Standard Operating Procedure CCTU/SOP022

Statistical Principals

1. Scope

This Standard Operating Procedure will be followed by statisticians working on Cambridge-Sponsored CTIMPs and research projects coordinated by the CCTU.

2. Purpose

- To outline statistical principles and considerations in the design, conduct, analysis, and reporting of intervention studies (trials). Some but not all points are also relevant to observational studies
- To define the role and responsibilities of the Trial Statistician and interactions with other members of the trial team

3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH); or the University of Cambridge (UoC); or jointly by CUH and UoC OR Sponsored by: Cambridge University Hospitals NHS Foundation Trust (CUH) or CUH jointly with the University of Cambridge or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge

3.2. Abbreviations

Abbreviation	Meaning
CONSORT	Consolidated Standards of Reporting Trials
CI	Chief Investigator
CRF	Case Report Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
NHS	National Health Service
QA	Quality Assurance
SAP	Statistical Analysis Plan
TMF	Trial Master File

4. Undertaken by

- Each trial should have a designated Trial Statistician, with appropriate qualifications and experience, who assumes ultimate responsibility for the statistical aspects of the trial.
- The designated Trial Statistician should be named in the trial protocol. Some tasks may be delegated to other statisticians involved in the trial; the Trial Statistician should exercise appropriate judgment about which tasks should be delegated and should check that these tasks are performed appropriately.
- The Trial Statistician will interact closely with other members of the trial team, including but not limited to the Chief Investigator, Principal Investigator, Project Lead, Clinical Trial Coordinators, Data Managers and Programmers.

5. Items Required

1. CCTU/SOP023 Statistical Analysis Plan
2. CCTU/TPL007 Statistical Analysis Plan Template
3. CCTU/TPL010 Data Monitoring Committee Charter Template
4. CCTU/SOP036 Open Label Randomisation
5. CCTU/SOP046 Blinded Randomisation
6. CCTU/SOP053 Paper Based Randomisation
7. CCTU/GD038 Storage and Access to Confidential Materials
8. CCTU/FRM106 Sample Size Justification
9. CCTU/SOP048 CTIMP Set up Procedures by the Regulatory Team
10. CCTU/SOP058 Randomisation using Sealed Envelope

6. Summary of Significant Changes

Use of Form 106 Sample Size Justification

7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

Access to statistical expertise is essential throughout the design, conduct, and analysis of the trial. Statistical considerations in the design and analysis of trials should broadly follow ICH Harmonised Tripartite Guideline: E9 Statistical Principles for Clinical Trials
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

Only the broad general principles of statistical procedures are considered in this document. More trial specific details are documented in trial-specific working instructions and guidance documents filed in the TMF for each trial. Refer to CCTU/SOP023 Statistical Analysis Plan for planning the analysis, and CCTU/TPL007 Statistical Analysis Plan Template to document the plan detail.

This document covers aspects of statistical work outside of the Statistical Analysis Plan.

7.1. Statistical Input into Grant Application

- Statistical input is required in grant applications to justify the sample size which impacts on study costs. Use CCTU/FRM106 Sample Size Justification
- The overall choice of study design, sample size, primary endpoint, and analysis must be recorded and should be reviewed by another statistician.
- If a study is funded from a grant application then all the relevant details will be ultimately be documented in the study protocol, however there must be a record of the preliminary discussions and key decisions regarding study design included in the statistics folder (File relevant emails section 7.11.1 and/or 7.11.2).
- A template form to record reviewing steps is available within the blank template folder (section 7.11.2).

7.2. Statistical Input to Trial Protocol

The following statistical considerations should be included in the trial protocol:

- Sample size justification. In general, this should be based on the trial primary endpoint
- A description of the method of treatment allocation should be given in enough detail (allocation ratios, stratification) to enable its theoretical reproduction. However, exact details, such as block size, that may enable inference of the actual allocation sequence should be avoided
- A brief summary of the methods of statistical analysis for the primary analyses to be employed (detailed in the Statistical Analysis Plan)
- The planned approximate timings of interim analyses, if appropriate

As a minimum the Trial Statistician should critically review the trial protocol throughout its development with special attention to:

- Details of the trial intervention(s)
- The trial design itself, for example parallel groups, crossover, factorial
- The trial outcome measures, split into a single primary endpoint and secondary endpoints and how this links to the broader aims of the trial
- Patient eligibility/ineligibility criteria
- Details regarding randomisation, blinding, matching and other measures to avoid bias and increase precision
- The designated trial statistician will approve the protocol review detailed in CCTU/SOP048 CTIMP Set up Procedures by the Regulatory Team. This can be by signature on the protocol page or by email. A copy of must be retained in the statistics folder.

7.3. Randomisation

- Randomisation refers to the random assignment of participants to one of two or more groups which are allocated different interventions. Its main purposes are:
    - To minimise differences between the groups in terms of baseline characteristics other than the interventions being compared that may influence clinical outcomes (prognosis)

- To avoid allocation bias
- To provide a basis for statistical inference

This SOP does not mandate the use of any particular method of randomisation provided the allocation to an intervention is unpredictable.

- For trials employing random permuted blocks a randomisation list (or dummy list) will be reviewed by a statistician for integration into the randomisation program. "Dynamic" methods of randomisation (e.g. minimisation) will, other than in exceptional cases are achieved through a randomisation server
- Refer to CCTU/SOP036 Open Label Randomisation, CCTU/SOP046 Blinded Randomisation and CCTU/SOP058 Randomisation using Sealed Envelope for further details of the documentation and testing of electronic randomisation systems
- Refer to CCTU/SOP053 Paper Based Randomisation for details of using physical envelopes for simple studies

7.4. Statistical Input to Data Collection and Handling

- The Trial Statistician should ensure, in collaboration with the CI or designee, Clinical Trial Coordinators and/or Data Programmers, that the design of the trial's main database/Case Report Form permits the efficient extraction of data in a format suitable for use in a statistical package
- Data items that are not strictly necessary for analysis or trial management should not be collected
- The trial statistician should raise any data queries that arise from performing the interim and final data analyses and consider it part of their responsibility to check that a valid and clean data set has been obtained
- Before any final reporting can take place any queries arising from these checks must be resolved with the Clinical Trial Coordinators/Data Managers

7.5. Statistical Programming

- The computer software used for statistical analysis will be one of the major statistical packages, for example R, Stata, SAS
- A copy of the statistical analysis files, derived datasets, and programs used in each interim analysis and the final analysis should be frozen and archived, preferably in separate folders
- Programs should be structured, and contain detailed descriptions and comments to enable them to be followed and understood by another statistician. In particular, all programs should have information identifying the trial for which they apply and a brief description of the program aims
- All analyses involving the primary endpoint should be quality controlled. Differing levels of QC may be used as appropriate
- As a minimum this will include reviewing the data for internal consistency and consistency with previous reports (and possibly any other relevant literature) to identify clear anomalies by an appropriately experienced person other than the statistician who performed the main analysis

- This may also include a visual review of the programs used to carry out the analyses or where appropriate a repetition of the analysis of the primary endpoint from the point of reading in data

7.6. Statistical Analysis Plan

- A statistical analysis plan (SAP) should be developed (refer to CCTU/SOP023) before the database lock for the primary analysis in line with the outline analysis plan in the trial protocol
- This can change at any time up to the database lock as the analysis may depend on unpredictable aspects of the data and new analytical ideas may be developed during the course of the trial
- The SAP must be finalised before database lock and followed for the primary analyses. If the data contradicts assumptions made in the SAP then supplementary analyses may be performed and justified in subsequent reports

7.7. Interim analyses/Independent Data Monitoring Committees (IDMC)

- The responsibilities and function of IDMCS are fully described in the IDMC Charter for each trial (CCTU/TPL010 Data Monitoring Committee Charter Template)
- Interim analyses are essential for monitoring the progress of a trial and for assessing data quality and completeness. For most trials, an IDMC will be established to periodically review unblinded data from interim analyses to assess the safety and/or efficacy of the trial interventions
- An outline of the analyses to be performed for potential inclusion in the IDMC report should be drafted by the Trial Statistician as early as possible and sent to the IDMC for their comment. The IDMC analyses will normally comprise a subset of those included in the final SAP and should not be overly detailed
- The IDMC report should contain all information that could materially affect the IDMC's decision on whether to recommend early closure, amendment or continuation of the trial
- The IDMC report should briefly describe the design of the trial, contain information on the rate of accrual (against predicted accrual), compliance with CRF return and present any new external evidence since the previous report
- Requests for additional analyses from the IDMC not included in the outline IDMC report (e.g. post hoc power calculations) should be critically examined by the Trial Statistician and may be referred to the Trial Steering Committee if necessary
- The Trial Statistician, while respecting the independence of the IDMC, should draw attention to the dangers of over-interpretation of early data if this is relevant during IDMC meetings
- The full IDMC report should only be seen by IDMC members, the Trial Statistician and any other statistician(s) involved in the analysis. The Chief Investigator may see the full report ONLY if they are NOT involved in the recruitment and management of trial participants

- The confidentiality of the report must be respected, and measures put in place to prevent unauthorised access to electronic and paper copies of the report. Refer to CCTU/GD038 Storage and Access to Confidential Material
- Unscheduled interim analyses comparing endpoints between randomisation arms should be performed only if approved by the Trial Steering Committee. The final statistical report should note when and why all interim analyses were performed

7.8. Sub-studies and Release of Data before Trial Closure

- Proposals for sub-studies not already documented in the trial protocol should be approved by the Trial Steering Committee
- Approval from the IDMC should be sought if the sub-study is to be conducted before the unblinding of trial participants
- The Trial Statistician should scrutinise any sub-study proposal or the publication of any data before the main trial is closed to ensure it does not compromise the main randomised comparison or the blinding if applicable
- In general, the trial data should not be released before the primary publication of the main trial

7.9. Statistical Reporting

- Tables and figures contained within statistical reports and presentations should, whenever possible, be obtained directly as the output from programs, and require minimal intervention to be directly reproducible
- If this is not possible then a "log" file should be produced by the statistical program against which the content of any tables is checked
- All reports including publications should be checked and endorsed by the Trial Statistician prior to their release. Any deviations from the statistical analysis plan should be documented and justified in the final trial report
- Results of statistical analyses should be reported according to the CONSORT guidelines for randomised trials (CONSORT is for randomised trials but it could be applied to non-randomised trials)
- The results of the analyses should be presented a manner likely to facilitate the interpretation of their clinical importance. More emphasis should be placed on estimates of the magnitude of the treatment effects or differences and confidence intervals rather than significance tests
- Avoid the phrase "p-values less than 0.05 are regarded as significant"

7.10. Document Approvals

- The Trial Statistician is responsible for reviewing and is in some instances a signatory to the following key documents:
    - Protocol
    - CRFs
    - Confirmation that randomisation is correctly implemented pre-trial
    - Final version of the statistical analysis plan
    - All reports of trial data or publications
    - IDMC charters

7.11. Document Management

- The core set of document that Statistics is responsible for are indexed within:
  - CCTU/TPL056 Statistics Index
  - CCTU/TPL053 Randomisation File Index

7.11.1. Paper Documents

- All studies have a paper folder for either or both Statistics and Randomisation.
- Wherever practically possible, documents should be printed out and included in the paper folder as soon as a major version change occurs (see CCTU/SOP31 Version Control of Trial Level Documents)
- All such documents must have a version number, date, and author included; if no formal section is included in a document with these details then hand-written annotations are acceptable
- The relevant index should be maintained at the start of a folder using tick marks to indicate if a document is present, or NA plus reasons if it is not required
- An empty indicator means that the document is absent, and will need to be produced in a timely fashion during the course of the study

7.11.2. Electronic Draft Documents

- For commencing a new study a copy of the blank study folder should be taken from the university drive V:/STATISTICS/STUDY PLANNING/Blank Template, and given a new name [the drive letter V:/ may vary between users]
- The earliest point this may occur is during initial grant application stages, but may occur at a later stage during a live study. Once a study is underway the folder should be transferred to within V:/STATISTICS/STUDY FOLDER
- In collaborating with staff who use IT systems which may or may not be accessible to statisticians, it is acceptable to delete parts of the folder template within the University drive if this avoids duplication
- Core documents will ultimately be printed off and filed in the Statistics or Randomisation Folder. Code is the exception as this is kept in electronic form to allow potential replication of analyses. Code will always be stored within the University drive
- If there is any duplication of documents the following indicates the hierarchy as to which version is to be regarded as the definitive version
  - Paper
  - NHS Drive
  - University Drive
  - Documents Outside of Remit
- General information may transpire during the course of a study that must be captured (data queries, definitions of derived variables, handling of unanticipated circumstances). If this information may affect any aspect of

decision making, data capture, or its subsequent analysis, then consider how it will be recorded in a GCP compliant fashion

- A process should exist for recording the information: data query, statistical analysis plan, file notes. It is unacceptable to use ad hoc documents or spread sheets as the only place where information is captured. Tracking documents may be created in addition as aids

7.12. End of Trial

- At the end of trial the following steps need to occur (in the following order):
  - Steps taken according to SOP32 Determination of Analysis Population
  - SAP v2.0 finalised and approved with signatures and dates
  - Formal unblinding to release randomisation and/or concealment lists
  - Database locking (check that approvals are in place)
  - Production of final statistical report
  - Entry of study results into EudraCT if required
  - Ensure that any documents that were stored according to GD038 Storage and Access of Confidential Information Guide are released and archived
  - Check all items in the statistical, and/or randomisation, index are present in the folder(s) in printed paper form, or a full file path is given for code
- The statistics and/or randomisation folders are transferred to be included in the main TMF
- For electronic documents that cannot be printed, ensure that there is one definitive version and no duplication across multiple folders or servers
- Change any relevant electronic folder permissions to read-only

8. Monitoring Compliance with and the Effectiveness of this Document

a. Process for Monitoring Compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

b. Standards/Key Performance Indicators

This process forms part of a quality management system and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

9. References

The Institute of Clinical Research, Abbreviations used in Clinical Trials.

MHRA, Good Clinical Practice "Grey Guide"

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1998, Statistical Principles for Clinical Trials
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

10. Associated Documents

NA

11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

Review date	2 years (or earlier in light of new evidence) from approval date
Owning department:	CCTU QA
Supersedes:	CCTU/SOP022 V4
Local reference:	CCTU/SOP022 V5