Title	**Procedures for storage and shipment of study medications**
SOP Code	2R2 SOP14_06Jul2020
Effective Date	06 July 2020

1.0 Purpose

The objective of this standard operating procedure (SOP) is to describe the procedures to follow for storage and shipment of study medication during the trial.
Information on study medication dispensing and recording are given in SOP04 (Blinding and dispensing of study medication) and are specific for each site.

The SOP will ensure:

- that actions are in compliance with the standards of Good Clinical Practice
- the safety and protection of study participants
- the quality of the data produced by the study

2.0 Persons/Areas affected

This SOP concerns the site principal investigators and the person in their respective research teams, involved in conducting research with human participants for the study entitled – $2R^2$- *Higher dose Rifampin for 2 months vs Standard dose Rifampin for Latent TB: a 3-arm randomized trial.*

3.0 Responsibilities.

The trial coordinating center is responsible for developing and maintaining this SOP and for making it available at the clinical research site. At the clinical trial site, the site principal investigator is responsible for adoption of the processes described in the SOP.

4.0 Definitions and abbreviations

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the Sponsor on each trial participant in a clinical research study.
Clinical Trial Coordinator: the site clinical trial coordinator, who, with the PI, supervises all trial operations at the site.

Clinical Trial Officer: The research assistant at the site, working in collaboration with CTC.
Coordinating centre: research staff involved in running the $2R^2$ study who are based at Research Institute of McGill University Health Centre (RI-MUHC)

5.0 Procedures

General Information

This SOP describes how study medication has to be shipped and stored during the study. For Canadian sites there are different procedures for the study medications used in high dose arms and in the standard arm. For study medications to use in the high dose arms: commercially available rifampin capsules are first shipped from the site pharmacy to Linda Frayne Pharmacy, in Montreal and then sent back to sites re-compounded. This process is repeated 2-3 times during the study, to avoid expiration of re-compounded medications. Rifampin for standard arm is purchased, stored and dispensed as per standard practices in each site. For Indonesia: Rifampin for high dose and standard dose arms is produced specifically for the study by a local pharmaceutical company and shipped once to the study site. For Vietnam: Rifampin for high dose and standard dose arms is produced specifically for the study

by a pharmaceutical company and shipped once to the Vietnam coordinating office for the study and from there to each study clinic.

5.1. Re-compounding procedures and shipment of study drugs

For Canadian sites:

5.1.1. Procurement of study medication: After consultation with the coordinating center, each Canadian site buys the commercialized rifampin (i.e. 300mg capsules of Rofact or 300mg capsules of Rifadin) that is needed for the high dose arms of 2R2, through the clinic usual pharmacy procurement path. The procurement is done by the hospital pharmacist in Montreal and Vancouver and by the pharmacist at Edmonton TB clinic, for both the Edmonton and Calgary sites, through Alberta Drug Depo.

5.1.2. Storage of rifampin before shipment: Rifampin procured for the 2R2 study must be kept at the hospital pharmacy (in Montreal and Vancouver) and at the Alberta Drug Depo following the conditions specified in the drug label. The storage area in which Rifampin is kept before shipping to Linda Frayne Pharmacy must be clean, secure, with restricted access and with temperature controlled and recorded. A plan for temperature control in case of electrical power outrage must be in place.

5.1.3. Shipment to re-compounding pharmacy: The coordinating center will communicate with pharmacist at these three sites to organize the shipment of rifampin to Linda Frayne Pharmacy in Montreal, where the re-compounding of rifampin is done. The re-compounding procedure is detailed in **Appendix 1.** The shipment to and from Linda Frayne Pharmacy is organized with commercial carriers, after agreement with coordinating center (note the carrier used can vary depending on the site). Requirements to be met during transportation has to be agreed upon with carrier before the shipment can take place and documentation of transport condition (time and place in which shipment was, type vehicle, temperature ranges provided) has to be collected and stored by the sending pharmacy.

The packaging of the rifampin to send, should be done with material (as Styrofoam) that will help keeping the drug within the acceptable temperature range. The package has to be clearly labeled with "Study medication- temperature sensitive".

A temperature measure device (as a TempTale), with preset delay of recording, time interval of measurements, and range of allowed temperatures has to be activated when shipment starts. The receiver (Linda Frayne Pharmacy) will read the TempTale record and send it back to sending pharmacist and coordinating center. The coordinating center will organize the procurement of TempTale for each site, before shipment starts.

5.1.4. Shipment from re-compounding pharmacy to sites. Once pharmacist at Linda Frayne Pharmacy agreed with coordinating center that the re-compounded capsules of rifampin 300mg and 450mg for the study are ready to be shipped back to the sites, the shipment will the organized with commercial carriers under the supervision of coordinating center or of site pharmacist, depending on agreement with each site. The procedures for the shipment are the same than at point 5.1.3.

5.1.5. If case of an excursion from recommended temperatures has occurred during transportation, the coordinating center must be informed by the party receiving the medication. Putting together all documentation relative to the shipment, the coordinating center will prepare a report and provide information regarding the possibility of use of the shipped medication, after taking necessary

consultation. Until a decision regarding utilization of the drugs is communicated by coordinating center, the drugs exposed to temperature excursions should be quarantined.

For International sites (Indonesia and Vietnam):

5.1.6. Shipment to study site will be arranged by site research team with the producing pharmaceutical company that will ship the study medications directly from production to study site. Monitoring of study drugs conditions during shipment has to be arranged by study coordinator at site or by coordinating center with the pharmaceutical company. The record of temperatures during shipment has to be kept by study site together with the other pharmacy essential documents in the study pharmacy master binder.

5.1.7. In case of occurrence of excursion from recommended temperatures during shipping, coordinating center must be informed. As for point 5.1.5 above, the coordinating center will recommend action regarding the stock of study drugs exposed to temperatures outside the recommended range, after having collected all the information and having had the necessary consultation. Awaiting the decision, the drugs exposed to temperature excursions should be quarantined.

5.2. Study medication storage

5.2.1. At sites, study medication must be stored in a secure (e.g. locked room), dry and clean place, with restricted access to qualified personnel.

5.2.2. The study drug for all arms of 2R2 is rifampin in solid form. Storage conditions for the study drug are specified on the label of the product.

5.2.3. The storage room must be equipped with a thermometer that can record the range of temperatures reached between readings. Periodic control and record of temperature exposure during storage has to be done at each site at minimum of 3 times per week, and reported in the **Log of study drug storage conditions (Appendix 2)**. The storage record has to be kept with other study documents, either by pharmacist (or the person designated by the site PI to have the role of pharmacist for the study), and be accessible during monitor visits**.** Research teams must ensure that conditions are in place to maintain the temperature within acceptable limits (for example: air conditioning system to avoid exposure to high temperatures), with plans for temperature control in case of electrical power outrage in place (for example: having a generator in cases of emergencies).

5.2.4. In case of excursions outside the recommended temperature range during storage at site, the study team at site needs to inform the coordinating center that would act accordingly (i.e. doing a risk analysis, informing, if deemed necessary, the regulatory authorities and making an evidence-based decision on the disposition of the study medication). Until a decision regarding utilization of the drugs is communicated to site by the coordinating center, the drugs exposed to temperature excursions should be quarantined.

5.3. Recording of drugs dispensed and returned

Please refer to **2R2 SOP04 "Blinding and dispensing"** of each site, for details on labeling, dispensing of study medication and for the necessary documentation to keep.

6.0 References

-Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069)- Health Canada- Health Products and Food Branch Inspectorate. January 28, 2011
-Research Institute of McGill University Health Center, SOP-CR-010_07 Management of Investigational Products 01-Sept-2018.

7.0. SOP Revision history

SOP code	Effective date	Summary of changes
2R2 SOP14_06Jul2020	06 July 2020	NA (original version)

Appendix 1. Procedures followed for re-compounding of the study drug

Narrative description of Rifampin capsules compounding – 27 June 2019
PHARMACIE LINDA FRAYNE

1. The capsule machine is initially cleaned, disinfected and dried using standard protocol, to avoid any cross-contamination with other products.

2. Every Rofact 300mg capsule is then opened manually and weighted to make batches of 100 capsules.

3. Croscarmellose sodium is also weighted to fill out the empty spaces. The amount used will depend on the dosage of Rifampin (300mg or 450mg). 85g of Croscarmellose sodium are required for 300 capsules of Rifampin 300mg (re-compound), and 40g of Croscarmellose sodium are required for 300 capsules of 450mg (re-compound).

4. The number of capsules used will depend on the hospital order, with the conversion rate of 1 Rofact 300mg capsule to make 1 re-compound Rifampin 300mg, and 3 Rofact 300mg capsules to make 2 re-compound Rifampin 450mg capsule. In total, 36,000 capsules of Rofact 300mg will be used to make a total of 36,000 capsules of rifampin 300mg and 54,000 capsules of Rofact 300mg will be used to make 36,000 capsules of rifampin 450mg.

5. The technicians will strictly follow the protocol and document every step of the preparation, including the manufacturer, the lot number and the expiry date for each component (Rofact capsules, croscarmellose sodium, and gelatin capsules).

6. The powders are then be mixed together thoroughly using a mixer.

7. The new gelatin capsules are placed into the capsule machine.

8. The powders are then spread onto the capsule machine evenly.

9. After making sure the powders are evenly distributed, the technician will close the capsules (with the capsule machine).

10. If the capsules are very powdery, they will be cleaned with NaCl in order to rid of the excess powder.

11. All capsules are inspected visually to ensure no defect is present.

12. Technicians will weight and document 10% of the final capsules, all capsules should have a weight ± 5% of each other.

13. The capsules will then be transferred to final container (polypropylene plastic vials) and labeled accordingly, depending on their strength. The vials will then be transferred to a carton box waiting for shipment.

Appendix 2. LOG of Storage conditions for study medication

Sponsor: RI-MUHC, 2155 Guy street, suite 500, Montreal, H2H 2R9, Canada		**Protocol Number:** < *protocol n at site*>
Site Number:	**Site Investigator**:	
☐ **Room Temperature** (15 to 30 C)	**Location**:	**Back-up Location**:
Serial Number of thermometer:	**Brand**:	**Model**:
Date of Calibration/Inspection:	**Expiry Date of Calibration/Inspection**:	
Emergency Contact 1 – Name:		**Phone:**
Emergency Contact 2 – Name:		**Phone:**

Year: _____	**Month:** _____	**Temperature (Range: _____)**			**Humidity (Range: _____)**			**Recorder Initials**	**Temperature Deviation?**		**If yes, please comment:**
Date	**Time (00:00)**	**Actual**	**Min.**	**Max.**	**Actual**	**Min.**	**Max.**		**Yes**	**No**	
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