Clinical Monitoring Plan

Protocol Number: SMA TB 001

Phase 2b Randomized double-blind, placebo-controlled trial to estimate the potential efficacy and safety of two repurposed drugs, acetylsalicylic acid and ibuprofen, for use as adjunct therapy added to, and compared with, the standard WHO recommended TB regimen

Document History:

Version No.	**Version date**	**Major changes**
V1 (Initial)	31 Mar 2020	Not Applicable
V2	14th November 2020	Change to Risk-based monitoring

By signing below, I acknowledge my agreement to this plan.

Sponsor

Name: Fundació Institut Germans Trias I Pujol

Signature: _____ Date: 12th November 2020

Site Name: _____

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1.0 LIST OF ABBREVIATIONS

All abbreviations used in the document, including appendices. Accepted international medical abbreviations should be used. All abbreviations should be spelled out when first used in the text, followed by the abbreviation in parentheses. Common units of measure like mg or mL don't need to be defined in the text or this list.

The following list is an example only. Add and delete abbreviations as appropriate for your clinical monitoring plan.

AE	Adverse Event
COV	Close-Out Visit
CMP	Clinical Monitoring Plan
CPI	Coordinating/Lead Site Principal Investigator
CRA	Clinical Research Associate
CRF	Case Report Form – paper and electronic
CRO	Clinical Research Organization
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
ED	Essential Documents
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonization
IP	Investigational Product
ISF	Investigator Site File
PI	Principal Investigator
PICF	Participant Information and Consent Form

PHRU	Perinatal HIV Research Unit
SAE	Serious Adverse Event
SC	Study Coordinator
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
USM	Urgent Safety Measure

2.0 ROLES & RESPONSIBILITIES

For the purpose of this study, sites will be monitored by a Georgian based Independent Clinical Research Associate (CRA). The CRA is qualified by education and experience to monitor the conduct of clinical research study sites according to applicable SOPs, Clinical Trials of Investigational Products, ICH GCP and applicable regulatory requirements.

3.0 INTRODUCTION

This Clinical Monitoring Plan (CMP) establishes the guidelines for conducting monitoring visits and related tasks for monitoring the National Center of Tuberculosis and Lung Diseases (Georgian site) for Protocol SMA TB, Phase 2b Randomized double-blind, placebo controlled trial to estimate the potential efficacy and safety of two repurposed drugs, acetylsalicylic acid and ibuprofen, for use as adjunct therapy added to, and compared with, the standard WHO recommended TB regimen and it is a requirement of the Integrated Addendum to ICH E6 (R1) and Guideline for Good Clinical Practice E6 (R2) Section 5.18.7.

The CMP was developed by the Independent CRA in collaboration with Dr. Cristina Vilaplana (Principal Investigator/Sponsor).

Monitoring tasks will be performed in accordance with the protocol-specific requirements, site SOPs, the Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice ICH

E6(R2) and applicable regulatory requirements.

The Trial Steering Committee (TSC) and Independent Data and Safety Monitoring Committee (IDSMC) also play a role in the monitoring of the SMA-TB trial.

4.0 TRIAL OVERSIGHT COMMITTEES

4.1. Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial and provide advice to the funder and the sponsor through its independent chairperson. The ultimate decision for the continuation of the trial lies with the TSC.

4.2. Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will provide a written recommendation to the Trial Steering Committee concerning the continuation of the study.

4.3. Trial Management Group (TMG)

The TMG will be responsible for the day-to-day running and management of the trial and will aim to meet/teleconference monthly. The TMG will be responsible for the review of trial monitoring reports and recommending arising actions.

5.0 MONITORING COMMUNICATION PLAN

The CRA will send monitoring communication including site visit confirmation emails, agendas, follow-up emails etc., to the following site staff members:

Sponsor details

Role	Representative
Sponsor leading Investigator	Dr. Cristina Vilaplana cvilaplana@igtp.cat
Sponsor SMA-TB project manager	Dr. Lilibeth Arias larias@igtp.cat

Participating Sites Contacts

Role	Representative
Site 3 Tbilisi, Georgia	
National PI	Dr. SergoVashakidze sergovashakidze@yahoo.com
Co-investigators	Dr. Nestani Tukvadze, marikushane@yahoo.com
	Dr. Lali Kupreishvili Email: lalikupreishvili@yahoo.com
	Dr. Ketevan Barbakadze keti_barbusa@yahoo.com

6.0 TYPES OF VISITS AND MONITORING ACTIVITIES

Note: Site Initiation is not considered a monitoring activity. The Sponsors and National Principal Investigator will be responsible for activities that occur during the SIV. These activities may be delegated to members of the research team at the Participating Sites.

There will be four types of monitoring visits for this study:

1) **Routine monitoring** by CRA to conduct **Interim Monitoring Visits (IMV),** hereafter referred to as Monitoring Visits will be conducted to verify that:

- The Investigator is conducting the study in accordance with the protocol, applicable SOPs, Good Clinical Practice (GCP) and applicable regulatory requirements;
- Participants' safety, rights and well-being are being protected;
- Data recorded on the case report forms are accurate, complete and verifiable from source documentation. These activities will be performed using on-site monitoring.

2) **Central monitoring:** the sponsor will perform central review of: monitoring of recruitment, adverse events, missing primary outcome data, visit schedules, and quality and timeliness of case report form (CRF) completion, return, data entry and review of data entry.

3) **For-cause visits** will be conducted to address any unanticipated issues that arise which require training, remediation or other situations in which the site requires assistance. For-cause visits can be mandated by the Sponsor according to the Risks identified during central monitoring, or can be requested by the site. These visits may involve either on-site monitoring or remote monitoring.

4) A Close-Out Visit (COV) will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled. The COV for the Coordinating Lead Site will be conducted on site. The COV for participating sites will be conducted on-site or via phone, depending on individual site circumstances.

7.0 ROUTINE IMV MONITORING

Routine monitoring by CRA will be performed in accordance with SOP-XX**.** CR: The purpose of the RMVs is to ensure that the safety and well-being of the study subjects are not compromised, that the data reported is accurate and complete, that the study protocol is adhered to and that the study is being conducted in accordance with the ICH-GCP guidelines.

The first routine monitoring visit will be performed **within 10 working days** of the first subject randomized at a site. The duration of each monitoring visit will be dependent upon the number of subjects enrolled and data pending review/SDV.

Visit frequency to low enrolling sites (i.e., 1 patient enrolled in between 2 consecutive RMVs) should not be prolonged due to need to confirm sites understanding of eligibility per protocol

requirements. Visits to sites with no enrolled patients since the previous visit should be performed only when approved by PM or PM-designees.

The frequency of routine monitoring visits will be **4-6 weeks** (dependent on agreed to scope and CRO SOPs), additional, visits may be scheduled based on the findings from central monitoring.

Prior to each site visit, the Monitor should:

- Verify that the eCRF data to confirm that all data expected to be entered have been entered into the Electronic Data Capture [EDC] system by the responsible site staff.
- Review Central Monitoring Report section as applicable for the specific site and check if there are any pending actions/action plans that need to be implemented or followed-up on during the onsite visit

Prior to scheduling visits outside of agreed to scope, approval from Sponsor is required prior to scheduling. If visits are not conducted consistently within the time frame identified above, the reason must be documented in the monitoring report.

8.0 CENTRAL MONITORING

The Central Monitoring strategy led by Sponsor includes: Key Risk Indicators Monitoring, Data Quality Monitoring and Central Safety Review, as specified in the Project Risk Management Plan.

The sponsor will facilitate early identification of risk(s)/issue(s) in the course of the study by means of periodic monitoring of KRIs, timely escalation of risk (s)/issue(s) to monitors and track of risk(s)/issue(s) until resolution, and will issue a report if necessary including all this information:

- list of KRIs for each site
- new risk(s)/issue(s) identified and action plan(s) suggested
- actions performed with regard to previously identified issues
- and the list of pending issues.

Central monitoring will also include:

- Attending Risk Review meetings with the relevant stakeholders to ensure that all risk(s)/issue(s) are properly tracked/control;
- Data quality monitoring,
- Preparing corrective action plans, and follow-up on identified issues until resolution Supporting Medical Monitors in central safety review, escalate issues to relevant stakeholders, and follow-up on these issues until resolution
- Supporting monitors in monitoring and adjusting the level of SDV if applicable.

9.0 KRIS AND DATA QUALITY MONITORING AND REPORTING

All KRIs included in the KRI List specified in the Annex 1 have one or more associated thresholds and the suggested action plan in case the threshold for a specific KRI is met. Additional/different actions may be agreed during the Risk Review Meetings. Central Monitoring Manager will perform KRI in a monthly basis, and generate the Central Monitoring Review reports in a monthly basis, and discuss them with the TMG and the monitors in accordance with the meetings schedule presented below to review site performance against the pre-determined KRIs and thresholds that have been identified. During the meetings, based on the outcome of this KRIs review, the number of patients enrolled at the site, in addition to any feedback on site performance from the project team, it will be decided:

- If the site health level should be adjusted (which will in turn adjust the level of SDV at that site), and/or
- If the frequency of onsite monitoring visits should be adjusted,
  and/or If any other corrective action(s) should be implemented.

Central Monitoring Manager will document the Risk review meetings by means of the Meeting Minutes. The minutes reviewed and approved by Project Manager will be filed in the eTMF system.

10.0 FREQUENCY/DURATION/RESOURCING ADJUSTMENTS FOR DATA SWEEPS

Increase in frequency or duration of monitoring visits can be considered in case of sites that require additional oversight. The Sponsor together with the monitors are in charge of making a decision on increasing the frequency or duration of monitoring visits on a case-by-case basis.

The frequency and/or duration of the monitoring visits will be adjusted depending on the volume and quality of the data received from a site (Key Risk Indicators (KRIs).

The sponsor will decide on adjustment visits frequency for sites based on:

- Volume of data (the number of CRF pages required SDV available at the site); Data entry (% of data missing);
- Query resolution (% of queries outstanding for longer than 15 days); Site issues (% of issues outstanding for longer than 60 days);
- Number of Protocol deviations per Subject visit;

- Number of Major Protocol deviations (number of major deviations in last 90 days); Number of Major Protocol deviations per Subject enrolled.

In the event a monitor thinks that a particular site needs more frequent or longer visits s/he will discuss it with CRO PM and the Sponsor and updates to the visits schedule will be made as necessary.

If significant quality issues impacting patient safety and data integrity have been revealed by the CRA monitor, the Sponsor will be notified within 24 hours of becoming aware of such a major issue.

CRAs will document and finalize visit findings on the Site Visit Reports according to the SOP requirements. CRAs will inform the sponsor CT or designee immediately of issues related to patient safety CRO SOPs and policies within 24 hours of becoming aware of such a major issue.

Outstanding site issues are documented in visit reports and tracked on subsequent report(s) until the issues are resolved.

IMV frequency can be adjusted considering recruitment rate at site, site performance, and other important indicators including but not limited to the number of CRF pages requiring available at the site, data entry status (% of data missing); query resolution, amount of opened site issues, number of Protocol deviations, number of total major Protocol deviations, number of major protocol deviations per subject enrolled.

6.1 Monitoring visits

6.1.1 First Monitoring visit

During the first visit at each study site, in addition to performing monitoring visit associated tasks, the CRA will confirm operational and facility related items as discussed with the study staff.

Items for confirmation may include:

• Roles and Responsibilities of site staff	• Participant source documentation
• Communication between team members	• Protocol submissions, deviations and associated regulatory reporting
• Site record keeping	• ISF
• Safety Reporting Process and Safety Reports to date	• Data collection methods, Case Report Forms Entry and Query resolution
• Office set up appropriate to GCP and patient privacy	• Assess Facilities appropriate to study execution
• Appropriate delegation of study	• Adequate facilities for study supply

tasks to qualified team members	storage, sample processing, and availability to necessary technology for data entry.

At the conclusion of the visit, or after review of the above, CRA will meet with the Site PI and Site Study Coordinator (SC) to determine a monitoring strategy for future visits.

Frequency of future IMVs will be based on the developed monitoring strategy taking into consideration the enrollment status, data quality, protocol compliance. The frequency of routine monitoring applies to sites with active participants. Monitoring frequency will be dependent on the participant enrolment status. The minimum interval in between on-site visits at each site is as follows:

Participant enrolment status	**CRA Days On-site (DOS)**
Pre-enrolment visits	3 DOS
3-5 Enrolled participants	2 DOS
20 Enrolled participants	3 DOS
60 Enrolled participants	4 DOS
1 Month after last participant completion	5 DOS
50 % Participants in follow-up	2 DOS
75% Participants in follow-up	3 DOS
COV	2 DOS

6.1.2 Routine monitoring visits

The CRA will work with the Participating Site PIs and Site Primary Contact to schedule monitoring visits. The Sponsor will be informed of visit scheduling at Participating Sites.

Prior to the visit, the PI will receive a visit confirmation email, agenda and a list of participant

files to be monitored. The CRA will ensure that this information is communicated to the site personnel within a mutually agreed upon timeframe to allow enough time for record requests. The PI and research staff will be expected to secure a workspace for the CRA and to be available during the visits to facilitate monitoring activities. The length of each monitoring visit will depend on the participant's enrolment status at each site.

The CRA will be available at the end of each monitoring visit day to discuss the findings/monitoring observations and answer questions from the study staff. The PI and Primary Site Contact are also expected to be available for a debriefing meeting at the conclusion of the visit, as schedules allow. These expectations will be explained in the visit confirmation email.

Each site will have an on-site monitoring visit at least 8 times during the study. The first on-site monitoring visit should occur within 10 business days of the first 5 participant's randomizations visit. Thereafter, monitoring visits will be conducted as necessary until the last participant has completed the follow-up evaluations according to the protocol. Additional visits will only be scheduled if required.

6.2 For-cause Visit Activities

During for-cause visits, the CRA may complete any of the activities listed for the IMV, discuss clinical operations and study management methods with the research staff, and/or provide training to the research staff.

6.3 Close-out Visit Activities

COV activities may require more than one visit to ensure the proper closure of the study. These activities may be conducted during a series of on-site visits or by telephone. Close-out visits may be conducted at study completion or earlier in the case of study termination by the Human Research Ethics Committee (HREC) or other Regulatory Authority. The outcome of the visit and other COV activities will be documented in a monitoring visit report and follow-up letter/email.

CRA will perform the activities below during the study COV process:

- **Consent Documents**
  - Confirm that consent was obtained for each participant prior to initiating study activities.

- Confirm that consents contain appropriate signatures and dates.
- Confirm that the correct version of the consent document was signed and dated.
- Confirm that additional consent was obtained for protocol amendments as required by the site's IRB.

- **Investigator Site File**
  - Ensure that essential document files are complete and current.
  - Identify any missing study documents.
  - Ensure that the Authorized Signature and Delegation Logs are complete and signed by the PI.

- **Source Documentation and CRF Review**
  - Reconcile the final status of all participants listed on the screening log.
  - Confirm that all required data fields have been verified against source.
  - Confirm that all data queries have been resolved.
  - Confirm that the PI has reviewed, signed, and dated all required CRF pages
  - Confirm that protocol deviations are noted in the source documents.

- **Unanticipated Problems, Adverse Events, and Serious Adverse Events**
  - Confirm that all AEs, and SAEs have been reported to the appropriate HREC and regulatory agencies as required.
  - Confirm that the site has and will continue to meet safety reporting requirements.
  - Ensure that copies of SAE reports are filed with the corresponding site files.

- **Investigational Product**
  - Confirm that all IP accountability records have been maintained appropriately and are consistent with the amount of remaining product.

- **Laboratory Samples**
  - Confirm that all lab samples have either been analyzed or stored for future analyses.
  - Confirm future use specimen disposition and labeling/de-identification, as appropriate.
  - Confirm site process for identification and disposition of future use samples connected to participants who withdraw consent.
- **Regulatory Obligations**
  - Confirm that the PI has met and will continue to meet regulatory obligations.
  - Confirm that the PI has provided written notification of study closure to the HREC and verify acknowledgement by the HREC of study closure.
  - If the study was terminated prematurely, the CRA will confirm that enrolled participants were informed, and that appropriate therapy and follow-up was initiated by the PI.
  - Inform the PI of the possibility of future audits by regulatory authorities.
- **Records Retention**
  - For IND/IDE studies, review the document retention requirement for all study-related records: 21 CFR 312.57 (c), 45 CFR 46.115 (b), 45 CFR Part 74, as well as institutional and local IRB requirements; emphasizing that the more stringent retention policy should be followed.
  - For IND/IDE studies, inform the PI that all study records and reports must be retained for 2 years after a market application approval for the drug, or until 2 years after shipment and delivery of drug for investigational use is discontinued and Food and Drug Administration (FDA) has been notified (21 CFR 312.57).]
  - HHS protection of human subjects' regulations (45 CFR 46.115) require institutions to retain records of IRB activities and certain other records for at least 3 years after completion of the research.

At the conclusion of the COV, the CRA will meet with the PI and site SC to discuss:

- Any findings noted during the visit.
- Retention timeframes for study-related documents.
- Safety reporting requirements.
- Notification of the IRB that the study has concluded.
- Outstanding issues at study closure and a plan for their resolution

11.0 ESSENTIAL DOCUMENTS/TRIAL MASTER FILE

7.1 Essential Documents to be filed by Participating Trial Sites

A hardcopy folder/file, which for purposes of this CMP will be defined as the Investigator Site File (ISF), will be maintained at each trial site and serve as the central source for essential document (ED) maintenance at the site. Documents with original signatures must also be maintained in a paper ISF. This includes study-level and participant-level documents (i.e. Clinical Trial Research Agreements and Participant Information and Consent Forms [PICFs]).

The following documents represent a complete site essential document packet and are to be maintained in the ISF:

- The original HREC-approved protocol and any amendments to the protocol, Protocol Amendment(s) and Signature Pages, sample Case Report Form
- All versions of the informed consent, advertisements for participant recruitment, diaries and study documents provided to families.
- The original Investigator's Brochure / Product Information and any amendments
- Documented evidence of submission of Investigator's Brochure (IB)/Product Information to the RCH HREC and written acknowledgment from RCH HREC of receipt of the IB/Product Information.
- Annual Reports, Annual Safety Reports, expedited safety reports, serious breach reports, notification of changes to the study team, submitted to HREC/local governance office for participating sites, as appropriate.

- All correspondence between the CPI/Site PI and RCH HREC/local governance office, as appropriate. Includes submissions, approvals and responses to questions/comments.
- Documented evidence (e.g. Note to File) and reporting of non-compliance to GCP, SOPs, protocol to Investigator-Sponsor.
- Principal Investigator's (PI) and Sub-Investigator(s) Curriculum Vitae (CV)
- Current and completed Delegation Log – all tasks appropriately delegated
- Training Log – incudes trial-specific and GCP trainings, valid for duration of involvement in study
- Laboratory Certifications
- Laboratory Reference Ranges
- Screen/enrollment log, listing all participants with a signed informed consent and, if the participant was randomized/treated. For any participant not randomized/treated, the reason they were not randomized/treated.
- Patient Identification Log

7.2 Essential Documents to be Filed by Sponsor in the Trial Master File (TMF) – excluding Site Information File subfolder

The Sponsor-Investigator is responsible for maintaining the Trial Master File (TMF). The Trial Master File is maintained in electronic formats and owned by the Sponsor-Investigator. Documents cited in Section 7.1 and 7.2 with original signatures must be maintained in the TMF/ISF. This includes study-level and participant-level documents. All other essential documents will be maintained in the electronic TMF only.

Essential Documents that are common to all sites and essential documents specific to the Coordinating Lead Site must be filed in the TMF.

For the lead site only – safety reporting to participating site Investigators/approving HREC and Regulatory Authority.

- SSIs
- USMs
- SUSARs
- Annual Safety Report (HREC and Regulatory Authority)
- Updated Product Information/Investigator Brochure, if applicable

8. Essential Documents to be Filed by Sponsor in the TMF and Site Information File subfolder)

Essential documents that are specific to a Participating Site must also be filed in a separate subfolder of the TMF called the Site Information File. The responsibility to hold and maintain an up to date TMF Site Information File, including all superseded documents, is with the Sponsor-Investigator.

Documentation that is site-specific includes the following:

- Study Contact List
- Site-specific PICF (current and superseded)
- Ethics and Regulatory Authority
  - Regulatory Authority approval letter (current and superseded)
  - Documentation of Regulatory Authority submission
  - Annual and final study reports
- Re-identifiable Screening Log
- Safety reporting to the Sponsor-Investigator:
  - All SAEs, except those identified in the protocol as not requiring immediate reporting
  - All SUSARs
  - All Urgent Safety Measures (USMs) instigated by the site

- AEs and laboratory evaluations critical to safety (specified in the protocol)
- All serious breaches

- Safety reporting to the HREC and Regulatory Authority
  - All SSIs

    Note: The Sponsor-Investigator will report SSIs, including USMs, to Investigators for forwarding to their local RGO.
  - All local SUSARs
  - All local serious breaches that have been confirmed by the Sponsor-Investigator
  - HREC and Regulatory Authority acknowledgement of submitted reports (SSIs, local SUSARs)
  - Any other safety reporting required by the local Regulatory Authority
- Monitoring reports and associated correspondence
- Local Lab(s)
  - Lab certification (Not required for labs undertaking exploratory testing)
  - Lab reference ranges
- Tissue log (if applicable)
- Sample tracking log (if applicable)
- Study Team Documentation
  - Delegation and Signature Logs
  - Qualifications (CV) and Training Logs
  - Copy of SIV Presentation and any other study training materials used at site
- Supplies Shipping Records - Documentation relating to provision of study supplies (excluding IP)

- Legal Documentation
  - Copy of agreements as applicable (e.g. Clinical Trial Research Agreement, Material Transfer Agreement, Confidentiality Agreement)
  - Correspondence with hospital CEO. Hospital Approval if applicable
- Finance Documentation
- Correspondence – all correspondence pertinent to study conduct at site
- Regulatory Documents – copies of all Regulatory authority correspondence, e.g. submission of Clinical Trial Application, Clinical Trial Application acknowledgement and approval.
- Investigational Product – During the study this section to contain a file note stating location of documents in the site Pharmacy Folder. At end of study, a copy of documentation in site Pharmacy Folder is to be filed in this section, including:
  - IP shipping records and delivery to site receipts
  - IP inventory including dispensing to and returns by participants, product expiry, product disposal
  - IP storage temperature logs

7.3 CRA's Role in Essential Document Maintenance

During routine monitoring visits, the CRA will review the TMF/ISF for accuracy and completeness.

As noted in section 7.2, the Sponsor is tasked with maintenance of the TMF. The CRA will support this endeavor by reviewing the essential documents for completeness and accuracy. No original documents will be collected. The CRA will alert the study staff to discrepancies and upcoming expiration dates.

12.0 REVIEW OF SOURCE DOCUMENTS AND CASE REPORT FORMS (CRFs)

Data quality analysis will be done by conducting 100% verification checks on a 10% random sample of participants CRF at 3 timepoints: when 25% of patients enrolled, 50% patients enrolled and 95% patients enrolled. Verification of original source documents will be conducted to determine data quality. During monitoring visits, comparison between source documents to data listings entered into the CRF will be made. If >5% of data variables are incorrect, a second 10% random sample (excluding files already sampled) would be extracted from the data set (as suggested by Houson et al, in Measuring Data Quality Through a Source Data Verification Audit). If a >5% error rate within electronic datasets is confirmed, a corrective measure will be applied.

At each on-site monitoring visit (IMV), the CRA will verify the following data/processes:

- Informed consent and or assent was obtained appropriately
    - Verify each participant entered into the study has a properly signed and dated HREC - approved informed consent or assent and there is documentation confirming that the study was explained to the participant and that consent was obtained before conducting any study-related procedures. In cases where the person giving consent (i.e. the participant or the parent/legal guardian) cannot read, the CRA must verify that an impartial witness has signed the form.
    - Verify the correct version of the informed consent and or assent was signed and revised versions of the consent or assent form are signed, if applicable. Deviations to the informed consent process are documented and all applicable parties are informed.
- The investigator is following Regulatory Authority and HREC-approved protocol and all approved amendment(s), if any.
- The participants enrolled/randomized in the study meet the protocol criteria for eligibility.
- If the Sponsor-Investigator has provided a waiver for the enrolment of an ineligible participant, the signed waiver must be filed in the participant's file.

- A serious breach is deemed to have occurred if an ineligible participant is enrolled without a waiver by the Sponsor. In such cases, the PI must report the serious breach to the Sponsor within 72 hours of becoming aware of the breach.

  Note: The Sponsor must report the serious breach to the reviewing HREC without delay and no later than 7 calendar days of confirming the serious breach occurred.

- If any Corrective and Preventative Action plans have been developed to address serious breaches related to enrolment, verify that these are being actioned by relevant site staff.

- For participants that are randomized/receive the IP, their medical record references the study and indicates that the participant is receiving an IP. The medical record should contain progress notes, laboratory reports (if applicable), concomitant therapies and adverse medical experiences.

- Conduct and documentation (in medical records, CRFs, participant study files (if used), TMF) are complete, accurate, consistent and adhere to the protocol for procedures and assessments related to:

  - Study endpoints

  - Protocol-required safety assessments

  - Evaluation, documentation and reporting of serious adverse events, SUSARs, Significant Safety Issues, participant deaths and withdrawals related to adverse events)

- Conduct and documentation (in medical records, CRFs, participant study files (if used), TMF) are complete, accurate, consistent and adhere to the protocol for procedures related to trial integrity, such as:

  - Any dose modifications (and the reason for the dose modification) for the investigational product are documented for each participant in both the medical record and the CRF.

- Documentation and reporting of serious breaches meet the principles of ALCOA (attributable, legible, contemporaneous, original, accurate), plus complete and traceable.

- Discrepancies between the source documents and the CRFs should be brought to the attention of the site staff and corrections made to the CRFs by the investigational site staff.

13.0 REVIEW OF INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY RECORDS

During the monitoring visit, the CRA will review the following aspects of the IP:

- That storage times and conditions are acceptable, and that supplies are enough throughout the trial.
- That the IP are supplied only to participants who are eligible to receive it and at the protocol specified dose(s).
- That participants are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s). (if applicable)
- That the receipt, use, and return of the IP at the trial sites are controlled and documented adequately.
- That the disposition of unused IP at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the Sponsor-Investigator's requirements (e.g. protocol, SOPs describing process for Investigational Product Accountability).

IP accountability should be completed by the CRA at each monitoring visit.

14.0 REVIEW OF INVESTIGATOR AND SITE STAFF SUITABILITY

At each monitoring visit, the CRA should confirm the continued ability and commitment of the Investigator and site staff to conduct the study. This includes the following tasks:

- Verify that the PI and site personnel are adhering to the protocol and conducting the study according to regulatory requirements, GCP and study-specific standard operating procedures (SOPs).
- Verify that the PI is providing adequate supervision to any individual or party to whom

they have delegated trial-related duties and functions. Evidence of supervision may include email correspondence, meeting minutes with attendees listed etc.

- Review the Delegations Log and Training Log to ensure it is complete, current and delegation is in accordance with qualifications and training.
- Ascertain the participant recruitment rate and determine if enrolment is adequate.

15.0 MONITORING REPORTS / ACTION ITEMS

The CRA should provide a written Monitoring Visit Report to the Principal Investigator after each monitoring visit. The report should provide enough detail to allow verification with the Clinical Monitoring Plan.

Monitoring visit findings and resulting action items will be documented in Monitoring Visit Reports. The CRA will complete a written Monitoring Visit Report and provide a follow up letter/email to identified study team members as noted in Section 4.0 within 10 business days of the visit. The follow-up letter should be signed and filed in the ISF and TMF. The Monitoring Visit Report will be shared with the sponsor and is not for distribution to the site, and should be filed in the TMF only.

The CRA will work with designated site staff to resolve any outstanding action items as communicated in the follow-up letter/email. At a mutually agreed upon time, or 4 to 6 weeks post visit, whichever is earlier, the CRA and site research staff designee will discuss via telephone conference or email all resolved, in process, and pending action items. At this time the need for, and frequency of subsequent meetings will be discussed.

ANNEX 1. RISK ASSESSMENT

Date of Assessment	**15th November 2020**	
Number of Risk Categories Identified	**17**	
Range of scores per category (min-max)	**1-25**	
Minimum Possible Total Score **Maximum Possible Total Score** (Sum maximum score possible i.e. 25 x number of categories)	**25** **750 (25 X 30)**	
Total Score for Trial (Sum of scores from all Categories)	**135**	
Mean Score for Trial (Calculated as total score/number of categories)	**7.94**	
Overall % Risk (Calculated as [Total score/maximum possible score] x 100)	**18%**	
Category of Risk (circle)	Low	If score ≤ 33%
	Moderate	If score ≥34 to ≤ 67%
	High	If score ≥ 68 to ≤ 100%

Risk Assessment Matrix

	1 Remote	**2 Unlikely**	**3 Possible**	**4 Likely**	**5 Certain**
1 Low	1	2	3	4	5
2 Moderate	2	4	6	8	10
3 Significant	3	6	9	12	15
4 Severe	4	8	12	16	20
5 Catastrophic	5	10	15	20	25

Risk Management Key

Action and time scales
Immediate action must be taken to manage the risk. Control measures should be put in place which will have the effect of reducing the impact of an event or the likelihood of an event occurring. A number of control measures may be required.
Significant resources may have to be allocated to reduce the risk. Where the risk involves work in progress urgent action should be taken.
Efforts should be made to reduce the risk, but the costs of prevention should be carefully measured and weighed against the impact of the event. Establish more precisely the likelihood of harm as a basis for determining the need for improved control measures.
On or below this level a risk is acceptable. Existing controls should be monitored and adjusted. No further action or additional costs are required. Consideration may be given to a more cost-effective solution or improvement that imposes no additional cost burden.
Acceptable risk. No further action or additional controls are required. Risks at this level should be monitored, and reassessed at appropriate intervals.

TRESHOLD FOR EACH RISK: DETECTION CHECKLIST AND ACTION TO BE TAKEN ACCORDINGLY

The presence of the risks will be evaluated as specified in section 9. A checklist will be used per each risk detected if surpass the threshold. Action to be taken will also be recorded.