SNAP TRIAL INTEGRITY SUITE: DOMAIN & INTERVENTION CHANGES

DOCUMENT APPROVAL

VERSION NUMBER	DATE	CREATED BY	APPROVED BY	SIGNATURE OF APPROVAL
1.1	11-05-2026 13:04:40 AEST	GTMG	Steven Tong	eSIGNED by Steven Tong on 31-03-2026
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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: Domain & Intervention Changes (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."

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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:

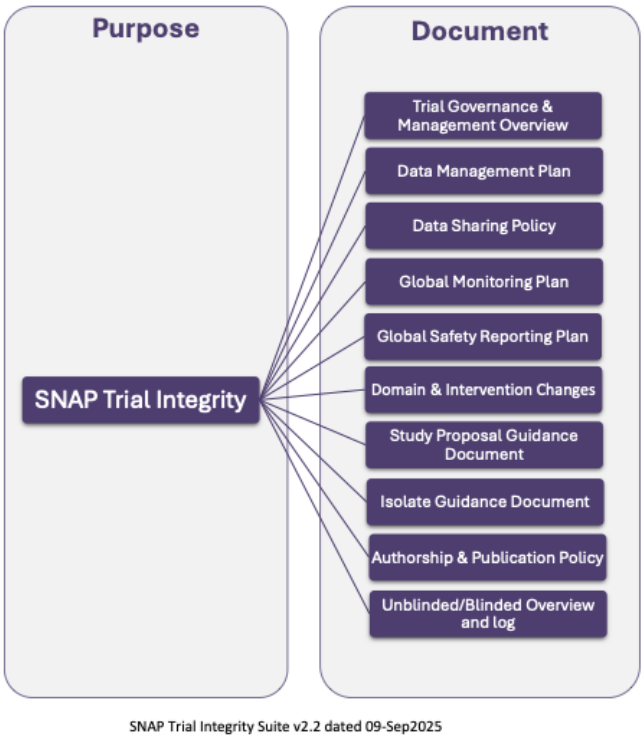


Figure 1 Trial Integrity Suite

3 INTRODUCTION

This document outlines the procedures undertaken when new treatment arms or domains are added, or existing treatment arms or domains are closed or temporarily suspended in the SNAP Trial. This includes the guidelines for making decisions regarding adding, closing, or suspending treatment arms or domains, procedures for informing HREC, and procedures for notifying sites and participants.

As an adaptive trial, it is crucial that the changes to interventions and domains are implemented quickly, when signals for stopping are made apparent or new treatments become available. This SOP provides clarity for how these changes can be implemented in a safe and time-sensitive manner.

4 DEFINITIONS & ACRONYMS

These definitions are consistent with the National Health and Medical Research Council (NHMRC) definitions for the categorisation of safety events for IMPs, as specified in the guidance document *Safety monitoring and reporting in clinical trials involving therapeutic goods*, NHMRC (2016).

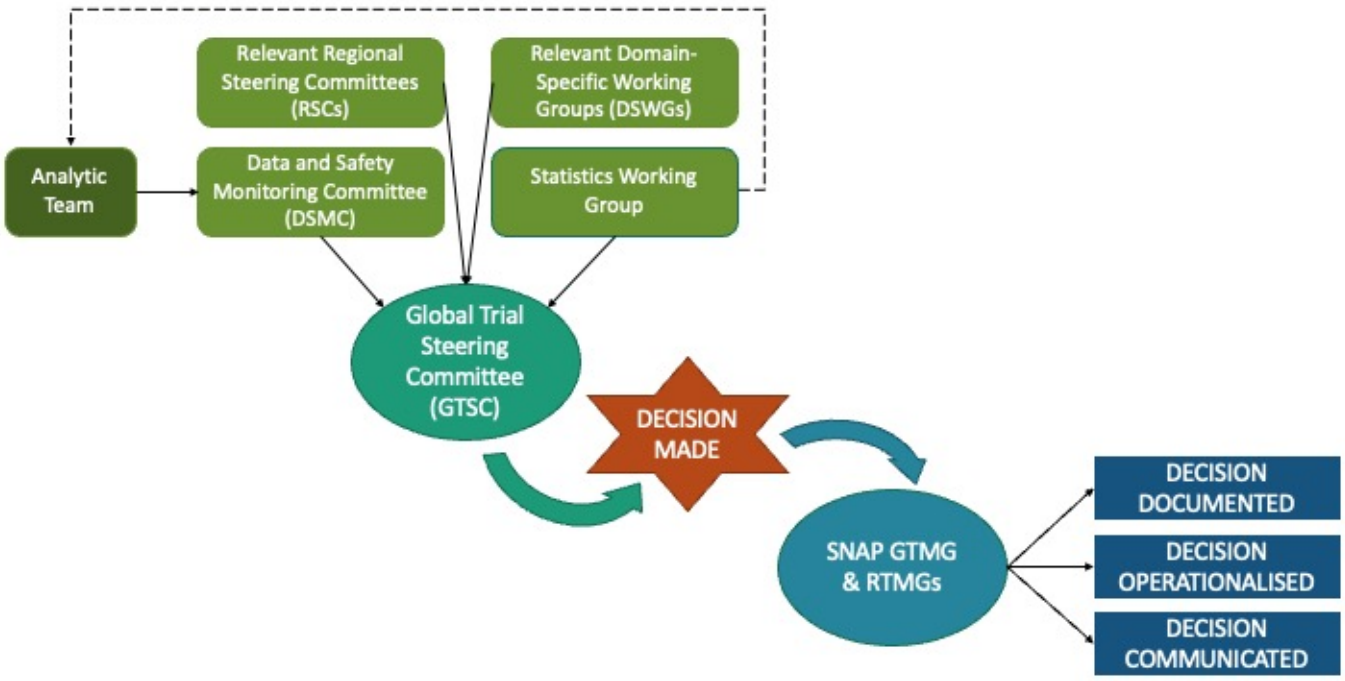
All definitions may be referenced by their acronyms throughout this document.

Term	Description

Ethical Review Body (ERB)	The international reviewing body responsible for providing ethical review of a multi-centre human research project in a specific region
Global Trial Steering Committee (TSC / Global TSC / GTSC)	The Global Trial Steering Committee keep abreast of emerging evidence from the SNAP Trial as well as external evidence, and discuss the advice provided by the other committees. The final decision on whether to add, close or suspend treatment arms rests with the GTSC.
Data and Safety Monitoring Committee (DSMC)	The Data and Safety Monitoring Committee review data arising from the trial and evaluate the safety of the interventions. The DSMC may provide recommendations to the GTSC to either continue with the trial, stop the trial, or continue with modifications, including closing domains or interventions when pre-specified thresholds are met
Domain-Specific Working Group (DSWG)	The Domain-Specific Working Groups evaluate emerging data, relevant to the domain, from sources external to SNAP and advise the GTSC if there is sufficient evidence to warrant closing or suspending a treatment arm, or if there is a promising new agent that would be potentially suitable for SNAP.
Domain-Specific Appendix (DSA)	Each intervention examined within the SNAP trial will be fully described within a DSA. Each DSA (and modifications) will be the subject of a separate ethics application or amendment as per regional requirements.
Case Report Form (CRF) / electronic Case Report Form (eCRF)	A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.
Local Site Review Body	The designated administrative area within an institution that is resourced to enable research proposals to be appropriately assessed so to assist the decision-maker to determine whether or not the research project will be authorised.
Site	An institution (or group of institutions) that resource, conduct and manage clinical trials that come under one final research governance authorisation sign off.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. This term refers to protocol and protocol amendments.
Amendment	A written description of a change(s) to or formal clarification of a protocol, Participant Information & Consent Form, or other study document(s).
Regulatory Authorities	Bodies having the power to regulate. In the ICH GCP Guideline, the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct Inspections. These bodies are sometimes referred to as competent authorities.

5 RESPONSIBILITIES

Table 1 Figure 1 Domain & Intervention Changes Responsibilities Overview



5.1 RESPONSIBILITY FOR MAKING THE DECISION

There are multiple committees who may be involved in the decision to add, suspend, or close treatment arms or domains in the SNAP Trial:

- The **Regional Steering Committees (RTSCs)** evaluate emerging data from the SNAP Trial as well as external evidence from their particular region, and discuss the advice provided by the other committees on their region. The RSCs advise the Global TSC of how the decision will impact their region.

- The **Domain-Specific Working Groups (DSWGs)** evaluate emerging data from sources external to the SNAP Trial and advise the Global TSC if there is sufficient evidence to warrant closing or suspending an intervention, or if there is a promising new agent that would be potentially suitable for the SNAP Trial.

- The **Analytic Team** perform interim analyses at pre-specified intervals for the DSMC to determine whether stopping rules have been met.

- The **Statistics Committee** provide statistical support for trial decisions, is responsible for the development of the statistical analysis plan and provides recommendations for the analysis of the outcome data.

- The **Data and Safety Monitoring Committee (DSMC)** review data arising from the trial and evaluate the safety of the interventions. The DSMC may provide recommendations to the Global TSC to either continue with the trial, stop the trial, or continue with modifications.

- The **Global Trial Steering Committee (GTSC)** keep abreast of emerging evidence from the SNAP Trial as well as external evidence, and discuss the advice provided by the other committees. The final decision on whether to add, close or suspend interventions rests with the GTSC.

An out-of-session meeting may be required if there are safety concerns related to an existing treatment or domain in the SNAP protocol, to ensure prompt action is taken to protect the safety of participants. Provided quorum is attained at the out-of-session meeting the decision will be considered final. Where there are no safety concerns, the GTSC will discuss at their usual meeting. Members not present will be provided with the minutes and will be given an appropriate timeframe (no shorter than 24 hours) to object to the decision or provide further information/argument.

The final decision, as well as the discussions and rationale leading to the decision, will be fully documented in the minutes from the relevant committee meetings and in a central Note to File.

5.1.1 CRITERIA FOR DECISION MAKING

The criteria for decision making are based on pre-specified rules are detailed in the core study documents. Where decisions are to be based on external evidence or operational considerations, the following criteria must be evaluated by those involved in making the decision:

- The type of trial – *decisions will not usually be made based on findings from observational trials. Findings from randomised controlled trials (RCTs) will provide the strongest evidence to warrant adding or closing a intervention arm.*
- The number of participants included in the analysis
- The characteristics of the population and the similarity of the participants to those in the SNAP Trial
- Whether or not any safety signals are present.
- The statistical significance of the findings
- The source of the information – *in many cases, a press release will not be sufficient to warrant the closure of an intervention or domain, however this will be decided on a case-by-case basis by the GTSC. If a press release contains sufficient detail of the statistical outcomes, is based on analysis of a large sample, and is from a reputable source then it may be considered sufficient.*
  Unpublished, preliminary data (e.g. early results from phase I/II trials commissioned by pharmaceutical companies) will not usually be sufficient to warrant addition or closure of an intervention or domain, however this will be decided on a case-by-case basis by the GTSC.
- Operational considerations:
  - The impact on trial participants (i.e., risk/benefit analysis).
  - The recruitment rate of the SNAP Trial and the likelihood that the trial would be able to answer any scientific questions (i.e. futility)
  - Operational or funding considerations that inform the feasibility of adding, closing, or suspending a domain.

5.2 RESPONSIBILITY FOR COMMUNICATING & DOCUMENTING THE DECISION

It is the ultimate responsibility of the SNAP Global Trial Management Group (GTMG) and Regional Trial Management Groups (RTMGs), on behalf of the International Sponsor Organisations (ISOs), to ensure all appropriate parties are notified of the decision and that the decision is documented appropriately and in a timely manner.

Sections 5, 6 and 7 describe the process for communicating and documenting the addition, suspension, or closure of a domain or intervention in the SNAP Trial.

6 ADDING AN INTERVENTION OR DOMAIN

A new domain or intervention may be incorporated globally, or in particular regions, as decided by that Regional TSC in consultation with the regional leads, site investigators and other regulatory and ethical bodies.

*Please see **Appendix 2: Flowchart for Adding a Domain or Intervention** for a summary of the process.*

6.1 REASONS FOR ADDING NEW INTERVENTIONS OR DOMAINS

Proposals received by SNAP Trial investigators, external researchers, or pharmaceutical companies will be reviewed by the GTSC. These proposals will be assessed for scientific plausibility, feasibility, and appropriateness for the SNAP Trial infrastructure.

A DSWG may identify potential new therapies based on the literature or recommendations from colleagues. These potential agents will be discussed by the DSWG, RSCs, and may be recommended to the GTSC for inclusion.

6.2 PROCEDURE FOR ADDING AN INTERVENTION OR DOMAIN

The **Statistics Committee** must be consulted prior to final decision about the addition of an intervention arm or domain so that they can provide important input regarding how the new intervention /domain will affect the overall study and statistical model.

When adding a new intervention or domain, the following steps must be taken to ensure that the decision is accurately documented, the relevant stakeholders are notified, and the decision is operationalised and appropriately communicated with the public and participants of the trial.

6.2.1 DOCUMENTATION

The following documents will be required as part of the domain/intervention addition process:

- **Minutes from the GTSC Meeting**
  The decision will be thoroughly documented in the minutes from the GTSC meeting and any committee meetings, including the Statistics Working Group, that provided input to the GTSC.

6.2.1.1 UPDATES TO STUDY DOCUMENTATION

- **Updates to study documents (e.g. domain-specific appendix, protocol, etc.)**
  Any ethically-approved documents requiring modification (including the core protocol) due to the addition of an intervention or domain will be submitted to the all relevant regional ethical review bodies for approval, as an amendment, prior to being implemented as part of the trial. This may also include the submission of new documents such as an Investigator's Brochure, additional participant facing documents, etc.
    - **Domain-Specific Appendix:**

      The intervention must be added to an existing domain-specific appendix, or a new domain-specific appendix must be created. The new domain-specific appendix must contain the following information:

      - Rationale for inclusion
      - Domain specific endpoints
      - Dose to be administered, administration route and duration of treatment
      - Intervention-specific inclusion/exclusion criteria
      - Intervention-specific data collection
      - Potential adverse events and safety monitoring procedures
      - Other considerations specific to the intervention(s)

- **Updates to the Master Participant Information & Consent Forms (PICFs)**

An updated version of the Master PICF will be submitted to the ethical review body for approval, as an amendment, prior to use for recruitment of participants into the new intervention or domain.

- **Updates to the Study Database/eCRF**
  The software company, Spiral, is responsible for maintaining the SNAP study database. The SNAP GTMG will work with the SNAP project manager at Spiral to update the study database. The study database must be updated prior to recruitment to the new intervention or domain.

6.2.2 NOTIFICATION

The following groups will be notified of the decision as soon as possible, following a final decision by the GTSC. As an adaptive trial, it is crucial that the changes to interventions and domains are able to be implemented quickly.

- **Relevant SNAP Committees and Working Groups**
  All relevant committees will be alerted to the addition of the new intervention or domain, including:
  - When the new domain or intervention will be made available on the study database
  - Any changes to the core study protocol
  - Any changes to the trial aspects overseen by the committee.

- **Spiral (Database Providers)**
  Spiral will be informed of the addition of the new intervention or domain, including:
  - Provision of updated study documents
  - Required timeframes for database build
  - Impact on existing participant data, domains or interventions already integrated into the database

  A formal change request will need to be approved before any work can begin.

- **Relevant Regional Ethical Review Bodies**
  A formal submission will be made to the relevant region-specific ethical bodies prior to the intervention or domain becoming active at any study site. Randomisation will not be enabled on the database until approval is obtained.

- **Relevant Regional Regulatory Authorities**
  If the additional treatment is an unapproved therapy or an approved therapy to be used for a different indication, the relevant regional regulatory authorities be notified.

- **Relevant Stakeholders (funders, collaborators, drug manufacturers/suppliers, lead sponsor, etc.)**
  - When the new domain or intervention will be made available on the study database
  - Changes to the Core Protocol
  - **Lead Sponsors:** will need to review for implications for insurance, changes to sponsorship conditions, agreements, etc.

- **Regional Sponsors**
  Regional sponsor will be alerted to the addition of the new intervention or domain, including:
  - When the new domain or intervention will be made available on the study database
  - Confirmation regarding whether the changes are global or region-specific
  - Provision of amended lead study documents, so a submission to the region-specific ethical body can be made

- Submission to the region-specific ethical body can occur prior to or after the lead ethical body has approved the amendment.
  Whether to submit before or after will depend on the region-specific ethical requirements, the urgency the change will need to be implemented and/or consideration of the alignment/similarity of study documents between regions (e.g. whether changes requested by the Lead ethical body impact information in the documents submitted to the region-specific ethical body). In most cases, the region-specific HREC will submit after approval is sought from the Lead ethical body, unless the change is only region-specific..

- **Sites**
  Sites will be alerted to the addition of the new intervention or domain, including:
  - When the new domain or intervention will be made available on the study database
  - Advice regarding the updating of study documents for local submission
  - Provision of amended study documents, so a submission to local governance bodies can be made
  - Consultation regarding the optional participation in the new intervention or domain (if applicable)
  - Provision of updated operational documents
  - Provision of updated/varied Clinical Trial Research Agreements (if applicable)

- **Local Site Review Bodies**
  Sites will submit a formal amendment to their local review body as required, with information including:
  - When the new domain or intervention will be made available on the study database
  - Confirmation of whether the site will be participating in the new intervention or domain
  - Provision of approved ethical submission documentation
  - Varied site Clinical Trial Research Agreements (if required)

  Randomisation will not be enabled on the database until all relevant site approvals have been obtained.

6.2.3 OPERATIONALISATION

The new domain or intervention will become available in the database at the time and date specified in the notification to the relevant groups. Individual sites will not be activated on the study database until all approvals, training and other relevant site activation procedures are finalised and reviewed by the regional and/or global sponsors.

Once sites have obtained the required approvals, their site will be **"switched on" in the database**, and they will be able to commence recruitment into that domain or treatment arm. A formal notification by the central SNAP GTMG will be sent once this has been completed.

6.2.4 COMMUNICATION WITH THE PUBLIC

The addition of the intervention or domain will be announced publicly via the SNAP website, and via media release where appropriate.

7 TEMPORARILY SUSPENDING AN INTERVENTION OR DOMAIN

Suspension of a domain or intervention may be enacted globally, in particular regions, or by particular participant cohorts, depending on region-specific requirements and implications.

*Please see **Appendix 3: Flowchart for Suspending a Domain or Intervention** for a summary of the process.*

7.1 REASONS FOR SUSPENDING INTERVENTIONS OR DOMAINS

Reasons why a domain or intervention may be suspended temporarily include, but are not limited to:

- Safety concerns arising from SNAP trial data
- Advised to pause by the DSMC
- If there is a loss of clinical equipoise due to emerging evidence regarding efficacy/lack of efficacy
- If there is a loss of clinical equipoise due to potential safety concerns
- If the evidence is not sufficient to close the intervention or domain completely, and whilst awaiting further evidence.
- Operational or budgetary restraints that require the temporary suspension of a domain or intervention

7.2 PROCEDURE FOR TEMPORARILY SUSPENDING A TREATMENT ARM OR DOMAIN

When temporarily suspending an intervention or domain, the following steps must be taken to ensure that the decision is accurately documented, the relevant stakeholders are notified, and the decision is operationalised and appropriately communicated with the public and participants of the trial.

7.2.1 DOCUMENTATION

The following documents will be required as part of the domain/treatment arm suspension process:

- **Minutes from the GTSC Meeting**
  The decision will be thoroughly documented in the minutes from the GTSC meeting and any committee meetings that provided input to the GTSC. Where GTSC discussions and decisions have occurred via email, the relevant emails will be retained and attached to the following GTSC meeting minutes.

- **Note to File**
  A note to file must be created documenting the reason for the decision, the committees involved and the date the decision was made. The Note to File must be stored in the Trial Master File.

7.2.1.1 UPDATES TO STUDY DOCUMENTATION

No updates to study documentation are required during the temporary suspension of the domain or intervention.

Ethically-approved study documents will be amended and formally submitted as a future amendment, subject to the final decision regarding the suspended intervention or domain. However, a notification will be submitted to the relevant region-specific ethical bodies, including a cover letter explaining the reason for temporary suspension of the intervention or domain. If there is a safety concern, a letter to participants may be included.

7.2.2 NOTIFICATION

Notification of the following groups should be considered, following a final decision by the GTSC; acknowledgment of the decision is *not required* for the domain or intervention to be suspended. As an adaptive trial, it is crucial that the changes to interventions and domains are able to be implemented quickly, when signals for suspension are made apparent.

When notified, each group will have the following aspects of the suspension communicated:

- **Relevant Committees**
  - Reason for the decision
  - Date/time of the decision
  - Who was involved in the decision

- The number of participants enrolled at the time of decision

- **Relevant Stakeholders (funders, collaborators, drug manufacturers/suppliers, lead sponsor, etc.)**
  - Reason for the decision
  - Date/time of the decision
  - The number of participants enrolled at the time of decision
  - **Drug Manufacturer (if applicable):** if the decision involves ceasing/discontinuing a study drug, the drug company will be notified of the temporary suspension of the intervention.

- **Relevant Regional Ethical Review Bodies**
  - Reason for the decision
  - Date/time of the decision
  - Date/time of any changes to study database
  - The number of participants enrolled at the time of decision
  - If there is a significant safety concern, a template letter informing participants.

  Acknowledgment or approval of the decision is not required for the changes to the trial to be implemented unless changes are required to patient-facing materials (e.g. participant letters).

- **Regional Sponsors**
  - Reason for the decision
  - Date/time of the decision
  - Who was involved in the decision
  - Date/time of any changes to study database
  - Confirmation regarding whether the changes are region-specific
  - If there is a significant safety concern, a template letter informing participants

- **Sites**
  - Reason for the decision
  - Date/time of the decision
  - Date/time of any changes to study database
  - Advice regarding contacting participants (if required)

- **Local Site Review Bodies**
  - Reason for the decision
  - Date/time of the decision
  - Date/time of any changes to study database
  - If there is a significant safety concern, a template letter informing participants.

  Acknowledgment or approval of the decision is not required for the changes to the trial to be implemented unless changes are required to patient-facing materials (e.g. participant letters).

7.2.3 OPERATIONALISATION

- **Database**

  The SNAP GTMG will **"switch off" the intervention arm or domain in the database** to prevent further randomisations until the intervention or domain is formally closed or re-opened.

- **Participant Treatment Continuation**
  - **Participants who have been randomised to the intervention or domain**, but have not yet completed day 90, will be followed up as per the protocol.

- If there is a **significant safety concern**, all active participants who have not yet completed the treatment will cease treatment immediately and continue to be followed up as per protocol. This must be recorded in the electronic Case Report Forms (CRFs) and in the patient's medical records.

7.2.4 COMMUNICATION WITH THE PUBLIC

- **Letter to Participants**
  If there is a significant safety concern and the intervention or domain must be ceased for all active participants, the SNAP GTMG & RTMGs will draft a letter to inform relevant participants of the decision to suspend the intervention or domain. If the significant safety concern impacts participants who are no longer active in the trial, but who were allocated to that treatment, the SNAP GTMG & RTMGs will draft a letter to inform them.
  This letter will be reviewed and acknowledged by the relevant reginal ethical bodies and local site review bodies before being distributed to participants by sites.
  The regional sponsor will provide the letter to sites who will be responsible for distributing them to the participants.

- **Website Announcement**
  If confirmed to be appropriate by the GTSC, the temporary suspension of an intervention or domain may be announced publicly via the SNAP website.

7.3 PROCEDURE FOR RESUMING THE INTERVENTION OR DOMAIN

- **If the decision is made to permanently close the intervention or domain**, the procedure described in **Section 7** must be followed.

- **If the decision is made to continue with the intervention or domain:**
  - This decision will be documented in a **Note to File** and filed in the Trial Master File.
  - The Lead HREC will be notified of the decision to re-open the domain
  - If required, **study documents will be updated** (e.g. updated safety information) and the amended documents will be **formally submitted to relevant regional ethical review bodies.**
  - The **local site review bodies** will be notified of the decision to re-open the intervention or domain and local acknowledgment will be requested prior to resuming the intervention or domain at each site
  - If confirmed to be appropriate by the GTSC, the recommencement of the treatment arm or domain can be **announced publicly via the SNAP website**

8 CLOSING AN INTERVENTION OR DOMAIN

A domain or intervention may be closed globally, in particular regions, or by particular participant cohorts, depending on region-specific requirements and implications.

*Please see **Appendix 4: Flowchart for Closing a Domain or Intervention** for a summary of the process.*

8.1 REASONS FOR CLOSING INTERVENTIONS OR DOMAINS

Reasons why a domain or intervention may close include, but are not limited to:

- Advised to close by the DSMC due to interim analyses revealing superiority, inferiority, or futility of the intervention(s) within a SNAP domain.
  Stopping rules are specified in the statistical appendix and domain-specific appendices.

- Sufficient external evidence reveals superiority, inferiority, or futility of the intervention(s). In this case the DSWG and the GTSC must evaluate the quality and reliability of the evidence when deciding whether to close the arm. The final decision lies with the GTSC.
- Advised to close by the DSMC due to signals of harm.
- Safety concerns raised from external sources (e.g. investigational product manufacturer).
- Operational or budgetary restraints that require the closure of a domain or intervention.

8.2 PROCEDURE FOR CLOSING AN INTERVENTION OR DOMAIN

When closing an intervention or domain, the following steps must be taken to ensure that the decision is accurately documented, the relevant stakeholders are notified, and the decision is operationalised and appropriately communicated with the public and participants of the trial.

8.2.1 DOCUMENTATION

The following documents will be required as part of the domain/treatment arm closure process:

- **Minutes from the GTSC Meeting**
  The decision will be thoroughly documented in the minutes from the GTSC meeting and any committee meetings that provided input to the GTSC.

- **Note to File**
  A note to file must be created documenting the reason for the decision, the committees involved and the date the decision was made. The Note to File must be stored in the Trial Master File (TMF).

8.2.1.1 UPDATES TO STUDY DOCUMENTATION

No updates to study documentation are required to implement the closure of the domain or treatment arm.

Ethically approved study documents will be amended and formally submitted with the next major amendment. However, a notification will be submitted to the ethics committee(s) including a cover letter explaining the reason for closure of the arm or domain and if there is a safety concern, a letter to participants may be included.

- **Master Participant Information & Consent Forms (PICFs)**
  The approved Master PICFs are modular to allow the removal of information pertaining to the closed domain or intervention at a site level. Therefore, these documents do not require a formal ethical submission before the domain is closed.

- **Updates to other study documents (e.g. domain-specific appendix, protocol, etc.)**
  Any ethically-approved documents requiring modification due to the closure of an intervention or domain will be submitted to the relevant regional ethical bodies for approval the next time a formal submission is made.

8.2.2 NOTIFICATION

The following groups will be notified of the decision as soon as possible, following a final decision by the GTSC. As an adaptive trial, it is crucial that the changes to interventions and domains are able to be implemented quickly, when signals for stopping are made apparent.

Each group requiring notification will have the following aspects of the closure communicated:

- **Relevant SNAP Committees and Working Groups (imcluding the DSMC & Analytic Team)**
  - Reason for the decision
  - Date/time of the decision

- Who was involved in the decision
- The number of participants enrolled at the time of decision
- Whether active participants will continue/cease treatment

- **Relevant Stakeholders (funders, collaborators, drug manufacturers/suppliers, lead sponsor, etc.)**
  - Reason for the decision
  - Date/time of the decision
  - The number of participants enrolled at the time of decision
  - Whether active participants will continue/cease treatment
  - **Drug Manufacturer (if applicable):** if the decision involves ceasing/discontinuing a study drug, the drug company will be contacted.

- **Regulatory Authorities**
  If the treatment to be ceased is an unapproved therapy or an approved therapy to be used for a different indication, the relevant regional regulatory bodies will need to be notified.

- **Relevant Regional Ethical Review Bodies**
  - Reason for the decision
  - Date/time of the decision
  - Date/time of any changes to study database
  - The number of participants enrolled at the time of decision
  - Whether active participants will continue/cease treatment
  - If there is a significant safety concern, a template letter informing participants.

  Acknowledgment or approval of the decision is not required for the closure of the domain/intervention(s) to the trial to be implemented.

- **Regional Sponsors**
  - Reason for the decision
  - Date/time of the decision
  - Who was involved in the decision
  - Date/time of any changes to study database
  - Confirmation regarding whether the changes are region-specific
  - If there is a significant safety concern, a template letter informing participants

- **Sites**
  - Reason for the decision
  - Date/time of the decision
  - Date/time of any changes to study database
  - Whether active participants will continue/cease treatment, and how to communicate this to participants (if required)
  - Advice regarding the updating of local PICF documents

- **Local Site Review Bodies**
  - Reason for the decision
  - Date/time of the decision
  - Date/time of any changes to study database
  - If there is a significant safety concern, a template letter informing participants.

  Acknowledgment or approval of the decision is not required for the changes to the trial to be implemented, unless changes are required to patient-facing materials (e.g. participant letters).

8.2.3 OPERATIONALISATION

- **Database**
  The SNAP GTMG will **"switch off" the treatment arm or domain in the database** to prevent further randomisations at the time and date specified in the notification to relevant groups

- **Participant Treatment Continuation**
  - **Participants who have been randomised to the intervention or domain**, but have not yet completed day 90, will be followed up as per the protocol
  - **Participants who have not yet completed the intervention or domain treatment** will continue as planned, unless the intervention has been closed due to safety concerns or inferiority.
    - If the intervention or domain is stopped for the above reasons, treatment may be stopped immediately, and this must be recorded in the electronic Case Report Forms (eCRFs) and in the patient's medical records.
  - If the significant safety concern impacts participants who are no longer active in the trial, but who were allocated to that treatment, the SNAP GTMG & RTMGs will draft a letter to inform the participants.

8.2.4 COMMUNICATION WITH THE PUBLIC

- **Letter to Participants**
  If the intervention or domain must be ceased for all active participants, the SNAP GTMG & RTMGs will draft a letter to inform them of the decision to close the intervention or domain. If there is a significant safety concern that impacts participants who are no longer active in the trial, the SNAP GTMG & RTMGs will draft a letter to inform them.
  This letter will be reviewed and acknowledged by the relevant regional ethical bodies and local site review bodies before being distributed to participants by sites.

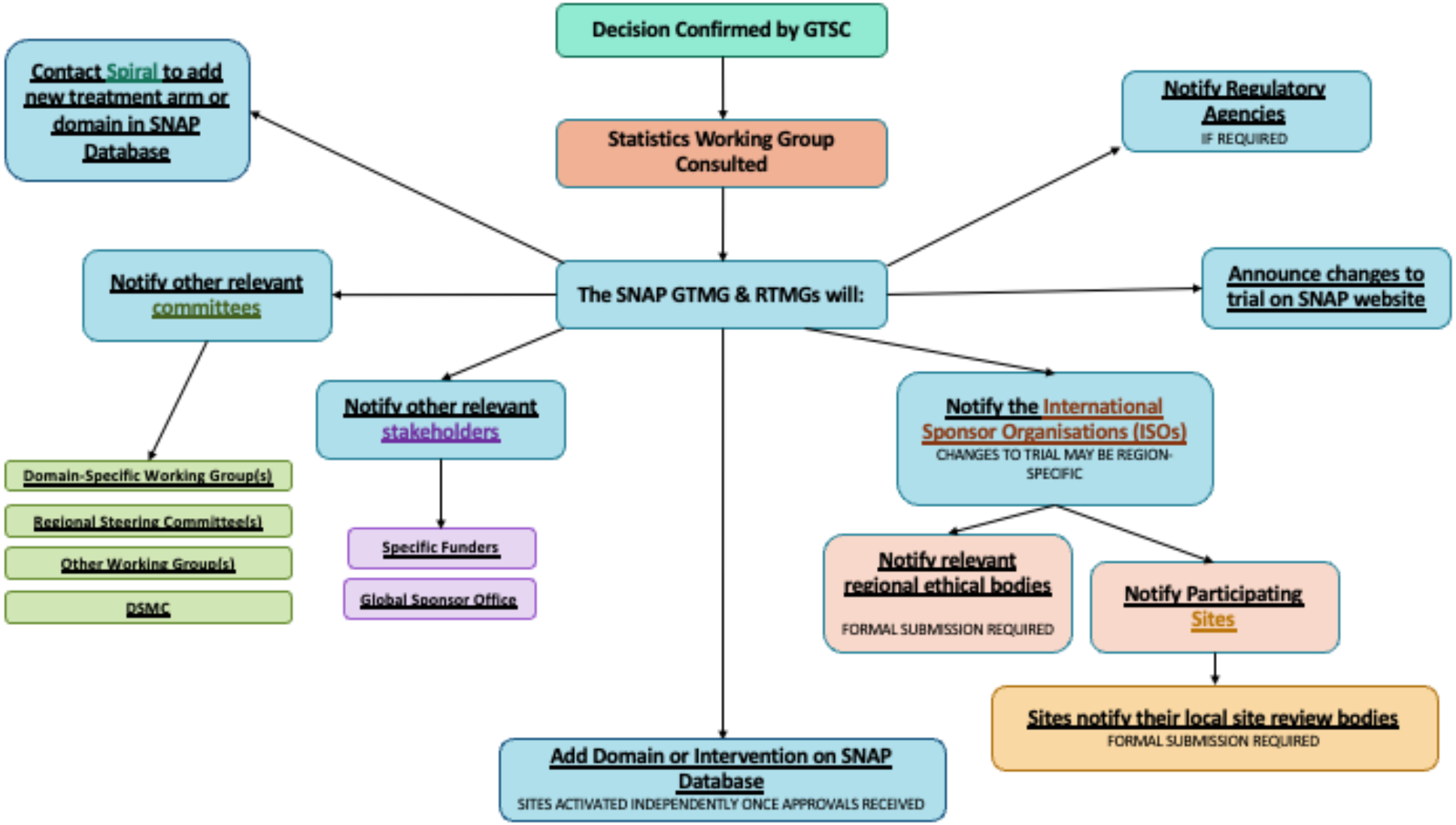
- **Website Announcement**
  The closure of an intervention or domain will be announced publicly via the SNAP website, and via media release where appropriate.

9 APPENDICES

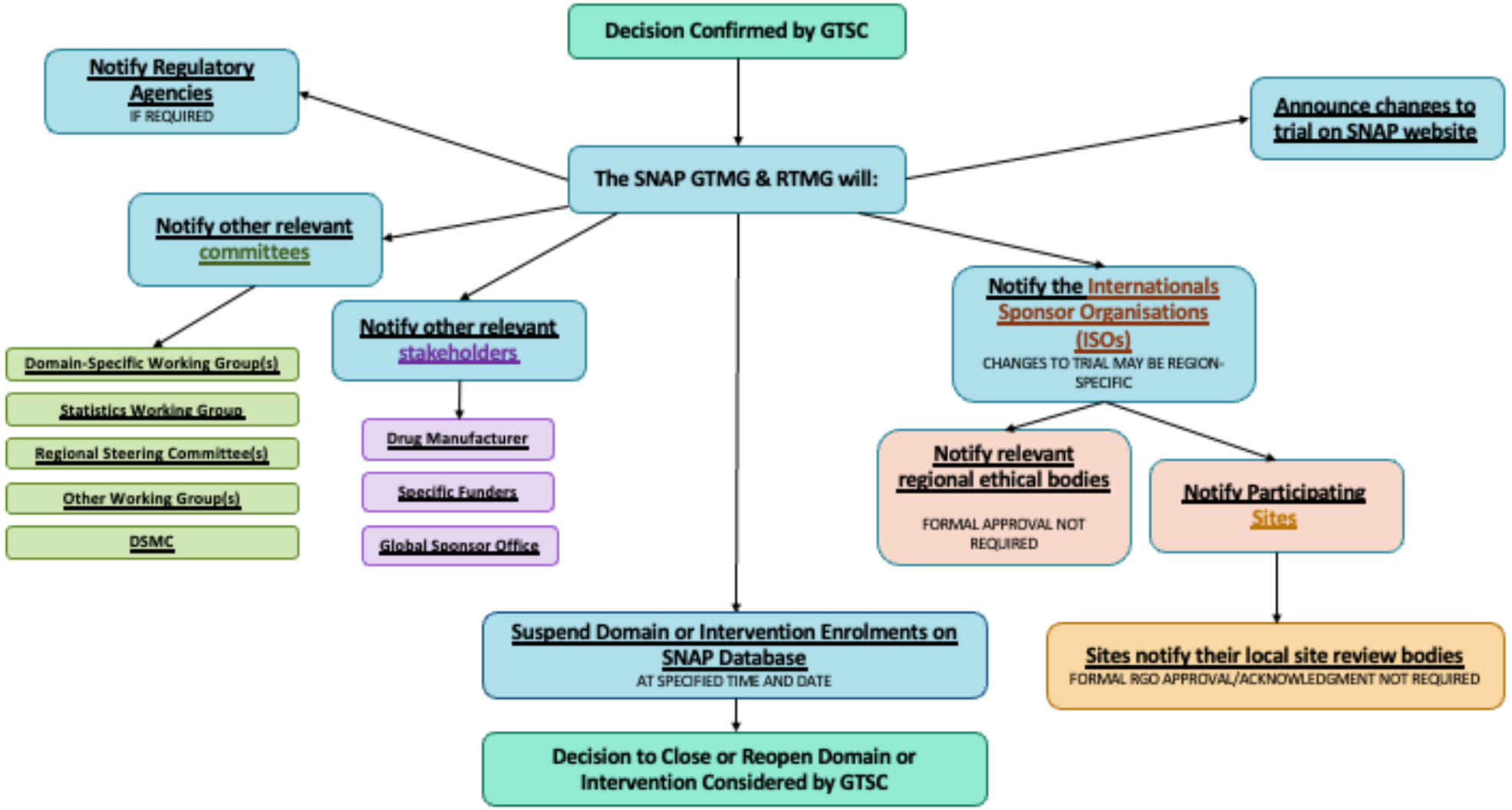
9.1 APPENDIX 1: RECORD OF CHANGES

VERSION NUMBER	VERSION DATE	SECTIONS AFFECTED	SUMMARY OF CHANGES	LEAD AUTHOR
1.0	15-Jul-24	-	-	Lauren Barina
1.1	31-Mar-26	All	Minor changes to terminology and formatting align with other Trial Integrity Documents	Lauren Barina

9.2 APPENDIX 2: FLOWCHART FOR ADDING A DOMAIN OR INTERVENTION



9.3 APPENDIX 3: FLOWCHART FOR SUSPENDING A DOMAIN OR INTERVENTION



9.4 APPENDIX 4: FLOWCHART FOR CLOSING A DOMAIN OR TREATMENT ARM