STANDARD OPERATING PROCEDURE FOR STATISTICAL ANALYSIS PLANS FOR CLINICAL RESEARCH

SOP NUMBER:	**Fife R&D SOP18**
AUTHOR:	**Julie Aitken**
ISSUE DATE:	**6th December 2018**
EFFECTIVE DATE:	**6th December 2018**
REVIEW DATE:	**6th December 2020**

1. PURPOSE

This document describes the purpose and content of the statistical analysis plan for clinical research and complies with the principles of Good Clinical Practice (GCP). It is the responsibility of all researchers using this SOP to ensure they are using the latest version of it. The latest version is available via the R&D pages on the NHS Fife Intranet (www.nhsfife.org/research). For guidance contact the R&D Department via fife-uhb.randd@nhs.net

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

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

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

The statistical analysis plan may either be incorporated into the protocol or presented as a separate document.

4. PROCEDURE

4.1 The statistical methods to be used for the analysis of the clinical research data should be included in the protocol. See Fife R&D WI35 - Writing a Protocol for further guidance.

4.2 The statistical methods should 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.

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

4.4 The statistical analysis plan 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 analysis plan should be explained in the analysis plan.

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 study may require the statistician to update the statistical analysis plan using version control.

4.6 The statistical authorship of the analysis plan, version and date should be clear.

4.7 The final statistical analysis plan should be discussed with the CI and ideally, where possible, a second independent senior statistician, with any modifications being subject to version control. The final version should be signed off by the CI, the study statistician and the second senior statistician, if applicable.

4.8 The statistical analysis plan should 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.

4.9 All primary and secondary outcomes should be clearly identified in the statistical analysis plan. 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 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.

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

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

4.13 The statistical analysis plan should 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

4.14 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 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

4.15 Provision should 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.

4.16 The analysis plan should be circulated by the statistician for review and comment to the CI or Principal Investigator and any others who may usefully comment.

4.17 The statistical analysis plan should be reviewed/updated immediately before the blinded code is broken at data lock (or before analysis begins in an unblinded study).

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

5. ASSOCIATED DOCUMENTS

Fife R&D WI35 - Writing a Protocol

6. ABBREVIATIONS

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

7. REFERENCES

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.
(https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)

Medicines for Human Use (Clinical Trials) Regulations 2004.
(http://www.legislation.gov.uk/uksi/2004/1031/contents/made)
It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.

8. 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.

9. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	6th December 2018