Clinical Trial Design: Overview Part I

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(Slides courtesy of BSE faculty)

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Welcome to this three-part series focused on clinical trial design and sample size justification.

Objectives

- Identify key characteristics of a clinical trial
- Identify ethical principles of clinical investigation
- Describe the main phases of clinical trial investigation

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Following the completion of this module, you will be able to

Identify key characteristics of a clinical trial
Identify ethical principles of clinical trials
Describe the main phases of clinical trials

Example 1

- Membrane sweeping at initiation of formal labor induction: A randomized controlled trial

  – *Obstetrics and Gynecology* 2006;107(3):569-577

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Before discussing design principles, let's begin with a few examples of clinical trial titles from the published literature that will highlight some of the terminology that we will be learning.

The first example is from a publication in the journal Obstetrics and Gynecology. The investigators report maternal and newborn outcomes from a randomized clinical trial investigating the effect of membrane sweeping versus no sweeping at initiation of formal labor induction.

Example 2

- Evaluation of epothilone B analog in advanced soft tissue sarcoma: a phase II study of the phase II consortium
  - *JCO* 23(13):3069-73,2005

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In a second example, published in the Journal of Clinical Oncology, investigators report results from a phase II clinical trial evaluating the biologic activity and safety of epothilone B analog in advanced soft tissue sarcoma.

Example 3

- Effects of oral L-carnitine administration in narcolepsy patients: a randomized, double-blind, cross-over and placebo-controlled trial.

PLoS One. 2013;8(1):e53707

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In a third example, investigators report the effects of oral L-carnitine administration among patients with narcolepsy using a randomized, double-blind, cross-over, placebo-controlled clinical trial.

Investigational Design

- Outline:
  - Question under investigation
  - Types of experimental studies
  - Advanced design topics: cluster randomization, intent-to-treat in longitudinal studies

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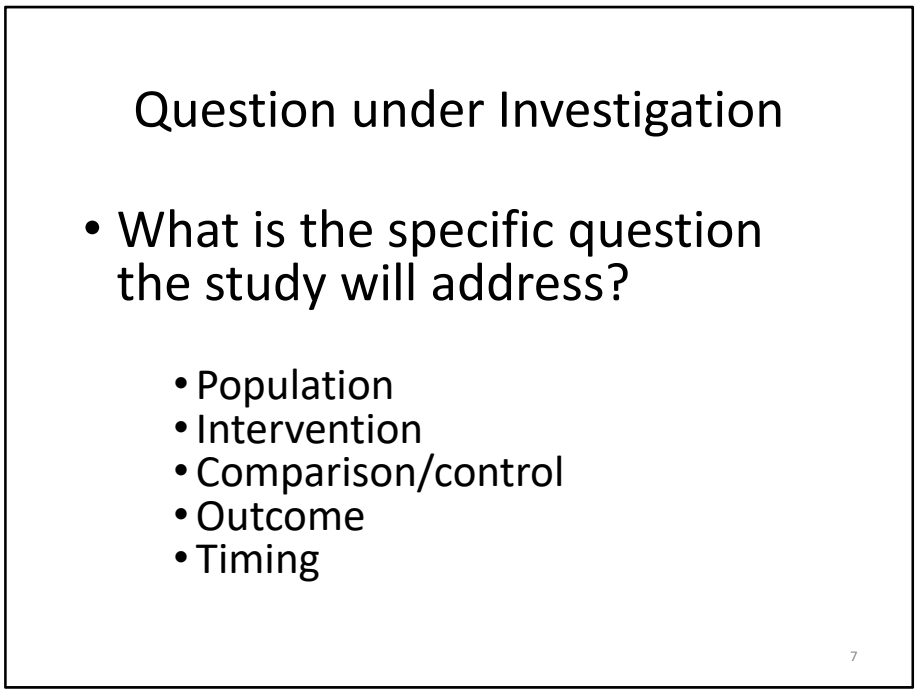
We will focus on three main areas of investigational design. We will begin reviewing key features of the question under investigation that drive the design and implementation of the clinical trial. Then, we will learn about a few of the main types and design features of clinical trials. Finally, we will briefly discuss advanced design topics.



The question under investigation will drive the clinical trial design.

When designing a clinical trial, it is critical to first establish a clear question of interest that includes five key components. First, we will define the clinical population of interest, specifying the clinical disease characteristics, demographic characteristics, and/or geographic characteristics that define the group of interest. Next, we will specify the intervention, including the agent or program, process or route of administration, and dose. Next, we identify the comparison or control program, which may be a placebo control or may be the standard of care to which the investigational agent will be compared. Then, we define the primary outcome of interest, which is the outcome of greatest importance for the clinical trial. Finally, we will identify the timing, including the duration of the intervention period and the time points for the outcome assessment.

Experimental Studies in Humans

- Clinical trials
  - "a prospective study comparing the effect and value of intervention(s) against a control in human beings" (Friedman, Furberg, DeMets, 1998)
- Key elements
  - Prospective
  - Comparative: assigned intervention versus control
  - Humans (ethical and safety issues, adherence to protocol)

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There are several key features of a clinical trial that distinguish it from other experimental studies. The definition provided by Friedman, Furberg and DeMets highlights the key features.

A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings. The key design elements are that a clinical trial utilizes prospective data collection, includes a comparison between an investigational intervention and a control, and is conducted in humans. Note that the prospective and comparative features may also describe experimental studies in basic science or animal study settings; however, the phrase "clinical trial" only refers to such studies among humans. When conducting research in human populations, there are important ethical issues, safety issues, and protocol implementation/adherence issues that need to be considered and are unique to human research studies.

Examples

- Prevention studies designed to prevent disease
- Diagnostic studies designed to look at ways to diagnose disease
- Treatment studies designed to study ways to treat disease

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Clinical trials may focus on different types of questions. Prevention studies are designed to test the efficacy and safety of interventions that aim to prevent disease. Diagnostic studies are designed to test the diagnostic accuracy of new tests. Treatment studies are designed to test the efficacy and safety of interventions aimed to treat existing disease.

Efficacy versus Effectiveness

- Efficacy
  - What the intervention accomplishes in an ideal setting
- Effectiveness
  - What the intervention accomplishes in actual practice (incomplete compliance to protocol)

More on this later (intent-to-treat)

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In discussing clinical trials, it is important to distinguish between efficacy and effectiveness. Efficacy refers to what the intervention accomplished in an ideal setting where we have carefully identified eligible patients, identified well-trained investigators, and provided optimal supportive care. In contrast, effectiveness refers to what the intervention accomplishes in actual practice where, for example, there may be less adherence with the intervention protocol, the patients may be more complex and variable in their disease states, investigators may have a broader range of areas of expertise, and resources may be more limited. We will begin by addressing the efficacy of an intervention, through a well-designed clinical trial, and then if the intervention is found to be efficacious, we will the evaluate the effectiveness through dissemination and implementation studies. We will revisit these topics when we discuss intention-to-treat.

Timing of Trials

- Trial must be feasible
  - Preliminary efficacy and safety data to justify design
  - Necessary tools and resources
- Must be a state of equipoise
  - Comfortable exposing patients to experimental or control arm
  - "uncertainty as to the benefits or harm from an intervention among the expert medical community" (FFD 1998)
- Intervention must be well enough established
  - Example: surgical procedure

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The timing of a clinical trial is an important consideration. First, the trial must be feasible; preliminary efficacy and safety data need to be available to justify the clinical trial design. Also, any necessary tools or patient and investigator resources need to be available.

When considering exposing patients to investigational agents, we need to be in a state of equipoise. This means that we are comfortable to exposing patients to either the experimental or the control arm. Equipoise means that there is uncertainty regarding the benefits or harms from an intervention as viewed by the expert medical community. While an individual clinician may have a strong opinion regarding the intervention's efficacy or safety profile, equipoise reflects the broader views of the expert medical community, which should be informed by published evidence. If there is sufficient information available such that the medical community is not in a state of equipoise, for example, if we consider an example where it has already been established that a certain type of infection can be effectively treated with antibiotic A, it would not be ethical to conduct a clinical trial that investigated the effect of antibiotic A versus placebo in the treatment of the infection.

Finally, the intervention must be well enough established to be implemented in a consistent manner, ideally by multiple investigators. As an example, some surgical procedures are highly technical that may require further development or training before a clinical trial could be conducted using multiple surgeons.

Ethics of Human Medical Research

- State of equipoise
- Informed consent
  - Inform patient of study aims, procedures (standard of care and experimental), risks, benefits (self and population at large), use of information or biologic specimens, alternatives
  - Patient decides whether to be involved or not
- Beneficence
- Justice
- Data monitoring
  - Interim analysis of outcome and safety data

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When conducting clinical trials in humans, we need to keep several ethical principles in mind. As previously discussed, before initiating a clinical trial, we should be in a state of equipoise regarding what is known about safety and efficacy of the intervention. Second, as investigators, we need to preserve patient autonomy. We do this by implementing an informed consent process whereby patients are informed of study aims, the planned procedures distinguishing between what is standard of care and what is experimental, risks, benefits to the patient and to the population at large, use of information or biologic specimens, and alternatives to trial participation. After discussing this information, patients then decide whether to participate in the clinical trial or not.

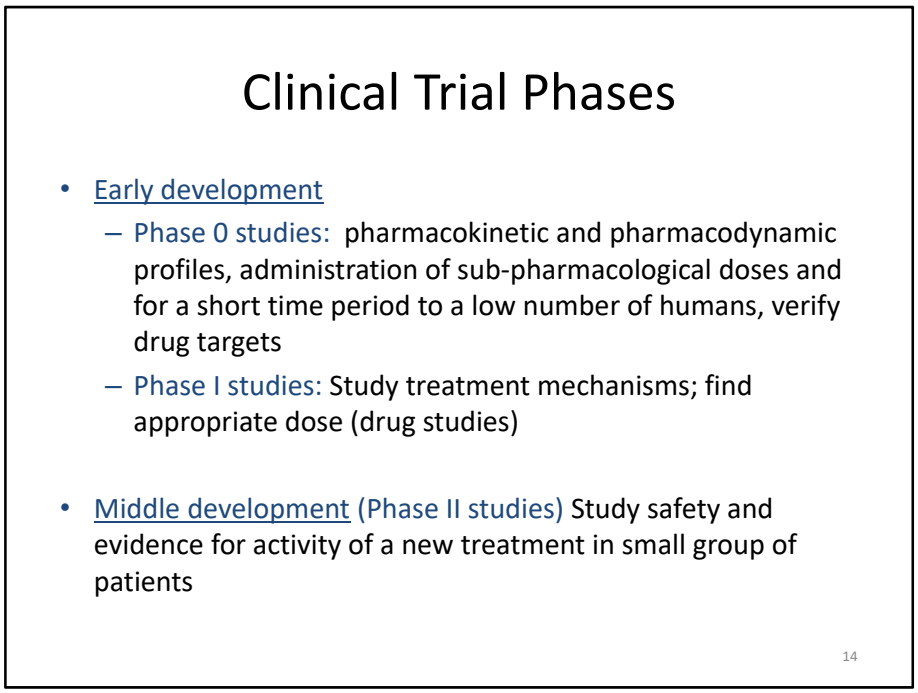
Another principle is beneficence. This relates to the balance between expected benefit and harm. As investigators, we will ensure that the methods and interventions that we use during the course of the clinical trial result in an appropriate balance between benefit and harm. This balance between safety and efficacy will differ among clinical settings. For example, we may tolerate higher levels of toxicity when investigating chemotherapeutic agents among cancer patients than what would be acceptable when considering a study of a dietary intervention to reduce obesity among grade school children.

The next principle is justice. When identifying target populations for clinical trials, it is important to allow participation of a broad population, to the extent that is relevant and

ethical to the given clinical question, by not excluding patients based on gender, race, ethnicity, or age as an example. It is also important to ensure that the patient population that is bearing the burden of the clinical trial investigation is the group that is likely to benefit from the clinical trial results. As an example, it is not ethical to only enroll prisoners or institutionalized individuals in clinical trials of investigational agents that will be used in broader populations.

Finally, as we accrue information during the conduct of a clinical trial, we will carefully monitor the accruing safety and efficacy data to determine if the balance between risks and benefits is still reasonable. If, for example, we find that the percentage of patients who develop severe complications from an investigational drug is unacceptably high, we may need to modify the protocol and consider a lower dose or different administration.

Now, with that background in mind, we will discuss the main phases of clinical trials. The general objectives of a clinical trial differ depending on the phase of the clinical trial.



The clinical trial phases are most relevant for drug development trials.

We begin with early development studies, that include Phase 0 and Phase I trials.

Phase 0 trials aim to describe the pharmakokinetic and pharmacodynamic profiles of drugs. A sub-pharmacological dose of the agent is given for a short period to a low number of patients. The main objective is to determine if the drug reaches the target in the body. For example, investigators may want to determine if an oral agent reaches the anatomic or cellular target of interest.

Phase I studies focus on understanding treatment mechanisms. Often times, the main objective is to identify the maximum tolerated dosage of an agent. These studies are often small in size, typically enrolling 20-60 patients.

Following early phase development, the agent then moves to middle development studies, which involve Phase II studies. Phase II studies focus on acquiring safety and preliminary efficacy data. Often, the efficacy endpoint includes what is termed a biologic endpoint, which might include tumor size, a surrogate marker, or biomarker levels such as cholesterol levels, as an example. These are endpoints that can be attained in a short period of time, compared to the ultimate, hard endpoint that might take years to develop, such as cancer

recurrence or death. These studies also typically involve a small number of patients. If the agent is found to have a promising activity level based on the biologic marker, and is reasonably safe, it will then move forward to Phase III testing.

Clinical Trial Phases (cont.)

- Comparative studies (Phase III studies): Compare the efficacy of two or more different treatments
- Late development (Phase IV studies): Expanded safety studies, designed to identify uncommon side effects and interactions with other therapies

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Phase III clinical trials are comparative, involve a larger number of patients than early or middle phase studies, and typically focus on hard clinical endpoints of interest. Design features of Phase III clinical trials will be the focus of the next video in this series.

After demonstrating efficacy and safety based on Phase III clinical trials, the agent will move to Phase IV, or late development, testing. These studies involve expanded use of the agent in clinical practice. The primary interest focuses on identify adverse events that were not evident from smaller, prior clinical trials. It may be that only after broader implementation that an agent is found to have an unacceptable adverse event. This discovery may lead to the product being recalled from the market. Keep in mind that with broader dissemination of the agent, it is more likely that the patients receiving the agent will have more complicated co-morbid conditions and concomitant medication practices than the patients who were enrolled in the Phase III clinical trials.

Summary

- Clinical trials are prospective, comparative and are conducted in human populations
- When conducting research among human populations, principles of equipoise, autonomy, beneficence, and justice guide our design and implementation approaches
- Clinical trial investigation progresses from early (Phase 0 or Phase I), middle (Phase II), comparative, to late studies, where each phase has a different objective and design

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In summary, clinical trials are prospective, comparative and are conducted in human populations. When conducting research among human populations, principles of equipoise, autonomy, beneficence, and justice guide our design and implementation approaches. Clinical trial investigation progresses from early (Phase 0 or Phase I), middle (Phase II), comparative, to late studies, where each phase has a different objective and design.