Efficacy of probiotic supplementation in preterm and small for gestational age infants. A multi-centre, placebo- controlled, individually-randomised trial

(Probiotics in preterm and small for gestational infants, PROPS trial)

Statistical Analysis Plan

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1. Introduction

1.1. Background and rationale

Preterm and small for gestational age (SGA) infants have a 2- to 10-fold higher risk of mortality than infants born at term and with normal birth weight, and are particularly vulnerable to infection, malabsorption, necrotizing enterocolitis, difficulty feeding, and growth failure. Numerous trials conducted in the last ten years have reported that probiotics can improve short- and long-term mortality, necrotizing enterocolitis and sepsis rates, and growth and neurodevelopment in preterm and low birth weight infants. However, most trials have been small and with high to moderate risk of bias. There have been no trials in SGA infants. The World Health Organization (WHO) guideline development group (GDG) and other organizations have recommended that further large high-quality trials are implemented to provide evidence of sufficient quality and applicability to inform policy and practice.

This large, multi-country trial will address this recommendation, by providing robust evidence on the effects of probiotic supplementation on mortality, morbidity, and growth in preterm or term SGA infants in the first 6 months of life in five countries in South Asia and Sub-Saharan Africa. Results from this trial will help inform policy and practice for probiotic supplementation in preterm and SGA infants, improve the certainty of evidence on critical outcomes and strengthen the understanding of optimal strains, dosing and duration of probiotic supplementation and related impact in high burden LMICs.

1.2. Objectives

The primary objectives are:

- For preterm infants, to assess the effectiveness of probiotic supplementation on mortality from enrolment to 6 months of age.
- For term SGA infants, to assess the effectiveness of probiotic supplementation on underweight-free survival from enrolment to 6 months of age.

The secondary objectives are, among preterm and term SGA infants:

- To assess safety of probiotic supplementation from enrolment to 6 months of age, assessed as:
    - Episodes of serious adverse events (SAEs)
    - Episodes of sepsis due to the probiotic strains *B. infantis* or *L. rhamnosus.*
- To assess the effect of probiotic supplementation on the following outcomes at hospital discharge, 1 month and 6 months of age:

  - All cause mortality (for the 6 month endpoint, this will be evaluated as a secondary outcome for term SGA infants, and as a primary outcome for preterm infants)
  - Cause specific mortality due to necrotising enterocolitis, sepsis, severe diarrhoea
  - Episodes of necrotising enterocolitis, sepsis, severe diarrhoea
  - Episodes of pathogen specific sepsis (including Streptococcus, Staphylococcus, Klebsiella, Escherichia coli, Acinetobacter spp) including their serotypes and genotypic sequences
  - Episodes of hospitalisation
- To assess the effect of probiotic supplementation on the prevalence of wasting, underweight, and mean weight for age z score (WAZ) and weight for length (WLZ) scores at 6 months of age
- To assess the effect of probiotic supplementation on the abundance of *B. infantis* and *L. rhamnosus* and other bacteria in infant faecal specimens at enrolment, 7 days, 28 days and 6 months of age; and in maternal faecal specimens at enrolment, including their serotypes and genotypic sequences.
- To assess the effects of probiotic supplementation on the primary outcome in the following subgroups:
  - prematurity (<32weeks, 32-<37weeks), among preterm infants only
  - birth weight (< 1.5kg, 1.5 to < 2.5kg, 2.5+ kg)
  - preterm and SGA status (preterm SGA, preterm AGA), among preterm infants only
  - vaccination (fully, partially, not vaccinated) from enrolment to 6 months of age
  - feeding type (exclusive, predominant, partial) at 1 month, 3 months, 6 months of age
  - early initiation of enteral feeding (including mother's milk, donor milk, infant formula) (within < 1hour, 2-< 24hour, 24+ hours after birth)
  - micronutrient supplement intake (multiple micronutrients, iron, vitamin A, vitamin D, zinc) from enrolment to 6 months of age
  - receipt of antibiotics from enrolment to 6 months of age

2. Study methods

2.1. Trial design

This is a multi-country, individually-randomised, double-blinded, parallel-group placebo-controlled superiority trial implemented among preterm and term SGA infants in five countries: Bangladesh, Pakistan, Ethiopia, Nigeria, Kenya.

2.2. Randomisation and blinding

Infants will be randomized in a 1:1 ratio to receive either intervention (*B. infantis* and *L. rhamnosus*) or control (placebo for *B. infantis* and *L. rhamnosus*) once daily for a period of 28 days. Randomisation will be stratified by site and by infant status (i.e. preterm, or term SGA), so that for each site there will be two randomisation lists, one for preterm infants and one for term SGA infants.

A statistician who is otherwise uninvolved with the study will generate the randomisation lists for each site using randomly permuted block sizes. This randomisation list will be embedded within the data

collection system. At the time of enrolment, a participant will be allocated to the next trial arm allocation on the randomisation list for their stratum.

Participants (i.e. infants and their care providers), hospital staff and all investigators (i.e. the site teams including the intervention, data collection, data management and data analysis teams, and the WHO team including the project managers and internal statistics team) will be blinded to the group allocation.

The intervention powder will be identical in appearance, consistency, taste and smell to the placebo powder. The intervention and placebo will be placed in foil sachets that are also identical in appearance and packaging. The sachets will be labelled, assembled into boxes and packs by an experienced packing team. The packing team will ensure that all labelling does not distinguish between placebo and intervention groups.

2.3. Sample size

The primary outcome for preterm infants is mortality at 6 months, which is assumed to be 10% in the control arm. A total of 8,602 preterm infants with data on this outcome would be needed for 90% power to detect a 20% relative reduction in mortality risk at 6 months in the intervention arm (i.e. 8% versus 10%), with 5% significance level. The 9,500 preterm infants expected to be enrolled across the 5 sites will allow 9% loss to follow up in determining the primary endpoint among preterm infants for a total of 9,453 preterm infants enrolled.

The primary outcome for term SGA infants is underweight free survival at 6 months, which is assumed to be 23% in the control arm. A total of 3,750 term SGA infants with data on this outcome would be needed for 90% power to detect a 20% relative improvement in underweight free survival in the intervention arm (i.e. 27.6% versus 23%), at 5% significance level. The 4,500 term SGA infants expected to be enrolled across the 5 sites will allow 16% loss to follow up in determining the primary endpoint among term SGA infants for a total of 4,465 term SGA infants enrolled.

2.4. Statistical interim analyses and stopping guidance

An independent Data Safety and Monitoring Board (DSMB) will review periodic data on trial progress and safety. No formal stopping rules relating to safety are planned, but the DSMB will be able to act on safety concerns at any point without alpha spending. Regarding efficacy, a formal interim efficacy analysis of primary outcome data will be done when 40-50% of trial participants have data available on the primary outcome (in each group, i.e. preterm and term SGA). The interim efficacy analysis will be governed by the Haybittle-Peto rule. An external statistician who is otherwise uninvolved in the trial will summarise primary outcome data by trial arm (A or B) but the DSMB will not know whether A or B are the intervention or control arms. These data will be discussed at a closed session DSMB meeting attended only by the DSMB members and the external statistician. The effect of the intervention on the primary outcome at this time point will be evaluated using the methods described in section 5.3. If there is strong evidence of a difference ($p<0.001$) in primary outcome between trial arms, then the trial arm will be unmasked to the DSMB who will then have the power to request that the trial be stopped or altered. Following the Haybittle-Peto rule, no adjustment to the significance level used in the final analysis will be made. These plans will be finalised by the DSMB at their first meeting and reflected in the DSMB charter.

Other than the formal interim efficacy analysis described above, no formal stopping rules relating to either efficacy or safety data are planned, with any recommendations from the DSMB to continue or discontinue to be guided by the balance of risks and benefits alongside other considerations such as

external new information. These aspects will be considered for the preterm and term SGA infant groups independently.

2.5. Timing of final analysis

Analysis for all outcomes will be done when all infants have completed the six-month visit (or have been censored before this visit), when all trial data have been cleaned, finalized and the database locked.

2.6. Timing of and sources for outcome assessments

Timing of, and sources for, primary outcome assessment

- The primary outcome in preterm infants, mortality from enrolment to 6 months of age, will be assessed based on SAE data capture during this period. Safety data, including on SAEs, will be actively solicited, daily from enrolment to 7 days post the last supplement dose, and then at 4-weekly visits. This will be supplemented by passive surveillance where all research staff, monitoring staff and health facility staff will be asked to report any SAE in a study participant that they become aware of.
- The primary outcome in term SGA infants, underweight-free survival from enrolment to 6 months of age will be assessed based on continuous SAE data capture (as described above) during this period, in combination with anthropometric data collected at the month 6 visit.

Timing of, and sources for, secondary outcome assessment

- Safety based on episodes of SAEs will be assessed based on continuous SAE data capture from enrolment to 6 months of age.
- Safety based on episodes of sepsis due to the probiotic strains *B. infantis* or *L. rhamnosus* will be assessed based on continuous SAE data capture from enrolment to 6 months of age.
- All cause and cause-specific mortality due to necrotising enterocolitis, sepsis, severe diarrhoea; episodes of necrotising enterocolitis, sepsis, severe diarrhoea; episodes of pathogen specific sepsis; and episodes of hospitalisation will be assessed based on continuous SAE data capture, supplemented by laboratory results from enrolment to 6 months of age. These data will be evaluated at three time points: at hospital discharge (on the basis of hospitalisation data), at age one month, and at age six months.
- Prevalence of wasting, underweight and mean WAZ and WLZ scores at 6 months of age will be assessed based on anthropometric data collected at the month 6 visit.
- Abundance of *B. infantis* and *L. rhamnosus* and other bacteria will be evaluated in laboratory tests done on infant faecal specimens at enrolment, 7 days, 28 days and 6 months of age; and in laboratory tests done on maternal faecal specimens at enrolment.

3. Statistical principles

3.1. Confidence intervals and p-values

All applicable statistical tests will be two-sided and 95% confidence intervals will be presented.

3.2. Adherence and protocol deviations

Compliance to the protocol schedule will be assessed based on the percent of participants who have attended the scheduled visits within the permitted time windows.

3.3. Analysis populations

The primary analysis populations will be:

- All randomised preterm infants (Preterm ITT)
- All randomised term SGA infants (Term SGA ITT)

For primary outcome 1 (mortality in preterm infants), all randomised preterm infants will be the analysis population.

For primary outcome 2 (underweight free survival in term SGA infants), all randomised term SGA infants will be the analysis population.

For all secondary outcomes, analyses will be conducted and presented separately for the two analysis populations.

The primary analysis will be done by intention to treat (ITT), i.e. participants will be included according to the trial arm they were randomised to, regardless of whether interventions were received. The only exception to this will be if the participant's mother withdraws their consent for their data to be used.

Missing data will be handled using complete case analysis as the primary approach. Multiple imputation methods may also be used as a sensitivity analysis if substantial missing data exist (>10% missing).

"Per-protocol" secondary analyses will also be conducted, among the following populations, with participants analysed according to the treatment received rather than the treatment to which they were randomised (if the two differ):

- Randomised preterm infants who receive all 28 days of intervention/control (Preterm PP): for primary outcome 1 and all secondary outcomes
- Randomised term SGA infants who receive all 28 days of intervention/control (Term SGA PP): for primary outcome 2 and all secondary outcomes

4. Trial population

4.1. Screening, eligibility, recruitment and loss to follow-up of participants

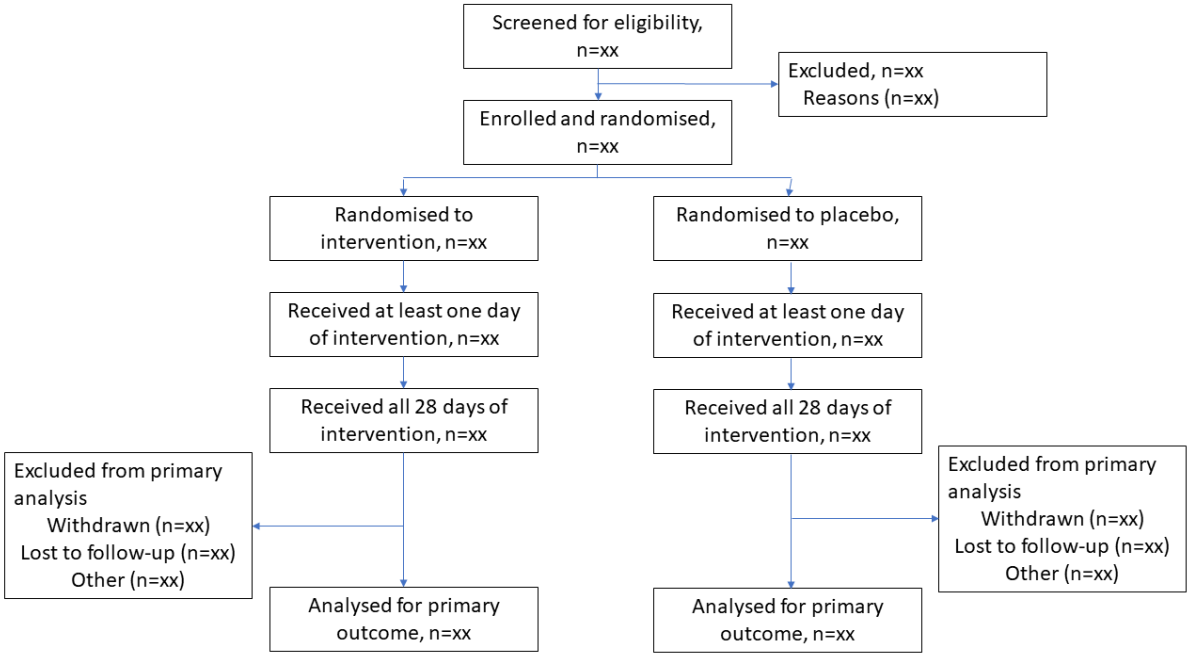
CONSORT flow diagrams will be used to summarise the number of participants in each trial arm who were:

• assessed for eligibility at screening • ineligible at screening* • eligible and randomised • received at least one dose of allocated trial intervention • received all 28 doses of allocated trial intervention • seen at 6 months • not seen at 6 months • censored before 6 months*

*reasons for these events will be provided.

The CONSORT flow diagrams will be shown separately for preterm infants and term SGA infants.

Figure 1. CONSORT flowchart



4.2. Baseline participant characteristics

Demographic and clinical characteristics of the enrolled groups at baseline will be described for each of the analysis populations. This will be done, overall, by trial arm, and by setting. Means and standard deviations will be used to summarise continuous, approximately normally-distributed characteristics; medians and interquartile ranges will be used to summarise continuous, non-normally-distributed characteristics; frequency and proportions will be used to summarise categorical characteristics.

4.3. Protocol adherence and participant follow-up

Protocol deviations are defined as any divergence from the approved study protocol. This includes enrolling ineligible participants, incorrect randomisation procedures, missing required data, and failure to follow approved study procedures. All important protocol deviations, including enrolment errors and procedural violations, will be summarized descriptively. The number and type of deviations will be presented overall and by study arm.

For each analysis population, the number and proportion of participants who receive each treatment dose will be summarised, for doses from days 1 through 28, overall and by trial arm. A summary of the number of doses received will also be calculated, as median and interquartile range, both overall and by study arm.

The number and proportion of participants who are seen at each 4-weekly visit and at the month six visit will also be summarised overall and by study arm. Characteristics of participants who are lost to follow-up will be compared to characteristics of participants who complete the six-month follow-up. Characteristics of participants who are lost to follow-up will be compared between trial arms.

5. Analysis of outcomes

5.1. Primary outcome definitions

- Mortality from enrolment to 6 months of age among preterm infants: the proportion of infants who die from any cause from enrolment to 6 months of age.
- Underweight-free survival from enrolment to 6 months of age among term SGA infants: the proportion of infants with WAZ ≥ -2 at 6 months of age and who have not died.

5.2. Secondary outcome definitions

- Episodes of serious adverse events (SAEs): SAEs will be defined as any AE that is considered serious if it (i) results in death, (ii) required inpatient hospitalisation, (iii) is life-threatening, (iv) results in persistent or significant disability/incapacity, (v) requires prolongation of the existing hospitalisation, or (vi) any other event that any person considers to be a trial SAE.
- Episodes of sepsis due to the probiotic strains *B. infantis* or *L. rhamnosus:* this will be defined as suspected sepsis (based on PROPS clinical case definitions described in Annex 1 of the protocol) with *B. infantis* and/or *L. rhamnosus* isolated from blood culture
- Mortality due to necrotising enterocolitis, sepsis, severe diarrhoea: this will be defined as the proportion of infants who die and who, at the time of death, meet the PROPS clinical case definitions for these conditions (as described in Annex 1 of the protocol).
- Episodes of necrotising enterocolitis, sepsis, severe diarrhoea: this will be defined as the incidence rate (number of episodes divided by person-time of follow-up) for each of these conditions, following the PROPS clinical case definitions.
- Episodes of pathogen specific sepsis (including Streptococcus, Staphylococcus, Klebsiella, Escherichia coli, Acinetobacter spp): this will be defined as the incidence rate (number of episodes divided by person-time of follow-up) of suspected sepsis with detection of specific pathogens.
- Episodes of hospitalisation: this will be defined as the incidence rate (number of episodes divided by person-time of follow-up)
- Wasting: this will be defined as the proportion of participants with WAZ< -2 at 6 months of age
- Underweight: this will be defined as the proportion of participants with WLZ < -2 at 6 months of age.
- Mean WAZ: this will be defined as the arithmetic mean of WAZ scores at 6 months of age, using WHO growth reference standards
- Mean WLZ: this will be defined as the arithmetic mean of WLZ scores at 6 months of age, using WHO growth reference standards
- Abundance of *B. infantis* and *L. rhamnosus* and other bacteria will be defined according to quantitative polymerase chain reaction (qPCR) testing of each species in faecal specimens

5.3. Analysis methods

Binary outcomes

The numerator, denominator and proportion with the outcome will be presented overall and by trial arm. A risk ratio comparing the proportion with the outcome in the intervention arm to the proportion

with the outcome in the control arm, along with a 95% confidence interval, will be calculated. As the randomisation is stratified by setting, the analysis will adjust for setting. This will be done using a binomial regression model with a log link function, and including both trial arm and setting as covariates. Binomial regression models can experience model convergence issues under certain circumstances; in this event we will instead use a modified Poisson regression approach with robust standard errors to estimate risk ratios and 95% confidence intervals.

Continuous outcomes

The number of participants, and the mean and standard deviation of the outcome will be presented overall and by trial arm. A difference in means comparing the intervention arm with the control arm, along with a 95% confidence interval will be calculated. As the randomisation is stratified by setting, the analysis will adjust for setting. This will be done using a multiple linear regression model, including trial arm and setting as covariates.

Rate outcomes

The number of episodes and the total person-time of follow-up will be presented overall and by trial arm. An incidence rate ratio comparing the intervention arm with the control arm, along with a 95% confidence interval, will be calculated. This will be done using Poisson regression with a random effects model to allow for multiple episodes occurring in some children, and including trial arm and setting as covariates. If the rate of the outcome varies over the follow-up time, then a Lexis expansion approach will be used to stratify the analysis, and allow the rate to vary by follow-up time period.

Checking assumptions

For statistical analyses of continuous outcomes that require data to be normally distributed, the normality assumption of the data will be checked using graphical assessment of normality (Q-Q plot) and a Kolmogorov-Smirnov test for normality. If the data are found to be non-normal, medians (IQR) or geometric means (GMs) will be presented instead of means (SD). A log transformation will be applied to achieve normality and if not achieved, alternative tests such as the Wilcoxon rank sum test will be used to compare outcomes between trial arms. If normality is achieved through log transformation, then the parametric tests described above will be applied to the log transformed data.

Covariate adjustment

Adjustment for baseline covariates that are prognostic for the outcome has been shown to increase power to detect an intervention effect. For the primary outcomes, we therefore plan to further adjust for birth weight, receiving human milk at the time of randomisation (yes/no) , receipt of any antibiotics at the time of randomisation (yes/no) and maternal education (none vs any), factors which have all been shown to be prognostic for the primary outcomes in their respective populations. Adjustment will be done within the binomial regression framework described above (or in the case of convergence issues, Poisson regression with robust standard errors).

5.5. Missing data

The primary analysis approach will be based on complete case analysis. However, for any outcome where >10% outcome data are missing, multiple imputation methods will be used, assuming that data are missing at random. Results from MI analyses will be presented alongside results from complete case analysis.

5.6. Subgroup analyses

We will assess whether the effect of probiotic supplementation on the primary outcomes differs in the following subgroups, listed according to whether the subgroups are defined pre-randomisation or post-randomisation.

Pre-randomisation:

- prematurity (2 groups): <32weeks, 32-<37 weeks, among preterm infants only
- birth weight (3 groups): < 1.5kg, 1.5 to < 2.5kg, 2.5+ kg
- preterm and SGA status (2 groups): preterm SGA, preterm AGA among preterm infants only
- early initiation of enteral feeding (including mother's milk, donor milk, infant formula) (3 groups): within < 1hour, 2-< 24hour, 24+ hours after birth

Post-randomisation:

- vaccination according to vaccine schedule from enrolment to 6 months (3 groups): fully vaccinated, partially vaccinated, not vaccinated
- feeding type at 1 month of age (3 groups): exclusive, predominant, partial
- feeding type at 3 months of age (3 groups): exclusive, predominant, partial
- feeding type at 6 months of age (3 groups): exclusive, predominant, partial
- any micronutrient supplement intake from enrolment to 6 months of age (2 groups): any, none
- iron supplement intake from enrolment to 6 months of age (2 groups): any, none
- vitamin A supplement intake from enrolment to 6 months of age (2 groups): any, none
- vitamin D supplement intake from enrolment to 6 months of age (2 groups): any, none
- zinc supplement intake from enrolment to 6 months of age (2 groups): any, none
- receipt of antibiotics from enrolment to 6 months of age (2 groups): yes, no

For subgroups defined pre-randomisation, this will be done by summarising results separately for each sub-group, and fitting a regression model including an interaction term between trial arm and subgroup indicator, and presenting the effect of the intervention within each subgroup. Interaction terms will be assessed for strength of evidence against the null hypothesis of no effect modification, using likelihood ratio tests.

For subgroups defined post-randomisation, we acknowledge the risk of bias in these analyses. During the protocol development for the trial, there was considered to be plausible reasons why the effects of treatment could be different in the different subgroups. For example, probiotics have been shown to reduce infection rates in preterm infants and to promote vaccine responses in normal infants. Vaccines may modify the effect of the probiotic intervention; there may be a greater effect of the probiotic intervention in vaccinated than non vaccinated infants.

Before conducting subgroup analysis using the approach described above for pre-randomisation subgroups, we will first determine whether the intervention has an effect on the stratifying variable; this will be done by comparing the proportions within each subgroup by intervention arm using chi-squared tests. If there is evidence from this test that the intervention impacts on the distribution of participants across subgroup, then we will still conduct the formal test for effect modification as

described above but as sensitivity analysis we will investigate the use of propensity score methods to adjust for bias.

5.7. Statistical software

All analysis will be conducted in Stata and R.

5.8. Sample tables for baseline characteristics, primary outcomes and selected secondary outcomes

Table 1: Baseline characteristics of **preterm infants** by trial arm, primary ITT analysis population

	Control arm		Intervention arm	
Characteristic	**n**	**Col%**	**n**	**Col%**

Table 2: Baseline characteristics of **term SGA infants** by trial arm, primary ITT analysis population

	Control arm		Intervention arm	
Characteristic	**n**	**Col%**	**n**	**Col%**

Table 3: The effect of probiotic supplementation on primary outcomes in preterm children and in term SGA children, primary ITT analysis populations

	Placebo	**Intervention**		
Population; outcome	**n/N (%)**	**n/N (%)**	**Risk ratio (95% CI)**	**P value**
Preterm children; All-cause mortality, enrolment to 6 months				
Term SGA children; Underweight-free survival, enrolment to 6 months				

Table 4: The effect of probiotic supplementation on secondary outcomes (all cause and cause specific mortality) among **preterm children**, primary ITT analysis populations

	Placebo	Intervention		
Outcome	**n/N (%)**	**n/N (%)**	**Risk ratio (95% CI)**	**P value**
All cause mortality at hospital discharge				
All cause mortality at 1 month				
Mortality due to necrotising enterocolitis at hospital discharge				
Mortality due to necrotising enterocolitis at 1 month				
Mortality due to necrotising enterocolitis at 6 months				
Mortality due to sepsis at hospital discharge				
Mortality due to sepsis at 1 month				
Mortality due to sepsis at 6 months				
Mortality due to severe diarrhoea at hospital discharge				
Mortality due to severe diarrhoea at 1 month				
Mortality due to severe diarrhoea at 6 months				

Table 5: The effect of probiotic supplementation on secondary outcomes (all cause and cause specific mortality) among **term SGA children**, primary ITT analysis populations

	Placebo	Intervention		
Outcome	**n/N (%)**	**n/N (%)**	**Risk ratio (95% CI)**	**P value**
All cause mortality at hospital discharge				
All cause mortality at 1 month				
All cause mortality at 6 months				
Mortality due to necrotising enterocolitis at hospital discharge				
Mortality due to necrotising enterocolitis at 1 month				
Mortality due to necrotising enterocolitis at 6 months				
Mortality due to sepsis at hospital discharge				
Mortality due to sepsis at 1 month				
Mortality due to sepsis at 6 months				

Mortality due to severe diarrhoea at hospital discharge				
Mortality due to severe diarrhoea at 1 month				
Mortality due to severe diarrhoea at 6 months				

Table 6: The effect of probiotic supplementation on secondary outcomes (episodes of necrotising enterocolitis, sepsis, severe diarrhoea) among **preterm children**, primary ITT analysis populations

	Placebo	**Intervention**		
Outcome	**n/pyr (rate)**	**n/pyr (rate)**	**Rate ratio (95% CI)**	**P value**
Episodes of necrotising enterocolitis up to hospital discharge				
Episodes of necrotising enterocolitis up to 1 month				
Episodes of necrotising enterocolitis up to 6 months				
Episodes of sepsis up to hospital discharge				
Episodes of sepsis up to 1 month				
Episodes of sepsis up to 6 months				
Episodes of severe diarrhoea up to hospital discharge				
Episodes of severe diarrhoea up to 1 month				
Episodes of severe diarrhoea up to 6 months				

Table 7: The effect of probiotic supplementation on secondary outcomes (episodes of necrotising enterocolitis, sepsis, severe diarrhoea) among **term SGA children**, primary ITT analysis populations

	Placebo	**Intervention**		
Outcome	**n/pyr (rate)**	**n/pyr (rate)**	**Rate ratio (95% CI)**	**P value**
Episodes of necrotising enterocolitis up to hospital discharge				
Episodes of necrotising enterocolitis up to 1 month				
Episodes of necrotising enterocolitis up to 6 months				
Episodes of sepsis up to hospital discharge				

Episodes of sepsis up to 1 month				
Episodes of sepsis up to 6 months				
Episodes of severe diarrhoea up to hospital discharge				
Episodes of severe diarrhoea up to 1 month				
Episodes of severe diarrhoea up to 6 months				