Adaptive Clinical Trials

Clinical trials

Clinical trials are performed to find out about the efficacy and safety of a new treatment. The outcome variable has a distribution of values in the population. When performing a hypothesis test, we want to find out if there is a shift in this distribution due to a possible treatment effect. We do this by calculating the probability to get this outcome from the sample, while there is no change. Then we show that this probability is less than some threshold which is usually 5% (type I error rate). In this way we control the probability of a false positive conclusion, that we conclude that an ineffective treatment is effective. Additionally we also have to restrict the probability of a false negative result, that we conclude that an effective treatment is ineffective. This type II error rate depends among others on the sample size, the variability and the treatment effect we want to identify. The sample size is chosen to restrict the type II error rate to 10 or 20% to achieve a power (1-type II error rate) of 80-90%. When we calculate a sample size for a clinical trial, we assume parameters such as variability and treatment effect. In trial designs without interim analyses, we only perform one analysis at the end of the trial with the data from the originally calculated number of patients.

What are adaptive clinical trials?

Patients are not all enrolled in a trial at the same time, but continuously. This means that interim analyses can be performed after the outcome of a certain number of patients is measured. Adaptive use accumulating data to stop the trial early or to continue and adapt the trial. We have to apply special analysis methods to maintain the validity of these kind of trials. The gain in flexibility can increase the robustness of the trial with respect to planning assumptions.
There are strict guidelines to avoid that incorrect usage of adaptive designs leads to inefficient trials, especially if adaptations are performed with small and highly variable first stage sample sizes.

How does it work?

Adaptive designs cover a wide variety of methodological approaches with differing complexity and freedom to adapt the trial at interim analyses while ensuring the validity of the trial, which means controlling the type I error rate* or in the case of multiple significance tests (at interim analyses and final analysis) the overall type I error rate. The time till the outcome is measured must be short in comparison to the accrual time.

*Overall type I error rate (or multiple type I error rate or familywise error rate): probability to reject at least one true null hypothesis under any configuration of true and false null hypotheses.

Possible adaptations

Stopping for efficacy or futility

Trials can stop early in case of overwhelming efficacy or if a positive result becomes very unlikely.

Sample size reassessment

The sample size can be adapted according to current estimates of parameters such as variability or treatment effect.

Changes in reallocation

More patients are allocated to better performing treatment arms.

Dropping/adding of treatment arms

Ineffective treatment arms can be dropped during a trial and promising arms added.

Selection of endpoints/subgroups

Suitable patient subpopulations and endpoints can be selected.

Seamless phase II/III trials

Phase II/III trials can be combined into one trial with an interim analysis, not only to reduce the organizational effort, but also the sample size by using the phase II data in the final analysis in phase III.

Asterix methods

Multi-arm group sequential designs* with a simultaneous stopping rule: We have derived optimal stopping boundaries to improve sample size and power. If the trial wants to show a treatment effect in at least one arm, we recommend a simultaneous stopping rule. To show efficacy in all arms we showed the advantage of a separate stopping rule.
Sample size reassessment and hypothesis testing in adaptive trials: Improved adaptive survival tests are constructed based on full interim data including patients who are censored at the interim analysis.

Adaptive Parametric Multiple Testing Procedures: We propose a multiple testing strategy using the joint distribution of the endpoints in which the correlations are estimated in an interim or final analysis and boundaries adjusted, while we still control the type I error rate of the trial.
Sequential designs with small samples: We have developed a method to decide on an optimal sequential design with normally distributed outcomes when we have some prior knowledge of the treatment effect and where there is a maximum number of patients available.

*Group sequential designs can be seen as a special form of adaptive designs, where all possible adaptations like stopping for efficacy or dropping of treatment arms have to be pre-specified in order to adjust the boundaries for rejecting a null hypothesis at interim analyses or at the final analysis. Patients are censored if the measured variable is time till a certain event, but the event has not happened for them at the time of the analysis.

Possible benefits for patients

- Effective treatments can become faster available because of the potential to stop the trial early for futility or efficacy.
- We need less patients to perform the clinical trial, making trials in rare diseases feasible.
- Patients are less exposed to inefficient and unsafe treatments/doses.
- The chance of success of a clinical trial increases because wrong assumptions at the start of the trial are adjusted and promising hypotheses selected at interim analyses.

Possible downsides

- Stopping earlier leads to less overall knowledge (e.g. lower precision of estimates of primary, secondary or safety endpoints, frequency of side effects) compared with a trial including more patients.
- With some adaptations the interpretation of the overall test decision could become difficult.
- Additional organizational efforts can be necessary and setup costs can arise because of complexity of the designs and due to regulatory issues, for example computer simulations for evaluation of design characteristics.

More information

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