable will be used for a sensitivity analysis (see section 9.5.1)

9.5 Primary Outcome

The primary outcome will be summarised overall, and by study site and active/control periods expressed as a rate per 1000 live births. Number of stillbirths (CEMACH definition) will be analysed on an intention to treat basis, incorporating all patients in the ITT population for whom outcome data are available. The number of stillbirths will be compared before and after implementation of the Active intervention using a logistic regression generalised linear mixed model following the model structure described in Hussey and Hughes [3]. The effect of implementation of the Active intervention will be presented as an odds ratio and its 95% CI. The intervention groups will be ordered in such a way that an odds ratio of less than one corresponds to a benefit for Active Phase over Control Phase

The event rate μ_{ij} in site i, study period j will be modelled in the linear component of the logistic regression as:

$$\mu + \alpha_i + \beta_j + \theta X_{ij}$$

where: μ is the overall mean event rate on the logit scale;

α_i is a zero-mean random effect for site i, $\alpha i \sim N(0, \tau^2)$;

β_j is the fixed effect log-odds ratio for time period j, with $\beta_1=0$ for identifiability;

θ is the fixed effect log-odds ratio for the intervention;

X_{ij} is a (0/1) variable to indicate whether the intervention is implemented in site i during period j.

A site by intervention interaction random effect will be included in the model and retained if it is found to explain an important proportion of the variability in outcomes.

The patient-level covariate included will be maternal age and number of babies (one; more than one).

A secondary analysis adjusting for a full list of patient-level covariates will also be included (maternal age, parity, smoking status during pregnancy, maternal BMI, number of babies (one or more) and ethnicity). This will be performed as a complete-case analysis.

A further secondary analysis not adjusting for patient level covariates will also be performed.

Also, a Scotland only model will be generated with the patient-level covariates included in the primary analysis plus the deciles of deprivation.

9.5.1 Sensitivity Analyses

One key exploratory analysis will be to explore the time lag over which the effect of the intervention builds up (and/or fades away) by using nonlinear nonparametric modelling of the intervention by time interaction.

Also the analysis in section 9.5 will be repeated for the “on treatment” variable (see section 9.4) according to the actual time of implementation of the intervention in each study site.

9.5.2 Subgroup analyses

A priori subgroups for the primary analysis will be explored for babies with and without fetal abnormalities. This analysis will be performed by including an interaction term between intervention and the relevant covariate in the model described in Section 9.5 above. A stricter level of statistical significance ($p<0.01$) will be used in this analysis to reflect its exploratory nature.

9.6 Discrete Secondary Outcomes

For the following binary outcome measures, we will use the same methods as for the primary outcome analysis which included adjustment for patient level covariates:

9.6.1 Stillbirth at 28 weeks gestation and above (WHO definition)

9.6.2 Stillbirth at 22 weeks gestation and above

9.6.3 Stillbirth at 37 weeks gestation and above

9.6.4 Stillbirth amongst normally formed infants of 22 weeks gestation and above, 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks gestation and above

9.6.5 Perinatal mortality

9.6.6 Rates of caesarean section

9.6.7 Rates of induction of labour (overall)

9.6.8 Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) overall

9.6.9 Rates of induction of labour at 39 weeks 0 days gestation or later

9.6.10 Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) in women delivered at 39 weeks 0 days gestation or later

9.6.11 Rates of admission to the neonatal unit

9.6.12 Rates of admission to the neonatal unit for more than 48 hours

9.6.13 Rates of admission to the neonatal unit for term babies (those born at 37 weeks 0 days or greater)

9.6.14 Proportion of babies with fetal growth restriction

9.6.15 Rates of spontaneous vaginal delivery

9.6.16 Proportion of babies born preterm

9.7 Continuous Secondary outcomes

For the following continuous outcomes a mixed linear regression model will be used to compare the means between the intervention groups adjusting by a random effect for site and fixed effects for the intervention implementation and study time periods. The result will be presented as an adjusted difference in means together with its corresponding 95% CI and p-values:

9.7.1 Gestation at delivery for women having induction of labour

9.7.2 Gestation at delivery

9.7.3 Birthweight centile

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9.8 Baby outcomes

The following will be presented and summarised by intervention and overall:

- Sex of baby
- Birthweight of baby
- Apgar score at 5 minutes
- Proportion of babies with 5 minute Apgar score < 4
- Proportion of babies with 5 minute Apgar score < 7
- Resuscitation required at birth

9.9 Process Outcomes

The following outcomes will be obtained from the study team audit and presented and summarised by intervention and overall:

9.9.1 Discrete - Number of women presenting with decreased fetal movements

9.9.2 Continuous - Interval between perceiving fetal movements and presenting to hospital

9.10 Exploratory Analyses

Associations between intervention effects on outcomes will be investigated:

- Change in stillbirth rate; and change in the rate of inductions at or above 37 weeks gestation

- Change in stillbirth rate; and change in proportion of babies undelivered by 40 weeks + 0 days who are less than the 10th centile in birthweight

Associations will be presented graphically using one data point for each study site; where feasible a correlation summarising the association will also be calculated.

9.11 Adverse Events

No other adverse event reporting will be undertaken

10 Data Sharing

A set of files containing the analysis code will be prepared. These will be stored alongside the analysis data set in the National Safe Haven.

11 References

(1) Tominey, Emma. 2007. Maternal smoking during pregnancy and early child outcomes. Discussion Paper no. 828, Centre for Economic Performance, London School of Economics.

(2) Campbell MK, Piaggio G, Elbourne DR, Altman DG; for the CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012;345:e5661..

(3) Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemporary Clinical Trials 2007; 28:182-191.

12 Appendix 1

Example 1, simple statistics

	Control		Intervention	
	n=xxx		n=xxx	
Demographics and lifestyle (participant)	**Mean or count (n)**	**SD or %**	**Mean or number (n)**	**SD or %**
Age (years)	xx.x	xx.x	xx.x	xx.x
Smoker during pregnancy	Xx	xx.x%	xx	xx.x%
Smoking history at booking	Xx	xx.x%	xx	xx.x%

Example 2, Discrete analysis

	Control		Intervention				
Primary outcome - Birth outcome (all births)	**number (n)**	**%**	**number (n)**	**%**	**OR**	**95 % CI**	**p-value**
Live birth at ≥ 28 weeks gestation	xxxx (xxx)	xx.x%	xxxx (xxx)	xx.x%	xxxx	-xxx, xxx	xxxx
Stillbirth at ≥ 28 weeks gestation	xxxx (xxx)	xx.x%	xxxx (xxx)	xx.x%			

Example 3, Continuous analysis

	Control		Intervention				
Outcome	**Mean (n)**	**SD**	**Mean (n)**	**SD**	**Adjusted mean difference**	**95 % CI**	**p-value**
Birthweight centile	xxxx (xxx)	xxxx	xxxx (xxx)	xxxx	xxxx	-xxx, xxx	xxxx