GAMIN II

MORDOR Project

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Statistical Analysis Plan

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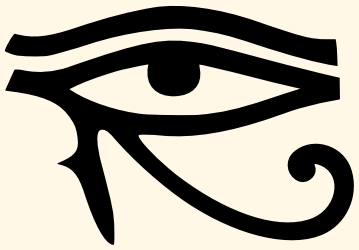

Introduction

This document (Statistical Analysis Plan, SAP) describes the planned analysis and reporting for the clinical trial, **GAMIN II: Gut and Azithromycin Mechanisms in Infants and Neonates in Burkina Faso**. It includes specifications for the statistical analyses and tables to be prepared for the interim and final Clinical Study Report. This study is a Phase IV clinical trial to compare methods to reduce childhood mortality using mass administration of azithromycin (Pfizer, CAS 83905-01-5) compared to placebo. The content of this Statistical Analysis Plan meets the requirements stated by the US Food and Drug Administration and conforms to the American Statistical Association's Ethical Guidelines.

The following documents were reviewed in preparation of this Statistical Analysis Plan:

- Azithromycin for the reduction of child and infant mortality: Longitudinal Component, Manual of Operations and Procedures
- GAMIN: Gut and Azithromycin Mechanisms in Infants and Neonates in Burkina Faso, Statistical Analysis Plan
- Statistical Analysis Plan, MORDOR Trial
- ICH Guidance on Statistical Principles for Clinical Trials

The planned analyses described in this SAP will be included in future manuscripts. Exploratory analyses not necessarily identified in this Statistical Analysis Plan may be performed to support the analysis. Unplanned analyses not delineated in this Statistical Analysis Plan will be documented as such in the final Clinical Study Report and manuscripts. Note that unplanned analyses will be broadly grouped into two categories:

1. Sensitivity analyses for pre-specified outcomes
2. Other unspecified analyses

Sensitivity analyses are defined as alternate ways of modeling the primary outcome to ensure the finding was not dependent on the analytic plan, and these will not be subject to a multiple comparisons correction. Other unspecified analyses will be declared hypothesis generating or subject to an alpha level of 0.001.

This document will be reviewed prior to the enrollment of patients. All subsequent changes will be indicated by detailed change log in the Appendix.

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1 Summary

1.1 Longitudinal Trial

The trial profile is given in the Manual of Operations. In the longitudinal trial, children are randomized to two arms: **Azithro** and **Control**. The trial is a placebo-controlled, double-masked (i.e., double-blind), individual-randomized clinical trial.

Objectives.

Determine the effect of a single dose of azithromycin for children aged 8 days-59 months on rapid diagnostic tests (RDT) for malaria positivity over a 14-day period. Children under 5 years of age will be randomized to a single dose of azithromycin or placebo. *We hypothesize that children randomized to a single dose of azithromycin will have significantly lower RDT positivity after a 14-day period, compared to those randomized to placebo.*

Determine the effect of a single dose of azithromycin for children aged 8 days-59 months on longitudinal changes in the intestinal microbiome over a 6-month period. *We hypothesize that children randomized to a single dose of azithromycin will exhibit a significant difference in the intestinal microbiome after a 6-month period, compared to those randomized to placebo.*

2 Statistical Analysis

2.1 Planned Analyses

2.1.1 Longitudinal Trial

Four hundred fifty children between the ages of 8 days and 59 months may be enrolled in the trial and be offered placebo or azithromycin in a masked fashion. Relevant indicators will be collected using finger prick and fresh frozen stool at days 0, 14, and 180. Children followed up within day 120 and day 240 will be included in primary day 180 analysis.

Primary Analyses. We will compare betweens arms RDT positivity using logistic regression. We will use permutation tests to estimate coefficient p-values.

We will compare profile of *Campylobacter*, *C. upsaliensis* and *C. hominis* based on L_1, L_2 distance, and PERMANOVA. We will compare diversity between arms at days 14 and 180 separately, using Shannon's Index and Simpson's Index.

Subgroup analysis. We will restrict the data set to participants RDT negative at baseline and compare between arms RDT positivity at 14-day visit using logistic regression. We will use permutation tests to estimate coefficient p-values.

Statistical considerations.

- Model adequacy will be checked by examination of residuals or other goodness of fit tests as needed. Inadequate model fit will prompt us to report alternative models.
- Multiple imputation will be used in case of missing baseline covariates (if applicable). Missing outcome variables will be handled by sensitivity analysis and reporting of conditional results.
- False Discovery Rate will be calculated for each estimated significant effect.

3 Sample Size Considerations

We assume 80% power to detect a significant effect. We also assume a sample size of 225 per group, no loss to follow-up, and RDT positivity prevalence in the control group of 10%. Given these assumptions, we estimate a detectable effect difference of -0.0659 in proportion of RDT positive participants.

4 Randomization

The randomization will be conducted using R. The function `sample` with option `replace=FALSE` will be used to conduct the random shuffling. Note that the choice of the random number seed completely determines the randomization.

5 Abbreviations

DSMC Data and Safety Monitoring Committee

RDT Rapid Diagnostic Tests for Malaria

SAP Statistical Analysis Plan

6 Revision History

02 Jul 2020 Example revision.