Standard Operating Procedure:

Statistics

# Purpose

This standard operating procedure (SOP) describes the statistical procedures involved in clinical research conducted within the University of Birmingham (UoB).

# Scope

This SOP applies to all clinical research where the UoB is sponsor or takes on sponsor responsibilities for the statistical procedures. Where clinical research is (co-)sponsored by another institution, this procedure should be followed as far as possible, and in line with the contractual agreement between the UoB and the other institution. This SOP also applies to clinical research approved by a UoB Research Ethics Committee (REC) that is required to follow the UoB Principles of Good Clinical Practice (GCP) for Clinical Research (UoB-GCP-POL-001). This SOP may be used as a guidance document in all other cases.

# Implementation plan

This SOP will be implemented directly after its effective date for all clinical trials and any clinical studies that are in set up. For existing clinical research that is already set up and in the recruitment phase (or further) at the time of implementation, this SOP will be implemented within three months of the effective date.

# Stakeholders

Note that where the UoB takes on the sponsor responsibility for statistics, the UoB will delegate the majority of these duties to the chief investigator (CI) and/or to a clinical trials unit (CTU), who may delegate these duties further to their research team(s). All delegation of duties will be documented e.g. using either the CI declaration and/or the Clinical Trials Task Delegation Log (UoB-SPO-QCD-001).

* CI: The CI may delegate activities to members of their research team, although evidence of CI involvement and approval is still expected and may not be delegated where ‘no delegation allowed’ is indicated. This SOP will state where delegation is possible. For clinical research approved by a UoB REC, the role of CI may be referred to as the principal investigator (PI), or the supervisor for the postgraduate research student.
* Statistician: The statistician must possess the relevant statistical knowledge and experience. This may be the CI (or delegate) where they have sufficient knowledge and experience to advise on and/or perform the required statistical elements of the clinical research.
* Statistical advisor: Where a statistical advisor is utilised, they may contribute to some, but not all, aspects of the clinical research design, conduct, analysis and reporting. The statistical advisor may take on the responsibility of the ‘statistician’ for specific statistical aspects of the clinical research that they will perform and will adhere to the relevant sections of this SOP.

# Background and rationale

For the purposes of this SOP the terms ‘clinical research’ or ‘project’ will cover clinical trials of investigational medicinal products (CTIMPs), other interventional trials (e.g. surgical trials, device trials and non-CTIMP trials, and any other projects deemed to be ‘interventional’ by the sponsor), clinical studies.

The purpose of this document is to describe the statistical procedures involved in clinical research conducted within the UoB. Statistics is a fundamental component of clinical research. The design, conduct, analysis of the resultant data and reporting must be scientifically sound in order to ensure that the results are reliable, minimise bias, and address the research question.

The statistician takes responsibility for the statistical methods, which may include (but not limited to): the design of the clinical research, protocol development, case report form (CRF) development, database design, input into the data management process, development of the statistical analysis plan (SAP), research project conduct, performance of interim analyses and the final analyses, interpretation of the results and contribution to the publication(s).

# Process map



\* A statistical advisor may take on the responsibility of the ‘statistician’ for specific statistical aspects of the clinical research that they will perform as documented in a memorandum of understanding or collaboration agreement.

# Procedure

## Identify statistical support

1. The CI (or delegate) will seek appropriate advice on project design and statistical methodology at the initial conceptualisation of the clinical research (e.g., at the grant application phase).
* This may be the CI where they have sufficient knowledge and experience to take on the statistician’s role as detailed below under ‘statistician’. In the small number of cases, where statistical review for determining the sample size is not deemed necessary, the CI (or delegate) will provide suitable justification for this in the protocol e.g. with reference to other published research using a similar sample size.
* Where appropriate, the CI (or delegate) will include appropriate funding for statistical support in the grant application.
* The CI may choose to work with a statistical advisor to contribute to some, but not all, aspects of the project design, conduct, analysis and reporting. The statistical advisor may take on the responsibility of the ‘statistician’ for specific statistical aspects of the clinical research that they will perform as detailed below.
1. The CI (or delegate) will ensure that where the statistical advisor is not, or will not be, a member of the research team, their responsibilities are clearly detailed in an agreement.
* For internal staff, this will be set out in a non-legally binding memorandum of understanding (e.g. CTU statistician advising an independent Investigator)
* For staff working in different organisations, this will be set out in a legally binding collaboration agreement (e.g. statistician from another organisation).
1. The CI (or delegate) will file evidence that the statistician and/or statistical advisor possesses relevant statistical knowledge and experience to fulfil their role in the project. See the Training SOP (UoB-TRN-SOP-001).
* It is expected that for clinical trials undertaken to support marketing authorisation applications, or large clinical trials where their publications may change prescribing practice or the standard care, an appropriate qualified and experienced statistician should take responsibility for the statistical aspects of the clinical trial.
1. The CI (or delegate) will document the level of ongoing input required from a statistician. For example, this may be documented in the protocol, a project-specific risk assessment, or local policies/processes.

## Project design and protocol development

1. Where applicable to the project, the CI (or delegate) will seek input from a statistician on the following aspects of the research:
* research design (e.g. observational, randomised clinical trial, inclusion of a feasibility/pilot study)
* formulating clinical research objectives
* suitability of outcome measures for meeting the objectives of the clinical research
* methods to minimise bias
* sample size
* randomisation
* stratification/minimisation variables
* blinding
* statistical stopping guidelines (e.g. futility, superiority)
* analysis methods (final and interim)
* the clinical research reporting requirement for registries. See also the Project Closure SOP (UoB-CLO-SOP-001).
1. The CI (or delegate) will maintain documented evidence of the statistician’s involvement in project/protocol design as applicable (e.g. emails, meeting minutes, comments on proposals/protocols).
* It is recommended that a second check of the statistical section of the protocol is performed prior to finalisation, in particular to check the sample size calculation (if performed), and where appropriate this should be performed by a second statistician.

## SAP development

1. The trial statistician will document the pre-specified statistical methodology for the project, either directly in the protocol and/or in a separate document, typically referred to as a SAP, which will be version-controlled. See also Protocol Template (CTIMPs) (UoB-ESD-QCD-001) and Protocol Template (non-CTIMPs and studies) (UoB-ESD-QCD-002).
2. The statistician will, as a minimum, include the following details for the primary and secondary outcomes (or equivalent terms) in the SAP:
* how the outcome will be measured
* appropriate statistical method(s) which will be used to analyse the data.
1. Where appropriate, the statistician will include details on these, and other, analytical aspects in the SAP:
* handling missing data
* handling protocol deviations
* adjustments for multiple testing or multiple comparisons
* pre-specified sub-groups
* rules for calculation of derived variables
* use of baseline data as co-variates in adjusted analysis
* levels of confidence/ statistical significance
* sensitivity analyses
* treatment interactions, particularly for factorial clinical trials.
1. The statistician will approve (each version of) the SAP, and the CI (or delegate) will retain documentation of this approval (e.g., emails, meeting minutes). It is expected that the first version of the SAP is in place prior to:
* data collection for an open label project
* unblinding the data for a blinded project.

## CRF design and data management activities

1. Where appropriate (as per the risk assessment), the CI (or delegate) will document the statistician’s involvement in developing the CRF, where this is being used to collect data, and the clinical research database. See the Case Report Form Development SOP (UoB-CRT-CRF-SOP-001).
* It is expected for CTIMPs that the statistician will review and formally approve the final version of the CRF, and any amendments which then impact on data items. However, this procedure (where appropriate) could also be applied in non-CTIMPs/clinical studies to support best practices.
1. Where appropriate (as per the risk assessment), the CI (or delegate) will document the statistician’s involvement in data management activities. See also the Data Management SOP (UoB-DMA-SOP-001).
* If applicable, it is recommended that the statistician will review the validation process (validation specification), which describes the checks to be performed as part of the data validation plan.
1. The CI (or delegate) will work with the statistician to document all protocol non-compliances and collate them prior to statistical analysis (where appropriate, prior to unblinding).
2. The statistician will review all significant protocol non-compliances for assessment of the impact on the analysis.

## Amendments

1. The CI (or delegate) will highlight amendments to the project that are likely to have an impact on the design and analysis of the clinical research, and the statistician will review and document these (as appropriate as per the risk assessment). This includes:
* review of the impact of the amendment on CRFs and project systems
* review of the impact of the amendment on the SAP
* whether the amendment introduces any risk of bias.
1. Where changes to the project necessitates an update to the SAP, the statistician will amend the SAP ensuring appropriate version control is employed and changes justified.

## Statistical programming, analysis and publication

1. Where appropriate, the CI (or delegate) will perform quality checks, data cleaning and data validation prior to analysis. For clinical trials, see the Data Management SOP (UoB-DMA-SOP-001) for further details.
2. The statistician will ensure that user-written code/macros and programs used during the analysis process are fit for purpose (validated). This will be on a risk-based approach with the detail and level of checking varying depending on the item begin checked. For example, output related to the primary objective of the clinical research should be checked.
3. It is expected that hardcoding during the analysis process is avoided. In extreme circumstances where hard coding is considered necessary, the statistician will retain documentation of its use and provide clear justification for this. For example, use of hard coding in free text fields for adverse event data.
4. Once data collection has been completed, the CI (or delegate) will lock the data from any further changes. This includes the procedures for unlocking the data for extreme circumstances where changes to the data are required. For qualitative data, an example of this may include converting transcripts to PDF or printing and signing finalised versions of the transcripts. For clinical trials, see the Data Management SOP (UoB-DMA-SOP-001) for further details.
5. The statistician will ensure an appropriate audit trail in the statistical analysis process, in order to allow the data analysis to be reconstructed from start to finish. An appropriate audit trail means that the final clinical research results for publication/reports can be traced back to the statistical program output and the datasets used. For example, a table of results including mean difference and 95% confidence interval should be verifiable against information that shows who undertook the analysis, and how and when this analysis occurred. This can be documented, for example, by email or a printout that has been signed and dated.
6. The statistician will apply version control to all outputs of the statistical process.
7. For clinical trials, where appropriate, the statistician will perform interim analyses at the intervals specified in the protocol (e.g. for data monitoring committee (DMC) meetings) and following the SAP.
* For this, a frozen copy (snapshot) of the dataset will be made for analyses, ensuring the frozen dataset is preserved so that the analysis can be reproduced if required at a later date.
* Where a decision is taken to cancel interim analysis (e.g. due to insufficient participant numbers), this must be documented.
* If the project is blinded, and interim unblinded analysis is required, ensure the clinical research team cannot gain access to unblinded data or the randomisation schedule. See the Randomisation and Blinding SOP (UoB-RND-SOP-001) for further information.
1. During final analysis, the statistician will ensure statistical packages remain unchanged e.g. by disabling automatic updates. Where updates have occurred e.g. if analysis undertaken over a period of time, these packages may require re-validation (see point 18 above).
2. The statistician will perform and document checks to ensure that the output of the statistical analysis process is accurate, and ensure that the SAP has been followed.
3. The statistician will prepare the analytical section of project reports (e.g. DMC, end of project report, reports to other third parties e.g. ethics, funder etcetera).
4. The statistician will review publications (including DMC reports) prior to submission, ensuring the results have been correctly transferred into the publication and that they accurately reflect the analysis data, and retain evidence of this review. For randomised clinical trials, the statistician will follow [The CONSORT (Consolidated Standards of Reporting Trials) Statement guideline](http://www.consort-statement.org/) for publication. Also see [Extensions of the CONSORT Statement](http://www.consort-statement.org/extensions) for “non-standard” randomised clinical trial with specific designs, data and interventions.
* For clinical trials, it is expected that all significant non-compliances that occurred during the trial and how these contributed to the analysis, and any changes to the planned statistical analysis with justification for these changes are reported.

## Essential documentation and archiving

1. The CI (or delegate) will retain adequate documentation to allow verification that data has been accurately handled and reported in accordance with the UoB Principles of GCP for Clinical Research (UoB-GCP-POL-001). This includes (but is not limited to):
* a SAP (where separate from the protocol)
* an audit trail (see previous section for details).
1. The CI (or delegate) will archive documentation related to statistical processes with the rest of the study/trial master file (S/TMF) at the end of the clinical research. See the Archiving SOP (UoB-ARC-SOP-001) for further information.

# List of expected outputs

* Documented evidence that the statistician has the relevant statistical knowledge and experience to perform the required tasks.
* Roles and responsibilities of the statistician are documented, with evidence of the level of ongoing input required and contracts and agreements to be in place (where appropriate).
* Evidence of the statistician involvement in the project design and protocol development. Where appropriate (as per the risk assessment), documented evidence of the statistician involvement in CRF design, clinical research database and data management activities.
* Evidence of a process to record and collate all protocol non-compliances and documented evidence that all significant protocol non-compliances have been reviewed by the statistician.
* Evidence of the pre-specified statistical methodology for the project in the protocol or in a separate document (SAP). As a minimum, it will detail how the primary and secondary outcomes will be measured and what statistical method(s) will be used.
* Documented evidence of the statistician’s approval of (each version of) the SAP.
* Where amendments to the project are likely to have an impact on the design and analysis of the clinical research: evidence that the impact of these have been reviewed by the statistician, with any changes justified and appropriate version control applied.
* Evidence of quality check, data cleaning and data validation processes. For clinical trials, this will be in accordance with the Data Management SOP (UoB-DMA-SOP-001).
* Evidence that the data has been locked (or a snapshot has been created) prior to the start of the statistical analysis. For clinical trials, this will be in accordance with the Data Management SOP (UoB-DMA-SOP-001).
* An audit trail in the statistical analysis process in order to allow the data analysis to be reconstructed from start to finish, with appropriate version control applied.
* Evidence of appropriate checks by the statistician to ensure the outputs of the statistical analysis process is accurate.
* Evidence that the SAP has been followed.
* Evidence that the statistician has reviewed publications prior to submission.
* Evidence that the documentation related to statistical processes has been stored as per the Archiving SOP (UoB-ARC-SOP-001).

# Related documents

* UoB-ARC-SOP-001 Archiving
* UoB-CLO-SOP-001 Project Closure
* UoB-CRT-CRF-SOP-001 Case Report Form Development
* UoB-DMA-SOP-001 Data Management
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-RND-SOP-001 Randomisation and Blinding
* UoB-SPO-QCD-001 Clinical Trials Task Delegation Log
* UoB-TRN-SOP-001 Training

UoB QMS documents can be found on the [CRCT website](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/index.aspx). Internal work instructions can be obtained from the CRCT (crct@contacts.bham.ac.uk) and/or from the RGT (researchgovernance@contacts.bham.ac.uk).

# References and frameworks

* The CONSORT (Consolidated Standards of Reporting Trials) Statement guideline: <http://www.consort-statement.org/>.
* Extensions of the CONSORT Statement: <http://www.consort-statement.org/extensions>.
* Medicines and Healthcare products Regulatory Agency (MHRA). Good Clinical Practice Guide, London: The Stationery Office, 2012.

# Abbreviations and definitions:

| Term | Description |
| --- | --- |
| **CI** | Chief investigator |
| CONSORT | Consolidated standards of reporting trials |
| **CRCT** | Clinical Research Compliance Team |
| **CRF** | Case report form  |
| **CTIMP** | Clinical trial of an investigational medicinal product |
| **CTU** | Clinical trials unit |
| DMC | Data monitoring committee  |
| **GCP** | Good Clinical Practice |
| **PI** | Principal investigator |
| **REC** | Research ethics committee |
| **RGT** | Research Governance Team |
| **SAP** | Statistical analysis plan |
| **SOP** | Standard operating procedure |
| **S/TMF** | Study/trial master file |
| **UoB** | University of Birmingham |

See also the [Glossary of Terms](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/Glossary-of-Terms.aspx).