Drug research an clinical trials

Purpose of Clinical Trials

- assessment of safety and drug efficacy
  - experimental treatments
  - new combinations of drugs
  - new approaches to surgery or radiation therapies
  - better disease prevention approaches
  - better diagnostic approaches

Human Subject Protection Guidelines

- International Conference of Harmonisation (ICH)
  Brings together the regulatory authorities of Europe, Japan, and the US to discuss scientific aspects of human research.
- Good Clinical Practices (GCP)
  Defines the roles and responsibilities of clinical trial sponsors, investigators, and monitors.
- Declaration of Helsinki
  was developed by the World Medical Association (WMA), as a set of ethical principles for the medical community regarding human experimentation
- Nuremburg Code
  set of principles for human experimentation set as a result of the Nuremberg Trials at the end of the second world war. Specifically, they were in response to the inhumane Nazi human experimentation carried out during the war by individuals such as Dr. Josef Mengele.

Good Clinical Practices (GCP)

- international ethical and scientific standards setting the minimum requirements for the development, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that involve the participation of human subjects

Types of Clinical Trials

- Treatment
- Prevention
- Screening and early detection
- Diagnostic
- Genetics
- Quality-of-life / supportive care

Treatment Trials

- test safety and effectiveness of new agents or interventions
- possible benefits:
  - early access to new treatments
- possible risks:
  - occurrence of unknown side effects

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Prevention Trials

- for people at risk of developing disease
- action studies vs. agent studies
- possible benefit:
  - early access to new interventions
- possible risk:
  - unknown side effects and effectiveness

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Screening and Early-Detection Trials

- assessment of new means of detecting disease earlier in healthy people
- possible benefit:
  - detecting disease at an earlier stage, resulting in improved outcomes
- possible risks:
  - discomfort and inconvenience
  - exposure to x-rays or radioactive substances if an imaging technique is studied

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Diagnostic Trials

- develop better tools for classifying types and phases of disease (e.g. cancer) and managing patient care
- possible benefits:
  - new technology may be better and less invasive
  - earlier detection of recurrences
- possible risk:
  - may require people to take multiple tests

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Genetics Trials

- to determine how one's genetic makeup can influence detection, diagnosis, prognosis, and treatment
- to broaden understanding of causes of cancer
- to develop targeted treatments based on the genetics of a tumor

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Quality-of-Life / Supportive Care Trials

aim:

- to improve quality of life for patients and their families
- possible benefit:
  - early access to new treatment
- possible risk:
  - may not benefit from participation

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Pre-clinical Phase

- involves *in vitro* (test tube or laboratory) studies and trials on animal populations
- wide ranging dosages of the compounds are introduced to the animal subjects or to an *in vitro* substrate
- obtain preliminary efficacy and pharmacokinetic information
- decisions are made during this phase regarding further development of the test compound, test item, or test article

Phases of Clinical Trials

Category	# of Participants	Purpose
Phase I	Less than 10	Tests how to administer a new therapy, exam, or preventive option
Phase II	30-40	Test patients responses to a new therapy, exam, or preventive option
Phase III	100-1000+	Compares new therapy exam or preventive option to a standard one
Phase IV	Varies	For marketing purposes, to compare the effectiveness of two therapies already on the market or to study new uses of therapies

Phase I

- First step in testing in humans.
- Researchers look for safety and potentially harmful side effects.
- Usually include only a limited number of human subjects (20-80).
- This phase of testing usually takes several months.

Phase II

- Once a drug has shown to be safe, then it must be tested for efficacy.
- This phase may last from several months to two years.
- Usually involves several hundred patients
- Most of these trials are *randomized* trials
- Only about 1/3 of these studies successfully complete both phase I and phase II due to poor patient activity or toxic effects.

Phase III

- Randomized control trials on large patient groups (300-3000).
- Compare the results of the patients on the experimental trial to those patients utilizing standard diagnostic studies or treatment
- Studies move into this phase only after a diagnostic agent, modality, or treatments have shown promise in phase I and II trials.
- These trials are typically *multi-center* trials.
- Many phase III trials are *randomized* and *blinded.*

Phase IV

- **Involve safety surveillance and ongoing technical support of a drug.**
- **Sometimes mandated by the Regulatory authorities for additional testing including interactions with other drugs and testing on certain populations.**
- **Adverse effects detected by Phase IV trials may result in withdrawal or restriction of a drug -recent examples include Vioxx.**
- **... ? marketing**

Clinical Trial Standard Language

Protocol	The planned course of action for the clinical trial. The protocol is established prior to the start of the trial and states the number of participants, eligibility requirements, agents that will be used, dosages, duration, how data is collected, etc.
Investigator	A researcher in a clinical trial.
Sponsor	The part of parties responsible for funding the clinical trial.
Institutional Review Board / Ethics Committee	An independent board of scientists, physicians, and nurses who review the clinical trial protocol to ensure patient safety.
Informed Consent	A patient's decision to participate in the clinical trial after being informed of the potential benefits and risks of participation. Participants may withdraw their consent at any time and leave the trial.
Double blind	Term used to describe a clinical trial in which neither the patient nor the researcher knows which agents are being administered to which patients. This helps prevent bias.
Invention group	The group of participants receiving the new preventive or treatment agent that is being evaluated in the clinical trial.

Clinical Trial Standard Language, continued

Control group	The group of participants receiving a standard treatment or placebo (see below) that is being compared to the new agent in the clinical trial.
Randomization	Assigning participants by chance to either the intervention group or the control group. Randomization is often done with a computer.
Placebo	An inactive substance that may be given to participant sin a clinical trial. Sometimes called a sugar pill.
Follow-up	Monitoring of participants for a specified time after the clinical trial is completed.
Prospective study	A study of a group of patients that is conducted as they are undergoing a treatment or preventive measure.
Retrospective study	A study of a group of patients after they have already undergone a treatment or preventive measure. "Recall bias," unintentional inaccurate reporting of certain information, can sometimes influence a retrospective study.

Blinding

- **in a <u>single blinded</u> study, the patient does not know which arm of the protocol they have been assigned to**
- **this approach avoids bias because when people know what they are taking, it might change the way they react**

  Example: Patients who know that they are assigned to the "new treatment" group might expect it to work better and report hopeful signs because they want to believe they are getting well. This could bias the study by making results look better than they are.

- **prone to researcher bias**

Blinding

<u>double blinded</u> studies are those studies where neither the patient or the research physician know whether the patient is receiving the actual study drug or standard drug (or placebo).

- **all patients are informed of the possibility of being assigned to the placebo arm of a study**
- **patients are "unblinded" only if it becomes medically necessary prior to the end of the study**
- **double blinding prevents scientists from introducing any unconscious bias into the data collection process**

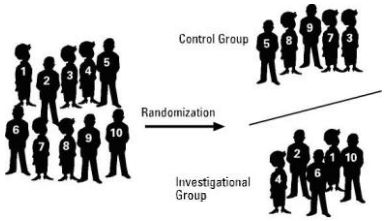
<u>triple blinded</u> studies:

- the patient, investigator and data-cleanup people are blind
- the statistician can only be partially blinded since he/she has to know which patients are in the same treatment group

Open Trials

- **Set-up where researchers and subjects know what treatment is being given**
- **Often used to test surgical procedures and medical devices, that by nature, cannot be done without subject or researcher knowing who is receiving the treatment**
- **More prone to error and bias than double-blind studies**

Randomization



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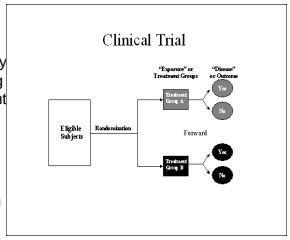
Randomization

- **Randomization** is the process by which patients are assigned a group for the Clinical Trial.
- Researchers assign patients by chance to either a group taking the new diagnostic or treatment agent. Similar to “flipping a coin”.
- Randomization helps avoid bias.
- The assigned groups are often referred to as “arms”.
- If one treatment is found superior, the trial is stopped so that the fewest patients possible receive the less beneficial treatment.



Types of Clinical Trials

- Controlled: One group receives the treatment and another group does not
- Randomized, double-blind trials
- Crossover trials
  Set-up where each participant gets both treatments being tested
- Open trials
- Orphan drug trials - Used to test drugs designed to treat rare diseases, tested on small number of participants who are very sick
  - If drug works, improved health is usually readily apparent

Crossover design

Placebo

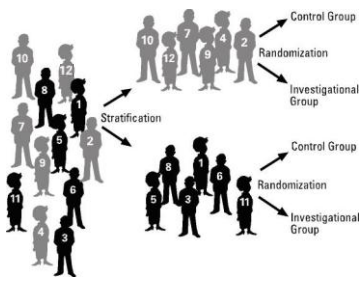
- in many studies, the new drug is compared to a **placebo**
- a **placebo** is a product that looks like the new drug, but it does not have the active ingredient in it
- people do not know that they are getting the placebo
- a component of every specific treatment effect can be attributed to the placebo response
- the question that a study should be asking is whether the treatment has any effect on outcome aside from the stress-relieving effect of study participation
- in actuality, a placebo effect is a psychosomatic effect brought about by relief of fears, anxiety or stress because of study participation
- it's not just the little white pill that brings about the effect; it's the additional attention and the belief that your condition might be being treated with a superior new treatment
- all outcomes affected by psychosomatics are prone to placebo effects

Clinical Trial Protocol

- **A study plan on which all clinical trials are based.**
- **Carefully designed to protect the health of participants**
- **Describes what types of people may participate in the trial (inclusion and exclusion criteria)**
- **Gives detailed schedule of tests, procedures, medications, dosages, and length of the study.**
- **Principal Investigator is responsible for assuring that the protocol is strictly followed for each participant**

Stratification

- categorizing subjects into subgroups by specific characteristics
  - enables researchers to look into separate subgroups to see whether differences exist



Ethics Committees

- independent institutions comprised of physicians, statisticians, community advocates, and others
- the role of the ECs is to do the following:
  - ascertain that clinical trials are scientifically worthy and that ethical guidelines are met
    - potential benefits for participants should outweigh risks
    - participants must be informed of all potential risks and agree to willingly participate and can drop-out at any time (called *informed consent)*
  - monitor the trial during its run and may even halt the trial if serious problems are reported
  - an EC can stop a clinical trial if there are safety concerns, inappropriate trial oversight, or if evidence becomes available that a new intervention is effective, in order to make it widely available

Informed Consent

- the process in which a patient learns key facts about a research study and then voluntarily agrees to take part or decides against it
- informed consent must be documented by the use of a written consent form approved by the EC
- consent forms must be signed by the subject or the subject's legally authorized representative
- a copy shall be given to the person signing the form

Consent Form Requirements

- **The consent form MUST include the following:**
  - **Statement that the study involves research**
  - **Explanation of the purposes**
  - **Expected duration of the subject's participation**
  - **Description of the procedures involved in the study**
  - **Identification of any procedures that are experimental**
  - **Risks or discomforts**
  - **Benefits**
  - **Alternatives to the research study**
  - **Statement of confidentiality**
  - **Statement about medical care and compensation should injury occur**
  - **Contact information for patients with concerns or questions**
  - **Statement that participation is voluntary and study withdrawal may take place at any time**

Barriers to Participation in Clinical Trials

Physicians and other health professionals may:

- Be unaware of appropriate trials
- Be unwilling to lose control of patient's care
- Believe that standard therapy is best
- Believe that clinical trials are more work

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Barriers to Adult Participation in Clinical Trials

Patients may:

- Be unaware of clinical trials
- Lack access to trials
- Fear, distrust, or be suspicious of research
- Have practical or personal obstacles
- Be unwilling to go against their physicians' wishes

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Clinical Trials Benefits & Risks

Possible Benefits of Trials	Possible Risks of Trials
• Having access to potentially more effective therapies than those currently available • Receiving quality medical care from leading physicians • Being closely monitored for possible negative effects • Sometimes receiving treatment at a reduced rate or free of charge • Helping to further new research that may result in significant medical advances • For patients in cancer therapy trials assigned to control groups, they still receive the top standard therapy available today	• Patients may not receive the therapy under investigation (may receive a placebo – inactive pill – instead) • The new therapy may not be more effective than the standard, thoroughly tested therapy • In Phase I trails, not knowing the safety consequences of the new therapy (risk is less in Phase III trials) • New therapy may have unexpected, possibly severe side effects or may be less effective than standard of care • Insurance companies may not cover all costs of clinical trials