# Phase 0 to IV

## Clinical Trials


Module 3 Topic 3

# When to begin Clinical Trials

- Clinical Trials may be contemplated when animals studies have demonstrated the safety of the drug in the intended therapeutic range, and the drug shows promise of superiority to existing treatment.
- Trials can be initiated only when the licensing authority has given a no objection to the trial application and the same has been approved by the institutional ethics committee.

# When to begin Clinical Trials

- The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

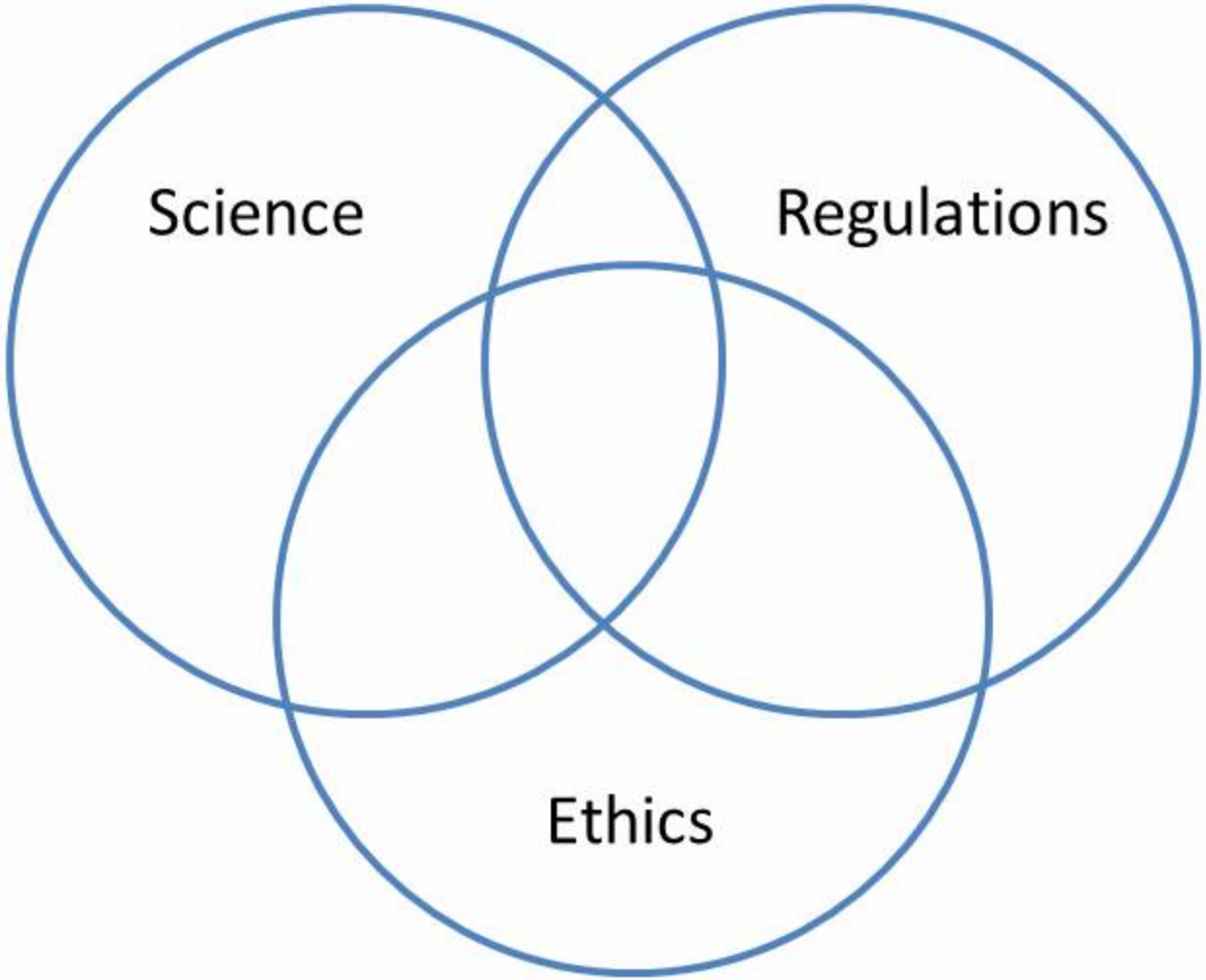
Nuremberg Code 1947

# When to begin Clinical Trials

- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

Declaration Of Helsinki

# Science, Ethics and Regulations



# Clinical Trials

**Aims**

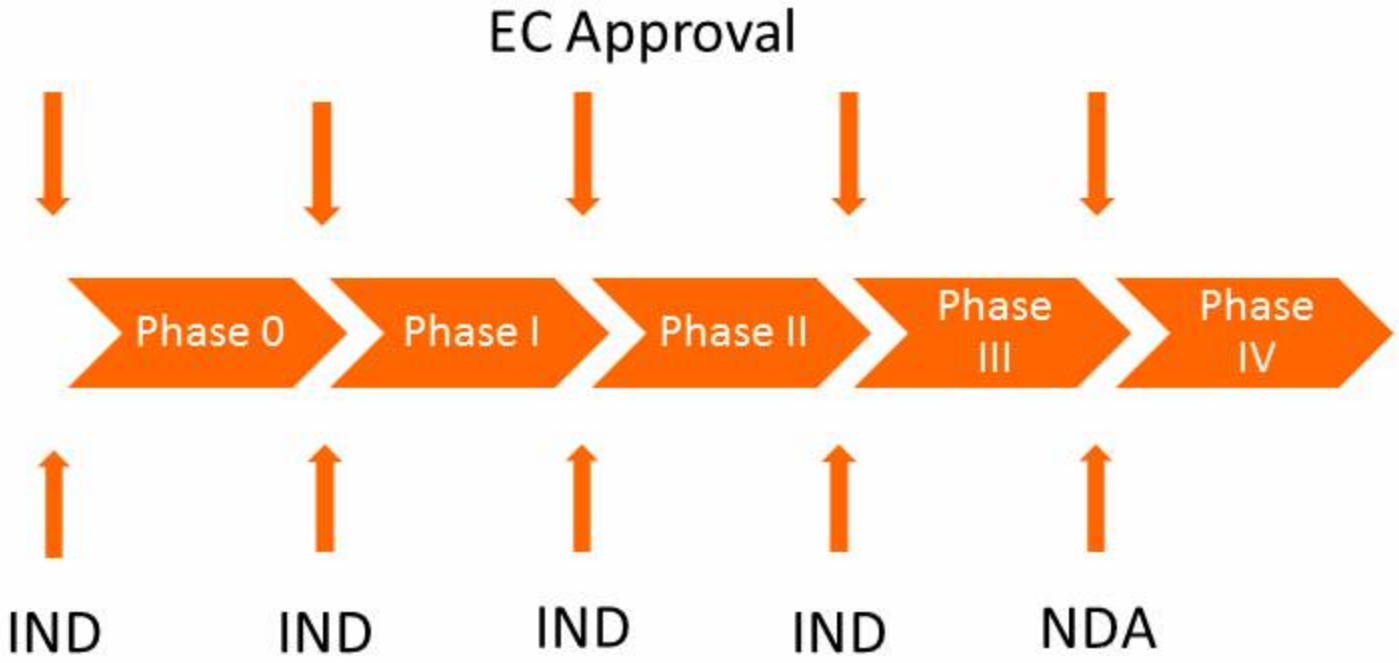
To evaluate the safety and efficacy of a new drug or that of an existing drug in new indication, that will provide advantage to the patients suffering from the disease.

**Objectives**

The primary and secondary objectives of each phase are different, but the objective for studies of a particular phase remain the same for most molecules.

# Phases of Trials

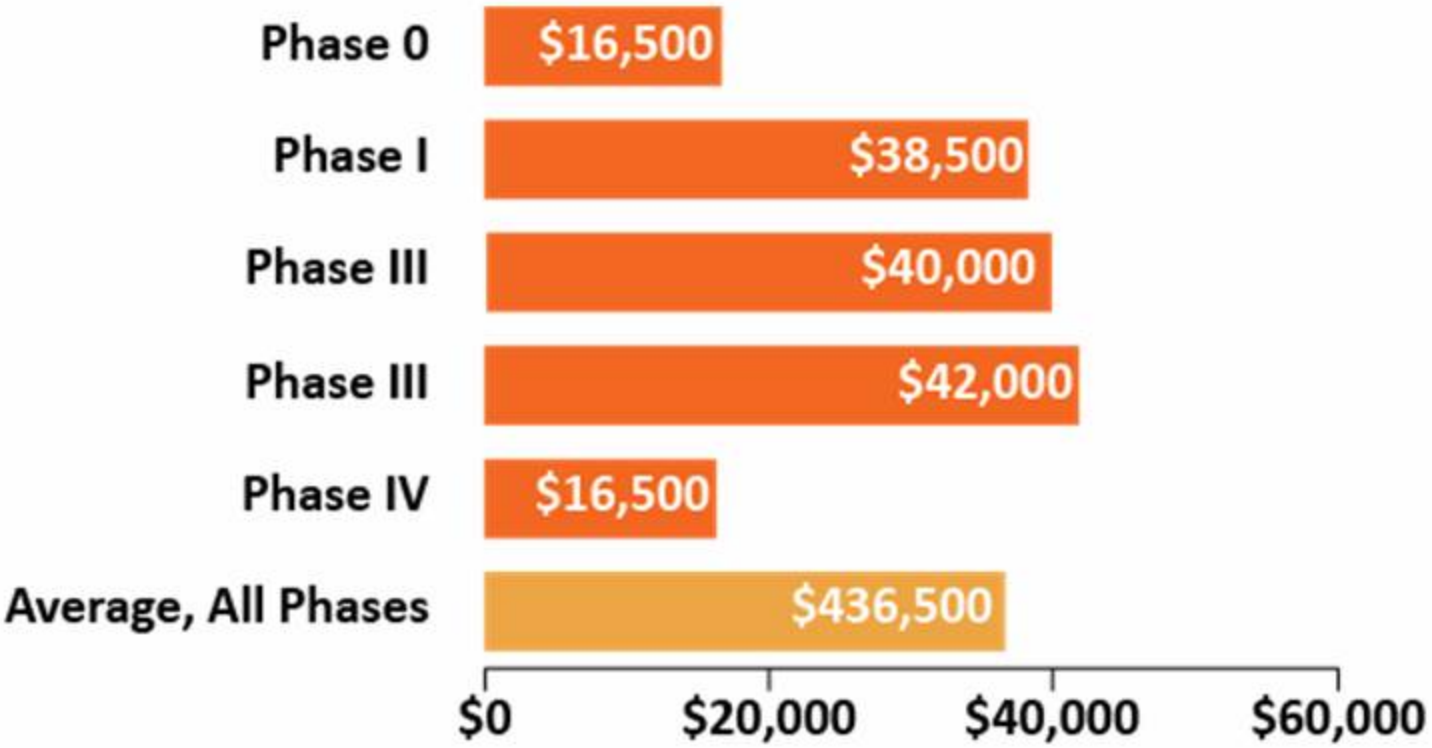
Clinical trials are conducted in phases 0 to IV, each phase being conducted sequentially



# Trial Phases

From I to IV the complexity of trial rises with more and more factors like blinding, randomization, choice of control and end points.

# Cost per patient (Phase wise)



# Trials in Progress Worldwide

| S.No | Phase | Total | Recruiting |
|---|---|---|---|
| 1 | Early Phase I | 2230 | 526 |
| 2 | Phase I | 37465 | 5190 |
| 3 | Phase II | 53444 | 8396 |
| 4 | Phase III | 33047 | 13857 |
| 5 | Phase IV | 23776 | 2993 |

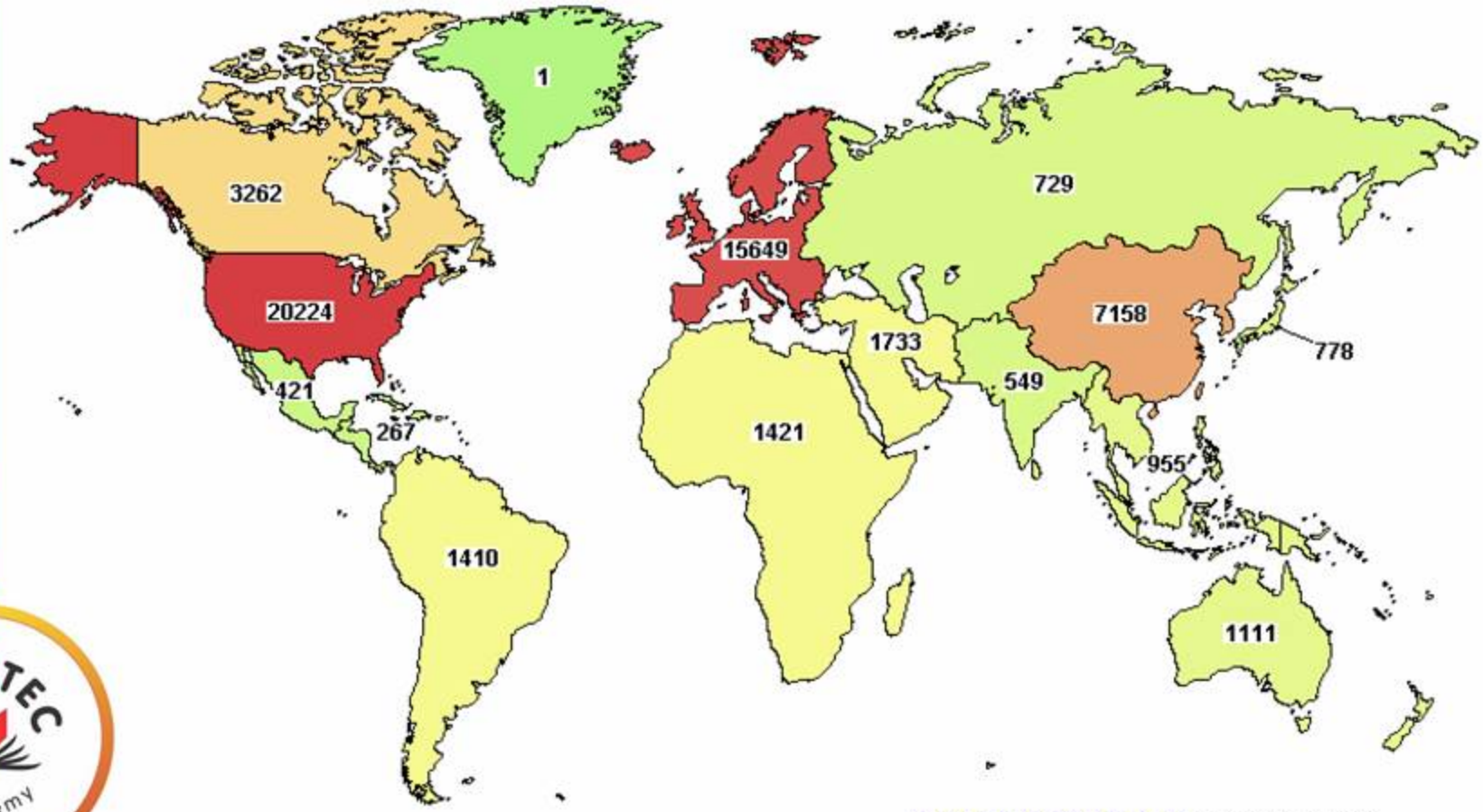
(www.clinicaltrials.gov as on 25.5.2018)

# Success Rate Phase-wise

| S.No | Phase | Total |
|---|---|---|
| 1 | Early Phase I | 85.3% |
| 2 | Phase I | 63.2% |
| 3 | Phase II | 30.7% |
| 4 | Phase III | 58.1% |
| 5 | NDA | 85.3% |
| 6 | Overall | 9.2% |

(www.bio.org)

# Clinical Trials Worldwide (Recruiting)




(www.clinicaltrials.gov as on 25.5.2018)

# Phase 0

- Phase 0 clinical trial is proposed by the US Food and Drug Administration and the Pharmaceutical Research and Manufacturers of America (PhRMA) to streamline the process of drug development.
- This phase requires less preclinical data, and involves administration of 1% of the therapeutic dose to verify the action of the drug on the target.
- The objectives of a phase 0 cancer clinical trial are to establish whether an agent is modulating its target in a tumour, and consequently whether further clinical development is warranted.
- Reported to be an outcome of the TGN 1412 tragedy.

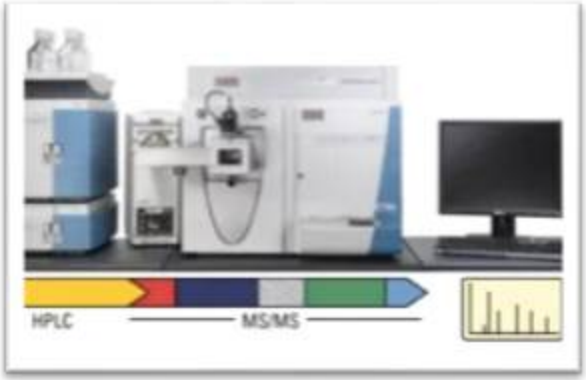
# Phase 0

- The aim is not to demonstrate efficacy, but to show whether the Pharmacodyamics and Pharmacokinetics warrant further development.
- Phase 0 is primary screen to weed out ineffective drugs, since a large number of drugs are failing in early trials.
- This is because in many drug classes (such as monoclonal antibodies) animal studies do not predict the safety or activity of the drug in humans.
- Using 1% of intended therapeutic dose eliminates the risk of toxicity.

# Phase 0

- 1% of the intended therapeutic dose (NMT 100 mcg) is injected in about 6 healthy adult males.
- Drug levels are traced in different body fluids and drug macromolecular interaction is studied if possible.
- Due to extremely low doses of the drug to be used, either very sensitive equipment is needed to detect the drug in body fluids or radiolabeling may be required.
- There are many objections to this phase, in any case the Phase 0 is not required for all drugs, but a selected few.

# Radiolabeling




| Phase I<br>First in Human | Phase II<br>First in Patient | Phase III<br>Multi-Site Trial | Phase IV<br>Post Marketing Surveillance |
|---|---|---|---|
| 10-100 participants | 50-500 participants | A few hundred thousand to a few thousand participants | Many thousands of participants |
| Usually healthy volunteers; occasionally patients with advanced or rare disease. | Patient-subject receiving experimental drug | Patient-subject receiving experimental drug | Patients in treatment with approved drug |
| Open Label | Randomized & controlled (can be placebo-controlled):may be blinded | Randomized and controlled (can be placebo-controlled; may be blinded | Open label |
| Safety and tolerability | Efficacy and dose ranging | Confirm efficacy in larger population | Adverse events compianlce, drug-drug interactions |
| Months to 1 year | 1-2 years | 3-5 years | No fixed duration<br>— |
| U.S. $10million | U.S. $20million | U.S. $50-100 million | — |
| Success rate: 50% | Success rate: 30% | Success rate: 25-50% | |
| Human Pharmacology | Therapeutic Exploratory | Therapeutic Confirmatory | Therapeutic Use |

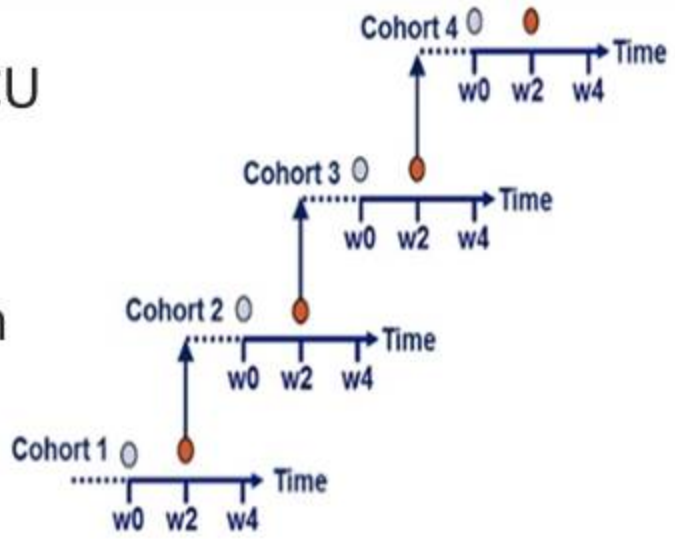
# Phase I

**Objective:** To study the safety of the drug in this first in human study. Additionally Pharmacokinetics may be studied. If the drug exhibits any pharmacodynamic properties, the same may be studied.

# Phase I

**Subjects:** 20 to 100 healthy subjects are studied in an ICU environment, measuring as many physiological parameters as possible both before and after the drug administration.

**Dosage:** Dosage of the drug calculated from NOEL/ NOAEL. The dose may be escalated, or repeated depending on the intended use of the drug.



# Phase II

**Objective:** To evaluate the efficacy of new drugs, the safety of said treatments and dosage specifications. Phase II research is conducted on patients afflicted with the condition the drugs intend to treat.

**Subjects:** Usually patients (about 300) suffering from the target disease, preferably with no or very few comorbidities. Patients within a narrow range of variables are preferred.

**Dosage:** Dosage is usually fixed in the Phase II Study, as is the schedule and the target group of patients. Appropriate end points help in evaluating both safety and efficacy of the product.

# Phase II

- Ideally, a Phase II trial should
  - Establish the proof of concept
  - Have a high benefit to risk ratio
  - Can be generalized to a maximum number of sub groups
  - Be adequate for approval or need a single Phase III study
- In practice
  - High rate of failure in this phase (60% in oncology)
  - Is not a true test of usefulness or futility
  - Often results are ambiguous

# Phase II/III

- Seamless II/III trials generally use an adaptive design and provide fundamentally better answers of safety and efficacy in a shorter time, with lower costs and more certainty.

- Phase II/III study that tests how well a new treatment works for a certain type of cancer or other disease and compares the new treatment with a standard treatment. Phase II/III clinical trials may also provide more information about the safety and side effects of the new treatment. Combining phases II and III may allow research questions to be answered more quickly or with fewer patients.

# Phase III

**Objective:** To confirm the activity and the safety of the new drug in comparison with a standard drug in practice.

**Subjects:** The participants should be like those encountered in a hospital or a clinic. Usually both men and women are studied in multicentric studies. The number of participants depends on the expected usage of the drug and often 1000's are used.

**Dosage:** The dosage of the new drug is decided in the Phase II trial, while the dosage of the standard drug is based on clinical reports. End points chosen to reveal both efficacy and safety of the drug.

# Phase IV

**Objective:** To study the efficiency of the drug as opposed to efficacy of the drug studied in Phase III, or the effect of the drug in real life conditions. They are also meant to collect more information on adverse effects when the drugs are used in clinical practice.

**Subject:** Very large number of subjects, many with comorbidities as are seen in routine clinical practice. Inclusion criteria are wide and exclusion criteria are at a bare minimum.

**Dosage:** The same as used in Phase III and as indicated by the license. Dose may be adjusted in case of co-morbidities or age considerations.

# Phase IV

- These studies usually use an observational design. They include patients of a wider variety, and have less oversight. Thus they reveal what is likely to happen when the drug is used in clinical practice.
- Large number of subjects help reveal side effects whose incidence is lower.
- The drug could be tried out for other indications which may be related to the main indication. Off label use is also tested sometimes in such trials.

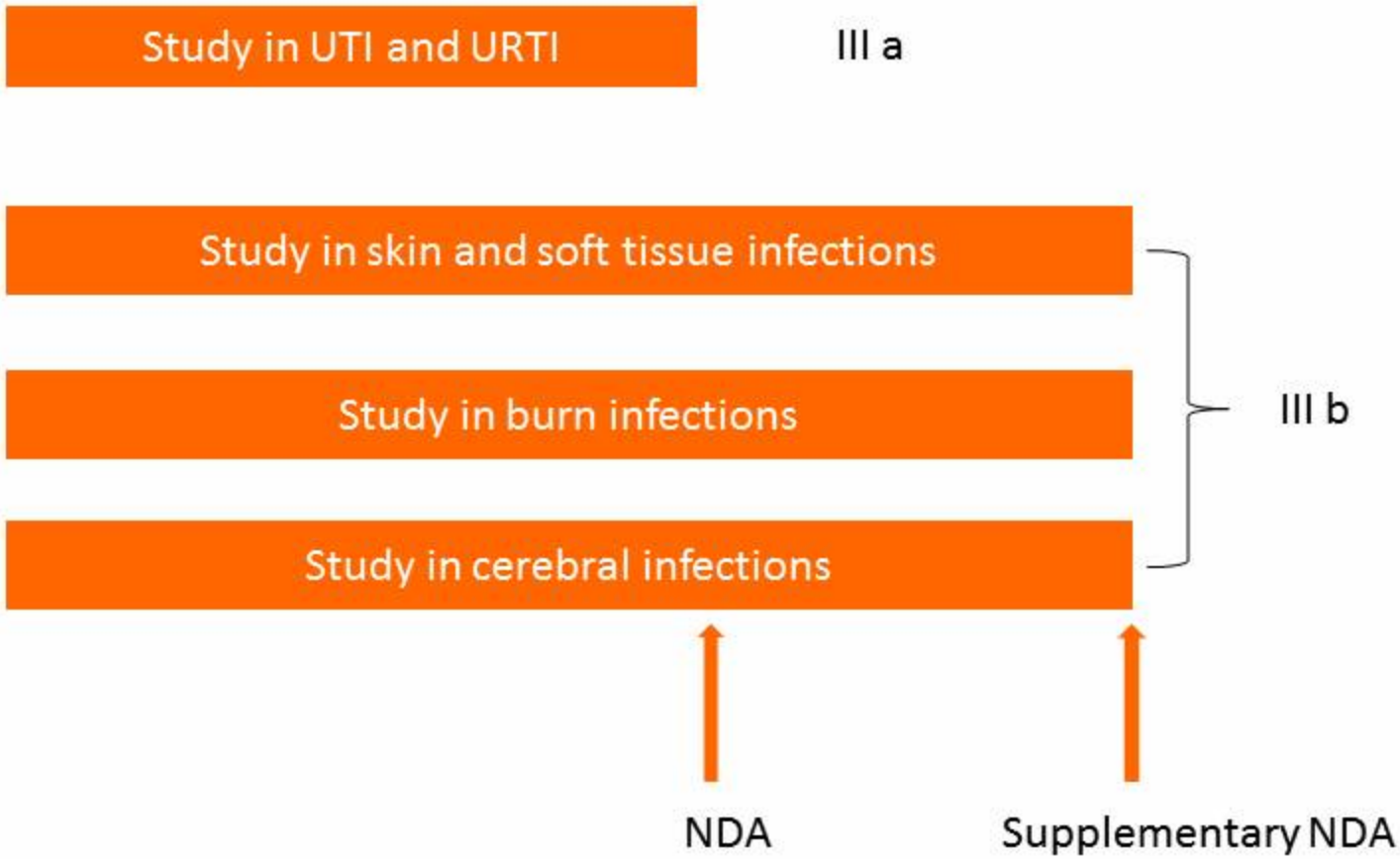
# Phase III a & b

Subtypes of Phase III

- Phase IIIa aims to get adequate data for NDA filing.
- Phase IIIb allows patients to continue treatment, for additional indications, and additional safety data.
- After Phase IIIa usually the NDA is filed, and the Phase IIIB continues as the NDA is under consideration.
- As soon as Phase IIIb data are in hand, supplementary NDAs are filed.

# Example of III a & b

A new Antibiotic

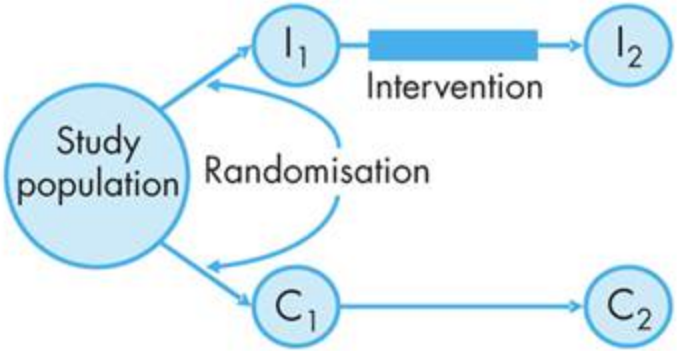


# Phase III

- The most common design for Phase III studies is
  - Interventional
  - Randomized
  - Double blind
  - Multicentric
  - Standard Controlled

In very specific cases a cross over design or an adaptive design may be used.

# Interventional




- A type of clinical study in which participants are assigned to groups that receive one or more intervention / treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.

# Randomized

- The process of assigning patients to different arms in a trial by chance is called randomization. In the simplest trial design, one group receives the new treatment this is the investigational group. The other group receives standard therapy, this is the control group. At several points during and at the end of the clinical trial, researchers compare the groups to see which treatment is more effective or has fewer side effects. A computer is usually used to assign patients to groups. Randomization is used to reduce allocation bias, and usually results in groups of patients with similar characteristics.

# Double Blind

- A double blind trial is a trial where neither the researchers nor the patients know what they are getting. The computer gives each patient a code number. And the code numbers are then allocated to the treatment groups. A patient's treatment arrives with a code number on it. Neither the patient nor the doctor knows whether it is the new treatment or not.

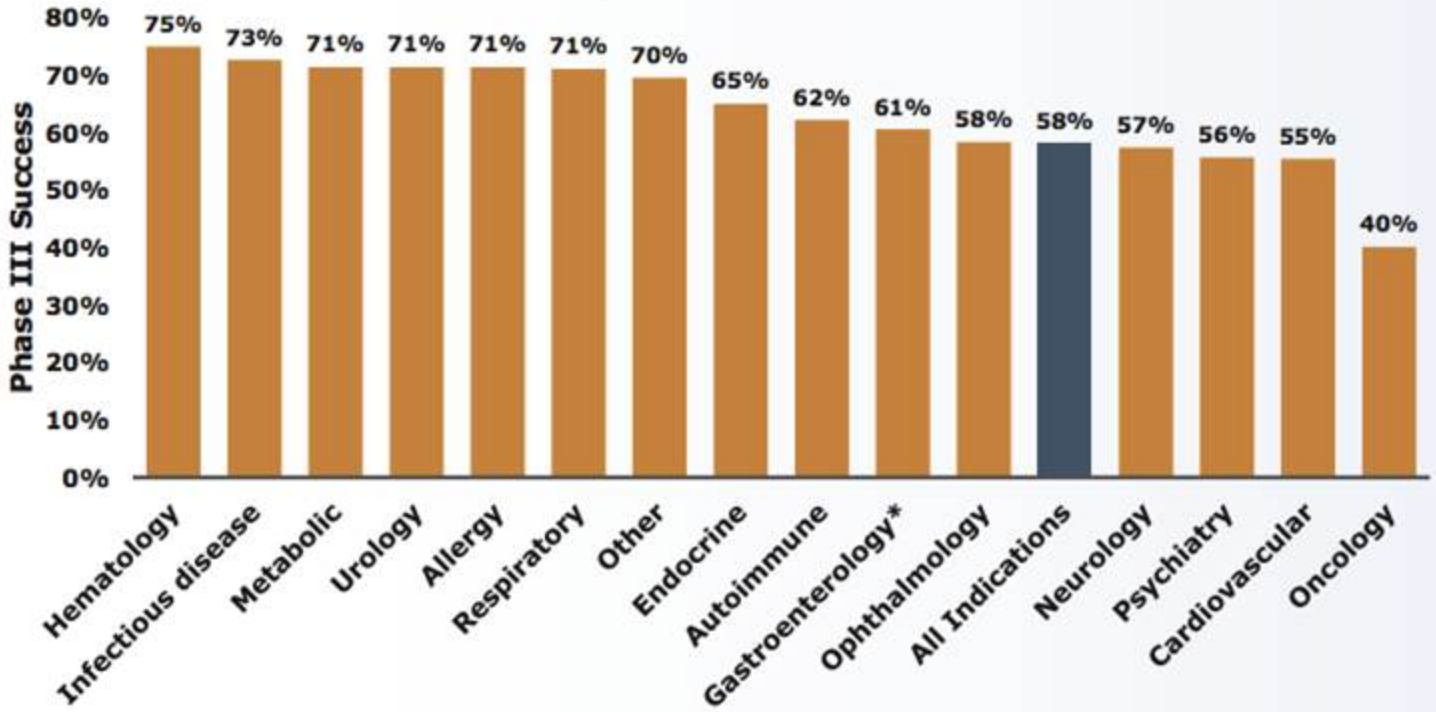
# Multicentric Trials

Multicentre trials are those that are conducted simultaneously in a number of hospitals or sites. This is done for two reasons:

- Firstly, a multicentre trial is an accepted way of evaluating a new technology more efficiently; it is a practical way of accruing sufficient subjects within a reasonable time frame.
- Secondly, it provides a better basis for the subsequent generalisation of its findings. This is due to recruiting of subjects from a wider population, and testing the drug in a broader range of clinical settings.

# Standard Controlled

- The control group in standard controlled trials receives the best available standard drug. This control is superior to placebo control, since
  - A comparison is done with a drug used by patients
  - Patients in the control group are not harmed by absence of treatment.
  - Patients in the control group receive the same therapy as they would have, if they were not a part of the trial.
  - Use of placebos in blinded trials amounts to cheating the patients.


Probability of Phase III Success
Phase III Success
80%
70%
60%
50%
40%
30%
20%
10%
0%
75%
73%
71%
71%
71%
71%
70%
65%
62%
61%
58%
58%
57%
56%
55%
40%
Hematology
Infectious disease
Metabolic
Urology
Allergy
Respiratory
Other
Endocrine
Autoimmune
Gastroenterology*
Ophthalmology
All Indications
Neurology
Psychiatry
Cardiovascular
Oncology

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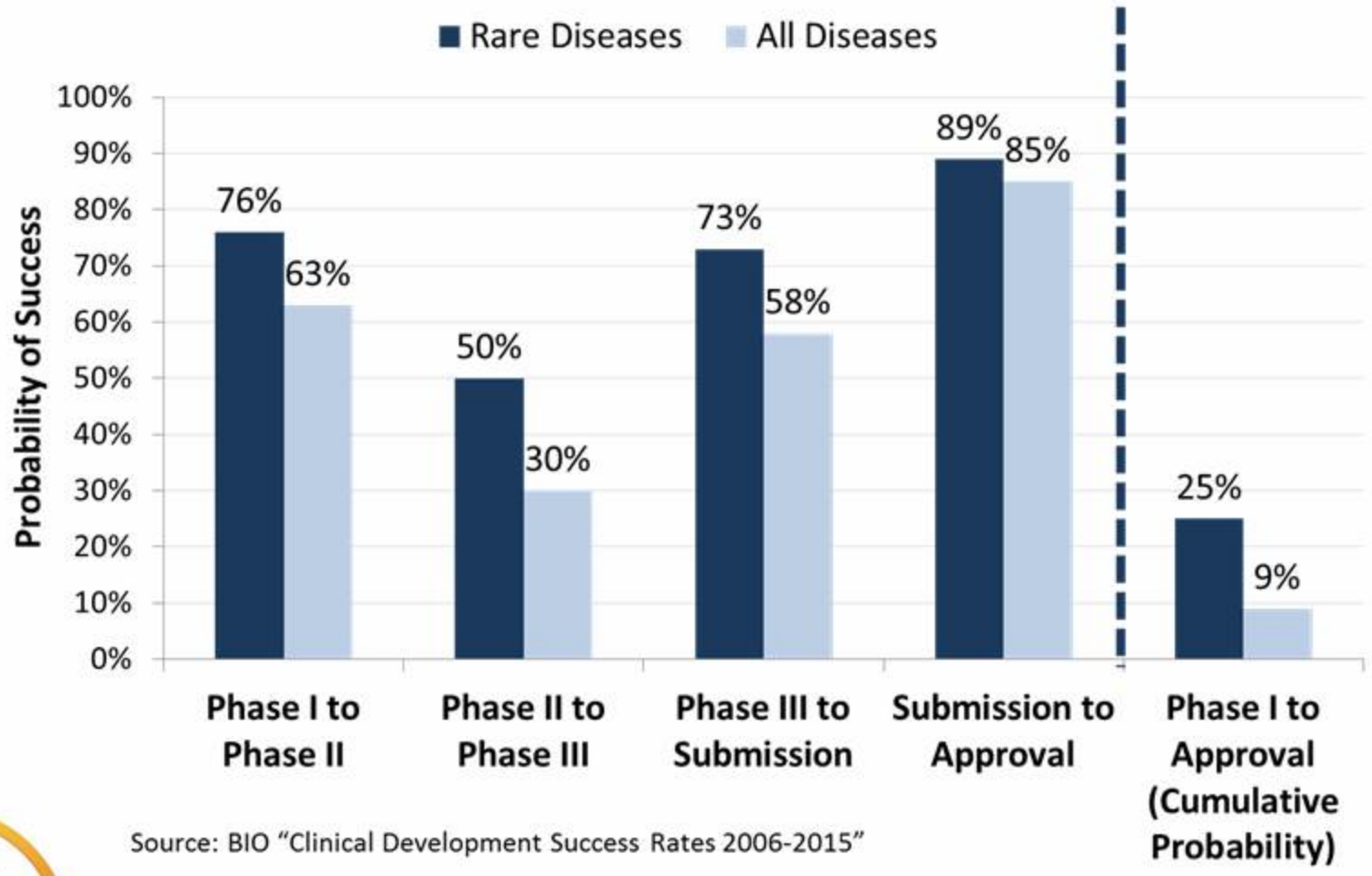


Source: BIO "Clinical Development Success Rates 2006-2015"

**Success Probabilities for Rare Diseases vs All Diseases**