Childhood Acute Illness & Nutrition Network

KEMRI | Wellcome Trust Clinical Trials

Pancreatic Enzymes and Bile Acids: A Non-Antibiotic approach to Treat Intestinal Dysbiosis in Acutely Ill Severely Malnourished Children

Study Specific Procedure	**SSP No:** CL07 **Version No:** 1.0 **Supersedes:** None **Effective Date:** 18th October 2021

Title: Safety Assessment Procedure

	NAME	SIGNATURE	DATE
PREPARER	Johnstone Thitiri		**15th June 2021**
Q.A. AUTHORITY	Aisha Bwika		**16th October 2021**
APPROVING AUTHORITY	Robert Bandsma		**17th October2021**

1.0 PURPOSE / INTRODUCTION:

- The purpose of this SSP is to guide reporting of serious adverse events (SAEs) and grade 3/4 toxicity events in the study.

2.0 SCOPE / RESPONSIBILITY:

- This SSP applies to all clinicians and nursing staff, involved in the clinical management of study participants.
- The SSP will also be used by Safety Review team centrally to coordinate the process of safety reporting.
- The Principal Investigator through the lead clinician retains the overall responsibility on implementation of this SSP.

3.0 DEFINITIONS/ INITIALS:

- **AEs** Adverse Events i.e. any untoward events occurring to a participant after receiving investigation product.
- **LSM** Local Safety Monitor
- **DSMC** Data & Safety Monitoring Committee
- **PI** Principal Investigator
- **SAEs** Serious Adverse Events
- **SOP** Study Operating Procedure
- **SUSAR** Suspected and Unexpected Serious Adverse Reaction
- **Serious Adverse Event (SAE)**: Any untoward medical occurrence or effect that Causes/Is:
  i. Death (from any cause at any time)
  ii. Re-hospitalization or an important medical event requiring medical or surgical intervention to prevent one of the outcomes listed above.
  iii. Life-threatening event (i.e., the subject was, in the view of the investigator, at immediate risk of death from the event that occurred).
  iv. Persistent or significant disability or incapacity (i.e., substantial disruption of ability to carry out normal life functions).
  v. Prolongs hospitalization whilst the child is still admitted in hospital

vi. Other serious medical event where medical intervention was required e.g. New diagnosis of TB, sickle cell disease etc

4.0 MATERIALS

- Serious Adverse Events Form
- Toxicity form

5.0 METHODOLOGY:

5.1 General considerations

5.1.1 Children admitted to hospital with complicated SAM are highly likely to experience many clinical events and deteriorations including mortality, often related to background clinical conditions.

5.1.2 The PB-SAM study will use marketed IPs that are routinely used for the treatment of other ailments including in children.

5.1.3 The IPs have good safety profiles. However, there are rarely reported adverse reactions that could result from the trial drugs. The 2 tables below summarize the known safety profile of the two IPs used in the PB SAM trial.

5.1.4 This SOP also serves as the safety management plan for the trial i.e. procedures adopted to monitor safety of IPs are captured in this SSP.

Reported side effects pancreatic enzymes	Specific side effect
Common/very common	Constipation
	Nausea/ Vomiting
Rare/very rare/unknown	Abdominal pain Dizziness
	Cough
	Diarrhea
	Fibrosing colonopathy
	Hypo-/hyperglycemia
	Allergic reaction/skin reactions

Table 1: Reported side effects of pancreatic enzyme replacement (per British National Formulary/BNF)

Reported side effects ursodeoxycholic acid	Specific side effect
Common/very common	Diarrhea
	Pale faeces
Rare/very rare/unknown	Abdominal pain
	Cholelithiasis calcification
	Nausea/Vomiting
	Exacerbation hepatic cirrhosis

Table 2: Reported side effects of ursodeoxycholic acid (BNF)

5.2 Safety Management

5.2.1 Safety reporting will apply to serious adverse events and toxicity only. Non-serious adverse events will not be recorded in the trial. However, participants will be clinically managed whenever the events require clinical intervention.

5.2.2 SAEs and Toxicities form part of trial objectives and are recorded and collected as trial data

5.2.3 There are 3 levels of safety management

a) Detection of safety events by clinical teams and notification to trial management team. This level may involve Local Safety Monitor.

b) Generation of reports for ethics and regulatory submission

c) Submission of reports to DSMC and subsequent review by the committee.

5.2.4 Safety events will be monitored continuously according to the plan in 5.2.3 above.

5.2.5 Routine summative reports will be curated and availed on demand and at scheduled intervals e.g. during annual progress reports.

5.3 Adverse events reporting (Toxicity reporting)

5.3.1 Report on adverse events considered to be causally related to the IPs i.e. toxicity.

5.3.2 Do not report on other adverse events considered unrelated to study IPs

	Grade 3	**Grade 4**
Allergic reactions	Generalized urticaria OR angioedema with intervention indicated OR symptoms of mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm OR laryngeal oedema
Hepatoxicity	ALT 5.0 to < 10.0 x ULN* OR Total bilirubin 2.6 to <5.0 x ULN	ALT > 10.0 x ULN OR Total bilirubin >5.0 x ULN
Diarrhoea	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)

Table 3: List of prespecified grade 3 and 4 events.

5.3.3 Important: Only grade 3 and 4 toxicities are reportable in the trial according to the protocol. The table below lists pre-defined grade 3 and 4 toxicities based on known safety profile of IPs.

5.3.4 Grade 3 and 4 reactions are considered significant enough to be SAEs. Ensure an

5.3.5 SAE form is completed as well.

5.4 Serious Adverse events reporting

5.4.1 Safety events considered Serious by a clinician must meet the criteria for SAEs (See appendix 1 below for definitions and criteria for SAE).

5.4.2 All SAEs are reportable to local IRBs, the Sponsor (and DSMC) and regulatory authority.

5.4.3 Timelines and procedures for reporting SAEs are dictated first by local IRB requirements. Ensure the site complies to these requirements at site.

5.4.4 Prioritize care of participant at detection of SAE. For emergency or serious safety concerns requiring input or assistance from the investigator team, notify the clinical lead/ chief investigator /LSM immediately using email, WhatsApp, or telephone contact.

5.4.5 Use the SAE form to document all adverse events that meet criteria for seriousness. The SAE form has 2 parts; the Initial reporting section i.e. Part A, completed upon detection of an SAE, and part B completed when the event has resolved/concluded, or the participant has been discharged from a hospital.

5.4.6 Use clinical notes, lab request forms, and other medical records to record all aspects of the SAE to include clinical signs and symptoms, assessment findings, investigations, treatments given, response to treatment and progress. Continue documentation throughout the progress of the event until final outcome.

5.4.7 Complete sections of SAE forms using information from 5.4.6 above.

5.4.8 Note that **ALL** prespecified grade 3 and 4 toxicities in PB SAM Trial meet criteria for SAE reporting.

5.4.9 Outline for reporting SAE

a) **Notification** – Upon detection of an SAE, immediately write to coordination team and the PI using the email: **sae@chainnetwork.org.** An acknowledgement will be sent to the site.

b) **Documentation**: Complete part 1 of SAE immediately.

c) **RedCap data entry**: Enter part 1 of SAE immediately onto RedCAP for SAE reports. This will be accessible by PI and reporting team.

d) **Review of SAE**: The site team will work with the study safety reporting team until a finalized report is ready. This will be shared as a pdf to site. This will be used for onward reporting to IRBs. If the PI/designee requires further details, clinical notes or their scan shall be provided to contribute to report writing.

e) **Local IRB, NDA and sponsor & DSMC reporting**: Submit report to IRBs and NDA within local reporting requirements. The PI/Designee will also report to the Sponsor and DSMC.

f) **Final reporting**: Repeat the same process of SAE completion for part B when the event has resolved or completed. Same review and reporting to IRBs, NDA, Sponsor and DSMB will follow as final reports for the SAE.

5.4.10 SAEs that are deemed causally related to the study drug (hence are toxicity events) and SUSARs will be initially reported to the sponsor, DSMC and regulatory bodies within 7 days of the investigators becoming aware of the event with a follow up report being provided within a further 8 calendar days. Local guidelines however take precedence over this requirement.

5.5 Safety reporting office of the PB SAM Trial

5.5.1 A safety reporting office within the data management team exists to manage all the safety reporting aspect of the trial.

5.5.2 The office is domiciled at University of Washington and will be responsible for monitoring, reviewing, report writing and onward notification of DSMC and other relevant authorities.

5.5.3 The office is also responsible for safety reports generation for purposes of submission to IRBs, drug agencies, sponsor and DSMC on demand or schedule.

5.6 Unblinding

5.6.1 If a safety event requires that clinicians taking care of the child are aware of the assignment of the study product (i.e. unblinding), this will be coordinated by site's local safety monitor.

5.6.2 Send (LSM) notification of intention to unblind to the central coordination team who will link LSM with trial statistician.

5.6.3 Trial statistician will reveal the required information directly to the LSM.

5.6.4 Document this break of blind by site team.

5.6.5 Subsequently, the participant will not continue to use study medication.

6.0 APPENDICES

6.1 Appendix 1: Definition of adverse events and reactions.

Term	**Definition**
Adverse Event (AE)	*Any untoward medical occurrence* in a patient or clinical investigation subject occurring in any phase of the clinical study whether or not considered related to the study drug. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or drug interactions. Anticipated day-to-day fluctuations of pre-existing conditions, that do not represent a clinically significant exacerbation, will not be considered AEs. Discrete episodes of chronic conditions occurring during a study period will be reported as adverse events in order to assess changes in frequency or severity. Adverse events will be documented in terms of a medical diagnosis(es). When this is not possible, the AE will be documented in terms of signs and symptoms observed by the investigator or reported by the subject. Pre-existing conditions or signs and/or symptoms (including any which are not recognized at admission but are recognized during the study period) present in a subject prior to the start of the study will be recorded on the medical history form within the subject's CRF.
Adverse Reaction (AR)	*An untoward and unintended response* in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects. *It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event*.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • results in persistent or significant disability/incapacity • rehospitalization for any reason (in a participant who was discharged) or an important medical event leading to severe

	clinical deterioration requiring medical or surgical intervention to prevent one of the outcomes listed above (i.e., a new diagnosis of TB not requiring admission) Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences. **NOTE:** The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which *hypothetically* might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction, the nature or severity of which is not anticipated based on the applicable product information is considered as an unexpected adverse drug reaction. Where the adverse reaction is also considered to have a possible, probable, or definite relationship with the drugs given, and also meets the criteria for a serious adverse reaction, it is termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). These events are subject to expedited reporting as for SAEs.

6.2 Appendix 2: Grading of adverse events according to Division of AIDs (DAIDs) criteria

Grade 1 Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate	Minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
Grade 3 Severe or medically significant but not immediately life-threatening	Hospitalization or prolongation of hospitalization; indicated disabling limiting self-care ADL.
Grade 4 Life-threatening consequences	Urgent intervention indicated.
Grade 5 Death related to AE.	Death

6.3 Appendix 3: PB SAM Trial pre-specified grade 3 and 4 toxicity events

7.0 References

- PB-SAM study protocol
- Pre-defined Grade 4 suspected toxicity events

- SAE CRF
- Toxicity CRF

8.0 DOCUMENT CHANGE HISTORY

Version Table:

Version 1.0: Title: **Safety Reporting Procedure**	Dated: **18th October 2021**	SSP No.: **CL07**	No. Pages: **10**
Version 2.0: Title:	Dated:	SSP No.:	No. Pages:
Version 3.0: Title:	Dated:	SSP No.:	No. Pages:
This document is effective from the date of training/last approval signature and will be reviewed in two years.			

SSP Review and Updating Logs

DATE	NAME OF REVIEWER	SIGNATURE	REASON FOR REVIEW AND CHANGES MADE

SSP AWARENESS LOG

I, the undersigned below, hereby confirm that I am aware that the accompanying SSP is in existence from the date stated herein and that I shall keep abreast with the current and subsequent SSP versions in fulfilment of Good Clinical Practice (GCP).

Number	Name	Signature	Date (dd/mmm/yyyy)
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