# SNAP TRIAL INTEGRITY SUITE: GLOBAL SAFETY REPORTING PLAN

## DOCUMENT APPROVAL

| VERSION NUMBER | DATE | CREATED BY | APPROVED BY | SIGNATURE OF APPROVAL |
|---|---|---|---|---|
| 1.1 | 11-05-2026 12:56:09 AEST | GTMG | Steven Tong | eSIGNED by Steven Tong on 31-03-2026 |
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| | | | Zoe McQuilten | eSIGNED by Zoe McQuilten on 11-05-2026 |

*Members of the SNAP Trial Global Trial Steering Committee (GTSC) and Regional Trial Management Groups (RTMGs) have had the opportunity to review this document, and it has been signed by the Chief Investigators and the Chair of the GTSC on behalf of the SNAP Trial.*

**IF ADAPTING THIS DOCUMENT, PLEASE ACKNOWLEDGE US VIA THE FOLLOWING STATEMENT:**

"This document has been adapted from the *Staphylococcus Aureus* Network Adaptive Platform (SNAP) Trial Integrity Suite: Global Safety Reporting Plan (Version 1.1), available from the SNAP Trial website: https://www.snaptrial.com.au/for-investigators#integrity.

The SNAP trial, globally coordinated by the University of Melbourne, is an international adaptive platform trial aimed at identifying the most effective treatments for *Staphylococcus aureus* bloodstream infections."

# 1 CONTENTS

# 2 SNAP TRIAL INTEGRITY SUITE

The SNAP Trial Integrity Suite is a comprehensive collection of essential documents that provide evidence and guidance for the conduct and oversight of the SNAP Trial globally and sets the minimum standards of compliance for the study.

The SNAP Trial Integrity Suite is comprised of the following documents:

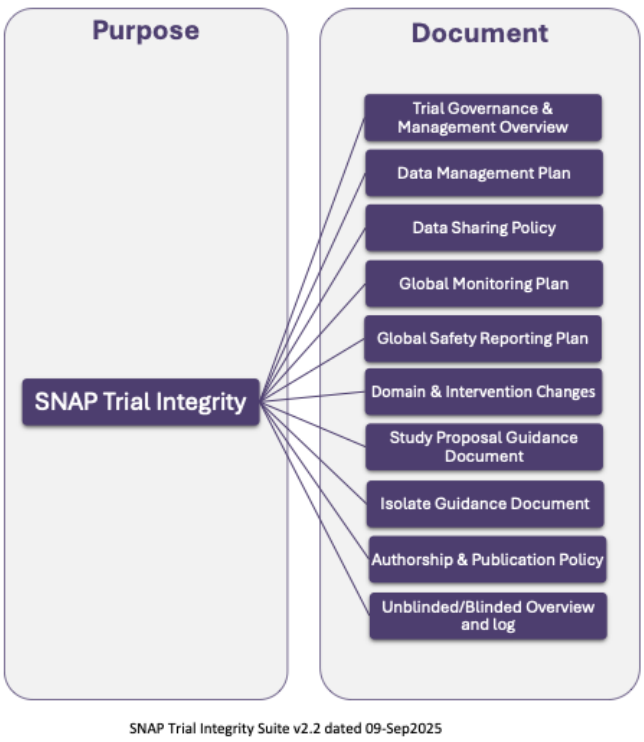



**Figure 1 Trial Integrity Suite**

# 3 INTRODUCTION

SNAP is a comparative effectiveness trial using registered interventions that are routinely used for treatment of *Staphylococcus aureus* bacteraemia (SAB). Patients eligible for the SNAP trial are at significant risk of morbidity or mortality from SAB and its complications. Regardless of participation in the trial, many such events would meet the conventional definitions of a Serious Adverse Event (SAE).

The safety reporting described here should be considered a minimum requirement, that can be applied to comparative effectiveness of known and registered interventions. This strategy aims to respect participant safety and rights whilst reducing the reporting of events that are likely to be part of the course of the illness or events that are already recognised as important and recorded as trial endpoints. Additional region-specific reporting above the minimum requirements will be documented in a region-specific safety reporting plan or SOP.

In the circumstance that novel, early phase or registrational trial interventions are included in the trial, additional safety monitoring and reporting procedures will be outlined in the relevant appendices and detailed in an update to this document.

This document should be read in conjunction with the **Data Management Plan** and **Monitoring Plan.**

# 4 DEFINITIONS

The term **'safety event'** will be used throughout this document to refer to an event that would meet the region-specific definition of an adverse event that requires recording and/or reporting.

Recording and reporting are defined separately in this document:

- **Recording** is the logging or documentation of the event
- **Reporting** is notification of the event to the relevant authorities (e.g., sponsor, ethical review body, regulatory bodies, etc.).

The definitions for the classification of safety events in the SNAP Trial are defined below. All definitions will be referenced by their acronyms throughout this document. These definitions are consistent with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH-GCP) *2016* and the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting 1995.

**Table 1 Safety Event Definitions**

| Term | Description |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a patient/trial participant that has been administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.<br>*An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the product.* |
| Adverse Reaction (AR) / Adverse Drug Reaction (ADR) | Any AE to a medicinal product related to any dose administered.<br>**Comment**: All adverse events judged as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship. |
| Reference Safety Information (RSI) | The information contained in a region-specific approved product information (or other country equivalent) that contains the information used to determine what adverse reactions are to be considered expected adverse reactions and, on the frequency and nature of those adverse reactions.<br>***Note***: *In the SNAP Trial, the RSI is the product information sheet available by the regulatory authorities in that region.* |
| Serious Adverse Event (SAE) | An SAE is any adverse event that:<br>o Results in death<br>o Is life-threatening<br>*The term "life threatening" 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 may have caused death, if it were more serious.*<br>o Results in unexpected prolongation of existing hospitalisation<br>o Results in persistent or significant disability/incapacity<br>o Is a medically important event or reaction |

| | |
|---|---|
| | ○ Is a congenital anomaly/birth defect<br><br>For the SNAP Trial, an SAE must fulfil a minimum of one of the above criteria and be assessed as a **grade 3 or higher** according to CTCAE, NAESS (neonates) or MFAET (foetal) criteria.<br><br>***Note***: *Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.* |
| Serious Adverse Reaction (SAR) / Serious Adverse Drug Reaction (SADR) | Any SAE that is suspected to be related (i.e., there is a reasonable causal relationship) to a randomised intervention allocated to the patient within the SNAP Trial used for *S. aureus* bacteraemia. In other words, this is an event which qualifies as both a serious adverse event AND an adverse reaction. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) / Unexpected Adverse Drug Reactions (UADR) | Any SAE that is both unexpected (i.e., its nature or severity is not consistent with the Approved Product Information) and suspected to be related to the medicinal product used for *S. aureus* bacteremia (i.e., there is a reasonable causal relationship with that medicinal product). |
| Significant Safety Issue (SSI) | A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.<br><br>**This term is not applicable in all regions* |
| Urgent Safety Measure (USM) | A measure required to be taken to eliminate an immediate hazard to a participant's health or safety. (A subset of significant safety issues).<br><br>**Note**: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from relevant ethics committees or institutions. |

# 5 PRESPECIFIED SAFETY EVENTS OF SPECIAL INTEREST

Trial endpoints designed to capture specific safety events will be referred to in this document as '**prespecified safety events of special interest'**.

These secondary endpoints, as outlined in the Core Protocol and appendices, are designed to record most safety events that might occur in the trial. Where required, domain-specific endpoints will be included in each domain-specific appendix to capture additional adverse events that may be specifically associated with a particular intervention.

# 6 SAFETY REPORTING REQUIREMENTS

All safety events are documented using the Safety Reporting CRF. Once available, all safety events will be logged in the Spinnaker database.

At a minimum, safety events should be documented for all participants between platform entry and platform day 90, or 30 days post-last treatment dose, whichever is earlier. Any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner) should be documented until 6 weeks post-delivery.

At a minimum, all regions will be required to:

- Record SARs as specified in the Core Protocol *(this includes SARs that occur from a SNAP treatment allocated as part of a domain or sub-study).*
- Report all SSIs including USMs (where applicable in the region) and SUSARs as specified in the Core Protocol.

The Safety Reporting CRF outlines the minimum safety reporting requirements for SNAP.

## 6.1 REGION-SPECIFIC SAFETY REPORTING REQUIREMENTS

The safety reporting requirements outlined in this document are the minimum requirements for SNAP. The level of additional recording and reporting required in each region will vary – the requirements will be outlined in each region-specific appendix and region-specific safety reporting procedure documentation. Additional recording and reporting of AEs and SAEs will be determined at a regional level.

Please see **Appendix 1** for a flowchart demonstrating the current region-specific reporting requirements; this will be updated with each review of this document to ensure correctness.

Events that meet the criteria of a safety event will be reviewed by the Regional Trial Management Group (RTMG). These events should be documented by the site as soon as becoming aware of the event, and within the timeframes specified in the region-specific guidelines and Core Protocol.

## 6.2 REQUIREMENT FOR EXTERNAL CLINICAL REVIEW

All reported serious safety events will require an independent assessment by a qualified, trained and delegated clinical reviewer. The clinical reviewer will confirm:

- The event meets the definition of a safety event (an event that requires recording or reporting in that region)
- The event has been assessed for seriousness, causality (relatedness) and expectedness against the region-specific Reference Safety Information (RSI)
- If the event is considered a SUSAR and/or SSI (if applicable in the region)

Each region can choose to nominate one or more clinical reviewers, who will provide this external review for each safety event documented. If the clinical reviewer is also an investigator of the SNAP trial, they will not be able to review safety events documented at their own site(s).

## 6.3 REQUIREMENT FOR MEDDRA CODING

MedDRA coding is based on a terminology belonging to the Medicines and Healthcare products Regulatory Agency (MHRA) of UK (previously named Medicines Control Agency) and was developed using the ICH process.

For the SNAP Trial, the safety events will be coded at the Lower-Level Term (LLT) using the most current version of the medDRA database, as per the following database specifications:

- **medDRA version:** *Most current version*
- **Browser view:** SOC
- **Coded by:** Lower-Level Term (LLT)

The RTMGs will be responsible for ensuring that all serious safety events that are documented within their region are medDRA coded. It is the responsibility of the RTMG to determine who will code the events; in some regions the medDRA coding must be applied by a specifically trained and qualified

individual and/or a medical doctor/clinician. It is also the responsibility of the RTMG to ensure the medDRA code and term are recorded for each safety event.

If the region does not have access to the medDRA online database, the following medDRA coding tools will be provided by the GTMG:

- **Most common medDRA terms (by LLT)** – this list is a subset of LLTs that has been derived from the most frequently reported SARs in the SNAP Trial
- **medDRA Coding REDCap database** – this REDcap database will provide access to the medDRA LLTs via an automated programming interface (API) that links in directly to the current version of the medDRA database.

If the event is unable to be coded using these tools, the RTMGs may reach out to the GTMG to discuss the event further.

The safety events will be summarised in reports by Preferred Term (PT) (and/or Higher-Level Term (HLT) and/or System Organ Class (SOC), if required). The hierarchical structure of medDRA will be applied to the LLT using the most current version of the database for each report, ensuring that all events receive the most up to date coding when reported.

For more information on medDRA hierarchy, please review this link: https://www.meddra.org/how-to-use/basics/hierarchy

# 7 SAFETY REPORTING RESPONSIBILITIES

The responsibilities described in this document apply to all site team members involved in the SNAP Trial. RTMG and GTMG responsibilities may be delegated to third parties, such as Clinical Research Organisations/Centres, Data Safety Monitoring Committees (DSMC) or Coordinating Investigators (CPIs), provided that arrangements are in place for oversight of any delegated activities.

## 7.1 SITE RESPONSIBILITIES

The Principal Investigator (PI) at each site maintains overall responsibility for the actions outlined in this section and is responsible for supervising any individual to whom they have delegated safety monitoring or reporting duties.

**The site PI (or their delegate) will:**

- Ensure all AEs are assessed for seriousness, causality (relatedness), and expectedness
- Ensure all safety events are documented at a minimum between platform entry and day 90, or 30 days post-last treatment dose, whichever is earlier.
- Ensure all safety events pertaining to congenital anomalies/birth defects are monitored out to 6 weeks post-delivery.
- Ensure all safety events are recorded as per region-specific requirements
- Ensure all safety events are reported as per region-specific requirements
- Ensure any follow-up information is recorded as soon as it is available, by completing a follow-up or final safety report.
- Ensure that all SSIs including USMs (where applicable in the region) and SUSARs are reported to the RTMG within 24 hours of becoming aware of the event
- Review all safety communications from the RTMG to ensure implications for trial participants are managed appropriately

## 7.2 REGIONAL TRIAL MANAGEMENT TEAM (RTMG) RESPONSIBILITIES

The RTMG will establish a region-specific safety reporting plan that complies with region-specific requirements that are based on the risk, size, and complexity of the research. The RTMG will ensure that this plan does not conflict with the minimum standards outlined in the global safety reporting plan.

The RTMG will evaluate all safety events documented by site investigators as well as safety information from other sources.

**The RTMG (or their delegate) will:**

- Review all safety events that are recorded or reported within the region
- Ensure that all safety events are reviewed by an external clinical reviewer to confirm event meets the region-specific safety reporting criteria
- Ensure medDRA codes are applied to each serious safety event and that these medDRA codes are applied and/or reviewed by a qualified clinical reviewer
- Ensure all safety events are reported to the GTMG within agreed upon timelines as per the International Sponsor Agreement for each region.
- Report, in an expedited manner to the GTMG, all safety events classified as SUSARs to the regulatory body, ethical review body according to local regulations and requirements
- Report to the GTMG, in an expedited manner, all safety events classified as SSIs (where applicable, including USMs) to the regulatory body, ethical review body, and sites according to local regulations and requirements
- Report all safety events classified as SSIs including USMs (where applicable in the region) to the regulatory body, ethical review body, and sites according to local regulations and requirements
- Communicate any impact that documented safety events may have on patient safety, trial conduct or trial documentation to the sites

## 7.3 GLOBAL TRIAL MANAGEMENT TEAM (GTMG) RESPONSIBILITIES

The GTMG will establish the global safety reporting processes for the trial based on the risk, size, and complexity of the research. The GTMG will compile all safety information that is recorded and reported for the interim analyses reporting, annual safety reporting, and final analysis reporting requirements.

**The GTMG will:**

- Ensure a safety reporting CRF/eCRF is implemented
- Ensure that global safety data is available for region-specific reporting requirements
- Ensure global safety data is compiled for the scheduled interim and final analyses, which undergo DSMC review
- Ensure that all RTMGs are provided with access to medDRA coding tools to appropriately code safety events
- Communicate any impact that documented safety events may have on patient safety, trial conduct or trial documentation to the RTMG and GTSC.

## 7.4 GLOBAL TRIAL STEERING COMMITTEE (GTSC), DATA SAFETY AND MONITORING COMMITTEE (DSMC), AND ANALYTIC TEAM (AT) RESPONSIBILITIES

The specific responsibilities of the Global Trial Steering Committee (GTSC), Data Safety Monitoring Committee (DSMC), and Analytic Team (AT) are outlined in detail in the committee or working group's Terms of Reference (ToR).

# 8 SAFETY REPORTING PROCEDURES

The site will assess all adverse events against the region-specific guidelines to determine whether the event meets the criteria of a safety event and requires recording and/or reporting.

## 8.1 ASSESSING ADVERSE EVENTS

AEs are expected to be assessed for all participants between platform entry and platform day 90, or 30 days post-last treatment dose, whichever is earlier. If the participant is pregnant, birth anomalies will be monitored past day 90.

For this study, all AEs should be evaluated for seriousness, causality, and expectedness prior to proceeding with any recording or reporting requirements:

1. **Seriousness** – *is the AE serious?*
2. **Causality (relatedness)** – *is there a reasonable causal relationship between the AE and the study treatment?*
3. **Expectedness** – *is the AE unexpected for that treatment?*

Further details for assessing adverse events for seriousness, causality and expectedness can be found in **Appendix 2**.

## 8.2 RECORDING & REPORTING SAFETY EVENTS

If an adverse event is determined to meet the region-specific criteria of a safety event, the site will be required to document the occurrence using the Safety Reporting CRF.

If a prespecified safety event of special interest occurs, these events will be recorded on the database as part of the regular CRF questions.

- If any of the pre-specified safety events of special interest are assessed as **both** 'serious' and 'related', they are considered an SAR and need to be logged additionally as a safety event using the Safety Reporting CRF.
- If any of the pre-specified safety events of special interest are required to be additionally documented as an AE/SAE as per region-specific requirements, they should be logged additionally as a safety event using the Safety Reporting CRF.

The site should record and/or report all safety events as per the timelines specified in their region-specific guidelines.

## 8.3 REVIEWING & CODING SAFETY EVENTS

All safety events will be reviewed by the RTMG for completeness, and the RTMG will be responsible for querying the site for any missing data.

The RTMGs will obtain review by an external clinical reviewer for each safety event to ensure that the event is assessed against the region's Reference Safety Information (RSI) as specified in **Section 5.2** of this document.

The RTMG will ensure that the medDRA coding is applied for each event by a qualified person as specified in **Section 5.3** of this document.

# 9 MAINTAINING TRIAL INTEGRITY IN REPORTS CONTAINING SAFETY EVENT DATA

To protect trial integrity, it is vital that the reporting of safety events does not inadvertently unblind the investigators and/or the wider public to the primary or secondary outcomes of the SNAP Trial.

The primary endpoint of the trial is 90-day mortality, and the objective of the trial is to identify differences in the primary endpoint that can be attributed to treatment allocation, which will often include treatments that are believed to be or known to be safe, and effective but for which it is not known whether some treatments are more effective than others.

Therefore, details regarding trial intervention and outcome of death will be omitted from reports provided to the blinded community – this includes open reports from the interim analyses as well as region-specific reports (such as DSURs). It is recognised that while certain safety events can be omitted from the line listings and summary tabulations, these omissions should be explained in the report.

See the **Data Management Plan** for more information.

## 9.1 REPORTING SAFETY EVENTS IN THE SCHEDULED ANALYSES

Safety events will form part of the scheduled interim analysis reports. The Analytic Team will be responsible for preparing both the open (blinded) and closed (unblinded) reports for review at each scheduled analysis.

- **Closed Report (unblinded):** will only be reviewed by the Data Safety Monitoring Committee (DSMC)
- **Open Report (blinded):** will be reviewed by the GTSC and GTMG and can be accessed by the RTMGs in order to complete region-specific reporting requirements.

***To note:*** *only events that are classified as 'serious' (SAEs/SARs) will be included in reports containing safety event data that are produced by the analytic team. As not all regions are collecting and reporting SAEs, SAE data summarised in the reports will only be reflective of the regions who are collecting and reporting these to the GTMG.*

Safety events will be summarised in the reports as table summaries and will be categorised by medDRA Preferred Term and Code (PT) and System Organ Class (SOC):

- **SAEs:** reported as tabulated cumulative summaries (by domain and overall)
- **SARs:** reported as tabulated cumulative summaries (by domain) and line listing summaries (overall).

See **Appendix 3** for an example of each style of summary table.

### 9.1.1 CLOSED (UNBLINDED REPORT)

Safety events included in the closed report will be summarised as follows:

- **Serious Adverse Events (SAEs; regions collecting SAEs):** will be stratified by domain and intervention and can contain outcome data and other information as requested by the DSMC.
- **Serious Adverse Reactions (SARs; all regions):** will be stratified by domain and intervention. These events will include outcome data and can include other information as requested by the DSMC.

### 9.1.2 OPEN (BLINDED) REPORT

Safety events included in the open report will be summarised as follows:

- **Serious Adverse Events (SAEs; regions collecting SAEs):** will be stratified by domain with events pooled across domain arms. SAEs will not be stratified by trial intervention or contain outcome data.

- **Serious Adverse Reactions (SARs; all regions):** will be stratified by domain with events pooled across domain arms. The relatedness of the trial intervention will be available, but the intervention itself will be excluded. Outcome data will be available (with the exception of death); events meeting the primary endpoint of death will be recoded as 'resolved'.

## 9.2 REPORTING SAFETY EVENTS IN REGION-SPECIFIC REPORTS

SAE and SAR data can be provided to RTMGs in order to develop region-specific annual reports (for example, DSURs). RTMGs will be responsible for communicating the reporting timelines to the GTMG.

- **Serious Adverse Events (SAEs; regions collecting SAEs):** can be included in region-specific report stratified by domain with events pooled across domain arms. SAEs cannot be stratified by trial intervention or contain outcome data.
- **Serious Adverse Reactions (SARs; all regions):** can be included in region-specific stratified by domain with events pooled across domain arms. The relatedness of the trial intervention will be available, but the intervention itself will be excluded. Outcome data will be available (with the exception of death); events meeting the primary endpoint of death will be recoded as 'resolved'.

***To Note:*** *If region's regulatory body disagrees with a DSMC decision based on data provided to them via a report and wishes to halt/stop recruitment to one or more interventions, this would be considered by the DSMC, but would only be implemented in that region (and not impact global recruitment).*

## 9.3 USEFUL EXAMPLES

A heart attack that is not related to study intervention, considered serious = SAE (region not recording SAEs)

This event is not considered a safety event and cannot be included in the reports as it will not be recorded.

- **Closed Report:** will not be included as event will not be recorded
- **Open Report:** will not be included as event will not be recorded
- **Region-Specific Report:** cannot be included as event will not be recorded

A heart attack recorded for a participant in the backbone domain that is not related to a study intervention that results in death = SAE (region recording SAEs)

This safety event medDRA name (PT) and System Organ Class (SOC) will be included in the reports in the following manner:

- **Closed Report:** included as part of the tabulated summaries; backbone domain and intervention allocation will be included.
- **Open Report:** included as part of the tabulated summaries; backbone domain allocation will be included but intervention allocation will be excluded.
- **Region-Specific Report:** can be included; backbone domain allocation can be included but intervention allocation must be excluded.

A heart attack recorded for a participant in the backbone domain that is possibly related to a study intervention (cefazolin), that results in death = SAR (all regions)

This safety event medDRA name (PT) and System Organ Class (SOC) will be included in the reports in the following manner:

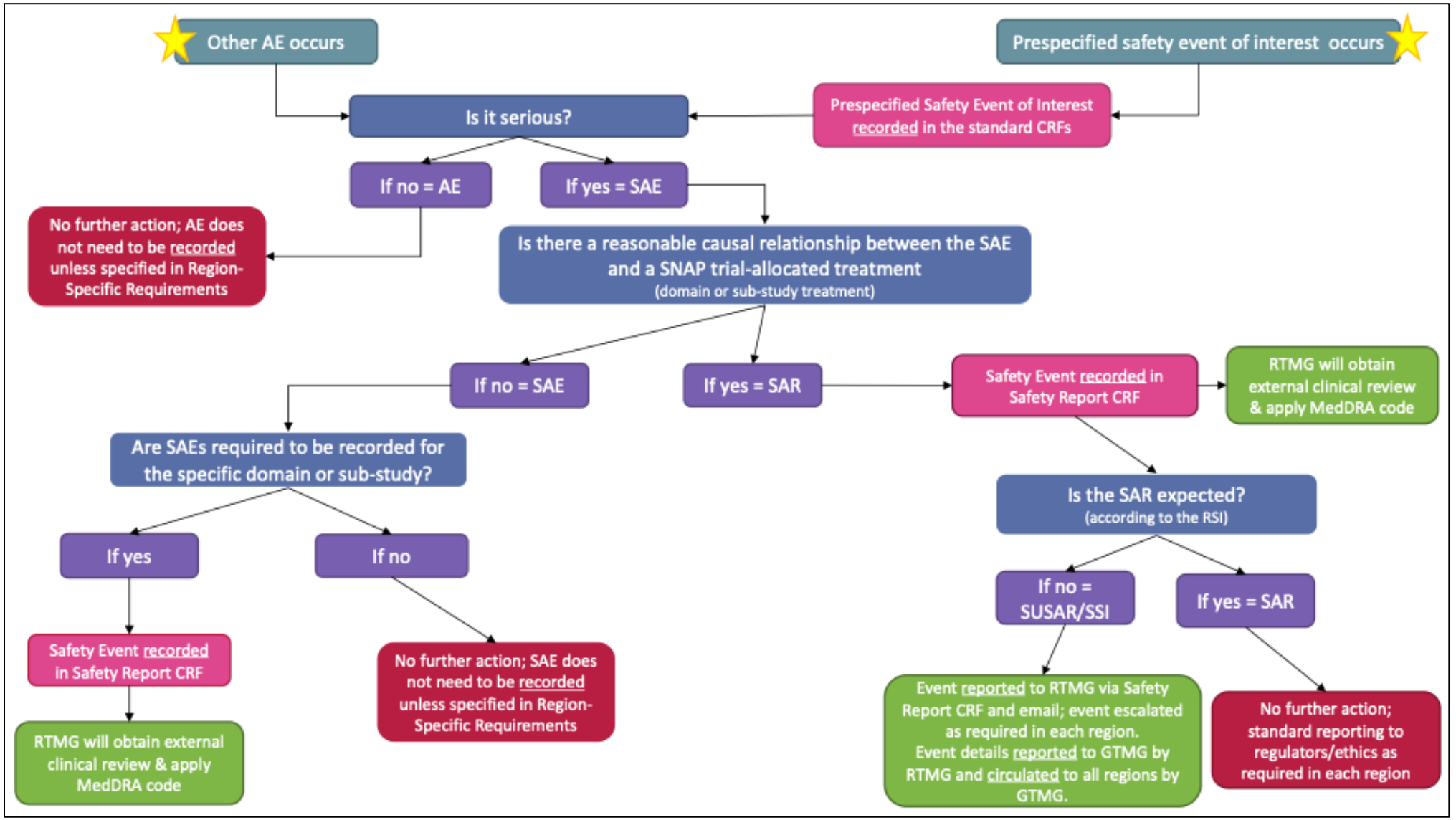
- **Closed Report:** included as part of the tabulated and line listing summaries; backbone domain and cefazolin intervention allocation will be included, as well as the outcome of death.
- **Open Report:** included as part of the tabulated and line listing summaries; backbone domain allocation will be included as well as the possible relatedness of the trial intervention (but the intervention itself will be excluded). The outcome of death will be recoded as 'resolved'.
- **Region-Specific Report:** can be included; backbone domain allocation can be included as well as the possible relatedness of the trial intervention (but the intervention itself must be excluded). The outcome of death will be recoded as 'resolved'.

# 10 APPENDICES

## 10.1 APPENDIX 1: RECORD OF CHANGES

| VERSION NUMBER | VERSION DATE | SECTIONS AFFECTED | SUMMARY OF CHANGES | LEAD AUTHOR |
|---|---|---|---|---|
| 1.0 | 01-Apr-25 | - | - | Lauren Barina |
| 1.1 | 31-Mar-26 | All | Minor changes to terminology and formatting align with other Trial Integrity Documents | Lauren Barina |

## 10.2 APPENDIX 2: FLOWCHART OF REGIONAL SAFETY REPORTING REQUIREMENTS



## 10.3 APPENDIX 3: ASSESSING SAFETY EVENTS

The below sections can be used as a guide for assessing safety events for seriousness, causality (relatedness) and unexpectedness.

### 10.3.1 SERIOUSNESS

An assessment of whether the AE meets the definition of a Serious Adverse Event (SAE).

**An SAE is any AE that:**

- Results in death
- Is life-threatening
- Results in unexpected prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a medically important event or reaction
- Is a congenital anomaly/birth defect

For the SNAP Trial, an SAE must fulfil a minimum of one of the above criteria and be assessed as a **grade 3 or higher** according to CTCAE, NAESS (neonates) or MFAET (foetal) criteria as per the below:

**Table 2 CTCAE, NAESS, MFAET Criteria for Seriousness**

| **Grading the Severity of Adverse Events according to CTCAE (Common Terminology Criteria for Adverse Events)** |
|---|
| • **Grade 1** - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.<br>• **Grade 2** - Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).<br>• **Grade 3** - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.<br>• **Grade 4** - Life-threatening consequences; urgent intervention indicated.<br>• **Grade 5** - Death related to AE.<br><br>More information:<br>https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf |
| **Grading the Severity of Adverse Events according to INC (International Neonatal Consortium) NAESS (Neonatal AE Severity Scale)** |
| • **Grade 1** - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behaviour*; no change in baseline care or monitoring indicated.<br>• **Grade 2** - Moderate; resulting in minor changes of baseline age-appropriate behaviour*; requiring minor changes in baseline care or monitoring*†<br>• **Grade 3** - Severe; resulting in major changes of baseline age-appropriate behaviour* or non-life-threatening changes in basal physiological processes†; requiring major change in baseline care or monitoring*‡<br>• **Grade 4** - Life threatening; resulting in life-threatening changes in basal physiological processes†; requiring urgent major change in baseline care.<br>• **Grade 5** - Death related to AE.<br><br>* Age-appropriate behaviour refers to oral feeding behaviour, voluntary movements and activity, crying pattern, social interactions and perception of pain.<br><br>† Basal physiological processes refer to oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning.<br><br>‡ Minor care changes constitute: brief, local, non-invasive or symptomatic treatments.<br><br>§ Major care changes constitute: surgery, addition of long-term treatment, upscaling care level. |

More information: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943241/pdf/archdischild-2019-317399.pdf

**Grading the Severity of Adverse Events according to MFAET (Maternal and Foetal Adverse Event Terminology)**

- **Grade 1** - Mild; clinical observation of uncertain significance; resolves spontaneously with low risk of long-term consequences.
- **Grade 2** - Moderate; likely to resolve spontaneously with low risk of long-term consequences; requires increased frequency of monitoring, but less than once a week; requires additional tests.
- **Grade 3** - Severe; requires increased frequency of monitoring, once a week or more; likely to lead to significant neonatal morbidity.
- **Grade 4** - Life-threatening; likely to lead to foetal injury or permanent disability; likely to lead to neonatal death; requiring a substantive change in management including changing the course of an interventional procedure or necessitating delivery.
- **Grade 5** - Foetal death.

More information: https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/pd.6047

### 10.3.2 CAUSALITY (RELATEDNESS)

A clinical assessment of whether there is a reasonable causal relationship between the AE and the allocated trial treatment(s). The PI (or medically qualified delegate) will be responsible for making this judgement.

The degree of certainty with which an AE is attributable to treatment, or an alternative cause will be determined by how well the event can be understood in terms of:

- Temporal relationship with the administration of the treatment or cessation of treatment
- Reactions of a similar nature previously observed in the individual or others following treatment

**The opinion of the relationship between the AE and the trial treatment(s) will be specified as per the table below:**

**Table 3 Definition of causality terms**

| Term | Description |
|---|---|
| Not related | There is not a causal relationship with a SNAP-trial allocated treatment. |
| Unlikely | The temporal association between a SNAP-trial allocated treatment and the adverse event is such that treatment is not likely to have any reasonable association. |
| Possibly | The AE could have been caused by a SNAP-trial allocated treatment. |
| Probably | The AE follows a temporal sequence from the time of the SNAP-trial allocated treatment and cannot be reasonably explained by the known characteristics of the participant's clinical presentation/history. |
| Definitely | The AE follows a reasonable temporal sequence from the time of SNAP-trial allocated treatment or reappears when the treatment is repeated. |

### 10.3.3 EXPECTEDNESS

An assessment against the AEs listed in the trial's Reference Safety Information (RSI; the relevant Production Information) as expected occurrences (considering the nature and frequency of the event).

The PI (or medically qualified delegate) will make a judgement as to whether an AE is unanticipated and/or unknown for the treatment given the current safety information available.

## 10.4 APPENDIX 4: SUMMARY TABLES FOR THE INTERIM ANALYSIS REPORTS (SAES AND SARS)

As a reminder, blinded reports (open interim reports and region-specific reports) cannot contain any data relating to intervention allocation or an outcome of death (trial primary outcome).

### 10.4.1 TABULATED CUMULATIVE SUMMARIES (SAES & SARS)

SAEs and SARs will be summarised in the open and closed reports as per the table below:

| MedDRA System Organ Class | MedDRA Preferred Term | Pooled Over both study arms |
|---|---|---|
| Blood and lymphatic system disorders | Anaemia | 8 |
| | Normochromic normocytic anaemia | 1 |
| | Pancytopenia | 1 |
| | **SOC total** | **10** |
| | | |
| Cardiac disorders | Sinus tachycardia | 1 |
| | **SOC total** | **1** |
| | | |
| Ear and labyrinth disorders | Tinnitus | 1 |
| | **SOC total** | **1** |
| | | |
| Gastrointestinal disorders | Abdominal hernia obstructive | 1 |
| | Abdominal pain | 2 |
| | Anal fissure | 2 |
| | Anal pruritus | 1 |
| | Colitis | 1 |
| | Colitis ulcerative | 3 |
| | Diarrhoea | 1 |
| | Gastrointestinal toxicity | 1 |
| | Inguinal hernia, obstructive | 1 |
| | Intestinal obstruction | 3 |
| | Oesophageal rupture | 1 |
| | Pancreatitis acute | 1 |
| | Proctitis | 2 |
| | Rectal haemorrhage | 1 |
| | Retroperitoneal haemorrhage | 1 |
| | Small intestinal obstruction | 2 |
| | **SOC total** | **24** |

**As part of the closed (unblinded report), the tables will contain columns for treatment allocation.*

### 10.4.2 LINE LISTING SUMMARIES (SARS ONLY)

SARs will also be summarised in the open and closed reports as per the table below:

| Country code | Age, gender | Date of onset | Adverse Reaction MedDRA PT | Outcome | Relatedness | Dates of treatment | Comments |
|---|---|---|---|---|---|---|---|
| USA | 23 M | 26-FEB-14 | Suicidal ideation | resolved | possibly | 04-DEC-12 - continuing | |
| | | | | | | | |
| ZAF | 36 F | 10-JUL-13 | Drug-induced liver injury | resolved with sequelae | probably | 12-DEC-12 - 09-JUL-13 | |
| | | | | | | | |
| THA | 44 F | 25-MAR-14 | Drug-induced liver injury | resolved | probably | 26-FEB-14 - 25-MAR-14 | |
| | | | | | | | |
| USA | 50 M | 06-NOV-13 | Major depression | resolved | possibly | 11-MAY-10 - continuing | |
| | | | | | | | |
| CHL | 47 M | 14-JAN-14 | Suicide attempt | resolved | probably | 30-APR-13 - 14-JAN-14 | |
| AUS | 30 M | 04-JUL-13 | Gastroenteritis viral | resolved | possibly | 10-MAR-13 - continuing | |
| | | | | | possibly | 10-MAR-13 - continuing | |

**As part of the closed (unblinded report), the tables will contain columns for treatment allocation and dosing details as well.*