Standard Operating Procedures for the LAKANA trial
SOP Data 02: Conducting interim analysis
Version 1.0 (2023-06-13)

1. Purpose and overview:

This SOP describes the steps for interim analysis in LAKANA trial. Interim analysis will be carried out when approximately 60% of the target person-years-at-risk has been collected. The interim analysis will consider the mortality and serious adverse event outcomes, and the aim is to have grounds for the decision about the continuation of the trial.

The DSMB may recommend stopping or modifying the trial if:

- In an interim analysis, there is strong evidence of a mortality benefit (reduced mortality) from quarterly or biannual azithromycin MDA (Peto rule, $p<0.001$).

- In an interim analysis, there is suspicion of harm (increased mortality or incidence of other SAEs) from quarterly or biannual azithromycin MDA. For harm assessment, no fixed statistical rules will be applied, but the DSMB will holistically consider point estimates and confidence intervals for mortality / SAE incidence differences, p-values from appropriate statistical tests and other relevant factors, when determining its recommendation about study continuation or discontinuation.

- In an interim analysis, there is strong evidence of futility (mathematical expectation predicting from the accrued data that the major study hypotheses cannot be supported with statistical significance with the originally planned sample size).

The scenarios guiding the decision will be:

1. There are no statistically significant mortality differences between any of the groups
   a. Continue trial as originally planned.

2. There is evidence of a mortality difference between the two azithromycin groups, but neither is statistically different from the placebo group.
   a. Continue trial as originally planned.

3. There is evidence of a mortality benefit in one but not both of the azithromycin groups as compared to the placebo group but no statistically significant difference between the two azithromycin groups.
   a. Continue trial as originally planned.

4. There is evidence of a mortality benefit in both of the azithromycin groups but no statistically significant difference between the two azithromycin groups.
   a. Drop the placebo arm and re-randomize the previous placebo-clusters into either of the two azithromycin groups.

5. There is evidence of a mortality benefit in one or both of the azithromycin groups and also a statistically significant difference between the two azithromycin groups.
   a. Stop the trial.

6. There is evidence of a mortality benefit in one azithromycin group and mortality harm in the other azithromycin group.
    a. Stop the trial.

7. There is evidence of a mortality harm in both of the azithromycin groups.
    a. Stop the trial.

8. There is evidence of a mortality harm in one but not the other azithromycin group and no statistically significant difference between placebo and the other azithromycin group.
    a. Drop the possibly harmful azithromycin arm and re-randomize clusters from this group into the placebo and the other azithromycin groups.

In addition to the aforementioned, the DSMB recommendation to continue or discontinue will be based on a comprehensive analysis, taking into account multiple issues around the trial.

After considering results of the interim analysis, the DSMB will report the LAKANA investigators one of the following recommendations:

a. Continue the trial implementation as planned
b. Continue, but re-randomize control villages into the two intervention villages
c. Stop and break the code: result is clear
d. Stop and break the code: futility
e. Possibly: Suggest increase in sample size, else continue as planned.

The actual findings from the interim analysis will not be shared with the study team members, unless there is a decision to stop the data collection entirely (options c and d above)

2. Applicability to and responsibilities of various staff members

Staff member	**Responsibility**
Trial Data Manager	Prepares the trial data for the DSMB statistician and coordinates the data sharing with CVD data manager
Trial Statistician	Conducts quality assurance on the analytical scripts
External statistician	Provides the treatment codes to the DSMB statistician
DSMB statistician	Runs the analysis on the trial data
LAKANA Principal Investigator (PI)	Member of LAKANA Project Steering Group
LAKANA Co-Principal Investigator (Co-PI)	Member of LAKANA Project Steering Group

3. Required materials

Item	Number	Specification
Data File without explicit group information	1	CSV-formatted file with the trial data for interim analysis
Treatment Code File	1	XLSX-formatted file with letter codes that correspond to placebo/Azithromycin treatment
Merging script	1	File of code that combines treatments (placebo/Azithromycin) to corresponding letter codes and creates the three-category intervention variable
Data file with group information	1	Data file that has the intervention code included as a variable
Analytical script	1	File of code that runs calculations for the inference
Analysis results	1	Pre-agreed tables and figures that will be produced by the Analytical script
Data Dictionary File	1	XLSX-formatted file with variables that are included in the interim analysis data

4. Definitions and general instructions

4.1. Definitions

4.1.1. Trial Data Manager: a LAKANA study team member who governs the data and prepares the data set to appropriate format for analysis.

4.1.2. Trial Statistician: a LAKANA study team member who, in collaboration with the Trial Data Manager, conducts quality assurance tests on the merging script.

4.1.3. External statistician: Person with expertise in data usage who will maintain the Treatment Code File, and who is not a LAKANA researcher.

4.1.4. DSMB statistician: Data Safety and Monitoring Board member with expertise in statistics who will conduct the interim analysis.

4.1.5. LAKANA Co-Principal Investigator: Member of the Project Steering Group with affiliation to CVD Mali, who will share the finalized version of the data to the DSMB and External Statistician.

4.1.6. Data File without explicit group information: CSV-formatted file consisting of the trial data on which the interim analysis on mortality will be conducted on, and that doesn't have the intervention variable included. The data file will be a matrix where each row represents eligible 1-11-month-old child, and columns represent the variables described in the Data Dictionary.

4.1.7. Treatment Code File: XLSX-formatted file consisting of the letter codes used in randomization, and to which class the letters correspond to (control/Azithromycin). At the merging, explicit expressions for each letter pair code (control, biannual, quarterly) as well as the pseudo codes for the groups (ie. "1", "2", and "3") will be included to the Treatment Code File. Example spreadsheet with mock information is presented in Appendix 1. Treatment Code File with pseudo-codes is presented in Appendix 2.

4.1.8. Merging script: Pre-prepared programmatic file of code that combines information from the Treatment Code File into the Data File without explicit group information.

4.1.9. Data file with group information: CSV-formatted file that has gone through the merging process, and thus has the three-category intervention variable included.

4.1.10. Analytical script: Pre-prepared programmatic file of code that runs the statistical models and creates the tables that report the incidence rates, standard errors, and statistical significance between the treatment arms.

4.1.11. Analysis results: Figures and tables presenting the analysis results that guide the DSMB decision.

4.1.12. Data Dictionary File: XLSX-formatted file with variables that are included in the interim analysis data. The variables will be:

- Village Identifier (*string*)
- Child Identifier (*string*)
- Village class: small/big village (*categorical*)
- Group intervention code (*categorical)*
- First MDA for the child (*integer*)
- Last MDA for the child (*integer*)
- Date of first treatment (*date*)
- Date of the last/latest treatment (*date*)
- Follow-up time in days (*integer*)
- MDA when the child was reported dead (*integer*)
- Date of Death (*date*)
- Person-years-at-risk (*numerical*)
- Vital status one year after the first treatment (*categorical*)
- SAE variables (*categorical*)

5. Step-by-step procedures

5.1. Prior to interim analysis, Trial Data Manager in collaboration with Trial Statistician produces programmatic scripts that combine mock treatment code information from a file that is formatted in same way as the actual Treatment Code File, and that run the analyses intended for the interim analysis.

5.2. In collaboration with the DSMB statistician, the Trial Data Manager agree on the contents of the Analytical Script: what will be the input data, and what should the output.

5.3. Once the trial has reached 60% of the target person-years-at-risk, the Trial Data manager will produce a pre-processed Data File without explicit group information and a corresponding data dictionary.

5.4. From the request of the LAKANA Principal Investigators, RTI shares the Treatment Code file with the External Statistician.

5.5. Trial Data Manager will share the merging script with the External Statistician and the External Statistician validates its functionality to a mock data set and mock intervention codes.

5.6. Trial Data Manager will then coordinate the material sharing with LAKANA Co-PI. LAKANA Co-PI will share the Data File without explicit group information in encrypted format to the DSMB statistician and the External statistician. The External Statistician will receive the encryption key via separate encrypted email to access the data.

5.7. The External Statistician will run the Merging Script to create the intervention variable, thus creating the Data File with group information. The group intervention variable will be a categorical variable with values 1, 2, or 3.

5.8. The External Statistician will then encrypt the Treatment Code File with a password and shares the Data File with group information and Treatment Code File with the DSMB statistician. The password for the Treatment Code File will be shared with the LAKANA Principal Investigators, and the DSMB may request the password should they find it necessary to open the Treatment Code File to verify the true intervention groups.

5.9. The External Statistician will delete the received data after completing the data sharing.

5.10. The DSMB statistician will run the Analytical Script, that produces the result tables and figures necessary for guiding the decision-making process.

5.11. The DSMB will make the decision on the recommendation on continuing the trial and informs the LAKANA Principal Investigators on the decision.

5.12. The DSMB statistician will delete the data after the decision on recommendation on continuing the trial has been made.

6. Occupational Safety Issues

None

7. Quality Assurance / Quality Control

The scripts will be tested beforehand using mock codes by the trial team. Trial Data Manager will propose drafts of code to the Trial Statistician, and the Trial Statistician will test the scripts with the mock code file and suggests corrections to the proposition should they be necessary. Trial Data Manager also discusses with the DSMB statistician to ensure both parties agree on how the information merging should happen, and how the analysis will be conducted.

8. Appendices and other related documents

Document number (Version)	Document content
Appendix 1 (1.0)	Example of mock Treatment Code File
Appendix 2 (1.0)	Example of mock Treatment Code File with pseudo-codes

9. Version history, authors and approvals

Version (date)	Edits to the SOP text (author)
1.0 (2023-06-13?	Original document (Juho Luoma). Approved by the LAKANA PSG.

Appendix 1: Example of mock Treatment Code File

Letter	Random intervention
A	Placebo
B	Azithromycin
C	Placebo
E	Placebo
F	Placebo
G	Azithromycin
H	Placebo
J	Placebo
K	Azithromycin
N	Placebo
P	Azithromycin
R	Azithromycin
S	Placebo
T	Azithromycin
U	Placebo
X	Azithromycin
Y	Azithromycin
Z	Placebo

Intervention type	Jan - June group	Jan - June intervention	Jul - Dec group	Jul - Dec intervention
Control	A	Placebo	F	Placebo
Control	H	Placebo	C	Placebo
Control	E	Placebo	J	Placebo
Azi-biannual	B	Azithromycin	N	Placebo
Azi-biannual	G	Azithromycin	S	Placebo
Azi-biannual	K	Azithromycin	U	Placebo
Azi-biannual	P	Azithromycin	Z	Placebo
Azi-quarterly	T	Azithromycin	R	Azithromycin
Azi-quarterly	X	Azithromycin	Y	Azithromycin

To re-randomise, write a new number to orange cell O3 and hit tab

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Combination number	June group	Jul - Dec group
1	T	R
2	H	C
3	X	Y
4	P	Z
5	E	J
6	B	N
7	A	F
8	K	U
9	G	S

Appendix 2: Example of mock Treatment Code File with pseudo-codes

Letter	Random intervention	Pseudo-code
A	Placebo	1
B	Azithromycin	2
C	Azithromycin	3
E	Placebo	2
F	Azithromycin	2
G	Placebo	2
H	Placebo	1
J	Azithromycin	2
K	Placebo	1
N	Azithromycin	3
P	Azithromycin	2
R	Placebo	2
S	Placebo	1
T	Azithromycin	2
U	Azithromycin	2
X	Placebo	2
Y	Placebo	2
Z	Placebo	2

Bin mapping | Treatment arms

Pseudo-code	Treatment arm
1	Placebo
2	Azithromycin, Placebo
3	Azithromycin

Bin mapping | Treatment arms