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Screening and Enrollment of Patients in EORTC Studies

ST-002-SOP
Version 2.1
ALWAYS REFER TO THE INTRANET TO CHECK THE VALIDITY OF THIS DOCUMENT

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1 PURPOSE

To describe the registration and randomization process as used by the EORTC Headquarters.

2 SCOPE

This SOP applies to all clinical studies where the patient registration and/or randomization is managed and executed by EORTC. In case of a blinded trial, CM-011-SOP is also applicable. In case a deviation from the eligibility criteria as stated in the study protocol is required, the procedure for an "Eligibility Deviation Request" as described in CM-010-WIN-01 will apply

3 POLICY

All patients entered in an EORTC study or research project database must be registered. The EORTC's policy is to have an automated procedure in place which allows study investigators to register a patient into a clinical study or research project with an automatic feedback of eligibility verification and a unique study-specific identification number for that patient. In case of a randomized clinical study, assignment to a treatment arm occurs in such a way as to produce comparable groups in terms of general patient characteristics and specific key factors that affect the probable course the disease would take, while minimizing potential selection bias by ensuring a degree of unpredictability in the treatment allocation.

4 DEFINITIONS

- **Registration**: process to add a subject in a study by allocating a patient identifier if the entry criteria are met.
- **Randomization**: process of assigning trial subjects to a single group when multiple groups are available using an element of chance to determine the assignments in order to reduce bias.
- **Randomization allocation log**: record created by the randomization program documenting the history of the performed patient registrations/randomizations and their characteristics.
- **On-line Randomized Trial Access (ORTA)**: Web based application developed at EORTC, used to register and randomize patients into EORTC trials.
- **VISTA:** Software developed at the EORTC and used for the clinical data entry, validation and descriptive analysis.
- **Randsup**: The administration tool for ORTA which allows for creating and managing studies in ORTA.

5 PROCEDURE

5.1 Before study activation

5.1.1 Design

Randomization parameters (timing, method, randomization ratio and stratification factors) are specified by the study Statistician (Stat) in the statistical chapter of the protocol according to the needs of the specific study, following the ST-002-WIN-02. Before study activation, when the eligibility and randomization requirements are sufficiently well documented in a study protocol, the study Data Manager (DM) contacts

the ORTA designers (OD) to create an ORTA program for each registration/ randomization step of the study. When creating the ORTA program(s), the template ORTA program is used as reference. The OD contacts the Stat in case questions are to be clarified. The ORTA Statistician (O-Stat) can be consulted in case of doubt on implementing the stratification factors.

An ORTA Study Definition and RandSup (administration tool) user guide explaining all the technicalities of the design of ORTA programs is available on the IT Help Pages on the intranet.

Once the registration/randomization programs are defined, the OD requests the creation of a test study to the ORTA-LDM (O-LDM) (if non-randomized) or the O-Stat (if randomized) to verify the eligibility questions are adequately defined and the randomization runs correctly. The OD submits the results of the tests for eligible and ineligible patients together with the ORTA programs and form ST-002-AF-01 to the O-LDM for review. The O-LDM approves the program by dating and signing form ST-002-AF-01, after verification of Form Review Committee approval. If a randomization step is involved, the O-Stat reviews the randomization allocation log generated by the randomization algorithm and approve the program by dating and signing form ST-002-AF-01 in addition to the O-LDM.

Upon approval, the O-LDM uploads the program on the server, prints and signs off the confirmation message of the upload. The O-Stat creates the study with the correct randomization parameters in RandSup.

The print-out of the approved program is annotated (explain what the program is doing, especially when functions and jumps are used) by the OD and stored in the TMF. A copy of the annotated ORTA program and the approval form are provided to the secretariat and the OD so that they can help a site when they call in case of problems with entering a patient in ORTA.

5.2 During the course of a study

During the course of a randomized study, the study statistician (or independent designee if the study is blinded) reviews the randomization allocation log generated by the randomization algorithm at the latest after the first 30 patients have been randomized. Inconsistencies indicating faulty randomizations are discussed with the O-Stat. The log is stored in the study TMF.

In case the registration or randomization program needs to be adapted after being uploaded, the DM first checks with O-LDM then requests the OD to do the necessary changes. The O-LDM summarizes the changes together with the justification on the ST-002-AF-01 form of that study.

For major changes (i.e. changes in the questions following an amendment, changes in questions following an error in the criteria) the version numbering is as follows: 1.0, 2.0, 3.0 etc. For minor changes (i.e. writing errors, modification instit function) the version numbering is as follows: 1.0, 1.1, 1.2 etc.

After the changes have been implemented and tested, the O-LDM reviews and approves the program by dating and signing form ST-002-AF-01. Adaptation of the instit function is not tested each time a site receives regulatory approval but only the first time it is implemented. If the changes affect the randomization of the study, both the O-LDM and the O-Stat need to review and approve the program by dating and signing form ST-002-AF-01. In case of an unplanned major change affecting the randomization, the O-Stat will inform the Head of Statistics.

Upon approval, the O-LDM uploads the program on the server, prints and signs off the confirmation message of the upload. The O-Stat changes the study randomization parameters in RandSup if needed.

The print-out of the approved program is annotated (explain what the program is doing, especially when functions and jumps are used) by the OD. A copy of the annotated ORTA program and the approval form are provided to the secretariat.

In case of a major change affecting the randomization, the study statistician (or independent designee if the study is blinded) reviews the randomization allocation log generated by the new version of the ORTA program at the latest after 30 patients have been randomized. Inconsistencies indicating faulty randomizations are discussed with the O-Stat. The log is stored in the study TMF.

6 FILING AND ARCHIVING

The DM files the initial and subsequently approved registration/randomization program, the test results and the ST-002-AF-01 approval form(s) provided by the O-LDM in the Trial Master File. A copy of the latest applicable, annotated registration/randomization program is provided to the secretariat so that they can help a site when they call in case of problems with entering a patient into a clinical study.

The Stat files the randomization allocation log as an electronic file in the appropriate J:\STAT TMF.

7 RACI MATRIX

Functions / Activities	CRP	Stat	DM	O-D	O-LDM	O-Stat
Design						
requirements documentation in the study protocol	C	A	C	C		
Implementation						
ORTA program creation	C	C	C	R	A	R[1]
Upload of the ORTA program(s)				R	A	R[1]
Filing			A			
Study conduct						
Allocation log check[1]		A				C
Modifying the ORTA program(s)	C	C	R	R	A	R[2]
Upload of the modified ORTA program(s)					A	R[2]
Filing			A			

R: responsible; A: accountable; C: consulted; I: informed.
Use ‘A’ when ‘A’ and ‘R’ are assigned to the same person.

[1]: for randomized studies.
[2]: if the change affects the randomization.

8 REFERENCES

- ICH Topic E9 (1998) Statistical Principles for Clinical Trials. CPMP/ICH/363/96.
- EMEA CPMP/EWP/2863/99 "Points to Consider on Adjustment for Baseline Covariates".

9 ASSOCIATED DOCUMENTS

Document title	Reference (file name or path)
Stat Dept Guideline 1 - Documentation on J STAT	J:\UNIT\Stat\Guidelines and Technical documents
ORTA Registration/Randomization Program Approval Form	ST-002-AF-01
Randomization Log Approval form	ST-002-AF-02
ORTA Study Definition Guide	Intranet-IT Help pages - Guides
ORTA RandSup Guide	Intranet-IT Help pages - Guides
Implementation of registration/randomization	ST-002-WIN-01
Design of randomization and stratification of clinical trials	ST-002-WIN-02

Forms are available from:
- Intranet, documentation section, Electronic Library of Quality Standard Documents page
- MS Word, File tab, New, My templates, forms tab, select the form

Work instructions (WINs) are available from Intranet, documentation section, Electronic Library of Quality Standard Documents page

10 DOCUMENT HISTORY

Version N°	Brief description of change	Author	Effective date
1.00	Initial release	Corneel Coens	23 Jun 2010
2.0	Complete revision of the process	Corneel Coens	09 Jul 2013
2.1	Revision of the process - extension of the documentation and testing process	Corneel Coens	18 Aug 2015