ECTU Central Office WPD_ST_W2: Statistical Input into Trial and Protocol Design

Version No:	4.0
Issue Date:	05 Sep 2023
Effective Date:	19 Sep 2023

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Document Revision History		
Version No.	Effective Date	Summary of Revisions
1.0	13 Mar 2017	Initial Creation
2.0	06 Nov 2018	Document moved to new template. Addition of Statistical Review Checklist, Section 2.4 now 2.2. Subsequent sections renumbered
3.0	13 Nov 2020	Scheduled review. Update to file references in Relevant Documents and References section. Minor text edits for clarity.
4.0	19 Sep 2023	Document moved to WPD Template V3.0. General review. Additional text in sections 2.1.1, 2.2.6 2.3 to 2.6

1. INTRODUCTION

This Working Practice Document provides guidance on statistical involvement in trial and protocol design both during initial set-up and for any further amendments made for the duration of the trial.

2. INSTRUCTIONS and GUIDANCE

2.1 Statistical Review Checklist

2.1.1 The Statistical Review Checklist should be used by the Trial Statistician (and designee) to record any statistical input into the trial. This checklist should be continuously updated throughout the trial as is necessary. The Trial Statistician should ensure that the current version of the Statistical Review Checklist ST007 template is used at all times.

2.1.2 The Trial Statistician or designee should document the instances where statistical input has been requested and where the evidence of this will be kept.

2.2 Input into Trial Protocol

2.2.1 When working up the trial protocol, edits and suggestions should be made via track changes directly onto the Word format copy of the protocol if possible. The tracked change version (or other comments document) should be saved in the relevant section of the Statistics Master File (SMF).

2.2.2 Ensure analysis populations are defined.

2.2.3 The protocol and any subsequent amendments should be signed off by the Trial Statistician.

2.2.4 The statistical methods section of the protocol should be read and sense checked by a second statistician and once done, this should be noted on the Statistical Review Checklist.

2.2.5 When the Trial Statistician is made aware of a protocol amendment either before or after completion of the final protocol, they should assess whether this impacts on the design or analysis of the trial and update the Statistical Analysis Plan (SAP) where necessary. The Trial Statistician's signature in the amended protocol is sufficient evidence that they have reviewed these aspects and dealt with any issues.

2.2.6 At this stage of the project, the trial statistician should consider the design of the end of trial data sharing process to ensure that this is a prospective rather than a retrospective task. This should take into account whether the trial protocol or consent

process permits participants to opt out of sharing of anonymised data, either at the point of informed consent or when withdrawing from the study.

2.3 Sample Size

The process for calculating the sample size and documenting the calculation is detailed in ECTU Central Office SOP ECTU_ST_01 Sample Size Calculation and this should be recorded using ST001 Sample Size Estimate Form and ST007 Statistical Review Checklist.

2.4 Case Report Forms (CRF) and Data Management activities

2.4.1 The stats input into CRF design and the data validation strategy will be evidenced and documented. For trials fully managed within ECTU, this documentation is gathered and filed by the Trial Manager. For trials managed externally to ECTU ensure related documentation is filed in the SMF.

2.4.2 Ensure that data needed to define analysis populations is being collected.

2.4.3 Where possible and relevant, ensure that data is collected on whether participants received the allocated treatment or not. If data will not be recorded on whether allocated treatment was received, store documentation of the reasons for this in the SMF.

2.4.4 Within the data validation strategy, ensure that consideration has been given to assessing the levels of missing data, particularly in key variables for the analysis e.g. primary and secondary outcomes, baseline variables. In time to event analyses, there should be no missing data for either the date last seen or primary outcome event date. Key visits or trial events not at correct times should have a mechanism for being assessed, as should too many withdrawals from the study.

2.4.5 Check that change of status form is consistent with the protocol, participant information sheet and consent form regarding the rights of participants to opt out from sharing of anonymised data at end of trial.

2.4.6 If an annotated CRF detailing the variable names in the database has been created, this should be scanned and saved as an electronic version in the trial folder. Creation of an annotated CRF is not mandatory.

2.5 Randomisation

2.5.1 The process for designing and documenting the randomisation scheme is detailed in ECTU Central Office WPD ECTU_WPD_ST_W6 Randomisation System Description and Confirmation.

2.5.2 During the trial, balance of the randomisation should be checked by minimisation and stratification variables and evidence recorded in the Statistical Review Checklist, ST007. This should be done for all trials, regardless of whether the trial has a data monitoring committee (DMC). For trials without a DMC, at least one check of randomisation balance should be made. This should be performed by the Unblinded Statistician early enough in the trial to allow timely corrective action where this is required, but after a sufficient period of recruitment so that the sample size is sufficient for the check to be informative.

2.6 Data monitoring committee (DMC) charter

For trials which have a DMC, the process for statistical oversight of the DMC charter and documentation of this is detailed in ECTU Central Office WPD ECTU_WPD_ST_W3 DMC Reporting.

3. RELEVANT DOCUMENTS AND REFERENCES

ST007 - Statistical Review Checklist Template (on shared drive):
ECT Unit/SOPs/Finalised SOP and WPD/ST/Supporting Document and Templates/Current

ST006A - SMF Essential Document Checklist Template (on shared drive):
ECT Unit/SOPs/Finalised SOP and WPD/ST/Supporting Document and Templates/Current

ST002 - Randomisation System Description and Confirmation Document Template (on shared drive):
ECT Unit/SOPs/Finalised SOP and WPD/ST/Supporting Document and Templates/Current

ST001 - Sample Size Estimate Form Template (on shared drive)
ECT Unit/SOPs/Finalised SOP and WPD/ST/Supporting Document and Templates/Current

ACCORD SOP CR013 Case Report Form Design and Implementation
www.accord.scot/research-access/resources-researchers/sop