

Main Topic: Design and analysis of clinical trials

**Title: Assessment of chronological bias in randomized clinical trials**

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In clinical trials patients are usually recruited sequentially over time. Often the recruitment takes place over several years. Especially in clinical trials studying rare diseases, low accrual rates and thus long recruitment phases are common. As a result of the prolonged recruitment time, time trends are suspected to occur. This can be due to several reasons, such as changes in the recruitment policy or learning effects in the application of the new methods. If treatment effects are confounded with time trends, this can result in the so called chronological bias.

Even in randomized clinical trials, time trends may impact the results, for instance if a long series of consecutive patients are assigned to the same treatment. To account for this, the ICH E9 guideline recommends the use of randomization in blocks. However, one major drawback of permuted block randomization with short blocks is the increase in the risk of selection bias.

Using different time trend models, we evaluate and compare the extent of chronological bias under the random allocation rule and the permuted block randomization with different block sizes. We present theoretical results regarding the extent of bias in the treatment effect estimate under different time trends. Further, the bias in statistical hypothesis testing is discussed considering the empirical type I error rate in simulations. An assessment of worst-case-scenarios as well as an overall assessment considering the choice of randomization is given.

This research is part of the IDeAI EU-FP7 project, Grant-Agreement No. 602 552.