Does Randomization protect against bias?
What can be done to improve the level of clinical evidence of effectiveness?

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The FDA guidance "Providing clinical evidence of effectiveness for human drug and biological products" states that among others details on the randomization is an important piece of information about a study, which can increase the likelihood that the study can be relied on to support an effectiveness claim. Further, the ICH E 9 guideline states that randomization is a key feature of randomized clinical trials aiming to protect against various types of bias. The interpretation of statistical measures of uncertainty of the treatment effect and treatment comparisons should involve consideration of the potential contribution of bias to the p-value, confidence interval, or inference.

Different randomization procedures have been introduced in the past decades and the analytical properties have been studied by various authors. Among others, balancing behavior, protection against selection via averaged number of best guesses etc. have been investigated. These theoretical properties do not apply to the practical setting of clinical trials and do not show the connection to the potential contribution of bias to the test size. So the question, whether or to which extend randomization protects against bias in clinical studies cannot be answered. The problems are more prominent in small clinical trials, where long run properties of randomization procedures are supposed to fail.

However, up to now, there is no specific recommendation neither in the regulatory nor in the scientific guidelines to study the potential of different randomization procedure with respect to impact of bias in a systematic way. This leads to the situation, that the selection of the randomization procedure does not follow scientific arguments, like e.g. sample size calculation does. Further, there is no tool available to perform such investigation.

Recently, our research group has developed a model within the IDeAl project (http://www.ideal.rwth-aachen.de) showing the direct connection between randomization procedures, bias and the test decision aiming to assess the value of a particular randomization procedure to avoid bias in a clinical trial.

In the talk we will propose a framework for a scientific evaluation of the connection between randomization procedures, bias and the test decision following a clinical evaluation scenario. We focus on selection bias and chronological bias with different time shapes in a clinical trial with parallel group design and continuous endpoint. Preliminary results in the direction of time to event endpoints where shown as well. Further, we will refer to our public available R software package "randomizeR", which can be used as a tool for the evaluation. The framework can be used as a template for providing scientific arguments to select a randomization procedure in the design phase of a clinical trial.

Dr. Ralf-Dieter Hilgers is Head of Department of Medical Statistics at RWTH Aachen University since 2001 and he founded the Clinical Trial Center Aachen in 2002. Currently he is coordinator of the IDeAl project (Integrated Design and Analysis of Small Population Group Trials) funded by the European Community (www.ideal.rwth-aachen.de), which will establish new methodologies for small population group trials. His research interest is in optimal design of experiments, randomizations procedure and clinical trials.