STATISTICAL ANALYSIS PLAN

EMPOWaR

Efficacy of Metformin in Pregnant Obese Women,
a Randomised Controlled Trial

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Signed: _____ Prof Norman, CI

Signed: _____ 10/11/2014 Prof Murray, Author and Statistician

Document Version History

Version Number	Reason for Update	Updated By:	Date
0.0	Creation of new statistical analysis plan	Gordon Murray	20 Nov 2012
1	Additional clarification text	Jane Norman	6 Oct 2014

1 Introduction

The EMPOWaR trial protocol (Version 8, dated 6 October 2014) describes the statistical analysis of the trial data. The purpose of this Statistical Analysis Plan is to give a more detailed and comprehensive description of the methods for the analysis of the trial data, to avoid post hoc decisions that may affect the interpretation of the results of the statistical analysis.

2 EMPOWaR Protocol

EMPOWaR is a double blind placebo controlled randomised trial designed to determine if metformin, administered to obese women during pregnancy, reduces the future life risk of obesity and metabolic syndrome in their babies. Birthweight centile and z-score of birth weight centile are being used as surrogate markers for future life events.

Embedded sub-studies will explore mechanisms of action of metformin.

The initial target sample size was 400 women (i.e. two groups of 200) randomised to receive either metformin (up to 2500mg daily from 12-16 weeks gestation up until the baby is delivered) or matching placebo. A higher than expected loss to follow up and poorer than expected compliance was noted during the study, so the sample size was increased to adjust for this. No formal recalculation of the sample size was performed, but the duration of the funding allowed 449 women to be recruited.

2.1 Outcome Measures as Specified in the Trial Protocol

2.1.1 Primary Endpoint

Z-score of birth weight centile for all live births in the study corresponding to the gestational age and sex adjusted birth weight centiles of the baby

2.1.2 Secondary Endpoints (see proposed tables for details)

- Maternal insulin resistance (HOMA-IR) at 36 weeks' gestation,
- Maternal anthropometry and body composition at 36 weeks' gestation
- Baby anthropometry and body composition at birth.
- Maternal inflammatory markers, including lipid and fatty acid profiles at 36 weeks' gestation as listed in the summary tables in the appendix.
- Neonatal CRP, glucose and insulin (measured in cord blood at birth) as listed in the summary tables in the appendix

- Adverse outcomes including:

  Maternal antenatal complications

  Maternal delivery complications (caesarean section and PPH)

Fetal and neonatal complications including incidence of low birth weight centile

Maternal symptoms up to 36 weeks' gestation

- Correlation between maternal insulin resistance and adverse pregnancy outcomes.

Other supplementary outcomes

- Maternal inflammatory and metabolic indices at baseline (to confirm no difference between groups) and at 36 weeks' gestation
- Maternal body composition at 3 months postpartum
- Baby anthropometry and body composition 3 months post partum

2.1.3 Data tables

Further details for the primary and secondary outcomes for this study are listed in the data tables in the appendices to this document (Appendix 1 [clinical data] and Appendix 2 [mechanistic data]. Additional information on some of these outcomes is listed below.

2.2 Statistical Considerations as Specified in the Trial Protocol

2.2.1 Sample Size Determination

Birth weight centile: In a previous study, the mean (SD) birthweight in a cohort of obese women (mean BMI 34 kg/m^2) was 4.0kg (0.6kg). We hypothesised that metformin would reduce mean birthweight by 200g, corresponding to a reduction in birthweight centile of 0.33SD. We believe that this reduction in birthweight is clinically relevant, but is a relatively conservative estimate of the likely reduction in birthweight centile induced by metformin, given that the mean birthweight in the study described above in a parallel non obese cohort was 3.4kg. A sample of 143 in each group will have 80% power to detect a difference in mean birthweight centile of 0.33SD (the difference between a placebo mean of 4.0kg and a metformin mean of 3.8kg) at the 5% significance level (2-sided) using a two-group t-test; a sample of 163 in each group will give the study 85% power to detect these differences. In practice we have recruited a larger sample size to allow for loss to follow up.

Insulin resistance: In our previous study of obese women with PCOS, fasting insulin was lowered by 25% after 6 months treatment with metformin 1500mg daily, consistent with meta-analysis. Based on published levels of fasting insulin in obese pregnant women (26.9 IU/L), and deriving the standard deviation as 15.7 IU/L from the published standard error of 3.5 IU/L with n=20, if a reduction in mean fasting insulin of 22% (5.4 IU?L) is achieved by metformin in pregnancy, a sample size of 306 is required for the study to have 85% power to demonstrate differences between placebo and metformin groups at the 5% significance level.

2.2.2 Randomisation

A central randomisation facility based at the Edinburgh Clinical Trials Unit (ECTU) will be available online via the web portal. Randomisation will be stratified by treatment centre and by BMI bands 30-39 kg/m^2 versus ≥40 kg/m^2.

2.2.3 Statistical analysis proposed in the study protocol

"Mean birthweight centile will be compared between the groups using essentially a two-sample t-test, but with the analysis stratified for the same factors as the randomisation. Correlations within the metformin and placebo groups will be used to determine association between IR and adverse pregnancy outcomes".

3 Responsibilities for the Statistical Aspects of the Trial

Trial Statistician, member of TSC: Prof Gordon Murray, Edinburgh

- Advising on the statistical design of the trial
- Drafting the Statistical Analysis Plan ahead of the trial being finished and the database locked.
- Overseeing the final trial analysis.

DMC Statistician, member of DMC: Mr Graeme MacLennan, Aberdeen

- Providing support to the DMC in interpreting the unblinded data presented to the DMC.

Independent Statistician, from ECTU: Ms Aryelly Rodriguez, Edinburgh

- Preparation of unblinded reports to go to the DMC.
- Undertaking the final analysis of the trial after the database is locked and unblinded.

4 Analysis Principles

4.1 Statistical Programming and Analysis

The statistician at ECTU will perform the statistical programming and analysis to produce all summary tables and figures using the statistical package SAS (v9.2 or a more recent version).

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) using the format presented in the examples 1 and 2 below. Data will be split by time point where applicable

Example 1. Data presentation for categorical data

Parameter	Time point / visit	Statistic/ category	**Placebo** **N=xx**	**Metformin** **N=xx**	**Overall** **N=xx**
Parameter	Time point x	Category 1	xx (%)	xx (%)	xx (%)
		…	…	…	…
		Category n	xx (%)	xx (%)	xx (%)

Example 2.Data presentation for continuous data

Parameter	Time point / visit	Statistic/ category	**Placebo**	**Metformin**	**Overall**
			N=xx	**N=xx**	**N=xx**
Parameter	Time point x	Mean	xx	xx	xx
		Median	xx	xx	xx
		SD	xx	xx	xx
		Q1, Q3	xx, xx	xx, xx	xx, xx
		Min, Max	xx, xx	xx, xx	xx, xx
		n	xx	xx	xx

In general, minimum and maximum will be quoted to the number of decimal places as recorded in the CRF or other appropriate source data. Means, medians and SDs will be quoted to one further decimal place. Percentages will be rounded to one decimal place.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots. Any severe deviation from the distributional assumptions for the parametric approach will be reported.

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level, leading to 95% (2-sided) confidence intervals (CIs).

The Intention-to-treat population (i.e. all randomised subjects) will be used to summarise all data.

The study is not adequately powered to analyse subgroup effects, but the primary results will be presented stratified by the factors used in the randomisation (treatment centre and BMI band) to allow an exploratory assessment of the consistency of treatment effect over these subgroups.

There are no plans to conduct any formal interim analyses, although the unblinded data will be reviewed regularly by an independent Data Monitoring Committee (DMC). The DMC would require a stringent level of statistical significance before recommending that the trial should be stopped early on the basis of efficacy, and so there is no intention of adjusting the significance level of the final analysis to take account of the possibility of premature termination.

4.2 Handling of Missing Data

The primary analyses will be based on all available data. If more than 5% of the outcomes are missing for any analysis then an additional sensitivity analysis will be run using multiple imputation.

4.3 Masking of treatment allocation

The clinical data for this project (data in the tables in Appendix 1) will be entered and the database "locked" before the treatment allocation codes are broken. Additionally, metformin levels in blood samples at 36 weeks' gestation will also be entered into the database prior to data lock.

It is unlikely that the complete mechanistic data (data in the tables in Appendix 2) will be available prior to data lock. The analysis of these data will still be performed blind but they will be entered into a separate MS Excel Spreadsheet that will be locked separately once analysis is complete. This is to avoid unnecessary delay in the analysis of the clinical data.

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

Isolated data errors detected in the database as a result of the QC checks that are deemed significant will be submitted for enquiry to the trial manager or designee.

Systematic data errors in the data reporting will be investigated further; the data will be corrected if necessary, and the appropriate table then re-checked.

4.4.1 QC - Summary Tables

A random selection of unique analysis and summary tables will be QC'd using manual methods (i.e. comparison of results in the table to results calculated by a calculator, spread sheet, database output or any alternative summarisation tool).

4.4.2 QC - Statistical Analysis

QC of statistical analyses will be performed by peer review of program code, log and output. The primary analysis will be replicated independently and the reasons for any discrepancies identified and resolved.

5 Populations for Analysis

5.1 Intention to treat population

The intention to treat (ITT) population will comprise all randomised subjects. The primary efficacy analyses will be performed using the ITT population.

5.2 Per-protocol population

The per-protocol (PP) population will comprise those members of the ITT population who completed the study without a major protocol violation and who complied adequately with the randomised treatment (see section 6.5).

The PP population will be determined from information entered into the database before database lock and will be used to perform sensitivity analyses for research questions relating to the mechanisms of action of metformin.

6 Patient Disposition, Demographics, Baseline/Clinical Characteristics

No formal statistical testing will be performed on patient disposition, or on demographic or baseline/clinical, or concomitant medication data. Summaries of patient disposition will be based on all patients and summaries of all other data described in this section will be based on the ITT population, unless otherwise stated.

6.1 Patient Disposition and Withdrawals

The number and percentage of patients randomised, dosed, completed and discontinued will be presented by treatment and overall. The number of patients discontinued early from the study will be summarised by reason for withdrawal and treatment.

6.2 Analysis Populations

A summary table will be produced detailing the number and percentage of patients in both populations for each treatment and overall. The reasons for exclusion from the PP population will be included in the summary.

6.3 Demographic Characteristics

Demographic data will be reported. Age will be calculated using the following formula:

Age (years) = FLOOR((intck('month', date of birth _,date of consent))/12);

and will be rounded down to the nearest year.

Clinician reported BMI is recorded in the database and it will also be calculated using the following formula:

BMI_calculated=Weight/(height_(in metres)*height_(in metres);

For the purpose of stratification of analysis we will use clinician reported BMI (ie the BMI used for stratification at randomisation), regardless of calculated BMI.

Summary statistics (mean, median, SD, minimum, maximum and n) will be presented for age, height, weight and BMI_calculated

6.4 Clinical Characteristics

Number and percentage of patients will be presented by treatment and overall for the clinical characteristics variables.

6.5 Extent of Exposure and Treatment Compliance

Treatment compliance will be determined using the following strategy.

Diary recordings and/or counting of returned medication will be used to determine the number of days the participant has taken medication. Compliant participants will be

assumed to be those who have taken any medication (regardless of dose) on at least 50% of possible treatment days.

Compliance will be also confirmed by assay of metformin levels at 36 weeks' gestation. For those in the "active" treatment group, any level of metformin above the detection level at 36 weeks gestation will be considered to indicate compliance. For those in the "placebo" treatment group, any blood sample which does not indicate metformin in the blood will be used to indicate compliance. Given that this latter group will include those in the placebo group who are taking their tablets, and those in the placebo group who are not taking their tablets, this analysis will be a secondary supporting analysis only.

7 Primary Outcome Measures Analysis

Z-score of birthweight centile

Birth weight centiles and z-scores of birth weight centiles (live births only) will be derived for each patient after adjustment for sex of the infant, gestational age, and parity (nulliparous versus multiparous). This will be done using the formulae and tables presented in Bonellie et al, "Centile charts for birthweight for gestational age for Scottish singleton births", *BMC Pregnancy and Childbirth* 2008; **8**:5.

The primary analysis will use a linear regression model to compare mean z-score between the metformin and placebo groups adjusting for treatment centre and by BMI band (30-39 kg/m^2 versus ≥40 kg/m^2). The result will be presented as an adjusted difference in mean z-score together with its corresponding 95% confidence interval.

The sex of the infants and gestational ages will be summarised by treatment group, and the mean birthweight will be summarised by treatment group, overall and stratified separately by sex of the infant, gestational age, and parity.

Also the birth weight centile will be summarised using the following categories: below 3rd centile, below 5th centile, below 10th centile, above 10th but below 90th, above 90th centile, above 95th above 97th centile again stratified as above..

8 Secondary Outcome Measures

8.1 Insulin resistance

Mean levels of glucose at the 36 weeks' gestation glucose tolerance test will be compared at baseline, and two hours between the randomised groups, adjusting for treatment centre and by BMI 30-39 kg/m^2 versus ≥40 kg/m^2. The results will be presented as adjusted mean differences together with their corresponding 95% confidence intervals.

HOMA-IR will be calculated using the following formula:

HOMA-IR (units) = (glucose x insulin / 22.5)

Mean HOMA-IR score at 36 weeks' gestation will be compared between the randomised groups, adjusting for treatment centre and by BMI 30-39 kg/m^2 versus ≥40 kg/m^2. The results will be presented as adjusted mean differences together with their corresponding 95% confidence intervals.

9 Safety/Adverse Events

9.1 Adverse pregnancy outcomes (secondary outcome) are listed in the data-tables in the appendices but include the following:

Pregnancy induced hypertension
Pre-eclampsia
Caesarean section
Post-partum haemorrhage
Incidence of the baby's admission to the neonatal unit

9.2 Significant adverse events (as reported to sponsor)

Mother died
Intrauterine death
Prolonged hospital admission
Persistent maternal disability/incapacity
Life threatening
Congenital anomaly or birth defect
Neonatal death

10 Changes to the Planned Analyses

Any changes to the planned analyses will be fully documented and explained.

11 Data sharing

A file, or set of files, containing the final data will be prepared, along with a data dictionary. These will be made available to the Chief Investigator at the end of the analysis phase by ECTU.