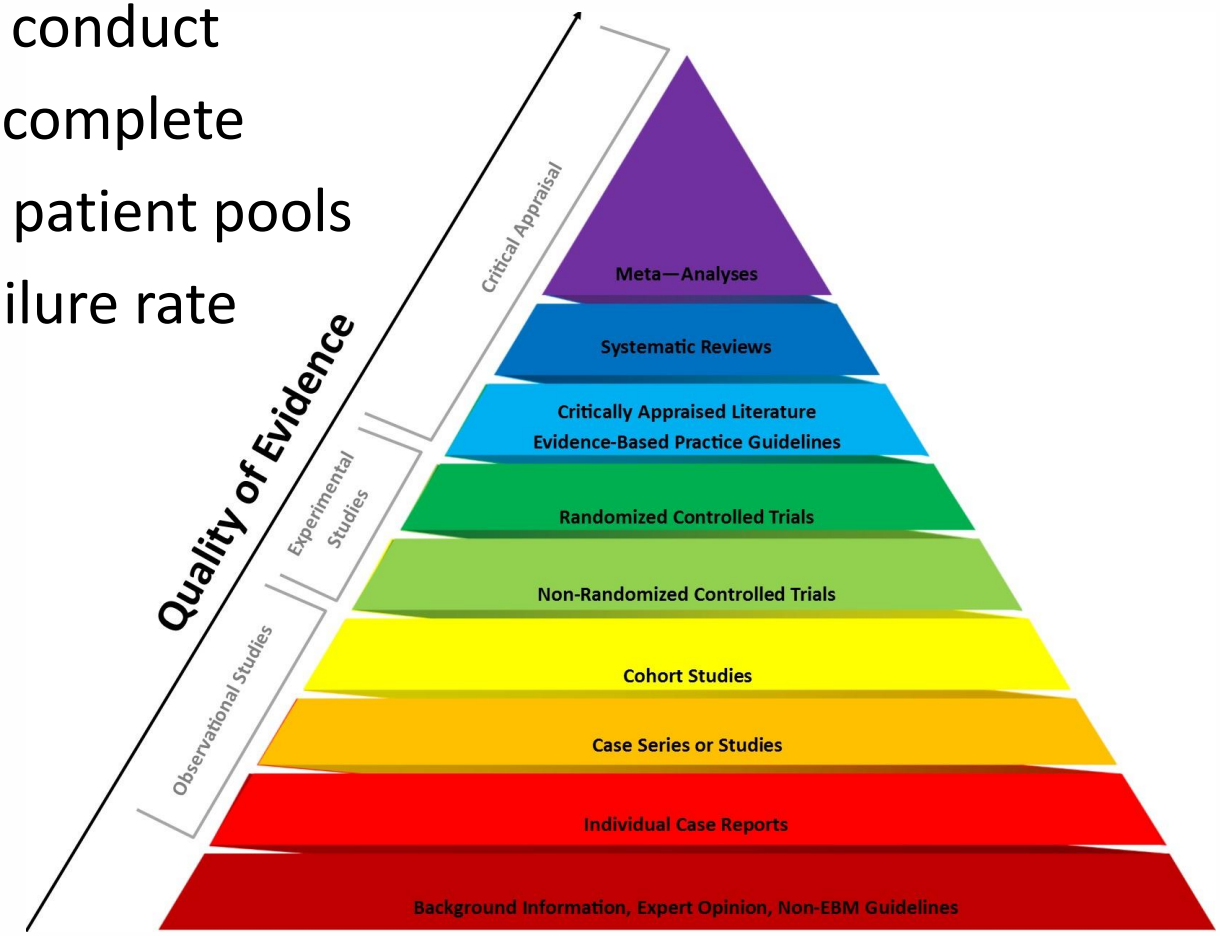
Introduction to Clinical Research Part II

Module 1 Topic 2

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



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.

Gold Standard

The randomized, controlled, trial (RCT) is the Gold Standard for testing the safety and efficacy of a new therapeutic agents. The new agent is usually compared to a standard therapy (in use currently), placebos are used only when there is no standard therapy available for the disorder. An RCT has three main attributes, namely :

1. Controls
2. Blinding
3. Randomization

Controlled trials using randomization and blinding, generally minimize subject and investigator bias.

Controls

Control groups have one major purpose: to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment. The control group experience tells us what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective.

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Blinding

- Blinding is intended to minimize the potential biases resulting from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment.
- In some trials, only the participants are blind to the treatment (single blind studies) while in others both the participants and investigators are blind to the treatment given to individual participants (double blind studies). Studies where the data handlers and statisticians are also blind are often known as triple blinded.

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Randomization

- Assurance that subject populations are similar in test and control groups is best attained by randomly dividing a single sample population into groups that receive the test or control treatments. Randomization avoids systematic differences between groups with respect to known or unknown baseline variables that could affect outcome. Inability to eliminate systematic differences between treatment groups is a major problem of studies without a concurrent randomized control. Randomization also provides a sound basis for statistical inference.

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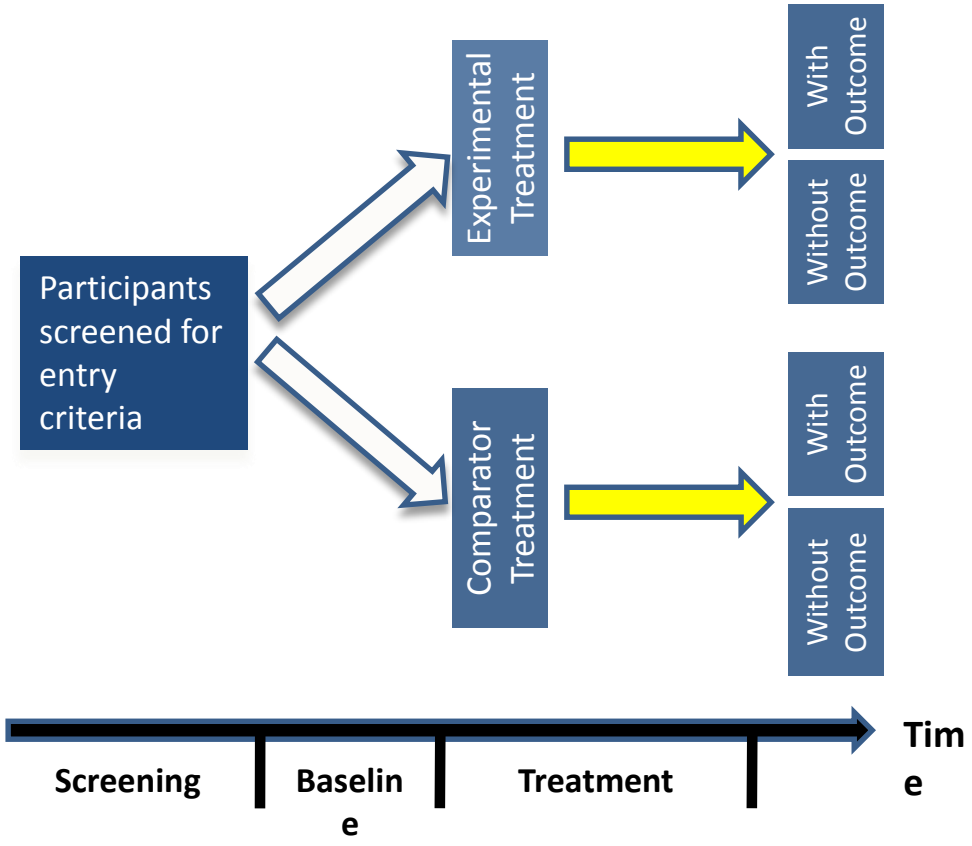
Trial Designs

- Prospective interventional trials are mainly of two types, parallel and cross over.
- Each design has its advantages and disadvantages, in terms of duration and sample size.
- Parallel studies take less time, while cross over studies require a less number of participants who fit in the inclusion exclusion criteria.
- Cross over studies are also unaffected by interindividual difference in response to the investigational products.

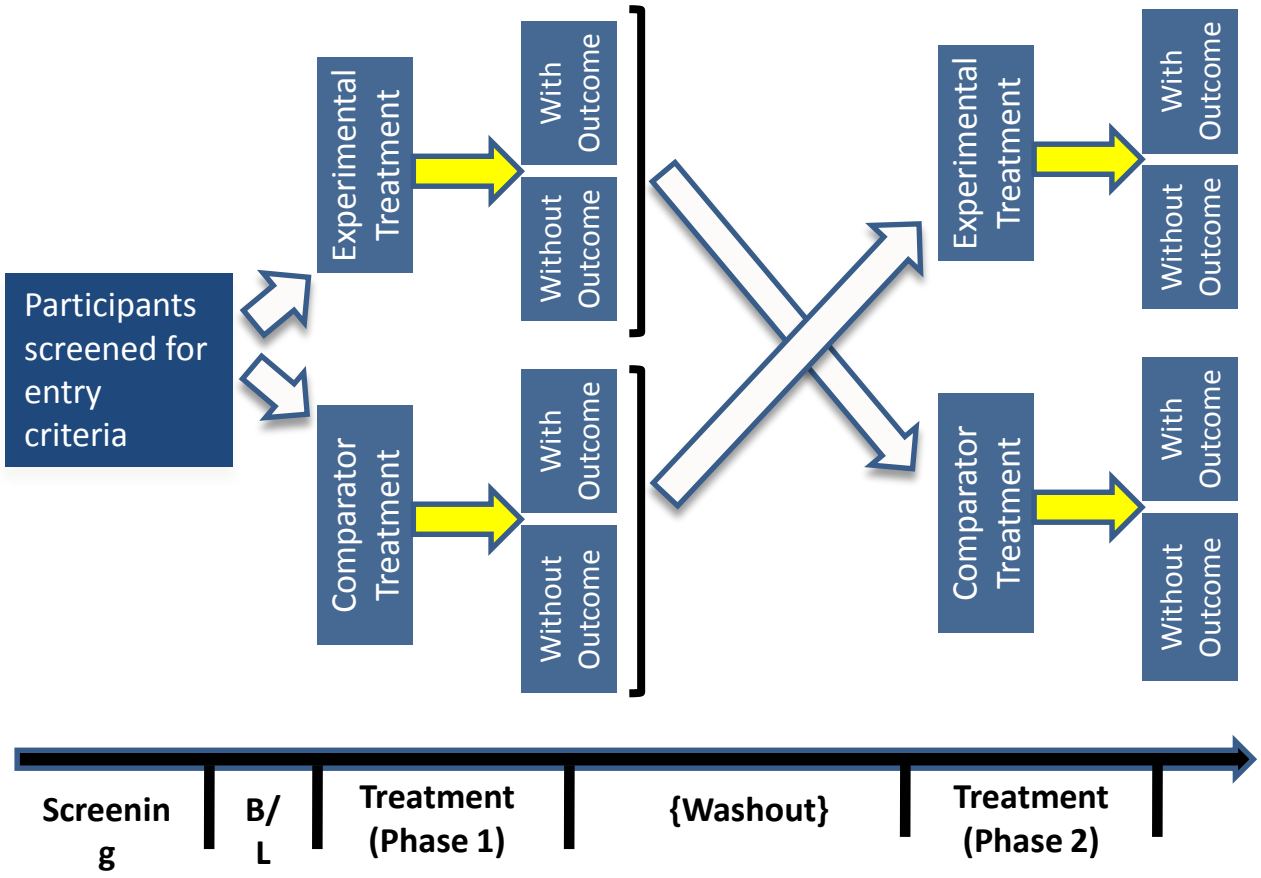
Multicenter Studies

- Most clinical trials are conducted in a number of centers spread across different geographies, which allows inclusion of participants with varying genetic make up.
- The use of a large number of centers ensures that the total number of participants required can be recruited at a faster rate, than if a single center is used.
- In multi center trials, it is essential that the study is conducted and results recorded at each site in an identical fashion, only then can the data obtained be merged into a single cohort.

Clinical Trial: Parallel Group Design



Clinical Trial: Crossover Design



Stakeholders in Trials

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

1.57 Subject/Participant: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

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.

Investigator

- A Principal Investigator is the person selected by the sponsor to conduct the clinical trial at the selected site on the new drug or device.
- The investigator must be qualified to conduct such a study, qualification by education, training and experience.
- The investigator has to be approved by the Regulatory authority and the Ethics Committee.
- He/she has to make a commitment to conduct the trial as per the protocol and the relevant regulations.

Trial Participants

- Trial participants are chosen by the investigator, according to pre-decided selection criteria known as Inclusion and exclusion criteria.
- Inclusion criteria are first applied to the population to be studied and then exclusion criteria are used to remove those who could be at a greater risk due to the investigational product.
- Very strict inclusion criteria may cause difficulty in recruiting the desired number of participants, while loose criteria may cause unsuitable participants to be included and hence are at risk.

I/E Criteria

- Common Inclusion Criteria are:
  - Age and gender of participants
  - Accurate diagnosis of the participants
    - Including severity, stage or extent of disease
  - Ability and readiness to provide written consent
- Common Exclusion Criteria are:
  - Pregnancy and lactation
  - Co morbidities that will increase risk to participants
  - Conditions that may prevent participant from complying to trial requirements

Sample Size

The number of participants chosen for a study is a balance between two opposing concepts:

- The need for high number of participants, that increases the accuracy of extrapolating the results to all patients of that disorder.
- The need to reduce the number of participants to reduce the number put at risk of adverse effects of an untested medication.

- This number is statistically derived after considering the expected results and required accuracy.

Objectives

- Every study has primary and secondary objectives.
- Primary objective relates to the principal intended effect of the product under investigation. The study must be able to answer whether the product produces that effect or not.
- Secondary objectives relate to other beneficial or desirable attributes the investigational product may possess. These are over and above the main benefit (primary objective) and may be regarded as a "bonus"

End Points

- There are two types of end points, primary and secondary; corresponding to the primary and secondary objectives of the trial.
- End points are single in nature, but sometimes may be a composite of different symptoms.

Example

- Primary end point for study of antihypertensive drug is fall in BP.
- Primary end point of an anti anxiety agent is reduction in anxiety score, which is calculated from a set of symptoms.

Parameters

- Biological parameters are chosen for measurement on the basis of the primary and secondary end points for the trial.
- Baseline levels of relevant parameters are required to be recorded before beginning the administration of the investigational product and the comparator.
- These parameters need to be recorded periodically depending upon their variability and propensity to change. All measurements should be repeated at the end of the study.
- Analysis of the values tells us, to what level the investigational drug and the comparator affects each parameter.

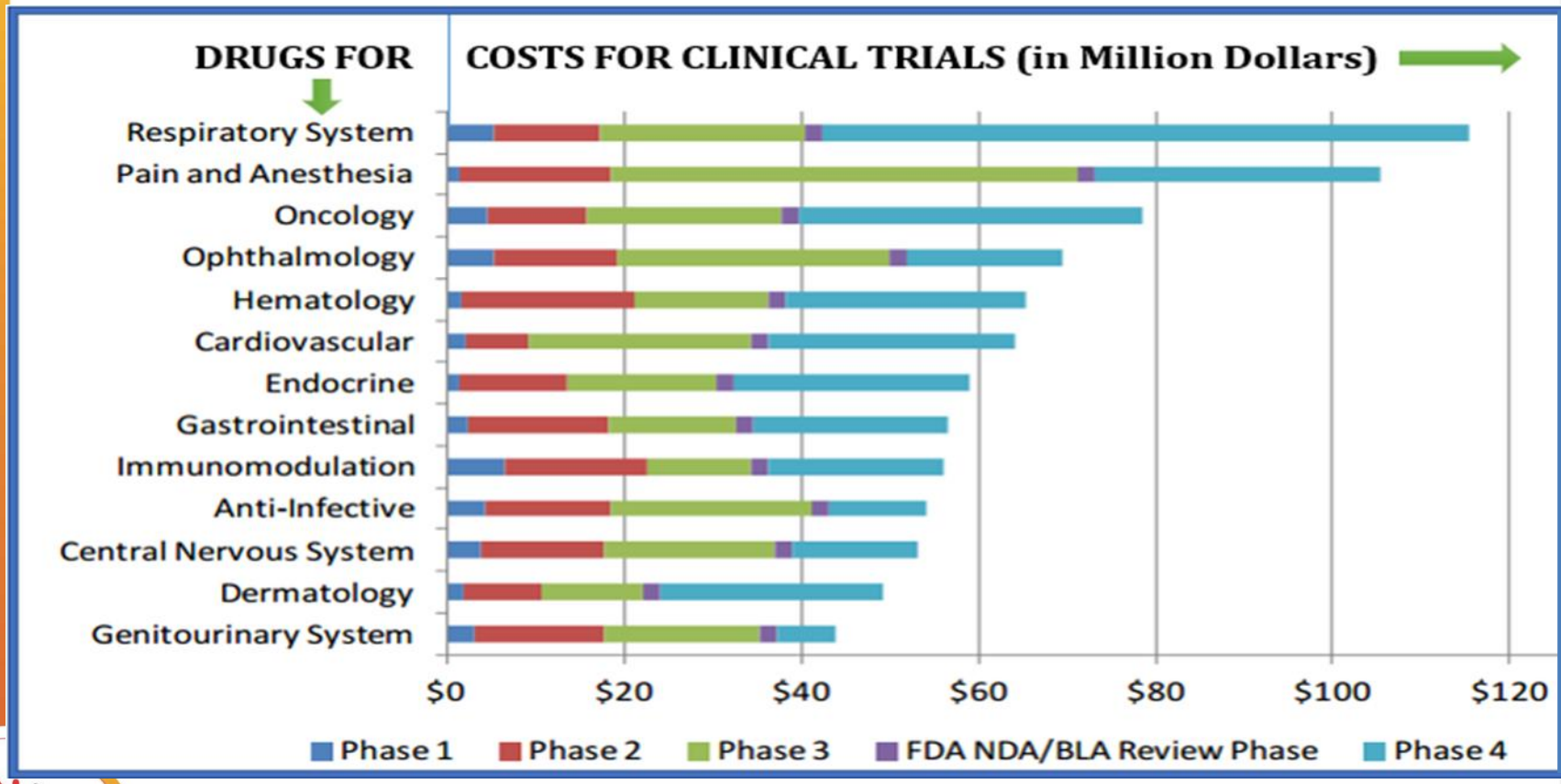
Data Analysis

- All data collected during the trial, needs to be accurately recorded. The recorded data are checked for missing values and errors if any.
- The cleaned data are statistically analysed to obtain results of the trial, which may be conveyed to the sponsor for preparing a report for the regulatory authority or for publication.
- The regulators, on going through the analysed data would decide if the claim made for the investigational product is valid, and may grant permission for marketing the product.

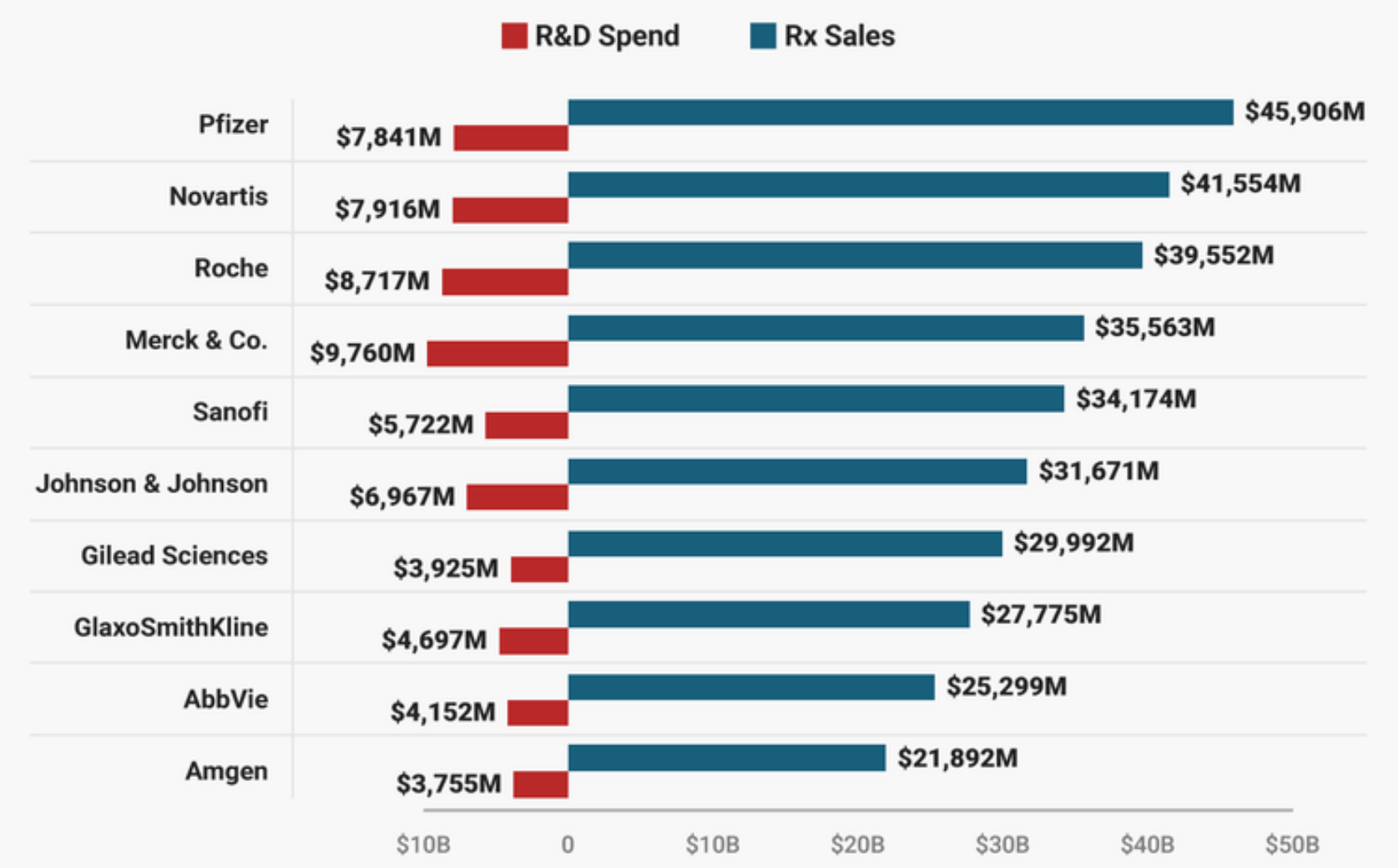
Archiving

- Since, data on drugs and devices is of significant public interest, they have to be preserved for a specified time period.
- The regulators may ask for the trial data, in case of any unexpected toxicity is noted with the product.
- Products are often recalled from the market, years after their initial introduction based on reanalysis of the data.
- Published reports on investigational products serve an important function, that is to provide information about the product to medical practitioners who prescribe them.

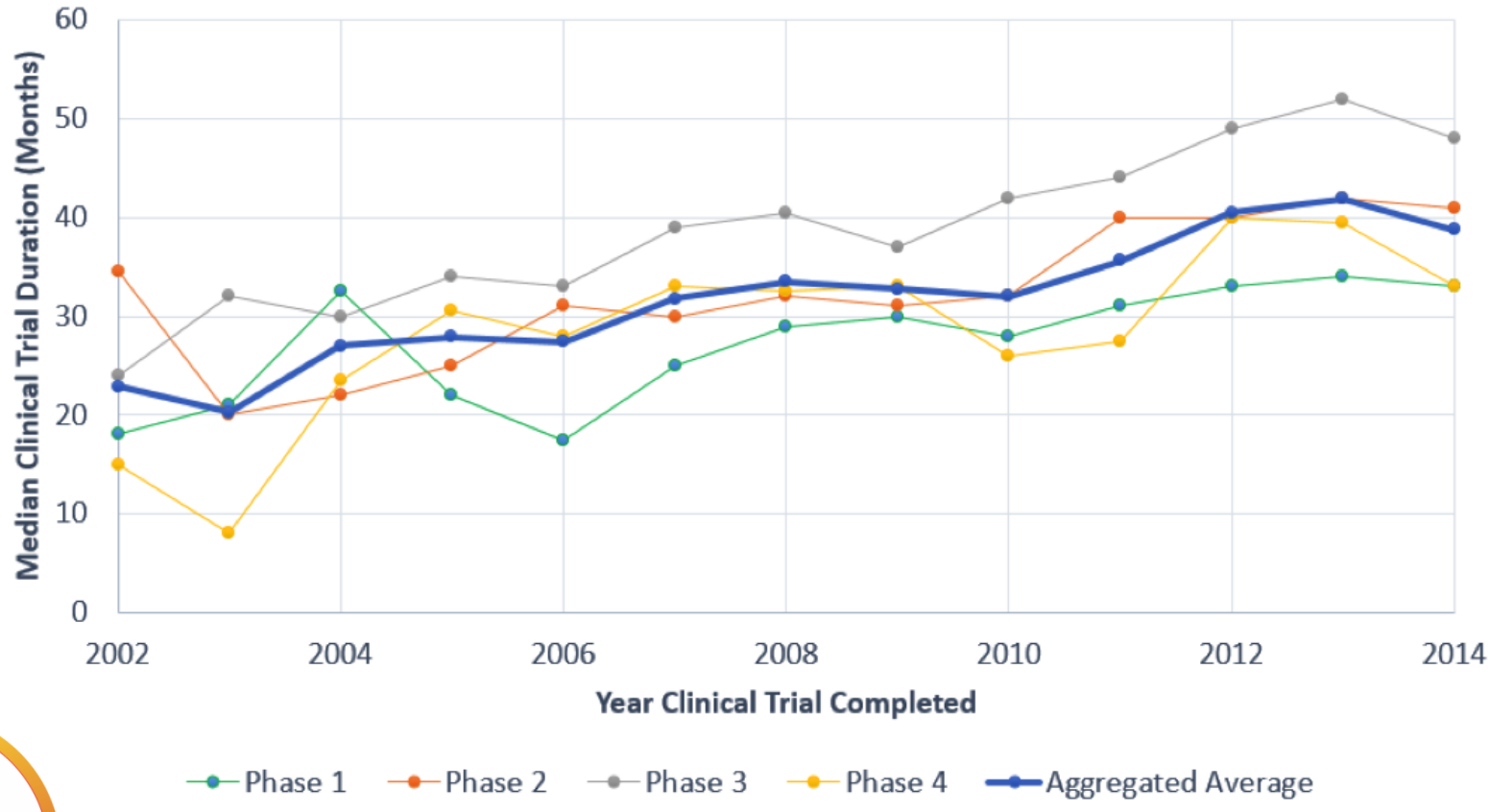
Costs in million dollars



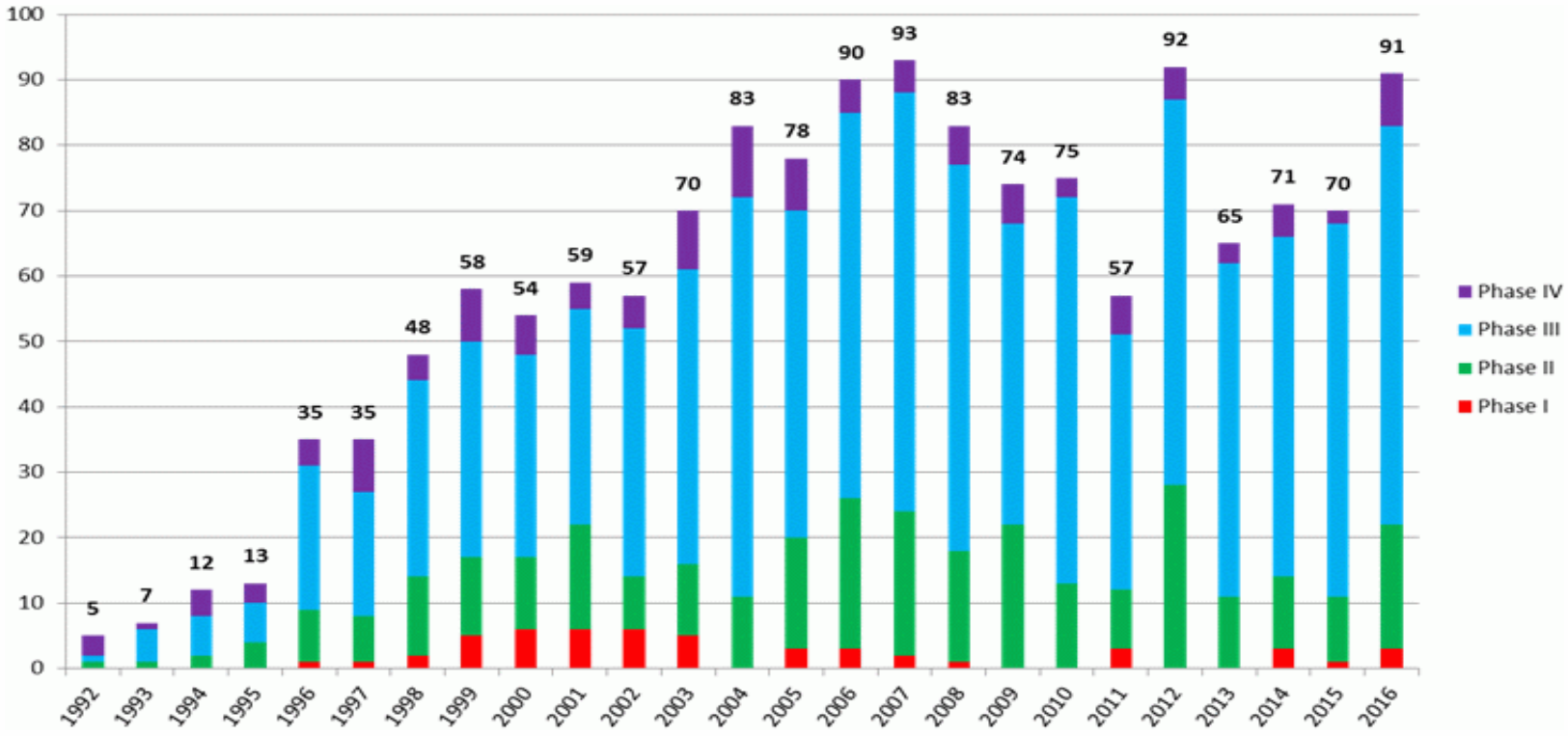
Drug Development



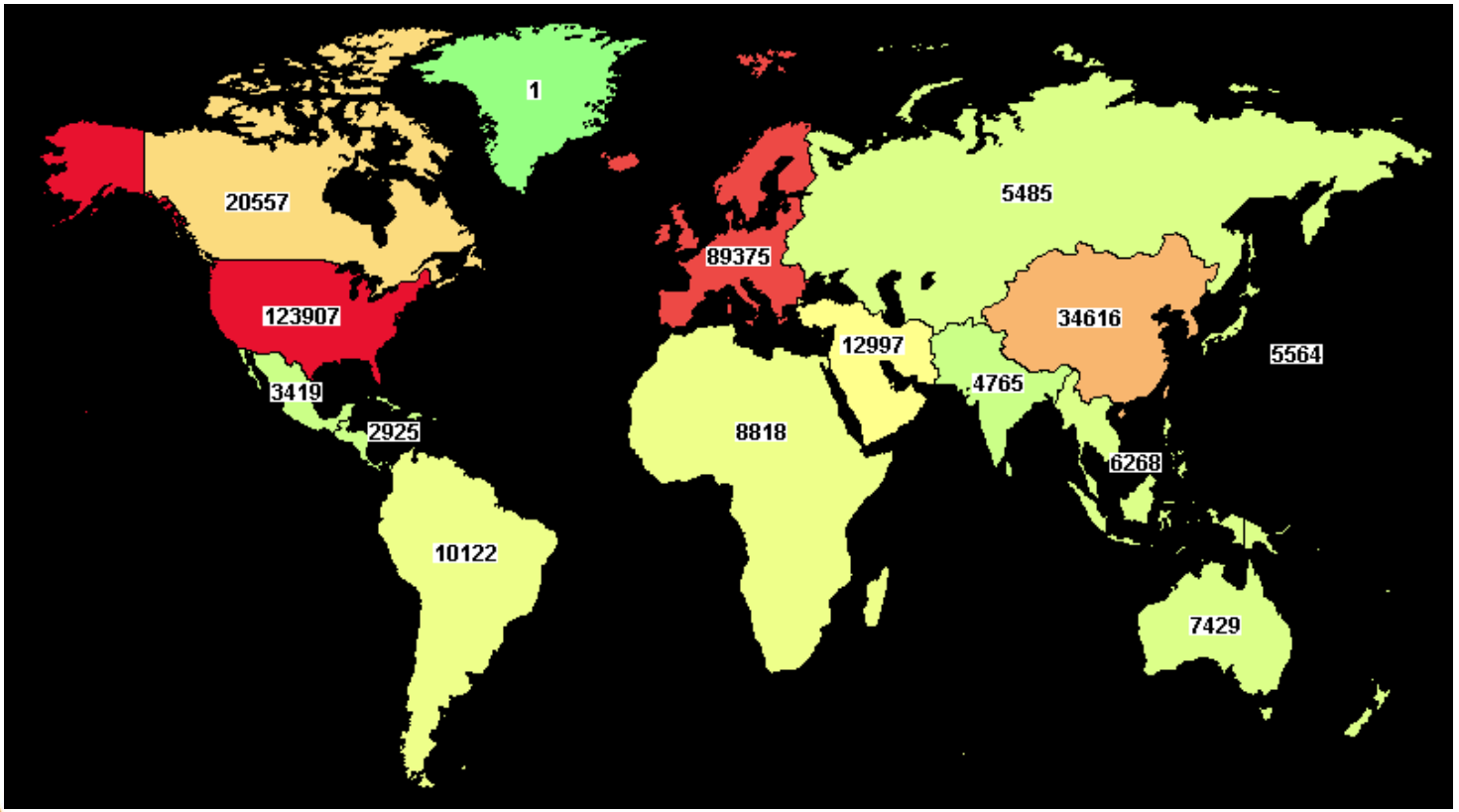
Duration of Trials is rising



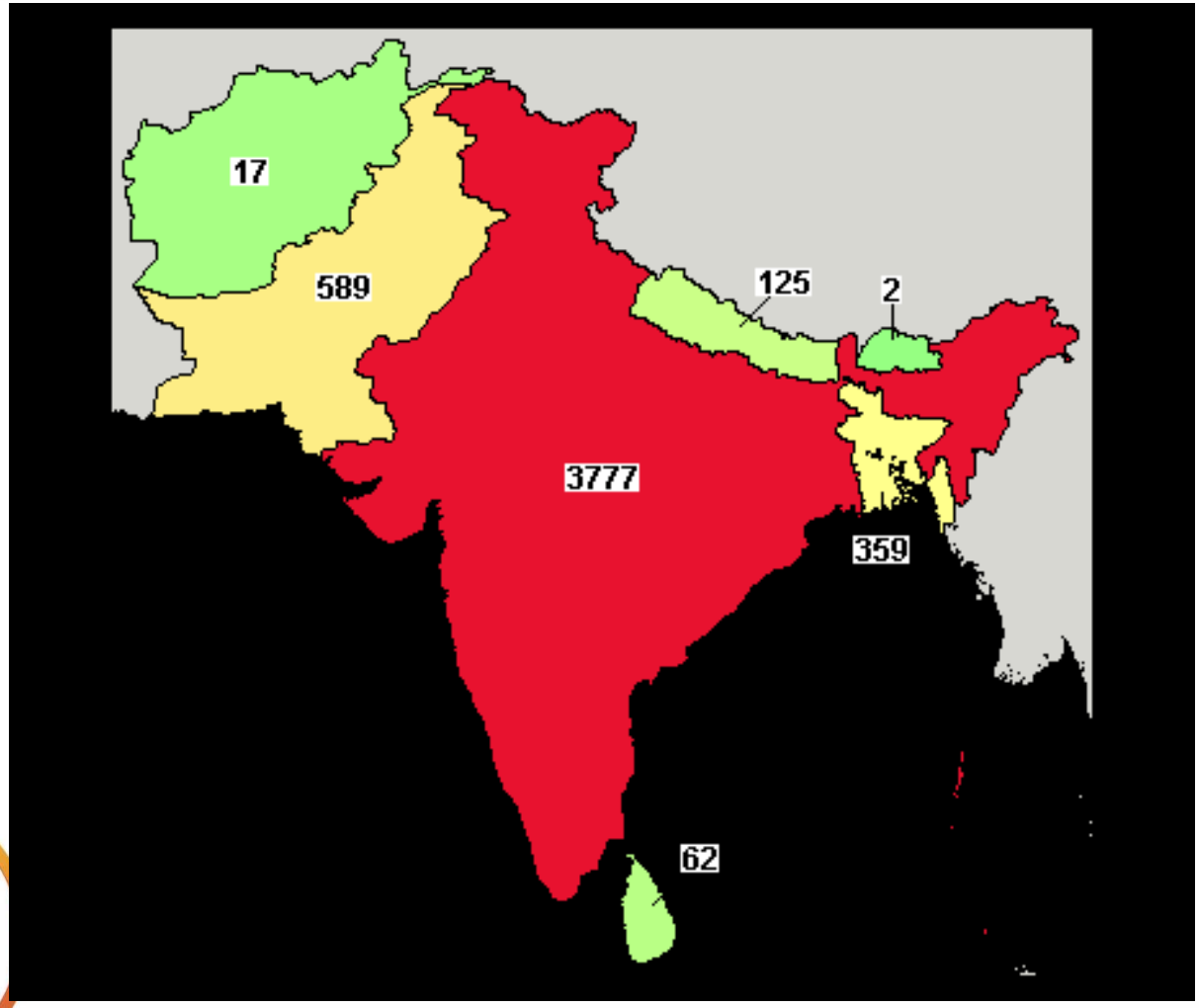
Distribution of Trials by Phase



The World of CR



Indian Subcontinent



As per US Registry on 15.8.2019

Clinical Trial Density

Country	Population (Million)	Clinical Trials	Trials/Million
World	7530	313819	41.68
Canada	37	20557	555.6
United Stated	329	123907	376.6
Europe	513	89357	174.2
China	1398	15074	10.7
Africa	1216	8818	7.2
Indian Subcontinent	1729	4765	2.76

As per US Registry on 15.8.2019

WHO/US Registry

Country	Trials	Country	Trials
Canada	25681	United States	132811
United Kingdoms	35166	Germany	37060
France	30017	Russia	7895
India	24592	China	39443

Questions?

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