

Clinical Trials :Overview and Opportunities



Dr. Kumud Sarin
Program Director
Bioinformatics Institute of India,
New Delhi



Clinical Trials

- *Clinical trials are studies performed with human subjects to test new drugs or combinations of drugs, new approaches to surgery or radiotherapy or procedures to improve the diagnosis of disease and the quality of life of the patient.*



Different Phases of Clinical Trials

- Clinical trials are also organized into different phases of research, in order to build up a greater understanding of the new treatment, before it is approved or recommended for routine use.
- **Phase 0** is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.
- Phase 0 trials are also known as **human micro dosing studies** and 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 and pharmacodynamics (how the drug works in the body).



Phase 0

- **Distinctive features of Phase 0 trials include**
- The administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug).
- A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect.
- Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best PK parameters in humans to take forward into further development.
- They enable base go/no go decisions to be based on relevant human models instead of relying on animal data, which can be unpredictable and vary between species.



Clinical Trials



- **Clinical trial: Phase I** - The first studies in humans are Phase I trials. They are performed with small numbers of patients or healthy volunteers and are used to answer questions **such as what dose of the drug is likely to be effective and what side effects might occur.**

Clinical trial: Phase II - The trials with larger numbers of patients and focus on **how well the treatment or procedure works, perhaps in particular situations or groups of patients.**

Clinical trial: Phase III - The trials enroll large numbers of patients and are used to compare the effectiveness and safety of the new treatment with that of the standard existing treatment. Information obtained from large

- **Phase III trials** demonstrates the benefits a new drug over the existing treatments are presented to regulatory authorities in order to obtain a license to market and sell the drug.

Phase IV

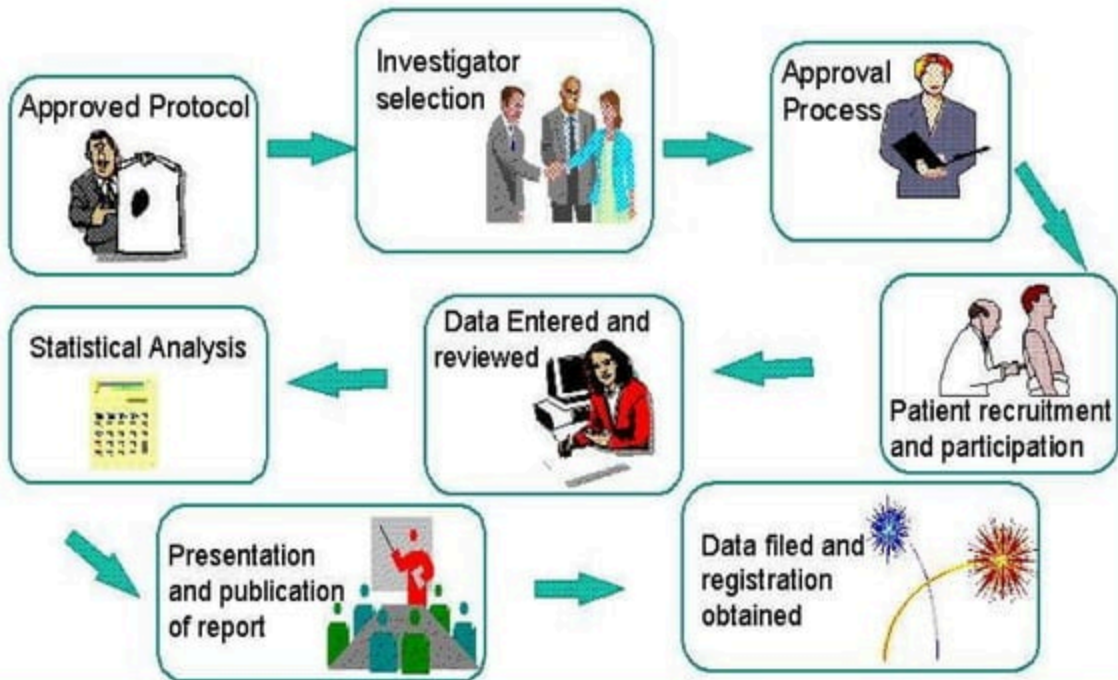
- Phase IV trial is also known as **Post Marketing Surveillance Trial**. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold.
- Phase IV studies may be required by regulatory authorities or may be undertaken 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. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses:
- Recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

Clinical trials



- Trials to evaluate the effectiveness and safety of medications or medical devices by monitoring their effects on large groups of people.
- **There are four possible outcomes from a clinical trial:**
- **Positive trial** -- The clinical trial shows that the new treatment has a large beneficial effect and is superior to standard treatment.
- **Non-inferior trial** -- The clinical trial shows that that the new treatment is equivalent to standard treatment. Also called a non-inferiority trial.
- **Inconclusive trial** -- The clinical trial shows that the new treatment is neither clearly superior nor clearly inferior to standard treatment.
- **Negative trial** -- The clinical trial shows that a new treatment is inferior to standard treatment.

Clinical Trials in a Nut Shell

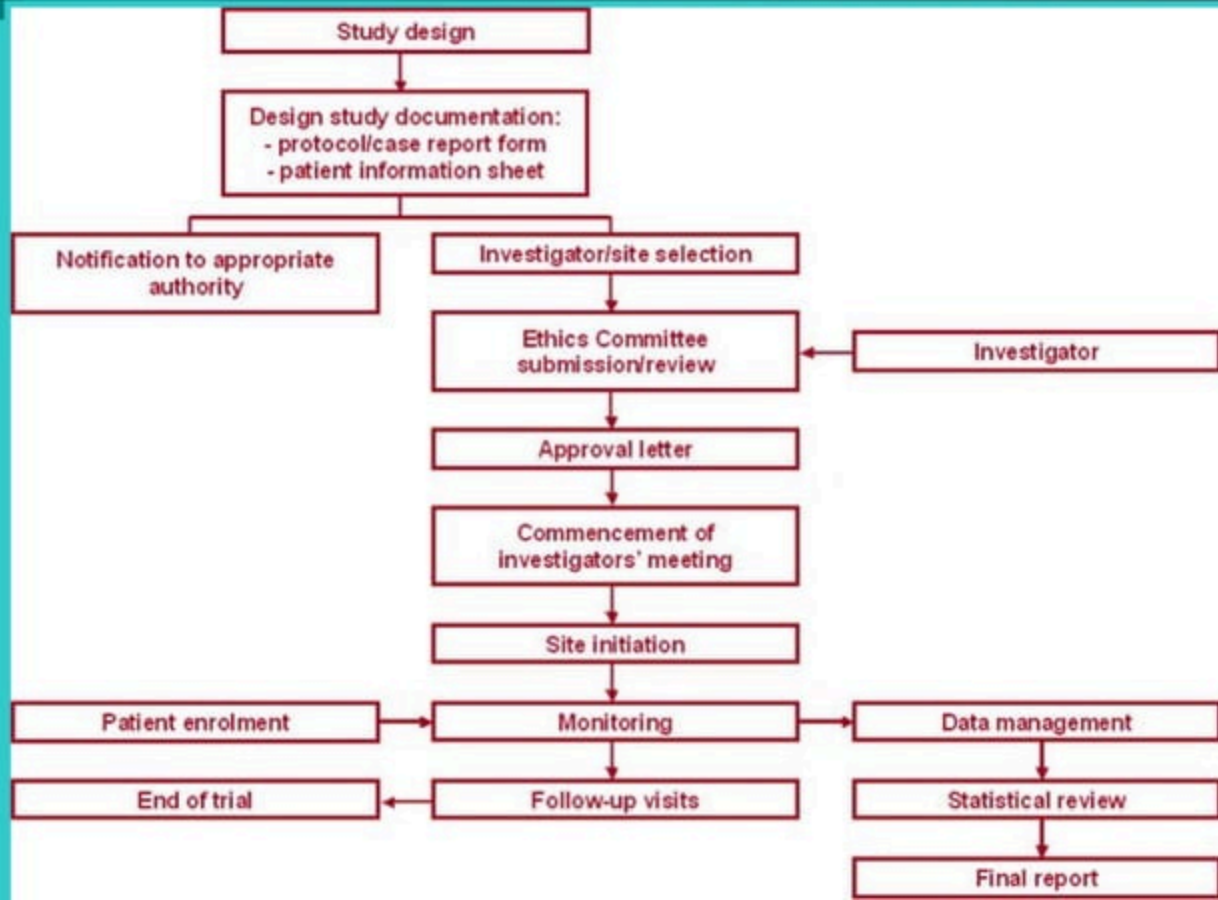


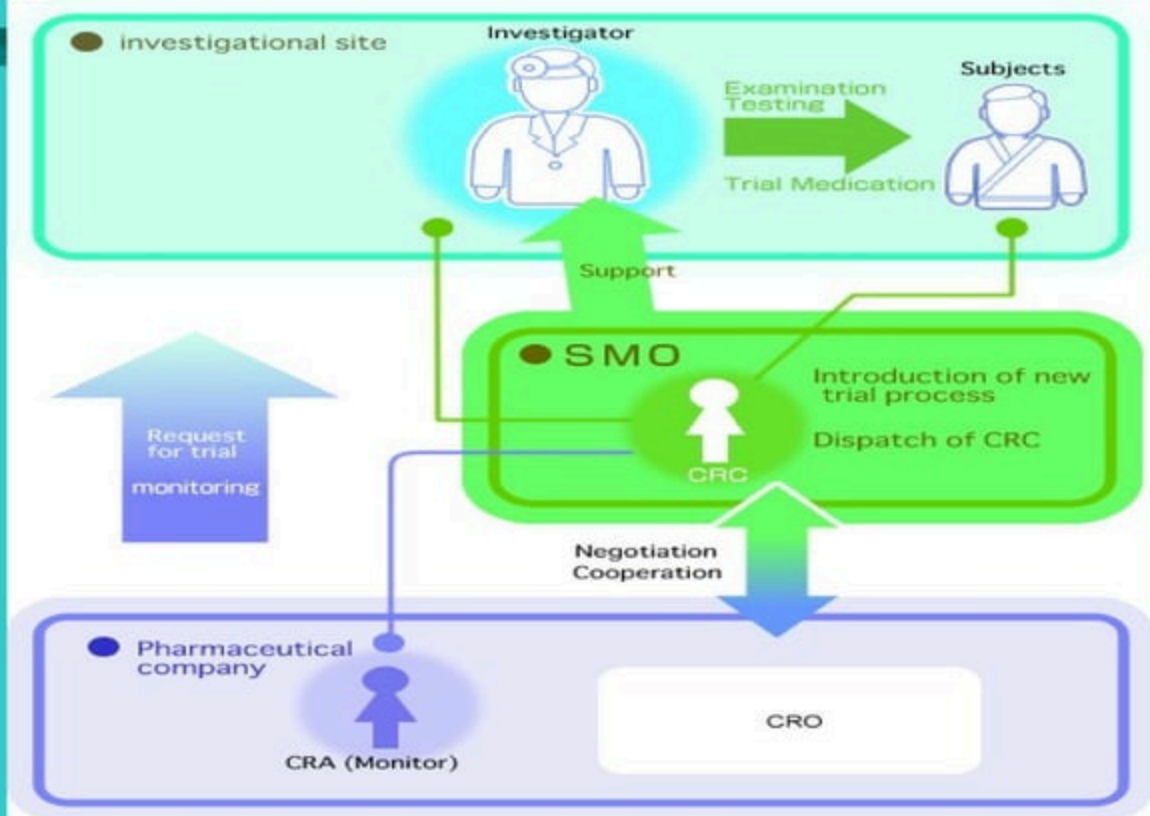
Clinical Trial :A Research Study

Why Do Research Studies?

- **To collect data on usual and unusual events, conditions, & population groups**
- **To test hypotheses formulated from observations and/or intuition**
- **Ultimately, to understand better one's world and make "sense of it"**



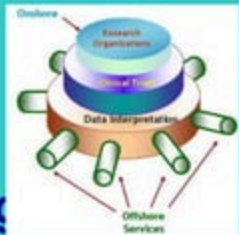




SMO: Site Management Organization
 CRO: Contract Research Organization
 CRA: Clinical Research Associate
 CRC: Clinical Research Coordinator

Core Components of Clinical Trials

- Involve human subjects
- Move forward in time
- Most have a comparison CONTROL group
- Must have method to measure intervention
- Focus on unknowns: effect of medication
- Must be done before medication is part of standard of care
- Conducted early in the development of therapies



Core Components of Clinical Trials

- Must review existing scientific data and build on that knowledge
- Test a certain hypothesis
- Study protocol must be built on sound & ethical science
- Control for any potential biases
- Most study medications, procedures, and/or other interventions



The Possible World of Clinical Trial Designs



- **Randomized/blinded trial**
- **Randomized/double blinded trial**
- **Non-randomized concurrent controlled trial**
- **Placebo trial**
- **Historical controlled trial**
- **Crossover Trial**
- **Withdrawal trial**

Simplified



- **Randomized:** Schemes used to assign participant to one group
 - Ex: Every 3 gets higher dose
- **Nonrandomized:** All with Hep. C = cases; others = controls
- **Protocol:** Study design - instructions
- **Blinded:** Participants do not know if in experimental or control group
- **Double Blinded:** Participants AND staff do not know group assignment
- **Placebo:** Inactive pill w/ no therapeutic value

Study Participant Recruitment



- Identify eligible participants
- Explain study
- Provide informed consent
- Reassess eligibility
- Assign to one group

Participants should be told:

- May have side effects (adverse effects)
- Time commitment
- Benefits & risks
- May withdraw at any time
- Enrollment 100% voluntary

Ethics of Clinical Trials: Protection of Participants



3 ethical principles guide clinical research:

- **Respect for Persons:** Treatment of person as autonomous
- **Beneficence:** Issue re: potential conflict between good of society vs. individual
- **Justice:** Treatment of all fairly & all equally share benefits & risks

Ethical Issues: Protection of Human Subjects



- Rely on integrity of Investigator but outside groups also have oversight
- Participants' rights protected by Institutional Review Boards [IRBs]
 - An IRB is defined as: "any board, committee or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects"

Human Subjects' Protection



IRB responsible for such tasks:

- Review research to ensure that potential benefits outweigh risks
- Develop and issue written procedures
- Review research for risk/benefit analysis & proper protection of subjects
- Issue written notice of approval/disapproval to the Investigator
- Review and respond to proposed protocol changes submitted by the Investigator

Human Subjects' Protection



- Review reports of deaths, and serious and unexpected adverse events received from the Investigator
- Conduct periodic continuing review of the study, study risks, selection of subjects, privacy of subjects, confidentiality of data, and the consent process



Informed Consent: A Part of Human Subject Protection



Objectives of Informed Consent

To Ensure:

- **Voluntaries**
- **Comprehension**
- **Information**

To Demonstrate That:

- **Person freely gave consent to participate**
- **Consent given by a competent person**
- **Person has been given all information**
- **Person knows this is research – not treatment**

Components of Informed Consent



- **Must Include the Following Information:**
- **Why research being done?**
- **What researchers want to accomplish**
- **What will be done and for how long**
- **Risks & benefits of trial**
- **Other treatments available**
- **Can withdraw from trial whenever desire**
- **Compensation for unexpected injuries**

Vulnerable Populations



Groups thought not to have autonomy to give informed consent:

- children
- mentally impaired, individuals with dementia
- Prisoners

OR

Who may be unduly influenced to participate:

- students
- subordinates
- pregnant women (actually, the fetuses)
- patients (care-giver vs. researcher)



Vulnerable Populations



To safe guard these groups, special requirements such as:

- Only parent can consent for minor
- Consents must be in subject's native lang.
- Prisoners: only some types of research allowed

Participation in Clinical Trials



Why Some Participate:

- Give back to society
- Exhausted all other txs
- Health care services
- Payment & incentives
- Support
- Others?? **Why Some Do Not?**
- Mistrust of studies
- Do not want to be “guinea pig”
- Do not meet criteria
- Cannot give up time for study visits
- Barriers: lang., distance



Conclusions



- Clinical trials often yield important results that affect health and well being
- Must follow guidelines & protocol
- Must ensure well-being of participant
- Clinical trials are susceptible to human error either on part of investigator or patient
- Research is soft science



Contract Research

- Large pharma companies- increasing trend towards outsourcing
 - R&D annual spend:US\$ 70 billion
 - Rapid increase in drug discovery targets



Contract Research

- **Compound Discovery & Development**
 - **Screening requirements of of the top 10 pharma companies will increase from 10-15 million primary screens per year to 200 million within 1-2 years**
- **Process Development & Synthesis**
 - **India's expertise in chemical synthesis can be utilized for development of cost-effective processes for new drugs and intermediates**
- **Clinical trials**
 - **One of the areas with greatest potential**
 - **Advantage India**
 - **Vast and diverse genetic pool**
 - **Cost effective**
 - **Increasing trend towards ICH/GCP**
 - **Trained physicians, ethics committees, Hospital infrastructure**
 - **Diversity of patient pool**



CLINICAL TRIAL INDUSTRY & CAREER PROSPECTS

Indian Clinical Research Industry

- India today unarguably is the most favored destination for the pharmaceutical R&D and clinical research. The key reasons are:
 - 100 million plus English speaking people (Largest outside US).
 - Over 2 million science post graduates. ■ Large pool of treatment-naïve patients from multiethnic and multiracial backgrounds.
 - Easy patient recruitment and compliance.
 - Favourable Regulatory Policies – Updated Schedule Y. ■ IPR / WTO, GATT on board.



Indian Clinical Research Industry

- Cost effective business operations
- International regulatory approvals for GMP/GLP/GCP.
- Maximum number of approved GMP plants outside USA. ■ Excellent quality management, Technology and infrastructure.
- Time zone difference facilities 24/7 support.
- Presence of all Pharma major & also in-house CROs set up by leading pharma companies.
- Presence of all leading international CROs and several domestic CROs – over 75 CROs.
- Strong IT industry availability of IT skilled manpower. ■ 30 million patients with cardiovascular diseases.
- 25 million with Type 2 diabetes
- .10 million with psychiatric disorders
- 2 million cases of cancer with 500,000 cases detected every year ■ 600,000 practicing physicians
- 14,000 hospitals
- .700,000 beds
- .17,000 medical graduates per year.

Clinical Trial Industry

	2003	2008	2010
<i>Value (million USD)</i>	50	200	1000
<i>Revenue (Crore INR)</i>	75	300	875
<i>Full time staff Requirement</i>	800	4000	20,000
<i>Site – staff Requirement</i>	1500	6000	30,000
<i>Patient Load</i>	10,000	50,000	300,000

Source: Mckinsey Report

Leading Companies in Clinical Trial

 <p>Clinigene</p>	 <p>ICON A Symbol of Excellence</p>	 <p>DR. REDDY'S</p>
 <p>gsk GlaxoSmithKline</p>	 <p>CDRI</p>	 <p>RANBAXY</p>
 <p>LUPIN</p>	 <p>CDRI</p>	 <p>torrent</p>
 <p>NOVARTIS</p>	 <p>ClinicaSpace[®] a division of BiSpace</p>	 <p>Johnson & Johnson</p>
 <p>Pfizer</p>	 <p>CORAL CORAL PHARMACEUTICALS LIMITED</p>	 <p>VIMTA LABS Determining Quality</p>
 <p>Zydus dedication for life</p>	 <p>CORAL CORAL PHARMACEUTICALS LIMITED</p>	 <p>ACT</p>
 <p>bioserve Leading Innovation</p>	 <p>dhanuka</p>	 <p>CLINTEC INTERNATIONAL</p>
 <p>Lilly Answers That Matter.</p>	 <p>glenmark PHARMACEUTICALS LTD.</p>	 <p>Clininvent Advanced Clinical Research Solutions A TCG LifeSciences Company</p>

Leading Companies in Clinical Trial

iGATE Clinical Research International



novo nordisk
The Blue Bull

INTAS
JINTAS BIOPHARMACEUTICALS
Building Global Biopharmaceuticals

CenterWatch
Clinical Trial Listing Service

Speed Accuracy & Reliability



AUROBINDO
CORPORATION OF INDIA

MATRIX
LABORATORIES LIMITED



NIH Clinical Center
NATIONAL INSTITUTES OF HEALTH

pharmanet
Development Group

QUINTILES
TRANSCORPORATE



Reliance
Clinical Research Services
Empowering Research & R&D

Roche

SERVIER

sanofi aventis
The Power of Health

SIRC
SIRC Clingham Pvt. Ltd.

Omnicare
Clinical Research
People who really care.
It's a company where it really matters.

SRL
RANBAXY
Clinical Reference Laboratories

SRISTEK
Your data. Our responsibility.

ORGANOSYS

Synchron
Good Science. Good People.

List of Major CROs

- Quintiles
- Synchron
- Lambda
- Siro Clinpharml-
- Gate
- Reliance Clinical Services
- PPD
- Onmnicare
- ICONClin
- TracPharmaNet
- Pharm-Olam

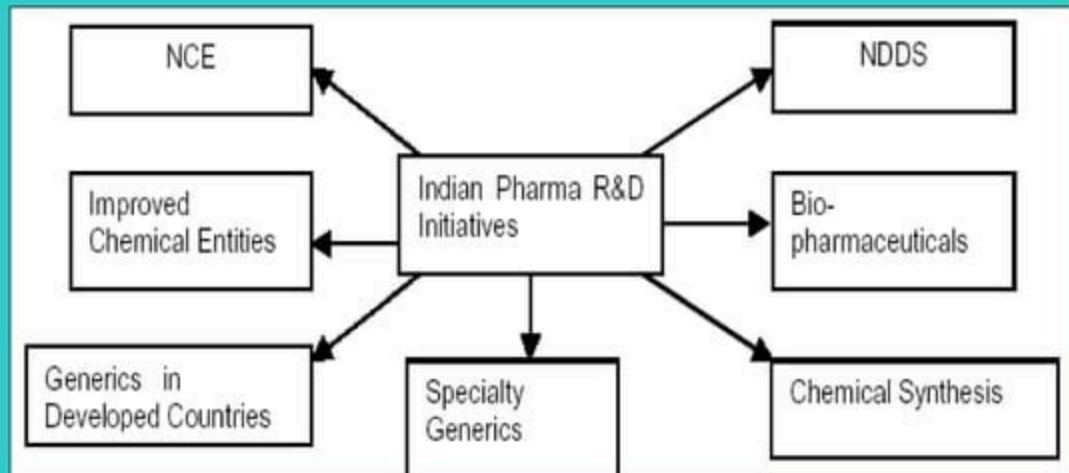


List of Major CROs

- Lotus Labs
- Vimta
- GVK
- BioServe Clinical Research
- Apothecaries
- Kendle
- Bioassay
- Clinworld
- Perinclinical
- Quest Life Sciences



Increased R&D Focus



**Shift from business-driven research
to research-driven business**

Contract Research

Clinical research

- USD 70 mn market (2001-02)
- Growing at 20% per annum
- **Outsourcing** - fastest growing area for new investment
- US\$ 1 bn opportunity by 2010

Custom synthesis

- Largest pool of trained analytical and development chemists
- Excellent track record of innovation
- US FDA approved manufacturing facilities
- 30-50% cost savings

API sourcing and contract manufacturing

- Global Outsourcing opportunity worth US\$ 15 bn by 2010
- Global majors to outsource manufacturing from India

Need for Training Programs

- Major gap in Demand & Supply of trained manpower – An unmet need.
- By 2010 Indian market would be over US\$1 billion, and would continue to grow at rapid pace.
- Over 75 CROs & 25 In-house Pharmaceutical Clinical Research & R&D Facilities in India.
- More and more international CROs are starting operations in India.
- Current trained manpower demand in the field of Clinical Research is over 10,000 trained personnel per annum.
- The current training facilities are able to train only 1,000 professionals.
- Untapped huge market potential for Full Time; Part Time, On-Line Course Distance Learning Courses & Workshops.
- The expected trained manpower requirement in the next 7 years is going to be over 50,000 persons.

Need for Training Programs

- There are only 2 - 3 training institutes currently offering courses in India.
- Most staff is provided on the job training, which wastes critical employer resources and time.
- Excellent Career Growth.
- Attractive Salaries Offered – Starting salaries from Rs.1.8 lakh to Rs.2.8 lakh.
- High Annual Salary Growth – 30 to 35% per annum, in comparison to average 15% growth in salaries

Careers in Clinical Research

Clinical Research Associate

Clinical Trials Auditor

Clinical Research investigator

Clinical Project Manager

Study Coordinator

Clinical Research Manager

Data manager

Business development Manger

Biostatistician

Drug Safety Associate

Regulatory Affairs Manager

Medical Writer

Career Opportunities

“More than 50,000 professionals will be required in the field of Clinical research in India alone.”

Source : Mckinsey Report

Thus science, pharmacy and medicine graduates can look forward to exciting and rewarding career opportunities in clinical research.



Clinical Trial Quotations

“India is an emerging market with growing number of entrepreneurs foraying into research and healthcare. Indian government is creating an effective regulatory framework. Protection of patents and IPR is now improving. India has a better place than countries like China in the clinical trials field”, Dr Charles Pierce, president Global Clinical Partners, Inc. USA, said

Source: Pharmabiz

“Indian contract research Organisations will have good chance to shine, Indian CROs are competitive compared to western companies. There are several advantages to global companies to outsource research service from us”Dr. Goutam Das ,CEO, Syngene International Pvt.Ltd.

Source: Chronicle Pharmabiz



Thanks