EORTC
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The future of cancer therapy

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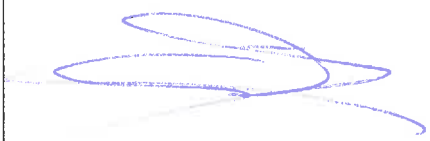
ST-000-GD-01:

Registration / Randomization Implementation

Version : 1

Author: *Lead Statistician* Corneel Coens	Signature: 	Date: *(ex:10-Feb-2017)* 31/5/2018
Approved and authorized by *Head of Statistics Department* Laurence Collette	Signature: 	Date: *(ex:10-Feb-2017)* 31.05.2018

1 PURPOSE

To describe the implementation of the MEDIDATA 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 Randomization implementation

When the eligibility and randomization requirements are sufficiently well documented in the study protocol, the **Study Statistican** writes a Randomization User Requirement detailing the randomization requirements.
The Randomization User Requirement is reviewed and approved by a **Randomization Expert** unless the study design is basic (ie. single randomization; not cohort or treatment period design).
The Study Statistician communicates the Randomization User Requirement to the **Study Designer** and **Clinical Data Manager** who implement the necessary stratification factor items for each randomization step of the study. The protocol or the CRFs do not need to be final before completing the Randomization User Requirement, but a stable draft of the screening/registration/randomization forms must be available.
In case of a complicated or non-trivial study, it is advised that the **Study Statistican** consults the **Study Designer** as early as possible to initiate the process and to start the randomization implementation process prior to protocol PRC approval. By doing so, the protocol can still be amended if needed to allow correct implementation.
The **Study Designer** and **Clinical Data Manager** ensures that the stratification factor states are collected according to the protocol. They consult the **study team** in case questions are to be clarified.
The stratification factors are listed with their corresponding levels in the statistical chapter of the protocol. The stratification factors are best programmed in the simplest possible way that correctly reflects the actual stratification categories: direct questions are preferred over derivations (e.g. risk group assessment). Unless specified in the protocol as a valid stratification state, missing data or 'unknown/other' responses need to cause ineligibility of the patient. Country and institution do not need to be programmed; any other geographical categorization is to be programmed. The database needs to retain the stratification states as given at the time of randomization.

The **Study Designer** informs the **Study Statistician** when the stratification state questions are complete and provides the name and values (codelists).
The **Study Statistician** verifies the stratification factor states are correctly implemented and completes the randomization setup in MEDIDATA.
The **Study Statistician** contacts a **Randomization Expert** in case parameters are to be clarified.

In the MEDIDATA software,the Study Statistician chooses the study design:

- Basic – single randomization; allows minimization.
- Cohort – single randomization per cohort (blocks only).
- Treatment Period – multiple randomizations and/or re-randomization (blocks only).

For each randomization step of the study (under the design tab), the **Study Statistician** must define the method: "Dynamic Allocation" or "Permuted Blocks", the treatment arms and the stratification factors.
For each treatment arm, the name, ratio and description needs to be entered in accordance with the protocol.
For each stratification factors, the **Study Statistician** specifies the name (variable name as provided by the **Study Designer**), values (state values as provided by the **Study Designer**), description and weight in accordance with the protocol. The default stratification factors are site/country, study and stratum. In order to remove a default stratification factor, its factor weight must be set to 0.
The following holds specifically for Dynamic Allocation: The Complete Randomization Probability should be set in accordance with the protocol.
The following holds specifically for Permuted Block: The Block Sizes should be set in accordance with the protocol with at least one block size from the possible length 1, 2, or 3 (x treatment arm ratios). The number of blocks per size within each strata needs to be specified as to adequately cover the intended sample size..
For non-randomized trials, but with different treatment arms (eg. phase I trial with dose levels), a Cohort design needs to be chosen with one treatment arm per cohort. Assigning patients to the correct cohort can then be controlled via the cohort inclusion criteria (if cohorts are to be opened in parallel) or via the enrollment status (if cohorts are to be opened mutually exclusive).

2.3 Testing the randomization implementation

Once the **Study Statistician** has completed the randomization setup in MEDIDATA, (s)he downloads the 'configuration report' and verifies that all characteristics listed there are in accordance with the protocol.

The **Study Statistician** then sets up a study specific test plan. This test plan will list the functional testing, user acceptance testing and performance testing procedures needed to validate the implementation. The test plan defines the clinical data requirements for the UAT execution and is provided at start of the study validation phase. The clinical data will be prepared in the UAT environment by the CDM in parallel with the database validation testing. The **Study Statistician** may consult the **Randomization Expert** and/or **Study Designer** to help complete the test plan. The test plan is reviewed by the **designated tester** to ensure that (s)he understands the requirements and the plan is approved by a **Randomization Expert.**
The **designated tester** will then perform the tests and inform the **Study Statistician** of the findings. The communication from the tester regarding anomalies, bugs or enhancements and actions triggered are summarized in the test report documentation. . The **Study Statistician** is responsible for implementing the necessary modifications. Whenever the randomization implementation is modified, the test plan must be repeated.
At the end of the testing, when the **designated tester** reports no critical findings, the test report is finalized and signed by the **Study Statistician**.

This test report contains:

- the CRF version used for the tests
- the environment used
- the date of execution

- the test results and randomization modifications (if any).
- the final configuration report

The signed test report is stored in the study TMF.

2.4 Activating the randomization implementation

After completion of the randomization test report, the **Study Statistician** signs the appropriate section on the database release report form for the study and ensures the stratification factors are collected correctly and have been tested by **CDM** user testing.
This database release report form is added to the study activation form. The study activation form is signed by the **Head of the Statistics Department** to authorize the official activation of the study.

2.5 Testing the allocation log

During the course of a randomized study, the **study statistician** reviews the randomization allocation log generated by the randomization algorithm to identify inconsistencies. This must be done for the first time after the first 30 patients have been randomized. Inconsistencies indicating faulty randomizations are discussed with the **Randomization Expert.** The log and the Randomization Log Report are stored in the study TMF.
For blinded studies, this process is performed by the **unblinded study statistician** rather than the **study statistician**.
Attention should be paid to patients who were removed from the allocation list (eg. double randomization).

2.6 Modification

Once the randomization implementation is activated, the parameters can only be changed in case of protocol amendment or if the implementation contains a mistake.
The need for and severity of a modification is assessed by the **Study Statistician**, who may consult the **study team**, **study designer** and/or **Randomization Expert**.
The **Study Statistician** requests a new study version to the **Study Designer**.
The **Study Statistician** implements the necessary changes and sets up a study specific test plan, particularly focusing on the required modifications. The content and execution of the test plan follows the procedure as in “Testing the randomization implementation”.

If a change involving a stratification factor or the 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 **Study Statistician**. 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. Patients already randomized may 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 will preclude any further recruitment into the existing strata.

This test plan will list the functional testing, user acceptance testing and performance testing procedures needed to validate the implementation. The **Study Statistician** may consult the **Randomization expert** and/or **Study Designer** to help complete the test plan.
At the end of the testing, when the designated testers report no critical findings, the test report is finalized and signed by the **Study Statistician**.
This test report contains:

- the CRF version used for the tests
- the environment used
- the date of execution
- the test results
- modifications from the previous version.
- the final configuration report

The signed test report is stored in the study TMF.
In case of an unplanned major change affecting the randomization, the **Study Statistician** informs the **Head of Statistics**. The **Study Statistician** must review the randomization allocation log generated by the new version at the latest after 30 patients have been randomized according to the procedure described in 'Testing the allocation log'.
After completion of the randomization test report, the **Study Statistician** signs the appropriate section on the database release report form for the study. This database release report form is added to the study activation form. The study activation form is signed by the **Head of the Statistics Department** to authorize the official activation of the modified version.

3 ASSOCIATED DOCUMENTS

Document title	Reference (file name or path)
Randomization User Requirement	ST-000-Temp-01
Randomization Test Plan	ST-000-Temp-02
Randomization Test Report	ST-000-Temp-03
Database Release Report	DM-000-Temp-04

4 DOCUMENT HISTORY

Version N°	Brief description of change	Author	Effective date
1	Initial release	Corneel Coens	01 Jun 2018