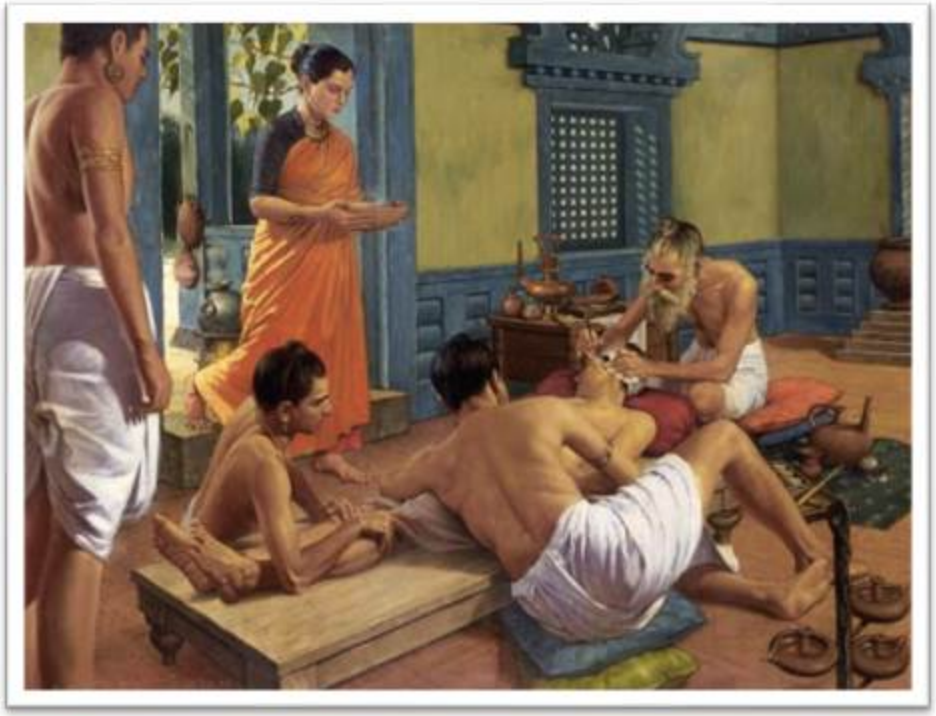
Clinical Research

In India and Worldwide

Module 1 Topic 3

Indian Medicine

Sushruta (~ 500 BC), the Indian Surgeon is believed to be the son of Vishwamitra. He was the author of Sushruta Samhita, which described in addition to anatomy, techniques for surgical repair. Indian medicine subsequently lost its leadership of the world and is only now regaining Its foothold.

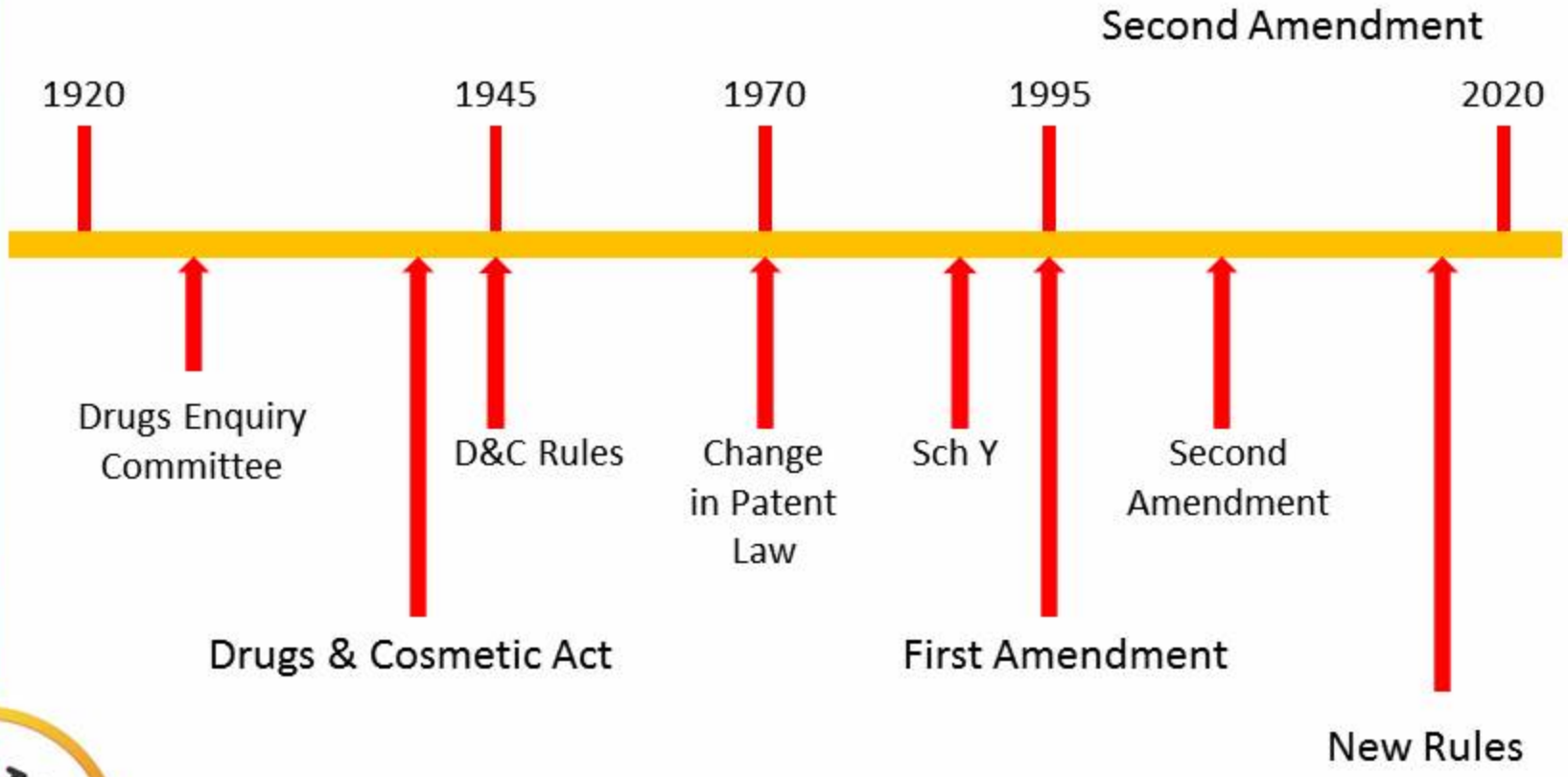


Drugs & Cosmetics Act & Rules

- The Indian Government in 1930 appointed the Drugs Enquiry Committee under Col. Sir Ram Nath Chopra.
- Its report formed the basis for the Drugs & Cosmetics Act 1940 and the Rules 1945.
- Both became effective in April 1947, they have been amended a number of times.

Sir. Col. Ram Nath Chopra

Regulations time line



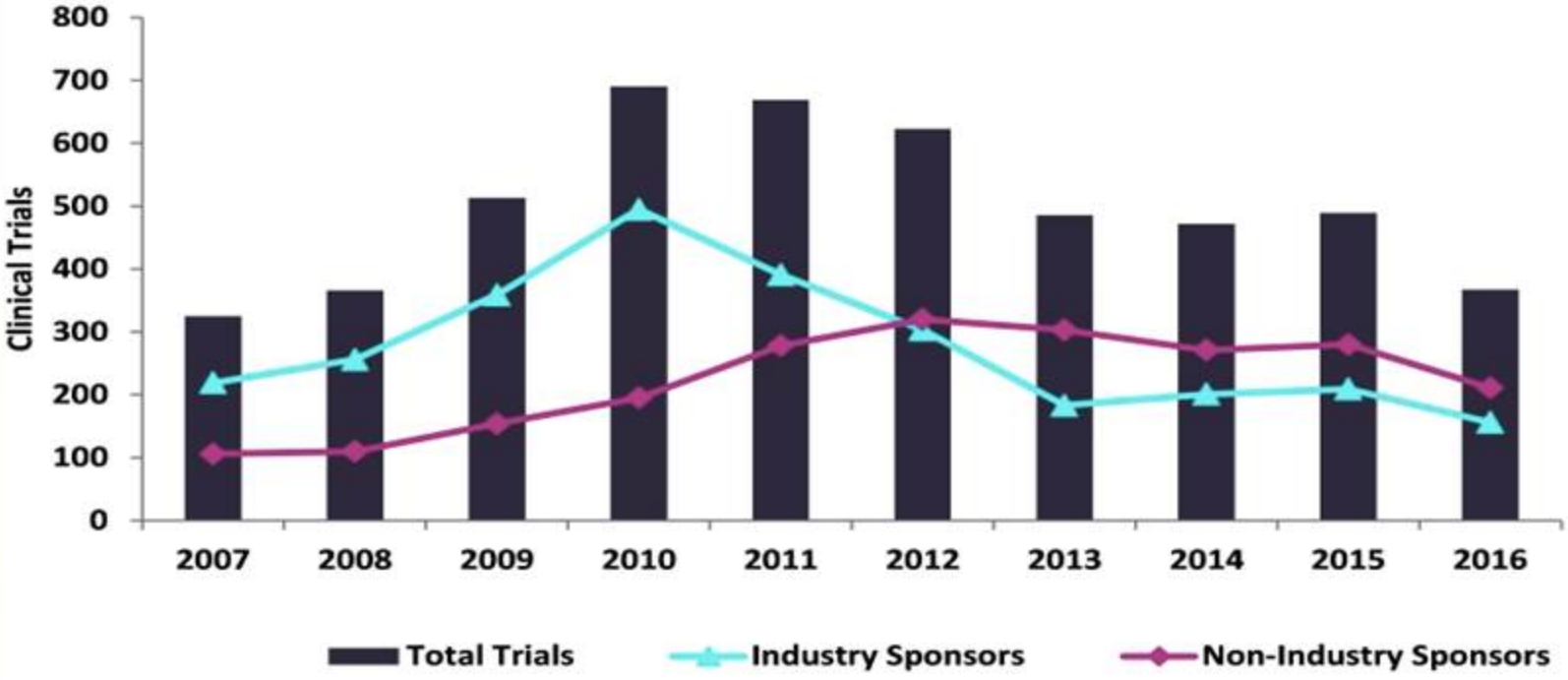
Trials in India

- Patent Act (1970) scrapped the product patent in India on foods and drugs.
- An inventor in India could get no patent protection in India for his inventions.
- This proved to be a disincentive for drug discovery, and the industry began to concentrate on “reverse engineering” all drug discovery related activities slowed down.
- A few clinical trials, mostly of overseas molecules were done in India.

Trials in India

- Government of India joined the WTO in January 1995, we were given a 10 year period to enforce the product patents on drugs and pharmaceuticals. It became clear that by January 2005, India would have to comply with Intellectual Property laws.
- The Indian Pharmaceutical industry began drug discovery and development in right earnest, setting up research centres and clinical pharmacology units.
- By 2004, India began to be talked of as a hub for outsourced clinical research.

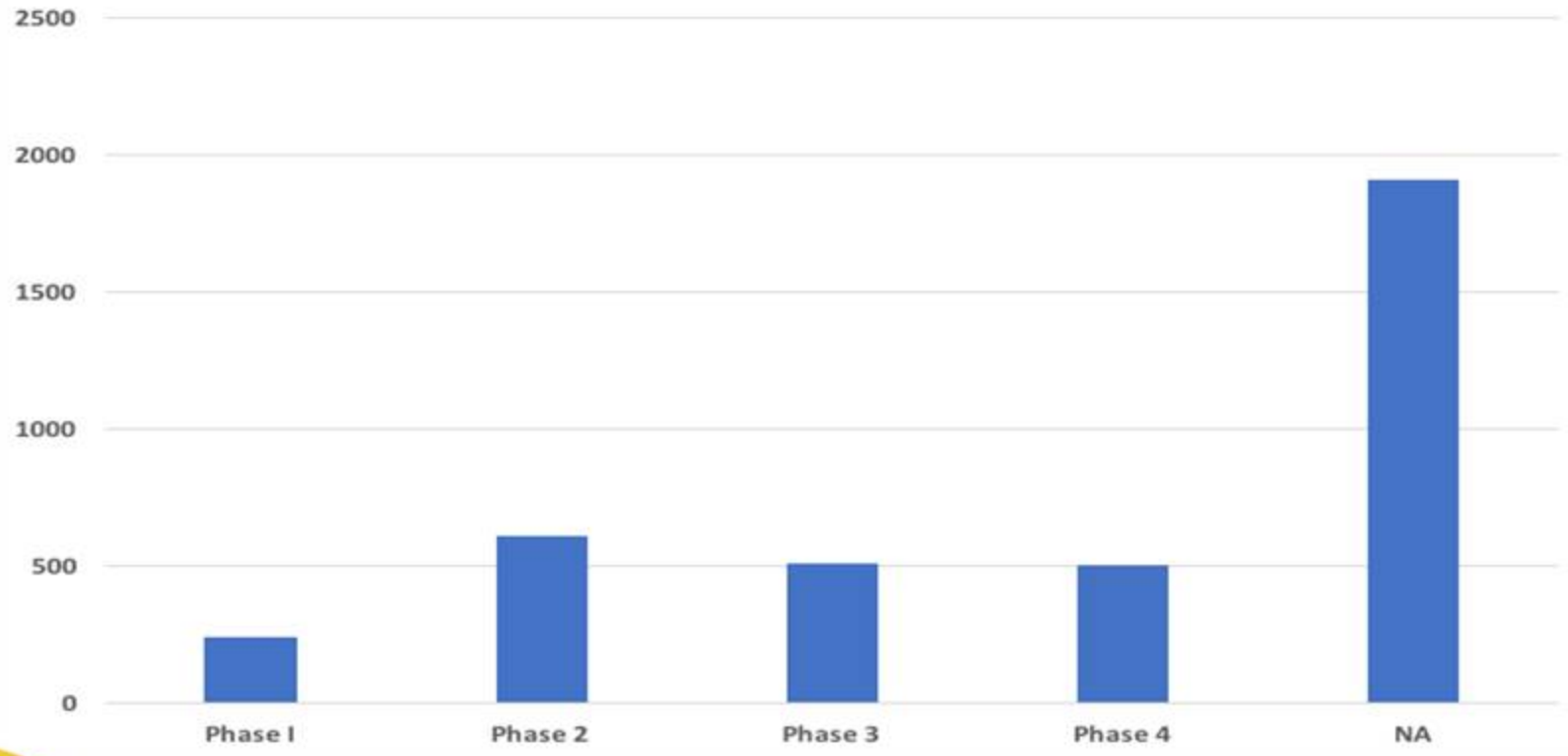
Clinical Trials in India



www.clinicaltrials.gov

KLINTEC Academy

Clinical Trials in India (as per CTRI)

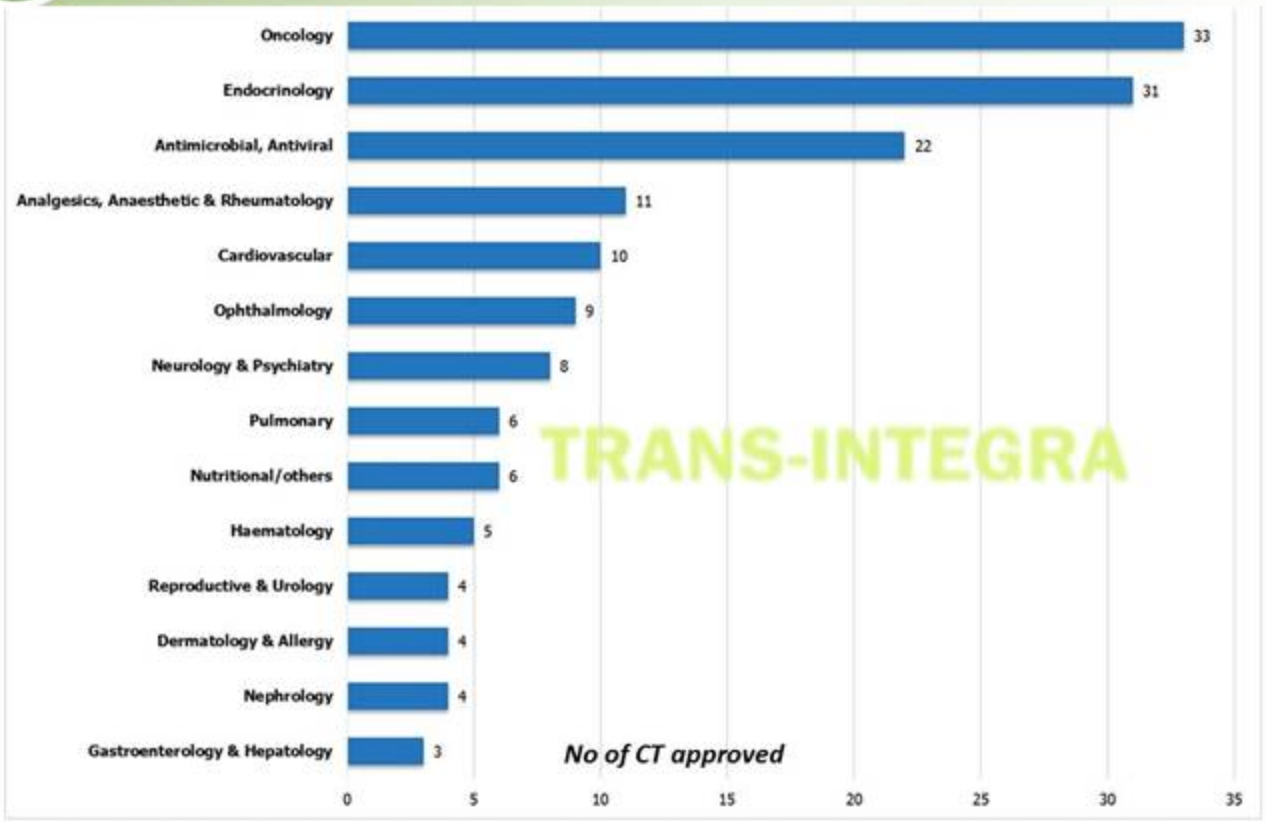


Clinical Trials in India

- It is difficult to know exactly how many trials are in progress in the country. Approvals by CDSCO do not give the correct figure, since trials go on for varying periods.
- Indian clinical trial registry is not user friendly, does not allow searches as the US site does. It is difficult to know the number of trials recruiting, closed to recruitment, completed etc.
- Analysis of CTRI data is only as good as the website.
- Registration of Indian Trials is not compulsory on the US registry, hence not all trials are registered, US data for India is not accurate.

REGIONAL REGULATORY UPDATE

"India: Therapeutic area-wise CT approvals (2014 - March 2015)"



Endocrine/Metabolic, Oncology and Anti-infective continue to be major areas of interest in Indian pharma market

Reference & Source of raw data: CDSCO India, available at http://www.cdsco.nic.in

Ethical Oversight

- Ethical oversight is provided by Ethics Committees, of individual institutes.
- Prior to 2013, there is no data as to how many ECs were operating and how many of them were complying to regulations.
- When the Rule 122 DD required ECs to be registered over 1200 were registered for three years.
- When their registration expired 2016, only about 500 applied for re registration.
- Now that NABH accreditation may become compulsory, so far only 233 have applied.

EC Competence

- Competence of ECs has been doubted by many workers, the DCGI requires EC members to be trained.
- There is no fixed syllabus for training, no formal training mechanism.
- There are no accredited bodies to conduct training.
- If EC members are to be trained, we estimate that about 200 training programs need to be held annually in our country.
- Neither ICMR, CDSA nor CDSCO has the resources to conduct so many programs.

Factors affecting growth

Positive

- Large patient pool with a variety of diseases
- Good quality hospitals, and highly qualified doctors
- English is the medium of communication
- Costs significantly lower than developed countries

Negative

- Large percentage of illiterate patients
- Poor medical services outside bigger cities
- Poor regulatory and ethical oversight
- Negative perception about trials among press and people

Negative Press

- Over the last decade, the press has been consistent in its criticism of research.
- Only negative aspects of research are published, the press avoids reporting gains due to research.
- Poor regulatory oversight gave more ammunition to the press.
- Greed among some doctors, led to the conduct of unethical trials, which were heavily publicized.
- The Supreme Court ordered the framing of proper rules in 2013.

Unethical Research

- Unethical clinical trials by a few investigators has brought disrepute to the entire industry.
- Inadequate training, resources, time of investigators could be responsible.
- Heavy clinical work load has been cited as a factor responsible for unethical research.
- Greed of sponsors and investigators has also been cited as a cause, and the regulator has failed to control such instances.
- All stakeholders are responsible for this.

HPV Vaccine Trial

- The trial sponsored by Program for Appropriate Technology and Health (PATH).
- It was conducted on nearly 23,500 girls in the 10-14 years age group in Khammam district (Andhra Pradesh) and Vadodra (Gujarat).
- Nearly 2,800 consent forms were signed by a hostel warden or headmaster, as the 'guardian', and not by the parent as required by D&C Rules.
- There were 7 deaths, all unrelated to the trial, but revealed the total lack of oversight.

Rota virus vaccine trials

- Rotavac (Bharat Biotech) and Rotasiil (Serum Institute of India), both rota virus vaccines have undergone clinical trials:
- The trials are under fire for the following reasons:
  - Comparison with placebo is not justified when rota virus vaccines are in the market
  - Numbers studied are too small to conclude about the safety of the vaccine
  - 56% protection with Rotavac seems to be poor in comparison with that offered by Rotarix (GSK)
  - Rotasiil seems to increase the incidence of non rotaviral diarrhea.

Benefits-Cancer

- Trastuzumab and its biosimilars have been studied in 29 clinical trials in India.
- In these trials, trastuzumab has been made available to hundreds of patients who had HER2 Positive cancers.
- Free access to the expensive drug was possible only because of the clinical trials in the country.
- Biosimilars of Trastuzumab (Herceptin) have been launched by Reliance, Biocon, Dr. Reddy and Intas. Many others are awaiting approval, this competition has brought down the cost of the drug.

Benefits Haemophilia

- Concentrates of coagulation factors or recombinant factors, which are very expensive, are used for the treatment of haemophilia
- In 15 trials on these products and their alternatives, patients have received the drugs free of cost, which they would not have otherwise received.
- Free of cost investigations offered in these trials are essential for many patients of economically deprived sections
- The survival and continued health of these patients depends on their entering a trial.

Benefits to society

- Clinical research benefits all stakeholders.
  - Hospitals – by adding new equipment
  - Investigators- by providing them experience
  - Patients- by providing new medications
  - Industry- by offering more economical test systems
  - Government- by increasing inflow of investment

Benefits to Indian Industry

- Trial costs in India are estimated to be 25 to 40% of those abroad.
- Drugs discovered and developed in India will not see the light of the day if no clinical trials were to be done in India.
- Ratio of Indian molecules to overseas molecules is slowly rising in the Indian clinical research industry.
- By and large, molecules of Indian origin are vastly cheaper to those developed abroad, more suited to our economy.

Regulatory Actions

- Jan 30, 2013 New rules for compensation of trial related injuries were published
- Feb 1, 2013 Rules for streamlining working of Ethics Committees published
- Feb 8, 2013 Rules requiring registration of Ethics Committees with CDSCO Published
- Jun 2013, RR Choudhary Committee recommends accreditation of ECs, Sites and PIs.
- Nov 19, 2013 Rules requiring audio visual recording of consent process published

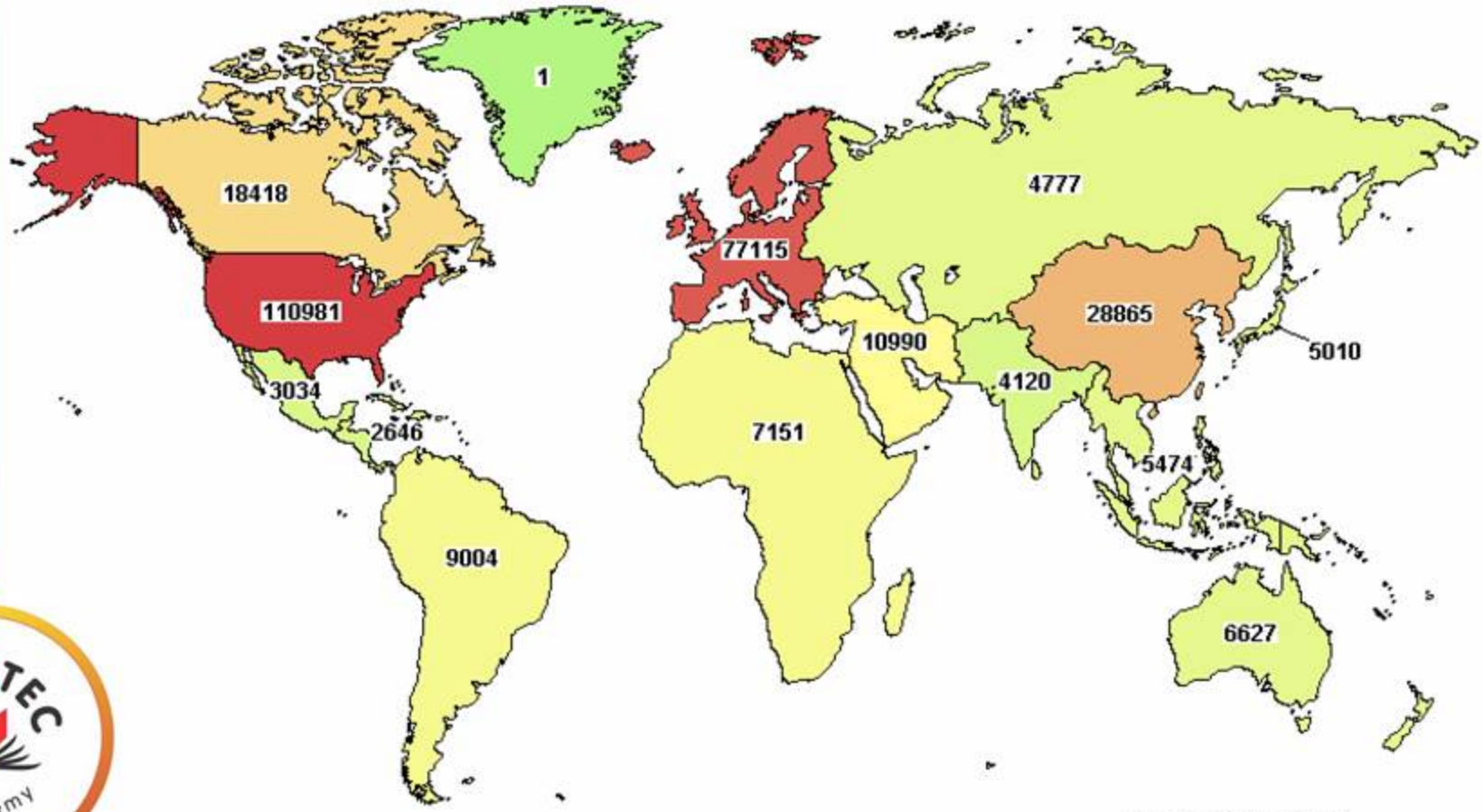
Regulatory approvals

- Regulators need to allow pre filing consultations and advice sponsors about their requirements.
- Regulators need to speed up approvals, presently there are no time lines for approval.
- New Drugs and Clinical Trial Rules (2018) provide for fixed time lines for approval, as follows:
  - For drugs developed and proposed to be marketed in India- 45 days
  - For drugs already approved outside India in select countries – 90 days

Ethics Committees

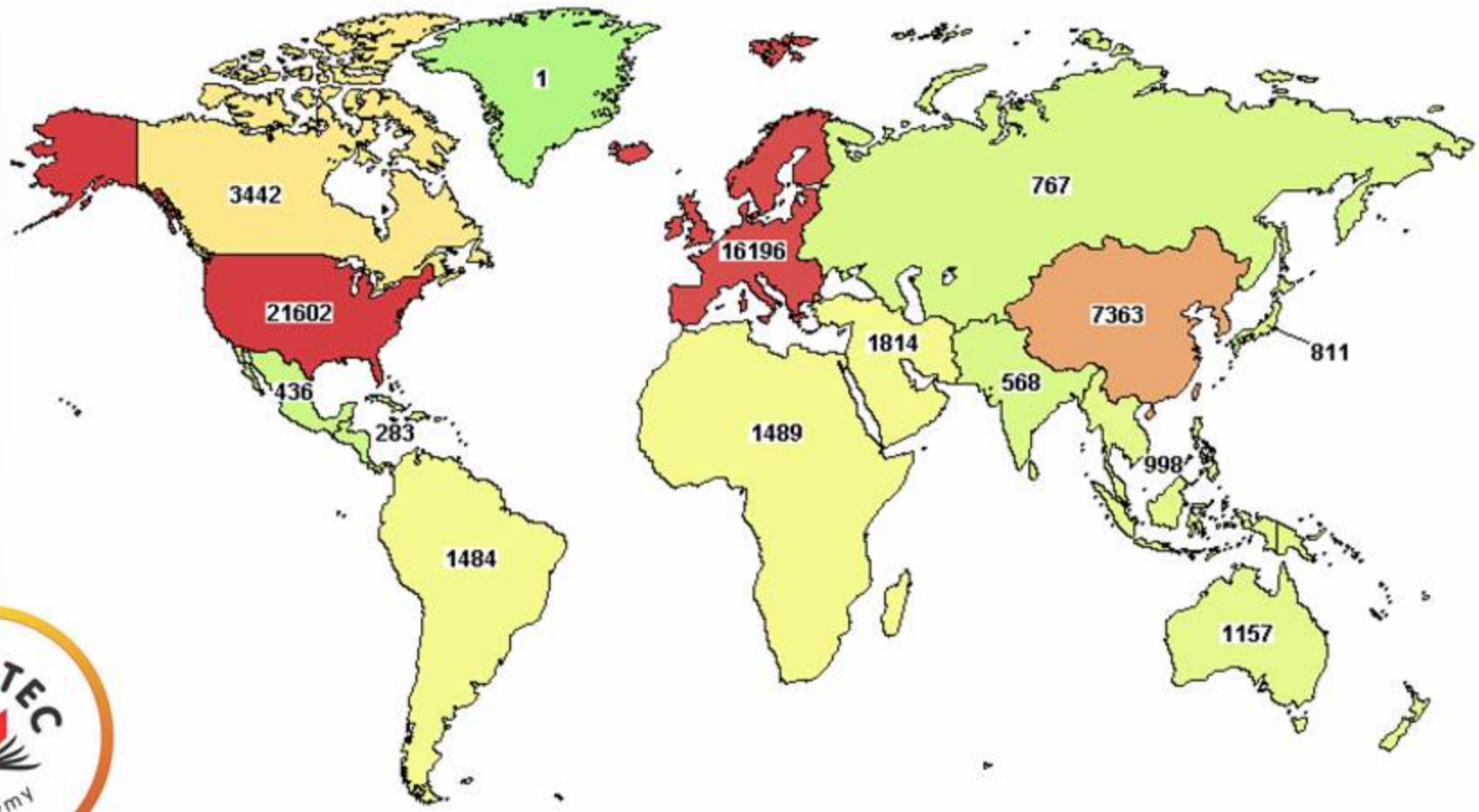
- In 2013 a total of 1257 ECs were registered with the CDSCO
- In 2016 only 533 ECs opted for re-registration
- In 2018 only 233 ECs have applied for accreditation by NABH
- Till October 2018, only 43 ECs have been accredited, and accreditation of 190 ECs is pending.
- NABH needs to speed up accreditation process and complete the assessment of pending ECs.

Clinical Trials Worldwide

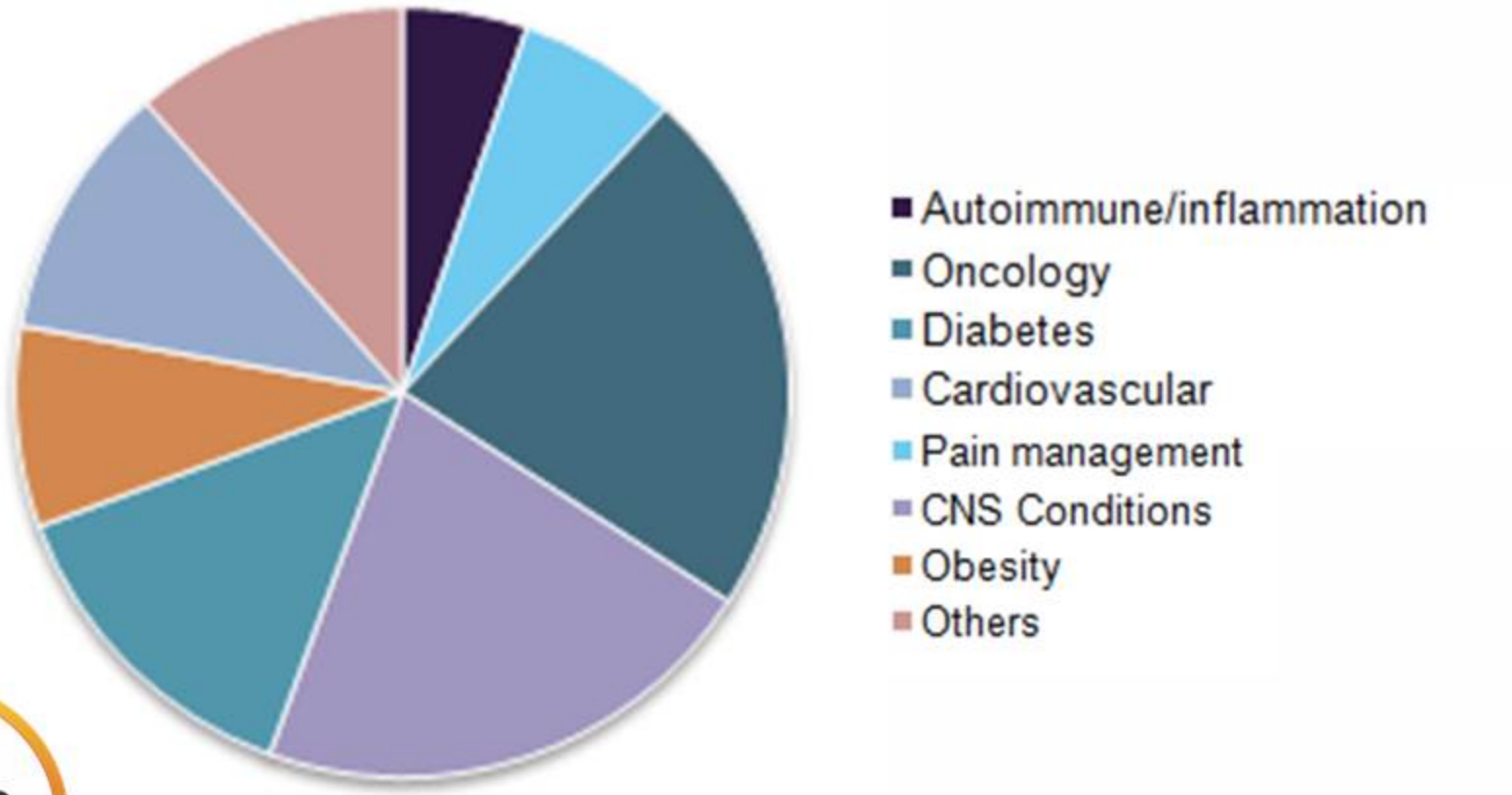


As on May 1, 2018

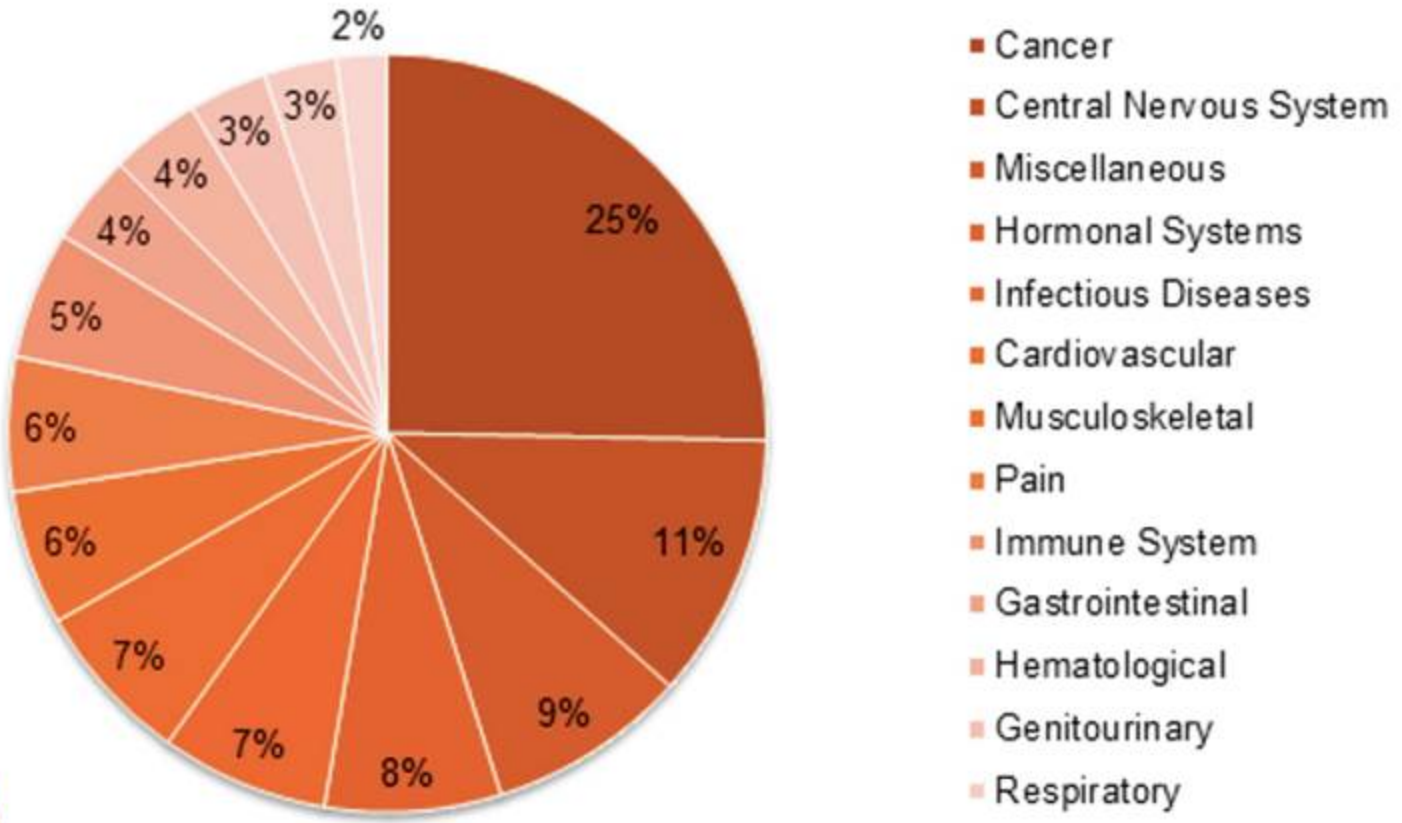
Clinical trials (Recruiting)



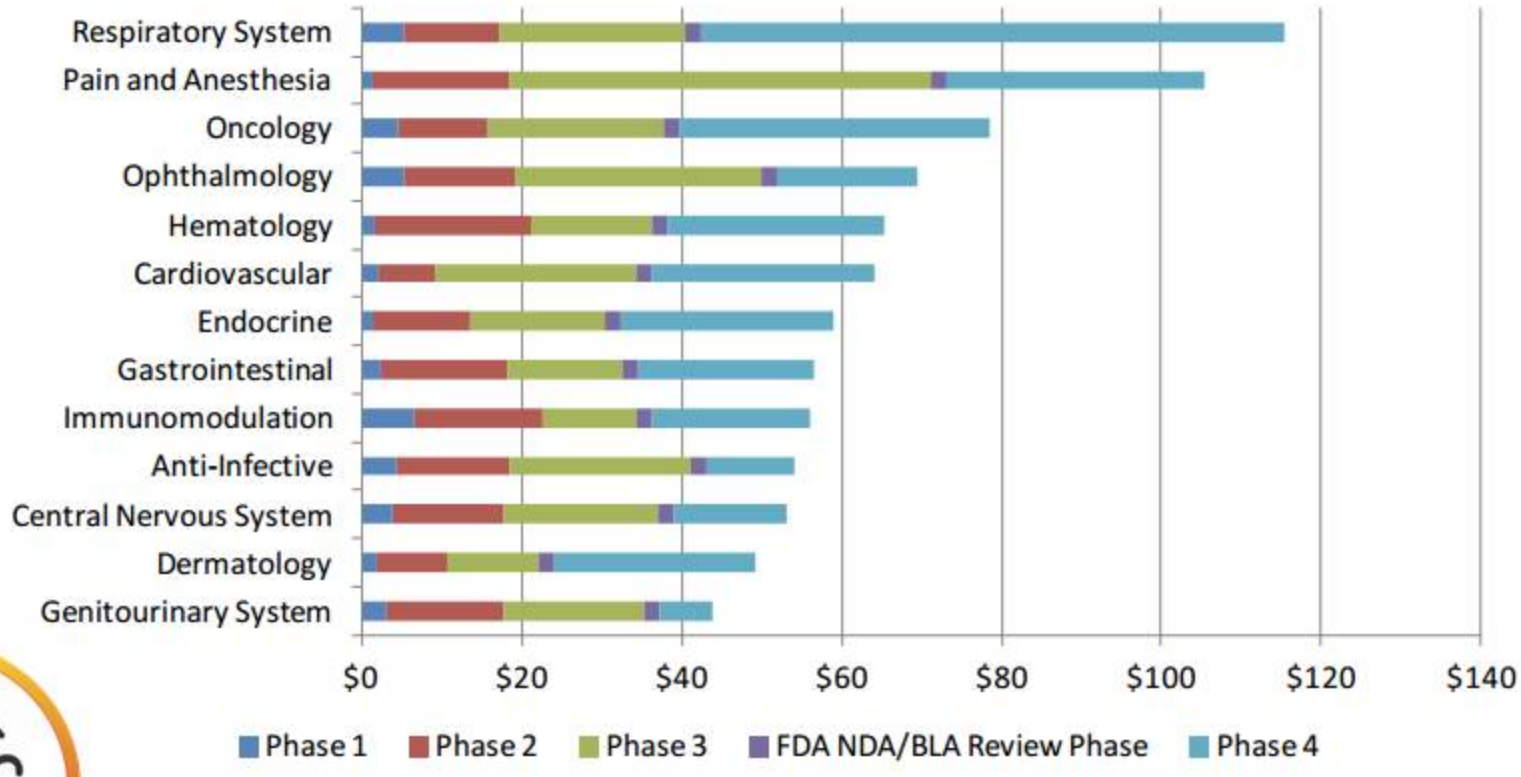
Global Trials by Indication



Trials Initiated in 2016



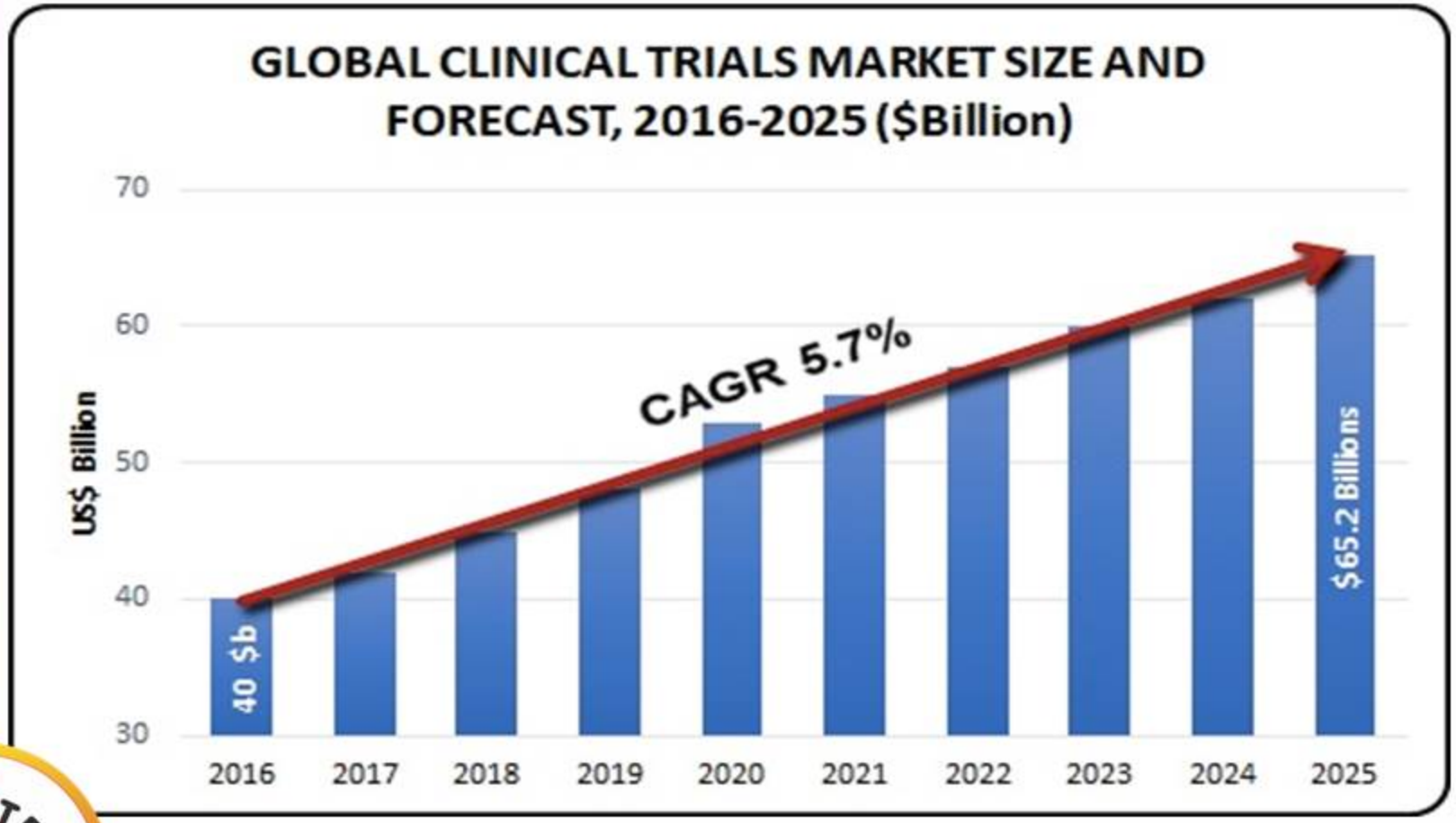
Clinical Trial Costs (in Million USD)



Trial Density

S.No	Country/Region	Number of Trials	Population in million	Trials/Million
1	United States	21602	325.7	66.32
2	Canada	3442	35.2	97.78
3	Europe	16196	510.3	31.7
6	China	7363	1415.1	5.2
7	Russia	767	143.9	5.33
8	Africa	1489	1256.3	1.19
9	South America	1484	428.3	3.46
10	Australia	1157	24.7	46.84
11	Mid. East	1814	254.5	7.12
12	India	568*	1342.5	0.42

* This figure may not be correct


GLOBAL CLINICAL TRIALS MARKET SIZE AND FORECAST, 2016-2025 ($Billion)
US$ Billion
70
60
50
40
30
CAGR 5.7%
40 $b
$65.2 Billions
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025