Implementation of different randomization algorithms in the web-based application RANDI2

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ABSTRACT

Background: The open source project RANDI2 provides a platform for the electronic randomization for clinical trials, in which course patients are allocated to different treatment arms. Formerly, the following methods are realized, namely: complete randomization, the simple block randomization, and the biased coin toss [1-3].

Material and Methods: The structure of RANDI2 has been presented elsewhere [1]. The application is built on the programming language JAVA and is subdivided into a user interface, application logic, and domain specific components to which also testing the randomization algorithms. The statistically validated randomization methods are based on several classes of objects, in which the boundary conditions as they result from the number of study therapies, study centers, and patient characteristics, play a key role [3].

Results: Newly implemented are the algorithms block randomization of unspecified length, variable block randomization, the urn model, the minimal stratification, and diverse stratification methods. The already existing algorithms have been revised. Generally, the randomization procedures consist of three parts: (i) configuration of the algorithm, (ii) temporary data, and (iii) execution of the operation. The assignment of study and algorithm is carried out in loose coupling in form of a strategy pattern [4].

Discussion: Since the study is independent from a concrete realization or implementation of the algorithm. With this procedure a variable approach is provided for the available randomization algorithms, in which after a testing and simulation process the procedure to be used can be chosen.

Conclusions: In the open source project RANDI2 are now the often used randomization processes available for most of the clinical trials, whereas the choice of the randomization procedure is supported by testing and simulating the process. Additional procedures can integrated easily due to the given program architecture.

INTRODUCTION

CLINICAL TRIALS
• Clinical trials are systematic predefined procedures to study and develop new therapies and treatments.
• New therapies have to be compared with standard treatments under the same boundary conditions.
• A clinical trial comparison with two or more treatment arms is usually randomized.

RANDOMIZATION
• In the randomization process patients are allocated to one of the treatment arms.
• The open source project RANDI2 provides a platform for the electronic randomization for clinical trials.
• In the first version the complete randomization, the simple block randomization, and the biased coin toss are realized.
• There is the need to adapt the randomization process to the study design and the patient recruitment.

METHODS

RANDI2 is based on the programming language JAVA.
• Divided into three layers:
  ◦ User interface
  ◦ Application Logic
  ◦ Domain specific components (including the randomization algorithm)
• The randomization methods are built from several classes of objects:
  ◦ Study therapies
  ◦ Study centers
  ◦ Patient characteristics

ARCHITECTURE OF THE RANDOMIZATION

TERMINOLOGY

ABSTRACT

FRAMEWORKS

HIBERNATE:
- Enables an independent usage of the randomization from the type and kind of data base.
- ICEFaces:
  - A Framework to form a dynamic and state-of-the-art graphical web-based user interface.
- Spring:
  - This tool makes the configuration of application components and allows the implementation of cross-cutting routines (i.e. security checks and logging).

FEATURES

• Single installation enables management of several studies and centers.
• Technology: JEE-application
• Activation for the first study: Late summer 2009

SPECIAL FUNCTIONS

Administration of roles and permissions
• predefined user roles:
  ◦ administrator
  ◦ principal investigator
  ◦ investigator
  ◦ statistician
• single user right’s customization

Configuration of patient data
• Types of properties:
  ◦ domicile change / enumeration
  ◦ name
  ◦ calendar data
  ◦ key
• Data validation

STRATIFICATION OF RANDOMIZATION

• Balancing of known covariates or prognostic factors for trials.
• Each influencing factor is defined as a stratum.
• Simple stratification: For each stratum an independent identical randomization process is established.
• Stratata are realized in RANDI2 by generating a stratum identifier on the basis of the patient properties and a separate randomization process per stratum is initialized.
• Thus, the stratification process is independent from the chosen randomization algorithm.

COMPLETE RANDOMIZATION
• The probability of every treatment is equal.
• For example: for two treatments a fair coin with probability 0.5.
• Every randomization is an independent Bernoulli variable.
• Suitable for more than 400 patients in the study sample.
• For small numbers it is not unlikely to get unbalanced treatment arms.
• Stratification plays no role, because of independent randomizations.

BIASED COIN
• Different probability in each single treatment.
• For example: to test a new treatment with a placebo (ratio 2:1).
• For stratification and the number of required patients there are the same conditions as in the complete randomization.

BLOCK RANDOMIZATION
• Permuted block design is used to avoid imbalances between treatment arms during the short course.
• Often used in trials with interim analyses.
• Blocks of length m are generated where the product m·n should be greater than the sample size.
• For example in case of two treatment arms m = 2 patients are assigned to each of the treatment arms.
• In each block the treatment allocation is done randomly.
• The maximum imbalance D is given by: max(0, 1/2 - m/n).

URN MODEL
• Initially a urn contains k balls of each type (2) of treatment.
• In the case the drawn ball is not replaced it is equivalent to the truncated randomization.
• Replacement of drawn balls can be defined in several ways:
  ◦ E.g., Replacement by a ball of the same color.
  ◦ Or in case of two colors replacement by k balls of the opposite color (resulting in a quicker compensation of the imbalance).

CONCLUSIONS

RANDI2 includes all the often used randomization processes.
RANDI2 supports the choice of the randomization procedure by testing and simulation.
RANDI2 integrates the possible additional procedures easily due to the given program architecture.

REFERENCES

Presented at the GMDV annual conference, September 7~10, 2009 in Essen, Germany.

RANDI2 source code is also hosted on
github.com (http://github.com/thirius RANDI2)