Design and interpretation of clinical trials

Week 3 Outcomes

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Hierarchy of outcomes (endpoints)

- Primary outcome

  Reflects objectives and primary hypothesis

  Design variable

  Related to stage/type of the research

  - Relevant and likely to be influenced by treatment
  - Accurate and reliable measurement
  - Evaluate in all participants
  - No bias
  - Power considerations: variability, frequency, anticipated differences

- Secondary outcome

  Other important potential treatment effects (defined safety outcomes, mechanism of effect)

  Allows more complete evaluation (risk-benefit)

- Other outcome

  Other data on patient's health or study participation (compliance)

  Exploratory

Objective & subjective outcome

- Objective: clinical events or measurements that are definitive, require little or no subjective judgments

  Rigorous definitions to limit confirmation

  May include test results for confirmation

- Subjective: assessments that rely on judgment

  Karnofsky score, histological evaluations, need for medications

  Masking more important

Influence of outcomes on design

- Efficacy & effectiveness trial

  Efficacy trials are usually those that are looking in to be able to evaluate the condition under the best of all circumstances: dose this intervention change outcomes given sort of benefit.

  Effectiveness trials are looking how intervention will work in a more real world.

Considerations for design: 3Bs

- Biology: does outcome reflect a clinical relevant fact/change
- Biostatistics: detectable difference between group is plausible and practical
- Budget: afford total N and to measure it reliably in every participant

Features to "protect" outcome

- Protect against bias by randomization to treatment group
- Defined primary outcome : avoid hoc definition or post hoc selection of primary outcome
- Standard methods for measurement
- Standard follow-up schedules: avoid differential follow-up by design or default
- Masking of patients, clinicians, and/or evaluators
- Limit observer variation
- Analyze all events from all patients

Analysis issues in clinical trials

- Analyses by assigned treatment (intention to treat , ITT)

  Analyze data based on purely on randomization.

  Ignore ineligibility, complete nonadherence, treatment terminations, treatment witches, partial adherence.

  ITT analyses require ITT data collection philosophy.

  - Data is collected per protocol regardless of adherence
  - Other analyses can be done on data collected for ITT

  We should not adjust adherence.

- Subgroup analyses

  It is necessary to check the consistency of treatment effect across subgroups. (demographic groups, disease groups)

  Stratification:

  - Estimation of treatment effect separately in subgroups.

- Allows testing whether relative treatment effect is significantly different from 1

Test for interaction

- Use of main effect and interaction terms in statistical model
- Allows estimation of subgroup treatment effects
- Tests whether subgroup treatment effects are statistically different

Important subgroups that may have an influence on the treatment effect should be specified in the protocol and statistical analysis plan.

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Week 4 Ethical issues on clinical tirals

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Equipoise

Genuine uncertainty regarding the comparative therapeutic merits of each intervention being tested.

- Theoretical equipoise: evidence of benefits of each therapy is well balanced.
- Clinical equipoise: no consensus within the expert clinical community on the preferred therapy.

Criteria for IRB approval

- Risks to subjects are minimized
- Risks are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Consent obtained and documented
- Adequate provisions made to protect privacy and maintain confidentiality
- Appropriate safeguards for vulnerable populations
- Adequate provision made for data monitoring

Basic elements of consent

- Purpose of research
- Reasonably foreseeable risks
- Benefits that may reasonably be expected
- Alternative courses of treatment
- Confidentiality of records
- Compensation for injury
- Contact information
- Voluntary participation, withdrawal

Selection of control therapy

- Placebo orthodoxy

  Placebo should be used unless there is an increased risk of serious harm (death or irreversible morbidity) in the absence of therapy.

  Arugument:

  - Without a placebo group, the finding of no difference between new and standard therapy is often misleading or uninterruptable
  - Placebo design is more efficient in determining efficacy
  - Standard of care is not universal

- Active control orthodoxy

  If an effective therapy exists, the use of placebo should be prohibited.

Argument: The clinical relevant question is not whether a new therapy is better than nothing but whether a new therapy is better than a standard treatment.

Quiz 4

1. In clinical trials today, ethics are an important consideration when designing and conducting a study.

   - (●) True
   - ( ) False

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2. Individuals are entitled to ask any questions and voice any concerns to the study staff before deciding to participate in a study.

   - (●) True
   - ( ) False

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3. Study participants are required to provide study staff with a good reason in order to withdraw from a study.

   - (●) False
   - ( ) True

4. In situations where the evidence clearly indicates that one treatment is superior to another, investigators should feel compelled to conduct another study in order to confirm these findings.

   - (●) False
   - ( ) True

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5. Before a study begins, all eligible participants should be aware of the known potential benefits and harms of participating in the study.

   - (●) True
   - ( ) False

6. The principle of distributing the benefits and burdens of the research fairly across study participants corresponds to which of the following basic ethical principles in the Belmont Report?

- ○ Respect for persons
- ○ Benificence
- ◉ Justice

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7. Research activities involving human subjects must be approved by an institution's Institutional Review Board (IRB) before those activities can be performed.

- ○ False
- ◉ True

8. If a study participant is uncomfortable with any part of the study protocol, the investigators are required to modify those aspects of the study for that particular study participant, even if the study has already been approved by the IRB.

- ◉ False
- ○ True

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9. HIPAA guidelines should be adhered to when transferring data.

- ○ False
- ◉ True

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10. All clinical trials should include both a placebo control and an active control.

- ◉ False
- ○ True