Clinical Trials Development and Design

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- What is a clinical trial?
- Study objectives
- Study population
- Basic study designs
- Randomization
- Blinding

What is a clinical trial?

- Any investigation in human subjects intended to discover or verify the clinical... effects of an investigational product, and/or identify any adverse reactions to an investigational product...with the object of ascertaining its safety and/or efficacy.

International Conference on Harmonization; Draft Guideline on Good Clinical Practice

What are the Features of a Clinical Trial?

- study using human subjects
- prospective rather than retrospective
- one or more *interventions* (e.g. prophylactic, diagnostic or therapeutic agents, devices, regimens, procedures)
- must contain a *control group*
- ideally, *randomized* and *double blind*

Study objectives

- each clinical trial must have a primary question the investigation seeks to address
- general objective is usually obvious (e.g. safety and effectiveness)
- the primary question as well as all secondary questions should be clearly defined and stated in advance

Study objectives - Examples

- Demonstrate an improvement in survival for patients implanted with an ICD, defined as a 46% reduction in the two-year mortality rate
- In a study of atherectomy vs. balloon angioplasty, demonstrate that the rate of restenosis at 6 months is reduced 20% by atherectomy

Study objectives - Primary question

- The primary question
  - is the one the study is most interested in answering
  - is used to determine sample size
  - usually framed in the form of a hypothesis

Study objectives - Specifying hypotheses

- Hypotheses for a two-sided test to demonstrate a difference between interventions
- $H_0 : S_T = S_C$
- $H_A : S_T \neq S_C$
- Want to reject the null hypothesis of no difference

Study objectives - Specifying hypotheses

- Hypotheses for a one-sided test to demonstrate "equivalence" between interventions
- $H_0 : S_T < S_C$
- $H_A : S_T \geq S_C$
- Want to reject the null hypothesis that the new intervention is worse

Study objectives - Secondary questions

- All secondary questions, like the primary question, should be stated in advance
- may be related to the primary question (e.g. cause-specific death in a study of mortality)
- may be related to a *subgroup* of patients

Study objectives - Secondary questions

- Results from subgroup analyses should be considered with caution
  - number of patients in a subgroup are usually too small to show any difference
  - if enough statistical tests are done, some will be significant by chance

Study population

- The study population is the subset of the general population defined by the *eligibility criteria*
- Eligibility criteria and reasons for them should be stated in advance
- Identify patients who have the potential to benefit from the intervention

Study population

- Most interventions are likely to have adverse effects; patients for whom the intervention is known to be harmful should not be enrolled
- Restrictive eligibility criteria could affect patient recruitment

Study population

- Those who volunteer for participation in clinical studies are different from non-volunteers
- All participants must sign informed consents
- Helpful to maintain a log of all patients eligible but not enrolled

Basic study designs

- A fundamental requirement in scientific investigations is the need for a *control*
- In a *parallel design* patients are assigned to one of the interventions (one of which is the control); patients are followed *prospectively*
- In a *paired design* patients receive both the experimental and control intervention (perhaps at different points in time)

Basic study designs

- *Randomized controlled clinical studies* are the standards against which all other studies are compared
- Randomization assigns patients to either the intervention group or control group “with the same probability”

Basic study designs - Randomized controls

- Advantages of randomizing treatment assignment
  - eliminates selection biases
  - produces comparable groups with respect to known (and unknown) risk factors
  - guarantees validity of statistical tests
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Basic study designs - Nonrandomized controls

- Patients are assigned to one of two groups, but not in a random fashion
- Patients are assigned *concurrently*
- Advantages: easier to convince patients and investigators to participate
- Disadvantages: potential of ending up with groups that are not comparable

Basic study designs - Historical controls

- New intervention is studied in all patients prospectively
- Results are compared to the outcome from a previous study of comparable patients
- Historical controls are nonrandomized, nonconcurrent

Basic study designs - Historical controls

- Arguments for historical controls
  - all patients receive the “new” intervention
  - greater participation from investigators, patients
  - shorter studies

Basic study designs - Historical controls

- Concerns when using historical controls
  - accuracy and completeness when collected
  - open to bias
  - changes in patient population or patient management over time

Basic study designs - Conclusion

- A historical control study is no substitute for a randomized control clinical trial

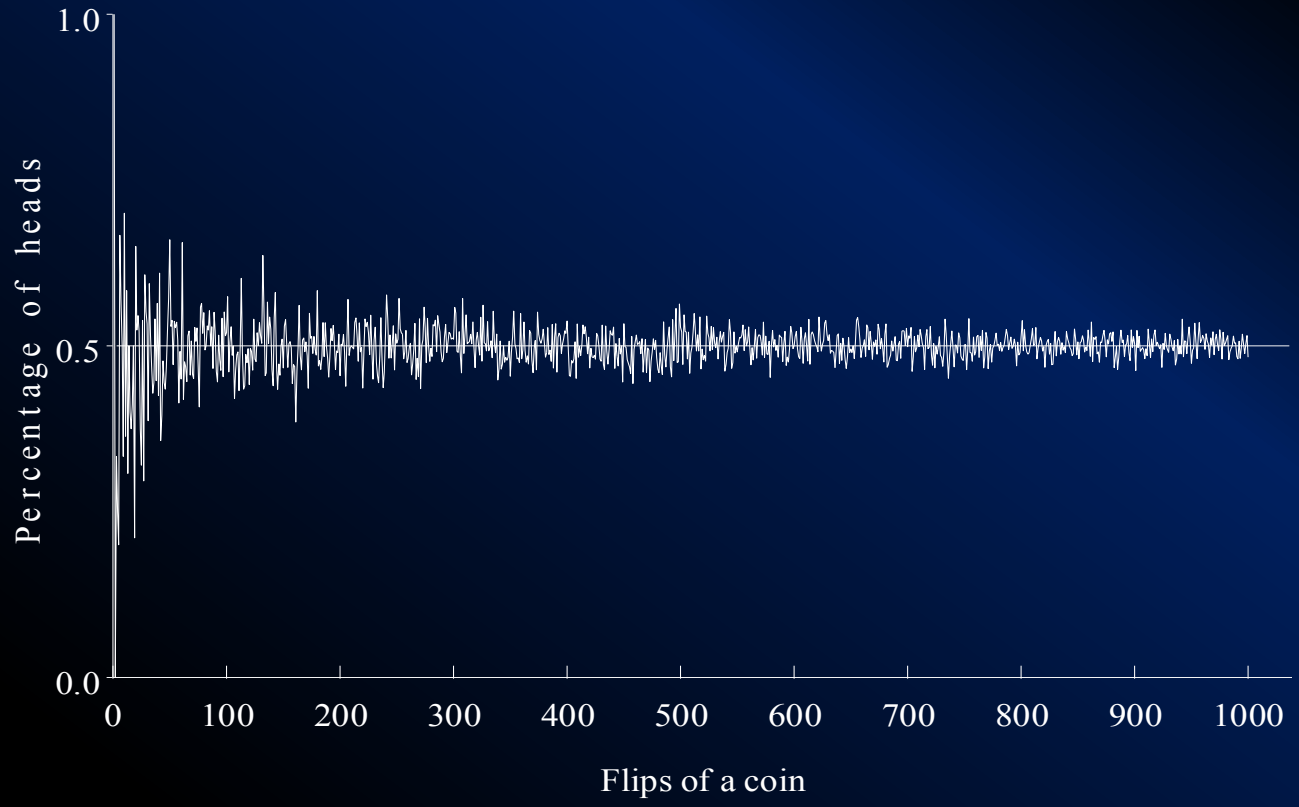
Randomization

- Randomization tends to produce study groups comparable with respect to known, as well as unknown, risk factors and guarantees the validity of statistical tests
- In its simplest case, randomization is a process by which each patient has the same chance of being assigned to either the new intervention or control

Randomization - Simple randomization

- Simple randomization - tossing of an unbiased coin
  - if heads, assign patient to new intervention; if tails, control
  - easy to implement
  - “in the long run,” equal numbers of patients are assigned to each group

Randomization - Simple randomization



Randomization - Blocked randomization

- Blocked randomization
  - used to avoid imbalance in the number of patients assigned to each group
  - guarantees that at no time in the study will the imbalance between the number of patients in each group be large, and at certain points in the study the numbers will be equal

Randomization - Blocked randomization

- For a study with two interventions
  - there are two blocks of size 2: AB, BA
  - there are six blocks of size 4: AABB, ABAB, ABBA, BBAA, BABA, BAAB
- One way of implementing is to randomly select a block size, then randomly select a block of that size

Randomization - Stratified randomization

- While randomization helps to produce groups that are comparable with respect to risk factors, there is a chance of finding an imbalance between some factors in small studies
- To prevent this from happening with important factors that can be identified upfront, *stratification* can be used

Randomization - Stratified randomization

- Identify factors for which it is important to have balance between intervention groups before starting the study
- Create separate randomization schedules for each stratum
- Do not use too many strata
- In most multi-center trials, randomization is stratified by institution

Blinding

- To avoid potential problems of bias a clinical study should be “double-blind”
- In a double-blind study, neither the patient nor the investigator know which intervention was assigned to the patient
- Studies in which the investigator is aware of intervention assignment but the patient is not are called single-blind

Blinding

- In a triple-blind study, monitoring committees are provide information on “interventions A and B” without knowing which is the new intervention and which is the control
- Device trials are less likely to be blinded

Conclusions

- Formulate a specific question to be answered by the study
- Identify the study population
- Include a concurrent control group
- Randomize patients to intervention groups
- Consult a statistician

References

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