brighton and sussex medical school

Brighton and Sussex University Hospitals NHS Trust

This is a controlled document
Any printed versions of this document will be classed as uncontrolled

SOP Statistical Review & Analysis

SOP Reference:	**SOP/RD/019**
Version Number	**Version 2.0**
Date:	**16th December 2015**
Effective Date:	16TH DECEMBER 2015
Review by:	18TH DECEMBER 2017

	Signature	**Date**
Author: Hannah Butler **Designation:** Quality Assurance Manager, Research & Development BSUH		16/12/15
Author: Stephen Bremner **Designation:** Senior Lecturer in Medical Statistics, Brighton and Sussex Medical School	SA Bremner	16/12/15
Authorised by: Scott Harfield **Designation:** Chair of Sponsorship Quality and Safety Committee		16/12/15

Version	**Date**	**Reason for Change**
1.0	**21st November 2013**	**Changes to sections 4.1, 4.2 and 4.3**

1.0 PURPOSE

This Standard Operating Procedure (SOP) describes the process for statistical review and analysis for research studies sponsored by Brighton & Sussex University Hospitals NHS Trust (BSUH).

2.0 INTRODUCTION

An appropriately qualified and experienced statistician must be involved if the research study is being undertaken to support a marketing authorisation application or if the publication of results may change current prescribing practice or standard of

care. There are a number of areas to consider for statistical review and analysis, which are addressed in this SOP.

3.0 RESPONSIBILITIES

Sponsor

The Sponsor is responsible for appointing personnel who have the relevant statistical qualifications and experience to advise on trial design and methodology as well as analysis of research data.

The Sponsor is responsible for ensuring there is an appropriate level of statistical input into a research study.

Trial Statistician

The Trial Statistician designated to a research study is responsible for the statistical aspects of the study.

4.0 PROCEDURE

It is recommended that a qualified statistician is consulted as early as possible in the design of the research study. Advice should be sought on formulating the trial objectives, suitability of the endpoint, potential sources of bias, sample size, randomisation, blinding and the methods of analysis. The sections below outline considerations in the statistical review and analysis of a research study.

4.1 Randomisation procedures (where applicable):

Randomisation of participants is important in research studies to minimise bias.
The randomisation method should be described thoroughly in the protocol.

4.1.1 Type of randomisation

Type of randomisation:

- Simple randomisation: Although easily implemented, can lead to substantial imbalance in participant numbers in each group, particularly if the study is small.
- Block randomisation: Can be used to avoid imbalance in number of patients assigned to each treatment arm
    - Define size of blocks (ideally choose blocks of different size e.g. randomisation could be in blocks of random size 2, 4 and 6 in the case of 2 treatment arms, with the sequences randomly ordered within each block to increase concealment)
- Stratified randomisation (usually with blocking): Used to ensure that strongly prognostic factors are evenly distributed between treatment arms
    - Define stratification variable and group cut off (e.g. <50 yrs old and 50+ rather than just "age")
    - Minimisation: Used to achieve balance between groups in small studies, and/or when there are several important prognostic variables.

There should be a random element to increase concealment e.g. the next patient recruited will have an 80% chance of being allocated to the group which minimises the imbalance on the minimisation variables.

- Patient or cluster randomisation: Will the patients be randomised individually or in groups (e.g. general practices, wards)?
- State allocation ratio: (e.g. 1:1 or 2:1)

4.1.2 Mechanics of randomisation

- How the randomisation will be generated
  - Who will generate the schedule
  - What software is to be used
- How the randomisation will be implemented
  - Mechanism of communication of the allocation
    - Sealed envelopes (not recommended)
    - Telephone allocation
    - Computerised randomisation
  - Out of hours procedure to be considered
  - Unblinding:
    - Define circumstances and procedures for breaking randomisation codes in blinded studies
- The randomisation should be carefully tested on dummy data to ensure it works as expected
- If randomisation is being done manually, ideally a statistician not involved in the study would action the randomisation requests

4.2 Sample size

The sample size should be calculated using appropriate statistical methods and sufficient information should be given for an independent statistician to reproduce the calculation.
The following should be considered when calculating the sample size:

- Definition of the primary outcome measure
  - Give descriptive measures: mean, standard deviation , proportions, median or proportion surviving to the end of follow-up
- Treatment allocation ratio
- Whether a one sided or two side test is to be used
- Threshold of significance for the statistical tests (e.g. 5% or 1%)
  - Allowance for planned subgroup analyses
  - Allowance for planned interim analyses
- Power of the statistical test (e.g. 80% or 90%)
- Size of the minimum clinically important effect to be detected
- Number of baseline measures, and time points at which the primary outcome will be measured
- Estimated attrition rate by the primary endpoint
- Assumptions made (e.g. normality, equivalence of variances etc.)
- Reference to formula/method and software used to calculate sample size

In order to ensure that the required sample size is attainable, the numbers required for analysis should be stated alongside accrual numbers for the trial:

- Expected number of eligible participants
- Expected number of recruited participants
- Expected attrition rate
- Expected number of participants for analyses.

A flow chart is recommended to illustrate the movement of participants through the study

4.3 Statistical Analysis Plan (SAP)

A SAP is the pre-specified statistical methodology documented for a trial in either the protocol or as a separate document. The SAP is often produced during the conduct of the trial and will likely go through several versions but should be finalised before the data is locked for analysis. The SAP should be finalised by appropriate personnel and approved by the designated trial statistician. It is good practice to have it reviewed by an independent statistician e.g. from an oversight committee.

The statistical analysis plan should include:

- Detail on where and how the data are stored and the procedure for quality checking them prior to analysis.
- Scoring algorithms for standard instruments
- Clear definitions of null hypotheses in term of parameters and hypothesised parameter values.
- The primary end-point(s)
- Secondary end-points
- The primary time-point or time-points for data analysis
- The primary analysis strategy, e.g. Intention to treat or per protocol
- Pre-defined subgroup analyses, including a definition of sub-groups of interest
- Statistical methods to be applied, distinguishing between primary and secondary analyses and any formal analyses of safety
- Any formal methods for dealing with multiple end-points
- Baseline variables to be adjusted for in the analyses and methods for adjustment
- Any other covariates to be included in the analysis (always selected a priori) with justification for choice of these. These should include all design variables e.g. stratification or minimisation variables.
- Methods for dealing with missing values
- Any formal methods for interim analyses, including when these will be carried out and formal stopping rules

4.3.1 Intention to treat or per protocol

Specify if per protocol or intention to treat analyses are to be conducted.

- *Intention to treat*: the analysis is conducted with patients as members of the treatment group they were randomized to regardless of compliance to treatment, protocol deviation or crossing over to the other treatment group. In practice, an ITT analysis is often carried out using available cases.
- *Per protocol*: only subjects who complied with treatment and for whom there were no protocol violations are analysed.

4.3.2 Interim analyses

Specify which method is to be used to adjust for the increase in type I error rate associated with group sequential methods (this will have been addressed at the sample size calculation stage). State the criteria for early termination of the trial.

4.3.3 Missing data

Details should be included for handling missing data, protocol deviations and withdrawals. All deviations from the protocol must be fully documented and collated. It is recommended that a Protocol Deviation Log is kept for the trial to ensure they are all recorded in one place.

4.3.4 *Planned subgroup analyses*

Give details of methods for taking multiple comparisons into account (e.g. Bonferroni correction).

4.3.5 *Descriptive statistics*

Define data types for all outcome and explanatory variables (continuous, nominal or ordinal).

Assess continuous variable distributions by calculation of descriptive statistics (mean, median etc.) and by visualisation (histograms, box plots etc.)

Describe all outcome and explanatory variables according to their data type:

- Summary measures
    - Continuous: mean and standard deviation, or median and interquartile range (IQR)
    - Nominal or ordinal: frequencies, proportions and percentages (contingency tables)

4.3.6 *Confidence intervals*

Give details on the calculation of confidence intervals.

4.3.7 *Tests of hypotheses*

- State which statistical tests are to be used considering the type (continuous, nominal, ordinal) and the structure (e.g. independent, paired, repeated) of the data.
- State the chosen threshold of significance.

4.3.8 Adjustment for confounders (observational studies)

List confounders and specify methods used for adjusting for confounders (e.g. paired analysis for matched case control; regression methods).

4.4 Amendments

Amendments to the research study should be reviewed by a statistician when appropriate, to assess the impact of the proposed amendment on the design and analysis of the trial. For BSUH sponsored research, please refer to the Sponsorship Approval SOP/RD/008.

5.0 Training

This is a 'read and understand' SOP. Please note that the R&D department discourages the retention of hard copies of SOPs and can only guarantee that the most up-to-date version is on the Trust website.

6.0 Cross Referenced SOPs

SOP/RD/008 Sponsorship Approval

7.0 References

MHRA, Good Clinical Practice Guide, Chapter 9, p311-328, Crown Copyright 2012

Bland, Martin *Statistics Guide for Research Grant Applicants*, http://www-users.york.ac.uk/~mb55/guide/guide.htm, 10 September, 2009