UNIVERSITY OF LINCOLN

# CLINICAL GOVERNANCE - STANDARD OPERATING PROCEDURE

# STATISTICAL ANALYSIS PLAN (SAP)

## CG-QMS SOP CGS2

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| **Version History** | **Reason for change** |
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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**OUT OF DATE DOCUMENTS MUST NOT BE USED AND HARD COPIES SHOULD BE DESTROYED**

# 1 PURPOSE

To describe the procedure for the preparation of a statistical analysis plan (SAP) for a trial that will comply with the study protocol, GCP guidelines and other statutory and regulatory requirements.

# 2 SCOPE

# 3 BACKGROUND

3.1 The Statistical Analysis Plan (SAP) gives a detailed description of the endpoints in the study and the corresponding analyses.

3.2 All clinical trials must have a Statistical Analysis Plan (SAP) which is a comprehensive description of the methods and presentation of data analysis proposed.

3.3 The overall responsibility for preparing the SAP is delegated to the CI, a suitably qualified statistician or Clinical Trials Unit (CTU). This delegation of duty shall be agreed before the study begins and shall be documented in the sponsorship/site agreements.

3.4 The SAP must be drafted, finalised and agreed before commencing the final statistical analysis of clinical trial data. Where possible, statistical analysis should be complete before unblinding (revealing the treatment allocation).

3.5 Changes to the SAP during the course of the clinical trial must be documented in the SAP and reasons for the change noted.

3.6 Chief Investigator (CI) and Trial Statistician prepare the Statistical Analysis Plan.

# 4 OTHER RELEVANT SOPs

4.1 CG-QMS SOP CGD2 Data management

4.2 CG-QMS SOP CGS1 Statistical Principles

4.3 CG-QMS SOP CGD6 Randomisation

# 5 PROCEDURE

The SAP shall document preparation of the SAP, including approval from the lead statistician overseeing preparation of the SAP (if required), and approval from the Chief Investigator.

The SAP shall contain:

## 5.1 DETAILS OF THE ANALYSIS

- The SAP states the hypotheses to be tested.
- The SAP states parameters that are to be estimated in order to meet the trial objectives stated in the trial protocol.
- The SAP provides details of the sample size calculation reported in the trial protocol.
- The SAP lists details of tables, figures and other data to be presented in the statistical report(s). This may also include the set of blank data tables reflecting the contents of the final report.
- The SAP should detail examination of key variables for outliers and any anomalies in data quality and notify these to the data manager in the form of data queries (hopefully the data manager would have resolved most issues already- as the data was gathered).
- This process may need repeating a number of times before all issues are completely resolved/clarified but at that point, it should be possible for the data manager to agree to implement formal “data lock” and final statistical analysis should take place. The process of data lock should be documented according to the data management SOP.
- The SAP defines population(s) within the clinical trial.
- The SAP may describe intention-to-treat, as randomised, sub-group analyses.

- The SAP describes all primary and secondary outcomes, and also describes in detail any algorithms required to derive outcomes as required.
- A check for comparison between arms to ensure balance.
- The SAP states the frequency of interim analyses and reports.
- A summary of patterns of missing data and compliance to the protocol

## 5.2 METHODS OF ANALYSIS

The SAP describes the methods for analysis and presentation of the data, including, where applicable:

- Regression models with interaction terms are typically used for analysis
- Observational period of analysis, defining pre- and post- end points.
- Methods for point and interval estimation.
- Levels of statistical significance to be used, one-tailed or two-tailed tests to be performed, and/or clinical relevance.
- Multiple comparison methods.
- Use of baseline and covariate data.
- Methods for handling multi-centre data.
- Methods for handling missing data.
- Methods for handling withdrawals and protocol deviations.
- Methods for dealing with censoring.
- Identification of fixed or random effects models.
- Planned interim analysis and statistical stopping rules.
- Methods for checking critical analysis assumptions and sensitivity of assumptions.
- Rules for introduction of methods for handling missing data.
- Specification of computer systems and packages to be used for statistical analysis.
- An evaluation of the efficacy of the treatment tested. Both p-values and confidence intervals should be provided with estimates of effect size for the primary endpoint(s).
- An adjustment for multiple comparisons to be specified if there is more than one primary endpoint or more than one primary comparison.

## 5.3 SECONDARY ANALYSIS

- If appropriate, a secondary analysis for treatment efficacy that is adjusted for predefined highly prognostic baseline characteristics and variables used in stratified randomisation.
- An evaluation of efficacy with respect to secondary outcomes.
- Confidence intervals should be provided with estimates of effect size.
- p-values should either be omitted or interpreted with caution as the study may not be appropriately powered.
- Such analyses should be considered as hypothesis generating rather than providing firm conclusions.
- Secondary analysis should include a sensitivity analysis that inputs missing data according to a range of assumptions.
- Any planned subgroup analyses as specified in the protocol.
- The addition of further subgroup analyses not specified in the protocol requires further justification.

## 5.4 FLOW OF PARTICIPANTS

A flow diagram following the Consort structure (http://www.consort-statement.org/)

Reporting requirements of regulatory agencies includes the numbers of:

- Screened, eligible and consenting participants
- Participants assigned
- Participants receiving the allocated treatment
- Participants completing the study protocol
- Participants analysed for the primary outcome
- A breakdown for each treatment group

A comparison of screening data between the participants included and excluded should be produced if any relevant data is recorded before consent to check how representative the study population is.

## 5.5 DATA TO BE OBTAINED

- The statistician/designee should work on a copy of the study database that has been downloaded by the data manager. The copy should not require manual intervention to obtain, but rather be an automated process where statistical code takes an internal temporary copy of the frozen data each time it is run.
- The statistician should refer data queries to the data manager to investigate.
- Any amendments to the study database should be documented and a new version supplied to the statistician.

# 6 FLOWCHART

None required.