MAGENTA

STATISTICAL ANALYSIS PLAN

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CONFIDENTIAL

SAP for Outcomes up to the time of primary hospital discharge

Approved by:

Name: Prof. Caroline A Crowther Version: 1.1 Date: 04/06/2020

SAP for Outcomes at two years corrected age

Approved by:

Name: Prof. Caroline A Crowther Version: 1.2 Date: 25/08/2020

CONTENTS

ABBREVIATIONS

ABBREVIATION	DEFINITION
APH	Antepartum haemorrhage
ARD	Absolute risk difference
MAGENTA	Magnesium sulphate for 30 to 34 weeks' gestation: neuroprotection trial.
GA	Gestational age
GEEs	Generalized estimating equations
IUGR	Intrauterine Growth Retardation
IVH	Intra-ventricular haemorrhage
NICU	Neonatal Intensive Care Unit
PVL	Cystic Periventricular leukomalacia
PSANZ-NDC	Perinatal Society of Australia and New Zealand Neonatal Death Classification
PSANZ-PDC	Perinatal Society of Australia and New Zealand Perinatal Death Classification
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
RRD	Relative risk difference
RTI	Respiratory tract infection
SAP	Statistical Analysis Plan
SD	Standard deviation
UK- WHO	United Kingdom- World Health Organization

1. GENERAL ISSUES:

1.1 PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the MAGENTA protocol (MAGENTA Study- Magnesium sulphate for 30 to 34 weeks' gestation: neuroprotection trial).

The following documents were reviewed in preparation of this SAP:

- The MAGENTA published Protocol (Crowther et al. *BMC Pregnancy and Childbirth* 2013,**13**:91).
- MAGENTA data collection forms

The reader of this SAP is encouraged to also read the clinical protocols for details on the conduct of this study and the operational aspects of clinical assessments in this study.

1.2 PURPOSE OF SAP

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the primary paper for the MAGENTA Study.

It will not cover any side studies, follow-up studies of the trial, nor cost analysis.

1.3 STUDY AIMS, HYPOTHESES AND ENDPOINTS

1.3.1 *Study Aims*

The study aims to determine whether giving magnesium sulphate compared with placebo to women immediately prior to preterm birth between 30 to 34 weeks' gestation reduces the risk of death or cerebral palsy in their children at two years' corrected age.

1.3.2 *Study hypotheses*

1.3.2.1 Primary Hypothesis

The primary hypothesis is that antenatal magnesium sulphate compared with placebo given to women at risk of preterm birth between 30 and 34 weeks' gestation when birth is imminent (defined as planned or definitely expected in the next 24 hours) reduces the risk of death or cerebral palsy in their children at two years' corrected age.

1.3.2.2 Secondary Objectives

The secondary hypotheses are that antennal magnesium sulphate, compared with placebo given to women at risk of preterm birth between 30 and 34 weeks' gestation when birth is imminent (defined as planned or definitely expected in the next 24 hours) has benefits:

- *Up to the time of primary hospital discharge,* relating to:

  The baby: of neonatal morbidity (including stillbirth, death of liveborn infant before discharge, and serious health outcomes); and **the mother**, of mode of birth and maternal morbidity (including serious adverse cardiovascular effects of the infusion, side effects of the infusion and postpartum haemorrhage).

- *At two years' corrected age,* relating to:

  Individual components of the primary outcome (mortality and cerebral palsy), and neonatal and childhood morbidity (including IVH and other neurosensory disabilities at two years' corrected age of blindness, deafness or developmental delay).

1.3.3 *Study Endpoints*

1.3.3.1 Primary Endpoint, measured in the children at two years' corrected age

The incidence of death or cerebral palsy defined as stillbirths, deaths of live born infants before hospital discharge and deaths after hospital discharge before two years' corrected age; or any cerebral palsy (abnormality of tone with motor dysfunction).

1.3.3.2 Secondary Endpoints

Secondary endpoints of the MAGENTA trials will be covered in detail in Section 2.4.

1.4 STUDY METHODS

1.4.1 *Overall Study Design and Plan*

Double-blind, multicentre, randomised, controlled trial.

1.4.2 *Selection of Study Population*

Eligibility Criteria: Women are at risk of preterm birth between 30 to 34 weeks' gestation where birth is planned or definitely expected within 24 hours, have a singleton or twin pregnancy, no contraindications to the use of antenatal magnesium sulphate (respiratory depression, hypotension, renal failure, myasthenia gravis) and give informed, written consent.

Exclusion Criteria: Women have a higher-order multiple pregnancy, have received antenatal magnesium sulphate in the current pregnancy or magnesium sulphate therapy is considered essential for the treatment of pre-eclampsia.

1.4.3 *Method of Treatment Assignment and Randomisation*

Once all entry details are given and eligibility is confirmed, the woman was randomised by contacting the central telephone randomisation service at the University of Adelaide. Women were assigned to one of two treatment groups: either the magnesium sulphate group or the placebo group. Randomisation was

stratified for collaborating centre, gestational age (30- 31 completed weeks or 32-33 completed weeks' gestation), and number of fetuses (1 or 2). A study number was allocated to the woman corresponding to a treatment pack, each of which looked identical and contained a 100 ml infusion bag.

1.4.4 *Treatment Masking (Blinding)*

This is a double- blind trial. The women, her caregivers, and paediatrician, psychologist or research staff assessing the trial outcomes are blinded to the treatment allocation.

Women in both study groups were administered 50 ml of a 100 ml infusion bag (containing 8g magnesium sulphate for women randomised to the magnesium sulphate group or isotonic sodium chloride solution 0.9% for those in the placebo group) through a dedicated intravenous infusion line over 30 minutes. After the infusion started, they were monitored accordingly to the individual obstetric unit protocols for intravenous administration of magnesium sulphate.

All surviving children were formally assessed at two years' corrected age by a developmental paediatrician and psychologist, who remain blinded to treatment group assignment.

1.5 SAMPLE SIZE DETERMINATION

A trial of 1676 children (838 per group), allowing for a design effect of 1.2 for clustering of babies within mothers and a 5% loss to follow up, with an absolute risk difference of 4.2% will have 80% power to detect a statistically significant difference at an alpha level of 0.05 (two-tailed) of a decrease in the combined outcome of death or cerebral palsy from 9.6% to 5.4% with magnesium sulphate compared with placebo.

1.6 GENERAL ISSUES FOR STATISTICAL ANALYSIS

1.6.1 *Analysis Software*

All analysis will be performed using SAS® software version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

1.6.2 *Analysis approach*

The planned analyses will be carried out using the intention-to-treat approach in which randomised participants will be analysed according to the initial treatment allocation. Only babies alive at randomisation are considered eligible for the analyses.

1.6.3 *Methods for Withdrawals, Missing Data, and Outliers*

We will include data of subjects until the point of withdrawal for the final analysis unless they have withdrawn consent to use their data. Data after the point of

withdrawal will be collected and used where permission has been obtained from the participant to do so.

Approach to handling missing data, i.e. complete case analysis approach versus complete case analysis and multiple imputation approach, will be decided after an assessment of the amount of missing data during the blinded review. Overall pattern of missingness, including amount, distribution across study groups and over different outcomes, and covariates to be adjusted for will be examined. If the missingness is expected to have little impact on the results, a complete case analysis will be performed. If the missingness is thought to have the potential to meaningfully impact on the results, multiple imputation will be used to create 100 complete datasets for analysis. Imputation will be performed separately by treatment group using the fully conditional specification method (also known as chained equations). Imputation models will include both baseline variables and outcomes, and sensitivity analyses will be performed using different imputation models. A complete case analysis will also be performed for comparison, but conclusions will be based on the imputed results.

We plan not to exclude outliers from the primary analyses.

1.6.4 *Protocol Violations and Deviations*

No subjects will be excluded from the intention-to-treat analyses due to protocol violations or deviations.

1.6.5 *Data Transformations*

No data transformations are planned. Data transformation may be investigated if assumptions about the distribution of the outcomes are invalid. Data transformations are not planned to correct for departures from normality, since the sample size is sufficient for the central limit theorem to apply (Lumley, Diehr et al. 2002).

1.6.6 *Multiple Comparisons and Multiplicity*

Multiple hypothesis tests will need to be performed to assess the effectiveness of the intervention due to multiple secondary outcomes, unadjusted and adjusted analyses, analyses based on raw and imputed data and planned treatment by covariate interactions.

No adjustment will be made for the number of secondary outcomes or any planned treatment by covariate interactions. As a result, any nominally significant results will be interpreted and reported with caution and considered in the context of consistency and biological plausibility.

1.6.7 *Clustering*

There were two sources of clustering in the trial, from collaborating centre (since multiple women were recruited from the same centre, and multiple centres were involved in the trial); and from mother (since some mothers had twins).

No adjustment is planned for clustering due to collaborating centre, since the effect of this potential clustering is expected to be negligible, given the standardised study

protocol. As the trial is an individually randomised trial with stratification by collaborating centre, the intraclass correlation coefficient is likely to be very small, and the design effect is conservative (Vierron and Giraudeau 2009).

The generalised estimating equations (GEEs) with exchangeable correlations will be used to take the effect of clustering of babies within mothers (infant level) into account.

1.7 ANALYSIS PRINCIPLES

The statistical analyses will be performed for all primary and secondary outcome variables. Statistical significance will be assessed at the 0.05 level using a two-sided comparative test of treatment effect, comparing the magnesium sulphate group (intervention group) to the placebo group (control group), unless otherwise specified.

Binary outcomes will be analysed using log binomial regression, and relative risk (RR) and corresponding 95% confidence interval (CI) will be reported. A log Poisson model with robust variance estimation will be used if the model fails to converge (Zou 2004). If the number of subjects experiencing the outcome is considered too small for the planned analysis to be sensible, a Fisher's exact test will be performed instead with no adjustment for baseline covariates. Additionally, the number needed to treat to benefit with its 95% CI will be computed for the primary outcome.

Count outcomes will be analysed using a log Poisson model. The data will be examined for evidence of over or under-dispersion, and an excess or lack of zero counts. If this occurs, alternatives to the log Poisson regression model will be used as appropriate, such as including a multiplicative dispersion factor in the model or fitting one of the following alternative models: zero-inflated Poisson, zero-truncated Poisson, negative binomial, zero-inflated negative binomial or zero-truncated negative binomial.

Ordinal outcomes will be analysed using a proportional odds model. If the proportional odds assumption is not met, separate logistic regression models for binary outcomes defined by different cut points will be fitted (Bender and Grouven, 1998).

Continuous outcomes will be analysed using linear regression. All model assumptions, including normality, will be assessed.

The UK-WHO Growth Reference (Cole TJ 2011) will be used to determine age and sex-specific percentiles and z-scores for weight, length and head circumference.

2. CHAPTER 2: STATISTICAL ANALYSIS PLAN FOR OUTCOMES UP TO THE PRIMARY HOSPITAL DISCHARGE:

2.1 SEQUENCE OF PLANNED ANALYSIS

2.1.1 *Interim Analyses*

There is no planned interim analysis.

2.1.2 *Final Analyses and Reporting*

Data will be analysed by a statistician independent of the clinical investigators.

Once the last participant has been discharged from the hospital, and all data have been entered, blinded reviews of the data without knowledge of treatment allocation will be conducted, and final changes will be made to this SAP. Following the approval of the final version of this SAP, analysis of the study outcomes will be performed blinded to the treatment allocation. A blinded data review meeting will be held prior to the treatment allocation unlock and completion of the final analysis.

Key statistics and study results will be made available to the trial investigators.

Any post-hoc, exploratory analyses which were not identified in this SAP but are completed to support the planned analyses will be clearly identified. Any deviations from the planned analyses detailed in this SAP will be clearly documented with reasons in a post-analysis version of the SAP.

2.2 OTHER ISSUES FOR STATISTICAL ANALYSIS

2.2.1 *Potential Confounders*

Both unadjusted and adjusted analyses will be carried out for each outcome. Conclusions about the effect of treatment will be drawn from the adjusted results; the unadjusted analyses will be used to potentially confirm the results of the adjusted analyses.

Analyses will make adjustment for the stratification variables; collaborating centre, gestational age at entry and plurality. Exploratory analyses will make additional adjustments for any important baseline predictors identified during the analysis which show evidence of substantial imbalance between the study groups.

Pre-defined potential confounding variables	Details
Collaborating centre	Categorical variable defined by hospital ID (Trial entry form, variable HospID). Collaborating centres with few participants, defined as < 10 women will be combined with the most similar centre.
Gestational age at trial entry	Binary variable (30-31 completed weeks vs. 32-33 completed weeks' gestation) (TrialEntry form Q1, variable GAentWk and GAentDy).
Number of fetuses	Binary variable (single vs. twins) (TrialEntry form Q2, variable Plurality).

If convergence is an issue, some potential confounders may need to be collapsed into fewer categories or excluded from the adjusted analysis for particular outcome(s). Any deviation from the planned adjustment for potential confounders will be clearly identified.

2.2.2 *Planned Treatment by Covariate Interactions*

Evidence of effect modification will be inspected for intraventricular haemorrhage, severe intraventricular haemorrhage and composite serious infant health outcome (See Section 2.4 for definition).

The analysis will be carried out to test for evidence of effect modification on these outcomes by including the relevant interaction term with treatment in the model. Subgroups will be defined using the categories specified in the following table. If data are insufficient, the subgroups may be combined, or only unadjusted analysis will be performed. No analyses will be carried out if the number of subjects experiencing the outcome is considered too small for the planned analysis to be sensible. Separate estimates of treatment effect will be obtained within each category, independent of whether the interaction is statistically significant or not, since these carefully chosen limited comparisons are of interest a priori.

Any unplanned treatment by covariate interactions must be considered exploratory and will be clearly identified.

Pre-defined effect modifiers	Details
Gestational age at trial entry	Continuous variable dichotomised as 30-31 completed weeks and 32-33 completed weeks' gestation (TrialEntry form Q1, variable GAentwk and GAentDy).
Main reason for risk of preterm birth	Categorical variable as Antepartum haemorrhage, PPROM, Preterm labour, Fetal compromise, Pre-eclampsia/Eclampsia, Cervical incompetence, and Other (TrialEntry form, Q12).
Gender	Binary variable as male and female (BabyDelivery form Q1.3, variable BSex)
Number of fetuses	Binary variable as single and twins (TrialEntry form Q2, variable Plurality).

2.2.3 *Planned exploratory sub-group analyses*

The treatment effect on intraventricular haemorrhage and other key secondary outcomes such as severe intraventricular haemorrhage, cystic periventricular leukomalacia, and composite serious infant health outcome will be also explored for each category of GA at delivery. No interaction test will be carried out for these exploratory analyses.

Exploratory sub-group analyses	Details
GA at delivery	Continuous variable categorized as <32, 32-< 34, 34-< 37 and ≥ 37 weeks' gestation, calculated from GA at entry (TrialEntry form Q1, variable GAentWk and GAentDy), date of randomization (Q8, variable RandDate) and date of birth (BabyDelivery form Q1.1, variable BDOB).

2.2.4 *Planned sensitivity analyses*

There are three planned sensitivity analyses:

2.2.4.1 Sensitivity analyses for infants whose cranial ultrasound examination and/or retinopathy assessment were not done.

Ultrasound examination and retinal examination are clinically indicated for infants experiencing any signs or symptoms or having additional risk factors warranting further assessment. Sensitivity analyses will be carried out for the below prematurity-related outcomes under an assumption that these outcomes are set to no

for infants whose GA at birth was 30 weeks' gestation or more, alive until the primary hospital discharge and having neither ultrasound nor retinopathy assessment done.

The sensitivity analyses will be carried out for the following outcomes: intraventricular haemorrhage, severe intraventricular haemorrhage, cystic periventricular leukomalacia, retinopathy of prematurity and composite serious infant health outcome.

2.2.4.2 Sensitivity analysis by treatment group allocated at randomization for women who received any of the trial medication by treatment group allocated at randomization.

This sensitivity analysis will be conducted for women receiving any of the allocated trial medication, by the treatment group allocated by randomization. The sensitivity analysis will be conducted for all outcomes of interest (section 2.4).

2.2.4.3 Sensitivity analysis by treatment group the women actually received.

This per-protocol analysis will be conducted by treatment group the women actually received, regardless of the treatment group allocated by randomization. The sensitivity analysis will be conducted for all outcomes of interest (section 2.4).

2.3 DESCRIPTIVE ANALYSIS

2.3.1 *Flow Chart of Participants*

Information will be presented by treatment groups (where appropriate) on:

- Number of women approached.
- Number of women excluded from the study
  - Number of women who did not meet inclusion criteria
  - Number of women who declined to participate, with reasons
  - Number of women who were excluded by other reasons
- Number of eligible women who consented and were randomised, and number of fetuses alive at randomisation.
- Number of women allocated to interventions
  - Number of women who did not receive allocated intervention, and reasons.
  - Number of women who received the allocated intervention and placebo.
- Number of women who withdrew from the study and timing of withdrawal.
- Number of stillbirths and liveborns.
- Number of women and babies included in the analysis.

- Number of infant deaths up to the time of primary hospital discharge, and number of survivors to the primary discharge.

2.3.2 *Baseline Characteristics*

An analysis of variables collected at baseline will be performed to compare the characteristics of subjects in each treatment group (see shell table). Any baseline covariates with important imbalance between the study groups will be controlled for in the exploratory adjusted analyses. Means and standard deviations, or medians and interquartile ranges will be reported for continuous variables where appropriate. Frequencies and percentages will be reported for categorical variables.

2.3.3 *Measurement of Treatment adherence*

Treatment adherence will be assessed descriptively based on whether the participants received allocated intervention (i.e., assigned drug package).

2.3.4 *Missing Data*

Missing data will be assessed descriptively by treatment group for each outcome variable in Section 2.4, and each potential confounder in Section 2.2.1.

2.4 STATISTICAL ANALYSES

The statistical analyses will be performed for all primary and secondary outcome variables. The analysis plan for each outcome includes the outcome variable description and analysis method(s). The outcome variable is described as the type of variable, the relevant variable(s) in the data collection forms and how it will be calculated. The analysis presents the type of statistical analysis used for each outcome and the measure of treatment effect to be reported.

2.4.1 *Infant Outcomes*

2.4.1.1 Any deaths before primary hospital discharge

Outcome: Binary infant level outcome, defined as either stillbirth (BabyDelivery form Q4, variable BStill) or liveborn deaths before primary hospital discharge (Neonatal form Q29, variable Death). Stillbirths before randomisation are not eligible for the analysis.

Analysis: Fit a log binomial GEE model to estimate relative risk of Death before discharge (magnesium sulphate relative to placebo).

A descriptive analysis of causes of any deaths before primary hospital discharge will be reported using PSANZ-PDC and PSANZ-NDC.

2.4.1.2 Stillbirth

Outcome: Binary infant level outcome (BabyDelivery form Q4, variable BStill). Stillbirths before randomisation are not eligible for the analysis.

Analysis: Fit a log binomial GEE model to estimate relative risk of stillbirth (magnesium sulphate relative to placebo).

A descriptive analysis of causes of death will be reported using The Perinatal Society of Australia and New Zealand Perinatal Death Classification (PSANZ-PDC).

2.4.1.3 Neonatal death before primary hospital discharge

Outcome: Binary infant level outcome, defined as liveborn deaths before primary hospital discharge (Neonatal form Q29, variable Death).

Analysis: Fit a log binomial GEE model to estimate relative risk of death before discharge (magnesium sulphate relative to placebo).

A descriptive analysis of causes of liveborn deaths before hospital discharge will be reported using The Perinatal Society of Australia and New Zealand Neonatal Death Classification (PSANZ-NDC)

2.4.1.4 Intraventricular haemorrhage (IVH)

Outcome: Binary infant level outcome defined as IVH identified from a cranial ultrasound within first 7 days (Neonatal form Q23.4, variable MaxIVHL1 or MaxIVHR1) or closest to 6 weeks (Neonatal form Q24.4, variable MaxIVHL2 or MaxIVHR2).

Only infants who had a cranial ultrasound performed within the first 7 days will be included in this analysis.

Analysis: Fit a log binomial GEE model to estimate relative risk of IVH (magnesium sulphate relative to placebo).

Secondary analyses will be carried out to test for evidence of effect modification by GA at trial entry, Main reason for risk of preterm birth, Baby gender and Number of fetuses (Section 2.2.2). The treatment effect will be explored for GA at delivery (Section 2.2.3).

Sensitivity analysis (Section 2.2.4) including all infants will be carried out under an assumption that IVH will be set to no for infants whose GA at birth was 30 weeks' gestation or more, alive until the primary discharge and having no ultrasound performed.

2.4.1.5 Severe intraventricular haemorrhage

Outcome: Binary infant level outcome defined as IVH grade 3 or 4 identified from a cranial ultrasound within first 7 days (Neonatal form Q23.4, variable MaxIVHL1 or MaxIVHR1) or closest to 6 weeks (Neonatal form Q24.4, variable MaxIVHL2 or MaxIVHR2).

Only infants who had a cranial ultrasound performed within the first 7 days will be included in this analysis.

Analysis: Fit a log binomial GEE model to estimate relative risk of severe IVH (magnesium sulphate relative to placebo).

Secondary analyses to test for evidence of effect modification (Section 2.2.2), or to explore the treatment effect for GA at delivery (Section 2.2.3), and sensitivity analyses (Section 2.2.4) will be carried out.

2.4.1.6 Cystic periventricular leukomalacia (PVL)

Outcome: Binary infant level outcome defined as PVL identified at a cranial ultrasound within first 7 days (Neonatal form Q24.3, variable CCysL31 or CCysR31) or close to 6 weeks (Neonatal form Q24.3, variable CCysL32 or CCysR32).

Only infants who had a cranial ultrasound performed within the first 7 days or close to 6 weeks will be included in this analysis.

Analysis: Fit a log binomial GEE model to estimate relative risk of PVL (magnesium sulphate relative to placebo).

Secondary analyses to explore the treatment effect for GA at delivery (Section 2.2.3), and sensitivity analyses (Section 2.2.4) will be carried out.

2.4.1.7 Neonatal encephalopathy

Outcome: Binary infant level outcome defined as encephalopathy (Neonatal form Q28, variable BHypIschEnc).

Analysis: Fit a log binomial GEE model to estimate relative risk of neonatal encephalopathy (magnesium sulphate relative to placebo).

2.4.1.8 Neonatal convulsions

Outcome: Binary infant level outcome (Neonatal form Q27, variable Convulsions).

Analysis: Fit a log binomial GEE model to estimate relative risk of neonatal convulsions (magnesium sulphate relative to placebo). A

descriptive analysis of causes and duration of neonatal convulsions will be reported.

2.4.1.9 Proven Necrotising Enterocolitis

Outcome: Binary infant level outcome (Neonatal form Q20, variable BNecEnt).

Analysis: Fit a log binomial GEE model to estimate relative risk of Proven Necrotising Enterocolitis (magnesium sulphate relative to placebo).

2.4.1.10 Retinopathy of prematurity (ROP)

Outcome: Binary infant level outcome (Neonatal form Q18, variable BROP).

Only infants who had an assessment for retinopathy performed will be included in this analysis.

Analysis: Fit a log binomial GEE model to estimate relative risk of ROP (magnesium sulphate relative to placebo).

Sensitivity analyses (Section 2.2.4) will be carried out.

2.4.1.11 Severe ROP

Outcome: Binary infant level outcome, defined as ROP stage 3 or worse in the better eye (Neonatal form Q18, variable BROPStageL or BROPStageR at stage 3 or 4).

Only infants who had an assessment for retinopathy performed will be included in this analysis.

Analysis: Fit a log binomial GEE model to estimate relative risk of ROP (magnesium sulphate relative to placebo).

Sensitivity analyses (Section 2.2.4) will be carried out.

2.4.1.12 ROP needing treatment

Outcome: Binary infant level outcome (Neonatal form Q19, variable BROPTrt).

Only infants who had an assessment for retinopathy performed will be included in this analysis.

Analysis: Fit a log binomial GEE model to estimate relative risk of ROP needing treatment (magnesium sulphate relative to placebo).

Sensitivity analyses (Section 2.2.4) will be carried out.

2.4.1.13 Patent ductus arteriosis requiring treatment

Outcome: Binary infant level outcome (Neonatal form Q14, variable BPdaTrt).

Analysis: Fit a log binomial GEE model to estimate relative risk of patent ductus arteriosis requiring treatment (magnesium sulphate relative to placebo).

2.4.1.14 Respiratory distress syndrome

Outcome: Binary infant level outcome (Neonatal form Q5, variable RDS).

Analysis: Fit a log binomial GEE model to estimate relative risk of respiratory distress syndrome (magnesium sulphate relative to placebo).

Secondary analyses will be carried out to test for evidence of effect modification (Section 2.2.2), and to explore the treatment effect will be explored for GA at delivery (Section 2.2.3).

2.4.1.15 Severity of any neonatal lung disease

Outcome: Ordinal infant level outcome. Defined as nil, mild (MAP< 7.0 and/or FiO_2< 0.40), moderate (MAP 7.0- 9.9 and/or FiO_2 0.40-0.79) or severe (MAP≥ 10.0 and/or FiO_2≥ 0.80) (Neonatal form Q9.1, variable BSevLung).

Analysis: Fit a proportional odds GEE model to estimate odds ratio of higher severity of neonatal lung disease (magnesium sulphate relative to placebo). If the proportional odds assumption is not met, fit separate logistic GEE regression models to estimate odds ratios for the 3 binary outcomes of at least mild lung disease (i.e. mild, moderate or severe disease), at least moderate disease (i.e. moderate or severe disease) and severe disease.

Secondary analyses will be carried out to test for evidence of effect modification by GA at trial entry, Main reason for risk of preterm birth, Baby gender and Number of fetuses (Section 2.2.2). The treatment effect will be explored for GA at delivery (Section 2.2.3).

2.4.1.16 Chronic lung disease

Outcome: Binary infant level outcome defined as any respiratory support, supplemental oxygen only, intermittent positive pressure ventilation or continuous positive airway pressure, including with oxygen or air only (Neonatal form Q6, variable BRespSupport and Q11, variable BSupO2) for chronic respiratory condition on

the day the baby reached 36 weeks postmenstrual age for an infant born at less than 32 weeks gestation, or a continuing oxygen requirement at 28 days of age for infants born at 32 weeks gestation or later. Age when support ceased determined from difference between date of final supplemental oxygen (Neonatal form Q11.1, variable BO2Dte or from 12 or 24 month Child's Ages and Stages questionnaire, variable homeono2datefinished) and date of birth (Baby delivery form Q1, variable BDOB) or sum of days spent on respiratory support (Neonatal form Q6.1-6.4, variables BMechdys, Mechhrs, BCPAPdys, BCPAPhrs, BOtherRespdys, BOtherResphrs, BO2Onlydys, BO2Onlyhrs). If the baby was discharged home on oxygen therapy and the date of final supplemental oxygen was not recorded, the date of discharge will be used.

Difference must be ≥36 weeks minus calculated GA at delivery for an infant born at less than 32 weeks' gestation, and must be ≥28 days for an infant born at 32 weeks' gestation or later.

Analysis: Fit a log binomial GEE model to estimate relative risk of chronic lung disease (magnesium sulphate relative to placebo).

2.4.1.17 Use of respiratory Support

Outcome: Binary infant level outcome, including endo-tracheal or CPAP support (Neonatal form Q6.1 and 6.2, variables BMechdys, Mechhrs, BCPAPdys and BCPAPhrs). Infants who received other respiratory support (Neonatal form 6.3 and 6.4, variables BOtherRespdys, BOtherResphrs) will be reviewed by a clinical expert to classify their respiratory support.

The outcome defined as no if infant received no respiratory support (Neonatal form Q6, variable BRespSupport) or if infant only received other support (Neonatal form 6.3 and 6.4, variables BOtherRespdys, BOtherResphrs), reviewed by a clinical expert as no respiratory support (Neonatal form Q6.3, variable BOtherRespSpecific).

Analysis: Fit a log binomial GEE model to estimate relative risk of respiratory support (magnesium sulphate relative to placebo).

Secondary analyses will be carried out to test for evidence of effect modification by GA at trial entry, Main reason for risk of preterm birth, Baby gender and Number of fetuses (Section 2.2.2). The treatment effect will be explored for GA at delivery (Section 2.2.3).

2.4.1.18 Duration of respiratory support (days)

Outcome: Count infant level outcome defined as the sum in days (i.e. hours will be converted to days) of duration of (i) endo-tracheal support (Neonatal form Q6.1, variables BMechdys and BMechhrs) and (ii) non endo-tracheal support (Neonatal form Q6.2 variables BCPAPdys and BCPAPhrs).

Duration of other respiratory support (Neonatal form Q6.3, variables BOtherRespdys and BOtherResphrs) will be used if other method of respiratory support is classified as respiratory support (i.e. not oxygen only support).

Analysis: Fit a log Poisson GEE model to estimate ratio of mean duration of respiratory support (magnesium sulphate relative to placebo).

2.4.1.19 Use of mechanical ventilation

Outcome: Binary infant level outcome (Neonatal form Q6.1, variable BMechdys or Mechhrs).

Analysis: Fit a log binomial GEE model to estimate relative risk of use of mechanical ventilation (magnesium sulphate relative to placebo).

2.4.1.20 Duration of mechanical ventilation (hours)

Outcome: Count infant level outcome defined as the sum in hours (i.e. days will be converted to hours) of duration of mechanical ventilation (Neonatal form, Q6.1, variable BMechdys and Mechhrs).

Analysis: Fit a log Poisson GEE model to estimate ratio of mean duration of mechanical ventilation (magnesium sulphate relative to placebo).

2.4.1.21 Use of oxygen therapy

Outcome: Binary infant level outcome, defined as the use of supplemental Oxy (Neonatal form Q11, variable BSupO2).

Analysis: Fit a log binomial GEE model to estimate relative risk of use of oxygen therapy (magnesium sulphate relative to placebo).

2.4.1.22 Need for oxygen therapy at 28 days or more of life

Outcome: Binary infant level outcome defined as need for oxygen therapy (Neonatal form Q11, variable BSupO2) at 28 days or more of life, defined as the difference between the timing of oxygen need (Neonatal form Q11.1, variable BO2Dte) and birth (BabyDelivery form Q1, variable BDob)≥ 28 days.

Analysis: Fit a log binomial GEE model to estimate relative risk of need for oxygen therapy at 28 days or more of life (magnesium sulphate relative to placebo).

2.4.1.23 Duration of oxygen therapy (days)

Outcome: Count infant level outcome defined as the difference in days between the date of final supplemental oxygen (Neonatal form Q11.1, variable BO2Dte) and birth (BabyDelivery form Q1.1, variable BDob). For the purpose of analysis of outcomes up to the time of primary hospital discharge, the date of discharge (Neonatal form Q35, variable DischDte) will be used for the date of final supplemental oxygen if babies are discharged home on oxygen. This definition will be modified in any subsequent analyses.

Analysis: Fit a log Poisson GEE model to estimate ratio of mean duration of oxygen therapy (magnesium sulphate relative to placebo).

2.4.1.24 Discharge home on oxygen

Outcome: Binary infant level outcome (Neonatal form Q12, variable BO2Home).

Analysis: Fit a log binomial GEE model to estimate relative risk of discharge home on oxygen (magnesium sulphate relative to placebo).

2.4.1.25 Air leak syndrome requiring treatment

Outcome: Binary infant level outcome (Neonatal form Q8, variable BAlSdrn).

Analysis: Fit a log binomial GEE model to estimate relative risk of air leak syndrome (magnesium sulphate relative to placebo).

2.4.1.26 Number of episodes of proven infection

Outcome: Ordinal infant level outcome (Neonatal form Q15, variable BNoEpis).

Analysis: Fit a proportional odds GEE model to estimate odds ratio of more episodes of proven infection (magnesium sulphate relative to placebo). If the proportional odds assumption is not met, fit separate logistic GEE regression models to estimate odds ratios for the 3 binary outcomes of at least one episode of proven infection, at least two episodes of proven infection and at least three episodes of proven infection.

2.4.1.27 Confirmed infection at less than 48 hours of life

Outcome: Binary infant level outcome defined as at least 1 episode of proven systemic infection (culture positive) < 48 hours of life (Neonatal form Q16.1, variable BSILConfNum).

Analysis: Fit a log binomial GEE model to estimate relative risk of confirmed infection less than 48 hours of life (magnesium sulphate relative to placebo).

A descriptive analysis of sites of infection and organisms will be reported.

2.4.1.28 Use of antibiotics at less than 48 hours of life

Outcome: Binary infant level outcome (Neonatal form Q16.3, variable BSILanti).

Analysis: Fit a log GEE binomial model to estimate relative risk of use of antibiotics less than 48 hours of life (magnesium sulphate relative to placebo).

2.4.1.29 Confirmed infection at 48 hours of life or more

Outcome: Binary infant level outcome defined as at least 1 episode of proven systemic infection (culture positive) ≥ 48 hours of life (Neonatal form Q17, variable BSIGConfNum).

Analysis: Fit a log binomial GEE model to estimate relative risk of confirmed infection after the first 48 hours of life (magnesium sulphate relative to placebo).

A descriptive analysis of sites of infection and organisms will be reported.

2.4.1.30 Use of antibiotics at 48 hours of life or more

Outcome: Binary infant level outcome (Neonatal form Q17.2, variable BSIGanti).

Analysis: Fit a log GEE binomial model to estimate relative risk of use of antibiotics after the first 48 hours of life (magnesium sulphate relative to placebo).

2.4.1.31 Gestational age at birth (weeks)

Outcome: Continuous infant level outcome, measured in weeks, calculated from GA at entry (TrialEntry form Q1, variable GAentWk and GAentDy), date of randomization (Q8, variable RandDate) and

date of birth (BabyDelivery form Q1.1, variable BDOB).

Analysis: Fit a linear GEE model to estimate difference in mean gestational age at birth (magnesium sulphate relative to placebo).

2.4.1.32 Weight at birth

Outcome: Continuous infant level outcome defined as both raw and a z-score (Cole TJ 2011).

The outcome defined using birth weight (BabyDelivery form Q1.8, variable BWght), sex (BabyDelivery form Q1.3, variable BSex) and gestational age at birth (MotherDelivery form Q2, variable GAdelwk and GAdeldy).

Analysis: Fit a linear GEE model to estimate difference in mean birth weight (z-score) (magnesium sulphate relative to placebo).

2.4.1.33 Length at birth

Outcome: Continuous infant level outcome defined as both raw and a z-score (Cole TJ 2011).

The outcome defined using birth length (BabyDelivery form Q1.9, variable BLngth), sex (BabyDelivery form Q1.3, variable BSex) and gestational age at birth (MotherDelivery form Q2, variable GAdelwk and GAdeldy).

Analysis: Fit a linear GEE model to estimate difference in mean birth length (z-score) (magnesium sulphate relative to placebo).

2.4.1.34 Head circumference at birth

Outcome: Continuous infant level outcome defined as both raw and a z-score (Cole TJ 2011).

The outcome defined using birth weight (BabyDelivery form Q1.10, variable BHeadC), sex (BabyDelivery form Q1.3, variable BSex) and gestational age at birth (MotherDelivery form Q2, variable GAdelwk and GAdeldy).

Analysis: Fit a linear GEE model to estimate difference in mean head circumference (z-score) (magnesium sulphate relative to placebo).

2.4.1.35 Weight at discharge home from birth

Outcome: Continuous infant level outcome defined as both raw and a z-score (Cole TJ 2011).

The outcome defined using weight at discharge (Neonatal form

Q37, variable DischWt), sex (BabyDelivery form Q1.3, variable BSex) and corrected age at discharge, estimated from the difference between Date of Weight at discharge measurement (Neonatal form Q37, variable DischWtDte) and Date of birth (Baby Delivery form Q1.1, variable BDob), and GA at entry (Trial Entry form Q2, variables GAentWk and GAentDy).

If weight at discharge is missing, weight at transfer (Neonatal form Q32, variables TransferWt and TransferWtDte) will be used. If neither weight at discharge nor weight at transfer is available, weight at birth (BabyDelivery form Q1.8, variable BWght) will be used for infants who have postnatal hospital stay of 7 days or less.

Analysis: Fit a linear GEE model to estimate difference in mean weight at discharge home from birth (z-score) (magnesium sulphate relative to placebo).

2.4.1.36 Length at discharge home from birth

Outcome: Continuous infant level outcome defined as both raw and a z-score (Cole TJ 2011).

The outcome defined using length at discharge (Neonatal form Q38, variable DischLen), sex (BabyDelivery form Q1.3, variable BSex) and corrected age at discharge, estimated from the difference between Date of Length at discharge measurement (Neonatal form Q38, variable DischLenDte) and Date of birth (Baby Delivery form Q1.1, variable BDob), and GA at entry (Trial Entry form Q2, variables GAentWk and GAentDy).

If length at discharge is missing, length at transfer (Neonatal form Q33, variables TransferLen and TransferLenDte) will be used. If neither length at discharge nor length at transfer is available, length at birth (BabyDelivery form Q1.6, variable BLngth) will be used for infants who have postnatal hospital stay of 7 days or less.

Analysis: Fit a linear GEE model to estimate difference in mean length at discharge home from birth (z-score) (magnesium sulphate relative to placebo).

2.4.1.37 Head circumference at discharge home from birth

Outcome: Continuous infant level outcome defined as both raw and a z-score (Cole TJ 2011).

The outcome defined using head circumference at discharge (Neonatal form Q39, variable DischHeadCirc), sex (BabyDelivery form Q1.3, variable BSex) and corrected age at

discharge, estimated from the difference between Date of Head circumference at discharge measurement (Neonatal form Q39, variable DischHeadCircDte) and Date of birth (Baby Delivery form Q1.1, variable BDob), and GA at entry (Trial Entry form Q2, variables GAentWk and GAentDy).

If head circumference at discharge is missing, head circumference at transfer (Neonatal form Q34, variables TransferHeadCirc and TransferHeadCircDte) will be used. If neither head circumference at discharge nor head circumference at transfer is available, head circumference at birth (BabyDelivery form Q1.10, variable BHeadC) will be used for infants who have postnatal hospital stay of 7 days or less.

Analysis: Fit a linear GEE model to estimate difference in mean head circumference at discharge home from birth (z-score) (magnesium sulphate relative to placebo).

2.4.1.38 Composite serious infant health outcome

Outcome: Binary infant level outcome defined as either stillbirth, death of liveborn infant before hospital discharge, severe respiratory disease, severe IVH (grade 3 or 4), chronic lung disease (oxygen dependent at 36 weeks post-menstrual age or 28 days of life if born after 32 weeks gestation), proven necrotising enterocolitis, severe retinopathy of prematurity (Stage 3 or worse in the better eye) or cystic periventricular leukomalacia.

Analysis: Fit a log binomial GEE model to estimate relative risk of composite serious health outcome (magnesium sulphate relative to placebo).

Secondary analyses to test for evidence of effect modification (Section 2.2.2), and to explore the treatment effect for GA at delivery (Section 2.2.3), and sensitivity analyses (Section 2.24) will be carried out.

2.4.1.39 Main Respiratory Diagnosis

Outcome: Binary infant level outcome for each of the following diagnoses: normal, non-specific, RDS (HMD), meconium aspiration, pneumonia, primary pulmonary hypertension, apnoea, congenital abnormality, respiratory support for surgical intervention, encephalopathy and other (Neonatal form Q10, variable BResDiag).

Analysis: Fit a log binomial GEE model for each diagnosis separately to estimate relative risk of each diagnosis (magnesium sulphate

relative to placebo).

2.4.1.40 Use of postnatal corticosteroids

Outcome: Binary infant level outcome (Neonatal form Q13.2, variable BPostCort).

Analysis: Fit a log binomial GEE model to estimate relative risk of use of postnatal corticosteroids (magnesium sulphate relative to placebo).

2.4.1.41 Use of surfactant

Outcome: Binary infant level outcome (Neonatal form Q7, variable BSurf).

Analysis: Fit a log binomial GEE model to estimate relative risk of use of surfactant (magnesium sulphate relative to placebo).

2.4.1.42 Use of Nitric oxide for respiratory support

Outcome: Binary infant level outcome (Neonatal form Q13.1, variable BNOxide).

Analysis: Fit a log binomial GEE model to estimate relative risk of use of Nitric oxide for respiratory support (magnesium sulphate relative to placebo).

2.4.1.43 Major congenital malformations

Outcome: Binary infant level outcome (Neonatal form Q21, variable BConMal).

Analysis: Fit a log binomial GEE model to estimate relative risk of major congenital malformations (magnesium sulphate relative to placebo).

A descriptive analysis of specific major malformations (variable BConMlSp) will be reported.

2.4.1.44 Other major problems

Outcome: Binary infant level outcome (Neonatal form Q23, variable BProblem).

Analysis: Fit a log binomial GEE model to estimate relative risk of other major problems (magnesium sulphate relative to placebo).

A descriptive analysis of specific other major problems (variable BProbSp) will be reported.

2.4.1.45 Abnormal level of consciousness

Outcome: Binary infant level outcome (Neonatal form Q26, variable BabnormConsc).

Analysis: Fit a log binomial GEE model to estimate relative risk of abnormal level of consciousness (magnesium sulphate relative to placebo).

A descriptive analysis of causes for abnormal level of consciousness (variable BProbSp) will be reported.

2.4.1.46 Need for admission to the neonatal nursery

Outcome: Binary infant level outcome defined as admission to either Observation ward (Neonatal form Q2, variable Bobs), Level 2 (Neonatal form Q3, variable Blvl2) or NICU (Neonatal form Q4, variable BNICU).

Analysis: Fit a log binomial GEE model to estimate relative risk of need for admission to the neonatal nursery (magnesium sulphate relative to placebo).

2.4.1.47 Length of stay in neonatal nursery (days)

Outcome: Count infant level outcome defined as the sum in days (i.e. hours will be converted to days) of duration of stay in (i) observational ward (Neonatal form, Q2, variable BObshr), (ii) level 2 (Neonatal form Q3, variable Blvl2dy), and (iii) NICU (Neonatal form Q4, variable BNICUdy).

Analysis: Fit a log Poisson GEE model to estimate ratio of mean length of stay (magnesium sulphate relative to placebo).

2.4.1.48 Need for admission to the NICU

Outcome: Binary infant level outcome (Neonatal form Q4, variable BNICU).

Analysis: Fit a log binomial GEE model to estimate relative risk of need for admission to the NICU (magnesium sulphate relative to placebo).

2.4.1.49 Length of stay in NICU (days)

Outcome: Count infant level outcome defined as duration of stay in days in NICU (Neonatal form, Q4, variable BNICUdy).

Analysis: Fit a log Poisson GEE model to estimate ratio of mean length of stay (magnesium sulphate relative to placebo).

2.4.2 *Mother Outcomes*

2.4.2.1 Serious adverse cardiovascular/respiratory effects of infusion

Outcome: Binary mother level outcome defined as one or more of the followings: maternal death (Treatment form Q9.5, variable DsMaternalDeath), cardiac arrest (Q9.3, DsCrdarr), or respiratory arrest (Q9.4, DsRsparr).

Analysis: Fit a log binomial model to estimate relative risk of serious adverse cardiovascular effects of infusion (magnesium sulphate relative to placebo).

2.4.2.2 Maternal side effects of the infusion

Outcome: Binary mother level outcome for each of the following side effects: nausea (Treatment form, Q10.1, variable DsMldnus);vomiting (Q10.2, DsVomit); flushing (Q10.3, DsWmth); infusion arm discomfort (Q10.6, DsSEarm); mouth dryness (10.8, DsMthdry), sweating (Q10.7, DsSwtng); dizziness (Q10.4, DsDizzy); blurred vision (Q10.5, DsBlurvs); respiratory depression, defined as respiratory rate decreased > 4 breaths/minute below baseline or < 12 breaths/minute (Q9.2, DsRspdep); hypotension, defined as blood pressure decreased> 15 mmHg below baseline level (Q9.1, DsHypotn);whether the infusion is discontinued because of side effects, defined as infusion discontinued before 30 minutes (Q7, DsInfstp) due to side effects (Q7.1, DsSEearly).

Analysis: Fit a log binomial GEE model for each maternal side effect separately to estimate relative risk of each diagnosis (magnesium sulphate relative to placebo).

2.4.2.3 Caesarean birth

Outcome: Binary mother level outcome (MotherDelivery form Q13.1, variable CSection).

Analysis: Fit a log binomial model to estimate relative risk of caesarean birth (magnesium sulphate relative to placebo).

A descriptive analysis of Indications for and Timing of Caesarean delivery will be reported.

2.4.2.4 Elective Caesarean birth

Outcome: Binary mother level outcome (MotherDelivery form Q13.1.1, variable CSElect).

Analysis: Fit a log binomial model to estimate relative risk of elective

caesarean birth (magnesium sulphate relative to placebo).

2.4.2.5 Emergency Caesarean birth

Outcome: Binary mother level outcome (MotherDelivery form Q13.1.2, variable CSEmerg).

Analysis: Fit a log binomial model to estimate relative risk of emergency caesarean birth (magnesium sulphate relative to placebo).

2.4.2.6 Postpartum haemorrhage

Outcome: Binary mother level outcome defined as estimated blood loss of 500ml or more (MotherDelivery form Q11, variable Bloss). Mother whose volume of blood loss was not recorded will be reviewed by a clinical expert blinded to treatment group to determine the appropriate outcome.

Analysis: Fit a log binomial model to estimate relative risk of postpartum haemorrhage (magnesium sulphate relative to placebo).

2.4.2.7 Major postpartum haemorrhage

Outcome: Binary mother level outcome defined as estimated blood loss of 1500ml or more (MotherDelivery form Q11, variable Bloss). Mother whose volume of blood loss was not recorded will be reviewed by a clinical expert blinded to treatment group to determine the appropriate outcome.

Analysis: Fit a log binomial model to estimate relative risk of major postpartum haemorrhage (magnesium sulphate relative to placebo).

2.4.2.8 Blood transfusion required

Outcome: Binary mother level outcome (MotherDelivery form Q12, variable BldTransf).

Analysis: Fit a log binomial model to estimate relative risk of blood transfusion required (magnesium sulphate relative to placebo).

2.4.2.9 Maternal perinatal infectious morbidity

Outcome: Binary mother level outcome defined as one or more of: Clinical chorioamnionitis requiring intrapartum antibiotics (MotherDelivery form Q11, variable Chorio) and/or Postnatal pyrexia requiring antibiotics (MotherDelivery form Q16, variable AntiB).

Description of other reason for the use of postpartum antibiotics will be reviewed by a clinical expert to determine whether its use was for infectious morbidity.

Analysis: Fit a log binomial model to estimate relative risk of maternal perinatal infectious morbidity (magnesium sulphate relative to placebo).

2.4.2.10 Postnatal pyrexia requiring antibiotics (up to 6 weeks postpartum)

Outcome: Binary mother level outcome (MotherDelivery form Q16, variable AntiB).

Analysis: Fit a log binomial model to estimate relative risk of use of postnatal antibiotics (magnesium sulphate relative to placebo).

2.4.2.11 Antenatal steroids given

Outcome: Binary mother level outcome (MotherDelivery form Q1, variable AnteSteroids).

Analysis: Fit a log binomial model to estimate relative risk of antenatal steroids given (magnesium sulphate relative to placebo).

2.4.2.12 Number of Antenatal steroids courses given

Outcome: Count mother level outcome (MotherDelivery form Q1, variable AnteSteroidsCourses).

Analysis: Fit a log Poisson model to estimate ratio of mean number of antenatal steroids courses given (magnesium sulphate relative to placebo).

2.4.2.13 Magnesium sulphate treatment since trial entry

Outcome: Binary mother level outcome (MotherDelivery form Q2, variable MgSO4SinceTE).

Analysis: Fit a log binomial model to estimate relative risk of magnesium sulphate treatment since trial entry (magnesium sulphate relative to placebo).

2.4.2.14 Pyrexia (≥ 38°C) after trial entry requiring antibiotics

Outcome: Binary mother level outcome (MotherDelivery form Q3, variable Pyrexia).

Analysis: Fit a log binomial model to estimate relative risk of pyrexia after trial entry requiring antibiotics (magnesium sulphate relative to

placebo).

2.4.2.15 Prelabour rupture of membranes

Outcome: Binary mother level outcome (MotherDelivery form Q4, variable PROM).

Analysis: Fit a log binomial model to estimate relative risk of Prelabour rupture of membranes(magnesium sulphate relative to placebo).

2.4.2.16 Induction of labour

Outcome: Binary mother level outcome (MotherDelivery form Q7, variable LabOns).

Analysis: Fit a log binomial model to estimate relative risk of induction of labour (magnesium sulphate relative to placebo). A descriptive analysis of Method of labour induction will be reported.

2.4.2.17 Augmentation of labour

Outcome: Binary mother level outcome (MotherDelivery form Q8, variable Augment).

Analysis: Fit a log binomial model to estimate relative risk of augmentation of labour (magnesium sulphate relative to placebo).

2.4.2.18 Chorioamnionitis requiring intrapartum antibiotics

Outcome: Binary mother level outcome (MotherDelivery form Q10, variable Chorio).

Analysis: Fit a log binomial model to estimate relative risk of chorioamnionitis requiring intrapartum antibiotics (magnesium sulphate relative to placebo).

2.4.2.19 Length of postnatal hospital stay of mother

Outcome: Count outcome defined as number of days between birth date (BabyDelivery form Q1, variable Bdob) and mother's postnatal discharge date (Complications form Q1, variable MatDis).

Analysis: Fit a log Poisson model to estimate ratio of mean length of stay (magnesium sulphate relative to placebo).

2.4.2.20 Maternal death within 6 weeks' postpartum

Outcome: Binary mother level outcome (Mother delivery form Q18, variable MDeath6wDis).

Analysis: Fit a log binomial model to estimate relative risk of maternal death within 6 weeks' postpartum (magnesium sulphate relative to placebo).

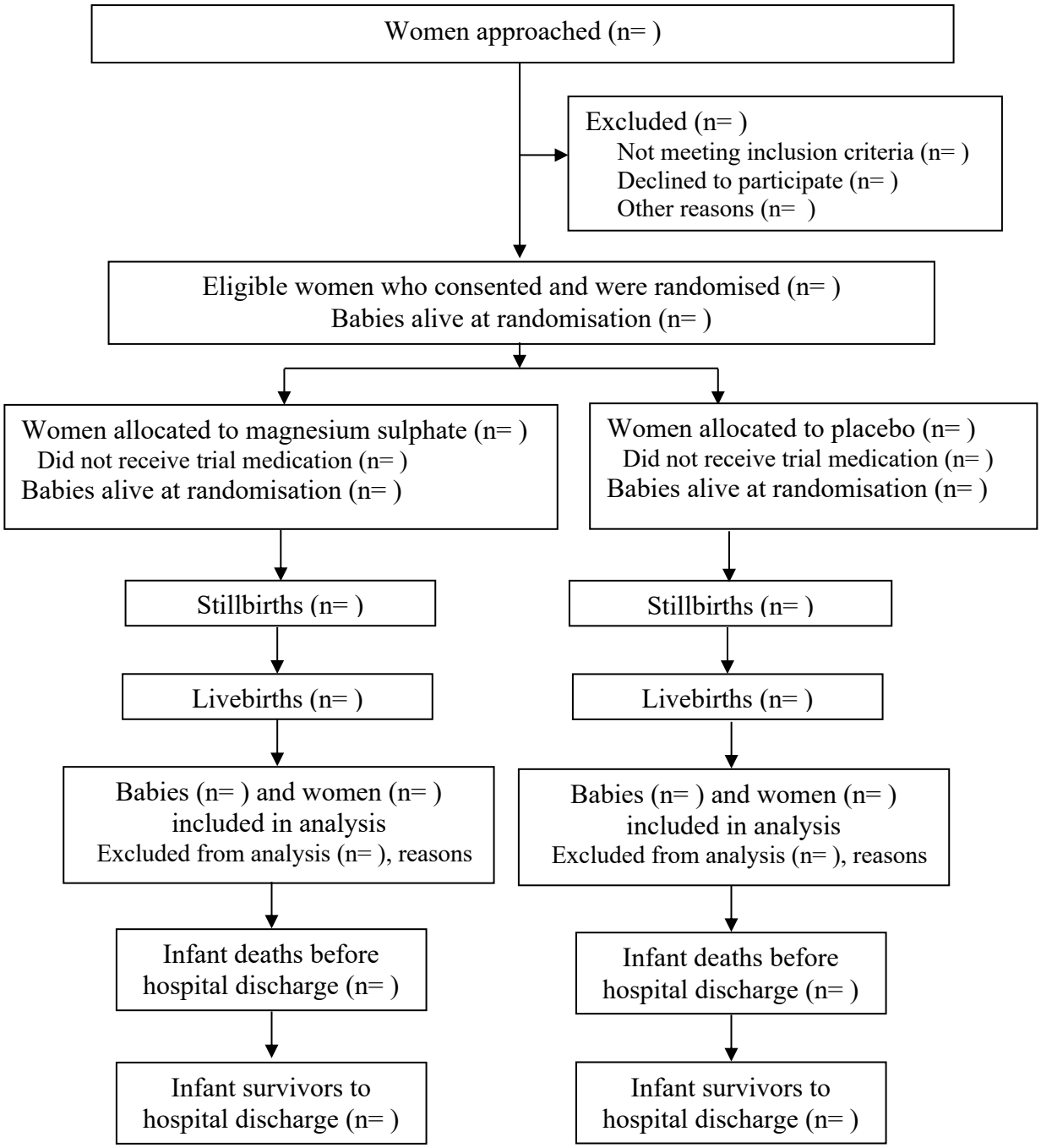
2.4.2.21 Serious maternal complications

Outcome: Binary mother level outcome (Mother delivery form Q18, variable MCompl).

Analysis: Fit a log binomial model to estimate relative risk of Any serious maternal complications (magnesium sulphate relative to placebo). A descriptive analysis of serious maternal complications will be reported.

2.5 SHELL TABLES

2.5.1 *Figure 1: Enrolment*



2.5.2 *Table 1: Baseline characteristics*

	Magnesium sulphate (N=)	Placebo (N=)
Age* (years)		
Primiparity		
Gestational age at randomization*(weeks)		
Body Mass Index* (kg/m^2)		
Body Mass Index Category		
- Underweight (<18.5kg/m^2)		
- Normal (18.5-24.9kg/m^2)		
- Overweight (25.0-29.9kg/m^2)		
- Obesity (≥ 30.0kg/m^2)		
Weight* (kg)		
Height* (m)		
Race		
- White		
- Asian		
- Other:		
. Aboriginal or TSI		
. Polynesian		
. Maori		
. African		
. Arabic		
. South American		
. Unknown		
Smoking during pregnancy		
Public patient		
Past Obstetric History		
- Previous pregnancy >20 weeks		
- Preterm birth		
- Stillbirth		
- Neonatal death		
Socioeconomic index†		
- Overseas		
- Most disadvantaged		
- Disadvantaged		
- Average		
- Advantaged		
- Most advantaged		
Twins		
Main reasons for risk of preterm birth		
- Antepartum haemorrhage		
. Placenta praevia		
. Placental abruption		
. Indeterminate antepartum haemorrhage		
- PPROM		
- Preterm labour		
- Fetal compromise		
. Severe IUGR		
. Fetal compromise		
. Vasa praevia		

. Twin-twin transfusion
- Pre-eclampsia/eclampsia
- Cervical incompetence
- Others
  . Chorioamnionitis clinically
  . Maternal disease
  . Fetal abnormality
  . Other

Values are number (%) unless otherwise indicated.
* Values are means (SD) or medians (IQR) where appropriate.
† Socioeconomic index as measured by SEIFA where higher index scores indicate decreasing levels of social disadvantage (ABS 2008).

2.5.3 *Table 2: Treatment- related information*

Treatment-related information	**Magnesium sulphate (N=)**	**Placebo (N=)**
Women received an assigned treatment		
Women who did not receive trial medication		
Reasons women did not receive trial medication		
Delivery before Treatment started		
Declined Treatment		
Other		
Women who did not complete the initial treatment		
Reasons women did not complete the initial treatment		
Delivery before Treatment started		
Adverse effect		
Other		
Any side-effects*		
Serious cardiovascular/respiratory side effects		
. Maternal death		
. Cardiac arrest		
. Respiratory arrest		
Hypotension		
Respiratory depression		
Calcium gluconate given		
Other		
Nausea		
Vomiting		
Flushing		
Dizziness		
Blurred vision		
Infusion arm discomfort		
Sweating		
Mouth dryness		
Sleepiness		
Headache		
Muscle weakness		
Palpitations		

Values are Numbers (%).
*: One woman might have more than one side effect.

2.5.4 *Table 3: Infant outcomes most likely to be influenced by Magnesium sulphate*

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
Intraventricular haemorrhage						
Severe intraventricular haemorrhage						
Cystic periventricular leukomalacia						
Neonatal encephalopathy						
Neonatal convulsions						
Causes of convulsions*						
. Asphyxia						
. Metabolic						
. Hemorrhage						
. Abnormality						
. Benign/Unknown						
. Infection						
. Other						
Duration of convulsions*						
. < 24 hours/						
. ≥ 24 hours						
Neonatal encephalopathy						
Composite serious health outcome						
Stillbirth						
Death of liveborn infant before hospital discharge						
Severe respiratory disease						
Severe intraventricular haemorrhage						
Chronic lung disease						
Proven necrotising enterocolitis						
Severe retinopathy of prematurity						
Cystic periventricular leukomalacia						

Values are Number (%); and Treatment effects are Relative risks (95% CI), unless otherwise indicated. Analyses are adjusted for collaborating centre, gestational age at trial entry, number of fetuses and clustering within mother.

2.5.5 *Table 4: Pre-defined interaction analyses*

Outcomes	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment effect (95%CI)	Unadj P-value	UnadjP-value for the interaction term	Adjusted Treatment effect (95% CI)	Adj P-value	Adj P-value for the interaction term
Intraventricular haemorrhage								
GA at trial entry								
30-31 weeks								
32-33 weeks								
Main reason at risk of preterm birth								
Antepartum haemorrhage								
PPROM								
Preterm labour								
Fetal compromise								
Pre-eclampsia/Eclampsia								
Cervical incompetence								
Other								
Gender								
Male								
Female								
Plurality								
Singleton								
Twins								
Other outcomes (severe intraventricular haemorrhage, composite serious neonatal health outcome)								

Values are number (%); and treatment effects are relative risks (95% CI). Analyses are adjusted for collaborating centre, gestational age at trial entry, number of fetuses and clustering within mother.

2.5.6 *Table 5: Pre-defined subgroup exploratory analyses based on post-randomisation variables*

Outcomes	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment effect (95%CI)	Unadjusted P-value	Adjusted Treatment effect (95% CI)	Adjusted P-value
Intraventricular haemorrhage						
GA at delivery						
< 32 weeks						
32-<34 weeks						
34-< 37 weeks						
≥ 37 weeks						
Other outcomes (severe intraventricular haemorrhage, cystic periventricular leukomalacia, composite serious neonatal health outcome)						

Values are number (%); and treatment effects are relative risks (95% CI) unless otherwise indicated. Analyses are adjusted for collaborating centre, gestational age at trial entry, number of fetuses and clustering within mother.

2.5.7 *Table 6: Secondary infant outcomes*

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
Any deaths before the primary						
hospital discharge						
. Stillbirth						
. Neonatal death						
Proven necrotizing enterocolitis						
Retinopathy of prematurity						
Severe retinopathy of prematurity						
Retinopathy of prematurity needing treatment						
Patent ductus arteriosis requiring treatment						
Respiratory distress syndrome						
Severity of any lung disease*						
Mild						
Moderate						
Severe						
Chronic lung disease						
Use of respiratory support						
Duration of respiratory support (days)‡						
Mechanical ventilation						
Duration of mechanical ventilation (hours)‡						
Oxygen therapy						
Duration of oxygen therapy (days)‡						
Need for oxygen therapy at 28 days or more of life						
Discharge home on oxygen						
Air leak syndrome						
Gestational age at birth (week) †						
Number of episodes of proven infection‡						
None						
1						
2 or more						
Confirmed infection at < first 48 hours						
Site of infection*						
. Blood						
. CSF						
Use of antibiotics						
Confirmed infection ≥ first 48 hours						
Site of infection*						
. Blood						
. CSF						
. Urine						
. Lung						
. Other						
Use of antibiotics						

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
Main respiratory diagnosis						
Non-specific (including TTNB)						
RDS (HMD)						
Meconium aspiration						
Pneumonia						
Primary pulmonary hypertension						
Apnoea						
Congenital abnormality						
Respiratory support for surgical intervention						
Encephalopathy						
Others						
Use of postnatal corticosteroids						
Use of surfactant						
Use of Nitric oxide						
Major congenital malformations						
Types of congenital malformation*:						
. Central nervous system						
. Cardio-vascular system						
. Urinary						
. Gastro-intestinal tract						
. Chromosomal						
. Metabolic						
. Multiple/non-chromosomal						
. Other						
Other major problems						
Abnormal level of consciousness						
Need for admission to the neonatal nursery						
Length of stay in neonatal nursery (days) §						
Need for admission to NICU						
Length of stay in NICU (days) §						
Any other major neonatal problems						
Other neonatal major problems*:						
. Congenital abnormality						
. Prematurity						
. Cardio-vascular problems						
. Infection						
. Neurological problems						
. Gastro-intestinal tract						
. Other						

Values are Number (%); and Treatment effects are Relative risks (95% CI), unless otherwise indicated. Analyses are adjusted for collaborating centre, gestational age at trial entry, number of fetuses and clustering within mother. * Values are Number (%); and Treatment effects are Odds ratio of higher severity (95% CI).
†Values are Means (SD); and Treatment effects are differences in means (95% CI).
‡ Values are Means (SD); and Treatment effects are ratios of mean duration (95% CI).

2.5.8 *Table 7: Outcomes relating to infant growth*

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
At birth						
Body-size measurement						
Weight						
Length						
Head circumference						
Z score						
Weight						
Length						
Head circumference						
At hospital discharge						
Body-size measurement						
Weight						
Length						
Head circumference						
Z score						
Weight						
Length						
Head circumference						

Values are Means (SD); and Treatment effects are differences in means (95% CI) unless otherwise indicated. Analyses are adjusted for collaborating centre, gestational age at trial entry, number of fetuses and clustering within mother.

2.5.9 *Table 8: Death details*

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
Stillbirth						
Causes of death (by PSANZ-PDC)*:						
. Congenital abnormality						
. Perinatal infection						
. Hypertension						
. APH						
. Maternal conditions						
. Specific perinatal conditions						
. Hypoxic death						
. Fetal growth restriction						
. Spontaneous preterm						
. Unexplained antepartum death						
. No obstetric antecedent						
Wigglesworth classification*:						
. Normally formed stillbirth						
. Congenital malformation						
. Immaturity						
. Asphyxia condition						
. Non-applicable						
. None of the Above						
Placental history*:						
. Vasculopathy						
. Abruption						
. Other						
. Not examined						
. None of the above						
. Infection and abruption						
Primary causes of death*						
Secondary causes of death*						
Neonatal death before discharge						
Causes of death (by PSANZ-PDC)*:						
. Congenital abnormality						
. Perinatal infection						
. Hypertension						
. APH						
. Maternal conditions						
. Specific perinatal conditions						
. Hypoxic death						
. Fetal growth restriction						
. Spontaneous preterm						
. Unexplained antepartum death						
. No obstetric antecedent						

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
Causes of death (by PSANZ-NDC)*:						
. Congenital abnormality						
. Extreme prematurity						
. Cardio-respiratory disorders						
. Infection						
. Neurological						
. Gastrointestinal						
. Other						
Wigglesworth classification*:						
. Normally formed stillbirth						
. Congenital malformation						
. Immaturity						
. Asphyxia condition						
. Non-applicable						
. None of the Above						
Placental history*:						
. Vasculopathy						
. Abruption						
. Other						
. Not examined						
. None of the above						
. Infection and abruption						
Primary causes of death*						
Secondary causes of death*						
Any deaths before hospital discharge						
Causes of death (by PSANZ-PDC)*:						
. Congenital abnormality						
. Perinatal infection						
. Hypertension						
. APH						
. Maternal conditions						
. Specific perinatal conditions						
. Hypoxic death						
. Fetal growth restriction						
. Spontaneous preterm						
. Unexplained antepartum death						
. No obstetric antecedent						
Causes of death (by PSANZ-NDC)*:						
. Congenital abnormality						
. Extreme prematurity						
. Cardio-respiratory disorders						
. Infection						
. Neurological						
. Gastrointestinal						
. Other						

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
Wigglesworth classification*:						
. Normally formed stillbirth						
. Congenital malformation						
. Immaturity						
. Asphyxia condition						
. Non-applicable						
. None of the Above						
Placental history*:						
. Vasculopathy						
. Abruption						
. Other						
. Not examined						
. None of the above						
. Infection and abruption						
Primary causes of death*						
Secondary causes of death*						

Values are numbers (%); and Treatment effects are Relative risk (95% CI). Analyses are adjusted for collaborating centre, gestational age at trial entry, number of fetuses and clustering within mother. Fisher's exact test is used with no adjustment for baseline covariates if the outcome events are considered too small for the planned analysis to be sensible.
*: Values are number (%).

2.5.10 *Table 9: Mother outcomes*

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
Serious adverse cardiovascular/ respiratory effects of infusion						
. Maternal death						
. Cardiac arrest						
. Respiratory arrest						
Maternal side effects of the infusion						
. Nausea						
. Vomiting						
. Flushing						
. Infusion arm discomfort						
. Mouth dryness						
. Dizziness						
. Blurred vision						
. Respiratory depression						
. Hypotension						
. Infusion discontinued due to side effects						
Antenatal steroids given						
Number of antenatal steroid courses given						
Magnesium sulphate treatment						
Pyrexia after trial entry requiring antibiotics						
Prelabour rupture of membranes						
Induction of labour						
Augmentation of labour						
Caesarean birth						
Elective						
Emergency						
Indications for Caesarean section*						
. Fetal distress						
. Haemorrhage						
Antepartum haemorrhage						
Intrapartum haemorrhage						
Placenta praevia/abruption/accreta						
. Hypertension						
Hypertension						
Pre-eclampsia						
. Previous Caesarean section						
. Breech/Abnormal lie						
. Failure to progress						
. Prematurity						
. Other						
Chorioamnionitis requiring intrapartum antibiotics						
Postpartum haemorrhage						
Major postpartum haemorrhage						

Outcome	Magnesium sulphate (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted Treatment Effect (95% CI)	Adjusted P value
Blood transfusion required						
Maternal perinatal infectious morbidity						
Postnatal pyrexia requiring antibiotics						
Length of postnatal hospital stay†						
Any maternal complications						
Maternal complications:*						
. Haemorrhage						
. Hysterectomy						
. Deep Vein Thrombosis						
. Pulmonary embolus						
. Eclampsia						
. Disseminated Intravascular Coagulation						
. Admitted to Intensive Care Unit						
. Diabetes						
. Hypertension						
. Severe sepsis						
. Haematoma						
. Puerperal sepsis						

Values are Number (%); and Treatment effects are Relative risk (95% CI), unless otherwise indicated.
* Values are Number (%).
† Values are Means (SD); and Treatment effects are ratios of mean length (95% CI).

3. CHAPTER 3: STATISTICAL ANALYSIS PLAN FOR OUTCOMES AT TWO YEARS CORRECTED AGE:

3.1 SEQUENCE OF PLANNED ANALYSIS

3.1.1 *Interim Analyses*

There is no planned interim analysis.

3.1.2 *Final Analyses and Reporting*

Data will be analysed by a statistician independent of the clinical investigators.

Once the assessment of the last participant has been conducted, and all data have been entered, blinded reviews of the data without knowledge of treatment allocation will be conducted, and final changes will be made to this SAP. Following the approval of the final version of this SAP, analysis of the study outcomes will be performed blinded to the treatment allocation. A blinded data review meeting will be held prior to the treatment allocation unlock and completion of the final analysis.

Key statistics and study results will be made available to the trial investigators.

Any post-hoc, exploratory analyses which were not identified in this SAP but are completed to support the planned analyses will be clearly identified. Any deviations from the planned analyses detailed in this SAP will be clearly documented with reasons in a post-analysis version of the SAP.

3.2 OTHER ISSUES FOR STATISTICAL ANALYSIS

3.2.1 *Potential Confounders*

Both unadjusted and adjusted analyses will be carried out for each outcome. Conclusion about the effect of treatment will be drawn from the adjusted results; meanwhile the unadjusted analysis will be used to potentially confirm the results of the adjusted analyses.

Analyses will make adjustments for the stratification variables, such as collaborating centre, gestational age at entry, plurality, and potential confounding variables, including child's gender, socioeconomic status and language spoken at home. The analyses also will make adjustment for any important baseline predictors identified during the analyses which show evidence of substantial imbalance between the study groups.

If convergence is an issue, some potential confounders may need to be collapsed into fewer categories or excluded from the adjusted analysis for particular outcome(s). Any deviation from the planned adjustment for potential confounders will be clearly identified.

Pre-defined potential confounding variables	Details
Collaborating centre	Categorical variable defined by hospital ID (Trial entry form, variable HospID). Collaborating centres with few participants, defined as < 10 women will be combined with the most similar centre.
Gestational age at trial entry	Continuous variable (TrialEntry form Q2, variable GAentWk and GAentDy). If a linear relationship with GA at trial entry is not appropriate, either a quadratic term will be added (if a quadratic relationship appears reasonable), or a continuous variable will be dichotomized (30 to < 32 weeks vs. 32 to < 34 weeks).
Number of fetuses	Binary variable (single, twins) (TrialEntry form Q1, variable Plurality).
Socioeconomic status	Categorical variable (i.e. most disadvantaged, disadvantaged, middle, advantaged, most advantaged), generated from the Australian disadvantage scores and the New Zealand deprivation index based on postal address (TrialEntry form, variable Address and Postcode).
Language spoke at home	Binary variable (English, other language) (Parent/Carer questionnaire Q7, variable Language).
Child's gender	Binary variable (male, female) (BabyDelivery form Q13, variable BSex)

3.2.2 *Planned Treatment by Covariate Interactions*

Evidence of effect modification will be inspected for the primary outcome (i.e. death or cerebral palsy) and other key secondary outcomes such as death; cerebral palsy); death or any neurosensory disability; death or major neurosensory disability; cognitive/language delay; and motor developmental delay.

The analyses will be carried out to test for evidence of effect modification on the above mentioned outcomes by each of gestational age at trial entry (30 to < 32 weeks vs. 32 to < 34 weeks), main reason for risk of preterm birth (antepartum haemorrhage, PPROM, preterm labour, fetal compromise, preeclampsia/ eclampsia, cervical incompetence and other), child's sex (male and female), number of fetus (single and twin), mother's socioeconomic status (most disadvantaged, disadvantaged, middle, advantaged, most advantaged), and ethnicity (Caucasian, Asian, other).

These subgroups may be combined if data are insufficient. Separate estimates of treatment effect will be obtained within each category, independent of whether the interaction is statistically significant or not, since these carefully chosen limited

comparisons are of interest a priori.

Any unplanned treatment by covariate interactions must be considered exploratory and will be clearly identified.

3.2.3 *Planned exploratory sub-group analyses*

The treatment effect on the primary outcome and secondary key outcomes mentioned in 3.2.2 will be also explored for each category of GA at delivery. No interaction test will be carried out for these exploratory analyses.

Exploratory sub-group analyses	**Details**
GA at delivery	Continuous variable categorized as (30 to < 32 weeks, 32 to < 34 weeks, 34 to < 37 and ≥ 37 weeks' gestation (TrialEntry form Q2, variable GAentWk and GAentDy, and BabyDelivery form Q1.1, variable BDOB).

3.2.4 *Sensitivity analyses*

3.2.4.1 Sensitivity analysis by treatment group allocated at randomization for women who received any of the trial medication by treatment group allocated at randomization

This sensitivity analysis will be conducted for women receiving any of the allocated trial medication, by the treatment group allocated by randomization. The sensitivity analysis will be conducted for all outcomes of interest (section 3.4)

3.2.4.2 Sensitivity analysis by treatment group the women actually received

This per-protocol analysis will be conducted by treatment group the women actually received, regardless of the treatment group allocated by randomization. The sensitivity analysis will be conducted for all outcomes of interest (section 3.4).

3.2.4.3 Sensitivity analysis by data availability from different sources

- *Primary outcome with cerebral palsy component* defined by: (i) Paediatrician's assessment, (ii) Paediatrician's assessment, and Parent questionnaire data, versus (iii) All data sources (Paediatrician, Parent questionnaire, and FU Minimal Info data).
- *Cerebral palsy* (CP) defined by: (i) Paediatrician's assessment, (ii) Paediatrician's assessment, and Parent questionnaire data, versus (iii) All data sources (Paediatrician, Parent questionnaire, and FU Minimal Info data).
- *Severity of cerebral palsy* classified: using (i) Paediatrician's assessment versus (ii) other data sources (Parent questionnaire and FU Minimal Info data).
- *Cognitive/language developmental delay* defined by: (i) Psychological assessment, (ii) Psychological assessment and ASQ data, (iii) Psychological assessment, ASQ and Parent questionnaire data, versus (iv) All data sources (Psychological, ASQ, Parent questionnaire and FU Minimal Info data).

- *Motor developmental delay* defined by: (i) Psychological assessment, (ii) Psychological assessment and ASQ data, (iii) Psychological assessment, ASQ and Parent questionnaire data, versus (iv) All data sources (Psychological, ASQ, Parent questionnaire and FU Minimal Info data).
- *Body size* data (Weight, Height and Head circumference) from different data sources: (i) Paediatrician's assessment, versus (ii) Paediatrician's assessment and other data sources (i.e. ASQ and Parent/Carer questionnaire).
- *Children with major malformation disorders* (Paediatrician data form Q4, variable Malform) or *postnatal CNS disorders* (Paediatrician data form Q3, variable CNSProbs) excluded.

3.3 DESCRIPTIVE ANALYSIS

3.3.1 *Flow Chart of Participants*

Information will be presented by treatment groups (where appropriate) on:

- Number of eligible women who consented and were randomised, and number of fetuses alive at randomisation.
- Number of women and number of fetuses alive allocated to interventions
- Number of women who withdrew from the study and timing of withdrawal.
- Number of stillbirths and liveborns.
- Number of babies who died before discharge and who survived to initial discharge.
- Number of children who died after discharge and who survived to 2 years
- Number of children at 2 years corrected age:
  - Had the primary outcome (overall)
    - From Paediatrician's assessment
    - From Paediatrician's assessment and Parent/Carer data
    - From all data sources (Paediatrician, Parent/Carer questionnaire and FU Minimal Info).
  - Had Paediatrician's assessment
  - Had Psychology assessment
  - Had Child Behavior Checklist assessment
  - Had Child Ages and Stages assessment
  - Had Parent/Carer questionnaire
  - Had FU Minimal Info form

3.3.2 *Baseline Characteristics*

An analysis of variables collected at baseline will be performed to compare the characteristics of subjects in each treatment group (see shell tables). Any baseline

covariates with important imbalance between the study groups will be controlled for in the adjusted analyses. Means and standard deviations, or medians and interquartile ranges will be reported for continuous variables where appropriate. Frequencies and percentages will be reported for categorical variables.

3.3.3 *Measurement of Treatment adherence*

Treatment adherence will be assessed descriptively based on whether the participants received allocated intervention (i.e., assigned drug package).

3.3.4 *Missing Data*

Missing data will be assessed descriptively by treatment group for each outcome variable in Section 3.4, and each potential confounder in Section 3.2.1.

3.4 STATISTICAL ANALYSES

The statistical analyses will be performed for all primary and secondary outcome variables. Analysis plan for each outcome includes the outcome variable description and analysis method(s). Outcome variable is described as the type of variable, the relevant variable(s) in the data collection forms and how it will be calculated. The analysis presents the type of statistical analysis used for each outcome and the measure of treatment effect to be reported.

3.4.1 *Primary Outcome*

3.4.1.1 Death or any cerebral palsy

Outcome: Binary child level outcome defined as death; or any cerebral palsy.

Death defined as stillbirth (BabyDelivery form Q4, variable BStill), deaths of live born infants before hospital discharge (Neonatal form Q25, variable Death) or after discharge (Baby database, variable PDDth), or known death until two years corrected age assessment (Tracking2yr database, variable Alive2yrCA, or FU Minimal Info form, Q1, variable KnownAlive).

Cerebral palsy (CP) defined for children with definite or probable diagnosis of CP (Paediatrician data form, Q17, variable CP). If missing, CP also defined for those unable to walk without assistance (Parent/Carer form Q18, variable DifWalkSp = 3), or unable to sit (Q19, variable DifSitSp = 3), or unable to control head without support (Q21, variable DifHeadSp = 2), or known as CP from parent interview (FU Minimal Info form, Q3 variable CP).

Analysis: Fit a log binomial GEE model to estimate relative risk of death or any cerebral palsy (magnesium sulphate relative to placebo). The number needed to treat to prevent one additional adverse outcome will be calculated.

Sensitivity analysis will be carried out for primary outcome with cerebral palsy component defined by: (i) Paediatrician's assessment, (ii) Paediatrician's assessment, and Parent questionnaire data, versus (iii) All data sources (Paediatrician, Parent questionnaire, and FU Minimal Info

data).

3.4.2 *Secondary Outcomes*

Neurosensory disability

3.4.2.1 Death

Outcome: Binary child level outcome defined as stillbirth (BabyDelivery form Q4, variable BStill), deaths of live born infants before hospital discharge (Neonatal form Q25, variable Death) or after discharge (Baby database, variable PDDth), or known death until two years corrected age assessment (Tracking2yr database, variable Alive2yrCA, or FU Minimal Info form, Q1, variable KnownAlive).

Analysis: Fit a log binomial GEE model to relative risk of death (magnesium sulphate relative to placebo).

3.4.2.2 Cerebral palsy

Outcome: Binary child level outcome defined for children with definite or probable diagnosis of CP (Paediatrician data form, Q17, variable CP). If missing, CP also defined for those unable to walk without assistance (Parent/Carer form Q18, variable DifWalkSp = 3), or unable to sit (Q19, variable DifSitSp = 3), or unable to control head without support (Q21, variable DifHeadSp = 2), or known as CP from parent interview (FU Minimal Info form, Q3 variable CP).

Analysis: Fit a log binomial GEE model to relative risk of cerebral palsy (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out for CP defined by: (i) Paediatrician's assessment, (ii) Paediatrician's assessment and Parent questionnaire data, versus (iii) All data sources (Paediatrician's, Parent questionnaire, and FU Minimal Info data).

3.4.2.3 Severity of cerebral palsy

Outcome: Ordinal child level outcome defined as severity of CP (Paediatrician data form, Q18, variable CPSp; 3: severe, 2: moderate, 1: mild, 0: no disease). If missing, severity of CP also classified as:

- *severe*: for children unable to walk without assistance (Parent/Carer form Q18, variable DifWalkSp = 3), unable to sit (Q19, variable DifSitSp = 3), unable to control head without support (Q21, variable DisHeadSp = 2) or known as severe CP from parent interview (FU Minimal Info form Q3, variable SCP = 3).

- *moderate*: for children known as moderate CP from parent interview (FU Minimal Info form Q3, variable SCP = 2).

- *mild*: for children known as mild CP from parent interview (FU Minimal Info form Q3, variable SCP = 1).

Analysis: Fit a proportional odds GEE model to estimate odds ratio of higher severity of cerebral palsy (magnesium sulphate relative to placebo).

If the proportional odds assumption is not met, fit separate logistic GEE regression models to estimate odds ratios for the 3 binary outcomes of at least mild cerebral palsy (i.e. mild, moderate or severe disease vs. no disease), at least moderate (i.e. moderate or severe disease vs. mild or no disease) and severe disease (i.e. severe disease vs. moderate, mild or no disease).

Sensitivity analysis will be conducted for severity of cerebral palsy classified using: (i) Paediatrician's assessment versus (ii) other data sources (Parent questionnaire and FU Minimal Info data).

3.4.2.4 Death or any neurosensory disability

Outcome: Binary child level outcome defined as death; or any neurosensory disability that includes the neurosensory impairment of cerebral palsy, blindness, deafness, and any developmental delay (such as cognitive/language developmental delay, motor developmental delay, or being unable to complete psychological assessment due to severe disability).

Death defined as stillbirth (BabyDelivery form Q4, variable BStill), deaths of live born infants before hospital discharge (Neonatal form Q25, variable Death) or after discharge (Baby database, variable PDDth), or known death until two years corrected age assessment (Tracking2yr database, variable Alive2yrCA, or FU Minimal Info form, Q1, variable KnownAlive).

Cerebral palsy (CP) defined for children with definite or probable diagnosis of CP (Paediatrician data form, Q17, variable CP). If missing, CP also defined for those unable to walk without assistance (Parent/Carer form Q18, variable DifWalkSp = 3), or unable to sit (Q19, variable DifSitSp = 3), or unable to control head without support (Q21, variable DifHeadSp = 2), or known as CP from parent interview (FU Minimal Info form, Q3 variable CP).

Blindness defined as corrected visual acuity worse than < 6/60 in the better eye (Paediatrician data form, Q14, variable VisBBlnd). If missing, blindness defined as blind/see light only in both eyes (Parent/Carer form Q23, variable DifSeeSp = 4) or known as blindness (FU Minimal Info form, Q4, variable Blind).

Deafness defined as severe auditory defect requiring hearing aids (Paediatrician data form, Q15.3, variable HrSAdDef). If missing, deafness defined as hearing not corrected with hearing aids (Parent/Carer form, Q25 variable DifHearSp = 3), or known as deafness (FU Minimal Info form,

Q5, variable Deaf).

Cognitive/language developmental delay defined as BSID-III cognitive (Psychologist Data form, variable CogComp), or language composite score (variable LangComp) of psychological assessment more than 1 SD below the mean (i.e. < 85), or children with severe cognitive/language developmental delay who are unable to complete the psychological assessment due to severe cognitive/language disability (who will be given a standardized score of -4 SD). If missing, cognitive/language developmental delay also defined as standardized scores for Communication (Child's ASQ 2-y form, variable SCComm) more than 2 SD below the mean, or having difficulty with communication (Parent/Carer questionnaire, Q26, variable DifCom), or known as cognitive/language developmental delay (FU Minimal Info form, Q6, variable DevelopDelayCog/ DevelopDelayLang).

Motor developmental delay defined BSID-III motor composite score of psychological assessment (Psychologist Data form, variable MotorComp) more than 1 SD below the mean (i.e. < 85), or children with severe motor developmental delay who are unable to complete the psychological assessment due to severe motor disability (who will be given a standardized score of -4 SD). If missing, motor developmental delay also defined as standardized scores for Gross motor (Child's ASQ 2-y form, variable SCGM) more than 2 SD below the mean, or for those less mobile than normal (Parent/Carer form Q18, variable DifWalkSp = 2), or sit only if supported (Q19, variable DifSitSp = 2), or unable to control head without support (Q21, variable DifHeadSp = 2), or known as CP from parent interview (FU Minimal Info form, Q3 variable CP), or as motor developmental delay from parent interview (FU Minimal Info form, Q6, variable DevelopDelayMotor).

Analysis: Fit a log binomial GEE model to estimate relative risk of death or any neurosensory disability (magnesium sulphate relative to placebo). The number needed to treat to prevent one additional adverse outcome will be calculated.

Sensitivity analysis will be carried out for primary outcome with neurosensory disability component defined by: (i) Paediatrician's and Psychological (BSID-III for cognitive/language and motor developmental delay) assessment, (ii) Paediatrician's, Psychological, and ASQ data, (iii) Paediatrician's, Psychological, ASQ, and Parent questionnaire data, versus (iv) All data sources (Paediatrician's, Psychological, ASQ, Parent questionnaire and FU Minimal Info data).

3.4.2.5 Death or major neurosensory disability

Outcome: Binary child level outcome includes Death or Major neurosensory disability that includes severe or moderate disability.

Death defined as stillbirth (BabyDelivery form Q4, variable BStill), deaths of live born infants before hospital discharge (Neonatal form Q25, variable Death) or after discharge (Baby database, variable PDDth), or known death until two years corrected age assessment (Tracking2yr database, variable Alive2yrCA, or Follow-up Minimal Info form, Q1, variable KnownAlive).

Major neurosensory disabilities defined as any of moderate or severe cerebral palsy, blindness, sensorineural deafness requiring hearing aids and major developmental delays.

Moderate/Severe cerebral palsy defined as recorded severity of CP as moderate or severe (Paediatrician data form, Q18, variable CPSever ≥ 2). If missing, moderate/severe CP defined as being unable to walk (Parent/Carer form Q18, variable DifWalkSp = 3), or unable to sit (Q19, variable DifSitSp = 3), or unable to control head without support (Q21, variable DifHeadSp = 2) or known as moderate or severe CP (FU Minimal Info form, Q2, variable SCP ≥ 2).

Blindness defined as bilateral blindness with vision < 6/60 binocular (Paediatrician data form, Q14, variable VisBBlnd). If missing, blindness defined as blind/see light only in both eyes (Parent/Carer form Q23, variable DifSeeSp = 4) or known as blindness (FU Minimal Info form, Q4, variable Blind).

Deafness defined as severe auditory defect requiring hearing aids (Paediatrician data form, Q15.3, variable HrSAdDef). If missing, deafness defined as hearing not corrected with hearing aids (Parent/Carer form, Q25 variable DifHearSp = 3), or known as deafness (FU Minimal Info form, Q5, variable Deaf).

Major cognitive/language developmental delay defined as BSID-III cognitive (Psychologist Data form, variable CogComp), or language composite score of psychological assessment (variable LangComp) more than 2 SD below the mean (i.e. < 70), or children who are unable to complete the psychological assessment due to severe cognitive/language disability (who will be given a standardized score of -4 SD). If missing, major cognitive/language developmental delay also defined as standardized scores for Communication (Child's ASQ 2-y form, variable SCComm) more than 3 SD below the mean, or for those who are unable to produce more than 5 recognisable sounds or does not produce recognizable sounds (Parent/Carer questionnaire, Q26, variable DifComSp ≥ 4).

Major motor developmental delay defined as BSID-III motor composite score of psychological assessment (Psychologist Data form, variable MotorComp) more than 2 SD below the mean (i.e. < 70), or children who are unable to complete the psychological assessment due to severe motor disability (who will be given a standardized score of -4 SD). If missing, major motor developmental delay also defined as standardized scores for Gross motor (Child's ASQ 2-y form, variable SCGM) more than 3 SD below the mean, or for those unable to walk without assistance

(Parent/Carer form Q18, variable DifWalkSp = 3), or unable to sit (Q19, variable DifSitSp = 3), or unable to control head without support (Q21, variable DifHeadSp = 2), or known as severe/moderate CP from parent interview (FU Minimal Info form, Q3 variable CP).

Analysis: Fit a log binomial GEE model to estimate relative risk of death or major neurosensory disability (magnesium sulphate relative to placebo).

3.4.2.6 Blindness

Outcome: Binary child level outcome defined as bilateral blindness with vision < 6/60 binocular (Paediatrician data form, Q14, variable VisBBlnd). If missing, blindness defined as blind/see light only in both eyes (Parent/Carer form Q23, variable DifSeeSp = 4) or known as blindness (FU Minimal Info form, Q4, variable Blind).

Analysis: Fit a log binomial GEE model to relative risk of blindness (magnesium sulphate relative to placebo).

3.4.2.7 Deafness

Outcome: Binary child level outcome defined as severe auditory defect requiring hearing aids (Paediatrician data form, Q15.3, variable HrSAdDef). If missing, deafness defined as hearing not corrected with hearing aids (Parent/Carer form, Q25 variable DifHearSp= 3), or known as deafness (FU Minimal Info form, Q5, variable Deaf).

Analysis: Fit a log binomial GEE model to relative risk of deafness (magnesium sulphate relative to placebo).

3.4.2.8 Cognitive/language developmental delay

Outcome: Binary child level outcome defined as BSID-III cognitive (Psychologist Data form, variable CogComp), or language composite score of psychological assessment (variable LangComp) more than 1 SD below the mean (i.e. < 85), or children with severe cognitive/language developmental delay who are unable to complete the psychological assessment due to severe cognitive/language disability (who will be given a standardized score of -4 SD). If missing, developmental delay also defined as standardized scores for Communication (Child's ASQ 2-y form, variable SCComm) more than 2 SD below the mean, or having difficulty with communication (Parent/Carer questionnaire, Q26, variable DifCom), or known as cognitive/language developmental delay (FU Minimal Info form, Q6, variable DevelopDelayCog/ DevelopDelayLang).

Analysis: Fit a log binomial GEE model to relative risk of cognitive/language developmental delay (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out for cognitive/language developmental delay defined by: (i) Psychological assessment, (ii) Psychological assessment and ASQ data, (iii) Psychological assessment, ASQ and Parent questionnaire data, versus (iv) All data sources (Psychological, ASQ, Parent questionnaire and FU Minimal Info data).

3.4.2.9 Severity of cognitive/language developmental delay

Outcome: Ordinal child level outcome defined as any of BSID-III Cognitive (Psychologist Data form, variable CogComp), or Language composite score (variable LangComp) more than 3 SD, 2 SD and 1 SD below the mean (or < 55, 70 and 85), respectively. Children who are unable to complete psychological assessment due to severe cognitive/language disability are classified as severe cognitive/language developmental delay (who will be given a standardized score of – 4 SD).

Analysis: Fit a proportional odds GEE model to estimate odds ratio of higher severity of cognitive/language developmental delay (magnesium sulphate relative to placebo).

If the proportional odds assumption is not met, fit separate logistic GEE regression models to estimate odds ratios for the 3 binary outcomes of at least mild cognitive/language developmental delay (i.e. mild, moderate or severe cognitive/language delay vs. no cognitive/language delay), at least moderate (i.e. moderate or severe cognitive/language delay vs. mild or no cognitive/language delay) and severe delay (i.e. severe cognitive/language delay vs. moderate, mild or no cognitive/language delay).

3.4.2.10 Cognitive and language developmental scores

Outcome: Continuous child level outcomes defined as separate BSID-III scores for Cognitive (Psychologist Data form, variable CogComp), and Language (variable LangComp).

Analysis: Fit a linear GEE model to estimate difference in mean BSID-III developmental scores for separate domains (cognitive and language domains) (magnesium sulphate relative to placebo).

3.4.2.11 Motor developmental delay

Outcome: Binary child level outcome defined as BSID-III motor composite score of psychological assessment (Psychologist Data form, variable MotorComp) more than 1 SD below the mean (i.e. < 85), or children with severe motor developmental delay who are unable to complete the psychological assessment due to severe motor disability (who will be given a standardized score of -4 SD).

If missing, motor developmental delay also defined as standardized scores

for Gross motor (Child's ASQ 2-y form, variable SCGM) more than 2 SD below the mean, or for those less mobile than normal (Parent/Carer form Q18, variable DifWalkSp = 2), or sit only if supported (Q19, variable DifSitSp = 2), or unable to control head without support (Q21, variable DifHeadSp = 2), or known as CP from parent interview (FU Minimal Info form, Q3 variable CP), or motor developmental delay known from parent interview (FU Minimal Info form, Q6, variable DevelopDelayMotor).

Analysis: Fit a log binomial GEE model to relative risk of motor developmental delay (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out for motor developmental delay defined by: (i) Psychological assessment, (ii) Psychological assessment and ASQ data, (iii) Psychological assessment, ASQ and Parent data, versus (iv) All data sources (Psychological, ASQ, Parent questionnaire and FU Minimal Info data).

3.4.2.12 Severity of motor developmental delay

Outcome: Ordinal child level outcome defined as motor composite score (Psychologist Data form, variable MotorComp) more than 3 SD, 2 SD and 1 SD below the mean (or < 55, 70 and 85), respectively. Children who are unable to complete psychological assessment due to severe motor disability are classified as severe motor developmental delay (who will be given a standardized score of – 4 SD).

Analysis: Fit a proportional odds GEE model to estimate odds ratio of higher severity of developmental delay (magnesium sulphate relative to placebo).

If the proportional odds assumption is not met, fit separate logistic GEE regression models to estimate odds ratios for the 3 binary outcomes of at least mild motor developmental delay (i.e. mild, moderate or severe motor delay vs. no motor delay), at least moderate (i.e. moderate or severe motor delay vs. mild or no motor delay) and severe delay (i.e. severe motor delay vs. moderate, mild or no motor delay).

3.4.2.13 Motor developmental score

Outcome: Continuous child level outcomes defined as BSID-III scores for Motor development (Psychologist Data form, variable MotorComp).

Analysis: Fit a linear GEE model to estimate difference in mean motor developmental scores (magnesium sulphate relative to placebo).

3.4.2.14 Neurosensory disability

Outcome: Binary child level outcome defined as any cerebral palsy (See 3.4.2.3),

cognitive/language developmental delay (See 3.4.2.7), motor developmental delay (See 3.4.2.10) blindness (See 3.4.2.5) or deafness (See 3.4.2.6).

Analysis: Fit a log binomial GEE model to relative risk of any neurosensory disability (magnesium sulphate relative to placebo).

3.4.2.15 Severity of neurosensory disability

Outcome: Ordinal child level outcome. Severity of neurosensory disability is classified as Severe (any severe cerebral palsy, severe cognitive/language developmental delay, severe motor developmental delay or blindness), Moderate (any moderate cerebral palsy, moderate cognitive/language developmental delay, moderate motor developmental delay or deafness), and Mild (any mild cerebral palsy, suspect, mild cognitive/language developmental delay or mild motor developmental delay).

See above definitions for severity of cerebral palsy (3.4.2.4), cognitive/language developmental delay (3.4.2.8), motor developmental delay (3.4.2.11), blindness (3.4.2.5) and deafness (3.4.2.6).

Analysis: Fit a proportional odds GEE model to estimate odds ratio of higher severity of neurosensory disability (magnesium sulphate relative to placebo).

If the proportional odds assumption is not met, fit separate logistic GEE regression models to estimate odds ratios for the 3 binary outcomes of at least mild disability (i.e. mild, moderate or severe disability vs. no disability), at least moderate (i.e. moderate or severe disability vs. mild or no disability) and severe disability (i.e. severe disability vs. moderate, mild or no disability).

3.4.2.16 Gross motor function

Outcome: Ordinal child level outcome defined by the Gross Motor Function Classification System (GMFCS) scoring (Paediatrician data form, Q16). The classification (Palisano R 1997) includes: 1 = child walks freely and toe-walk); 2 = child sits hands free for play and creeps/crawls on hands and knees; 3 = child uses hands for sitting support, or sits hands free for play but not creeps/crawls on hands and knees; 4 = child sits with external support for lower trunk; 5 = child has good head control in supported sitting or is unable to maintain anti-gravity head and trunk postures in prone or sitting.

Analysis: Fit a proportional odds GEE model to estimate odds ratio of higher score of GMFCS (magnesium sulphate relative to placebo).

If the proportional odds assumption is not met, fit separate logistic GEE regression models to estimate odds ratios for the 2 binary outcomes with

different thresholds (0 vs. 1+; 0 and 1 vs. 2+; 0, 1 and 2 vs. 3+; 0, 1, 2 and 3 vs. 4+; 0, 1, 2, 3 and 4 vs. 5).

3.4.2.17 Gross motor dysfunction

Outcome: Ordinal child level outcome defined as substantial (level 2+), minimal (level 1) or nil (level 0) using the GMFCS scoring (Paediatrician data form, Q16).

Analysis: Fit a proportional odds GEE model to estimate odds ratio of higher severity of gross motor dysfunction (magnesium sulphate relative to placebo).

If the proportional odds assumption is not met, fit separate logistic GEE regression models to estimate odds ratios for the 2 binary outcomes of at least minimal dysfunction (i.e. minimal or substantial dysfunction vs. nil), and substantial dysfunction (i.e. substantial dysfunction vs. minimal or nil).

3.4.2.18 Child Development Stages

Outcome: Continuous child level outcomes defined as separate standardized scores for Communication (Child's ASQ 2-yr form, variable SCComm), Gross motor (variable SCGM), Fine motor (variable SCFM), Problem solving (variable SSPSol), Personal-Social (variable SCPSoc), and total score (variable TotScr). The scores are computed using the Ages and Stages scoring process.

Analysis: Fit a linear GEE model to estimate difference in mean development stages for separate domains (magnesium sulphate relative to placebo).

3.4.2.19 Delayed Child Development Stages

Outcome: Binary child level outcome defined as any of standardized scores more than 2 SD below the mean (< -2 SD) for Communication (Child's ASQ 2y form, variable SCComm), Gross motor (variable SCGM), Fine motor (variable SCFM), Problem solving (variable SSPSol), Personal-Social (variable SCPSoc), and Total score (variable TotScr). The scores are computed using the Ages and Stages scoring process. The threshold of 2 SD below the mean is derived from ASQ Manual for each specific domain.

Analysis: Fit a log binomial GEE model to relative risk of any delayed child development stages (magnesium sulphate relative to placebo).

3.4.2.20 Delayed Child Development Stages for specific domain

Outcome: Binary child level outcomes defined as any of standardized scores more

than 2 SD below the mean (< -2 SD) for each of Communication (Child's ASQ 2y form, variable SCComm), Gross motor (variable SCGM), Fine motor (variable SCFM), Problem solving (variable SSPSol), Personal-Social (variable SCPSoc), and total score (variable TotScr). The scores are computed using the Ages and Stages scoring process. The threshold of 2 SD below the mean is derived from ASQ Manual for each specific domain.

Analysis: Fit a log binomial GEE model to relative risk of separate delayed child development stages (magnesium sulphate relative to placebo).

General health of the child

3.4.2.21 Use of health services since discharge

Outcome: Binary child level outcomes for separate health services (Parent/Carer questionnaire, Q13) such as physiotherapy (variable PhysRef, PhysRecd), Occupational therapy (variable OccRef, OccRecd), Speech therapy (variable SpchRef, SpchRcd), Special education service (variable SpEdRef, SpEdRcd), Psychology (variable PsychRef, PsychRcd), and Other (OthRef, OthRcd).

Analysis: Fit a log binomial GEE model to relative risk of separate health services since discharge (magnesium sulphate relative to placebo).

3.4.2.22 Use of supportive interventions since discharge

Outcome: Binary child level outcomes for separate supportive interventions used since primary discharge after birth (Paediatrician data form Q5) such as any intervention (variable SpecInt), special play group (variable SIspPlay), physio only (variable SIphys), both special play group and physio (SI1&2), play group (organized) (variable SIplay), day care/crèche (variable SIcreche), and other (variable SIother).

Analysis: Fit a log binomial GEE model to relative risk of separate supportive interventions since discharge (magnesium sulphate relative to placebo).

3.4.2.23 Hospital readmission

Outcome: Binary child level outcome defined as any hospital readmission since primary discharge after birth (Parent/Carer questionnaire, Q13, variable HospAdm, and ASQ questionnaire, variable Admit).

Analysis: Fit a log binomial GEE model to relative risk of any hospital admission (magnesium sulphate relative to placebo).

3.4.2.24 Blood pressure

Outcome: Continuous child level separate outcomes defined as a z-score (Rosner

1993) for (i) systolic, and (ii) diastolic blood pressure.

The outcome defined using blood pressures (Paediatrician's Data form Q12 and Q13, variable GrowSyst and GrowDias for systolic and diastolic blood pressure, respectively), sex (BabyDelivery form Q1.3, variable BSex) and age at assessment (Paediatrician data form, Q2, variable calcCAmth, calcCAdays).

Analysis: Fit a linear GEE model to estimate difference in mean blood pressures (z-score) (magnesium sulphate relative to placebo).

3.4.2.25 Hypertension

Outcome: Binary child level outcomes defined separately as (i) Systolic hypertension (z-score of systolic blood pressure> 95th percentile), (ii) Diastolic hypertension (z-score of diastolic blood pressure> 95th percentile), and (iii) Hypertension (z-score of either systolic or diastolic blood pressure> 95th percentile) (Rosner 1993).

Analysis: Fit a log binomial GEE model to estimate relative risks of hypertension (magnesium sulphate relative to placebo).

Child behavior checklist domains

3.4.2.26 Child behavior checklist score

Outcome: Continuous child level outcome defined as total scores of child behavior checklist domains (Child behavior checklist questionnaire, variable TotalScore).

Analysis: Fit a linear GEE model to estimate difference in mean total score for child behavior checklist domains (magnesium sulphate relative to placebo).

3.4.2.27 Scores of separate child behavior checklist domains

Outcome: Continuous child level outcomes defined for separate child behavior checklist domains (Child behavior checklist questionnaire), such as Anxious or depressed (variable Score1), Withdrawn (variable Score2), Sleep problems (variable Score3), Somatic complaints (variable Score4), Aggressive behavior (variable Score5), Destructive (variable Score6), Other problems (variable Score7) and total score (variable TotalScore).

Analysis: Fit a linear GEE model to estimate difference in mean scores for separate child behavior checklist domains (magnesium sulphate relative to placebo).

3.4.2.28 Child behavior checklist scores within clinical range

Outcome: Binary child level outcomes for separate child behavior checklist domains indicating further assessment is warrant. The outcomes defined as the scores at the top 2.5 percentile for each domain, such as Anxious or Depressed (scores ≥ 9), Withdrawn (≥ 6), Sleep problem (≥ 9), Somatic complaints (≥ 7), Aggressive behavior (≥ 25), Destructive (≥ 18), Other problems (≥ 25) and total score (≥ 61).

Analysis: Fit a log binomial GEE model to estimate relative risks of hypertension (magnesium sulphate relative to placebo).

Body size

3.4.2.29 Weight

Outcome: Continuous child level outcome defined as both raw and a z-score (Cole TJ 2011).

The outcome defined using weight at Paediatrician's assessment (Paediatrician data form Q7, variable GrowWt), sex (BabyDelivery form Q1.3, variable BSex) and corrected age at assessment (Paediatrician data form, Q2, variable calcCAmth, calCAdays). If missing, weight and corrected age reported from ASQ questionnaire (variable Weight), or Parent/Carer questionnaire (Parent/Carer form Q16, variable ChldWt) will be used.

Analysis: Fit a linear GEE model to estimate difference in mean weight (z-score) (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out using data from Paediatrician's assessment, versus data from all available sources (Paediatrician, ASQ, and Parent/Carer questionnaire).

3.4.2.30 Weight >90th, >97th, <10th, or <3rd percentile

Outcome: Binary child level separate outcomes defined as z-score (Cole TJ 2011) (i) > 90th, (ii) > 97th, (iii) < 10th and (iv) <3rd percentile.

Analysis: Fit a log binomial GEE model to estimate relative risks of weight > 90th, 97th percentile, and weight < 10th, 3rd percentile (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out using data from Paediatrician's assessment, versus data from all available sources (Paediatrician, ASQ, and Parent/Carer questionnaire).

3.4.2.31 Height

Outcome: Continuous child level outcome defined as both raw and a z-score (Cole

TJ 2011). For children unable to stand, length supine will be used instead.

The outcome defined using height at Paediatrician's assessment (Paediatrician data form Q8, variable GrowHght), sex (BabyDelivery form Q1.3, variable BSex) and age at assessment (Paediatrician data form, Q2, variable calcCAmth, calcCAdays). If missing, height and corrected age reported from ASQ questionnaire (variable Height) or Parent/Carer questionnaire (Parent/Carer form Q16, variable ChldHt) will be used.

Analysis: Fit a linear GEE model to estimate difference in mean height (z-score) (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out using data from Paediatrician's assessment, versus data from all available sources (Paediatrician, ASQ, and Parent/Carer questionnaire).

3.4.2.32 Height >90th, >97th, <10th, or <3rd percentile

Outcome: Binary child level separate outcomes defined as z-score (Cole TJ 2011) (i) > 90th, (ii) > 97th, (iii) < 10th and (iv) <3rd percentile.

Analysis: Fit a log binomial GEE model to estimate relative risks of height > 90th , 97th percentile, and height < 10th, 3rd percentile (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out using data from Paediatrician's assessment, versus data from all available sources (Paediatrician, ASQ, and Parent/Carer questionnaire).

3.4.2.33 Head circumference

Outcome: Continuous child level outcome defined as both raw and a z-score (Cole TJ 2011).

The outcome defined using head circumference at Paediatrician's assessment (Paediatrician data form Q10, variable GrowHead), sex (BabyDelivery form Q1.3, variable BSex) and age at assessment (Paediatrician data form, Q2, variable calcCAmth, calcCAdays). If data in Paediatrician's assessment is missing, head circumference and corrected age reported from ASQ questionnaire (variable HC) or Parent/Carer questionnaire (Parent/Carer form Q16, variable ChldHC) will be used.

Analysis: Fit a linear GEE model to estimate difference in mean head circumference (z-score) (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out using data from Paediatrician's assessment, versus data from all available sources (Paediatrician, ASQ, and Parent/Carer questionnaire).

3.4.2.34 Head circumference> 90th, >97th, <10th, or <3rd percentile

Outcome: Binary child level separate outcomes defined as z-score (Cole TJ 2011) (i) > 90th, (ii) > 97th, (iii) < 10th and (iv) <3rd percentile.

Analysis: Fit a log binomial GEE model to estimate relative risks of head circumference > 90th, 97th percentile, and head circumference < 10th, 3rd percentile (magnesium sulphate relative to placebo).

Sensitivity analysis will be carried out using data from Paediatrician's assessment, versus data from all available sources (Paediatrician, ASQ, and Parent/Carer questionnaire).

3.4.2.35 Mid-arm circumference

Outcome: Continuous child level outcome defined as raw score (Paediatrician data form Q11, variable GrowArm).

Analysis: Fit a linear GEE model to estimate difference in mean mid-arm circumference (magnesium sulphate relative to placebo).

Other outcomes

3.4.2.36 Postnatal CNS problems

Outcome: Binary child level outcome defined as any of postnatal CNS problems (Paediatrician data form Q3, variable CNSProbs).

Analysis: Fit a log binomial GEE model to relative risk of any postnatal CNS problems (magnesium sulphate relative to placebo). Descriptive analyses for specific CNS problems will be carried out.

3.4.2.37 Malformations

Outcome: Binary child level outcome defined as any of malformations (Paediatrician data form Q4, variable Malform).

Analysis: Fit a log binomial GEE model to relative risk of any malformations (magnesium sulphate relative to placebo). Specific malformations will be also described.

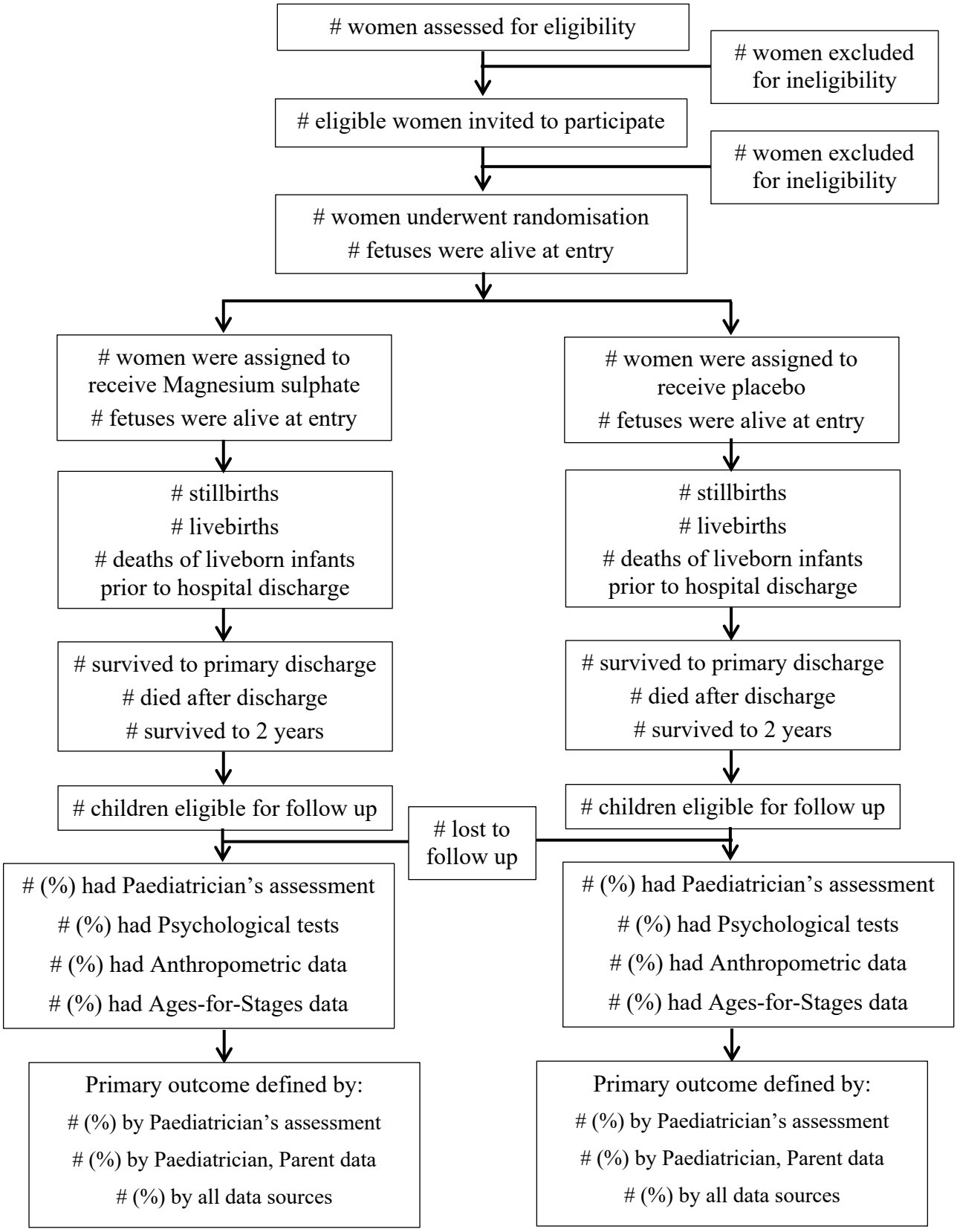
3.4.2.38 Seizures

Outcome: Binary child level outcome defined as any of seizures (Paediatrician data form Q6, variable Seizure).

Analysis: Fit a log binomial GEE model to relative risk of any Seizures (magnesium sulphate relative to placebo).

3.5 SHELL TABLES

3.5.1 *Figure 1: Enrolment*



3.5.2 *Table 1: Baseline characteristics*

	Magnesium sulphate (n=)	Placebo (n=)
Maternal age (years)		
Ethnicity		
Caucasian		
Asian		
Aboriginal or Torres Strait Islanders		
Polynesian		
Maori		
Other		
Parity		
0		
1-3		
4+		
Smoking during pregnancy		
Gestational age at entry* (wk), Median (IQR)		
30 to < 32 weeks		
32 to <34 weeks		
Twin pregnancy		
Previous preterm delivery (< 37 weeks)		
Previous perinatal death (≥ 20 weeks)		
Main reason for risk of preterm delivery		
Antepartum haemorrhage		
PPROM		
Preterm labour		
Cervical incompetence		
Preeclampsia/Eclampsia		
Fetal compromise		
Other		
Socioeconomic status		
Least disadvantaged		
Disadvantaged		
Middle		
Advantaged		
Most advantaged		
Highest level of maternal education		
Never attended school/Primary school		
Some/completed High school		
Completed other qualification		
Some study towards a tertiary degree/diploma		
Completed tertiary degree/diploma		
Language spoken at home		
English only		
English and other language		

	Magnesium sulphate (n=)	Placebo (n=)
Treatment given		
Women received some of the trial medication		
Women received all of the trial medication		
Women did not receive trial medication		
Women gave birth before treatment started		
Staff unable to find treatment pack		
Other reasons treatment not given		
Sex of child		
Male		
Female		
Gestational age at birth* (wk), Median (IQR)		
Birth weight* (g), Mean (SD)		

Values are number (%) unless otherwise indicated.
* Values are Means (SD) or Medians (IQR) where appropriate.

3.5.3 ***Table 2: Primary outcome, assessed at 2 years of corrected age***

Outcome	MgSO4 (N=)	Placebo (N=)	Unadjusted Treatment Effect (95% CI)	Unadjusted P value	Adjusted* Treatment Effect (95% CI)	Adjusted* P value
Death or any cerebral palsy						
- Data from Paediatrician's assessment						
- Data from Paediatrician's assessment and Parent questionnaire						
- Data from Paediatrician's assessment, Parent questionnaire and FU Minimal Info form						

*: Adjusted for collaborating centres, GA at trial entry, number of fetuses, language spoken at home, mother's socioeconomic status and child's gender. Analyses are also adjusted for clustering within mother

3.5.4 ***Table 3: Pre-defined interaction analyses for primary outcome, and key secondary outcomes at two years' corrected age***

Outcomes	MgSO4 (N=)	Placebo (N=)	Unadj Treatment effect (95% CI)	Unadj P value	Unadj P value for interaction term	Adj* Treatment effect (95% CI)	Adj* P value	Adj* P value for interaction term
Death or any cerebral palsy								
GA at trial entry								
. 30 to <32 weeks								
. 32 to <34 weeks								
Main reasons for risk of preterm birth								
. Antepartum haemorrhage								
. PPROM								
. Preterm labour								
. Fetal compromise								
. Pre/eclampsia								
. Cervical incompetent								
. Other								
Child's gender								
. Male								
. Female								
Number of fetuses								
. Single								
. Twin								
Mother's socioeconomic status								
. Most disadvantaged								
. Disadvantaged								
. Neutral								
. Advantaged								
. Most advantaged								
Ethnicity								
. Caucasian								
. Asian								
. Other								

Other outcomes include death; cerebral palsy; death or any neurosensory disability; death or any major neurosensory disability; cognitive/delay; and motor developmental delay.

*: Adjusted for collaborating centres, GA at trial entry, number of fetuses, language spoken at home, mother's socioeconomic status and child's gender. Analyses are also adjusted for clustering within mother.

3.5.5 ***Table 4: Pre-defined exploratory subgroup analyses for primary outcome, and key secondary outcomes at two years' corrected age***

Outcomes	MgSO4 (N=)	Placebo (N=)	Unadjusted Treatment effect (95% CI)	Unadjusted P value	Adjusted* Treatment effect (95% CI)	Adjusted * P value
Death or any cerebral palsy						
GA at delivery						
.30 to <32 weeks						
.32 to < 34 weeks						
. 34-< 37 weeks						
. ≥ 37 weeks						

Other outcomes include death; cerebral palsy; death or any neurosensory disability; death or any major neurosensory disability; cognitive/language delay; and motor developmental delay.

*: Adjusted for collaborating centres, GA at trial entry, number of fetuses, language spoken at home, mother's socioeconomic status and child's gender. Analyses are also adjusted for clustering within mother.

3.5.6 *Table 5: Secondary outcomes at two years' corrected age*

Outcomes	MgSO4 (N=)	Placebo (N=)	Unadjusted Treatment effect (95% CI)	Unadjusted P value	Adjusted* Treatment effect (95% CI)	Adjusted* P value
Death						
Cerebral palsy						
Severity						
. Mild						
. Moderate						
. Severe						
Death or any neurosensory disability						
Blindness						
Deafness						
Any developmental delay						
Death or major neurosensory disability						
Moderate/severe cerebral palsy						
Blindness						
Deafness						
Any moderate/severe developmental delay						
Developmental delay:						
Cognitive/language developmental delay						
Severity:						
. Mild						
. Moderate						
. Severe						
Cognitive/language developmental scores						
. Cognitive						
. Language						
Motor developmental delay						
. Mild						
. Moderate						
. Severe						
Motor developmental scores						
Neurosensory disability						
. Mild						
. Moderate						
. Severe						
Gross motor dysfunction						
. Minimal						
. Substantial						
Child developmental stages scores						
. Communication						
. Gross motor						
. Fine motor						
. Problem solving						
. Personal- social						
.Total						

Outcomes	MgSO4 (N=)	Placebo (N=)	Unadjusted Treatment effect (95% CI)	Unadjusted P value	Adjusted* Treatment effect (95% CI)	Adjusted* P value
Delayed child developmental stages						
. Communication						
. Gross motor						
. Fine motor						
. Problem solving						
. Personal- social						
.Total						
General health						
Use of health services since discharge:						
. Physiotherapy						
. Occupational therapy						
. Speech therapy						
. Special education services						
. Psychology						
. Other						
Use of supportive interventions since discharge						
. Special play group						
. Physio only						
. Both special play group and Physio						
. Day care/crèche						
. Other						
Hospital readmission						
Systolic blood pressure						
Diastolic blood pressure						
Hypertension						
. Systolic						
. Diastolic						
Child behavior checklist domains:						
Child behavior checklist score						
. Anxious						
. Sleep problems						
. Aggressive behavior						
. Destructive						
. Other						
Child behavior checklist scores within clinical range						
. Anxious						
. Sleep problems						
. Aggressive behavior						
. Destructive						
. Other						

Outcomes	MgSO4 (N=)	Placebo (N=)	Unadjusted Treatment effect (95% CI)	Unadjusted P value	Adjusted* Treatment effect (95% CI)	Adjusted* P value
Body size						
Weight						
. Raw						
. Z-score						
. > 90th percentile						
. > 97th percentile						
. < 10th percentile						
. < 3rd percentile						
Height						
. Raw						
. Z-score						
. > 90th percentile						
. > 97th percentile						
. < 10th percentile						
. < 3rd percentile						
Head circumference						
. Raw						
. Z-score						
. > 90th percentile						
. > 97th percentile						
. < 10th percentile						
. < 3rd percentile						
Mid-arm circumference						
Other outcomes						
Postnatal CNS problems						
Malformations						
Seizures						

*: Adjusted for collaborating centres, GA at trial entry, number of fetuses, language spoken at home, mother's socioeconomic status and child's gender. Analyses are also adjusted for clustering within mother.

4. REFERENCES

Bender R, Grouven U. Using binary logistic regression models for ordinal data with non-proportional odds. *J Clin Epidemiol* 1998; 51(10):809-816.

Cole TJ, Williams AF, Wright CM; RCPCH Growth Chart Expert Group. Revised birth centiles for weight, length and head circumference in the UK-WHO growth charts. *Ann Hum Biol.* 2011 Jan;**38(1)**:7-11.

Crowther CA, Middleton PF, Wilkinson D, Ashwood P, Haslam R; MAGENTA Study Group. Magnesium sulphate at 30 to 34 weeks' gestational age: neuroprotection trial (MAGENTA)--study protocol. *BMC Pregnancy Childbirth* 2013 Apr 9;13:91.

Lumley, T., P. Diehr, et al. The importance of the normality assumption in large public health data sets. *Annu Rev Public Health* 2002;23:151-169.

Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997 Apr;39(4):214-23.

Vierron, E. and B. Giraudeau. Design effect in multicenter studies: gain or loss of power*?* *BMC Med Res Methodol* 2009;9: 39.

Zou, G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159(7): 702-706.