Statistics

Research & Development

Standard Operating Procedure for Statistical Input into Clinical Research Studies

SOP Number : SOP-34-02	**Effective Date:** October 2021
Version Number: v02	**Review Date:** 2-3 years

1.0 BACKGROUND

This document sets out the procedure for all West Hertfordshire Hospitals Trust (WHHT) staff who are involved in the statistical guidance for the 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 WHHT.

2.0 PURPOSE

This document defines the Trust's procedures for the responsibilities of Statisticians and Chief Investigators (CI) in the development, review and approval of Statistical Analysis Plan (SAP), clinical trial protocols and Case Report Forms (CRF) for research projects managed or sponsored by WHHT.
To review statistical principles and considerations in the design, conduct, analysis and reporting of research studies.

The monitoring of study data to ensure its validity is outside the scope of this SOP.

3.0 APPLICABLE TO

Any Trust employee involved with Clinical Trials sponsored by WHHT including, but not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Consultants, Co-investigators, Research Fellows, Clinical Trial Pharmacists, Research Managers, Statisticians, Research Nurses, Allied Health Professionals, Trial Coordinators, the Research & Development Steering Group (RDSG) & Data Managers.

4.0 RESPONSIBILITIES

This document applies to all personnel that are conducting research at the Trust including: staff that are full or part-time employees of the Trust, those working at the Trust with employment contracts funded partially or wholly by third parties.

The sponsor, or their delegated representative, is responsible for ensuring the quality of their trial through the use of appropriately qualified 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 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 CRF. Any data that is not strictly necessary for analysis or trial management should not be collected.(see SOP-15)

5.0 PROCEDURE

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

5.1 Statistical Input into Trial Design

5.1.1 All research studies should obtain statistical input at the protocol development stage.(see SOP-14)

5.1.2 For Clinical Trials of an Investigational Medicinal Product (CTIMP), each trial must have its own designated trial Statistician who must be suitably experienced.

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

- Initial advice on appropriate trial design and indicative sample size
- Formal and ongoing input into trial design, conduct, analysis, interpretation and publication
- Developing a SAP in conjunction with the CI, project team and any necessary external stakeholders

5.1.4 All CTIMPS will be given the following:

- Sample size based on the trial's primary outcome
- Method of treatment allocation: e.g. randomisation
- Summary of statistical analyses for the primary outcome
- Approximate timings of any interim analyses

5.1.5 The CI and Research Team are responsible for identifying clinically important primary and secondary outcomes. Input from the 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.

5.1.2 The final SAP should be reviewed and agreed upon between the Statistician and project team members. All SAP versions should be signed and dated by the Statistician and CI, and kept in the TMF.

5.2 Randomisation

The method of randomisation will be agreed by the project team.

5.3 Statistical input into Data Collection and Handling

5.3.1 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).

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

5.3.3 The trial Statistician in collaboration with the Data Manager should develop batch 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.

5.3.4 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

5.4.1 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.

5.4.2 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.

5.4.3 All programmes/files should be adequately labelled to identify the trial for which they are applicable.

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

5.4.5 Whenever possible, all analyses involving the primary outcome measure should be quality controlled by an appropriately experienced person other than the main 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)

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

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

5.5.3 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.

5.6 Interim analysis

5.6.1 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.

5.6.2 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.

5.6.3 Interim analyses are considered in detail in the SAP.

5.7 Statistical Reporting

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

5.7.2 The SAP should be reviewed periodically.

5.7.3 The Statistician should prepare summary reports for the clinical trial project team and external stakeholders as required.

5.7.4 The Statistician's reports should be used in the writing of trial publications.

5.7.5 Any table and figures presented within statistical reports and presentations 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.

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

6.0 RELATED DOCUMENTS

- SOP-14- Writing Research Protocols
- SOP-15- CRF and Data Management (Sponsored)

7.0 APPENDICES

Appendix 1 – Definitions

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-34-02	**October 2020**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. Other minor changes and clarifications of terms following review
gSOP-34-01	**October 2017**	New document

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R & D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Case Report Form (CRF)
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has coordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. An investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions, or c) to study absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products.

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

Good Clinical Practice (GCP)
Good Clinical Practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

Independent Data Monitoring Committee (IDMC)
A group of experts (including Clinical Experts, Statisticians and if appropriate Ethicists and Patient Advocates) not associated with the trial and all independent of WHHT that monitor safety and efficacy data while a trial is ongoing. The role of the Independent Data Monitoring Committee (IDMC) is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants attention or any reasons for the trial not to continue.

International Conference on Harmonisation (ICH)
International Conference for Harmonisation, a collaboration between regulators and the pharmaceutical industry in Europe, the United States and Japan to establish common standards for clinical trials. ICH GCP is a widely recognised standard for Good Clinical Practice in clinical trials.

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted and recorded in accordance with the protocol, Standard Operating Guidelines (SOP's), Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC)
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

The Regulations
Medicines for Human Use (Clinical Trial) Regulations 2004 transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

Trial Master File
The Trial Master File contains all essential documents held by the sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

Trial Steering Committee (TSC)
The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.