NMST532 Design and Analysis of Medical Studies

Slide set III.

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Design issues

Types of study design

- Multi-arm design: Compare several treatments or several doses of the same treatment.
- Factorial design: Investigate two different treatments simultaneously in a single trial. Two independent randomizations: treatment A vs. control and treatment B vs. control. Efficient when the treatments do not interact.
- Cross-over design: Apply two treatments to each patient in a random order, leave *washout period* between them. Randomization: the order of treatments. Useful for treatments that act immediately and their effects do not persist when withdrawn.

Types of study design

- Non-inferiority trials: Show that the new treatment is not less effective than the standard. Used when the expected advantage of the new treatment is fewer side effects or more convenient dosage/administration. Needs special statistical approach (the null hypothesis is “the new therapy is worse than the old”).
- Group-randomized trials: Randomize groups of subjects rather than individuals (regions, villages, clinics, schools). Useful for investigating population effects on infectious diseases (e.g., testing new vaccines) or health interventions that have a social impact beyond the individual (prevention campaigns). The unit of randomization and analysis is the group.

Types of study design

- Meta-analysis: Analyze the results of several completed trials of insufficient size, merge them and obtain a more precise result. Also used in epidemiology.

Follow-up

- The follow-up should be long enough to demonstrate the treatment effect on the primary outcome and to investigate the safety profile of the drug.
- Frequently, the follow-up duration in Phase III trials is too short to fully understand the long-term effects of the new drug.
- Follow-up procedures should not be too hard for the participants (painful, inconvenient, time-consuming). The priority is evaluation of the primary outcome.
- Follow-up procedures must be the same regardless of randomization. Blinding is ideal to assure this.

Ethical issues

The conduct of clinical trials (and human subject research in general) is subject to strict ethical standards. Main principle: you must not do harm.

- IRB review. The protocol is approved by an IRB (Institutional Review Board) at each participating institution. The review is repeated at regular intervals (annually).
- Informed consent. Each participant signs an informed consent before enrollment. Purpose: describe the purpose of the study, explain randomization, give information about study procedures, reveal risks of participation, inform about rights.
- Justification for randomization: clinical equipoise.

Ethical issues

- Every participant has the right to terminate participation at any time for any reason.
- DSMB review. The Data and Safety Monitoring Board is an independent group of external experts (including a statistician) that reviews the results of the ongoing study and has the right to terminate the study at any occasion.

Analysis issues

Before analysis

- A detailed Statistical Analysis Plan is developed, approved and archived.
- When data collection is completed, the data are cleaned, verified and locked. After locking, no data item can be changed.
- Locked data can be unblinded and the analysis proceeds according to the SAP.

Analysis set

- Clinical trials are analyzed according to the intent-to-treat principle. This means that each participant is kept in the group to which he was originally randomized – even if the treatment never started or was not fully provided.
- The ITT principle means: we do not test the effect of the drug on the subjects who take it (efficacy) but we are testing the policy of *prescribing* the drug to the study population (effectiveness).

Analysis set

- The willingness of the participants to follow the treatment as prescribed is called adherence or compliance. This can be measured and recorded but it is not taken into account in the primary analysis. Deleting patients who were not compliant violates the randomization principles and reintroduces confounding.
- Participants who dropped out of the study should be included in the analysis as long as the primary outcome is available. Otherwise, they must be excluded (with the danger of confounding hanging on).
- If the number of dropouts is substantial, the integrity of the study is compromised.

Analysis methods

Analysis methods should be:

- simple
- robust (as few model assumptions as possible)
- focused on a clinically relevant alternative
- able to evaluate the treatment effect and provide a confidence interval

Analysis methods

Common methods for two-arm trials: Two-sample tests

- **Continuous outcomes:** Welch t-test
- **Binary outcomes:** two-sample test of proportions
- **Time-to event outcomes:** logrank, Cox model with group as predictor, weighted logranks

Rank tests such as Wilcoxon or Kolmogorov-Smirnov are not suitable (lack of treatment effect)

Adjusting for baseline

- Suppose a continuous outcome is measured twice on each participant:
  - At baseline (randomization): Y_i^0
  - At the end of the follow-up: Y_i^1
- Treatment effect: $\theta = \mathrm{E}[Y_i^1 \mid \text{treatment}] - \mathrm{E}[Y_i^1 \mid \text{control}]$
- Treatment effect can be estimated
  - from Y_i^1 by a two-sample test (ignoring Y_i^0)
  - from $Y_i^1 - Y_i^0$ by a two-sample test (change from baseline)
  - most efficient approach: linear model

Adjusting for baseline

- Recommended approach: Use the model

$$Y_i^1 = \mu + \theta \cdot I(\text{treatment}) + \beta Y_i^0 + \epsilon_i$$

  with sandwich variance estimator
- Advantages: robust, distribution-free approach, provides the best power for testing θ