Standard Operating Procedures for the LAKANA trial
SOP Proc-01: Provision of study drug
Version 5.0 (2020-11-17)

1. Purpose and overview:

The purpose of this SOP[1] is to provide detailed instructions on how to prepare and administer study drug to eligible infants participating in the LAKANA trial. This SOP refers to data collection forms (DCF) DCF02 and DCF02a.

2. Applicability to and responsibilities of various staff members

Staff member	Responsibility
LAKANA Data collector	- Provides information about treatment process to caregiver, requests consent for study drug provision. - Prepares study drug. - Administers study drug.
Relais Communautaire	- Facilitates discussion with caregiver

3. Required materials

Item	Number	Specification
Weighing scale	1	Electronic baby hanging scale.
Batteries for weighing scale	*Number required*	
Medical disposal paper sheet	*Number required to meet the daily target*	Paper sheet to be placed in the weighing sling/trouser designed for single use that can be discarded after each infant to help in preventing cross-infection.
Commercial drinking bottled water	1	Water to be used for study drug reconstitution: Bottle of 500 ml (15 ml is needed to reconstitute one drug bottle)

[1] Abbreviations: SOP = standard operating procedure, LAKANA = Large-scale Assessment of the Key health-promoting Activities of two New mass drug administration regimens with Azithromycin, DCF = Data Collection Form, CSCom = Centre de Santé Communautaire, FAQ = Frequently Asked Question.

Item	Number	Specification
Disposable cup	*Number required to meet the daily target*	To transfer water from bottled water and measure 15 ml to reconstitute a bottle of study drug.
Study drug bottle	*Number required to meet the daily target*	Each bottle of study drug contains the same amount of dry powder, either including 1.2 g of azithromycin or respective amount of placebo powder.
Plastic disposable syringe	*Number required to meet the daily target*	Volume: 5ml; 0.2ml graduations
Bag for waste collection	1	
Tablet computer	1	Data collection tablet Samsung Tab A 9-inch GSM tablet, model number SM-T295. The Tangerine application will be used to conduct the data collection process. The LAKANA App (providing access to SOPs, FAQs) will be installed.
Personal Protective Equipment (PPE) individual kit	1	1 Kit/ LAKANA staff member (For details on the kit composition and utilization, refer to *SOP-Safety 01 Hygiene and PPE*)

4. Definitions and general instructions

4.1. Definitions

4.1.1. Eligible infant: Infant aged between 1 and 11 months (age 29-364 days) and weighing at least 3.0 kilograms at the time of study drug provision, and for whom there is no record of allergy to macrolides.

4.1.2. Caregiver: person who is responsible for looking after a child. The caregiver is the individual responsible for providing consent for study drug administration to eligible infants.

4.1.3. Study drug: Azithromycin or placebo powder packed in non-opaque, plastic bottles. Study drug bottle are labelled with a letter code. At any village (cluster), all infants will receive study drug of the same letter code, one for visits between January and June and the other one for visits between July and December (there will be a total of 9 two-letter study drug regimens, of which 3 will be allocated to control (both letter codes for placebo), 2 will be for azithromycin-quarterly

(both letter codes for azithromycin) and 4 will be for azithromycin-biannual (one letter code for placebo, the other one for azithromycin).

4.2. General instructions

4.2.1. During the Covid-19 epidemic, physical distancing will be enforced: a distance of at least 1 meter (3.3 feet) will be maintained between any two individuals (exception will apply when administering the study drug to an infant).

4.2.2. The data collection team members will wear a mask at all times when in a village.

4.2.3. The data collector will explain the purpose and process for the treatment verbally to each 1-11- month-old infant's caregiver and seek permission to provide study drug.

4.2.4. For each infant for whom a caregiver has given a permission, the data collector will check eligibility criteria i.e. having no allergy to macrolides and weight above 3.0 kg.

4.2.5. An infant whom the data collector considers very sick and needing a referral to a health facility for diagnostics or treatment or who can not swallow oral medication, will not be treated. Before making a non-treatment decision, the data collector will consult a study coordinator or study physician. In such cases, there is no plan for a revisit for giving the child study drug during this MDA cycle.

- Infants with non-severe illness will be treated normally, unless a caregiver refuses it. If the infant has respiratory symptoms, the data collectors will follow national guidelines on possible referral for covid-19 testing.

4.2.6. Study drugs are packaged in powdered form and need to be reconstituted prior to administration. For consumption, a study drug bottle will be reconstituted with 15 ml of clean commercial bottled water to make 30 ml of study drug suspension.

4.2.7. At any village (cluster), all infants will receive study drug of the same letter code. Hence, a bottle can be reconstituted and used for several infants on the same day. The data collector will make sure that a bottle that has been opened is emptied before opening a new one.

4.2.8. The dose given to eligible children will be 20 mg / kg, i.e. 0.5 ml / kg, rounded up to the nearest 0.2 ml. The daily dose (ml) of study drug to provide will be automatically calculated based on infant's weight recorded in the tablet computer.

4.2.9. The data collector will measure the dose of reconstituted drug to be given and will give the dose to each eligible infant. The sterile syringe is a single use device i.e. designed to be used once, for a single infant, and then disposed of.

- If the team is composed of 3 members, the data collector will prepare the study drug dose, one member will verify that the dose is correct.

4.2.10. If the data collector becomes aware that an infant has vomited soon after the study drug ingestion (within approximately 15 minutes), a new similar-size dose will be given to the infant in question.

4.2.11. There will not be any planned observation period of the infant immediately after the study drug administration, but the data collector will instruct the caregivers to: 1) seek the help of a health professional/visit a health facility if the child gets any major symptoms in the next 14 days, and 2) notify the event to a Relais or a LAKANA data collector or supervisor.

5. Step-by-step procedures

5.1. Caregiver consent

5.1.1. The data collector will provide information to the 1-11- month-old infant's caregiver about the purpose and process of the treatment verbally.

5.1.1.1. The data collector will answer any questions that may arise (*Refer to FAQs*).

5.1.2. The Relais Communautaire and the data collector will request a permission to weigh and provide study drugs.

5.1.2.1. The caregiver response will be given verbally, and the data collector will document it electronically in the tablet computer (form DCF02).

5.1.3. If the caregiver is not authorized to provide consent, the data collector will record the information, stop and return later.

5.1.4. If consent is not granted, the data collector will thank the caregiver, and record the refusal.

5.1.5. If consent is granted, recording the approval in the tablet computer will unlock the treatment form DCF02 and allow further data collection.

5.1.6. During the Covid-19 epidemic, the consent seeking procedure will primarily happens outdoors and in a private space: the data collection team will ask the caregiver to come out of the household with the concerned infant. If consent is granted, the data collection team will implement the data collection and treatment-related activities outdoors.

5.1.6.1. If the activity must be carried out indoors, the data collection team will make sure to use the most well-ventilated areas available.

5.1.6.2. As far as possible, the data collection team will ensure adequate privacy for administering trial drug/conducting interviews.

5.2. Infant Eligibility verification

5.2.1. Check Allergies

5.2.1.1. The data collector will ask the caregiver if the infant is allergic to azithromycin or to any other macrolide antibiotics.

- If available, the data collector will check the infant's health card or any other health document to verify if the information is reported.

- If there is no health document available, the data collector will rely on the information that the caregiver reports.

5.2.1.2. If the infant is allergic to macrolides, the data collector will record the information, explain to the caregiver that the infant cannot be treated and will not participate in the trial, and thank the caregiver.

5.2.1.3. If the infant is not allergic to Azithromycin or any other macrolide antibiotics, the data collector will proceed with measuring the infant's weight.

5.2.2. Measure weight

5.2.2.1. The Relais Communautaire is a familiar figure to infants in the community which can help minimize possible resistance, fear or discomfort. Thus, s/he will assist the data collector during the weighing procedure.

5.2.2.2. Weighing requires touching and handling an infant, Measurer and Assistant will disinfect their hands using the hand sanitizer provided in the PPE kit before and after handling an infant.

- During the Covid-19 epidemic, the data collection team will enforce extra precaution measures: before weighing a child, the data collector will make sure to position a disposal paper sheet in the weighing sling/trouser before placing an infant. The data collector will remove the paper once the infant is measured and place a new one before measuring the next child.

5.2.2.3. The data collector will explain the weighing procedure to the caregiver.

5.2.2.4. Step-by-step guide for taking the child weight using the scale is described in Appendix 1.

5.2.2.5. The data collector will record the child weight in Kilograms (Kg) with 3 decimal places into the tablet computer.

- The weight will determine infant eligibility and, if eligible, the drug dose to be given, it is thus very important to cautiously report the measure into the tablet computer.

5.3. Study drug preparation and administration

5.3.1. Drug Preparation:

5.3.1.1. The data collector must apply hand sanitizer provided in the PPE kit before and after study drug preparation.

5.3.1.2. The steps for reconstituting the study drug supplied in powdered form are:

- Tap the bottle to loosen powder.
- Open the bottle by removing the cap.
- Transfer a small amount of clean commercial bottled water in a clean disposable cup. Measure 15 ml of water using a sterile syringe (take three times 5 ml with the syringe) and pour the water into the drug bottle.
    - Do not discard the syringe, it will be used to treat the first child.

- Replace the drug bottle cap and shake vigorously to dissolve all the powder. The total volume of the study drug suspension will be 30 ml.
- Mark on the bottle's label the date the study drug was reconstituted.
- A bottle reconstituted can be used for several participants on the same day. Reconstitute a new bottle only after running out of an old one.

5.3.2. Drug Administration:

5.3.2.1. The Data collector must apply hand sanitizer provided in the PPE kit before and after study drug administration.

5.3.2.2. The steps for the data collector for preparing the study drug to an eligible infant are:

- Check on the tablet computer the dose (ml) of study drug to administer.
- Shake the study drug bottle well just before measuring a dose.
- Remove the bottle cap and place the bottle on a firm, flat surface. Hold it steady with one hand, and with the other hand insert a sterile syringe into the bottle and draw the prescribed dose. Make sure only the sterile syringe, and not your finger, touches the liquid.
    - For the first child to treat after a drug bottle has been reconstituted, use the syringe that was used for drawing water from the cup.
- Replace the cap on the bottle.
- Ask the mother/caregiver to bring the infant and to hold him/her while s/he is treated. The mother/caregiver will hold the infant at a 45-degree angle.
- Put the tip of the syringe carefully into the infant's mouth.
- Point the tip of the syringe towards the inside of the infant's cheek.
- Slowly push down the plunger of the syringe: Do not squirt it out quickly.
- Allow the child some time to swallow the drug.
- While administering the drug, do not hold the child's nose closed, shake the child or push the head backwards to force the child to swallow.
    - If a child is uncooperative or anxious, ask the caregiver to calm the child, before administering the drug.
    - If after multiple attempts to administer the drug (try at least 10 mins), the child keeps resisting and cannot calm down, the data collector should register the child as having refused the drug, stop and come back on the following day for a new attempt.
- Once a child is treated, record the information on the tablet computer (form DCF02).
- Place the syringes used and other waste in the designated waste bag.

5.3.2.3. Thank the caregiver and advise him/her that in case the infant vomits within approximately 15 minutes, he/she should alert the LAKANA Staff so that the infant can be re-treated (form DCF02a).

- Specify to the caregiver that if the vomiting happens later than 15 minutes after drug administration, there is no need to contact the staff.

5.3.2.4. Instruct the caregivers to 1) seek the help of a health professional/visit a health facility if the child gets any major symptoms in the next 14 days, and 2) notify the event to a Relais or LAKANA data collector or supervisor.

6. Occupational Safety Issues

In a non-epidemic situation, there are no specific occupational safety issues.

During the COVID-19 epidemic, procedures for safe and proper work will be used to reduce the risk of exposure to a hazard and prevent transmission between the study team and the study participants. Special considerations due to COVID-19 are presented *SOP-Safety 01 Hygiene and PPE*.

7. Quality Assurance / Quality Control

See SOP Pharm 01 Study drug management.

8. Appendices and other related documents

Document number	**Document content**
Appendix 1	Step by step guide for measuring a child weight

9. Version history, authors and approvals

Version (date)	Edits to the SOP text (author)
Version 1.0 (2020-08-25)	Authored by Laura Adubra in consultation with LAKANA investigators. Approved by the LAKANA PSG
Version 2.0 (2020-09-24)	Updated instructions on actions if a study infant has illness symptoms (4.2.5). Authored by Laura Adubra, approved by the LAKANA PSG.
Version 3.0 (2020-10-07)	Edits: Record weight in kg with 3 decimal places (5.2.2.5) Authored by Laura Adubra, approved by the LAKANA PSG.
Version 4.0 (2020-10-20)	Edits: Removed drug provision from the responsibilities of the Relais. The data collector will handle both drug preparation and administration (Edits in Table 2; section 4.2.9, sections 5.3.2.1 and 5.3.2.2) Authored by Laura Adubra, approved by the LAKANA PSG.
Version 5.0 (2020-11-17)	Changed instructions regarding study drug administration to infants with illness (section 4.2.5). Authored by Laura Adubra, approved by the LAKANA PSG.

Appendix 1: Step by step guide for measuring a child weight

1. **Assistant:** Using the hook designed as a handle, hold the scale with your hand.

2. **Measurer:** Fix the pair of weighing pants/sling to the lower edge of the scale by the second hook, position a disposal paper sheet in the weighing sling/trouser, and calibrate to zero; then remove the pants/sling.

3. **Measurer:** Ask the caregiver to remove the infant's clothing.

    - *Infants should be weighed with minimal clothing (if possible, remove diaper before weighing).*

    - *If blankets or cloth are required, the scale will be recalibrated with the item on the scale before weighing*.

4. **Measurer:** Put your arms through the leg holes of the weighing pants (if used). While the caregiver holds the child, grasp the child's feet and pull his or her legs through the leg holes. Make sure that the strap of the pants is in front of the child. OR (if sling used) place the infant on his/her back in the weighing sling.

    - *If a child is under severe stress and is crying excessively, the data collector will return the child to the caregiver for a moment until he/she has calm down before proceeding with the weighing.*

5. **Measurer:** Attach the strap of the pants/sling to the lower hook of the scale held by the assistant. Do not carry the child by the strap alone.

6. **Measurer:** Allow the child to hang free.

7. **Assistant:** Keep the child under observation, check the child's position and make sure s/he is hanging free and not touching anything. Make sure that nobody touches the pants or the scale during weighing.

8. **Measurer:** When the baby is stable and the scale reading is not changing, the data collector will record the weight in Kg with 3 decimal places into the tablet computer.

9. **Measurer:** remove the child slowly and safely. If weighing pants used, do not lift the child by the strap of the weighing pants; Take hold of the child in one arm and gently lift him/her; release the strap from the hook of the scale with the free hand. Discard (in the bag for waste collection) the disposal paper sheet placed in the weighing sling/trouser.