Standard Operating Procedures for the LAKANA trial
SOP Pharm-01: Drug Management
Version 4.0 (2021-05-11)

1. Purpose and overview:

The purpose of this SOP[1] is to describe the procedure for documenting the receipt of clinical trial drug supplies, the dispensing, use and accountability of the supplies, the handling of damaged bottles and disposal of drug bottles.

2. Applicability to and responsibilities of various staff members

Staff member	Responsibility
Study Pharmacist (CVD-Mali Bamako)	• Maintains and submits all study drug documentation needed for the trial. • Receives study drug from Pfizer and oversees storage at the CVD Mali central storage facility in Bamako. • Communicates with LAKANA personnel about the study drug supply and guidelines for storage at all levels. • Notify temperature excursion events to principal investigators. • Oversees disposal process of study drugs.
Drug manager (at Kita hub/district hub)	• Orders study drugs and makes trips to Bamako to retrieve the supplies. • Monitors and records the temperature of the CVD Mali storage facility in the Kita hub/district hub and reports to the study pharmacist. • Communicates with field supervisors.
Field supervisor	• Manages study drugs at the data collection hub. • Prepares study drugs supply for selected villages. • Distributes the drugs to data collectors on the day of administration. • Writes and transmits administration and accounting reports to the district supervisor. • Manages the used drugs bottles.

[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, CSCom = Centre de Santé Communautaire, MDA = Mass Drug Administration.

3. Required materials

Item	Number	Specification
Study drug importation log	1	At the main storage facility and at the district level.
Study drug administration and accounting log	1	
Study drug temperature log	1	Stock cards at the storage facility.
Study drug disposal certificate	1	In Kita and Bamako for incineration of bottles used.
Thermometer Min/Max (Delta logger) with warning light.	3 per storage facility	3 thermometers per room (+1 back up) for central storage facility in Bamako and secondary storage facilities in Kita Hub/Another District hub. Those thermometers record the temperature and it is possible to download the data recorded.
Min-Max thermometer min/max with audible alarm.	2 per storage facility	To be used at storage facilities (central, secondary, data collection hubs) and for monitoring temperature during transport.
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

4.1.1. Study Drug (SD): 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 (for each cluster, we will use bottles with two letter codes, one for visits between January and June and the other one for visits between July and December).

4.1.2. Temperature excursion: an event in which the study drug is exposed to temperatures outside the range prescribed (i.e. between +15 ° C and + 30 ° C) for storage and/or transport.

4.1.3. Central storage: central facility identified by the country for the longer-term storage of the study drugs. In Mali, the location of the central storage will be CVD-Mali in Bamako.

4.1.4. Secondary storage: refers to a hub with the required capacities for storage of study drugs at the district level. Kita hub is a secondary storage hub.

4.1.5. Drug manager: a LAKANA staff member in charge of managing study drugs at the Kita hub or at another district.

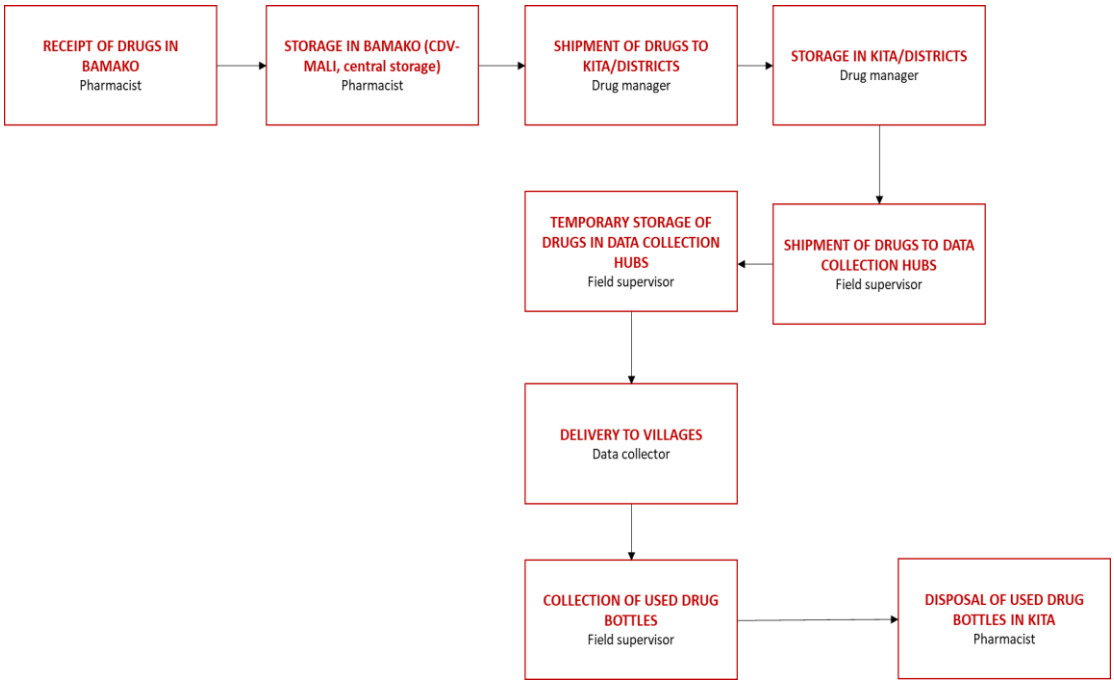
4.1.6. Field Supervisor: a LAKANA staff member responsible for coordinating data collection teams' activities and for managing study drugs at a data collection hub.

4.1.7. Data collection hub: a secure location where the research team will preposition drugs and other study material prior to village MDAs. Daily activities such as packing of rucksacks, meetings with data collection team and data transmission will be carried out at a hub (a CSCom can be a data collection hub).

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.

4.2.2. There will be 9 separate phases for the study drug management as illustrated below. The detailed instructions for each phase are described in *Section 5 Step-by-step procedures*.



5. Step-by-step procedures

5.1. Receipt of drugs in Bamako (central storage facility)

5.1.1. Pfizer logistic officer and the freight forwarder from World Courier will ship study drugs to Mali annually. The Finnish PI will discuss the details with Pfizer team for arranging the shipments.

5.1.1.1. Due to the ongoing Covid-19 epidemic, flight restrictions may impact the planned frequency of shipment.

5.1.1.2. An Import License for the study drugs is required and is to be renewed every 6 months. The Malian co-PI and study pharmacist will make sure there is a valid Import License.

5.1.2. The study pharmacist will receive study drugs and all importing documents at the central storage facility.

5.1.3. Upon receipt, the study pharmacist will inspect the shipment and record on the study drug receipt form: the date, time, batch numbers, temperature, number of drugs containers delivered classified by letter code, and quantity of study drugs bottles delivered. He will send a copy of the drug receipt form to the Finnish PI and Malian co-PI.

5.1.3.1. The study pharmacist will verify that the shipping slip and labels from the supplier specify the quantity of study drug received.

5.1.3.2. The study pharmacist will open the Active Shipping Containers (Cocoons) to count the total number of cartons, the number of containers per carton, and the total number of study drug bottles received.

5.1.3.3. The study pharmacist will verify that the number of drugs bottles marked on the container matches the number specified on the receipt or invoice from the supplier.

- The contenair will not be opened to count the number of drug bottles. The study pharmacist will only count the number of contenair and estimate the number of bottles. One contenair contain 48 bottles of the same letter code. The container has a bar code and letter code identical to the bottles inside.

5.1.4. After filling the study drug receipt form and for each study drug carton, the study pharmacist will scan the bar code to link the carton to the individual study drug bottles inside.

5.1.5. The study pharmacist will keep the shipping slip and all the shipping documents in a Study Drug Accountability Binder.

5.2. Storage of drugs in Bamako (central storage facility)

5.2.1. The study pharmacist and his team will move the containers with the drugs to a lockable, temperature-controlled room reserved for drug storage.

5.2.2. The study pharmacist will make sure that the temperature is continuously monitored and maintained between +15 and +30°C. At the storage facility, a min/max thermometer will be installed in addition to two data loggers.

5.2.2.1. If the data loggers record a temperature outside of the set temperature range, they will show a red light.

5.2.2.2. If the min-max thermometer records a temperature outside of the set temperature range, it will give an audible alarm as well as show a red light.

5.2.2.3. The alarms of the thermometers will have narrower range set (14-31°C) and will be used to keep the study drug within the study drug temperature range. The temperatures from these min-max thermometers will not be recorded and are only to prevent an excursion.

5.2.3. Two times daily, the study pharmacist will check (visual checking) the data loggers. The study pharmacist/other designated person will record the current temperature displayed on the data logger, the time, and his initials on the paper log available at the storage facility.

5.2.3.1. Temperature excursions: Upon a visual inspection, if either data logger is outside of range (the red light is flashing), the study pharmacist/other designated person will follow the steps outlined in *Appendix 1 Management of excursion event*.

5.2.4. The study pharmacist will export the data from the data logger on a weekly basis.

5.2.4.1. The study pharmacist will proceed with one data logger at a time so that there is constant temperature monitoring.

5.2.5. The study pharmacist will share the records with CVD-Mali researchers and Project Steering Group members through a designated mailing list.

5.3. Shipment of drugs from Bamako central storage to Kita secondary storage hub (and other secondary storage hubs at district level)

5.3.1. The drug manager, in consultation with the district supervisor, in Kita hub (and other districts hubs) will prepare orders for study drug supply and send the request via e-mail to the study pharmacist in Bamako.

5.3.2. Shipment preparation:

5.3.2.1. The study pharmacist will prepare the orders accordingly to the needs specified. The study Pharmacist will agree with the drug manager on the date for picking up the supplies in Bamako so that the drug manager can prepare his trip to retrieve the supplies.

5.3.2.2. The study pharmacist will place the study drugs in isolated boxes. The study pharmacist will prepare the boxes the day before delivery and the temperature will be monitored and recorded every 30 minutes until it stabilized within the specified temperature range (between 15 ° C and 30 ° C).

5.3.2.3. The study pharmacist will make sure to equip each box with a min/max thermometer or a data log thermometer and with a sensor to monitor the temperature during transport to storage location at the district level. The study pharmacist will place the sensor of the thermometer in an appropriate carton and he will place the carton in the isolated box.

- The study pharmacist will add accumulators in the boxes if the temperature is too high or remove accumulators if the temperature is too low. The study pharmacist will not place the sensor directly on the accumulators and always place the study drugs in a carton before placing them in a box.

5.3.2.4. For transport, the study pharmacist will make sure that a second box containing frozen/non frozen accumulators is available. The accumulators will be used if the temperature rise above 30 ° C or decrease below 15 ° C.

5.3.2.5. The study pharmacist will record date and time in the study drug log for every study drug shipment prepared.

5.3.3. Transport (if the study drugs are transported via the frigonette, no need to use the isothermal boxes):

5.3.3.1. The drug manager will pick up the boxes at the central storage facility.

5.3.3.2. The drug manager will arrange the transport of the study drugs in an air-conditioned vehicle (*frigonette*) in a temperature-controlled environment, or in isothermal boxes equipped with air conditioning accumulators (ice box reservoirs).

5.3.3.3. During transportation process, the drug manager will monitor the temperature of the boxes or *frigonette* and he will document it on the temperature sheet at departure and upon arrival.

5.3.3.4. If during the process the temperature has gone outside of the study drug temperature range in an isothermal box, the drug manager will adjust the temperature by removing or adding accumulators.

- Once the temperature has been adjusted, the drug manager will notify the excursion event as soon as possible. He will lock the box until further notice (*see Appendix 1 for management of excursion event*).

5.4. Storage in Kita secondary storage hub (and other secondary storage hubs at district level)

5.4.1. Once the study drugs arrived in the Kita hub (or other district hub), the drug manager will make sure that the temperature is continuously monitored and maintained between +15 and +30°C. The drug manager will follow the steps described in *section 5.2.2 to section 5.2.4.*

5.4.2. The drug manager will send the records from the data loggers via e-mail to the study pharmacist.

5.4.3. The study pharmacist will review the records and share with CVD-Mali researchers and Project Steering Group members through a designated mailing list.

5.5. Shipment of drugs from Kita secondary storage hub (and other secondary storage hubs at district level) to data collection hubs.

5.5.1. The field supervisor will prepare orders for study drug supply required for each data collection hub and send the request via e-mail to the drug manager of the concerned district.

5.5.2. Shipment preparation:

5.5.2.1. The drug manager will prepare the orders accordingly to the needs specified.

5.5.2.2. The drug manager will place the study drugs in isolated boxes. The drug manager will prepare the boxes the day before delivery and the temperature will be monitored and recorded every 30 minutes until it stabilized within the specified temperature range (between 15 ° C and 30 ° C).

5.5.2.3. The drug manager will make sure to equip each box with a min/max thermometer or a data log thermometer and with a sensor to monitor the temperature during transport to sites. The drug manager will place the sensor of the thermometer in an appropriate carton and he will place the carton in the isolated box.

- The drug manager will add accumulators in the boxes if the temperature is too high or remove accumulators if the temperature is too low. The drug manager will not place the sensor directly on the accumulators and always place the study drugs in a carton before placing them in a box.

5.5.2.4. For transport, the drug manager will make sure that a second box containing frozen/non frozen accumulators is available. The accumulators will be used if the temperature rise above 30 ° C or decrease below 15 ° C.

5.5.2.5. The drug manager will record the date and time of departure in the study drug log for every study drug shipment prepared.

5.5.3. Transport (if the study drugs are transported via the frigonette, no need to use the isothermal boxes):

5.5.3.1. Prior to village MDAs (< 1 week), the field supervisor will transport drugs from Kita hub (or other district hubs) to the data collection hubs under his supervision. For villages close to district offices, the drug will be kept on site.

5.5.3.2. The field supervisor will transport the drugs in an air-conditioned vehicle (*frigonette*) in a temperature-controlled environment, or in isothermal boxes equipped with air conditioning accumulators (ice box reservoirs).

5.5.3.3. During transportation process, the field supervisor will monitor the temperature of the boxes or *frigonette* and he will document it on the temperature sheet at departure and upon arrival.

5.5.3.4. If during the process the temperature has gone outside of the study drug temperature range in an isothermal box, the drug manager will adjust the temperature by removing or adding accumulators.

- Once the temperature has been adjusted, the field supervisor will notify the excursion event as soon as possible. He will lock the box until further notice (*See Appendix 1*).

5.6. Temporary storage at the data collection hubs

5.6.1. Once the study drugs arrive in a data collection hub, the field supervisor will move the boxes with the drugs to a lockable room reserved for LAKANA drugs storage. Only the field supervisor will have the keys of the storage room.

5.6.1.1. The field supervisor will keep the drugs at the data collection hub for less than a week and there will be no formal monitoring of temperature in the storage room.

5.6.2. The day before entry in a village, the field supervisor will choose the data collectors and pack the rucksacks at the data collection hub.

5.6.2.1. For villages close to a district office, the district office itself will be the data collection hub, thus the packing will happen on site.

5.6.3. The field supervisor will make sure when packing that the right drug (i.e. intended for the village to be visited) is selected.

5.7. Delivery of study drugs to villages

5.7.1. In a village, the drug bottles will be stored in the data collector's rucksack or, if available, in a cooler box.

5.7.1.1. If drugs are kept in a cooler box, the data collectors will record twice a day the temperature. The data will be documented in the dedicated registry.

5.7.2. In a village, each data collector accompanied by 1 or 2 Relais will administer study drugs to eligible infants in the village (*See SOP Proc 01*) and will report to the field supervisor at the end of each day.

5.7.2.1. The data collectors will return the remaining reconstituted drugs to the field supervisor, as well as remaining unused drugs (still in dry format) to the field supervisor who will follow the procedure described in section 5.8.1.

5.7.2.2. The field supervisor will collect the syringes that were used to provide study drugs to infants in a waste bag for incineration on site or at the district level.

5.8. Study drug collection and disposal

5.8.1. At the end of each week, the field supervisor will collect and organize the drug bottles in dedicated boxes (used bottles and unused drugs that have been stored in rucksacks kept separate from unused drugs that have been stored in a cooler box). S/he will return the bottles to Kita hub.

5.8.2. Upon receipt, the Kita hub drug manager will:

5.8.2.1. Place the opened bottles and unused ones that were kept in rucksacks in a "to be discarded" pile.

5.8.2.2. Check temperature logs, for the unopened bottles. If temperature excursions occurred, these bottles will also be added to the "to be discarded" pile. If no excursions detected, the drug manager will temporarily store the bottles in a dedicated storage space. The bottles will be re-used (i.e. sent back to field) the next working day when the same letter code will be used

5.8.2.3. Every 3 months, the study pharmacist, in consultation with the drug manager, will prepare and transmit a disposal report to the Finnish PI and Malian co-PI and seek their approval for proceeding with the incineration of the used bottles.

5.8.2.4. Upon approval from PIs, the study pharmacist will proceed with the disposal process in attendance of the study monitor, the study coordinator, and the drug manager.

5.8.2.5. The study pharmacist will prepare a report of the disposal procedure (Study drug disposal certificate) with photos attesting of the event. He will share the report to CVD-Mali researchers and Project Steering Group members via the designated mailing list.

5.8.3. Disposal of bottles exposed to temperature excursion:

5.8.3.1. The study pharmacist will proceed as instructed by Pfizer.

6. Occupational Safety Issues

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

During 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 in *SOP-Safety 01 Hygiene and PPE*.

There will be a fire extinguisher in the storage facility in Bamako which will be checked regularly by the pharmacy personnel. The pharmacy personnel will be trained to use the extinguisher.

7. Quality Assurance / Quality Control

8. Appendices and other related documents

Document number	Document content
Appendix 1	Management of Temperature excursions.

9. Version history, authors and approvals

Version (date)	**Edits to the SOP text (author)**
Version 1.0 (2020-08-25)	Authored by Mamoudou Kodio and Laura Adubra in consultation with LAKANA investigators. Approved by LAKANA PSG.
Version 2.0 (2020-10-09)	Removed instruction to monitor rucksack temperature with thermometers during village MDAs (former 5.6.4) Authored by Mamoudou Kodio and Laura Adubra. Approved by LAKANA PSG.
Version 3.0 (2020-11-17)	Added precision that when in a village, drugs are stored in data collectors' rucksacks or cooler box (if available) (section 5.7.1) Authored by Mamoudou Kodio and Laura Adubra. Approved by LAKANA PSG.
Version 4.0 (2021-05-11)	Added precisions on procedures to follow when unused drugs (still in dry format) are returned to Kita pharmacy(sections 5.7.1.1 / 5.8.1 / 5.8.2.1-5.8.2.2). Authored by Mamoudou Kodio and Laura Adubra. Approved by LAKANA PSG.

Appendix 1: Management of Temperature excursions

Management of Temperature excursions at Bamako/Kita/Data collection hub /during transport

The data loggers will be equipped with an audible and light alarm for the detection of temperature excursions. In the event that the data loggers record a temperature outside of the set temperature range, they will show a red light. In the event that the min-max thermometer records a temperature outside of the set temperature range, it will give an audible alarm as well as show a red light.

If at any point the study pharmacist, the drug manager, or the field supervisor checks the data logger or the min/max thermometer and the alarm has gone off, the following steps must be taken:

1. Move drugs to a correct temperature (if possible).
2. Identify the cause of the deviation and resolve the issue as quickly as possible (e.g. Adjust the air conditioning to bring the temperature back into the study drug temperature range or Remove or add accumulators into the box containing drugs (if applicable) or Adjust the air conditioning in the vehicle during transport (if applicable)).
3. Note the time that the excursion started on the study temperature log
4. Affix a label on the affected drug container stating: Do not use until further notice, pending the PIs approval.
5. Drug manager/Field supervisor: Call the study pharmacist and notify the excursion event and explain the measures taken.
6. Study pharmacist: Call the Malian co-PI and Finnish PI to notify the excursion event and explain the measures taken.
7. Move drugs back (if applicable)
8. Inform Study pharmacist/PIs that drugs were returned (if applicable)
9. Fill in the protocol deviation form

Any time an excursion is reported at any level, the study pharmacist, in consultation with the Malian co-PI and Finnish PI, will prepare a report and submit it to Pfizer via e-mail and to the designated mailing list.

1. Pfizer will respond with information regarding whether the drug can be released or must be destroyed, and the study pharmacist will follow their instructions.
2. If the drug can be released, it can be reintegrated into regular usage.
3. If the drug cannot be used, it must be destroyed, following instructions from Pfizer.