Standard Operating Procedure CCTU/SOP032

Determination of Analysis Populations

1. Scope

This Standard Operating Procedure applies to The Cambridge Clinical Trials Unit staff, Chief Investigators and their trial teams working on Cambridge Sponsored CTIMPs or clinical studies coordinated by the CCTU.

2. Purpose

The purpose of this SOP is to describe a framework for determining whether to include or exclude a subject from a specific population when it is not clearly defined.

Any statistical analysis or summary table must clearly state which set, group or population of observations, patients or subjects it is based upon.

Different populations may be needed to address different questions in the same study. Names and definitions of populations should be specified in a study protocol and/or statistical analysis plan. However such definitions do not always capture every eventuality.

3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH); or the University of Cambridge (UoC); or jointly by CUH and UoC or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Population	A group of patients, subjects or observations

3.2. Abbreviations

Abbreviation	Meaning
SAP	Statistical Analysis Plan
CTIMP	Clinical Trial of Investigational Medicinal Product
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
PI	Principal Investigator
DM	Data Manager
TMF	Trial Master File

DMC	Data Monitoring Committee
TMG	Trial Management Group

4. Undertaken by

CI, PIs, Statistician, Data Manager, TMG

5. Items Required

Study Protocol
Statistical Analysis Plan (CCTU/SOP023)
Trial Specific Data Management Plan (CCTU/TPL009)
Analysis Population Database Approval Form (CCTU/FRM029)
Database Locking (CCTU/SOP033)

6. Summary of Significant Changes

Change in items required

7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

7.1. Overview

In most clinical studies there is a degree of non-compliance with the treatment regime(s) or investigations specified. Depending on the nature of the study, several different populations of subjects or patients will be defined for different purposes (ICH E9 section 5.2). For example: Safety, Full Analysis, Per-Protocol.

Examples of population definitions:

- Full Analysis Population:
  - All subjects who received any study drug and who participated in at least one post-baseline assessment
- Safety Population:
  - All subjects who received any study treatment
- Per Protocol Population:
  - All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis.

It is expected that these examples will need to be revised for each trial.

The decision of whether or not to include or exclude a subject from a specific population is distinct from any consideration of which treatment group to assign a patient to when comparing treatments.

The terms "intention-to-treat" and "as-treated" are commonly used to describe how to assign a patient to a treatment group (assuming that the patient belongs to the relevant analysis population). These two terms should not be used as names for populations. Commonly an Intention-to-Treat grouping is used on a Full Analysis population to assess efficacy and an As-Treated

grouping is used on a Safety population to assess safety, but, if justified, any combination of treatment grouping and analysis population can be used.

Definitions and criteria for membership of each population

- The population for the primary objective should be given in the study protocol if necessary with further refinements in the statistical analysis plan
- In some cases subjective or expert judgement is required. Unanticipated circumstances can arise, where input from Clinicians, Data Managers or Statisticians is required to decide to include or exclude a subject from a population
- Such judgements should be considered as part of the study data and the process for capturing such data must be documented

7.2. Key Steps

- A finalised charter, described in 7.3, will be signed and dated by the CI, or delegate and Study Statistician and included in the TMF before the dataset lock for the primary analyses
- When all outstanding queries of the main study database have been addressed, but before the initial lock occurs, the committee assembled will meet to examine the data provided as per the charter
- The committee will produce a Population Database that indicates for each subject or patient whether or not they belong to each population as per the terms of the charter. In many studies the populations will be easily determined automatically for the majority of patients
- The committee's primary role is to determine the populations for the minority of patients where population membership is not clear, and confirm for the majority of patients
- Any queries or further data requested by the committee will be addressed by an external consultant(s) as specified in the charter until the Population Database is completed
- The finalised version of the database will be approved by the committee and released to the Data Manager for the initial lock

7.3. Charter Document

The purpose of the charter is to describe the process of assigning subjects to analysis populations in sufficient detail to allow its theoretical reproduction

The charter should contain the following sections:

7.3.1. Membership of Committee

- The charter document should contain details of what roles will be required on the committee
- If a Data Monitoring Committee (DMC) has been assembled, the members of the DMC may be suitable for this role
- A typical minimal composition includes two Clinicians and a Statistician

7.3.2. Analysis Population Definitions

- The definitions of each of the populations should be given

- The definitions should be agreed with the CI, or delegate, TMG and study Statistician and be consistent across the protocol and Statistical Analysis Plan (SAP)
- The definitions used in the charter document should be verbatim copies taken from the protocol or SAP; any alterations will need to be reflected in a revision protocol or SAP
- It is acceptable for the definition to give more detail than provided in the protocol. Clarification should be given to distinguish between cases of missing data as opposed to exclusion from an analysis population
- If the study protocol undergoes an amendment then the Charter may need to be revised

7.3.3. Review Data

- It will be stated what data will be provided for each subject. This will contain all data referred to in the definition of the populations. It may include:
- Subject ID number
- Dosing Records
- Visit dates, including randomisation, treatment compliance, withdrawal
- Reasons for withdrawal
- The charter will describe who, or what role, is responsible for providing the data to the committee, in what format and on what timescales
- Wherever possible and practical, the review data will contain suggested membership of populations based on automatic rules and highlight any cases lacking clarity

7.3.4. Unblinding of treatment

- It will be determined in the charter if the assignment of subjects to populations can be judged without knowledge of which treatment regime a subject was assigned to. In general it is preferable not to have such data
- If data on treatment is required then terms of membership of the committee should prevent any further input into the final analysis of the study data
- Depending on the risk and nature of the study, for example an open-label exploratory phase I study, such restrictions may be relaxed if fully documented in the charter

7.3.5. Analysis Populations Database

- Details of which data will be recorded at the committee meeting is stated in the charter
- Typically this will consist of the review data augmented with one extra variable per population with the values "yes" or "no" indicating inclusion or exclusion respectively
- Depending on the scale of the study, a Statistician or Data Manager may write code to automatically provide suggested values based on the data provided and the population definitions

7.3.6. Further Queries

For any subjects where assignment is not possible, details of whom to consult (for example CI, Steering Committee) and what documentation will be provided are to be described in the charter.

7.4. Committee Meeting

The committee meeting(s) will be documented with an agenda and minutes to be included in the TMF, along with documents as detailed in the charter.

7.5. Final Approval

- The approval document will be signed (CCTU/FRM029) and dated by all members of the committee and the study Data Manager
- The signed approval form is filed in the TMF
- The Population Database and the main study database should then be initially locked for release to the study Statistician (CCTU/SOP033)

8. Monitoring Compliance with and the Effectiveness of this Document

a. Process for Monitoring Compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

b. Standards/Key Performance Indicators

This process forms part of a quality management system and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

9. References

The Institute of Clinical Research, Abbreviations used in Clinical Trials.

MHRA, Good Clinical Practice "Grey Guide"

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Statistical Principles for Clinical Trials E9

10. Associated Documents

Trial Specific Data Management (CCTU/TPL009)

11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

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