NMST532 Design and Analysis of Medical Studies

Slide set II.

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Statistical aspects of Phase III clinical trials

- We will focus on Phase III clinical trials
- Phase III trials are randomized experiments comparing an experimental therapy (new drug, a novel treatment regimen) to a standard therapy (current practice) or placebo (no therapy)
- We will describe issues that are related to the role of the statistician
  - at the planning stage
  - during the conduct of the trial
  - at the analysis stage
- Some aspects are also relevant to Phase I and II trials, or observational studies in epidemiology and medicine

Clinical trial protocol

- Clinical trials are conducted according to a protocol that describes all aspects of the study
- Among attachments to this course are: example Phase III protocol and a contents of a typical protocol
- A statistician must be involved in the development of the protocol from the very beginning

Important parts of the protocol

- Study objectives
- Study endpoints
- Study design
  - treatment assignment
  - blinding
  - follow-up
- Study population
- Endpoint assessment
- Statistical considerations
  - sample size and power
  - analysis methods

Study objectives

- **Study objectives (aims)** specify goals of the study, scientific hypotheses to be verified
- Primary objective: a single hypothesis about the effectiveness of the experimental drug/therapy
- The primary objective decides whether the new drug will be approved or not
- Secondary objectives: additional supplementary hypotheses about the potential effects of the drug
- There may be multiple secondary objectives, they have no direct influence on the approval decision

Study endpoints (outcomes)

Variables to be measured in order to assess the objectives of the study

- Primary endpoint (outcome): a single variable chosen to measure the effect of the experimental drug specified in the primary objective
- Secondary endpoints (outcomes): additional variables to be measured
  - as alternative ways to assess the effect in primary objective
  - to evaluate the secondary objectives

Study endpoints must agree with the study objectives

Hard endpoints

Variables that can be measured objectively, with minimal assessment error, cannot be manipulated and are immediately relevant to the well-being of the patient

- death
- time to a serious undesirable event (relapse of tumor, heart failure, some life-threatening condition, etc.)

Hard endpoints are preferable but sometimes they cannot be used:

- the drug cannot be expected to affect a hard outcome but may still be beneficial in other ways
- the sample size or follow-up duration would be excessively large

Soft endpoints

Variables that lack some of the properties of hard endpoints

- are self-reported (pain, quality of life)
- are subjectively assessed (hospitalization, need for serious surgery)
- are less relevant to the patient (blood pressure, ECG, detection of pathogenic bacteria, some screening procedure)
- are not entirely reliable (certain laboratory procedures)

Surrogate endpoints

Variables that are not immediately relevant to the patient but are related to future more serious outcomes

- blood pressure, cholesterol levels
- presence of cardiac arrhytmias
- measurements of various blood markers
- ultrasound assessment of atherosclerosis

Surrogate endpoints are dangerous and should only be used when no more relevant endpoints are available. Results obtained on surrogate endpoints may be different from the true long-term effects of the drug.

Study population

The protocol includes eligibility criteria (inclusion and exclusion rules) that clearly define who can and who cannot participate in the study.

The study population should be selected with the following considerations

- must have the condition (disease) of interest verified
- must not be too ill to complete the study
- must not be in particular danger of serious adverse events
- must be likely to benefit from the therapy (if effective)
- there must be a chance of detecting the desired effect

Study population

The choice of the study population is also important to consider from the following aspects

- is there enough patients who satisfy the eligibility criteria?
- how quickly can be patients enrolled?
- what is the expected enrollment duration?

If enough patients cannot be enrolled from a single center, multi-center trials are conducted.

Treatment assignment

Treatment is assigned to the participants by randomization, usually with equal probability to be assigned to each treatment arm.

- Randomization methods are the responsibility of study statistician
- It is essential to guarantee that randomization cannot be manipulated or guessed
- Random assignment is usually done by a computer program accessible by internet, phone or other methods
- Before randomization, eligibility must be verified
- Randomization with equal probabilities alone assures approximately equal sizes in each arm and prevents confounding; the estimated treatment effects are causal

Blocked randomization

Assures better balance in sample sizes

- choose an even block size, e.g., 2 or 4
- instead of randomizing each patient separately, randomize the whole block while keeping balance
- with block size two, randomize between {AB} (the first patient gets treatment A, the next gets B) and {BA} (the first gets B, the second gets A)
- with block size four, randomize between {AABB}, {ABAB}, {ABBA}, {BAAB}, {BABA}, {BBAA}
- block sizes may randomly vary to prevent predictability of randomization outcomes

Variants of randomization

Stratified randomization

Perform block randomization within subgroups, e.g. men vs. women. This assures balance in randomization outcomes in the subgroups.

- Blocked and stratified randomization are popular
- They are important with small sample sizes (e.g. 20–30)
- With large sample sizes ($>$ 100) common in Phase III trials, these methods are not necessary
- Blocked randomization may violate the assumption of independence between participants

Blinding

Blinding means hiding the randomization result from the participants and study staff

- Blinding assures equal approach to all trial participants during the study (visit schedule, assessments of outcomes and adverse events, dropouts)
- Who should be blinded: patient, physicians, study staff, statisticians
- Who is not blinded: pharmacist, DSMB (Data and Safety Monitoring Board)
- Blinding can be broken if adverse events or serious health problems occur
- Procedures for unblinding must be described in the protocol
- All data are unblinded after the study is closed, data are cleaned, databases are locked and final analysis is about to start