Introduction to Clinical Research

History of Clinical Trials

Module 1 Topic 1

What is Clinical Research?

Clinical research is a branch of healthcare science that determines the safety and effectiveness (efficacy) of medications, devices, diagnostic products and treatment regimens intended for human use. These may be used for prevention, treatment, diagnosis or for relieving symptoms of a disease.

Types of Clinical Research

- **Treatment Research** involves interventions such as medication, psychotherapy, new devices, or new approaches to surgery or radiation therapy
- **Prevention Research** is search for better prevention of occurrence or recurrence of disorders
- **Screening Research** is to develop better techniques to detect disorders
- **Quality of Life Research** explores ways to improve comfort and the quality of life for individuals with a chronic illness.

Types of Clinical Research

- **Genetic studies** aim to improve the prediction of disorders by identifying and understanding our genes and illnesses are related.
- **Epidemiological studies** seek to identify the patterns, causes, and control of disorders in groups of people.

- US FDA (2018)

What are Clinical Trials?

'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.

Clinical trials may be conducted on:
Experimental drugs, medical devices, vaccines cells and other biological products surgical and other medical treatments and procedures psychotherapeutic and behavioural therapies preventive care strategies and educational interventions.

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Australian Government
National Health and Medical Research Council

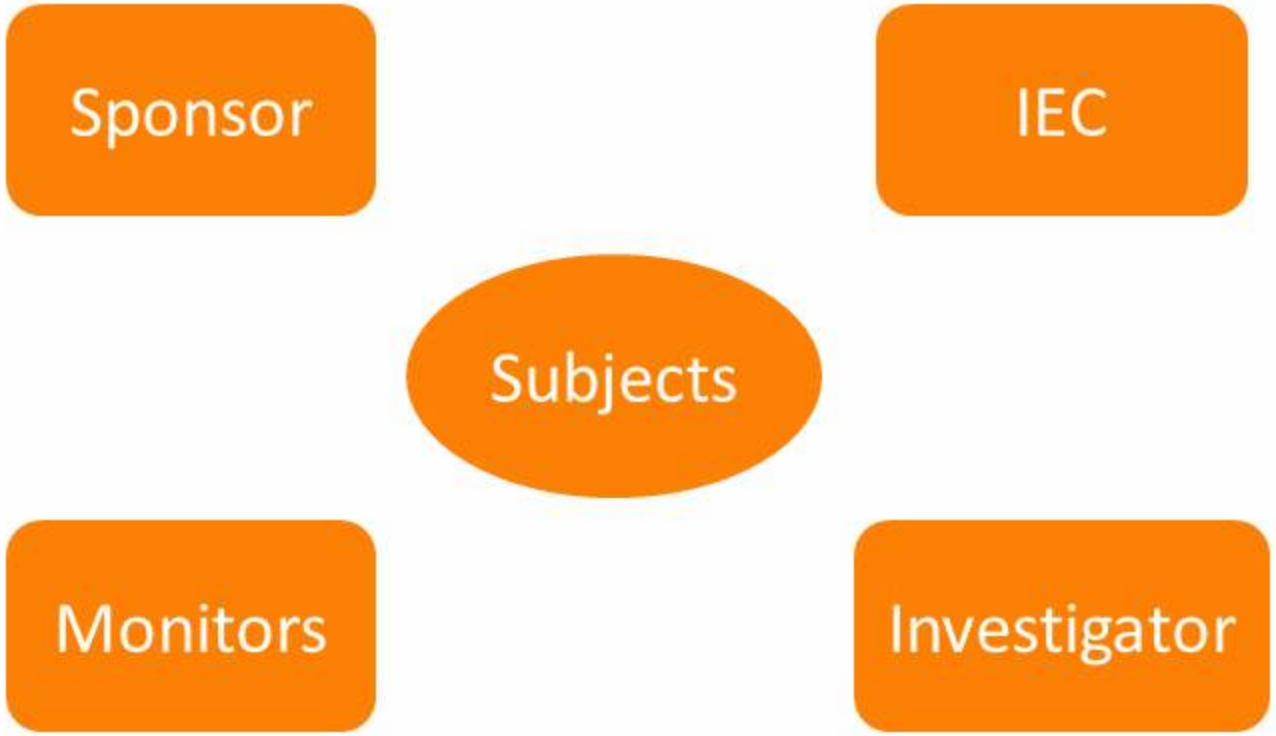
Phases of Clinical Trials

- **Phase I trials**
  New drugs are tested in a small group of people (usually healthy) for the first time, to evaluate safety, determine safe dosage, study pharmacokinetics and identify adverse effects.
- **Phase II trials**
  The experimental drugs are given to a larger group of people(usually suffering from the disease intended to be treated) to check if they are effective and to further evaluate their safety.

Phases of Clinical Trials

- **Phase III trials**
  The experimental study drug or treatment is given to large groups of people (who represent the patients that are seen in hospitals and clinics) to confirm its effectiveness, monitor side effects, in comparison with commonly used drugs for the same indication.
- **Phase IV trials**
  Post-marketing studies, conducted after a drug is approved for use, to provide additional information on drug's risks, benefits, and best use.

Key Stakeholders



Sponsor

NOVARTIS

1.53 Sponsor

- An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

-ICH GCP E6 R2

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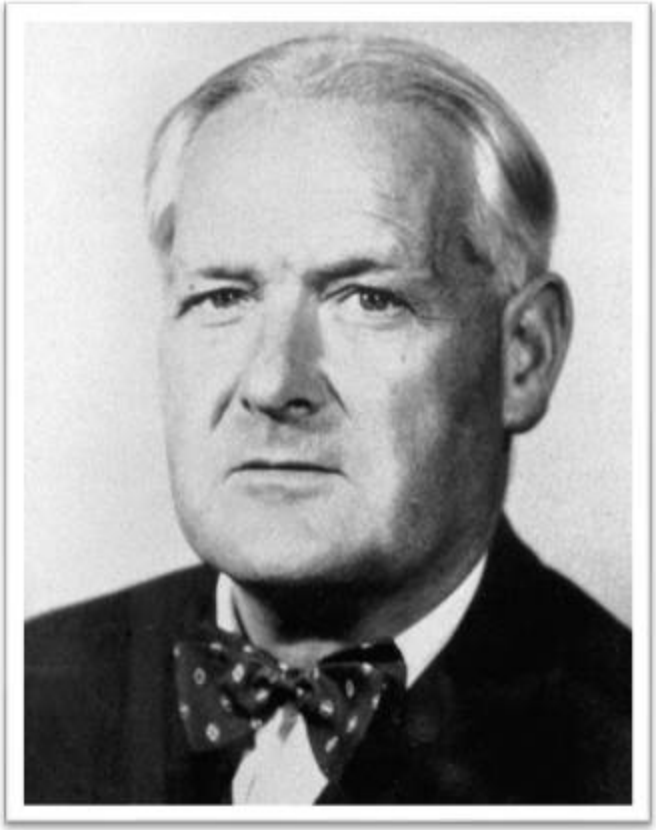
Principal Investigator

1.34 Investigator

- A person responsible for the conduct of the clinical trial at a trial site.
- If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.



Sir Austin Bradford Hill
1897-1991

Regulatory Authority

1.49 Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP Guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

-ICH GCP E6 R2

In India, the Regulatory Authority is the Central Drugs Standard and Control Organization that is headed by the Drugs Controller General of India.

Ethics Committee

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

-ICH GCP E6 R2

Monitors

Monitors are responsible for monitoring, that is defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures(SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Modified from ICH GCP E6 R2

Words in blue are added to the original definition

Trial Participants

Also known as Trial Subjects are healthy or a sick individuals who voluntarily participate in a clinical trial, either as recipients of the investigational product(s) or as controls.

Modified from ICH GCP E6 R2

Words in blue are added to the original definition

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced

They include

- The Protocol
- Investigators Brochure
- Informed consent forms
- Case Report Form
- Clinical Trial Agreement
- Insurance Statement
- Regulators approval
- IEC Approval
- CVs of Investigators
- Normal values of laboratory
- COA of IP

Essential Features of a Clinical Trial

1.24 Good Clinical Practice (GCP)

- A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Essential Features of a Clinical Trial

1.10 Blinding/Masking

- A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Essential Features of a Clinical Trial

1.28 Informed Consent

- A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Essential Features of a Clinical Trial

Randomization

- Random allocation is a procedure in which identified sample participants are randomly assigned to a treatment and each participant has the same probability of being assigned to any particular treatment

University of West England

Essential Features of a Clinical Trial

Bias

- Bias is the intentional or unintentional adjustment in the design and/or conduct of a clinical trial, and analysis and evaluation of the data that may affect the results. It may affect the results of a clinical trial and cause them to be unreliable.
- Bias can occur at any phase of research, e.g. during trial design, data collection, data analysis and publication.

The Beginning

James Lind, surgeon of the HMS Salisbury, began a study of sailors suffering from scurvy. Twelve affected sailors were divided into 6 groups and they received either cider, vitriolic elixir (diluted sulfuric acid), vinegar, sea water, two oranges and a lemon, or a purgative mixture. He ran out of oranges and lemon by the sixth day, but by then those receiving them were almost cured. This was the first recorded clinical trial.

James Lind
(1716-94)

Biblical References

Daniel 1:12 describes a study in which some servants were given vegetables and water for ten days while others were given the King's Food. At the end of the period, those on vegetables and water were found to be better off compared to the other group. Unfortunately details are scanty and differ in different versions of the Bible.

Avicenna

- Laid down the basic concepts for drug testing.
- “Testing a medicine on a horse or a lion, may not tell us much about the effect of the medicine in man”
- “A medicine must produce its effect on most if not all patients, to be useful”

Abū ʿAlī Ḥosayn Ebn Sīnā
(980-1037)

Placebos

- Ambroise Paré (1510-90) is believed to have introduced placebos in medicine following the dictum "Guérir quelquefois, soulager souvent, consoler toujours” (or "cure occasionally, relieve often, console always).
- John Haygarth conducted the first placebo controlled study in 1799.
- James Lind’s work on scurvy was a placebo controlled multiple arm study.

Blinding

The French Academy of Sciences recorded the first blind experiments in 1784: the Academy set up a commission to investigate the claims of animal magnetism proposed by Franz Mesmer. Headed by Benjamin Franklin and Antoine Lavoisier, the commission carried out experiments asking mesmerists to identify objects that had previously been filled with "vital fluid", including trees and flasks of water. The results showed that when properly blinded, objects with vital fluid could not be identified by so called Mesmerists.

Statistical Significance

The first clinical trial of streptomycin organized by the Medical Research Council (UK) in 1948 is considered to be the first randomized clinical trial based on statistical methodology. Early clinical trials had little to do with statistical theory and much more to do with the more fundamental and less technical concept of a fairness.

Chalmers 2011

Control group

I solemnly affirm and believe, if a hundred or a thousand men of the same age, same temperament and habits, together with the same surroundings, were attacked at the same time by the same disease, that if one half followed the prescriptions of the doctors of the variety of those practising at the present day, and that the other half took no medicine but relied on Nature's instincts, I have no doubt as to which half would escape.

Francisco Petrarca (1304-74)

Informed Consent

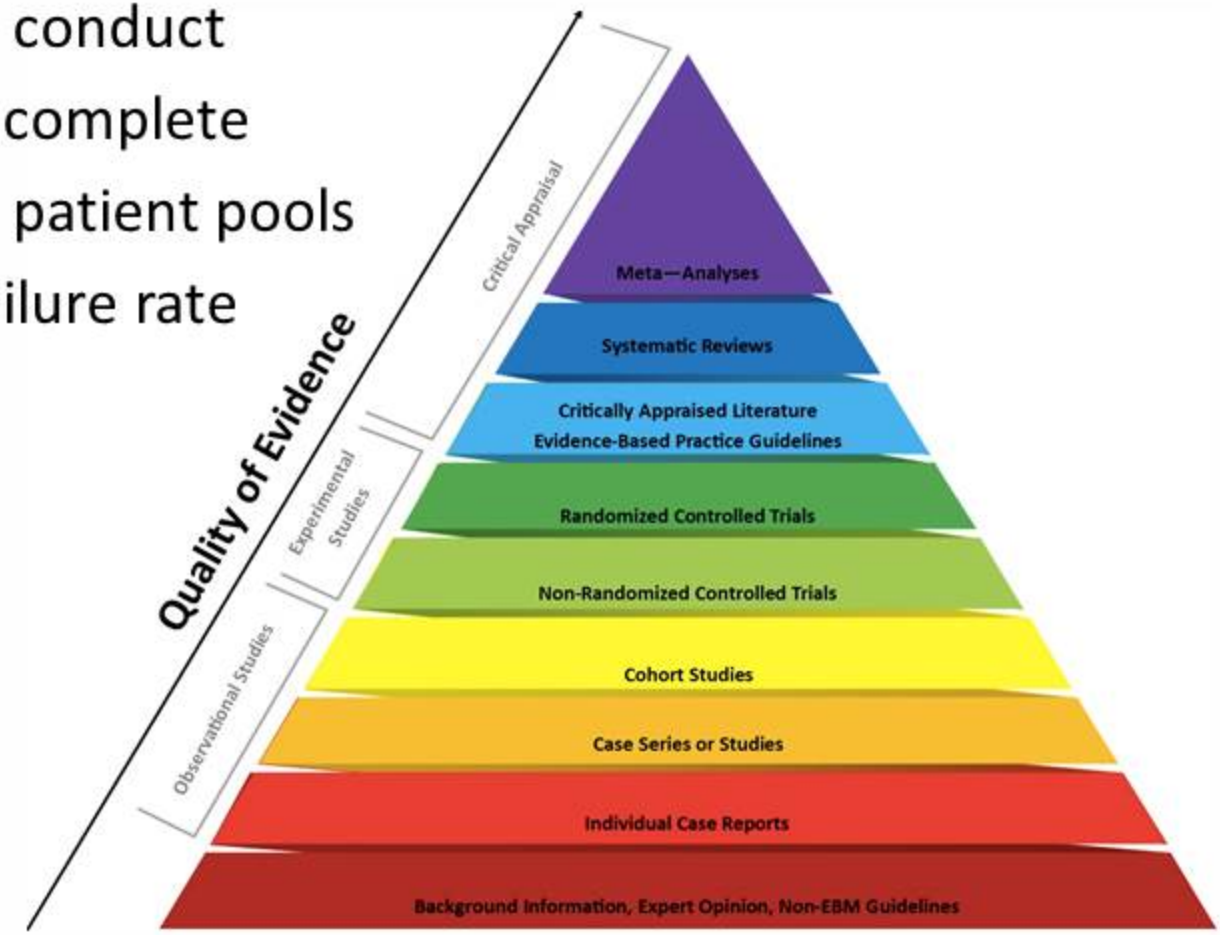
The concept of Informed voluntary concept was introduced independently by Walter Reed in the US in 1900 and recommended in the Berlin Code (1900). The code was developed by a commission headed by Rudolf Virchow to enquire into the human experiments conducted by Albert Neisser on commercial sex workers.

Reed's Informed Consent

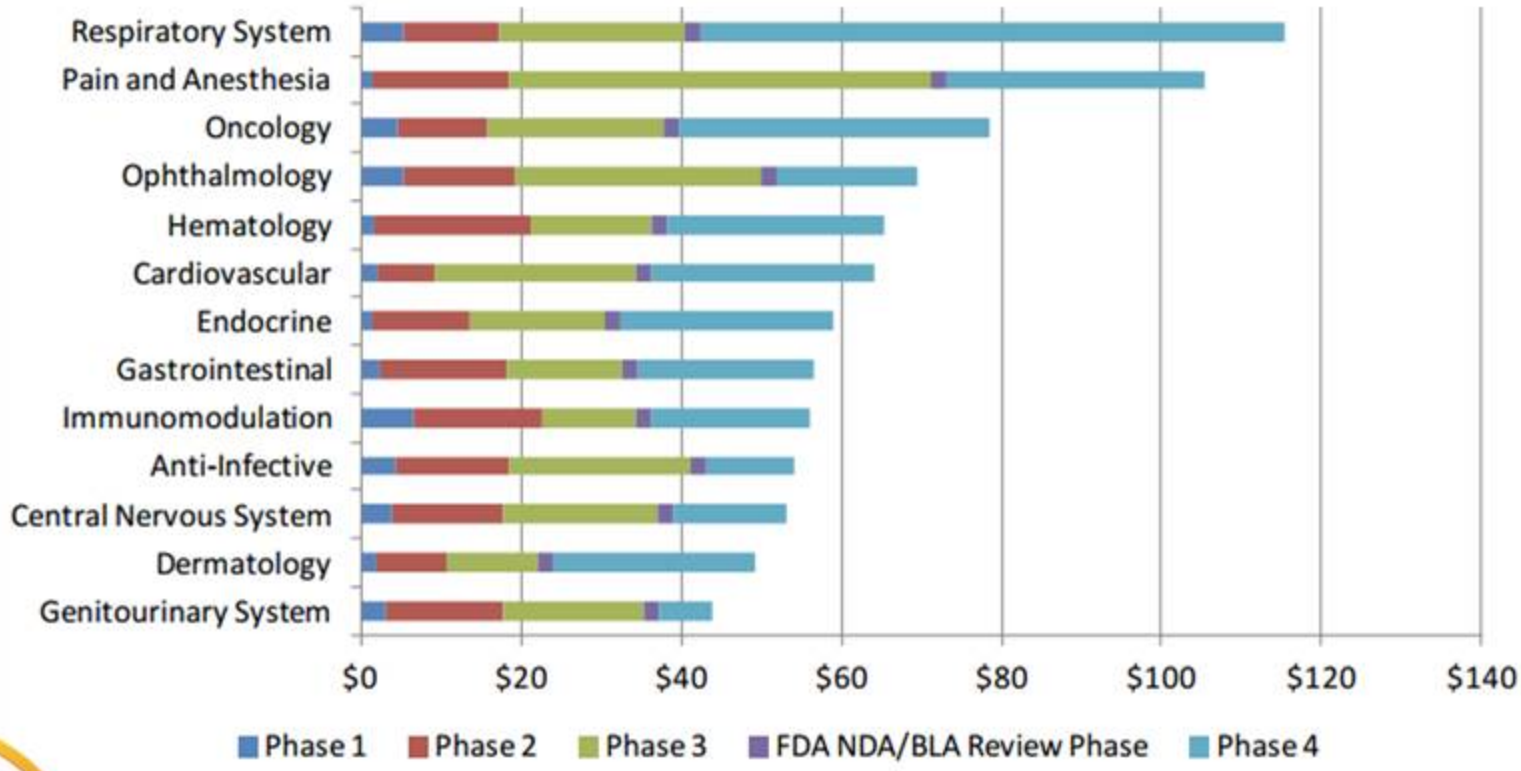
Randomized Controlled Trials have the highest acceptability among experimental Studies.

But they are:

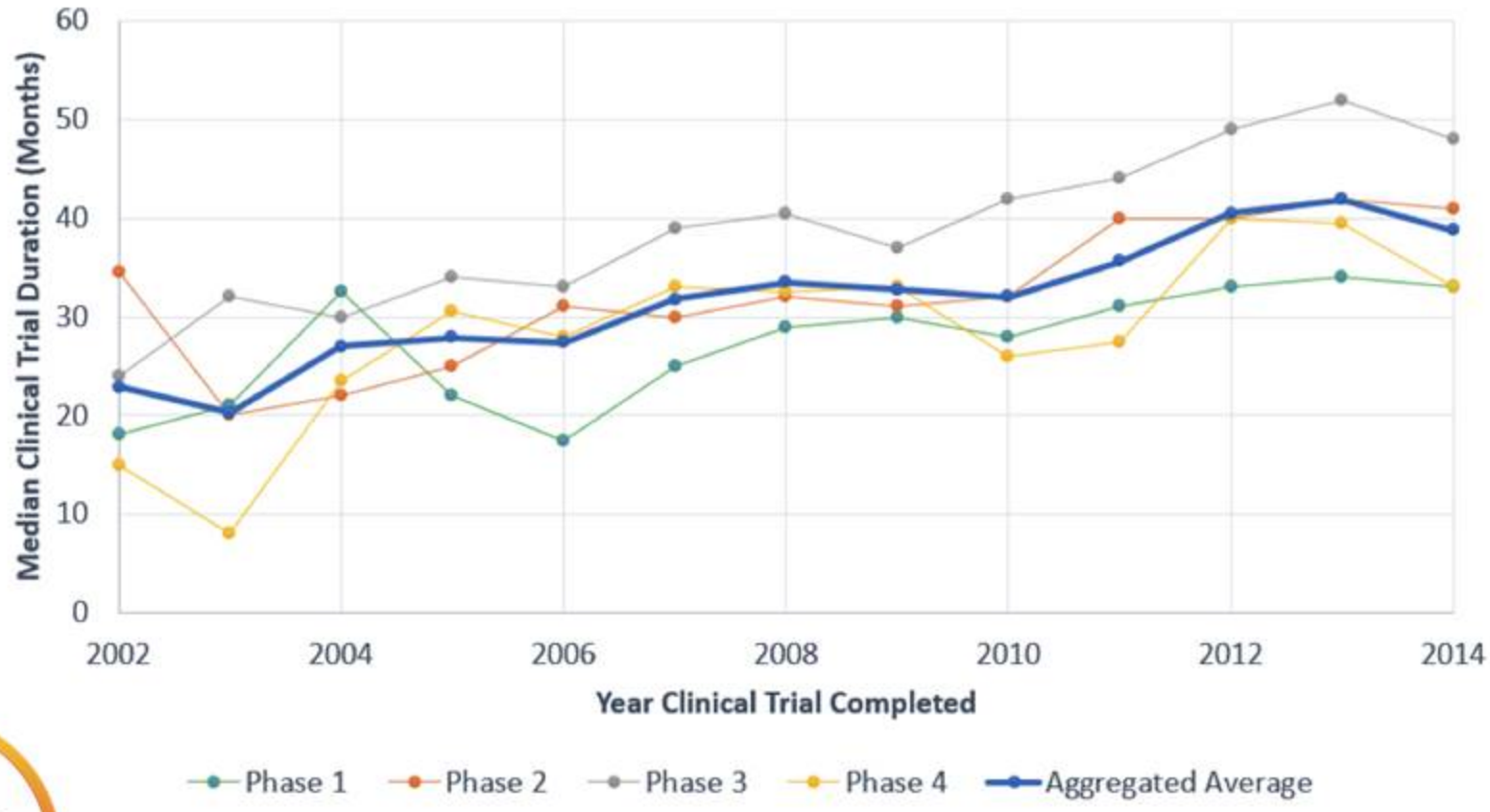
- Expensive to conduct
- Take time to complete
- Involve large patient pools
- Risky-High failure rate



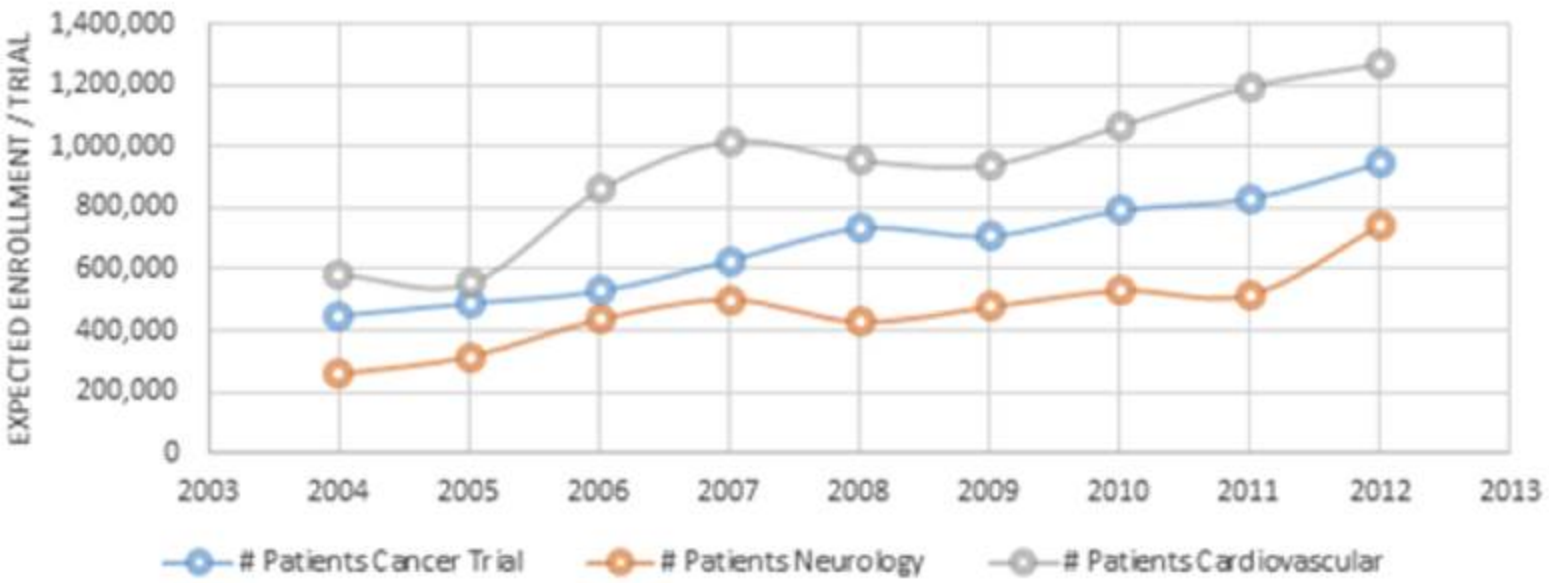
Cost of Clinical Trials (in Million USD) in 2014



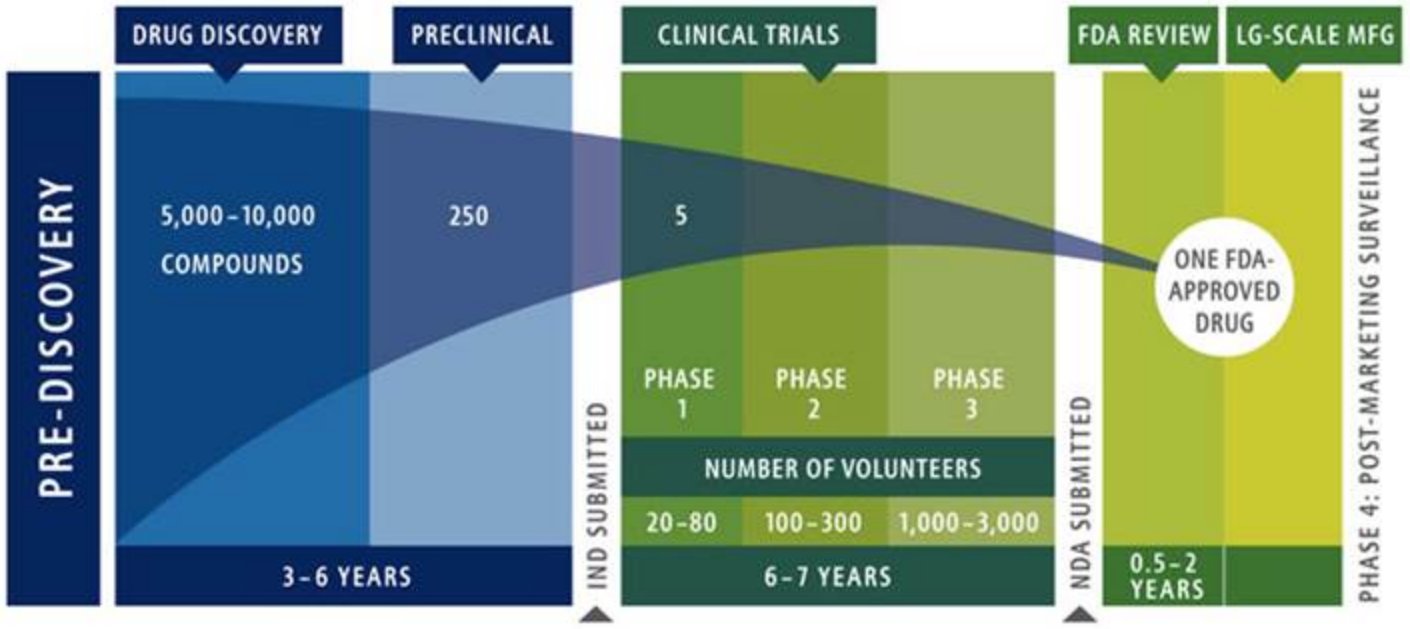
Duration of Trials is rising



Rising number of patients in Trials



Drug Discovery and Development: A LONG, RISKY ROAD



Source: Pharmaceutical Research and Manufacturers of America

Distribution of Trials by Phase