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Should the standard recipe for RCTs be revised?

Randomized clinical trials (RCTs) are often said to constitute the gold standard among statistical methods for establishing a causal relationship in medical research. A large majority of RCTs are designed following the standard recipe: formulate a null hypothesis in a statistical test, select a significance level to limit the error rate of false positives, specify the smallest clinically meaningful effect size and the corresponding target power, compute the required sample size, randomize the participants equally to the different treatment arms, and run the trial. Finally, after all outcome data are in, check the p-value to decide whether the null hypothesis can be rejected.

An alternative to such standard designs of fixed sample size is to follow a sequential scheme, where the execution of the trial can depend adaptively on the so far accumulated outcome data. In traditional group sequential designs such a possibility is restricted to a few pre-selected time points at which an interim analysis is made, and the consequent multiple testing problem is handled by adjusting the significance level in such analyses. In this talk, we consider some further alternatives, based on the direct consideration of the posterior probabilities arising from comparing the different treatments. If a treatment is found to be sufficiently clearly inferior to the currently best candidate, it can be closed off either temporarily or permanently from further participant accrual. The former possibility provides a method for adaptive treatment allocation, and the latter for treatment selection, including early stopping of the trial.The main development of the talk is in terms of binary outcomes, but some extensions, notably for handling time-to-event data, are discussed as well. The presentation is to a large extent comparative and expository. (The talk is based on joint work with Dario Gasbarra.)