STANDARD OPERATING PROCEDURE (SOP)

TITLE: MANAGEMENT AND REPORTING OF SAFETY EVENTS

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1. PURPOSE:

The purpose of this SOP is to outline the procedures for the management and reporting of safety events (encompassing adverse events (AEs), serious adverse events (SAEs), adverse events of special interest and suspected unexpected serious adverse reactions (SUSARs)) for clinical trials at Epworth in compliance with ICH GCP guidelines[1], *NHMRC guidelines on Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (November 2016)*[2] and regulatory requirements.

2. SCOPE:

All clinical research conducted at Epworth.

3. APPLICABILITY:

This applies to all Epworth employees, non-employed staff and Visiting Medical Officers (VMOs) and to all relevant external persons or parties engaged in the research activity at Epworth.

4. GLOSSARY OF TERMS:

Please refer to Epworth SOP Glossary of Terms (see *Related Documents*).

For clarity an **Adverse Event** (AE) is any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure[1].

5. PROCEDURE:

The Principal Investigator (PI) for the clinical trial retains overall responsibility for ensuring safety events are assessed, recorded and reported in the correct manner. The PI can delegate at his/her discretion certain trial duties to individuals where appropriately qualified by education, training and experience (see also *SOP-TM-14 Delegation of Duties*). Delegation of trial activities must be recorded on the delegation log. The PI remains responsible for any delegated activity.

5.1 Identification and recording of AEs

- The PI has overall responsibility for ensuring AEs are recorded accurately in the medical records and managed in a way that protects the safety of participants (see also *SOP-TM-07 Source Document Management*). Documentation must be in accordance with the Epworth *Health Information Documentation Protocol* and *Scanned Medical Record – Access and Management Protocol*.

- A thorough medical history must be obtained at the commencement of the trial by a medical practitioner or registered nurse delegated to this task to identify any pre-existing medical conditions, and to ensure these are not reported as new AEs once the participant begins active involvement in the trial.

- If a pre-existing medical condition worsens after the participant has signed informed consent this is usually recorded as a new AE. It could be documented as "worsening of…" or "exacerbation of…" the event described in the medical history.
- Where an AE is first identified at a visit it is the responsibility of a doctor to record this in the medical records.
- The PI may be alerted to the occurrence of a new or worsening AE in between visits by:
    - the clinical research nurse (RN) or non-nurse clinical research coordinator (CRC),
    - the participant (self-reported), and/or
    - non-trial clinical staff.
- Where the RN/CRC has collected the data for an AE in between visits, they must alert the PI or delegated Sub Investigator in a timely manner to ensure medical oversight and consultation.
- The PI must be alerted immediately by delegated trial staff of all SAEs or SUSARs.
- Changes to a trial participant's health should be recorded in the participant's research notes when Epworth clinical research staff become aware of them, either at a trial visit or between visits (see *SOP-TM-07 Source Document Management*).
- Where potential AEs have been documented in the medical records by non-delegated clinical staff the PI or the delegated Sub Investigator will need to assess whether they fulfil the GCP definition of an adverse event and if so grade them, attribute causality and ensure they are recorded as AEs in the trial Case Report Form (CRF). As part of standard of care practices, non-delegated clinical staff will use their clinical judgement to escalate potential AEs for real-time review to an investigator if they feel this is clinically appropriate. Potential adverse events that are documented by non-delegated clinical staff will be reviewed by delegated clinical trial staff within the mandatory timeframe stated in the protocol. The final decision of whether potential adverse events documented by non-delegated clinical staff are to be considered as true adverse events and documented in the CRF lies with the reviewing investigator.
- The beginning and end of the AE should be recorded in the participant's notes. If the participant cannot remember an exact date, then an approximate date should be recorded and identified as an "estimated date".

5.2 Assessment and evaluation

- Assessment of an AE and whether or not it is related to any trial medication or a trial-related process must be determined by a medical practitioner.
- The PI has overall responsibility for ensuring all AEs are assessed and managed in line with trial protocol requirements and standard of care practice.

- AEs should be graded for severity and seriousness as indicated in the protocol or by using an established assessment tool such as the *Common Terminology Criteria for Adverse Events* criteria.
- Consistent terminology will be used to describe an AE at each participant visit so as to avoid recording an existing AE as an entirely new one.
- The final terminology used to describe an AE or SAE (i.e. the formal diagnosis) must be made by a medical practitioner such as the PI or Sub Investigator.

5.3 Response and follow-up

- The PI may be able to implement a change in the trial protocol to eliminate an immediate risk to any trial participant without prior approval from the Sponsor or Human Research Ethics Committee (HREC)[2]. However, these parties should be notified as soon as possible after this has occurred.
- The PI and all delegated trial staff are responsible for monitoring the event as instructed by the trial protocol (e.g. until the event resolves or the trial closes) and documenting the outcome.
- A cumulative log listing should be created for each participant in each trial to record all AEs in a central place (see also suggested *TEMPLATE-01*). The log records event terminology, severity and changes in level of severity over time, start and stop dates, and relationship to trial medication(s). The treating medical practitioner (i.e. PI or Sub Investigator) signs in wet ink against every recorded event to confirm accuracy and also to provide evidence of medical oversight.

5.4 Safety Reporting Requirements

- The PI is responsible for ensuring reporting of adverse safety events to the Sponsor, HREC and institution takes place as specified in the trial protocol and the *NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (November 2016)*[2]. All submitted documents must have no identifying information of the participant.
- It is the responsibility of the PI or delegate to record all Epworth research participant serious adverse events and adverse events of special interest in RiskMan (Appendix 1 -2) before the end of the month that the event occurred.
- Where reporting to Epworth is required, written notification must be emailed to the Research Development and Governance Unit (RDGU) *research@epworth.org.au* within the required reporting timeframe.
- The reporting timeframes to the RDGU are inclusive of weekends except where notification occurs after 5pm on a Friday. In these instances the clock start will start from 9am on a Monday.

6. REFERENCES & RELATED DOCUMENTS:

The Epworth Research Policy, handbook, SOPs and supporting forms and templates can be found on the *Epworth Resources for Researchers* webpage.

1. *Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) – Annotated with TGA comments*
2. *NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (November 2016)*
3. *Epworth, 2017. Health Information Documentation Protocol*
4. *Epworth, 2019. Scanned Medical Record – Access and Management Protocol*
5. *Epworth, 2021. Epworth Incident Management Protocol*

7.1 Related Forms and Templates

- SOP-TM-06-TEMPLATE-01 Adverse Event Log

7.2 Related SOPs

- SOP-TM-07 Source Document Management
- SOP-TM-14 Delegation of Duties
- SOP-Glossary-of-Terms

7. VERSION CONTROL

Document History	
Version	**Summary of Changes**
1.0	N/A First Issue
1.1	**Section 5.1** inclusion of an additional point in relation to PI oversight of potential AEs documented by non-trial staff. **Section 5.3** clarification SUSARs or SSIs must be reported to the RDGU with 72 hours Appendices – safety reporting flowcharts removed as information provided in the NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (November 2016)
3.0	**Glossary** – added definition for adverse (safety) event **Section 5.1** – information previously outlined in this section (Handling of AEs) restructured into 5.1 (Identification and recording of AEs), 5.2 (Assessment and evaluation), 5.3 (Response and Follow-up). These sections now include additional

	points on obtaining medical history, recording changes to medical history over time, recording unknown dates, use of an established tool for grading AEs, ensuring consistent use of terminology to describe AEs, requirement for medical determination of AE terminology and causality, and use of a cumulative log for recording AEs over time. **Section 5.4** - (previously section 5.2 & section 5.3) – safety reporting requirements combined and condensed. SOP formatting and hyperlinks to referenced documents updated.
4.0	**Section 5.1** – Further guidelines provided in relation to reporting of potential adverse events by non-delegated clinical staff. **Section 5.4 –** Requirement to record all adverse events relating to Epworth patients on RiskMan stated. Hyperlinks updated.
5.0	Added Appendix 1 to clarify list of serious adverse events and adverse events of special interest to be reported in RiskMan (Section **5.4**). Added Appendix 2 to provide guidelines on RiskMan reporting. Broadened the SOP scope to include all clinical research.

8. Appendix

Appendix 1: List of adverse events that should be reported in RiskMan:

- Death – following the adverse event
- Life-threatening – if the patient has a substantial risk of dying at the time of the adverse event
- Hospitalisation (initial or prolonged) – due to the adverse event
- Disability or Permanent Damage
- Required Intervention to prevent permanent impairment or damage
- Development of drug dependence or drug abuse
- Other serious events – where the event may jeopardize the patient and may require medical or surgical intervention/treatment to prevent one of the above outcomes from occurring (for e.g. seizures, allergic reactions etc…).
- Adverse events of special interest. These are adverse events (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required.

The following should also be reported:

- Readmissions to Epworth following the trial (if it is believed to be caused by the trial)
- Formal complaints received by participants or family members
- Any correspondence from third party legal counsel (including writs or requests for information)

Appendix 2: Important details to include in RiskMan

1. Please note that all mandatory fields (yellow) need to be completed before submitting.
2. Please take note of the instructions below for further clarity regarding research related adverse events.