University of Hertfordshire

STATISTICAL INPUT INTO CLINICAL TRIALS

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for Statistical Input into Clinical Trials at the University of Hertfordshire

SOP Number: gSOP-34-02	**Effective Date:** 16th March 2022
Version Number: 2.0	**Review Date:** 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire (UH) standard operating procedure (SOP). UH acknowledges West Hertfordshire Hospitals NHS Trust (WHHT) Research & Development (R&D) which has allowed UH to use the SOPs developed by WHHT where possible, modified for local implementation.

This SOP sets out guidance for the statistical aspects of planning, monitoring, analysis and reporting of research studies and clinical trials, to ensure compliance with Good Clinical Practice (GCP) for research projects managed or sponsored by University of Hertfordshire (UH). Where there are potential conflicts between different collaborating organisations' SOPs, project level working instructions should be developed, to determine precedence.

2.0 PURPOSE

This document defines the University's procedures for the responsibilities of Trial Statisticians and Chief Investigators (CI) in the development, review and approval of Statistical Analyses Plan (SAP), clinical trial protocols and Case Report Forms (CRF) for research projects managed or sponsored/co-sponsored by UH.

To review statistical principles and considerations in the design, conduct, analysis and reporting of research studies.

To comply with 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 subjects are protected.'

This SOP is specifically for CTIMPs, however in the absence of a documented procedure can be used as guidance for any other clinical study.

Full details of monitoring of study data to ensure its validity is outside the scope of this SOP (see gSOP-12).

3.0 APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored by UH, including but not limited to: Chief Investigators, Principal Investigators, Research Fellows, Consultants, Trial Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Coordinators, Clinical Studies Officers, Data Managers, Research Assistants and Students.

4.0 RESPONSIBILITIES

The sponsor, or their delegated representative, is responsible for ensuring the quality of their trial through the use of appropriately qualified Trial Statisticians in the trial design, interim and final analysis.

The Trial Statistician is responsible for:

- Ensuring that the protocol is statistically sound and for providing input into the design of the case report form (CRF).
- Reviewing and approving all statistical sections before a document (protocol, grant application or manuscript) is submitted for funding, approval or publication.
- Ensuring that all data required for the analysis of outcome measures specified in the trial protocol are accurately captured on the CRF. Any data that is not strictly necessary for analysis or trial management should not be collected.
- Ensuring oversight on all data management (coding and definitions of variables).

5.0 PROCEDURE

Only general principles of statistical procedures are described below. More detailed sources of information are in the Trial Master File (TMF) for a particular study or the statistical analysis plan (SAP).

5.1 Statistical input into Trial Design

i) All research studies should obtain statistical input at the protocol development stage.

ii) For Clinical Trials of an Investigational Medicinal Product (CTIMP), each trial must have its own designated Trial Statistician who must be a qualified statistician.

iii) For clinical trials, statistical input will involve all of the following:

   a) Initial advice on appropriate trial design and indicative sample size (including potential power of the study).

   b) Formal and on-going input into trial design, conduct, analysis, interpretation and publication.

   c) Developing a SAP in conjunction with the Chief Investigator, project team and any necessary external stakeholders.

iv) All CTIMPS will be given the following:

a) Sample size based on the trial's primary outcome.

b) Method of treatment allocation: e.g. randomisation.

c) Summary of statistical analyses for the primary outcome.

d) Approximate timings of any interim analyses, if applicable.

v) The CI and research team are responsible for identifying clinically important primary and secondary outcomes. Input from the trial statistician should be obtained to ensure the study is feasible based on sample size calculations, ease of data collection via CRF, and transformations or changes of scale more suitable for analysis.

vi) The final SAP should be reviewed and agreed upon between the Trial Statistician and project team members. All SAP versions should be signed and dated by the Trial Statistician and CI; and kept in the Trial Master File.

5.2 Randomisation

The method of randomisation will be agreed by the project team. See gSOP-047 for further information.

5.3 Statistical input into Data Collection and Handling

i) The Trial Statistician, in collaboration with the Trial Coordinator or manager, should ensure that the design of the trial's main database permits the efficient extraction of data in a format suitable for use in a statistical package (statistical analysis file).

ii) The SAP should include a document specifying variables; their named, formats and the overall structure of the data that the Data Manager will provide to the Trial Statistician on database lock.

iii) The Trial Statistician in collaboration with the Data Manager should develop programs that can perform extensive range and consistency checks on the variables in the statistical analysis files. This is in addition to any checking that is incorporated within the trial database. These checks should be run prior to each analysis of the study data.

iv) Errors that are identified should be detailed in a data queries log so that any amendments can be made to the data set. Case sensitivity analysis may be considered.

5.4 Statistical Programming

i) A copy of the statistical analysis files, derived datasets and programs used in each interim analysis and the final analysis should be locked and archived at the end of the project preferably in separate folders.

ii) Programs should be structured and contain enough detail to allow them to be easily followed by another Statistician. They should also contain a brief header description of what they do.

iii) All programs/files should be adequately labelled to identify the trial for which they are applicable.

iv) Clear documentation on statistical analysis file specification procedures should exist for exporting from the trial database.

v) Whenever possible, all analyses involving the primary outcome measure should be quality controlled by an appropriately experienced person other than the main Trial Statistician. As a minimum, this will include reviewing the data for internal consistency, and consistency with other reports so as to allow the identification of clear anomalies. As a maximum, this will include a repetition of all analyses for the primary outcome.

5.5 Statistical Analysis Plan (SAP)

i) The SAP is a comprehensive and detailed description of all statistical methods to be used in a trial.

ii) The SAP should provide enough detail for a qualified statistician with no previous experience of the trial to perform the final analyses.

iii) The SAP should provide full details of all planned summaries and analyses, including templates of tables and figures to be presented in the statistical report. All primary and secondary outcomes should be clearly identified in the SAP.

iv) The SAP should not be written by anyone with unblinded access to the data prior to the database lock. Specifically, in blinded trials, the analysis plan should not be written by anyone unblinded to treatment arm. If the analysis plan is written by someone who is initially blinded to the data but later becomes unblinded during the trial, then this person cannot continue to write the analysis plan after they have become unblinded. In this case, authorship must be transferred to someone blinded.

v) Some parts of the SAP may change, and be version controlled, to account for unpredictable features of data, or to incorporate new analytical ideas. Any changes between the original protocol and the final SAP must be explained.

vi) The SAP must be finalised prior to the database lock (see gSOP-46 Database Lock and Data Extract Authorisation) or snapshot for interim analyses.

vii) As specified in section 5.1, the final SAP should be reviewed and agreed upon between the Trial Statistician and project team members. All SAP versions should be signed and dated by the Trial Statistician and CI; and kept in the TMF.

5.6 Interim Analysis

i) For interventional and larger observational studies, partial interim analyses are essential for monitoring the progress of a trial and for the regular assessment of data completeness and quality. Interventional studies will periodically consider interim analyses to assess safety and/or efficacy through their Data Monitoring or Trial Steering Committees.

ii) A full interim analysis should only be required if detailed in the study protocol or for safety concerns. This must be requested via the sponsor or data monitoring committee.

iii) Interim analyses are considered in detail in the SAP.

5.7 Statistical Reporting

i) Data should not be released to third parties before the primary publication of the main trial.

ii) The SAP should be reviewed periodically.

iii) The Trial Statistician should prepare summary reports for the Clinical Trial project team and external stakeholders as required.

iv) The Trial Statistician's reports should be used in the writing of trial publications.

v) Any table and figures presented within statistical reports and presentation should be obtained directly as an output from programs used to generate them wherever possible. This will ensure that minimal intervention is required to reproduce them.

vi) All reports should be checked and endorsed by the Trial Statistician prior to their release.

6.0 ARCHIVING

Consideration should be given for the archive of both paper and electronic data (such as databases). Please refer to gSOP-17 Archiving Essential Documents for guidance. Clinical trial documents should not be archived until the final report has been submitted. The 'green' open access deposit of all research outputs in the UH Research Archive (UHRA) is mandatory. A complete set of study data including programming information for the analysis is to be deposited in the EDRMS. Deposit is to be carried out by the author or relevant Principal Investigator. For research data there are various repositories into which data can be deposited, see gSOP-22 End of Trial Study Reports for guidance.

7.0 RELATED DOCUMENTS

- gSOP-14- Writing Research Protocols
- gSOP-047 Randomisation, Blinding and Unblinding
- gSOP-46 Database Lock and Data Extract Authorisation
- UPR-IM11 Records Management and the Archiving and Retention of Prime Documents and Business Records
- gSOP-17 Archiving Essential Documents for guidance
- gSOP-22 End of Trial Study Reports

8.0 APPENDICES

Appendix 1.0 - Definitions

9.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
2.0		Scheduled review

10. AUTHORSHIP & APPROVAL

Author Solange Wyatt

Signature  **Date 15/03/2022**

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature  **Date 01/03/2022**

11. AGREEMENT

Please detach and retain within your training files

I have read and understood the contents and requirements of this SOP (ref gSOP-034-01) and accept to follow University policies implementing it.

Recipient

Signature: ……Date: ……..

Name & Position: ……

Please retain copy of the signed form for your reference in your training file

Appendix 1: Definitions

Chief Investigator (CI)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Trial
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

Delegated Individual (DI)
An individual delegated by the PI to carry out their task(s).

Good Clinical Practice (GCP)
As defined in the Regulations.

International Conference on Harmonisation (ICH)
The ICH produced a series of guidelines in 1996, E6 being the guideline on Good Clinical Practice, otherwise known as (ICH-GCP).

Trial Master File
The Trial Master File (TMF) will be held at the principal site by the sponsor, Chief Investigator or at the coordinating Centre. The TMF should contain all essential documents defined as documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. A Trial Master File should be set up at the beginning of a trial and maintained up-to-date throughout the trial until trial conclusion.

For trials currently running, it is recommended that Section 8 of the ICH-GCP Guideline is followed as guidance in order to meet statutory requirements. However, some of the documents listed may not be available or applicable in many non-commercial trials. The appropriate documentation will vary according to the trial and sponsor requirements.