Statistical Analysis Plan

The Baby Milk Trial: a randomised controlled trial of a theory-based, multicomponent intervention to prevent excessive weight gain during infancy.

July 2015

1 Introduction

This is the plan for the main trial analyses of the primary and secondary efficacy outcomes and safety outcomes from a randomised controlled trial of a theory-based, multicomponent intervention to prevent excessive weight gain during infancy. The analyses described in this document will be performed by Stephen Sharp, Senior Statistician, University of Cambridge MRC Epidemiology Unit, once the data have been entered, cleaned and released for use.

Other planned analyses of data arising from this trial include cost-effectiveness analyses, cohort analyses and cross-sectional analyses; these will be performed separately by members of the trial team/PhD students/post-doctoral researchers and defined in future analysis plans.

The analyses described in this document are compatible with the recommendations of the CONSORT 2010 statement (www.consort-statement.org).

2 Study outcomes

2.1 Primary efficacy outcome

- Change from birth to 12 months in weight standard deviation score (SDS), adjusted for weight SDS at birth.

2.2 Secondary efficacy outcomes

2.2.1 Baby's anthropometry

- Change from **baseline** to 6 months in weight SDS.
- Change from **baseline** to 6 months in BMI SDS.
- Change from **baseline** to 12 months in BMI SDS.
- Change from **baseline** to 12 months in abdominal circumference.

All the changes defined above will be adjusted in the analysis for the value of the relevant variable at baseline (see section 5.2).

- Rapid weight increase, defined as an increase in weight of ≥0.67 SDS between **birth** and 12 months.
- Rapid weight decrease, defined as a decrease in weight of ≥0.67 SDS between **birth** and 12 months.

Measures at 12 months of:

- sum of skinfold thicknesses (cm).
- subcutaneous abdominal fat thickness (cm).
- visceral fat thickness (cm).

2.2.2 Baby's dietary intake

- Milk intake at 2, 3, 4, 5 and 6 months (ml/day).
- Energy intake at 8 months (kcal/day).
- Age at introduction of solid foods.

2.2.3 Parental anthropometry

- Change from **baseline** to 12 months in mother's BMI (kg/m^2).

- Change from **baseline** to 12 months in father's BMI (kg/m^2).

2.3 Safety outcomes

- Adverse events.

- Change from **baseline** to 6 months in length SDS.
- Change from **baseline** to 12 months in length SDS.
- Change from **baseline** to 6 months in head circumference.
- Change from **baseline** to 12 months in head circumference.

- Change from **baseline** to 6 months in SF-8 mental health summary score.
- Change from **baseline** to 6 months in SF-8 physical health summary score.
- Change from **baseline** to 6 months in EuroQoL visual analogue scale.
- Change from **baseline** to 12 months in EuroQoL visual analogue scale.
- Change from **baseline** to 6 months in anxiety score (Spielberger inventory).

For the safety change outcomes, if a measure of the relevant anthropometric variable at birth is not available, the measure at baseline will be used instead.

2.4 Hypothesized mediators of behaviour change

- Change from **baseline** to 6 months in the following psychological mediators, of which the first three are informed by Social Cognitive Theory:
    - self-efficacy (general and situation-specific) in relation to following the feeding recommendations.
    - outcome expectancies (perceived benefits) in relation to following the feeding recommendations.
    - Intention to follow the feeding recommendations.
    - general attitudes about the baby's growth and feeding the baby.

3 Analysis populations

The primary analysis of efficacy and safety outcomes will use an **Intention To Treat (ITT) population**, which includes all babies in the group to which they were randomised, regardless of whether the intervention was actually received.

A secondary analysis of **the primary efficacy outcome only** will use a **Per Protocol (PP) population.** Babies randomised to the intervention group will be included in the PP population if at least 4 out of the 5 intervention sessions were completed and the parents had not opted out of the intervention; babies randomised to the control group will be included in the PP population if at least 4 out of the 5 "control" sessions were completed. The PP population will be finalised once clean data are available, but before the start of any trial analyses.

4 Descriptive analyses

The following baseline characteristics of the study population will be summarised separately within each randomised group:

- Baby's sex.
- Baby's weight SDS at **birth**.
- Baby's weight SDS at **baseline**.
- Baby's length SDS at **baseline**.
- Baby's BMI SDS at **baseline**.

- Mother's age.
- Age mother completed education.
- Mother's highest educational qualification.
- Mother's ethnicity.
- Mother's occupation.
- Mother's marital status.
- Mother's BMI.
- Mother's smoking status during pregnancy (smoker/non-smoker).
- Mother's alcohol consumption during pregnancy.
- Duration of pregnancy.
- Weight change from before pregnancy to delivery.
- Type of delivery.
- Number of previous children.
- Feeding practice at baseline (fully formula fed/mixed feeding).

For continuous variables, means and standard deviations will be presented, unless the variable has a highly skewed distribution, in which case medians, 25th and 75th percentiles will be presented. For categorical variables, the number and percentage of participants (mothers or babies) within each category will be presented. For each variable (continuous or categorical), the % of missing values will be reported.

No p-values will be calculated for these tables.

5 Analyses of study outcomes

5.1 Primary efficacy outcome

The primary efficacy outcome will be analysed using a linear regression model, in which the outcome is change (12 months minus birth) in weight SDS, with weight SDS at birth included as a covariate in the model, together with a binary control/intervention indicator variable. (Note – this is also known as an analysis of covariance model). An estimate of the difference in change between the intervention and control groups, together with a 95% confidence interval and p-value, will be calculated from this model.

Where values of weight SDS at birth are missing, the missing indicator method will be used to enable these babies to be included in the analysis (section 6.1).

5.2 Secondary efficacy outcomes

5.2.1 Baby's anthropometry

For each of the **continuous anthropometry change outcomes** defined in section 2.2.1, an estimate of the difference in change between the intervention and control groups, together with a 95% confidence interval, will be calculated from a linear regression model, in which the outcome is change (6 or 12 months minus birth/baseline) in the relevant variable, with the variable at birth/baseline included as a covariate in the model, together with a binary control/intervention indicator variable.

Where values of the variable at birth/baseline are missing, the missing indicator method will be used to enable these babies to be included in the analysis (section 6.1).

Any of the change outcomes whose distribution is skewed will be log transformed prior to analysis, in which case a ratio of geometric means (and 95% confidence interval) will be reported.

For the **rapid weight increase and rapid weight decrease outcomes**, an estimate of the difference in percentage of rapid weight increasers between the intervention and control groups, together with a 95% confidence interval, will be calculated from a binomial regression model, with weight SDS at birth included as a covariate in the model, together with a binary control/intervention indicator variable.

For the **outcome measures at 12 months**, an estimate of the difference in mean value of the outcome between the intervention and control groups, together with a 95% confidence interval, will be calculated from a linear regression model including a binary control/intervention indicator variable.

5.2.2 Baby's dietary intake

An estimate of the difference in mean milk intake at each of 2,3,4,5 and 6 months between the intervention and control groups, together with a 95% confidence interval, will be calculated from a linear regression model, in which the outcome is milk intake at the relevant time point, and including a binary control/intervention indicator variable.

A similar analysis will be performed for energy intake at 8 months, and for the age at introduction of solid foods.

5.2.3 Parental anthropometry

An estimate of the difference in change in mother's BMI between the intervention and control groups, together with a 95% confidence interval, will be calculated from a linear regression model, in which the outcome is change (12 months follow-up minus baseline) in BMI, with BMI at baseline included as a covariate in the model, together with a binary control/intervention indicator variable.

Where values of BMI at baseline are missing, the missing indicator method will be used to enable these individuals to be included in the analysis (section 6.1).

A similar analysis will be performed for father's BMI.

5.3 Safety outcomes

The numbers and types of adverse events within each randomised group will be reported. No p-values or confidence intervals will be calculated.

The safety change outcomes will be analysed using the method defined in section 5.2.1. For change in length SDS and head circumference, the missing indicator method will only be applied if both the values of the relevant variable at birth and baseline are missing. If the variable is missing at birth but not at baseline, then the baseline value will be used.

5.4 Hypothesized mediators of behaviour change

Items will be recoded as appropriate so that higher scores mean stronger intentions, self-efficacy, etc. Internal consistency (Cronbach's alpha) will be calculated for outcome expectancies (5 items), situation-specific self-efficacy (3 items), and intention (2 items). If Cronbach's alpha is satisfactory ($0.6 \leq \alpha < 0.7$ is considered satisfactory; > 0.70 is considered good), the items will be combined in a scale. The general attitude items will not be combined in a scale (i.e. they will be analysed as individual items) as they were not designed as indicators of a theoretical construct.

For each of the four theory-based constructs (outcome expectancies, situation-specific self-efficacy, general self-efficacy, and intention) and for general attitudes, an estimate of the difference in change in the measure between the intervention and control groups, together with a 95% confidence interval, will be calculated from a linear regression model, in which the outcome is change (6 months follow-up minus baseline), with the measure at baseline included as a covariate in the model, together with a binary control/intervention indicator variable.

Where values of the measure at baseline are missing, the missing indicator method will be used to enable these individuals to be included in the analysis (section 6.1).

Note – no p-values will be calculated for any the analyses described in sections 5.2, 5.3 or 5.4.

6 Considerations for analysis

6.1 Missing data

Missing values of outcomes

If a baby has a missing value for an efficacy outcome, they will be excluded from the analysis. The pattern of missing data for the primary efficacy outcome will be described. Levels of missing data are expected to be low, but if this is not the case, the potential impact of missing data on the analysis of the primary efficacy outcome will be explored in sensitivity analyses using a pattern mixture model (White 2012).

Missing values of outcomes at birth/baseline

For the continuous anthropometry change outcomes, those babies with a missing value of the variable at birth/baseline will be included in the analysis using the missing indicator method (White 2005), which is a valid method for pre-randomisation measures in trials ensuring that no further babies are excluded while maintaining the advantage of improved precision.

6.2 Subgroup analyses

For the primary efficacy outcome, an interaction between intervention/control and feeding practice at baseline (fully formula fed/mixed feeding) will be tested in the linear regression model defined in section 5.1. Estimates of the difference in change in weight SDS between the intervention and control groups, together with 95% confidence intervals, will be calculated within each of the 2 feeding practice subgroups.

6.3 Multiplicity

The only p-values calculated and reported will be for the primary efficacy outcome analysis (section 5.1) and the interaction test (section 6.2). Given the large number of secondary outcomes, safety outcomes and hypothesized mediators of behaviour change, interpretation of effect sizes and confidence intervals for these outcomes will be made with due caution.

7 References

White IR, Thompson SG (2005) Adjusting for partially missing baseline measurements in randomized trials. Stat.Med 24: 993-1007.

White IR, Carpenter J, Horton NJ (2012) Including all individuals is not enough: lessons for intention-to-treat analysis. Clinical Trials 9: 396-407.