STANDARD OPERATING PROCEDURE

STATISTICAL PRINCIPLES

LinCTU SOP 08

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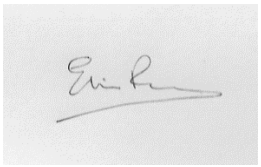
Version History	**Reason for change**
1.0	First LinCTU version

NOTE: All SOPs are subject to regular review.

Please ensure that the version of this SOP is the most up-to-date.

OUT OF DATE DOCUMENTS MUST NOT BE USED AND HARD COPIES SHOULD BE DESTROYED

List of those who have read, reviewed and advised on the SOP

Reviewer name	**Role**	**Date**	**Signature**
Vanessa Botan	Statistician and reviewer	07/04/2022	
Elise Rowan	Data manager	24/05/2022	
Zahid Asghar	Lead of Statistician's Group	07/04/2022	
LinCTU Steering Committee		23/06/2022	

1 PURPOSE

- To outline statistical principles and considerations in the design, conduct, analysis, and reporting of clinical trials. Some, but not all, points may also be relevant to observational studies.
- To define the role and responsibilities of the Statistician/Analyst and interactions with other members of the trial team.

2 SCOPE

This Standard Operating Procedure will be used by statisticians/analysts working on research projects coordinated by the Lincoln Clinical Trials Unit.

3 BACKGROUND

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.

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[1].

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 for each trial.

4 CROSS REFERENCES

CG-QMS SOP CG04 Protocol development

CG-QMS SOP CG12 Amendment

CG-QMS SOP CG15 Archiving (Clinical Data).

LinCTU SOP 02 Data Management

LinCTU SOP 05 Randomisation

LinCTU SOP 06 Sample Size Calculations

LinCTU SOP 07 Statistical analysis plan

RG-QMS RG03 Document Control – (Study documents)

5 PROCEDURE

5.1 The Trial Statistician will interact closely with other members of the trial team, including but not limited to the Chief Investigator (CI), Principal Investigator (CI), Project Lead, Clinical Trial Coordinator(s), Data Manager(s) and Programmer(s) as necessary.

5.2 The CI and/or statistician should refer to CG-QMS SOP CGS2 Statistical Analysis Plan for planning the analysis.

Statistical Input into Grant Application

5.3 At the start of the trial, the overall choice of study design, sample size, primary endpoint, and analysis must be recorded and should be reviewed by another statistician or one other key trial team member (usually the CI, health economist or similar).

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

5.4 Statistical input is required in grant applications to justify the sample size. Use CG-QMS CGS3 Sample Size Calculations.

5.5 All the relevant details should be documented in the study protocol.

Statistical Input to the Trial Protocol

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

- Sample size justification. In general, this should be based on the trial primary outcome.
- A description of the method of treatment allocation should be given in enough detail (allocation ratios, stratification) to enable its theoretical reproduction.
- A brief summary of the methods of statistical analysis for the primary analyses to be employed (to be detailed in the Statistical Analysis Plan).
- The planned approximate timings of interim analyses, if appropriate.

5.7 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.
- Patient eligibility/ineligibility criteria (taking into account clinical factors).
- Details regarding randomisation, blinding, matching and other measures to avoid bias and increase precision.
- The designated trial statistician will review and approve the protocol and send confirmation to the Chief Investigator. This can be by signature on the protocol page or by email.

RANDOMISATION

5.8 Randomisation refers to the random assignment of participants to one of two or more groups which are allocated different interventions, or different order of intervention. 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.

5.9 Use CG-QMS SOP CGD6 Randomisation. This SOP does not mandate the use of any particular method of randomisation provided that the allocation to an intervention is unpredictable.

5.10 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, be achieved through a randomisation system

STATISTICAL INPUT TO DATA COLLECTION AND HANDLING

5.11 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 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.

5.12 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.

5.13 Before any final reporting can take place, any queries arising from these checks must be resolved with the Clinical Trial Coordinators/Data Managers as appropriate.

STATISTICAL PROGRAMMING

5.14 The computer software used for statistical analysis shall be one of the major statistical packages, for example R, Stata, SAS, SPSS.

5.15 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 in accordance with CG-QMS SOP CG15 Archiving (Clinical data).

5.16 Programs should be structured and contain detailed descriptions and comments to enable them to be followed and understood by another statistician. All programs should have information identifying the trial for which they apply.

5.17 All analyses involving the primary endpoint should be quality controlled by the appropriate Data Monitoring Committee or equivalent.

5.18 As a minimum, quality control 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.

5.19 This may also include a review of the programs used to carry out the analyses or where appropriate a repetition of the analysis of the primary endpoint.

STATISTICAL ANALYSIS PLAN (SAP)

5.20 A Statistical Analysis Plan (SAP) should be developed in accordance with CG-QMS SOP CGS2 Statistical analysis plan before the database lock for the primary analysis in line with the outline analysis plan in the trial protocol

5.21 It is encouraged that the SAP is published in advance, either in a peer-reviewed journal or in Lincoln ePrints (http://eprints.lincoln.ac.uk).

5.22 The SAP should be developed by the statistician and data manager together to ensure that the data collected can be coded appropriately at the data capture system design phase.

5.23 The SAP may 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.

5.24 The statistical analysis plan must be finalised before database lock and followed for the primary analyses.

INTERIM ANALYSES / INDEPENDENT DATA MONITORING COMMITTEES (IDMC)

5.25 The responsibilities and function of IDMCs shall fully described in the IDMC Charter for each trial where one is required. The Data Monitoring Committee Charter should be produced using CG-QMS Data Monitoring Committee.

5.26 Interim analyses are essential for monitoring the progress of a trial and for assessing data quality and completeness. For most trials, an IDMC shall be established to periodically review unblinded data from interim analyses to assess the safety and/or efficacy of the trial interventions.

5.27 An outline of the analyses to be performed for potential inclusion in the IDMC report shall be drafted by the Trial Statistician (in accordance with CG-QMS SOP CGS2 Statistical analysis plan as early as possible and sent to the IDMC for their comment. The IDMC analyses should not be overly detailed.

5.28 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.

5.29 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.

5.30 Requests for additional analyses from the IDMC not included in the outline IDMC report should be critically examined by the Trial Statistician and may be referred to the Trial Steering Committee, or equivalent, if necessary.

5.31 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.

5.32 The full IDMC report should only be seen by IDMC members, the Trial Statistician and any other statistician(s) and data managers involved in the data set creation and analysis. The Chief Investigator may see the full report ONLY if they are NOT involved in the recruitment and management of trial participants.

5.33 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.

SUB-STUDIES AND RELEASE OF DATA BEFORE TRIAL CLOSURE

5.34 Proposals for sub-studies not already documented in the trial protocol should be approved by the Trial Steering Committee and approvals (including ethics) must be obtained prior to the commencement of data collection. Where this is after permissions have been given, an amendment should be made in accordance with CG-QMS SOP CG12 Amendment.

5.35 Approval from the IDMC should be sought if the sub-study is to be conducted before the unblinding of trial participants.

5.36 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.

5.37 In general, the trial data should not be released before the primary publication of the main trial. Any exceptions should be discussed with the CI.

STATISTICAL REPORTING

5.38 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.

5.39 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.

5.40 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.

5.41 Results of statistical analyses should be reported according to the Consolidated Standards of Reporting Trials (CONSORT[2]) guidelines for randomised trials (CONSORT is for randomised trials but it could be applied to non-randomised trials), STROBE[3] for observational epidemiology studies, TREND[4] for evaluations with non-observational designs and EQUATOR [5]for general health research.

5.42 The results of the analyses should be presented in 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.

5.43 Avoid the phrase “p-values less than 0.05 are regarded as significant”.

DOCUMENT APPROVALS

[2] http://www.consort-statement.org/
[3] https://www.strobe-statement.org/
[4] https://www.cdc.gov/trendstatement/index.html
[5] https://www.equator-network.org/

5.44 The Trial Statistician is responsible for reviewing and, in some instances, a signatory to the following key documents:

- Protocol.
- CRFs.
- Confirmation that randomisation is correctly designed for implementation pre-trial.
- Final version of the statistical analysis plan.
- All reports of trial data and/or publications.
- IDMC charters.

ELECTRONIC DOCUMENTS

5.45 All data should be recorded electronically.

5.46 All data must have version and/or dates in accordance with RG-QMS RG03 Document Control – (Study documents).

5.47 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.

END OF TRIAL

5.48 At the end of trial, the following steps need to occur (in the following order):

5.49 Database lock (check that approvals are in place). This may include confirmation that the final outcome assessment has been obtained and recorded for the last patient in the trial. There should also be confirmation from the data manager and CI that all queries have been resolved and data is clean.

5.50 Formal unblinding (to release randomisation and/or concealment lists).

5.51 Production of final statistical report.

5.52 Ensure that any trial documents are archived in accordance with SOP CG15 Archiving (Clinical Data).

5.53 Check all items in the statistical, and/or randomisation, index are present in the folder(s) with a full file path given for code.

5.54 Change any relevant electronic folder permissions to read-only.

FLOW CHART

None required.