Royal Papworth Hospital
NHS Foundation Trust

Document Title: Statistical Input into Clinical Trials

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Staff involved in development: *Job titles only*	Senior R&D Manager, R&D Operational Manager, Clinical Project Managers
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For use by:	NHS Staff Trust-Wide
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Summary of Amendments

Version No:	Modification:
4.0	Amendments throughout.

Key Points of this Document

- It sets statistical guidance for the planning, designing, monitoring, analysis and reporting of research studies and clinical trials, to ensure compliance with good clinical practice (GCP) for research projects managed by Royal Papworth Trials Unit Collaboration (PTUC) or sponsored by Royal Papworth NHS Foundation Trust.

1 Purpose and Contents

a. This document defines the Trust's procedures for the responsibilities of Statisticians and Chief Investigator(s) (CI) in the development, review and approval of statistical analyses plan (SAP, see Guidance Document GD003: Statistical Analysis Plan), clinical trial protocols and case report forms (CRF) for research projects managed by PTUC or sponsored by Royal Papworth NHS Foundation Trust.

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

c. 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'.

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

2 Roles & Responsibilities

a. This Policy applies to all personnel that are conducting research at the Trust..

b. 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 analyses.

c. For single centre non-CTIMPs projects an appropriately qualified non-statistician may carry out the duties of the Trial Statistician with oversight from an appropriately qualified statistician.

d. The Trial Statistician is responsible for:

1. Ensuring that the protocol is statistically sound and for providing input into the design of CRF. This responsibility is shared with the PI who should seek involvement from the statistician as early on in the study design as possible.
2. Reviewing and approving all statistical sections before a document (protocol, grant application or manuscript) is submitted for funding, approval or publication.
3. 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.

e. The PI will provide the statistician with a copy of the protocol (SOP019). In addition, the PI will provide as accurate information as possible for the statistician to perform analyses.

f. A delegation of duties log must be completed to clarify the division of responsibilities. If statistical analysis is undertaken by anyone outside of the Papworth Trials Unit statistical team, then this must be detailed in the trial delegation log

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance with may result in disciplinary procedures.

4 Procedure

a. Only general principles of statistical procedures are described below. More detailed sources of information are: the Trial Master File for a particular study, GD003: Statistical Analysis Plan (SAP), SOP018: Randomisation of Royal Papworth Sponsored Clinical Trials and SOP009: Project Management of Royal Papworth Sponsored Studies.

4.1 Statistical Input into Trial Design

a. All research studies should obtain statistical design input at the protocol development stage.

b. For clinical trials of an investigational medicinal product (CTIMP), each trial must have its own designated trial Statistician who must be suitably experienced.

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

1. Initial advice on appropriate trial design and indicative sample size.
2. Advice on appropriate choice of a (usually) single primary endpoint, used to address the main research question, normally on which the trial is to be powered.
3. Advice on appropriate choice of secondary and exploratory endpoints, which are additional outcomes of interest for which the trial may not be powered.
4. Formal and on-going input into trial design, protocol development, conduct, analysis, interpretation and publication.
5. Developing a Statistical Analysis Plan (SAP) (see GD003: Statistical Analysis Plan), in conjunction with the CI, project team and any necessary external stakeholders.

d. All CTIMPs will be given the following (see GD003: Statistical Analysis Plan):

1. Sample size based on the trial's primary outcome.
2. Method of treatment allocation: e.g. randomisation or minimisation.

3. Summary of statistical analyses for the primary outcomes.
4. Timings of any interim analyses.

e. 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, etc.

f. The final SAP should be reviewed and agreed upon between the Statistician and project team members and the data management team. All SAP versions should be signed and dated by the Statistician and CI, and kept in the Trial Master File.

4.2 Randomisation (see SOP018)

a. The method of randomisation (simple, block, minimisation, etc.) will be agreed by the project team. See SOP018 for further information.

4.3 Statistical Input into Data Collection and Handling

a. The Trial Statistician, in collaboration with the Trial Coordinator or Manager and a member of the Data management team, 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).

b. The Statistical Analysis Plan (SAP) should include a document specifying variables; their names, and the overall structure of the data that the Data Management will provide to the Trial Statistician on database lock.

c. 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.

For CTIMPS errors that are identified by the Trial Statistician must be detailed in a data queries log - FRMXXX: Statistician Data Queries, so that any amendments can be made to the data set if necessary. Case sensitivity analysis may be considered. For non-CTIMPs an alternative process can be used with agreement from the Trial Statistician and Data Manager.

4.4 Statistical Programming

a. 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 their project, preferably in separate folders.

b. 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.

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

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

e. 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.

4.5 Statistical Analysis Plan (SAP)

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

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

c. Some parts of the SAP may change, and 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 in the latter.

d. See GD003: Statistical Analysis Plan for further details.

4.6 Interim Analysis

a. 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.

b. 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.

c. Interim analyses are considered in detail in GD003: Statistical Analysis Plan. Interim analysis for reasons other than safety or monitoring of the recruiting rate should be carefully discussed at a design stage of the trial to ensure statistical control of error probabilities.

4.7 Statistical Reporting

a. The SAP should be reviewed periodically but certain parts of the SAP should be decided and fixed before the study starts, e.g. the criteria for triggering a futility stopping rule.

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

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

d. Any tables 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.

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

f. Results of statistical analyses should be reported according to clinical trial reporting instruments such as Consolidated Standards of Reporting Trials (CONSORT/STROBE).

5 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: *Managment/Clinical Directorate Group*	Research and Development Directorate
Approval date: (this version)	[Current active version approved date]
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care Research (2018)
Key related documents:	Trust Research Policy SOP009: Project Management of Royal Papworth Sponsored Studies, SOP016: Monitoring Royal Papworth Sponsored Studies, SOP018: Randomisation of Royal Papworth Sponsored Clinical Trials, SOP021: Trial Closure and End of Trial Reportin SOP061: Research Data Queries, SOP063: Research and Development: Internal Good Clinical Practice (GCP) Audit, GD003: Statistical Analysis Plan, Guidance Good Clinical Practice for Clinical Trials www.gov.uk/good-clinical-practice-for-clinical-trials

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Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO
Positive/Negative							

Review date:	July 2025

I certify the contents of this SOP has been reviewed and ratified

DocuSigned by:
Dr Patrick Calvert
81A52758BFFF421...

13-Jul-2022

Signed by Dr Patrick Calvert, Clinical Director of R&D

Date