Ingham Institute and SWSLHD Standard Operating Procedures
for Clinical Trials

Approved Version

Document Title: **Management of safety reporting for clinical trials sites**

Version: Version 2, Dated 18th April 2017

Effective Date: 18th April 2017

Review Before: April 2019

Author: Kelsey Dobell-Brown – Clinical Trials Manager – Ingham Institute/SWSLHD

Author Signature: _____ Date: _____

Author: Professor Meera Agar – Clinical Trials Director – Ingham Institute/SWSLHD

Author Signature: _____ Date: _____

Reviewed and Approved by:

Research Committee for SWSLHD

Signature: _____ Date: _____

1. AIM

To describe the procedures related to the Safety reporting for the site management of clinical trials with reference to Investigator, Sponsor Responsibilities, HREC and TGA reporting requirements.

2. SCOPE

To facilitate guidance for the collection verification and reporting of adverse events that occur in clinical trials that involve investigational products or devices, conducted under the clinical trial notification (CTN) or Clinical Trial Exemption (CTX) scheme.

3. APPLICABILITY

Principal Investigator, Sub-Investigators, Clinical Trial Coordinators and all other staff delegated trial-related activities by the Principal Investigator.

4. PROCEDURE

4.1 Safety monitoring and reporting responsibilities

a) Responsibilities of the Sponsor include;

i. Establishing safety monitoring processes that are based on the risk, size and complexity of the proposed clinical research.

ii. Having a systematic, prioritised, risk-based approach to monitoring clinical trials.[3]

iii. Have an established Independent Data Safety Monitoring Committee (IDSMC) or medical monitor for low risk studies, to oversee the safety profile of the Clinical Trial. [2]

iv. Constantly and consistently evaluate all safety information that is reported by investigators as well as safety information from other sources.

v. Ensure the trial protocol has clear instruction regarding the safety reporting process.

vi. Is required to keep a detailed record of all reported adverse events such as the use of an Electronic Case Report Form (eCRF)[1]

vii. Effectively communicate and clarify the impact of each report on patient safety, trial conduct or trial documentation to the HREC, IDSMC and the trial sites as required, in accordance to current NHRMC guidelines.[1]

viii. Constantly assess and categorise the safety reports including any deviations received from investigators and report all suspected unexpected serious adverse reactions occurring in Australian participants to the Therapeutic Goods Administration for fatal or life threatening Australian SUSARs, immediately, but no later than 7 calendar days after being made aware of the case, with any follow-up information within a further 8 calendar days.[1]

ix. Is required to review and provide an updated the Investigator Brochure on an annual basis or when relevant information becomes available to the relevant HREC and clinical trial site(s)[2]

x. Is required to provide the HREC with and annual safety report including a concise summary of the safety profile of the investigational product or device.[1]

Approved Version

xi. Ensures that all sponsor responsibilities for safety monitoring and reporting (e.g. reporting significant safety issues to the TGA) are appropriately allocated or delegated.

xii. Is responsible for notifying the TGA, HREC and investigators of all significant safety issues that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. [1]

b) Responsibilities of the Principal Investigator

i. As per ICH-GCP guidelines[2] Investigators and/or delegates are required to assess all local safety events and should act on any events as clinical care dictates ensuring the immediate safety and ongoing clinical management of the participant is maintained at all times.

ii. Consistently provides the sponsor with all relevant information so that an appropriate safety analysis can be performed.[1]

iii. Conducts the clinical trial in compliance with the protocol and regulatory authorities at all times. Any deviation from the protocol without prior approval from the Sponsor is required to be reported directly to the Sponsor with all relevant information so that an appropriate safety analysis can be performed. See appendix for further guidance in reporting non compliance events such as Deviations/Violations and a Serious Breach otherwise contact the Sponsor directly

iv. The investigator is however, able to **implement a change in the protocol to eliminate an immediate risk to a trial participant without prior approval from the Sponsor or HREC**

v. Ensure that adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations are reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

vi. Report to the Sponsor within 24 hours of **learning of any serious safety** events including Serious Adverse Events (SAE's) and Sudden Unexpected Serious Adverse Reactions (SUSAR). **Refer to the definitions in the glossary below**.[2]

vii. Ensure comprehensive documentation for any serious safety event even if the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting.

viii. Ensure participant safety and clinical care priorities are maintained at all times

ix. Ensure that all local site SAE, and SARs are reported to the local institution within 72 hrs. from being aware of the event .

x. Ensure that for all information relating to a SAE or SAR is provided to the Sponsor as requested.

c) Responsibilities of the institution

i. An institution's responsibilities and oversight of safety information in clinical trials will differ depending on whether they are hosting externally sponsored clinical trials or sponsoring locally led, non-commercial trials. In both cases they should help ensure that their site(s) understands and complies with sponsor requirements. Institutions should have oversight of any issues that may require management, such as disputes or litigation resulting from trials. **Where the institution is also named as the trial sponsor, the institution will also assume the sponsor responsibilities**.[1]

Approved Version

ii. To assess whether any safety reports received impact on medico-legal risk, the responsible conduct of research, adherence to contractual obligations or the trial's continued site authorisation and, where applicable, facilitate the implementation of corrective and preventative action.[1]

iii. Develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials.

d) Responsibilities for the Therapeutic Goods Administration (TGA)

i. The clinical use of unapproved therapeutic goods are conducted in Australia under either the Clinical Trial Notification (CTN) Scheme or the Clinical Trial Exemption (CTX) Scheme. Responsibility for the regulatory control of therapeutic goods in Australia lies with the Therapeutic Goods Administration (TGA).[1]

ii. The TGA may, conduct an audit of a clinical trial where necessary on safety ground and/or stop a trial where the ethical conduct of the trial is at risk.[1]

5. GLOSSARY

Adverse Event [2]

An adverse event for medicines is also referred to as an adverse experience, any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal(investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event (SAE) – Drug/Device

Any untoward medical occurrence that, at any dose:

a. results in death;
b. is life-threatening;
c. requires in-patient hospitalisation or prolongation of existing hospitalisation;
d. results in persistent or significant disability/incapacity; or
e. is a congenital anomaly/birth defect, and fits the SAE criteria as specified in the relevant clinical trial protocol.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations or a s determined by the trial protocol.

Any Serious Safety Event refers to the determination of a causality. This is defined by the following classifications;

- Definitely related
- Probably related
- Possibly related

Approved Version

- Unlikely/Remotely related
- Definitely not related

The determination of the casualty then defines whether the event is reported as one of the following;

- Serious Adverse Event (SAE)
- **Serious Adverse Reaction (SAR)**

If the SAR is then considered by the PI as **Unexpected,** it then referred to as an Sudden Unexpected Serious Adverse Reaction (SUSAR)

Please refer to the diagram in Appendix 3.

Clinical Trials Notification (CTN)

An online notification scheme whereby all material relating to the proposed trial, including the trial protocol is submitted directly to the TGA by the Sponsor. The TGA does not review any data relating to the clinical trial. Follow link for further information;

https://www.tga.gov.au/form/ctn-scheme-forms

The HREC is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine or device and the ethical acceptability of the trial process, and for approval of the trial protocol.

CTN trials cannot commence until the trial has been notified to the TGA and the appropriate notification fee paid and acknowledgement is received.

Clinical Trials Exemption (CTX)

An online approval process whereby a sponsor submits an application to conduct clinical trials to the TGA for evaluation and comment. Follow link for further information;

https://www.tga.gov.au/form/ctn-scheme-forms

A TGA Delegate decides whether or not to object to the proposed Usage Guidelines for the product. If an objection is raised, trials may not proceed until the objection has been addressed to the Delegate's satisfaction.

If no objection is raised, the sponsor may conduct any number of clinical trials under the CTX application without further assessment by the TGA, provided use of the product in the trials falls within the original approved Usage Guidelines. Each trial conducted must be notified to the TGA.

A sponsor cannot commence a CTX trial until written advice has been received from the TGA regarding the application and approval for the conduct of the trial has been obtained from an ethics committee and the institution at which the trial will be conducted. There are two forms, each reflecting these separate processes (Parts), that must be submitted to TGA by the sponsor.

Part 1 constitutes the formal CTX application. It must be completed by the sponsor of the trial and submitted to TGA with data for evaluation.

Approved Version

Part 2 is used to notify the commencement of each new trial conducted under the CTX as well as new sites in ongoing CTX trials. The Part 2 form must be submitted within 28 days of the commencement of supply of goods under the CTX. There is no fee for notification of trials under the CTX scheme.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participant s are protected.

Human Research Ethics Committee (HREC)

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines.

The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

Research and Ethics Office/Governance Office

Reviews and makes recommendations to the Chief Executive about the satisfactory governance of research projects within the SWSLHD

Independent Data Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) is an independent group of experts that periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and makes recommendations concerning the continuation, modification, or termination of the trial. The IDSMC considers study-specific data as well as relevant background knowledge about the disease or patient population.

International Conference on Harmonisation (ICH)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Investigator

An individual responsible for the conduct of a clinical trial at a trial site ensuring that it complies with GCP guidelines. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. In this instance they may delegate tasks to other team members.

The Trial Sponsor

The sponsor of a clinical trial is defined as 'an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study.

Approved Version

Sponsor functions may be delegated to third parties, such as clinical research organisations/centres, Data Safety Monitoring Boards or Coordinating Principal Investigators, provided that arrangements are in place for oversight of any delegated activities.

A sponsor should be identified for all clinical trials. Although the definition of trial sponsor allows an individual to be named as sponsor, for non-commercial trials it is usually more appropriate for an institution, rather than an investigator, to perform this role. It is also common practice for a group of non-commercial partners to make collaborative arrangements to initiate, manage and fund trials and, in such circumstances, it is important to ensure that all sponsor functions, including safety monitoring and reporting, are clearly allocated or delegated.

Protocol Deviation

Minor protocol deviations which do not carry significant ethical / administrative implications or consequences do not need to be reported to the HREC. However, all such deviations must be recorded in the study file and reported to the sponsor.

Protocol Violation

A protocol violation is any change, divergence, or departure from the study design or procedures of a research protocol that affects the participant's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data.

Serious Breach

Major Deviations that pose a significant and or prolonged risk to participant safety, or have significant ethical implications are required to be reported to the Sponsor and Approving HREC directly and/or within a 24hrs period of being aware of the event.

Sub Investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

Therapeutic Goods Administration (TGA)

Australia's regulatory agency for medical drugs and devices.

6. REFERENCES

1. NHMRC Guidance: Safety monitoring and reporting I clinical trials involving therapeutic goods. November 2016
2. ICH E6 Guidelines for Good Clinical Practice, section 4.
3. Integrated addendum to ICH E6 (R1) Guideline for Good Clinical Practice. Version 4, 9th November 2016
4. Access to Unapproved Therapeutic Goods - Clinical trials in Australia October 2004.
5. TGA - https://www.tga.gov.au/
6. http://www.swslhd.nsw.gov.au/ethics/default.html

Approved Version

7. APPENDICES

Appendix 1: SOP Change Log

Appendix 2: Safety Event Reporting for clinical trial sites and Investigators

Appendix 3: Deviation reporting Template via http://www.swslhd.nsw.gov.au/ethics/default.html

DOCUMENT END

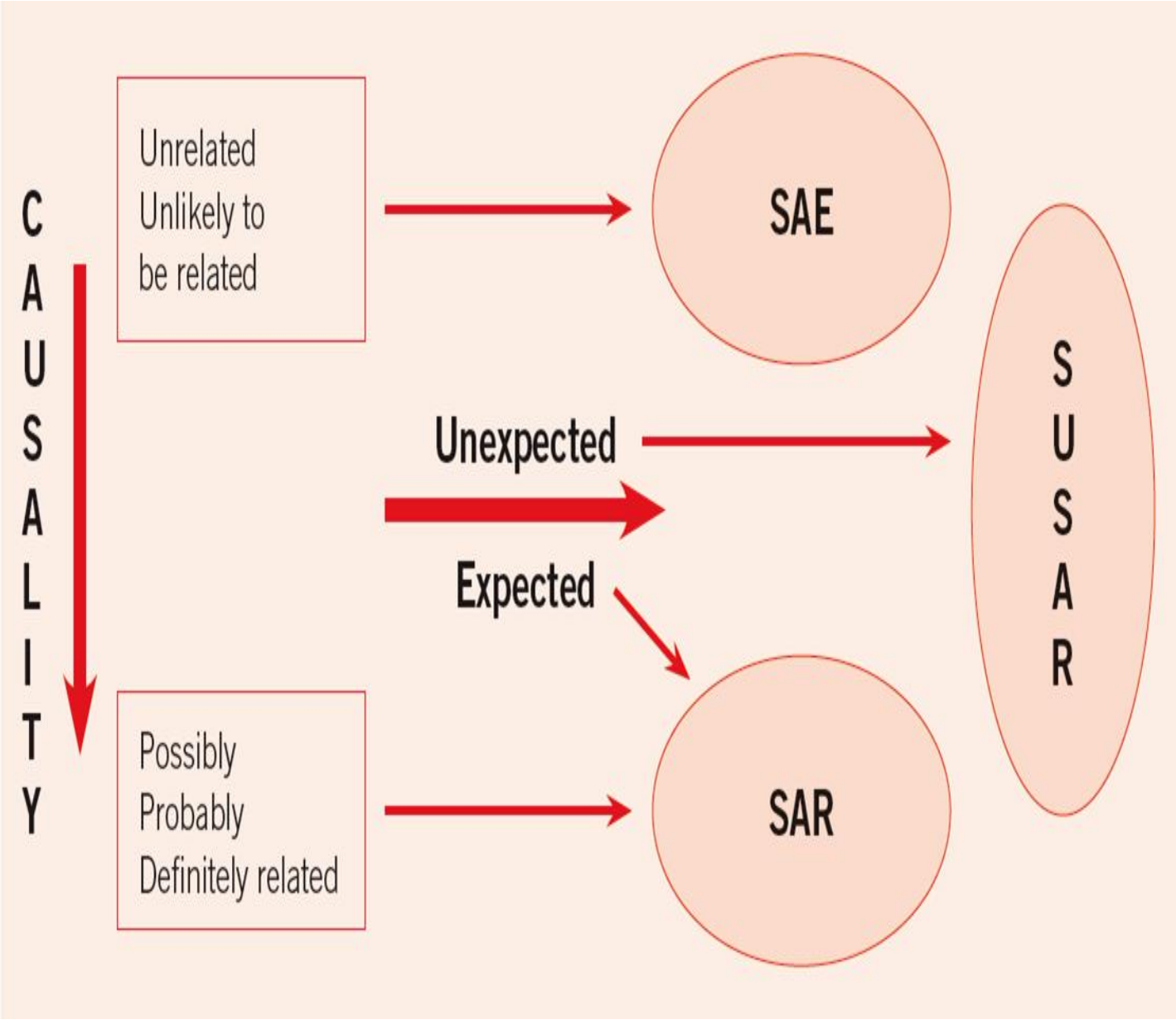
Approved Version

APPENDIX 1: SOP CHANGE LOG

Version No.	*Reason for Issue*
1.0 August 4th 2015	First issue
2.0 April 18th 2017	Updated as per ICH-GCP and NHMRC guidelines.

Approved Version

APPENDIX 2


CAUSALITY
Unrelated
Unlikely to
be related
SAE
Unexpected
Expected
SUSAR
Possibly
Probably
Definitely related
SAR