STANDARD OPERATING PROCEDURE FOR STATISTICAL ANALYSIS PLANS FOR CLINICAL RESEARCH

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1. PURPOSE

This document describes the purpose and content of the statistical analysis plan for clinical research.

It is the responsibility of all staff using this SOP to ensure they are using the latest version of it. The latest version is available via StaffLink, the R&D section of the NHS Fife website (www.nhsfife.org/research) and EDGE (https://www.edge.nhs.uk). For guidance, contact the R&D Department via fife.randd@nhs.scot

2. APPLICABILITY

This document applies to clinical research sponsored or co-sponsored by NHS Fife.

This SOP applies to the individual or individuals (hereafter referred to as the statistician) responsible for the statistical planning and analysis associated with a clinical research study. Responsibility for the statistical analysis plan may be transferred to groups or individuals outside NHS Fife but this must be done using a formal clinical study service agreement.

3. POLICY

3.1 The statistical analysis plan must be a comprehensive and detailed description of the methods and presentation of analyses proposed for a clinical study to avoid *post hoc* decisions that may affect the interpretation of the statistical analysis.

3.2 The statistical analysis plan must be determined for individual research studies by discussion between the statistician and the Chief Investigator (CI).

3.3 The statistical analysis plan must either be incorporated into the protocol (See Fife R&D SOP05 - Writing a Protocol for further guidance) or presented as a separate document.

4. PROCEDURE

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

4.2 The statistical analysis plan must specify the hypotheses to be tested and any parameters that are to be estimated in order to meet study objectives.

4.3 The statistical analysis plan must define the populations (e.g., intention-to-treat, modified intention-to-treat, as randomised or efficacy evaluable) to be used, and the analyses that will be applied to these populations 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 analysis plan must be explained in the analysis plan.

4.4 All primary and secondary outcomes must be clearly identified in the statistical analysis plan. Ideally, a single primary measure of outcome must be identified. Where co-primary outcomes are specified, the reasoning and effect on power and significance level must be stated.

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

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

4.7 The statistical analysis plan must include, as a minimum, for each primary and secondary outcome measure:

- how the outcome will be measured
- any transformations of 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

4.8 Consideration must 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 studies and for factorial designs
- interim or sequential analyses
- rules for stopping the study, 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

4.9 Provision must be made within the statistical analysis plan 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.

4.10 The statistician must circulate the statistical analysis plan for review and comment to the CI, Principal Investigator and any others who may usefully comment. Ideally, where possible a second independent senior statistician should also review the analysis plan.

4.11 Prior to the start of the study, the statistician must review the data collection forms to ensure that primary and secondary outcome measures are collected appropriately. Any changes to the data collection forms or protocol during the course of the study must be assessed by the statistician to determine if an update to the statistical analysis plan is required.

4.12 All changes to the statistical analysis plan must be justified, subject to version control, fully documented in the statistical report and presented in any peer-reviewed publications.

4.13 The statistical analysis plan must be reviewed, finalised and signed off by the CI, the study statistician and the second senior statistician, if applicable immediately before data lock, before analysis begins and before the blinded code is broken on a blinded study.

5. ASSOCIATED DOCUMENTS

Fife R&D SOP05 - Writing a Protocol

6. ABBREVIATIONS

CI	Chief Investigator
GCP	Good Clinical Practice
R&D	Research and Development
SOP	Standard Operating Procedure

7. DOCUMENT HISTORY

Version Number	Edited by (job title)	Effective Date	Details of Revisions Made
1	David Chinn Senior Research Advisor	31/10/2014	New - Adapted from TASC SOP 05, version 5
2	Julie Aitken R&D Trials Facilitator	06/12/2018	Reformatted in line with current SOP template. Minor changes to clarify that this SOP applies to all clinical research and to reflect current practice.
3	David Chinn Senior Research Advisor	14/04/2021	Location of latest version of the SOP updated. Text updated for clarity.

8. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	14 Apr 2021