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Implementation of Registration/Randomization

ST-002-WIN-01
Version: 2
ALWAYS REFER TO INTRANET TO CHECK THE VALIDITY OF THIS DOCUMENT

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1 PURPOSE

To describe the implementation of the ORTA registration/randomization process in trials handled by the EORTC.

2 INSTRUCTION

2.1 Design

The necessary registration/randomization steps and requirements must be specified in the protocol. Eligibility criteria must be clearly listed for each required step in the dedicated protocol chapter (see PD-002-SOP on protocol development). Randomization parameters (timing, method, randomization ratio and stratification factors) are to be specified by the Stat in the statistical chapter of the protocol according to the needs of the specific study (see ST-002-SOP on randomization/registration).

2.2 Before study activation

When the eligibility and randomization requirements are sufficiently well documented in a study protocol, the DM will contact the ORTA Designers to create an ORTA program for each registration/ randomization step of the study. The protocol or the CRFs do not need to be finalized before contacting the ORTA designers, but the eligibility criteria must be confirmed and a stable draft of the registration/randomization forms must be available. In case of a complicated or non-trivial study, it is advised to consult the OD as early as possible to initiate the process and to start the ORTA creation process prior to protocol PRC approval. By doing so, the protocol can still be amended if needed to allow correct ORTA implementation.

2.2.1 Creation of the ORTA program

Note: An ORTA userguide explaining all the technicalities of the design of ORTA programs is available on the IT help pages on the intranet.

The ORTA designer should start by inferring from the eligibility criteria defined in the protocol and/or the eligibility checklist (or equivalent form) which answers render the patient ineligible. No deviation of the eligibility criteria defined in the protocol is allowed.

The ORTA designer will create an appropriate file for each step required by the protocol (all the steps together are considered one program). The OD will discuss with the study team if the needed number of ORTA steps deviates from the number listed in the protocol. When defining the ORTA program, the template ORTA program should be used as reference.

Some items don't need to be defined in the ORTA program as they are asked in the identification screen. These are:

- Institution number
- Protocol number
- Step
- Name of the responsible physician
- Identification of the patient which consist of:

- Patient code: maximum 4 alpha-numeric characters
- The patient's birth date

- Intergroup reference number

The ORTA program should always start with the age function unless there are no age limits defined in the protocol. For the further questions, the order of the questions on the eligibility checklist should be maintained.

The questions but also the possible labels, units and dates format to be used should be described in the "prompt" section of the questions definition.

Ranges have to be defined for each question whenever applicable. For categorical values this corresponds to the labels. For numerical values this corresponds to the limits defined in the protocol. If no limits are defined then the ORTA designer should check with the CRP what should be put as limit. For date values this corresponds to the minimum date before which no date can be entered.

For categorical values, if possible, the code introduced should be the same as the numbering of the answer proposed (e.g. 0 = no → code = 0; 1 = yes → code = 1). Exceptions are if it concerns a stratification factor, in which case it is possible that two different answers have the same code for stratification purposes (e.g. performance status as stratification factor: PS 0 versus 1 and 2, which gives the code 0 for PS 0 and code 1 for PS 1 and 2), and if the code needs to be used in a function (e.g. 0 has code 0 and 1 has code 10). For scalar values, a code also needs to be attributed which is almost never the same as the value entered (e.g. for age: 0 gets code 0, 18 gets code 1, 50 gets code 2). The codes are very often attributed in a certain way so that they can be used in a function.

The stratification factors are listed with their corresponding levels in the statistical chapter of the protocol. The stratification factors should be programmed in the simplest possible way that correctly reflects the actual stratification categories: direct questions will be preferred over derivations (e.g. risk group assessment). In case of doubt on stratification factors programming, the statistician responsible for review of ORTA programs should be consulted.

For randomized trials using minimization with unequal randomization ratios, each treatment arm should be clearly identified with each corresponding ratio in both the protocol and the ORTA program and the order in which the treatments are listed should be consistent throughout the process. Eg. a 2:2:3 randomization should be implemented by defining 2 x arm A, 2 x arm B and 3 x arm C for a total of 7 treatment arms. For randomized trials with unequal ratios but using blocks, the number of treatment arms is equal to the number of distinct treatments, ie. each treatment arm is listed exactly once.

For non-randomized phase I trials all dose levels that are foreseen should be defined in the original program. The treatment exclusion is used to exclude all the dose levels except the active dose level.

2.2.2 Testing the ORTA program

Before testing, the ORTA designer needs to complete the ST-002-AF-01 form, together with the ORTA Stat (O-Stat) if needed. A test study named tYYYY, whereby YYYY is the study number, is created via RandSup (by the O-Stat or the ORTA LDM (O-LDM)) with the same parameters as required for the actual study. The tYYYY program is uploaded on the server by the ORTA designer.

The tests should always be made with the institution number 1. A minimum of 5 patients should be registered/randomized to test the defined program. However as many patients as required should be

registered/randomized to ensure that the eligibility and ineligibility of the dummy patients as well as all functions are adequately tested. All the different possible answers should be tested (e.g. male versus female, childbearing potential versus not of childbearing potential). During the test procedure the "Java console" is mandatory for documentation of ineligible patients. To document the ineligible answers in java, the ORTA designer should press twice on the button "next" during the test procedure. After testing, the output of java should be saved according to CM-007-SOP.

If necessary, corrections should be made in the program. It should be saved again according to CM-007-SOP and tYYYY and new tests should be performed to make sure that the implemented changes are correct.

2.2.3 Review, approval & upload on server

Once the test procedure has been successfully performed, it has to be submitted to the O-LDM. The ORTA designer needs to submit a package of the eligibility checklist, the ORTA program, completed ST-002-AF-01 form and the performed tests for eligible and ineligible patients (printouts of patient entry from ORTA tools and Java console). In case there are comments, the program should be adapted and new testing should be done. ST-002-AF-01 will be completed and signed by the O-LDM and in case of randomized trials also by the O-Stat who will check the treatments definition, the stratification factors and the allocation log. After approval, the program should be annotated (explain what the program is doing, especially when functions and jumps are used) by the ORTA designer.

For RDC trials with crgX forms the corresponding ORTA question number needs to be added in VISTA form definition by the study Data Manager after approval of the ORTA program.

Upon approval, the O-Stat will create the study in RandSup. Before the approved program can be uploaded on the server for patient entry, the program should be saved as YYYY.stx (with YYYY being the study number). When the approved program is uploaded on the server by the O-LDM, a printout of the confirmation needs to be made by the O-LDM, signed off and filed together with the approved program.

After uploading, the annotated program and ST-002-AF-01 will be attached and filed according to CM-007-SOP together with the signed tests. A copy of the annotated ORTA program and ST-002-AF-01 is provided to the secretariat so that they can help a site when they call in case of problems with entering a patient in ORTA.

2.3 Testing the allocation log

During the course of a randomized study, the study statistician reviews the randomization allocation log generated by the randomization algorithm for inconsistencies indicating faulty randomizations. This is to be done for the first time 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 of a blinded study, this needs to be done by the unblinded statistician rather than the study statistician.

2.3.1 Minimization

The randomization log of any EORTC-based study can be exported into Excel format via the ManaRand program. In addition to the actual treatment assignment, the randomization log includes also:

- protocol number
- login ID
- date of randomization

- patient ID
- institution number
- step number
- institution inclusion
- threshold level
- random component
- total matrix scores
- random allocation numbers

The resulting excel file can then be imported into SAS via PROC IMPORT and checked via the %STRATCHECK macro for inconsistencies.

Attention should be paid to patients who were removed from the allocation list (eg. double randomisation). These should be identifiable for exclusion by having a seqid equal to "0".

2.3.2 Permuted block

The randomization log of any EORTC-based study can be exported into Excel format via request to the IT Office. In addition, the generated block lists can be obtained as well via request to the IT Office.

Verification of the allocations is then straightforward by comparing the observed allocations to the generated block list.

2.4 Modification

Once the ORTA program is approved and uploaded on the server and the entry of patients has started, the ORTA program can only be changed in case of protocol amendment or if the program contains a mistake. If a modification is needed, this should be done in strict agreement with O-LDM. The current program should be downloaded from the server and the field "study name" should be changed with the new version number. For major changes (e.g. changes in the questions following an amendment, changes in questions following an error in the criteria) the version numbering should go as follows: 1.0, 2.0, 3.0 etc. For minor changes (e.g. writing errors, modification instit function) the version numbering should go as follows: 1.0, 1.1, 1.2 etc.

In case of an unplanned major change affecting the randomization, the O-Stat will inform the Head of Statistics.

It is not allowed to delete questions or to add questions between already defined questions once the program has been put on line and patients have been entered. New questions can only be added at the end. The "go to" function should be used to display the question at the correct place during registration/randomization.

To check the changed program, tests should be performed particularly focusing on the changes made. For review and approval by the O-LDM the same procedure should be followed as in paragraph 2.2.3. The O-LDM summarizes the changes together with the justification on the ST-002-AF-01 form of that study. 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. If the changes affect the randomization (if any) 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.

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 current version should be saved according to CM-007-SOP.

In case a modification to the program is needed due to a protocol amendment, the INSTIT function should be used, except in case of an amendment due to urgent safety measures. In the last case the changes are immediately applicable. The INSTIT function will ensure that centers reply to the questions for the version of the protocol for which they received regulatory approval. To use the INSTIT function all the authorized institutions should be put in ascending order in the range field (include 1 to allow testing the INSTIT function). Codes need to be assigned to make sure that the correct questions are asked to the correct sites, meaning questions asked before the amendment will still be asked to sites who didn't get approval yet and questions developed due to the amendment will only be asked to sites who did get it. If a site gets regulatory approval, the code should be adapted. This new program should not be tested each time a site receives regulatory approval but only the first time the INSTIT function is implemented. It should be approved and uploaded by the O-LDM as described in section 2.2.3.

If a change involving a stratification factor or a change in treatment arms is needed after a number of patients have already been randomized, the impact on the overall trial needs to be assessed by the O-Stat. For the minimization method, the change should be implemented preferably in such a way that the resulting overall trial balance is achieved as much as possible. Already randomized patients can be counted or not towards the complete calculation of the imbalance scores. A sensitivity analysis of the primary endpoint with stratification according to pre-/post-amendment accrual needs to supplement the main analysis when appropriate. For the permuted blocks method, creating additional strata will not disturb allocations to existing strata. Modifying existing strata (eg. splitting one strata into 2 distinct strata) however will require the creation of new strata and exclude the further recruitment into the existing strata. In case of a major change affecting the randomization, the Stat reviews the randomization allocation log generated by the new version of the ORTA program at the latest after 30 patients have been randomized according to the procedure described in ‘Testing the allocation log’.

2.5 Eligibility deviation

In case a minor eligibility deviation (waiver) was granted (see "Eligibility Deviation Request" as described in CM-010-WIN-01), the ORTA program should be adapted accordingly. The field "study name" for this adapted ORTA program should be coded as study number - patient's code - patient's birth date. This program needs to be tested if possible and submitted to the O-LDM together with the e-mail correspondence and the completed and signed "eligibility deviation form" (CM-010-AF-01). After approval, the program needs to be uploaded to allow the entry of this patient with an eligibility deviation, a printout of the confirmation needs to be made by the O-LDM, signed off and filed together with the approved program. Once the patient for whom an eligibility deviation was granted has been registered / randomized, the last normal approved ORTA program should be re-uploaded on the server and a printout of the confirmation needs to be made by the O-LDM and filed together with the documentation of the eligibility deviation.

3 ASSOCIATED DOCUMENTS

Document title	Reference (file name or path)
ORTA Registration/Randomization Program Approval Form	ST-002-AF-01
Randomization Log Approval form	ST-002-AF-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

4 DOCUMENT HISTORY

Version N°	Brief description of change	Author	Effective date
1.00	Initial release superseding WP1105 version 2.00 section 4.2	Claire Aerts	23 Jun 2010
2	Removal of the technicalities that are defined in the ORTA user guide available on intranet. Redistribution of responsibilities between specialized people (ORTA designer, ORTA statistician and ORTA lead data manager)	Corneel Coens	18 Aug 2015