STANDARD OPERATING PROCEDURE FOR STATISTICAL ANALYSIS PLANS FOR CLINICAL RESEARCH

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1. PURPOSE

This document defines the purpose and content of the Statistical Analysis Plan (SAP) for Clinical Research Studies and complies with the principles of Good Clinical Practice (GCP).

2. SCOPE

This document applies to Clinical Trial of Investigational Products (CTIMP) and other clinical research studies as required sponsored or co-sponsored by the University of Dundee (UoD) and/or NHS Tayside (NHST).

This Standard Operating Procedure (SOP) applies to the individual or individuals responsible for the statistical planning and analysis associated with a clinical research study (the "Study Statistician"). The Chief Investigator (CI) may be the statistician. Responsibility for the SAP may be transferred to groups or individuals outside UoD or NHST, but this must be done using a formal clinical trial service agreement.

3. RESPONSIBILITIES

The SAP should be a comprehensive and detailed description of the methods and presentation of analyses proposed for a clinical trial to avoid *post hoc* decisions that may affect the interpretation of the statistical analysis. The SAP will be determined for individual research studies by discussion between the Study Statistician and the CI.

The definition of the SAP will include all those procedures that are required to write a SAP in accordance with the protocol, the principles of GCP and the applicable statutory and regulatory requirements.

The SAP may be incorporated into the protocol but is usually presented as a separate plan.

4. PROCEDURE

4.1 The statistical methods to be used for the analysis of the trial data should be included in the protocol. Refer to the TASC SOP on writing a protocol for further guidance.

4.2 The statistical methods should reflect the design of the trial, that is, proposed analyses should account for type of randomisation such as minimisation, stratification, factorial designs, matching, clustering, etc., where appropriate.

4.3 The details provided in the protocol may be sufficient. If not, a separate more detailed SAP should be written.

4.4 The SAP should be finalised prior to data analysis, data lock and before any treatment unblinding and may include templates of tables, listings, and figures to be presented in the statistical report. Any differences between methods described in the protocol and those in the SAP should be explained in the SAP.

4.5 The Study Statistician should review the data collection forms to ensure that primary and secondary outcome measures are collected appropriately. Changes to the forms or protocol during the course of the trial may require the Study Statistician to update the SAP with version control.

4.6 The SAP should state who the Study Statistician is.

4.7 The initial SAP and any subsequent amendments should be signed by the CI and the Study Statistician (may be the same person). Ideally, an independent statistician should review the SAP. The initial SAP and any subsequent modification to it must be version controlled and dated.

4.8 The SAP should define the populations (e.g., intention-to-treat, modified intention-to-treat, as randomised, efficacy evaluable, etc.) to be used, and the analyses that will be applied to these populations.

4.9 All primary and secondary outcomes should be clearly identified in the SAP. Ideally, a single primary measure of efficacy should be identified. Where co-primary outcomes are specified the reasoning and effect on power and significance level should be stated.

4.10 If a novel approach to statistical analysis is suggested in the protocol and SAP, a justification for the preference of this method over more standard methods should be provided. This justification should be backed up by literature references.

4.11 Where a composite primary outcome is proposed, it should be clearly defined along with each component. Multiple analyses of each component should also be described.

4.12 The unit of analysis should be clear for all outcomes and if necessary, methods for multi-level analysis described.

4.13 The SAP should specify the hypotheses to be tested and any parameters that are to be estimated to meet trial objectives.

4.14 The SAP should include, at a minimum, for each primary and secondary outcome measure:

- how the outcome will be measured
- any transformations on the data likely to be required before analysis
- appropriate statistical tests which will be used to analyse the data
- how the missing data mechanism will be assessed, and what assumptions are made to account for 'missingness' in the analyses
- methods for handling more than two treatment groups and multiple comparison methods (if appropriate)
- any pre-specified subgroup analyses.

4.15 Consideration should be given to the following:

- methods for handling multiple outcome observations
- rules for calculation of derived variables including definitions that can be programmed from the data
- use of baseline values and covariate data
- methods for handling multi-centre data
- treatment interactions, particularly with centre, sub-groups, crossover trials and for factorial designs
- interim or sequential analyses
- rules for stopping the trial, and allowance for them in the analysis
- levels of statistical significance (one-tailed or two-tailed) and clinical relevance
- methods for handling outliers or influential observations
- methods for point and interval estimation
- approach to handling concomitant medications
- definition of the safety population
- specification of computer systems and packages to be used for statistical analysis
- any sensitivity analyses.

4.16 Provision should be made within the SAP for checking the statistical model for assumptions, goodness-of-fit and influential observations and then for alternative methods to be used if the test assumptions are not met.

4.17 The analysis plan should be circulated for review and comment to the CI or Principal Investigator (PI) and any others who may usefully comment.

4.18 The SAP should be reviewed/updated immediately by the Study Statistician before the blinded code is broken at data lock (or before analysis begins in an unblinded trial).

4.19 Changes to the SAP should be justified, fully documented in the statistical report, and presented in any peer-reviewed publications.

5. ABBREVIATIONS & DEFINITIONS

CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Products
GCP	Good Clinical Practice
NHST	NHS Tayside (Tayside Health Board)
PI	Principal Investigator
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TASC	Tayside Medical Science Centre
UoD	University of Dundee

6. ASSOCIATED DOCUMENTS & REFERENCES

None

7. DOCUMENT HISTORY

History of reviewers prior to 2021 are in the archived SOPs available from TASC QA Dept.

Version Number:	Reviewed By (Job Title):	Effective Date:	Details of editions made:
10	Tracy Petrie (Quality Assurance Support Officer)	01/02/2021	Uploaded to new TASC SOP template which shows the new TASC website in the footer. Physical scan converted to electronic pdf as a requirement for upload to new TASC website.
11	Peter Donnan (Co-director, TCTU; Director, Dundee Epidemiology and Biostatistics Unit)	09/04/2021	Scheduled review date. No changes made.
12	Petra Rauchhaus (Clinical Trials Statistician)	05/04/2023	Addition of justification of Novel methods for analysis in Section 4.

8. APPROVALS

Approved by:	**Date:**
Dr Valerie Godfrey, TASC Quality Assurance Manager, on behalf of TASC Clinical Research Guidelines Committee	04 Apr 2023