



CLINICAL TRIALS

A Real World Application of the
Scientific Method

How do you know if the medicines you take are safe?

- All medical drugs, treatments, preventions and even medical devices have to go through a thorough testing process with human beings or animals before they are available to you
- This process is call a **Clinical Trial**.
 - an experimental epidemiological method.
 - an interventional study on individuals, usually on patients



First “Clinical Trials”

- Clinical Trials have a long history – even if not acknowledged as *Clinical trials*
- Formal record of clinical trials dates back to the time of the “*Trialists*”:
 - Dr. Van Helmont’s proposal for a therapeutic trial of bloodletting for fevers [1628]
 - A ship surgeon - Dr. Lind’s, trial of oranges & limes for scurvy [1747]
 - 1909: Paul Ehrlich - Arsphenamine
 - 1929: Alexander Fleming - Penicillin
 - 1935: Gerhard Domagk - Sulfonamide
 - 1944: Schatz/Bugie/Waksman – Streptomycin
 - By 1950, the British Medical Res. Council developed a systematic methodology for studying & evaluating therapeutic interventions

Core Components of Clinical Trials

- Most study medications, procedures, and/or other interventions
- Focus on unknowns: effect of medication
 - Must be done before medication is part of standard of care
 - Conducted early in the development of therapies
- Involve human subjects
- Most have a comparison CONTROL group
- Must have method to measure intervention
- Must review existing scientific data & build on that knowledge
- Test a certain hypothesis
- Control for any potential biases

Clinical Trial vs. Randomized controlled trial

- CT: "...a pre-planned clinical study of the safety, efficacy, or optimum dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques in humans selected according to predetermined criteria of eligibility and observed for predefined evidence of favorable and unfavorable effects."
- RCT: "...a [controlled] **clinical** trial that involves at least one test treatment and one control treatment, concurrent enrollment and follow-up of the test- and control-treated groups, and in which the treatments to be administered are selected by a random process, such as the use of a random-numbers table."

What is an RCT?

- Individuals from both groups are treated exactly the same
 - If sign differences, we can say they are due to treatment of interest
- Randomization list is created **before** trial begins
- Many ethical issues to consider when designing RCTs
 - Withholding treatment; experimental treatment; clinicians are hesitant to try something new if they have something that works

When Clinical Trials are Done

- When the margin of the expected benefit or the outcome of an intervention is doubtful or very narrow (10 to 30%) only.
- When the margin is large, obvious, and beyond doubt, it will be unnecessary to conduct clinical trials.

Sponsors

- Clinical trials are usually sponsored or funded by companies that make pharmaceuticals or medical devices.
- Trials can occur at sites as varied as hospitals, universities, doctors' offices, community clinics, or in the offices of clinical-trial contractors.



Objectives?

- **Intervention trials** determine whether experimental treatments or trials are safe and effective under controlled environments
- **Observation trials** address health issues in large groups of people in natural settings.

Types of Clinical Trials:

(as defined by the National Institutes of Health)

- Treatment Trials - test new treatments, new combination of drugs or new approaches to surgery or radiation.
- Prevention Trials - look for better ways to prevent diseases and disease recurrence.
- Diagnostic Trials - determine better tests or procedures for diagnosing a particular disease or condition (symptoms).
- Screening Trials - test the best way to detect or treat diseases (no symptoms).
- Quality of Life Trials - explore and measure ways to improve the comfort and quality of life of people with a chronic illness.

Differences between Screening and Diagnostic tests

	Screening tests	Diagnostic tests
Purpose	To detect potential disease indicators	To establish presence/absence of disease
Target population	Large numbers of asymptomatic, but potentially at risk individuals	Symptomatic individuals to establish diagnosis, or asymptomatic individuals with a positive screening test
Test method	Simple, acceptable to patients and staff	maybe invasive, expensive but justifiable as necessary to establish diagnosis
Positive result threshold	generally chosen towards high sensitivity not to miss potential disease	Chosen towards high specificity (true negatives). More weight given to accuracy and precision than to patient acceptability
Positive result	Essentially indicates suspicion of disease (often used in combination with other risk factors) that warrants confirmation	Result provides a definite diagnosis
Cost	Cheap, benefits should justify the costs since large numbers of people will need to be screened to identify a small number of potential cases	Higher costs associated with diagnostic test maybe justified to establish diagnosis.

Basic Research Terminology

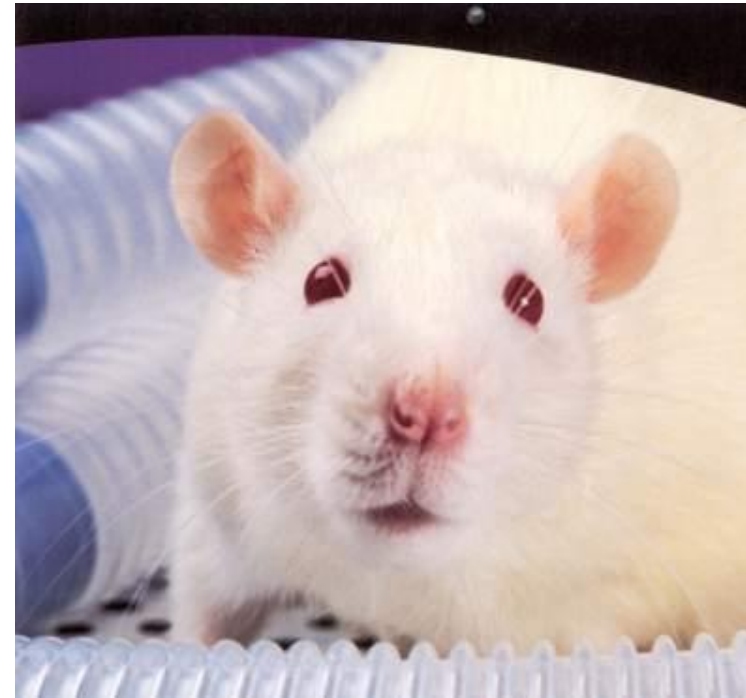
- **Retrospective:** Refers to time of data collection (past)
- **Prospective:** Refers to time of data collection (future)
- **Case Control Study:** Persons w/ disease & those w/out are compared
- **Cohort Study:** Persons w/ and/or w/out disease are followed over time

Terminology (Cont.)

- **Cross-sectional Study:** Presence or absence of exposure to possible risk factor measured at one point in time. Prevalence obtained.
- **Prevalence:** The # of new cases and existing cases during specified time period (how widespread).
- **Incidence:** The # of NEW cases per unit of a population at risk for disease occurring during stated time period (rate/risk).

Phases of Clinical Trials:

- **Pre-clinical trial** – research on a new drug or a new medical device or procedure, usually done on **animals**, to learn about mechanisms of action, determine how well the treatment works, and see if it is safe to test on humans.



Design of clinical trial

• **Selecting the reference population**



**Selecting the experimental population
(Exclude non-participants)**



**Selecting the study population
(Participants)**



Random allocation into



Intervention group



Comparison group



Apply intervention



No intervention



Uniform assessment of outcomes



Protocol (study plan)

- Study plan is carefully designed
 1. to safeguard the health of the participants and
 2. to answer the specific research question

- Protocol describes
 1. what types of people can participate,
 2. the schedule of tests, procedures, medications, dosages
 3. The length of study

Explaining the benefits

- Participants play active role in their own health care
- They gain access to the new treatments before they are widely available
- They obtain expert medical care
- They can help others by contributing to research



Explaining the risks

- Unpleasant, serious, or even life-threatening side effects
- Failure of treatment
- Time waste for the participants



Selecting reference population

- The population to which the results of the trial are applied and who benefits from the trial.
- It can be the whole or part of the country
- It can be any specific population like school children, specific age groups, sex groups or disease groups

Selecting Experimental Population

Criteria

A sample selected from the reference population as per the feasibility and practicability.

1. Sufficiently large to neutralize confounding variables
2. Non-response restricted to $<10\%^*$
3. Sufficient number of end-points, preferably measurable and objective type.
4. Feasibility to inform the participants and to do the follow-up throughout and also after the trial

The Study Population

- Actual participants on whom the trial will be conducted
- Drawn from the experimental population after excluding the non- participants
- **Inclusion /exclusion criteria**
- To identify appropriate participants and keep them safe
- Help ensure that researchers will be able to answer the questions
- Based on such factors as age, gender, the type and stage of the disease, previous treatment history, other medical conditions

Where do the people come from?

- Clinical Trials require people to volunteer to be tested - They are often paid.
- Would you volunteer to be a subject in a Clinical Trial?
- What if it meant you received a treatment for a disease that wasn't available to anyone else?
- What if it meant you weren't receiving effective treatment?



Phases of Clinical Trials:

- **Phase I**
- Researchers test an experimental drug or treatment in a small group of people (approximately 20-80) for the first time. The purpose is to evaluate its safety and identify side effects. If this is a veterinary study, it is conducted in animals.



Phases of Clinical Trials:

- **Phase II**

- The experimental drug or treatment is administered to a larger group of people/animals (approximately 100-300) to determine its effectiveness and to further evaluate its safety.



Phases of Clinical Trials:

- **Phase III**
- The experimental drug or treatment is administered to a large group of people/animals (300-3,000 or more) to confirm its effectiveness, monitor side effects, and compare it with standard or equivalent treatments.



Summary of Phases I-III

	# P's	Length	Purpose	% Drugs Successfully Tested
Phase I	20 – 100	Several months	Mainly Safety	70%
Phase II	Up to several 100	Several months-2 yrs.	Short term safety; mainly effectiveness	33%
Phase III	100s – several 1000	1-4 yrs.	Safety, dosage & effectiveness	25-30%

Placebos

- 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.
- Placebo effect
 - Psychological relief of symptoms, not true biological relief, is often reported
- Hawthorne effect
 - Sometimes the participants in comparison group may exaggerate the effects/outcomes to please the investigator or when they like the study or for some other reasons.

Research Concepts

- **Randomization** is the process by which patients are assigned a group for the Clinical Trial.
- Groups are assigned randomly, not purposefully to avoid selection and confounding biases.
- Some people will receive the new treatment, some may receive an already approved treatment, and some may receive a placebo.
- If one treatment is found superior, the trial is stopped so that the fewest patients possible receive the less beneficial treatment.

Research Concepts

- **Blocking is** done when the study population is heterogeneous consisting of men, women, patients with different levels of severity of illness and suspected to give results of varying frequency
- Done before random allocation.
- Sub –groups are stratified and blocked to make the trial more accurate.
- Participants are randomly allocated from these various blocks or groups so that the trial's internal validity will be increased.

Research Concepts

- A **Blind Trial** is a trial in which the patients do not know if they are receiving the treatment or a placebo.
- A **Double Blind Trial** is a trial in which the patients **and** the researchers do not know who is receiving the treatment.
- Assessors can also be blind



Approval must be gained:

- Once a drug has proven satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life.
- This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities like the U.S. Food And Drug Administration (FDA) so they can then grant the sponsor approval to market the drug, device or treatment.

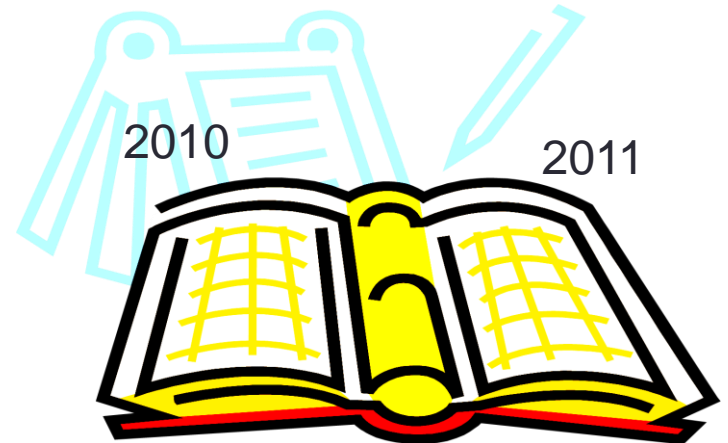
The Results!

- For approximately every 5,000 to 10,000 compounds that enter preclinical testing, only **one** is approved for marketing.
- Cost of the failures has to be borne by the price of the one success.



Phases of Clinical Trials:

- **Phase IV**
- After a drug is licensed (approved by the FDA) or treatment is launched, researchers track its safety, seeking more information about a drug or treatment's risks, benefits, and optimal use. These long-term studies involve large groups of participants and are designed to reveal if any unexpected side effects occur in a small percentage of individuals.



Crossover designs

- Each person serves as own control.
- Two period crossover.
 - 1/2 receive A first and 1/2 B.
 - Order of interventions excluded.
- Multiple Period crossover.
 - Order and sequence effects eliminated by design.
- Insertion of “Washout Period”.

EXPERIMENTAL DESIGN OF TWO PERIOD CROSSOVER

	Period 1	Period 2
Group 1	a	b
Group 2	b	a

	Period 1	2	3	4	5
Group 1	Baseline	a	wo	b	Control
Group 2	Baseline	b	wo	a	Control

Advantages of crossover

- Assessment of Each Individual Against Self as Control.
 - Reduces variability.
- Efficiency of Design
 - 2.4 X participants if parallel design used.

Disadvantages of crossover

Assumptions

- No carry over effects.
 - Carry over effects do occur.
- Completion of other experimental periods: no intervening events.
- Difficult to detect.
- Selling job results.

Timeline Estimate

- Some estimates on the amount of time it takes for this process in cancer treatment research:
- Pre-clinical Trials - 4.5 years
- Phases I-III - 8.5 years
- FDA Approval - 1.5 years
- Phase IV - Ongoing for the duration of the use of the drug



Costs

- On average, pharmaceutical companies are spending anywhere between \$100 and \$800 million per each drug tested!
- Spending on clinical trials in the U.S. in 2014: ~ 30-40 million before approval and again after approval

Table 1: Total Per-Study Costs (in \$ Millions), by Phase and Therapeutic Area [a] [b]

Therapeutic Area	Phase 1	Phase 2	Phase 3	Phase 1, 2, & 3 Subtotal [d]	FDA NDA/BLA Review Phase [c]	Phase 4	Total [d]
Anti-Infective	\$4.2 (5)	\$14.2 (6)	\$22.8 (5)	\$41.2 (3)	\$2.0	\$11.0 (12)	\$54.2 (10)
Cardiovascular	\$2.2 (9)	\$7.0 (13)	\$25.2 (3)	\$34.4 (10)	\$2.0	\$27.8 (4)	\$64.1 (6)
Central Nervous System	\$3.9 (6)	\$13.9 (7)	\$19.2 (7)	\$37.0 (6)	\$2.0	\$14.1 (11)	\$53.1 (11)
Dermatology	\$1.8 (10)	\$8.9 (12)	\$11.5 (13)	\$22.2 (13)	\$2.0	\$25.2 (7)	\$49.3 (12)
Endocrine	\$1.4 (12)	\$12.1 (10)	\$17.0 (9)	\$30.5 (12)	\$2.0	\$26.7 (6)	\$59.1 (7)
Gastrointestinal	\$2.4 (8)	\$15.8 (4)	\$14.5 (11)	\$32.7 (11)	\$2.0	\$21.8 (8)	\$56.4 (8)
Genitourinary System	\$3.1 (7)	\$14.6 (5)	\$17.5 (8)	\$35.2 (8)	\$2.0	\$6.8 (13)	\$44.0 (13)
Hematology	\$1.7 (11)	\$19.6 (1)	\$15.0 (10)	\$36.3 (7)	\$2.0	\$27.0 (5)	\$65.2 (5)
Immunomodulation	\$6.6 (1)	\$16.0 (3)	\$11.9 (12)	\$34.5 (9)	\$2.0	\$19.8 (9)	\$56.2 (9)
Oncology	\$4.5 (4)	\$11.2 (11)	\$22.1 (6)	\$37.8 (5)	\$2.0	\$38.9 (2)	\$78.6 (3)
Ophthalmology	\$5.3 (2)	\$13.8 (8)	\$30.7 (2)	\$49.8 (2)	\$2.0	\$17.6 (10)	\$69.4 (4)
Pain and Anesthesia	\$1.4 (13)	\$17.0 (2)	\$52.9 (1)	\$71.3 (1)	\$2.0	\$32.1 (3)	\$105.4 (2)
Respiratory System	\$5.2 (3)	\$12.2 (9)	\$23.1 (4)	\$40.5 (4)	\$2.0	\$72.9 (1)	\$115.3 (1)

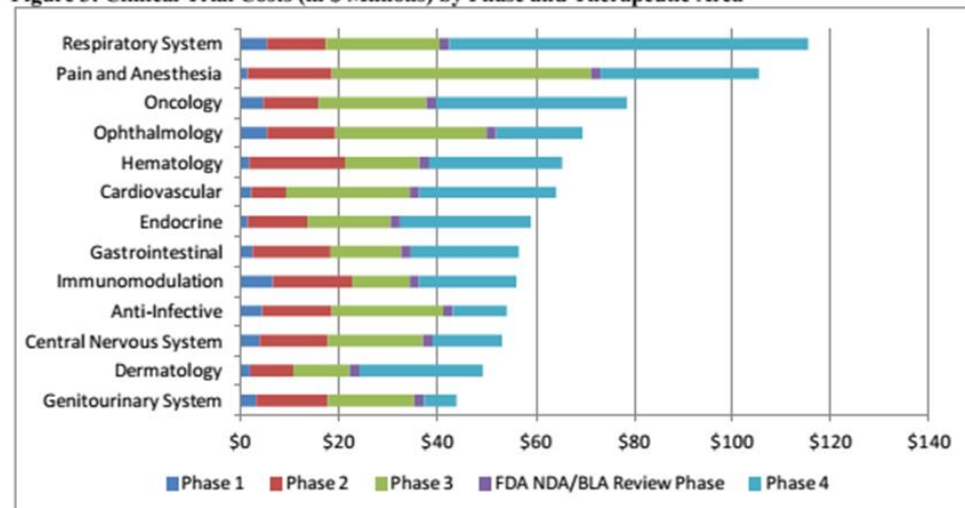
[a] The numbers in parentheses represent the rank in descending order.

[b] The cost for each phase assumes that a single trial (i.e., study) is conducted.

[c] The category represents the New Drug Application (NDA)/Biologic License Application (BLA) filing fee for an application requiring clinical data and does not include any establishment or product fees that the filing entity might need to pay in addition.

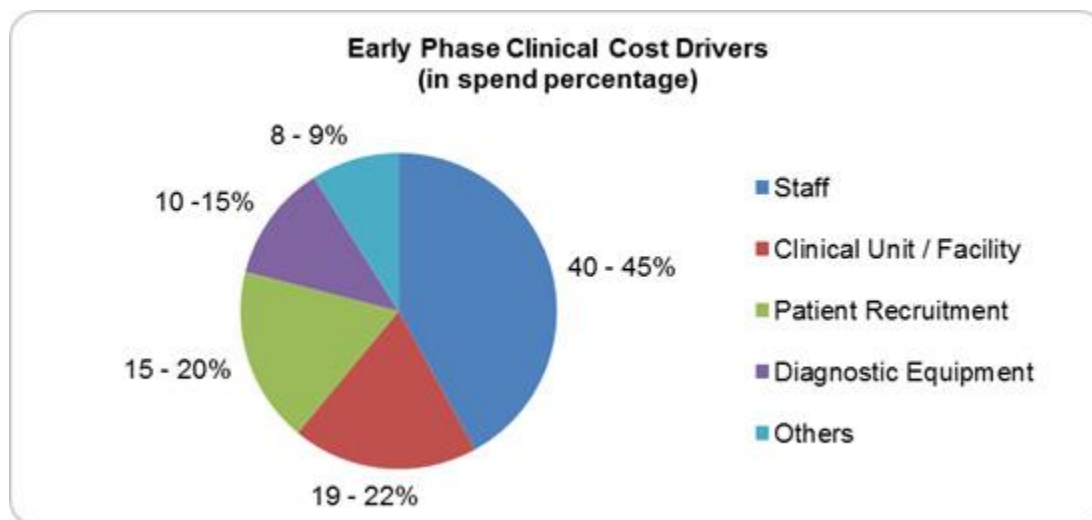
[d] Totals may not add up due to rounding.

Figure 3: Clinical Trial Costs (in \$ Millions) by Phase and Therapeutic Area



Costs

- Why would **anyone** spend that much money on drug development?
 - Why does it cost so much to conduct a clinical trial?
 - Why does it take so much time to conduct a clinical trial?



Follow-up

- Better compliance will lead to better validity, which in turn enables better generalizability
- Both the groups are similarly followed in all aspects like duration, type of follow-up

Treatment fidelity

- Is the intervention being delivered as planned?
- Operationalize the intervention
 - Manuals
 - Protocol – procedures regarding administration of the treatment
 - Assessment
- Training of interventionists
- Supervision of interventionists
 - Fidelity checks

Maintenance of compliance

- Selecting high risk people as participants in study population*
- Frequent contacts with the participants through phone calls, home visits, clinic visits
- Providing calendar packs to the participants and asking them to stick to calendar packs without fail.
- Giving incentives like free medical aid in future, giving some gifts.

Non-compliance

- Non-compliance decreases the statistical power of the trial which speaks about the validity (truth of the results)
- Extent of non-compliance is directly proportional to the duration and complexity of the trial.
- Compliance is difficult when the end –points are time taking like incidence of cancers or death

Preventing missing data

- Clear informed consent document and thorough informed consent process
- As few assessment appointments as possible
- Rapport between participants and study staff members
- When possible, get family members involved since they might be willing to help motivate participants to continue with the trial
- Work to continue to collect data even if the participant drops out of treatment

Handling missing data

- Intention-to-treat/Intent-to-treat analysis
 - Whole of the experimental population including non –participants, once randomized, whether they are participating in the trial , have to be considered for evaluation as intention is to treat all the people randomized
 - “Once randomized, always analyzed”
- Completer analysis
 - Only analyze data of participants who have completed the study

Assessment criteria

Whether the outcomes or end-points are single or multiple, subjective or objective, uniform & similar type of evaluation of end-points for both the groups is to be carried out.

- Subjectivity of the outcome e.g., reduction of pain, may lead to observer error and poor assessment.
- Double blinding eliminates observer bias to a large extent.

Participant Safety

- Human Subject Institutional Review Board (HSIRB)
- Data and Safety Monitoring Board (DSMB)
 - Group of independent experts (at least 3)
 - Role: To ensure that the trial is being conducted correctly and participants are not being harmed
 - DSMB members have the power to stop a trial
 - Early positive findings
 - Participants are being harmed (e.g., side effects)
 - Futility – Questions are not going to be answered
 - Low study power (# of recruited participants is low and/or many drop-outs)
 - A drug is not any better than one currently on the market
 - Something has changed such that the study cannot be conducted as planned