CLINICAL TRIALS - PROTOCOL

PROCEDURE ©

DOCUMENT SUMMARY/KEY POINTS

- The purpose of this procedure is to ensure that protocols being developed by SCHN Investigators comply with NSW Health, SCHN and regulatory as well as best practice recommendations.
- The procedure must be followed by all personnel involved in the conduct of clinical trials

CHANGE SUMMARY

- Not applicable – New Sydney Children's Hospitals Network Procedure.

READ ACKNOWLEDGEMENT

- Read/Acknowledge Only – Personnel involved in the conduct of clinical trials.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st May 2022	**Review Period**: 3 years
Team Leader:	Clinical Research Manager	**Area/Dept**: Kids Research

TABLE OF CONTENTS

Purpose/Scope

The purpose of this procedure is to ensure that protocols for clinical trials used or developed by SCHN Investigators comply with NSW Health, SCHN and regulatory and best practice recommendations. This procedure must be followed by all personnel involved in the conduct of clinical trials.

Background

A protocol or clinical investigation plan (for investigational devices) describes the background, justification, objective(s), design, methodology, statistical considerations, organisation of the study, study duration, and a timeline for a clinical trial.

In accordance with the TGA Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Section 2.5, clinical trials should be scientifically sound and described in a clear, detailed protocol. The protocol provides a common reference document for Investigators and their Delegates, enabling clinical trials to be undertaken consistently by one or more participating sites. It is also a document that enables other Investigators to precisely replicate the study in order to validate the integrity of conclusions drawn.

Protocol development is the iterative process by which a research question or idea is expanded upon through the collaborative efforts of a multi-disciplinary team contributing their expertise to ensure the robustness and validity of the protocol generated.

Procedure

Development

As per Chapter 4.2 of the NHMRC National Statement, clinical research involving children and young people can raise additional ethical issues related to equipoise, informed consent, and the nature of procedures/assessments. Careful consideration should be given to these aspects during protocol development, as well as overall protocol design.

The team involved in protocol development should include, but is not limited to: Health professionals with subject matter expertise (e.g. therapeutic area, investigational agent or class of agent), statisticians, experts with clinical research regulatory and operations (coordination, quality assurance and data management) experience and individuals or groups who can provide insight into the lived experience, values and priorities of consumers and communities.

Resources, such as the Australian Clinical Trials Alliance (ACTA) Consumer Involvement and Engagement Toolkit (2022), provide practical advice on how to engage consumers in clinical research protocol development and delivery.

As per the SCHN Policy – Sponsorship [DRAFT], early engagement with the SCHN Research Governance Office (RGO) is mandatory if SCHN is being requested to act as Sponsor for an investigator-initiated or cooperative group clinical trial.

Protocol Content

Protocols must comply with scientific and ethical standards. In Australia, Investigators must meet the requirements of the TGA Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) which provides a standardised format for the content of protocols in Section 6.

SCHN-initiated protocols must use the Standard Protocol Items for Randomised Trials (SPIRIT) template[3] to ensure compliance with the requirements of ICH GCP as adopted by the TGA. Templates are available on the SCHN HREC website.

As there are additional considerations for clinical trials involving paediatric populations, the use of the SPIRIT-C (Child) extension guidance and checklist[4] is recommended. The SPENT (SPIRIT extension for n-of-1 trials) checklist[11] may help to improve the completeness and transparency of n-of-1 trial protocols.

Additional information to supplement the protocol may be included in separate documents, such as an Investigator's Brochure or Study Manual(s). Supplementary information, such as country or region-specific variations to protocol requirements, may be documented as annexures to the protocol.

Registration

In accordance with the NHMRC National Statement (2007) Section 3.1.7, clinical research that involves the prospective assignment of participants to health-related interventions to evaluate the effects on health outcomes must be registered on a publically accessible register prior to the recruitment of the first participant by the Sponsor.

Inclusion on a registry is important to ensure improved research transparency, to facilitate research participation and avoid duplication of effort. It can also aid the identification of evidence gaps and/or areas of unmet need, promote research collaboration and improve clinical research quality.

The register used by Investigators must comply with international standards, as detailed on the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) (2009).

The use of the Australian New Zealand Clinical Trials Registry (ANZCTR - http://www.anzctr.org.au/), a primary registry fulfilling the criteria defined by the WHO, is recommended. Listings on the ANZCTR, as well as those contributed from all WHO endorsed primary registries plus the US-based registry, ClinicalTrials.gov, are visible via the ICTRP global search portal (https://www.who.int/trialsearch), with links to the original record.

The Sponsor or Delegate is responsible for ensuring that clinical research is registered prior to recruitment of the first participant, ensuring that information is accurate and complete and that the record is kept up-to-date. The language used in the general title and the lay summary of the registration record should be brief, clear, and written in plain English so that it is understood by a lay person.

Implementation

As per the TGA Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Section 4.5, the Investigator/Institution must conduct the trial, approved by the responsible HREC/RGO and regulatory authorities (if applicable), in compliance with the protocol. The Investigator and the Sponsor should sign the protocol, or an alternative contract, to confirm their agreement, prior to commencement.

The Investigator must not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and documented approval from the responsible HREC/RGO for the amendment. The only exception to this is where a deviation is necessary to eliminate an immediate hazard(s) to participants, or when the change(s) involves only logistical or administrative aspects of the trial.

In the event of deviations from the Protocol, the Investigator is responsible for ensuring that the issue is documented and reporting to the Sponsor and regulatory bodies (as applicable), as soon as possible after its occurrence. The documentation of deviations should specify the nature of the deviation or change, the reason for it and the notification to the Sponsor and regulatory bodies (if required). The use of Corrective and Preventative Action Plans (CAPAs) is recommended. The CAPA should incorporate:

- Identification of the issue, including scope and impact
- Identification of the root cause of the issue (e.g. how and why it occurred)
- The actions taken to prevent recurrence of the issue (corrective) and/or prevent an identified issue from occurring (preventative)
- The actions that were taken to address the issue identified and its resolution

The use of a Protocol Deviation and Violation Log and CAPA Plan (**Appendix**) is recommended.

Appendices

Protocol Deviation and Violation Log

Corrective and Preventative Action Plan (CAPA)

Abbreviations and Definitions

ACSQHC	Australian Commission on Safety and Quality in Healthcare
ACTA	Australian Clinical Trials Alliance
ANZCTR	Australian New Zealand Clinical Trials Registry
CAPA	Corrective Preventive Action Plan
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
IB	Investigators Brochure
ICH	International Conference on Harmonisation
ICTRP	International Clinical Trials Registry Platform
NHMRC	National Health and Medical Research Council
NSW	New South Wales
PD	Policy Directive
RGO	Research Governance Office
SCHN	Sydney Children's Hospitals Network
SPENT	SPIRIT Extension for n-of-1 Trials
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TGA	Therapeutic Goods Administration
WHO	World Health Organisation

Related Documents

1. ACTA (2022) – The Consumer Involvement and Engagement Toolkit - https://involvementtoolkit.clinicaltrialsalliance.org.au/
2. ACSQHC. (2020) - National Clinical Trials Governance Framework and User Guide [DRAFT] - https://www.safetyandquality.gov.au/publications-and-resources/resource-library/national-clinical-trials-governance-framework-and-user-guide
3. Chen, A. et al. (2013). SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. British Medical Journal, 346:e7586 - https://www.bmj.com/content/346/bmj.e7586
4. Clyburne-Sherin, A. V. P et al. (2015). Recommendations and evidence for reporting items in pediatric clinical trial protocols and reports: Two systematic reviews. Trials, 16:417 - https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-0954-0
5. Declaration of Helsinki - https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
6. NHMRC – Consumer Involvement - https://www.nhmrc.gov.au/guidelinesforguidelines/plan/consumer-involvement
7. NHMRC (2016) – Guidance - Safety Monitoring and Reporting in clinical trials involving therapeutic goods - https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods
8. NHMRC - National Statement on Ethical Conduct in Human Research (2007) - Updated 2018 - https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018
9. NHMRC – Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trial Involving Therapeutic Goods – https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1
10. NSW Health PD2017-039 – Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations - https://www1.health.nsw.gov.au/pds/Pages/doc.aspx?dn=PD2017_039
11. Porcino, A. J. et al. (2020). SPIRIT extension and elaboration for n-of-1 trials: SPENT 2019 checklist, British Medical Journal, 368:m122 - https://www.bmj.com/content/368/bmj.m122.full
12. SCHN Policy – Clinical Research [DRAFT]
13. SCHN Policy – Sponsorship [DRAFT]
14. SCHN Policy 2015-9060 – Research – Authorisation of Proposals to Conduct Research on Humans - http://webapps.schn.health.nsw.gov.au/epolicy/policy/3604
15. SCHN Policy 2012-9029 – Research – Ethical and Scientific Review of Human Research - http://webapps.schn.health.nsw.gov.au/epolicy/policy/2683
16. SCHN Procedure 2019-145 – Clinical Research - Record Keeping - http://webapps.schn.health.nsw.gov.au/epolicy/policy/4661
17. SCHN Procedure 2019-024 – Clinical Research - Statistical Design, Analysis and Reporting - http://webapps.schn.health.nsw.gov.au/epolicy/policy/4665
18. SCHN Procedure 2016-9002 - Consent to Participate in Human Research – Participant Information and Consent - http://webapps.schn.health.nsw.gov.au/epolicy/policy/3666
19. SPIRIT Statement - http://www.spirit-statement.org/spirit-statement/
20. TGA - Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) - https://www.tga.gov.au/sites/default/files/ich13595an.pdf
21. WHO (2009) - International Clinical Trials Registry Platform (ICTRP) – Registry Criteria Version 2.1 - https://www.who.int/clinical-trials-registry-platform/network/registry-criteria