Introduction to Clinical Research

and Drug development

Module 1

What is Clinical Research?

Clinical research is a branch of healthcare science that determines the **safety and effectiveness** (efficacy) of drugs, devices, diagnostic products and treatment regimens intended for human use.

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

Types of Clinical Research

- **Quality of Life Research** explores ways to improve comfort and the quality of life for individuals with a chronic illness.
- **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.

KLINTEC Academy

Australian Government
National Health and Medical Research Council

Need for New Drugs & Diagnostics

Existing ones do not cover all diseases,
are not uniformly safe and effective
and are too expensive.

Lack of Drugs

There are no drugs for a large number of diseases including the most simple ones like Leucoderma.

Other disorders that defy treatment are

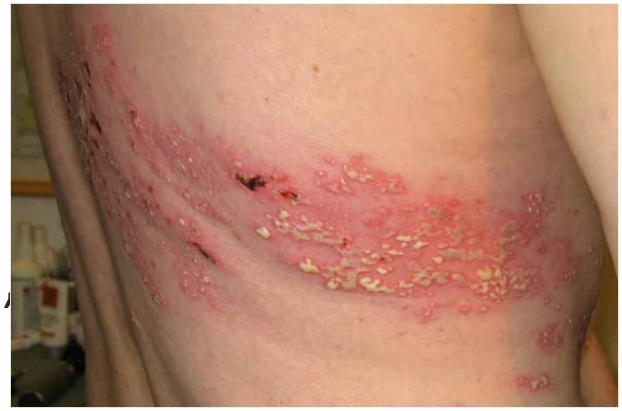
- Down's Syndrome
- Haemophilia
- Thalassemia
- Alzheimer's Disease
- Multiple Sclerosis
- Psoriasis

Ineffective/Unsafe Drugs

Drugs for cancers and viral infections are ineffective/unsafe.

Many diseases have no cure, drugs only suppress the disease. When treatment stops, the disease is back with a vengeance

- Various cancers
- Viral Infections
- Microbial Infections



Diseases with no cure:
Asthma
Hypertension
Diabetes

Expensive Drugs

Eteplirsen (Rs. 3,45,000/vial)

Herceptin (Rs. 75000/vial)

Actilyse (Rs. 37500/vial)

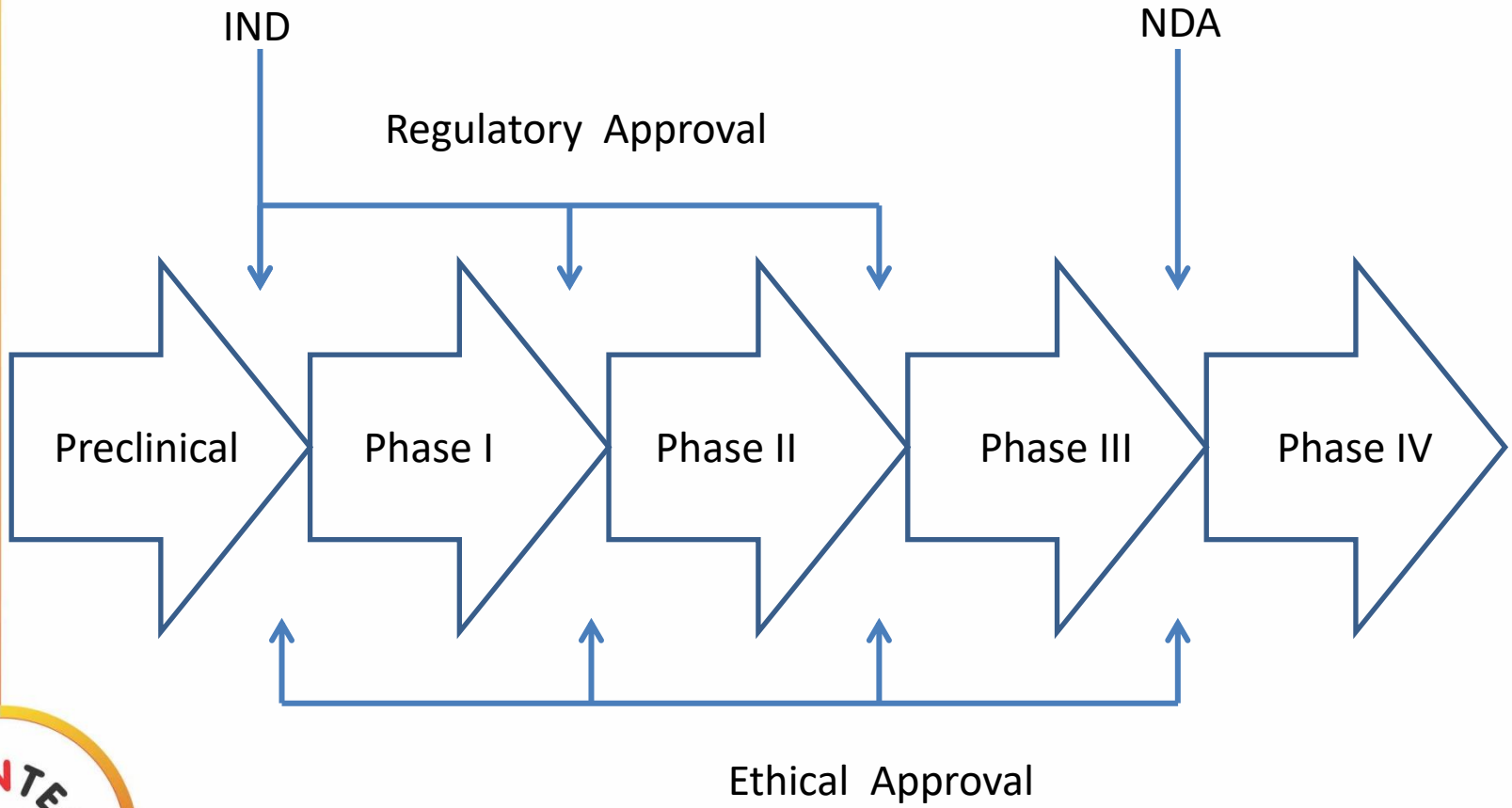
Avastin (Rs. 33416/vial)

Mabthera (Rs. 14323/vial)

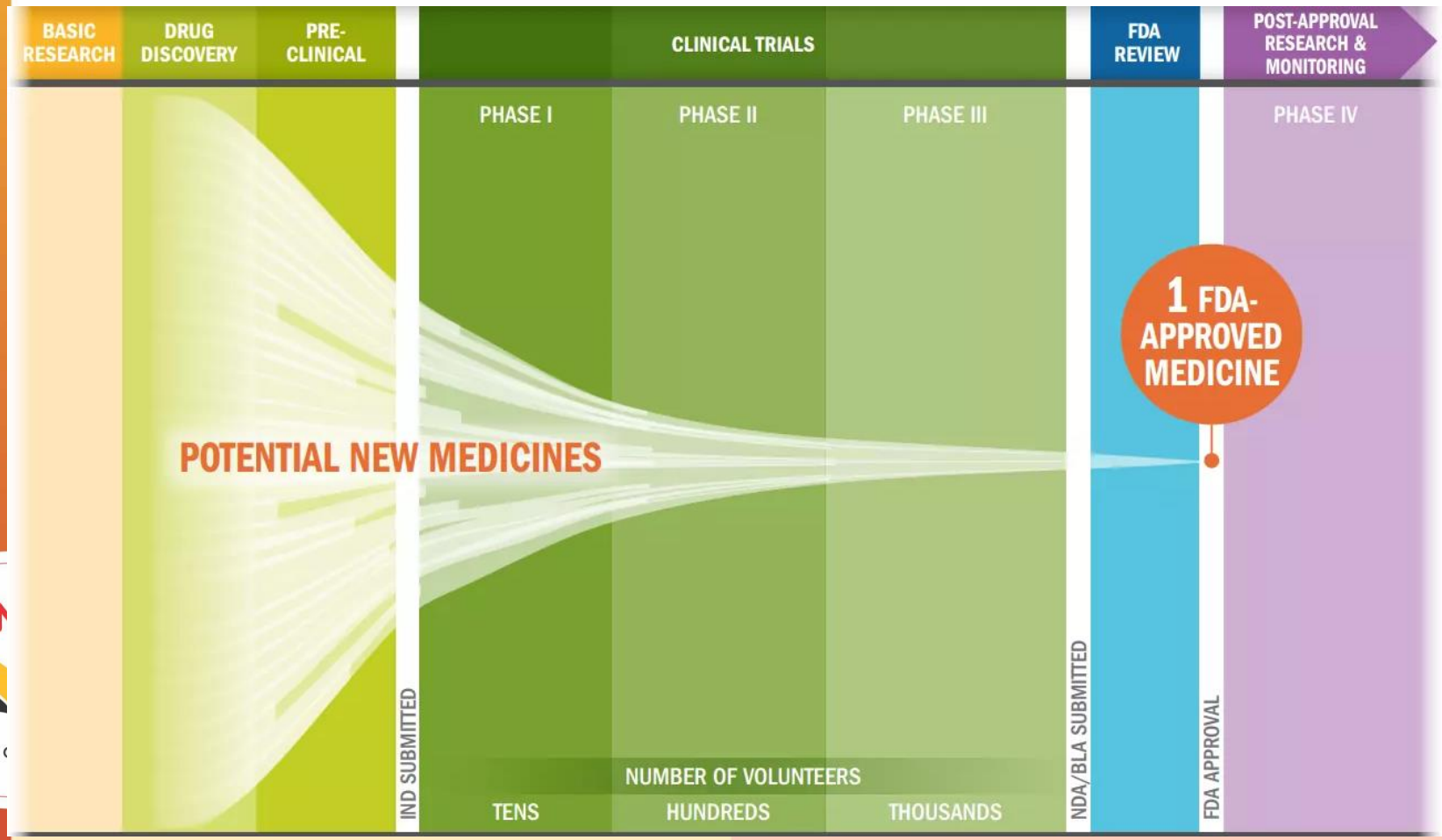
Sitagliptin (Rs. 50/tab)

Can we afford to fall sick?

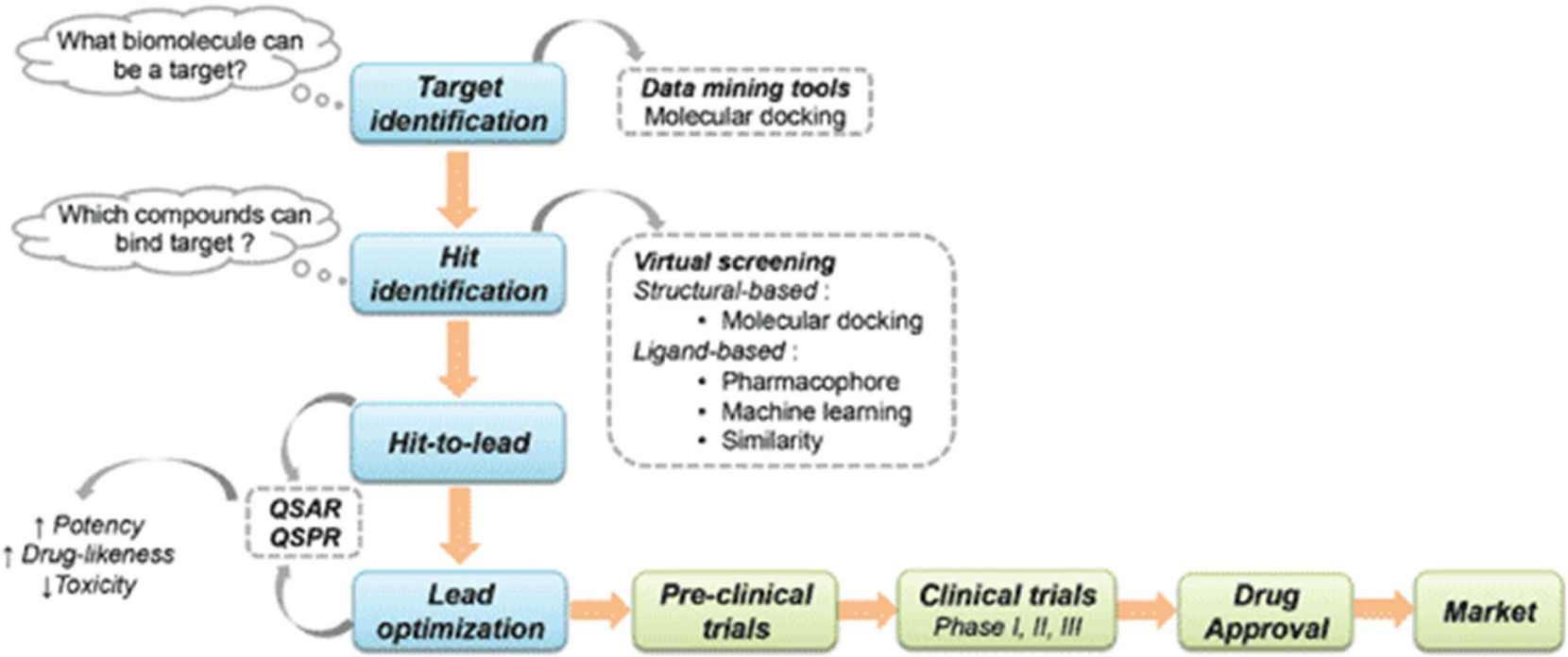
New Drug Development



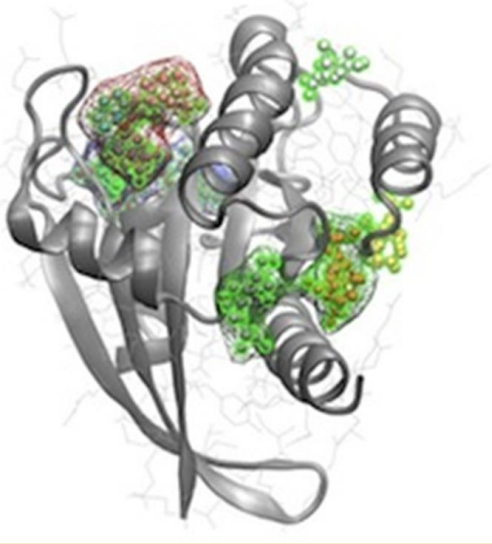
Conventional Development

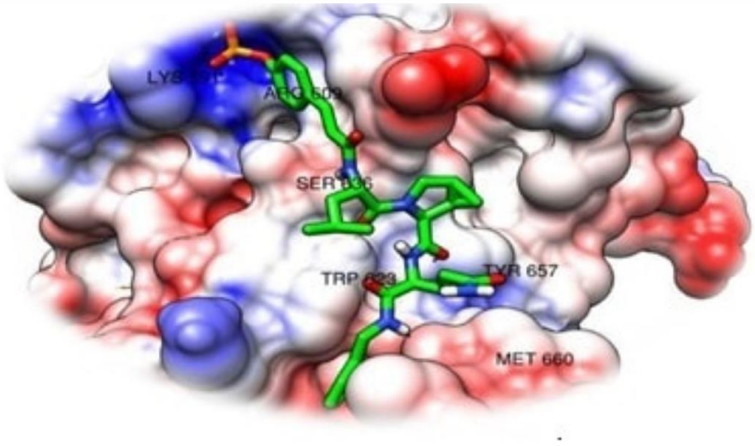


Computer Aided Drug Design

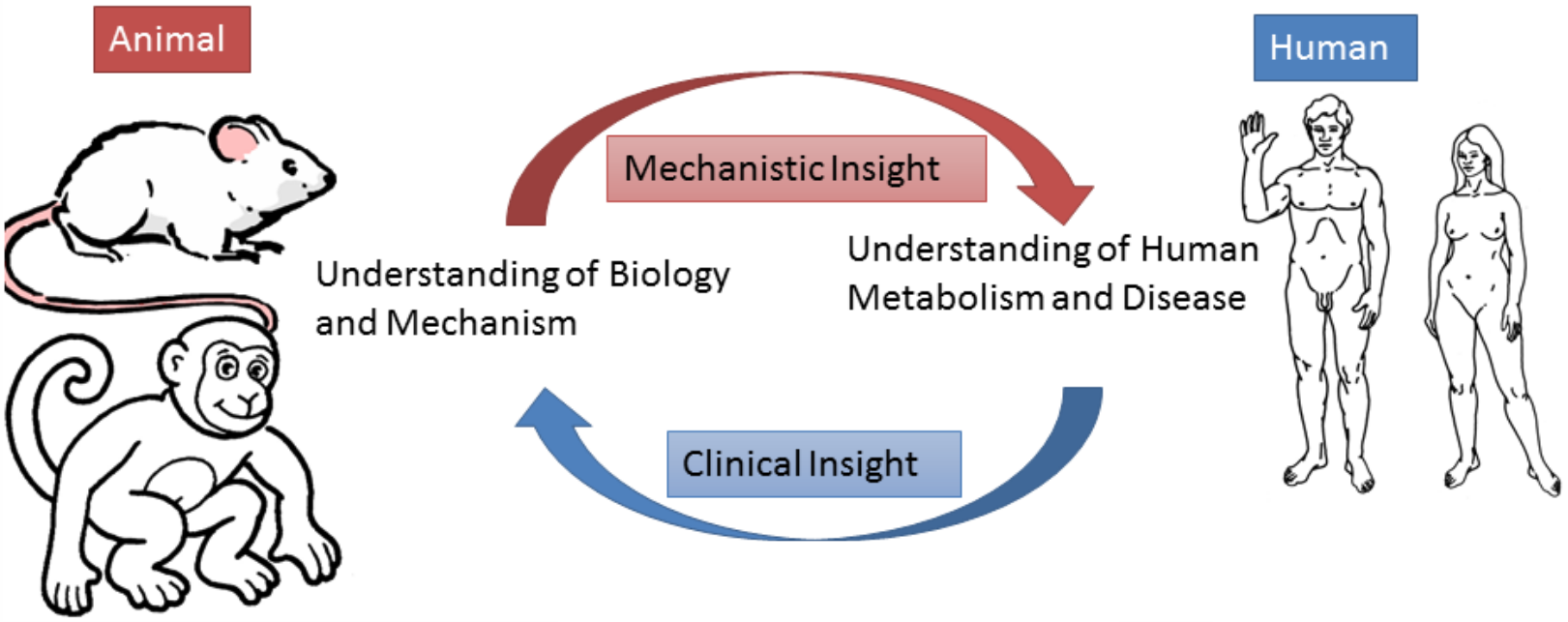


Targets have changed





Animal Studies are a pre-requisite



Clinical Trials

the final test….

Phases of Clinical Trials

Phase 0 Trials

Also known as human microdosing studies, Phase 0 trials have been recently introduced (2006). They are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the **drug** or agent behaves in human subjects as was expected from preclinical studies.

These are not required for all drugs, but only certain drugs as determined by the regulators may be subjected to these studies.

Phases of Clinical Trials

Phase I trials

Formerly referred to as “first-in-man studies” these are the first stage of testing in human subjects. They are designed to test the safety, side effects, best dose, and formulation method for the drug.

Normally, a small group of 20–80 healthy volunteers are recruited. These trials are often conducted in a specialized unit, where the subject can be observed by full-time staff.

Phase I trials usually include dose-ranging, also called dose escalation studies, so that the best and safest dose can be found. New drugs are tested at doses that are a fraction of the dose that produces toxicity in animals testing. Mostly include healthy volunteers, but some times patients are used, in case of anti cancer or HIV drugs.

Phases of Clinical Trials

- **Phase II trials**
  These are performed on larger groups (100–300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rate. High failure rates have been noted in Phase II trials, when the drug is found to lack efficacy or safety
  - Phase IIA studies are usually pilot studies designed to demonstrate clinical efficacy or biological activity ('proof of concept' studies);
  - Phase IIB studies look to find the optimum dose at which the drug shows biological activity with minimal side-effects (‘definite dose-finding’ studies)

Phases of Clinical Trials

Phase III Trials

Phase III is designed to assess the effectiveness of the new intervention and, hence its value in clinical practice. Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. Phase III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice. This phase precedes marketing of the drug and is sometimes called the "pre-marketing phase".

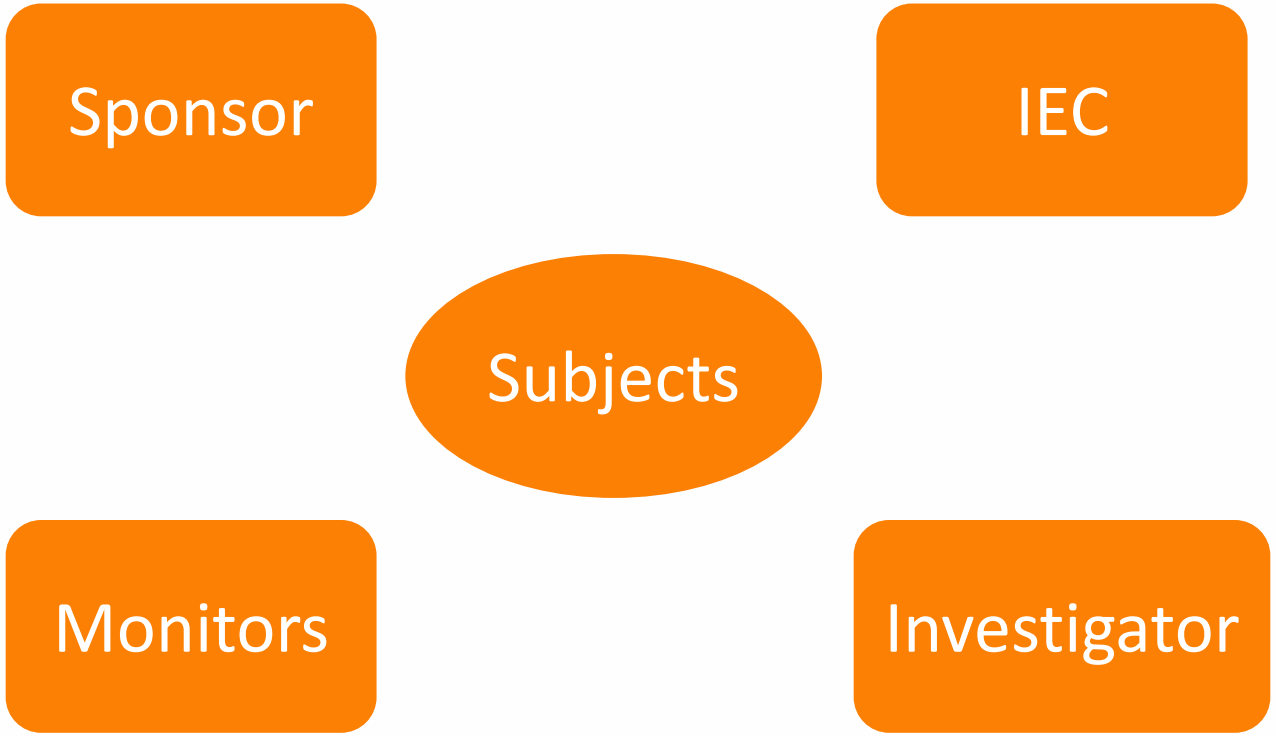
Phases of Clinical Trials

Phase IV Trials

Also known as post-marketing studies, and these trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be marketed.

Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials.

Key Stakeholders



Sponsor

1.53 Sponsor

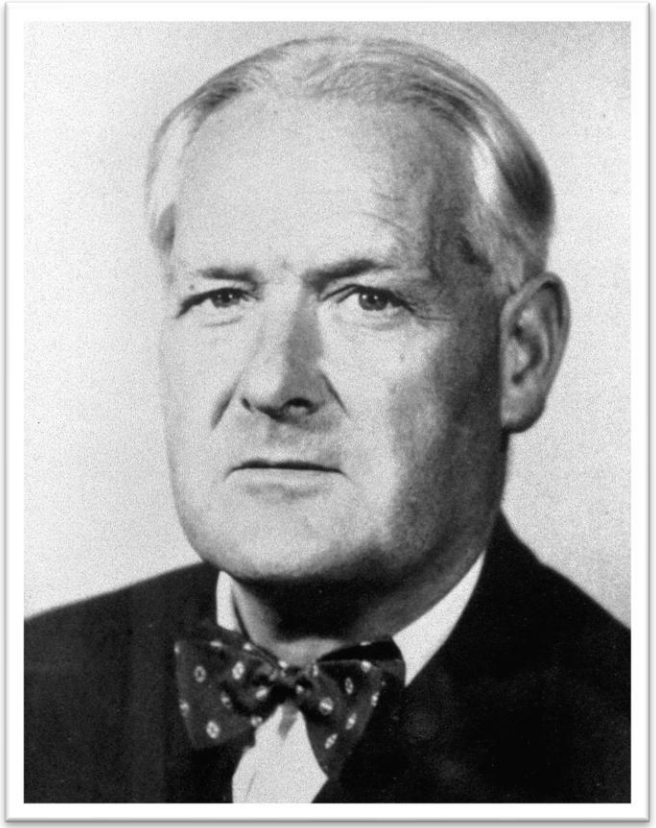
- An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

-ICH GCP E6 R2

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.

Regulations in India

- The Drugs and Cosmetics Act 1940 lays down the principles of drug law.
- The Drugs and Cosmetics Rules 1945 provide details how the ACT is to be implemented.
- New Drugs and Clinical Trail Rules 2019 lay down the procedure for conducting clinical trials on new drugs.
- ICMR in its National Ethical Guidelines for Biomedical and Health Research involving Human Participants provides guidelines for ethical research.

Good Clinical Practices

GCP guideline by the International Council for Harmonization: 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.

CDSCO GCP

On the lines of ICH GCP the Indian Regulator CDSCO has developed the Indian GCP Guideline. This has brought Indian Guidelines at par with the international ones.

Trials conducted in India must be in accordance to the CDSCO GCP Guidelines.

All trials should be conducted in accordance to ethical principles laid down in the Declaration of Helsinki and the ICMR Guidelines.

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

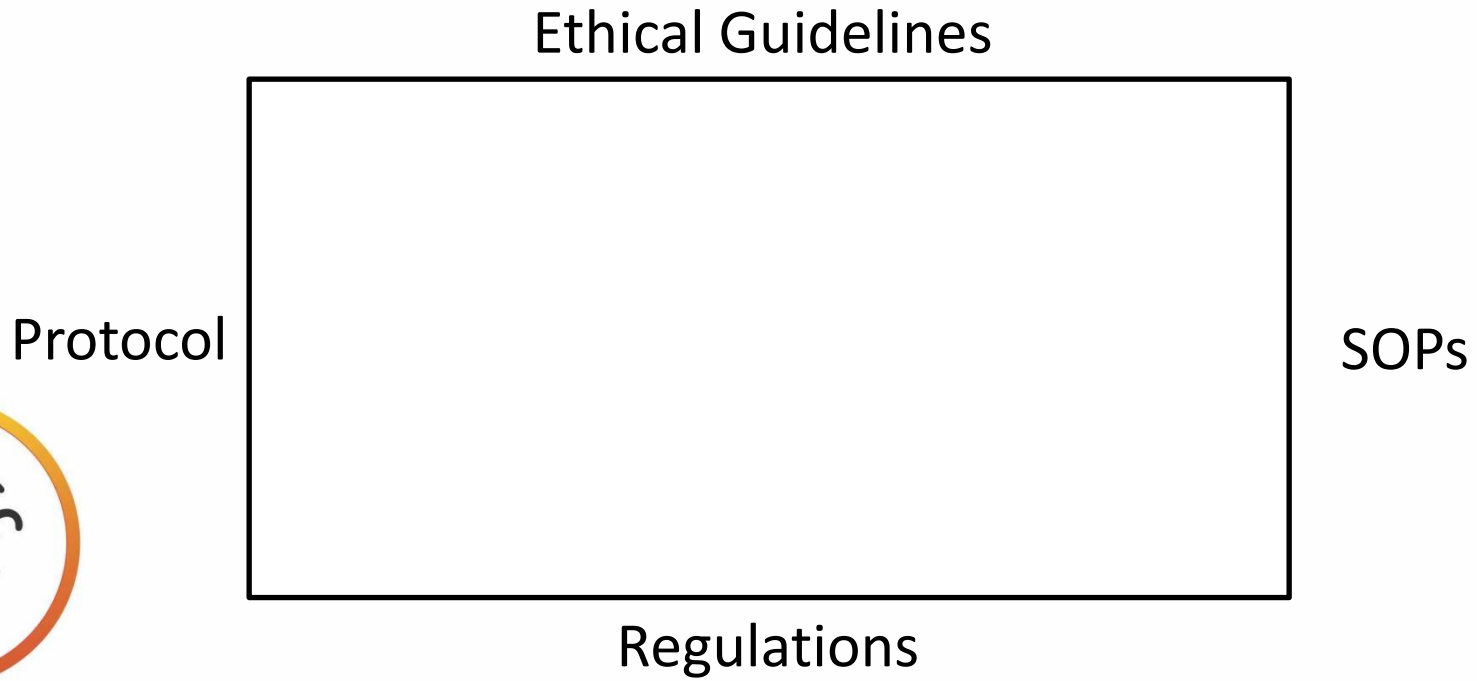
They include

- 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

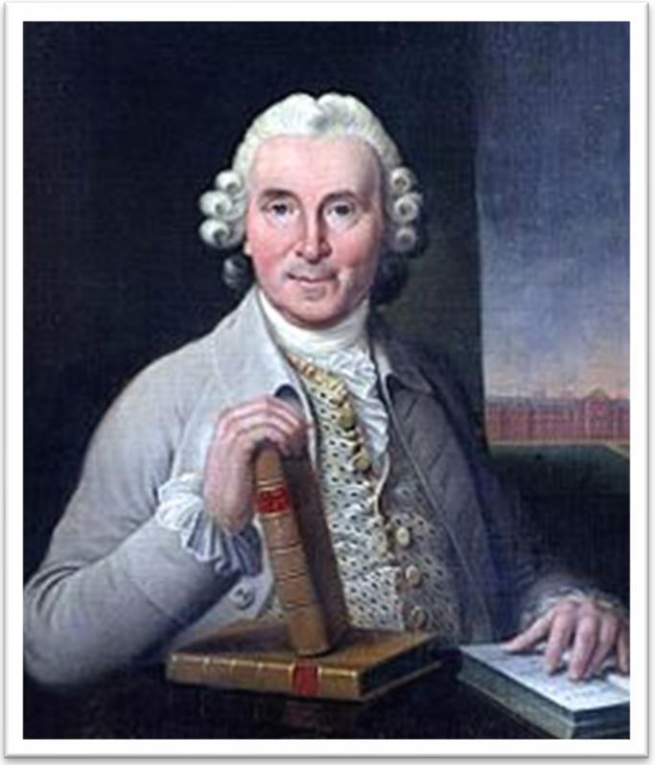
Compliance

Clinical trials need to comply to all relevant rules, guidelines, and SOPs.



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.



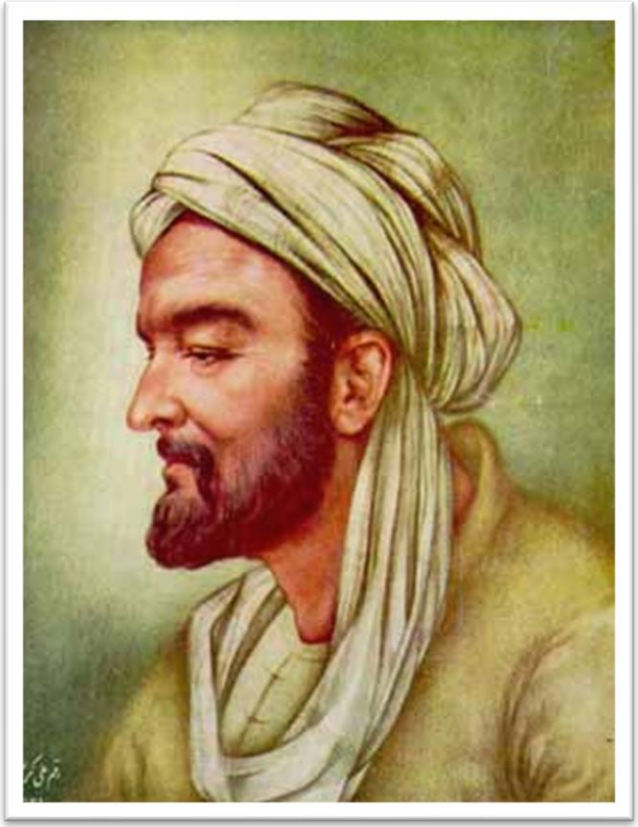
James Lind
(1716-94)

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”

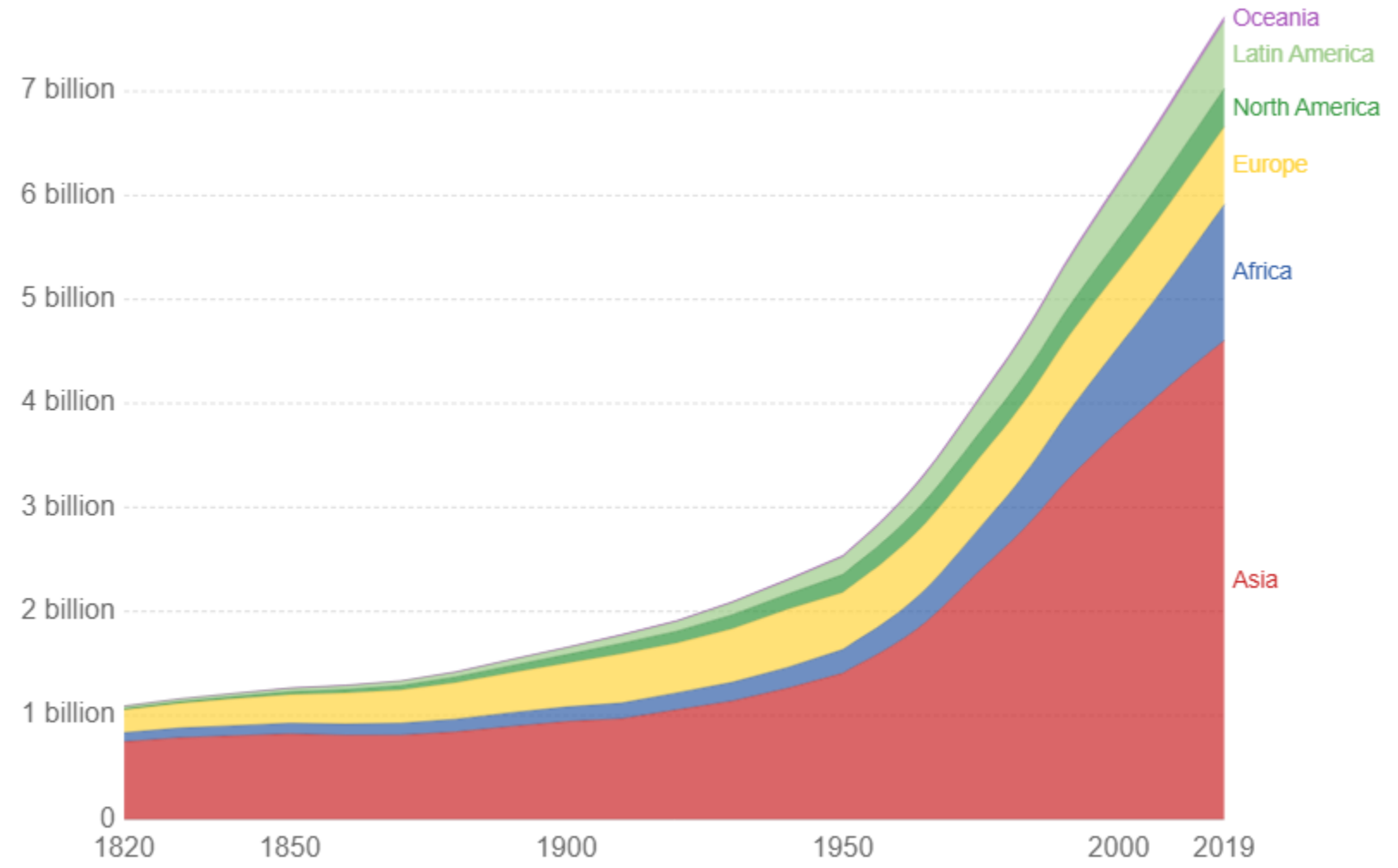


Abū ʿAlī Ḥosayn Ebn Sīnā
(980-1037)

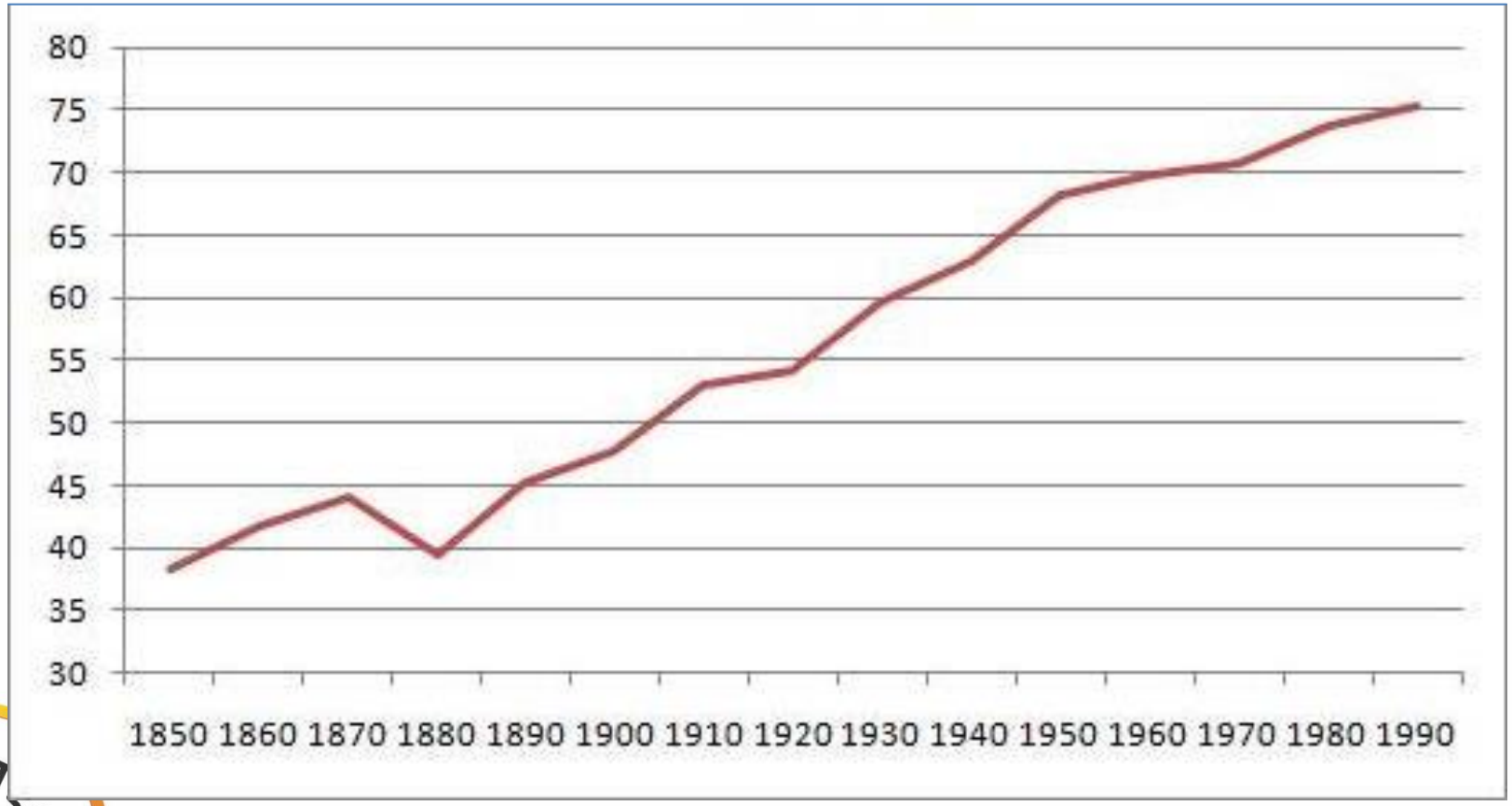
New Drugs

- Have impacted human life, in such a way that the human race is growing in numbers.
- Average human beings are living longer and a healthier life.
- The average human is taller and heavier.
- Mortality due to various causes has gone down, notably due to disease.
- Mortality among mothers and children is going down.
- Are we happier?

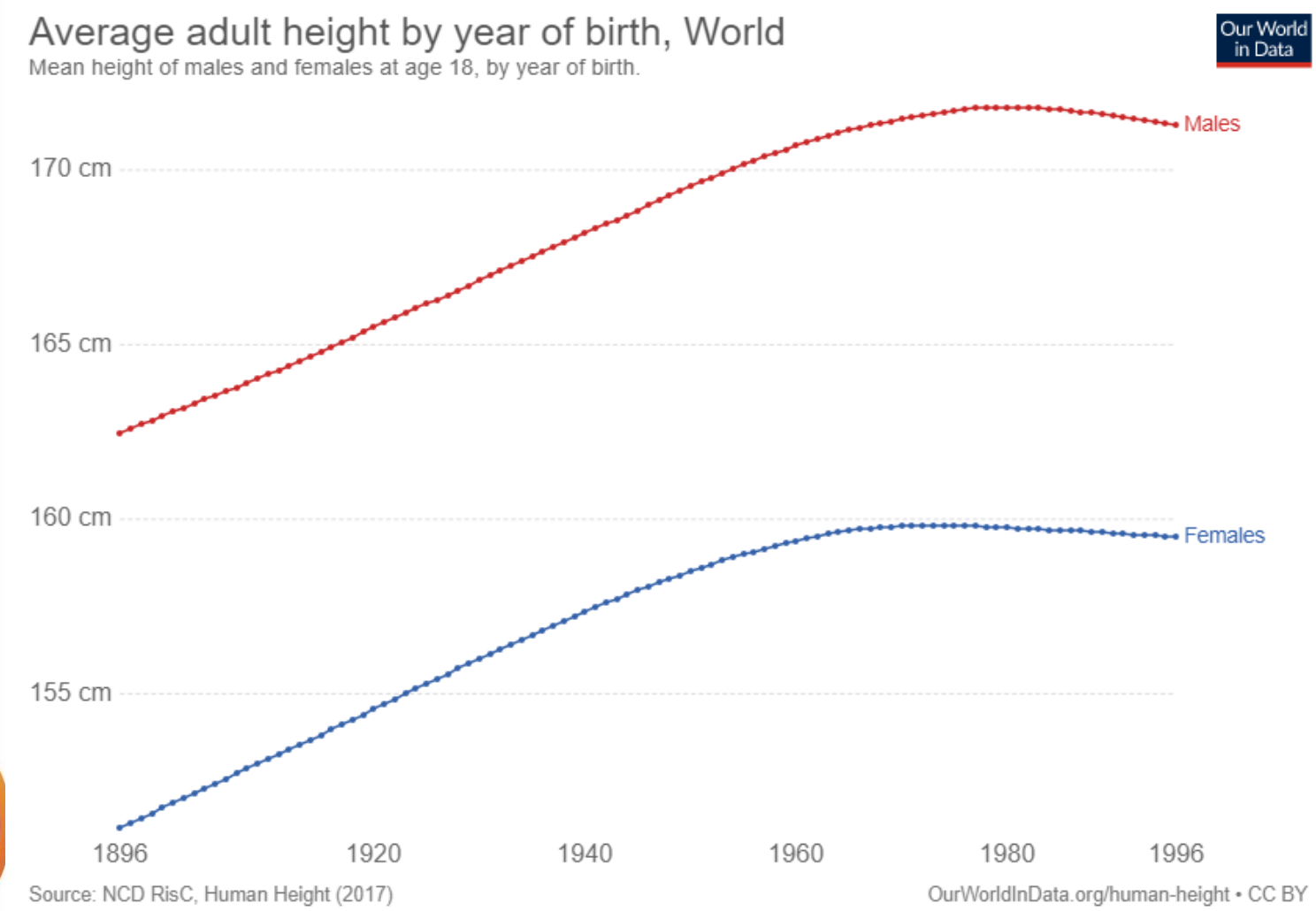
World Population



Life Expectancy

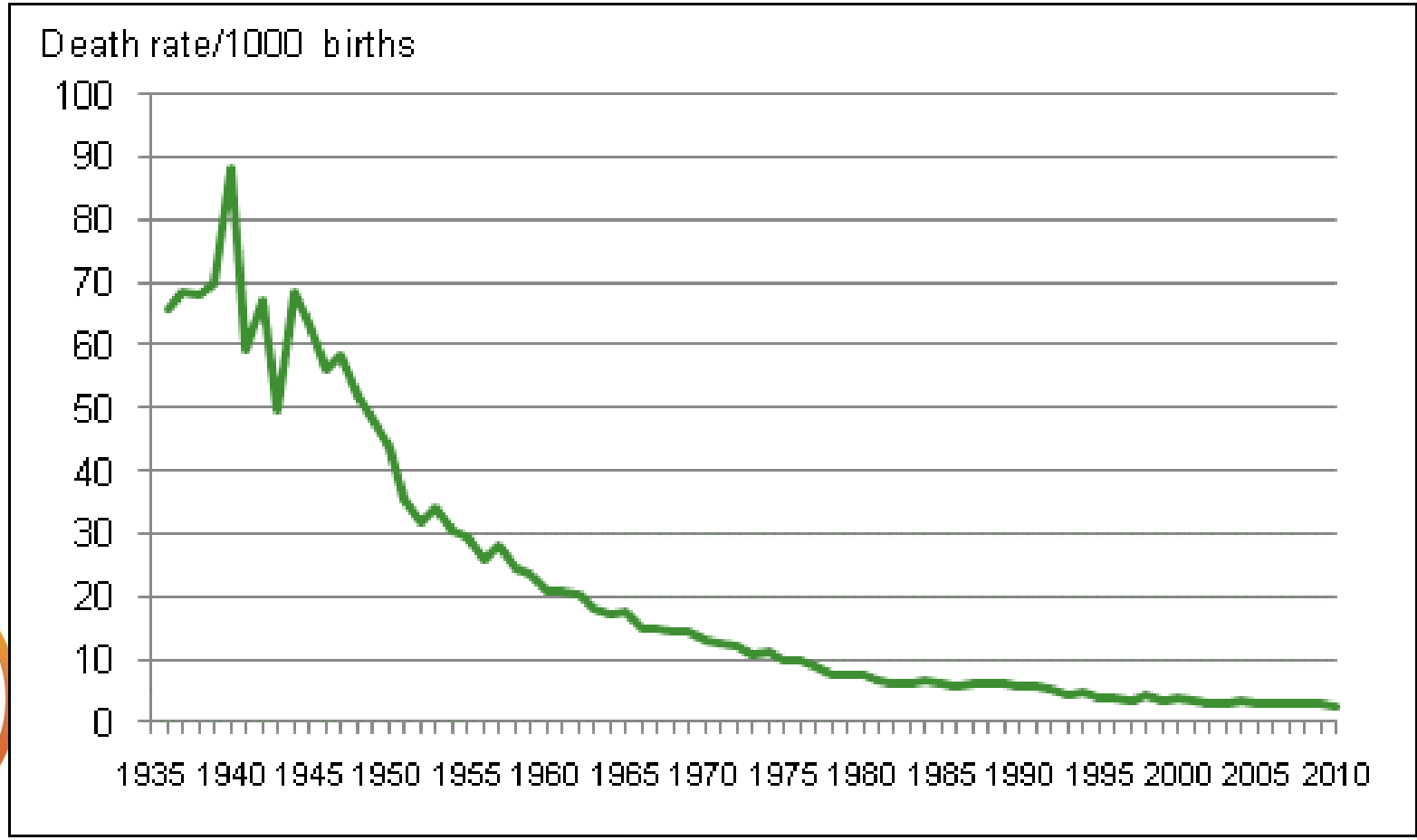


Average Height

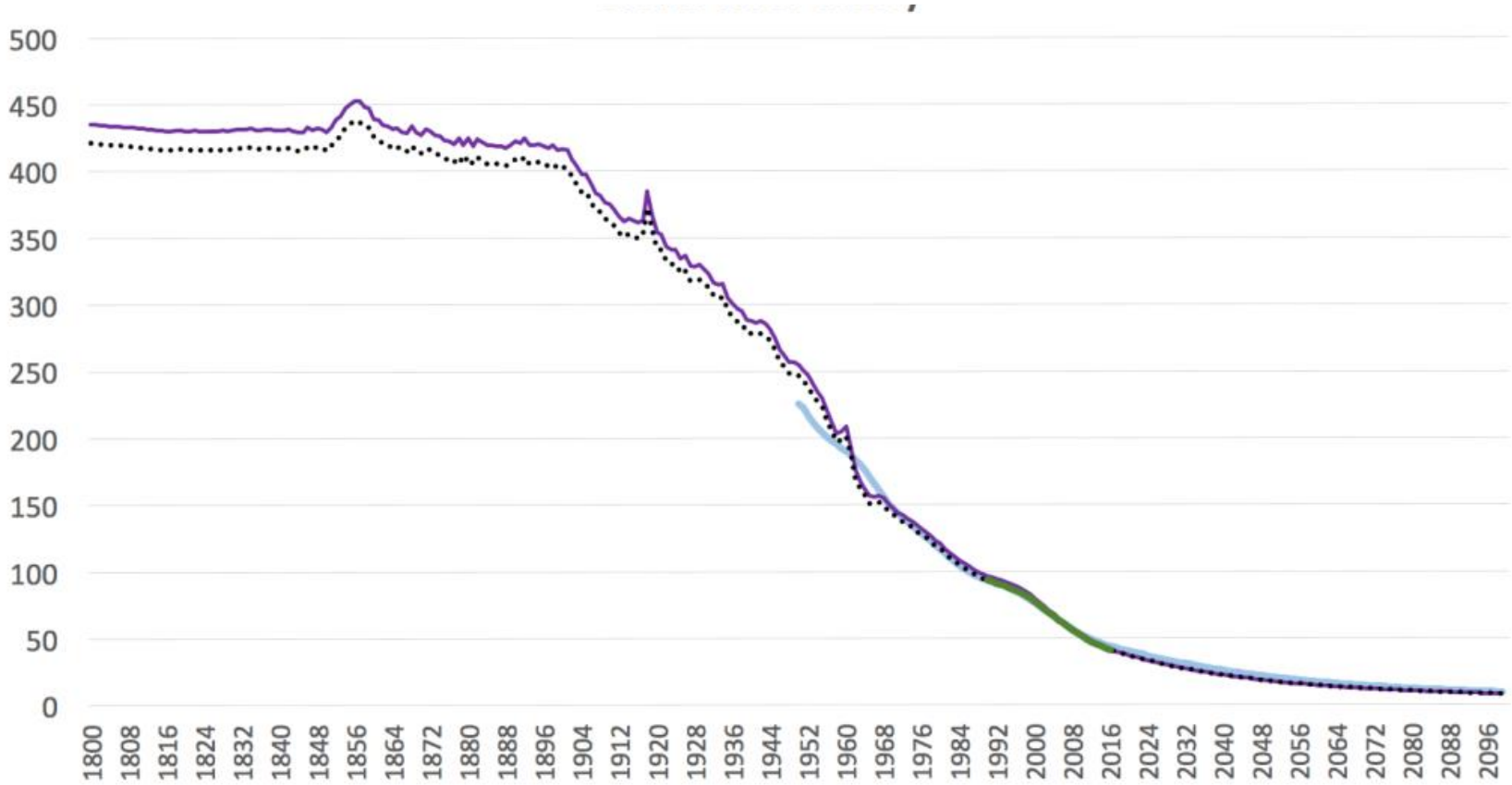


Infection and Life Span

Maternal Mortality



Child Mortality

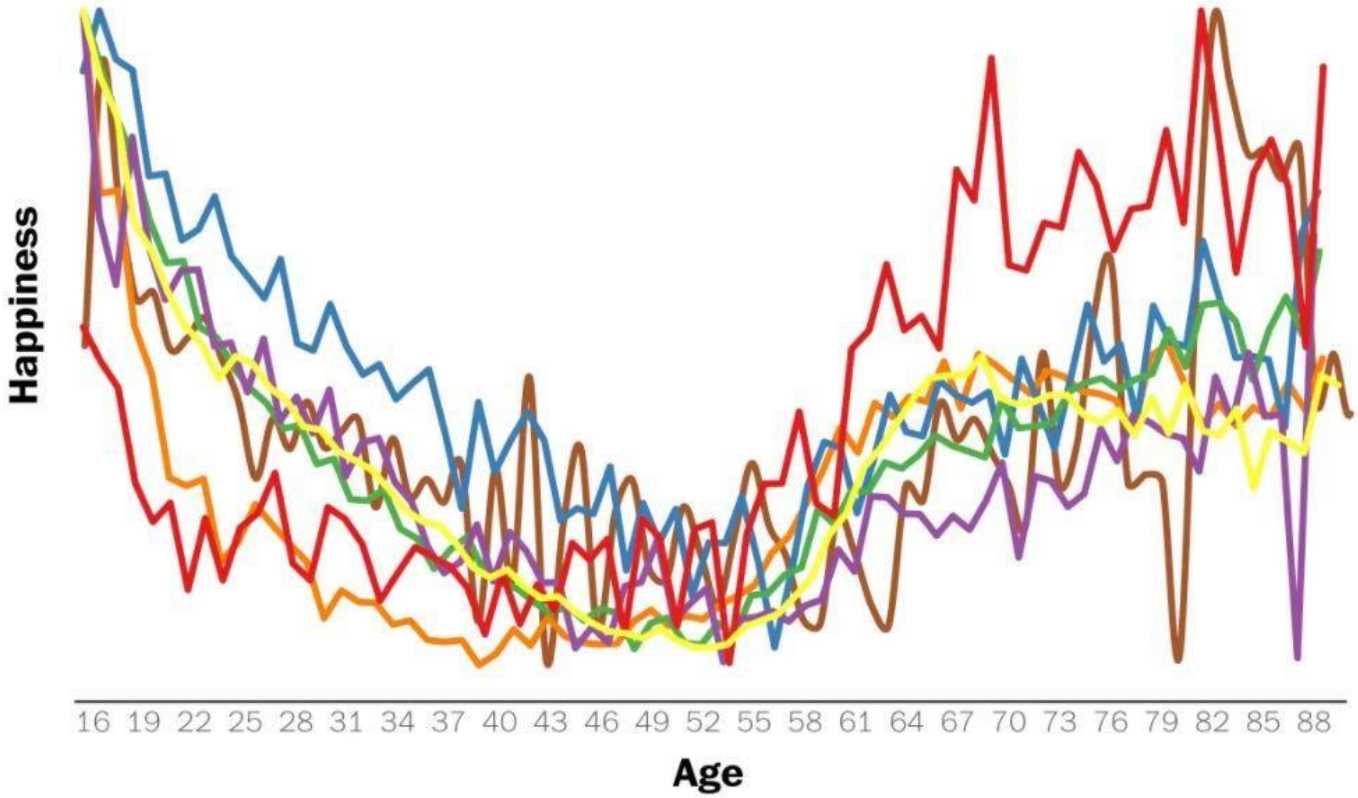


Happiness

The shape of happiness

Relationship between happiness (or life satisfaction) and age across seven major surveys

Note: Trend lines are scaled to a common minimum and maximum range



The need for new drugs is not likely to abate, as medicine comes up with challenges of new diseases and older diseases becoming resistant to existing drugs.

Clinical trials, the final test of a drug are here to stay as long a new drugs are required. There will be changes in design, control, conduct, reporting of trials, but the human participant and the investigational product will always remain.

Questions?

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