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Trial Design

ST-001-SOP

Version 2.4

ALWAYS REFER TO THE INTRANET TO CHECK THE VALIDITY OF THIS DOCUMENT

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1 PURPOSE

To describe the process of developing and reviewing the design of the clinical studies conducted by the EORTC.

2 SCOPE

This procedure applies to all new studies in which EORTC is involved, whether they are designed at the EORTC Headquarters (HQ) or designed externally to the EORTC HQ but endorsed by EORTC.

3 POLICY

All clinical studies in which EORTC participates should have an appropriate design that will ensure the trial to provide the answer to its objectives within the limits of existing statistical methodology.

4 DEFINITIONS

- **Design:** the statistical and methodological setup of the trial, including elements such as randomization, stratification, planning of the statistical testing of primary and secondary endpoints, adjustment of those comparisons for covariates, sample size calculation taking into account type I and type II errors

5 PROCEDURE

5.1 Development of the design

The Statistician develops the study design including any interim analysis plan in cooperation with the study coordinator, the clinical research physician and the clinical scientist . The Statistician is proactive in getting the information needed for statistical design from the clinicians.

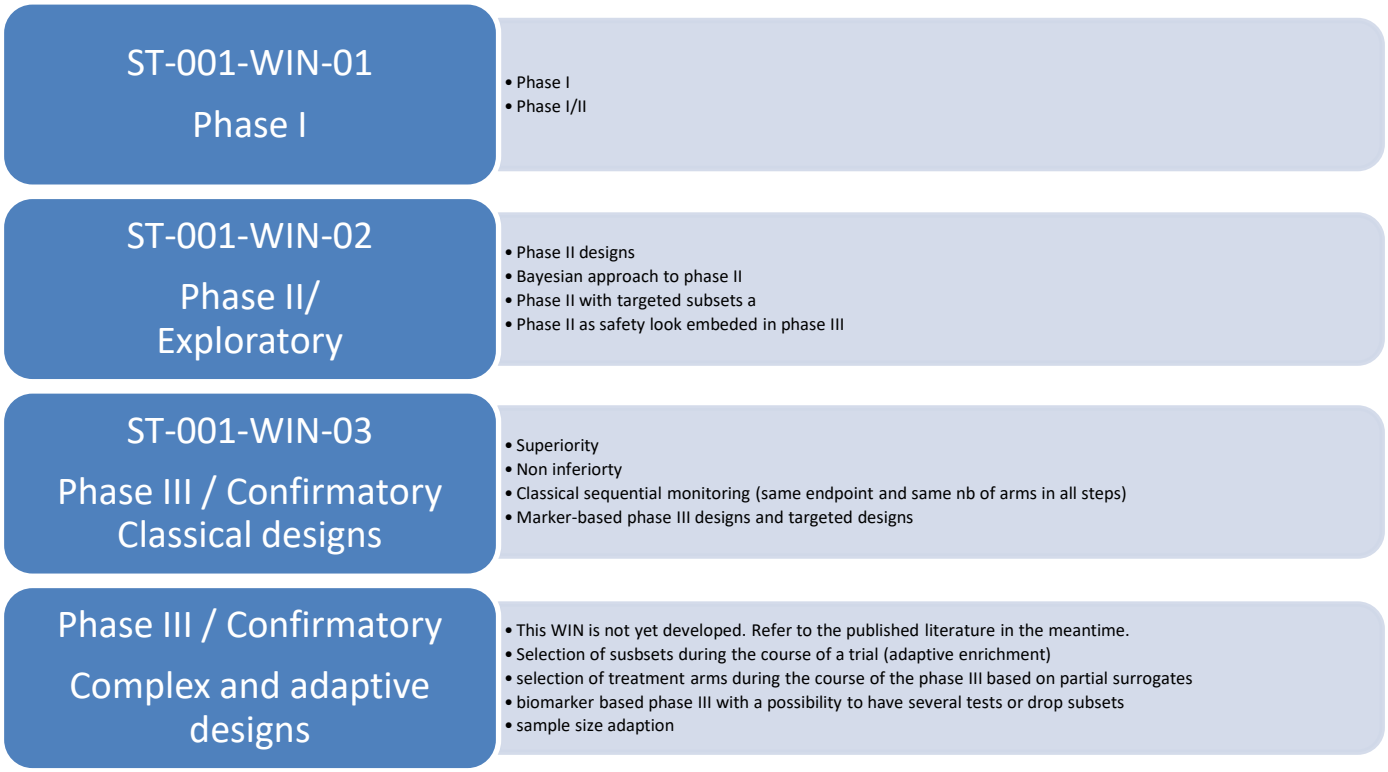
It is generally expected that the study coordinator should make the rationale, the objectives and the clinical background of the study clear and that he/she will supply the information about the population, and available data/studies with accompanying estimates that are needed to inform the statistical design of the study. The Clinical Research Physician (CRP) is expected to help in this process by in particular providing input regarding implications of the design for the medical and ethical aspects of the study from the HQ perspective. Preliminary discussions should also identify the practical constraints of the study, particularly in terms of potential accrual and overall study duration. Input from any pharmaceutical company involved is expected at this stage, as necessary for informing the trial design. It is worthwhile to identify already at this stage the important prognostic factor(s) that may influence the outcome and need to be considered if stratification is envisaged.

With these elements in hand, the statistician will propose a statistical design for the study. The statistician must ensure that the design has the potential to provide an answer to the objectives of the study within the framework of current statistical knowledge, with appropriate Type I and Type II errors. Several options are typically discussed before a final design is agreed upon by all parties including pharmaceutical companies when some are involved. In case the trial is fully supported by a pharmaceutical company, the statistician and CRP jointly ensure that independence in design is maintained.

If the EORTC is proposed to join an existing trial conducted by another group, the EORTC statistician identifies any element of the design that is not according to the EORTC procedures, to assess their impact on the study, and for reporting them clearly to all EORTC bodies that will review the study

Below is a description of the level of detail concerning the trial design that is expected to be available at the various stages of review by EORTC bodies.

Figure 1: Where to find more guidance regarding trial designs:



5.2 Elements of study design at study pre-development and protocol development

The study pre-development and protocol development procedures are covered in PD-001-SOP and PD-002-SOP (and associated WINs) respectively.

5.2.1 Study pre-development and review by the EORTC Board

The primary goal of this review is to assess if the proposed study is in line with the strategy of EORTC. To assess the trial feasibility and scientific merit, a rough estimate of the sample size and the main features of the proposed statistical approach must be available at that time. Not all details are needed at that moment. However the following elements must be available:

- the primary objective of the trial and the proposed approach to statistical design of the trial,

- sample size can be given as a threshold or range (i.e. preliminary computation), including magnitude of effect and statistical parameters (type I and type II error) and if early monitoring is envisaged (details of the stopping rules need to be fully clarified at this time)
- secondary endpoints: a first list can be given
- key eligibility criteria defining the proposed population

5.2.2 Outline and review by PRC

At this time, the complete design must have been worked out. The statistician ensures that they are complete and clearly described in the study outline. The statistician validates the complete outline before the green light is given to the PRC review of the outline.

As primary responsibility, the statistician ensures that the following elements are clearly stated in the outline by the time it is submitted to PRC:

- the primary objective of the trial and the resulting statistical design of the trial,
- the sample size calculation, including alternative treatment effect, type I and type II error- early stopping rule(s) and interim analyses
- secondary endpoints including quality of life
- key eligibility criteria
- preliminary calculations for any planned ancillary study (translational study, imaging …)
- for the parts of the design related to quality of life, imaging or biological side studies, the study statistician liaises with the member of the statistics department that is specialized for the relevant matter, for obtaining guidance and support. It is strongly recommended to do this as early as possible in the development of the outline.

If the design is very complex from the statistical standpoint, the statistician is invited to present it during the bi-weekly meeting of the statistics department prior to the IPRM to allow more time to the statistics department to debate of the details of the design.

When the study design emanates from a third party, the statistician should obtain clarification about the design from that third party and must describe the design, as well as any deviations from the usual EORTC procedures and if applicable, the elements of the design that they do not fully support. Whenever the PRC issues questions regarding the statistical design, the study statistician transmits the comments to the responsible statistician who produced the design to obtain clarifications.

5.2.3 Full protocol

If and when approved, the statistician ensures that the design is appropriately written out and documented into the draft and final protocol. The protocol addresses in detail all the elements of the design:

- Objectives of the trial, including endpoints

- Patient selection criteria
- Trial design and schema
- Criteria of evaluation, definition of endpoints (as a co-writer)
- Statistical considerations (as primary writer), including
  - Design: sample size, patient accrual rate, duration of follow up, study feasibility, the parameters that decides timing of the analysis (i.e. when and under which conditions will it be done)
  - Randomization/stratification: randomization procedure, stratification factors
  - Statistical analysis plan: primary and secondary endpoints, analysis populations, statistical methods, sensitivity or exploratory analyses, prognostic factor analyses, data recoding and display (Ref.: ST-005-SOP)
  - Interim analyses, early stopping rules
- Data monitoring (as primary writer)
- Quality of Life: description, planned analyses
- Translational research: description, planned analyses

Central review procedures when an endpoint or study parameter is to undergo such procedures

5.3 Modifications of the study design during the course of a trial

If and when, during the course of the study, it becomes clear that the trial cannot be run as per its design (as stated in the protocol), and steps to make it run have failed, it needs to either be stopped or amended. The study coordinator (SC), CRP and the statistician take steps to monitor if this is the case, and may need to consult the IDMC if changing the design is needed.

In order to maintain trial integrity, changes to the study design that affect the main statistical characteristics of the design (power, type 1 error, target effect size) must be done **prior to any data analysis and must be done or proposed by a statistician not directly involved in the conduct of the study**. The list of independent statisticians is maintained by the associate Head of the Department.

The study statistician provides the independent statistician with:

- Study documents: protocol; original statistical considerations and SAP, if any; non confidential IDMC recommendations, if any.
- Study data: dates of start and end of patient entry and accrual by year; number of patients by recruitment period; summary statistics (including Kaplan-Meier curves if applicable) for duration of follow up and for the primary endpoint in the control arm only.
  Note: if summary statistics for all treatments arms pooled together have previously been communicated, no additional data should be provided for the control arm only or separately by treatment group.
- Any information regarding feasibility or any other than purely statistical consideration that need to be taken into account in the re-design of the study.

Changes to the statistical considerations of the trial are major changes to the study that most often require a formal amendment to the study.

The revisions must be justified and documented in the form ST-001-AF-01 and signed by the head of the statistics department (or delegate, the associate head of the department). The approved ST-001-AF-01 is then transmitted to the study statistician.

In addition, the IDMC may need to be consulted.
It is generally agreed that:

- Early publication plans are regarded as early disclosure of study results and must therefore be submitted to the EORTC IDMC.
- Changes that involve modifying the primary trial endpoint must also be submitted for approval to the EORTC IDMC.
- Simple increases to the sample size that maintain the trial operational characteristics (target difference and definition of data maturity) need not to be submitted to the EORTC IDMC.
- Changes to the interim analysis plan of the study that consist in suppressing a planned review need to be notified to the IDMC with justification not to perform the interim analysis. Changes that involve addition of an un-planned interim analysis must be submitted to the EORTC IDMC for approval prior to conducting the interim analysis.

Finally, since such modifications may affect the patient risk/benefit ratio and as such are major amendments to the study. They must therefore be submitted to the PRC for approval.

5.3.1 Trials closed before reaching the target sample size ("closed prematurely") not according to planned stopping rules or IDMC recommendations.

Trials that are closed early may also require a revised statistical analysis plan (as per CM-005-SOP-03). Such revised analysis plans will be developed using the same process as described above by a statistician not directly involved in the conduct of the study

6 FILING AND ARCHIVING

All relevant documents that were generated to develop the design (mostly statistical tool files and other software output) are kept on the trial Statistician's specific directory on EORTC S drive according to Statistics Department guidelines.

Filing in the trial master file follows the EORTC procedure on trial master file CM-007-SOP-01.

7 RACI MATRIX

Functions / Activities	Study Statistician	CRP	SC	Head of stat (or delegate)	Independent stat
Statistical trial design	A	C	C	C	
Revision of trial design	I			A	R*
Filing and archiving of documents pertaining to the statistical design	R			A	
R: responsible; A: accountable; C: consulted; I: informed. Use 'A' when 'A' and 'R' are assigned to the same person.					

8 REFERENCES

- Committee for Proprietary Medicinal Products (CPMP) (2005) Guidelines on the Evaluation of Anticancer Medicinal Products in Man. CPMP/EWP/205/95/Rev.3/Corr.2
- CPMP Working Party on Efficacy of Medicinal Products. (1990) EEC Note for Guidance: Good Clinical Practice for Trials on Medicinal Products in the European Community. Pharmacology and Toxicology, 67: 361-372.
- CPMP Working Party on Efficacy of Medicinal Products (1995) Note for Guidance III/3630/92-EN, Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorizations for Medicinal Products. Statistics in Medicine, 14: 1659-1682.
- ICH Topic E8 (1997) General Considerations for Clinical Trials. CPMP/ICH/291/95.

ICH Topic E9 (1998) Statistical Principles for Clinical Trials. CPMP/ICH/363/96.

9 ASSOCIATED DOCUMENTS

Document title	Reference (file name or path)
Trial design - Phase I	ST-001-WIN-01
Trial design - Phase II and Feasibility studies	ST-001-WIN-02
Trial design – Phase III Confirmatory studies - classical	ST-001-WIN-03
Revised Statistical Design Template	ST-001-AF-01

10 DOCUMENT HISTORY

Version N°	Brief description of change	Author	Effective date
1.00	Initial release.	Jan Bogaerts	03 Mar2009
2.00	Introduction of the Revised Statistical Design Template and its approval process.	Jan Bogaerts	02 Feb2010
2.01	More detailed development process. Introduction of several new references.	Jan Bogaerts	25 Feb2011
2.1	Update section 6.2	Jan Bogaerts	25 Mar 2013
2.2	Update sections 5 and 6.2 (different statistician responsible for re-design in case of open label versus blind study)	Jan Bogaerts	16 Apr 2013
2.3	Update of the text to reflect advances in statistical methodology and revision of the ST-001-WINs. Implementation of the RACI matrix. Referencing to CM-005-SOP-03 for trials closed prematurely.	Laurence Collette	11 Dec 2015
2.4	Update to reflect updated job description and titles. Even for blind trials the revisions are done by an independent statistician.	Laurence Collette	14 Sep 2017