CLINICAL RESEARCH - STATISTICAL DESIGN, ANALYSIS AND REPORTING

PROCEDURE ©

DOCUMENT SUMMARY/KEY POINTS

- The purpose of this procedure is to ensure that due consideration is given to statistical design, analysis and reporting for clinical research sponsored by SCHN, as applicable, in compliance with NSW Health, SCHN, regulatory and protocol requirements.
- The procedure must be followed by all personnel involved in statistical design, analysis and reporting of clinical research sponsored by SCHN.

CHANGE SUMMARY

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

READ ACKNOWLEDGEMENT

- Training/Assessment Required – Personnel involved in statistical design, analysis and reporting of clinical research sponsored by SCHN.

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st March 2019	**Review Period**: 3 years
Team Leader:	Clinical Trials Program Manager	**Area/Dept**: Kids Research Institute

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Purpose/Scope

The purpose is to outline is to ensure that due consideration is given to statistical design, analysis and reporting for clinical research sponsored by SCHN, as applicable, in compliance with NSW Health, SCHN, regulatory and protocol requirements.

Adherence to this procedure will contribute to ensuring the accuracy, validity and integrity of results drawn from the analysis of data for clinical research through use of appropriate statistical design, methodology and practices.

This procedure must be followed by all personnel involved in statistical design, analysis and reporting for clinical research sponsored by SCHN.

Background

As per the TGA Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Section 6.9, the protocol or equivalent must detail the statistical methods to be used including, but not limited to, the nature and timing of any analysis(ses). Further, per Section 5.5.1, the Sponsor should “use appropriately qualified individuals to supervise the conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial report”.

This guidance is expanded upon by ICH E9 and SPIRIT which recommend the development of an accompanying SAP, to be read in conjunction with the protocol or equivalent. The SAP is intended to provide a comprehensive and detailed description of the methods and presentation of data analysis for the study, including both the main and any interim analyses, consistent with the protocol or equivalent.

It is recommended that the Investigator assigns some or all duties relating to the statistical design elements of protocol development and the performance of statistical analyses for clinical research to appropriately qualified and trained personnel, such as a clinical biostatistician or epidemiologist, operating under their supervision, in accordance with the SCHN Procedure – Clinical Research – Personnel Roles and Responsibilities [DRAFT].

Procedure

Principles

- The Investigator or Delegate is responsible for consulting with a qualified biostatistician or epidemiologist to provide input into the statistical aspects of the protocol including its overall design an early stage;
- The biostatistician or epidemiologist should provide expert comment with consideration of the context of the protocol, the population of interest and the research question to be addressed;
- At a minimum, input is recommended on the choice of design including treatment allocation methodology, sample size, endpoints, outcome measures and the nature and timing of any analysis(ses) including any criteria to be used for early termination;
- Where randomisation, the random assignment of participants to one of two or more groups which are allocated different interventions, is required, consideration should be given to the need to avoid allocation bias, minimise differences between the groups in terms of baseline characteristics other than the interventions being compared that may influence clinical outcomes (prognosis) and providing a basis for statistical inference;
- The Investigator or Delegate is also encouraged to consult with the biostatistician or epidemiologist to ensure that the design of data systems and/or CRFs is conducive to the efficient extraction of the data, as required for analysis.

Development of SAP

- The development of a SAP is to be considered for complex interventional clinical research, with consideration of the comprehensiveness of the protocol or equivalent, and the recommendation of the biostatistician or epidemiologist;
- Gamble et al (2017)[3] provides an outline of the type of information that may be appropriate to detail within an SAP;
- If a SAP is deemed to be required, it should be considered in parallel with the development of the protocol;
- For studies involving no interim analysis(ses), the SAP should be completed prior to the final data lock for use in the final statistical analysis;
- For studies involving interim analysis(ses), the SAP should be drafted prior to any data freeze/lock (as applicable) and/or the conduct of the interim analysis(ses), and finalised prior to the final data freeze/lock for use in the final statistical analysis;
- Adequate records must be maintained, in accordance with the SCHN Procedure – Record Keeping [DRAFT] to enable the appropriate version of the SAP to be linked to the data set and corresponding results of the analysis(ses);
- The SAP should provide sufficient detail to allow a qualified biostatistician or epidemiologist, without former knowledge of the clinical research, to perform the corresponding analyses;

- Prior to finalisation by the Investigator or Delegate, the SAP should be circulated for comment to relevant Committee members and/or collaborators (if applicable), with consideration of their role in the clinical research.

Analysis

- Prior to commencing the analysis(ses), the Investigator or Delegate must verify that the data has been cleaned and the corresponding CRFs or data system frozen/locked (if applicable) in preparation;
- The data set export must be undertaken in accordance with the request made by the Investigator or Delegate;
- The Investigator or Delegate must be satisfied that the data set used for the purpose of analysis(ses) is complete, corresponds to the source, and that no modification of the data has occurred outside of approved procedures for data management including data querying and cleaning;
- Any additional data queries identified by the Investigator or Delegate as part of the statistical analysis(ses) process (e.g. missing, out of range or discrepant values) should be raised and referred for resolution as per the SCHN Procedure – Data Management [DRAFT];
- Any amendments to the data post provision of the data set extract, must be appropriately documented and a new version of the data set extract provided to the Investigator or Delegate for analysis;
- The software used for analysis(ses) (e.g. R, Stata, SAS, SPSS) will vary in accordance with the preference of the Investigator or Delegate performing the analysis and the required statistical method, but must be a product that is robust and validated for its intended use;
- The Investigator or Delegate must perform the analysis(ses) in compliance with the protocol and the SAP (if applicable), ensuring that an audit trail permitting reproducibility is maintained through avoiding hard coding of changes to source data and ensuring the detailing of annotations for any outputs including, but not limited to, date and time, code file reference(s), comments and associated meta-data;
- Any tables and figures contained within reports of analyses should be, whenever possible, obtained directly as the output of statistical programs, in order to be reproducible. If this is not possible, then a log file should be provided for cross-checking the output;
- The Investigator or Delegate is responsible for ensuring that any manipulation and presentation of the data set complies with applicable regulatory requirements, including those of international agencies such as EudraCT and/or the FDA; as well as the requirements of any journals being targeted for publication;
- For any reports subject to periodic review by the (I)DSMC or equivalent, all information which could materially affect the (I)DSMC's decision on whether to recommend early closure, amendment or continuation of the clinical research, should be included for comment;

- Any requests for additional or unscheduled analyses, not included in the SAP, should be critically assessed to ensure that the performance of the analyses will not compromise the integrity of the clinical research and any conclusions to be drawn and if performed, should be reported as post-hoc or exploratory analyses;
- The results of statistical analyses must be reported according to the CONSORT guidelines (or alternatively, the STROBE or TREND guidelines);
- Results must be presented in a manner which aids the interpretation of their clinical importance (e.g. emphasis should be placed on estimates of the magnitude of the treatment effects or differences and confidence intervals rather than only on significance tests);

Abbreviations and Definitions

CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
GCP	Good Clinical Practice
(I)DSMC	Independent Data Safety and Monitoring Committee
ICH	International Conference on Harmonisation
NHMRC	National Health and Medical Research Council
NSW	New South Wales
SAP	Statistical Analysis Plan
SCHN	Sydney Children's Hospitals Network
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TGA	Therapeutic Goods Administration
TREND	Transparent Reporting of Evaluations with Non-Randomised Designs

Related Documents

1. Australian Code for the Responsible Conduct of Research (2018) - https://www.nhmrc.gov.au/guidelines-publications/r41
2. CONSORT Statement (Consolidated Standards of Reporting Trials) - http://www.consort-statement.org/
3. Gamble et al (2017). Guidelines for the Content of Statistical Analysis Plans in Clinical Trial. , 318(23): 2337-2343 - https://jamanetwork.com/journals/jama/fullarticle/2666509?alert=article
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Statistical Principles for Clinical Trials (E9) - http://www.ich.org/home.html
5. International Conference on Harmonisation General Considerations for Clinical Trials (E8) - https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf
6. National Statement on Ethical Conduct in Human Research (2007) - Updated 2018 - https://www.nhmrc.gov.au/guidelines-publications/e72
7. SCHN Policy – Clinical Research [DRAFT]

8. SCHN Procedure – Clinical Research – Committees [DRAFT]
9. SCHN Procedure – Clinical Research – Data Management [DRAFT]
10. SCHN Procedure – Clinical Research - Personnel Qualifications and Training Records [DRAFT]
11. SCHN Procedure - Clinical Research – Personnel Roles and Responsibilities [DRAFT]
12. SCHN Procedure – Clinical Research - Record Keeping [DRAFT]
13. STROBE Statement (Strengthening the Reporting of Observational Studies in Epidemiology) - http://www.strobe-statement.org/
14. TGA - Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) - https://www.tga.gov.au/sites/default/files/ich13595an.pdf
15. TREND Statement (Transparent Reporting of Evaluations with Nonrandomized Designs) - http://www.cdc.gov/trendstatement