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General Review On Clinical Trials And Regulatory Guidelines

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ABSTRACT:
Clinical research is an important part of the drug discovery process to ensure the safety and efficacy of any new drug. In today's global scientific era, clinical trials are the compulsory for bringing newer and better drugs to market. Clinical trials test potential treatments in human volunteers (subjects) to see whether they should be approved for wider use in the general population. India stood as a global hub for clinical trials in past years due to various factors.In this paper we discuss about clinical trials and clinical trials in India.Good clinical practice (GCP) is an international ethical analysis and scientific quality standard for designing, conducting, and auditing clinical trials that involve the participation of human subjects.FDA 21 Code of Federal Regulations (CFR) Part 11 refers to the FDA's regulations on electronic records and electronic signatures for clinical trials. Since most sponsors and research sites now use electronic documents, Part 11 has become more important than ever.

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I. INTRODUCTION:

Clinical trials as the name suggests are set of experiments and observations done for clinical research.In human subjects. They are carried out in search of new treatments, interventions or tests as a means to prevent, detect, treat or manage various diseases or medical conditions. Clinical Trials helps in determining if a new intervention works, its safety & efficay, and is it better than already available treatments. According to WHO defines clinical trial as:

'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'.

The main aspect of research in drug discovery leads to newer, safer and more efficacious drugs being made available for mankind. Before a new drug is introduced in the market, it has to go through various phases of rigorous methods of trials first in animals and then in humans subjects. They are most important and decisive part for new drug to come in market. Without clinical trials, researchers cannot properly determine whether new medicines developed in the laboratory or by using animal models are effective or safe, or

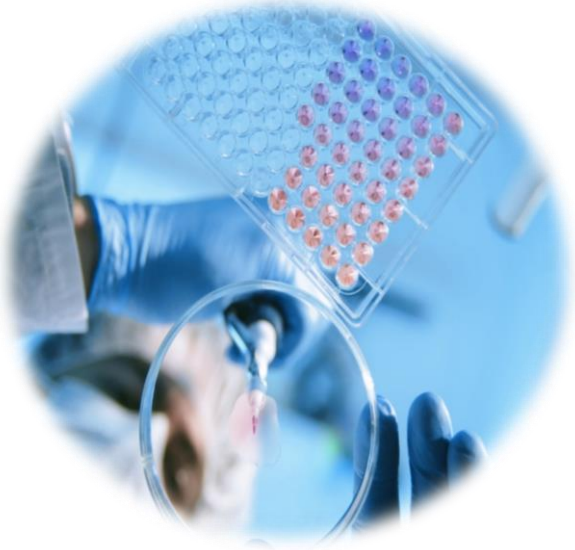
Whether a diagnostic test works properly in a clinical setting1-3.Randomized controlled trials (RCTs) with placebo- control and blinding fashion is the only accepted form of clinical trials with few exceptions. Besides explanatory, descriptive clinical research is also useful for certain types of studies such as epidemiological research.Clinical trials are research studies that test a medical, surgical, or behavioral intervention in people. These trials are the primary way that researchers determine if a new form of treatment or prevention, such as a new drug, diet, or medical device (for example, a pacemaker), is safe and effective in people.[6]

II. TYPES OF CLINICAL TRIAL:

Clinical trials can be classified in to various ways one way is to classify clinical trials on basis of mode of study:

1) **INTERVANTIONAL STUDY:-**In this study researchers measure how the subjects' health changes. They give the research subjects a particular medicine and then compare the treated subjects with those receiving no treatment or the standard treatment. This is a type of a comparative study.[7]
2) **CLINICAL OBSERVATIONAL STUDY:-**In this study the researchers observe the subjects given with new medicine and measure their outcomes.[6]

Fig.A:Clinical observation and laboratory sampling.



III. CLASSIFY TRIALS IS BY THEIR PURPOSE:

- Prevention trials to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.[9]
- Screening trials test the best way to detect certain diseases or health conditions.[3]
- Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.[1]
- Treatment trials test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.[2]
- Quality of life trials (supportive care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.[5]
- Compassionate use trials or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. This involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials.[10]

IV. PHASES OF CLINICAL TRIAL:

PHASE I STUDIES:

This phase assess the safety of a drug or device. This is initial phase of testing, which may take about several months to complete. This phase usually includes a small number of healthy volunteers (20 to 100). The purpose of phase 1 trial is to determine the effect/ effects of the drug or device on humans including how it is absorbed, metabolized, and excreted (ADME). This phase also investigates the dose related side effects. About 70% of experimental drugs pass this phase of testing.[12]

PHASE II STUDIES:

This phase assesses the efficacy of a drug or device. This is second phase of testing. It takes several months to two years for completion, and involves up to several hundred patients. Most phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded" which means that neither the patients nor the researchers know who has received the experimental drug. This allows researchers to provide the pharmaceutical company and the FDA with comparative information about the relative safety and effectiveness of the new drug. About one-third of experimental drugs successfully complete both Phase I and Phase II studies.[11]

PHASE III STUDIES:

This phase assess randomized and blind trials in several hundred to several thousand patients. This is large-scale testing, which lasts up to several years. It provides the researchers and regulatory authority with a more thorough understanding of the effectiveness of the drug or device, the benefits and the range of possible adverse reactions. About 70% to 90% of drugs that enter Phase III trial successfully complete this phase of

testing. Once Phase III is complete, a pharmaceutical company can request FDA approval for marketing the drug.[14]

PHASE IV STUDIES:

This phase is also called as Post Marketing Surveillance Trials. They are conducted after a drug or device has been approved for consumer sale after approval from regulatory authority. Pharmaceutical companies have several objectives at this stage: (1) to compare a drug with other drugs already in the market; (2) to monitor a drug's long-term effectiveness and impact on a patient's quality of life; and (3) to determine the cost-effectiveness of a drug therapy relative to other available and new therapies. Phase IV studies can result in a drug or device being taken off the market or restrictions of use could be placed on the product depending on the findings in the study4-6.[13]

V. TRIAL DESIGN:

ADAPTIVE CLINICAL TRIAL:

Purpose of an adaptive trial is quickly identifying drugs that have a therapeutic effect done by adjusting dosing levels. This trial evaluates a medical device or treatment by observing participant outcomes on a prescribed schedule, and modifying parameters of the trial protocol in accord with those observations. Modifications parameters include dosage, drug undergoing trial, patient selection criteria, sample size and mix.[16]

RANDOMIZED TRIAL:

Purpose of Randomized trial is to reduce bias for testing new drug treatment. In this trial, each study subject is randomly assigned to receive either the study treatment or a placebo. Group receiving placebo is control group.Randomized trial are used to check effectiveness and efficacy of drug.[19]

BLIND TRIAL:

In blind trials, the subjects involved in the study do not know which study treatment they receive and for what purpose. In double blind trials, subjects and investigator / doctor do not know which medication is given. Neither the patients nor the researchers monitoring the outcome know which patient is receiving which treatment, until the study is over. It is very effective to reduce bias.[12]

CODE OF FEDERAL REGULATIONS (CFR):

The CFR is a codification of the general and permanent rules that were published in the FR by the Executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation.

Most of FDA's medical device and radiation-emitting product regulations are in Title 21 CFR Parts 800-1299. These final regulations codified in the CFR cover various aspects of design, clinical evaluation, manufacturing, packaging, labeling and post market surveillance of medical devices. In addition, the regulations address standards and product reports that apply to radiation-emitting products.[13][12][9][6][3][1]

21 CFR searchable database

Parts 1 – 99 (product jurisdictions, protection of human subjects, institutional review boards, etc)

Parts 100 – 799 (food, human and animal drugs, biologics, cosmetics)

Parts 800 – 1299 (medical devices and radiation emitting products)

Parts 1300 – 1499 (controlled substances)eCFR.

The Electronic Code of Federal Regulations (e-CFR) is a currently updated version of the Code of Federal Regulations (CFR). It is not an official legal edition of the CFR. The e-CFR is an unofficial editorial compilation of CFR material and Federal Register amendments produced by the National Archives and Records Administration's Office of the Federal Register (OFR) and the Government Printing Office. The OFR updates the material in the e-CFR on a daily basis. The current update status appears at the top of all e-CFR web pages.[2]

VI. BENEFITS:

EARLY ACCESS TO THE LATEST ADVANCES:

Research participants are among the first to benefit from the latest medical breakthroughs.[1]

IMPROVED CARE:

Research studies involve detailed care plans (protocols). As a result, you may have more frequent check-ups and other services you normally wouldn't receive.[8]

FREE OR LOW-COST HEALTH CARE:

Most studies at Penn Medicine Lancaster General Health don't involve added costs for you or your insurer. The study's sponsor usually covers costs that are specific to the study and not standard of care.[9]

MAKING A DIFFERENCE:

When you participate in research, you help providers learn better ways to prevent, treat, and care for people now and in the future. You can also help improve medical care for our community. Many of the studies at Penn Medicine Lancaster General Health focus on conditions that affect people in the Lancaster area, including heart disease, stroke, and diabetes.[10]

VII. PATIENT SAFETY IN CLINICAL STUDIES:

HUMAN RESEARCH PROTECTION PROGRAM (HRPP):

The Penn Medicine Lancaster General Health Human Research Protection Program includes the Lancaster General Hospital Institutional Review Board. Together, they ensure all research studies follow ethical, federal, state, and Research Institute standards and regulations for human research. Penn Medicine Lancaster General Health has maintained accreditation from the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) since 2015. AAHRPP accreditation shows that our research exceeds standards established by regulatory organizations like the U.S. Food and Drug Administration (FDA).[4]

INSTITUTIONAL REVIEW BOARD (IRB):

The IRB is made of more than a dozen representatives, including physicians, nurses, PhD scientists, and other nonmedical professionals. The primary purpose of the IRB is to protect the rights and welfare of research participants and monitor ongoing studies for safety and patient privacy concerns. Periodically, internal and external monitors inspect individual study records for compliance with the protocol and other safety standards.[3]

DATA AND SAFETY MONITORING BOARDS (DSMBS):

Studies that test specific devices, treatments, or procedures have their own independent Data and Safety Monitoring Board. DSMBs regularly meet to review study data and monitor protocol compliance and patient safety. They are sometimes called Data Monitoring Committees (DMCs).[1]

VIII. ROLES/REPONSIBILITIES:

1. The Vice President of Research Administration, as Institutional Official, shall oversee the LG Health HRPP and ensure that all human subject research conducted at LG Health complies with all federal and state laws and regulations and ethical standards to safeguard the health and welfare of human research subjects.[8]
2. The LG Health IRB shall implement policies and procedures, consistent with federal and state laws, establishing the application and review process of proposed human subject research, including research that qualifies for exempt status. The IRB shall approve, require modifications, or disapprove all proposed human subject research Projects.[4]
3. The LG Health HRPP shall implement policies and procedures governing research with human subjects to ensure compliance with federal and state laws and regulations and shall review and approve revisions to such policies and procedures. All LG Health HRPP policies and procedures shall be available on the LG Health research Institute website. The LG Health HRPP will keep IRB members as well as investigators, research staff, and other individuals engaged in human subject research apprised of new information and revisions to applicable policies and procedures. Material revisions to HRPP policies and procedures will be communicated to IRB members during IRB meetings and to investigators and research staff by email, in-person education sessions, or other appropriate communication methods.[2]
4. The LG Health IRB Office is responsible for accepting applications for human subject research projects,communicating substantial revisions of HRPP and IRB policies and procedures to IRB members, investigators,and other research staff, and ensuring the IRB functions in an efficient manner.[1]
5. Investigators and others involved in the conduct of research are responsible for obtaining IRB approval or determination of exempt status before initiating research activities and for conducting research in accordance with LG Health's ethical standards and policies, applicable rules and regulations, and the requirements and determinations of the IRB.[17]

IX. PROCEDURES:

ORGANIZATIONAL REPORTING:

- The RQAO reports to the Human Research Protection Program Institutional official – Vice president of Research Administration.

- The activities of the RQAO are governed by the Research Compliance Committee. This committee comprises the Administrative Director of the Lancaster General Research Institute; Vice President of risk Management and Corporate Compliance; Senior Vice President, General Counsel; Vice president of Research Administration; Medical Director of the LG Research Institute; and Executive director of the Ann B. Barshinger Cancer Institute.
- At any time the RQAO identifies an immediate subject safety concern, the finding(s) will be reported directly to the Human Research Protection Program Institutional Official and the IRB chair.
- Findings by the RQAO will be reviewed by the Research Compliance Committee. The Research Compliance Committee will report cases of non-compliance to the IRB and provide recommendations for corrective action. The IRB reviews cases to make a final determination as to whether non-compliance is serious or continuing and establishes a corrective action plan.
- A representative of the RQAO, typically the HRPP / IRB Manager, attends meetings of the IRB.The RCC to address current concerns identified through the monitoring procedures outlined in this policy.
- Findings by the RQAO may be further reported and triaged by the Research Compliance Committee.To the Audit and Compliance Committee.

TRAINING/EDUCATION:

A)The RQAO will administrate use of the CITI Program coursework for training and certification of the IRB Chair, IRB members and LG Health research personnel.

- A new IRB chair, new IRB member or new researcher identified on an IRB application will be assigned required modules to be completed for certification before commencement of IRB or research duties and responsibilities.[18][2][1]
- Renewal of all certifications will be required every 3 years.[3][1]
- HRPP Manager shall be responsible for monitoring certifications of researchers by running monthly reports from CITI database.[6]
- Failure by researchers to maintain certifications will result in initial approval or continuing review approval being withheld or by cessation of individual research activities, as applicable.[2]
- Failure by IRB members to maintain certifications will result in recusal from IRB activities.[1]
- The RQAO will organize education sessions for the IRB, typically in conjunction with scheduled meetings. [12]
- The RQAO will facilitate educational sessions or seminars to address real-time institutional needs. [11]

ROUTINE ON-SITE REVIEW:

For studies with ongoing data collection, the RQAO will conduct routine on-site reviews according to the following tiered approach:

- **Tier 1:**Tier 1 studies are defined as investigator-initiated and greater than minimal risk. These studies will be identified at the time of IRB review. The intent is to conduct an on site **r**eview of 100% of these studies within 1 year of the start of subject enrollment.[13]

- **Tier 2:**Tier 2 studies are defined as externally sponsored and greater than minimal risk, not monitored on-site by any Sponsor representative. These studies will be identified at the time of IRB review. The intent is to conduct an on-site review of 100% of these studies within 1 year of the start of subject enrollment.[11]

- **Tier 3a:**Tier 3a studies are defined as externally sponsored and greater than minimal risk, monitored on-site by a Sponsor representative. A sampling of these studies will be chosen for on-site review at the time of IRB review. The focus of the review will be aspects less likely to be monitored by the Sponsor, such as recruitment activities, the consent process, and medical record documentation of research activities. IRB reporting will also be monitored to ensure consistent application of the LG Health IRB policy. Tier 3a studies will not be reviewed more than once without cause.[9]

- **Tier 3b:**Tier 3b studies are defined as low/minimal risk. A sampling of these studies will be chosen for on-site review at the time of IRB review. The focus of the review will be on data security. Tier 3b studies will not be reviewed more than once without cause.[5]
- On-site review is mandatory for those studies selected; however, the review will be scheduled at a time that is convenient to the Principal Investigator, but must be completed within 3 months of notification.[2]
- A review template outlining the objectives of the visit will be provided by the RQAO within 30 days prior to the scheduled review.[1]
- A report outlining the findings, recommendations, and/or corrective actions, as needed, resulting from the

routine, on-site review will be completed by the RQAO within 30 days after the scheduled review. The report will be provided to the Principal Investigator and to any other person supervising study personnel. The report or summary findings also will be shared with the Research Compliance Committee.[1]

FOR-CAUSE REVIEW:

- The RQAO will conduct a for-cause review of a study at the request of the IRB or the Research Compliance Committee.[4]
- The investigator and/or research staff have demonstrated poor adherence to IRB policies.[6]

PROCEDURE:

- credible internal complaint has been reported (i.e., from a research subject or family member, LG Health personnel).[8]
- An external complaint has been reported (i.e., from OHR, the FDA or a Sponsor) of a significant protocol violation involving issues of patient safety, privacy or confidentiality, regulatory non-compliance or Scientific misconduct.[4]
- A report outlining the findings, recommendations, and/or corrective actions, as needed, resulting from the for-cause review will be completed by the RQAO within 30 days after the scheduled review. The report will be provided to the Principal Investigator and to the Research Compliance Committee.[2]

IRB REVIEW:

- The RQAO conducts periodic, routine review of the IRB to assess compliance with federal, state and local laws and LG Health policies.[6]

- The RQAO examines IRB records for inclusion of required documents such as protocols,investigator brochures, consent documents, recruitment materials, subject injury reports,unanticipated problems, progress reports, data and safety monitoring reports, new findings, and all Correspondence between the IRB and researchers.[2]

- The RQAO examines IRB minutes for required elements, such as documentation of attendance,Recusals, deliberations, controverted issues and resolutions, votes, actions taken, the basis for actions taken, and approval periods.[1]

- The RQAO may identify opportunities for improvement and suggest modified processes for adherence to current policies.[8][5][2][1]

RESEARCH SUBJECT COMPLAINTS:

- The RQAO manages and performs the initial investigation of all research subject complaints reported to the IRB Chair, via the Research Institute website, directly to the Investigator and/or Research staff, or via other documented means.[19][11][8]
- For serious complaints (e.g., complaints of study-related injury, safety concern, violation of subjects' rights, etc.), the RQAO will involve other institutional entities as appropriate (e.g., Legal services, the IRB, Risk Management, Medical and Dental Staff Office).[4][1]
- The RQAO will report all complaints and resulting actions to the Research Compliance Committee on a quarterly basis.[3][1]

INDIRECT MONITORING OF CLINICAL RESEARCH:

- The RQAO compiles and assesses Data and Safety Monitoring Board reports. Any immediate subject safety concerns will be reported directly to the Human Research Protection Program institutional Official and the IRB Chair. Other pertinent, but non-immediate concerns will be summarized and reported to the IRB for review.[2]
- The RQAO compiles and assesses reports of external monitors (i.e., typically sponsor representatives). Any immediate subject safety concerns will be reported directly to the Human Research Protection Program Institutional Official and the IRB Chair. Other pertinent, but non-Immediate concerns will be summarized and reported to the IRB for review.[3]

FINANCIAL CONFLICT OF INTEREST:

- The RQAO is responsible for gathering Financial Conflict of Interest Forms from the IRB Chair, IRB members and LG Health research personnel.[9]

- The RQAO will review the Financial Disclosure Forms on record for project personnel at the time of IRB submission and compile Significant Financial Interests for referral to the Research Compliance Committee. The Research Compliance Committee is responsible for determining whether any significant Financial Interests constitute a Financial Conflict of Interest and for recommending Management plans to the IRB as needed (see policy 'Conflicts of Interest in Research').[16]

ACTIVITIES THAT REQUIRE IRB REVIEW:

Activities involving the collection of data, for the purpose of contributing to generalizable knowledge, through intervention or interaction with a living individual, or involving identifiable private information including protected health information of a living individual or a decedent, must be reviewed by the IRB. Specific activities that require IRB review include, but are not necessarily limited to:

- Any clinical investigation that is regulated by the U.S. Food and Drug Administration (FDA) or that will support an application for research or marketing permit for a product regulated by the FDA.[4]
- Systematic investigation of an innovative preventative strategy, screening procedure, diagnostic Procedure, treatment, or alteration of a standard procedure or treatment, to evaluate feasibility, efficacy, or safety for scientific purposes, including comparison to an accepted standard.[5]
- The assignment of subjects to any social or behavioral intervention for research purposes.[2]
- Systematic collection and evaluation of data such as patient demographics, health history, treatments,and outcomes, including studies of approved or standard procedures or treatments to provide additional evidence on feasibility, efficacy, or safety or to compare procedures or treatments.[9][2][1]
- Collection of data for educational research, including evaluation of instructional strategies, curricula, or classroom management methods, or analysis of educational test results. (These projects may qualify for exemption from further IRB review; see policy on Exempt Research).[4]
- Analysis of an existing data set or a data set abstracted or extracted from existing records. (These projects may qualify for exemption from further IRB review if the data are de-identified and publicly available; see policy on Exempt Research).[6]
- Collection, storage, distribution, or analysis of specimens of human cells or tissues for research purposes. (Human cell or tissue repository activities do not require IRB review under certain circumstances, discussed in section 4).[4]

SPECIAL CATEGORIES OF ACTIVITIES REQUIRING IRB REVIEW:

Some activities do not follow all of the usual Research review processes but are required by regulation to follow a specialized IRB review process.

- Emergency use of an investigational drug or device to treat a life-threatening or serious condition with no available, standard, acceptable treatment. Such treatment could be initiated with or without prior IRB notification, depending on the timing and urgency of the situation, but must be submitted to the IRB no later than 5 days following the emergency use. Refer to the policy Emergency Use of an Investigational or Unlicensed Test Article.[3][1]
- Use of a device under a Humanitarian Device Exemption given by the U.S. Food and Drug administration. The use of humanitarian use devices must be reviewed by the IRB. Refer to the policy humanitarian Use Devices.[7]

ACTIVITIES THAT REQUIRE IRB REVIEW FOR PRIVACY CONCERNS:

The LGH IRB is authorized to review activities that may not meet the definition of research but that involve the use of protected health information or that might reasonably identify subjects by the specificity of the information disclosed:

- Use of individual patients' protected health information preparatory to research, including use to Identify patients who may be eligible for the research. (See section 2 for the circumstances when activities preparatory to research to do not require IRB review.) The investigator must provide assurance that 1) the use or disclosure is requested solely to review PHI as necessary to prepare a Research protocol or for similar purposes preparatory to research; 2) the PHI will not be removed from the covered entity in the course of review; and 3) the PHI for which use or access is requested is necessary for the research.[9]
- Secondary research uses of identifiable private information or identifiable biospecimens that, though meeting criteria for exemption from IRB review are still subject to regulation under HIPAA (see policy on Exempt Research).[5]
- Student scholarly activities for academic programs. These activities may not meet the definition of Research that will contribute to generalizable knowledge. However, if the student uses protected health Information of LG patients, living or deceased, the LGH IRB must review the project. The LGH IRB has the authority to require consent when determined to be warranted.[14]

- Case report, case series, or other publication in a professional journal or presentation to a professional society. If such activities involve the use or disclosure of protected health information, or if there is a reasonable chance that subjects could be identified by the specificity of the information, the LGH IRB should review the activity. The LGH IRB is authorized to require consent when determined to be warranted.[20]
- Any other research activities that LG Health is engaged in per OHRP guidance.
- Engagement of Institutions in Human Subjects Research.[21]

ACTIVITIES NOT SUBJECT TO IRB REVIEW:

Activities that do not meet the definition of research because they do not involve intervention or interaction with a living individual or use protected health information of a living Individual or decedent, or they do not contribute to generalizable knowledge, do not need to be reviewed by the IRB. Investigators may request documentation from the IRB that the activity is not subject to IRB review.An Initial Application must be submitted in IRBManager for human research determination. Research status will be determined by the IRB Chair or designee under the revised Common Rule, and the definition of Research and human subjects set forth by the FDA. The determination that the submission does not constitute Research with human subjects will be documented by the IRB Chair or designee on the Initial Application form in IRBManager. The determination documentation will be maintained by the IRB office in the protocol file. The researcher will be informed of the determination by written correspondence by letter sent via email and may not begin the research until correspondence is received. Notification of approval of the project will be provided to IRB members via the agenda of the next convened meeting.specific activities that do not require IRB review include, but are not necessarily limited to:

- Proposals that lack definite plans for involvement of human subjects.[2]
- Activities such as quality assurance or quality control, program and fiscal audits, and certain disease monitoring as prescribed by the Pennsylvania Department of Health.Collection for, storage in, or distribution from a repository of specimens of human cells or tissues, if material satisfies both of the following conditions.[12]
- The material, in its entirety, was collected for purposes other than submission to the repository (e.g., the material was collected solely for clinical purposes, or for legitimate but unrelated Research purposes, with no "extra" material collected for submission to the repository).[11]
- The material is submitted to the repository without any identifiable private data or information (i.e., no codes or links of any sort may be maintained, either by the submitter or by the Repository that would permit access to identifiable private data or information about the living Individual from whom the material was obtained).[3]
- Use of health information preparatory to research.

●A provider accesses health information of their patients only.

●An investigator obtains only aggregate data (e.g., number of patients meeting certain criteria) or De-identified data through an LGH data broker.[3]

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal Research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.[2]

- Public health surveillance activities, including the collection and testing of information or Biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify,Monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public Health (including natural or man-made disasters).[4]

- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.[7]

- Operational activities (as determined by each agency) in support of intelligence, homeland security, Defense, or other national security missions.[2]

FAILURE TO SUBMIT PROJECT FOR IRB REVIEW:

The implications of engaging in activities that qualify as Research that are subject to IRB review

without obtaining such review are significant. If an investigator begins a project without prospective IRB review and approval and later learns of the review requirement, the Investigator should promptly notify the IRB. The IRB, under rare circumstances, may allow use of the data.If an investigator begins a project and later finds that the data gathered could contribute to generalizable knowledge, has changed in some fashion as to now require IRB review, or that they may wish to publish the Results, the investigator should submit a proposal to the IRB for review as soon as possible. If the IRB does not approve the research, data collected cannot be used as part of a study nor may the results of the research be Published.[1]

INVESTIGATIONAL DRUG OR BIOLOGIC:

A drug or biologic, not FDA approved, which is being tested in a clinical trial for Safety and efficacy. Investigational drugs and biologics also include drugs and biologics with marketing approval if they are being tested for a different formulation, strength, route of administration or packaging other than what is approved. An FDA approved drug or biologic could also be investigational if it is being tested for an indication which is not approved or to gain further information about an approved use. An investigational drug or biologic may also be referred to as "study medication" or "study drug." [4]

PLACEBO:

An inactive substance used as a control in a randomized clinical trial. The active drug or biologic together With the matching placebo, if applicable, may jointly be referred to as "study medication" or "study drug."[27]

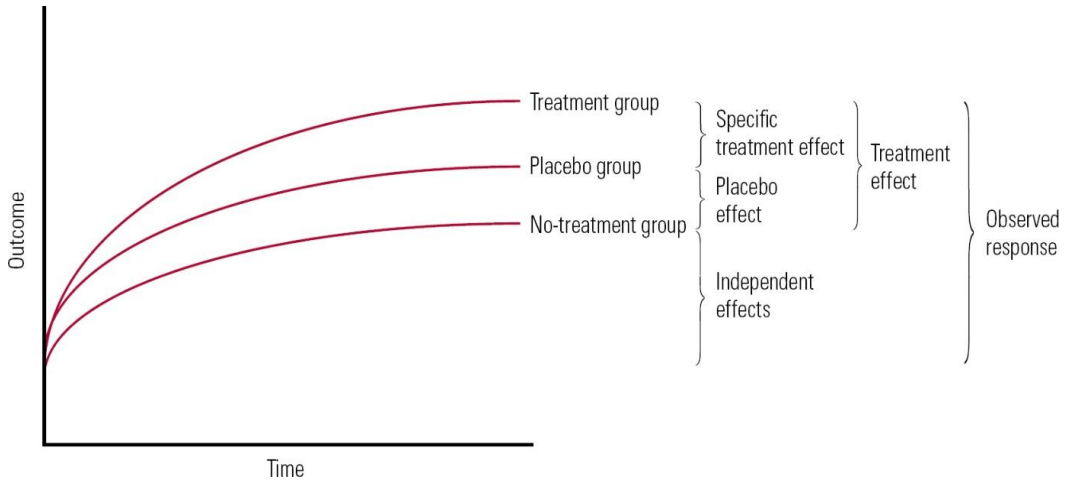


Fig. C : Placebo effects and specific treatment effects.

INVESTIGATIONAL DEVICE:

A device that is used in a clinical study designed to evaluate the effectiveness and/or safety of the device. Investigational devices also may be modifications of devices with marketing approval, or an approved device may be considered investigational if it is being tested for an indication that is not approved. An investigational device may also be referred to as a "study device".[18]

REFERENCE DOCUMENTS

- Investigational Product Accountability Log Template.
- Investigational Product Transportation Log Template.

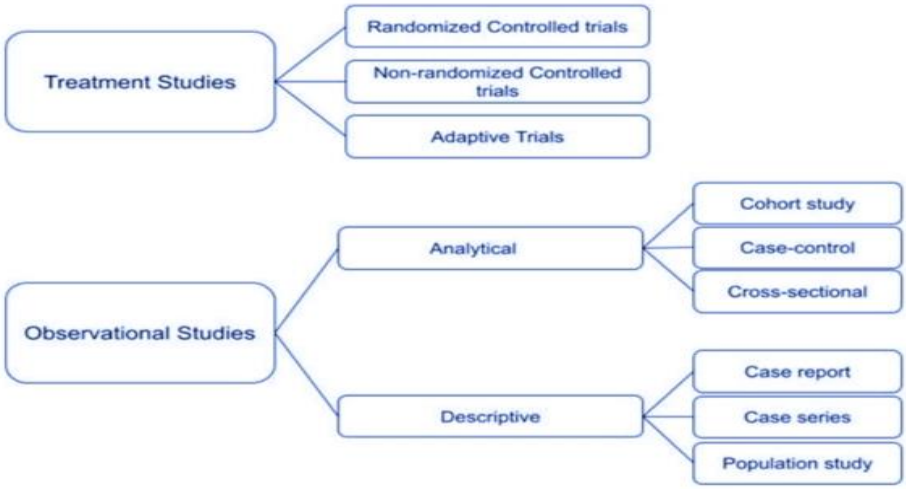


Fig. D. Observation Studies & Data Reports.

CLINICAL TRIALS IN INDIA:

India is looked upon as a favorable destination for conducting global clinical trials. It is estimated that nearly 20% of all global clinical trials are conducted in India. Being the second largest populated country in the world, India can contribute significantly to global drug development programs. India provides an opportunity in terms of availability of large patient populations, highly educated talent, a wide spectrum of disease, lower costs of operations, low cost of medication compared to other developed countries and a favorable economic, intellectual property environment, and importantly, use of English as the primary language make it easy to set up clinical sites in India. India's equivalent to the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) is the office of the Drugs Controller General (India) (DCGI).[4]

The DCGI is federal official responsible for all Pharmaceutical related issues in India. The DCGI is equivalent to the commissioner of FDA. India follows schedule Y for drug trials and Schedule Y is equivalent to the IND regulations 21CFR:312. In India, DCGI is not subdivided into several centers and offices to individually regulate different kinds of products. But, the DCGI himself signs on all applications filed with his office. These include not only clinical trial applications but all applications for marketing approval of drugs and medical devices, for import and export of regulated products and for manufacturing. India follows ICH E6 guidance for clinical trials7-9. The Indian Council of Medical Research (ICMR) released an Indian version of GCPs to for India specific issues for conducting clinical operations. An IEC in India is similar to an Institutional Review Board (IRB) in the US. All sites need to have IEC approval, in addition to the DCGI's approval, before enrolling any subject. In India clinical trial application process takes about 4-8 weeks for starting a trial, while in US, other European countries and Australia, it takes about 2- 4 weeks for processing an application for trial.[3]

X. CONCLUSION:

A Clinical trial is compulsory for a drug/device to ensure its safety & efficacy in humans before their usage. Clinical trials can provide answers regarding the use or not of a therapeutic agent that can benefit millions of patients worldwide. Although, the filing process of the clinical trial application in India is a lengthy process.

It Involves many committees like NDAC, Technical review committee, Apex Committee, Ethics Committee but clinical trials in India have undergone many changes from 2008 to till date, still altering. These changes made India to be a global hub for clinical trials. Being the second most populated country in the world, India can contribute significantly to global drug development programs.[11][8][3][1]

REFERENCES:

[1]. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A Comparison Of The Pharmacokinetics And Pharmacodynamics Of Pregabalin And Gabapentin. Clin Pharmacokinet. 2010;49(10):661–669. Doi:10.2165/11536200-000000000-00000.
[2]. Bartoszyk GD, Hamer M. The Genetic Animal Model Of Reflex Epi-Lepsy In The Mongolian Gerbil: Differential Efficacy Of New Antic-Onvulsive Drugs And Prototype Antiepileptics. Pharmacol Res Commun. 1987;19(6):429–440. Doi:10.1016/0031-6989(87)90082-8.
[3]. Berlin RK, Butler PM, Perloff MD. Gabapentin Therapy In Psychiatric Disorders: A Systematic Review. Prim Care Companion CNS Disord.2015;17(5). Doi:10.4088/PCC.15r01821.
[4]. Clinical Trial Wikipedia, The Free Encyclopedia. Available From: URL Http://En.Wikipedia.Org/ Wiki/Clinical_Trial.
[5]. Crawford P, Ghadiali E, Lane R, Blumhardt L, Chadwick D.Gabapentin As An Antiepileptic Drug In Man. J Neurol Neurosurg Psychiatry. 1987;50(6):682–686. Doi:10.1136/Jnnp.50.6.682.

[6]. Hannan, E. L. (2008). "Randomized Clinical Trials And Observational Studies: Guidelines For Assessing Respective Strengths And Limitations". JACC:Cardiovascular Interventions.1 (3): 211–7.
[7]. Hart CL, Haney M, Collins ED, Rubin E, Foltin RW. Smoked Cocaine Self-Administration By Humans Is Not Reduced By Large Gabapentin Maintenance Doses. Drug Alcohol Depend. 2007;86(2–3):274–277. Doi:10.1016/J.Drugalcdep.2006.05.028.
[8]. Hart CL, Ward AS, Collins ED, Haney M, Foltin RW. Gabapentin Maintenance Decreases Smoked Cocaine-Related Subjective Effects, But Not Self-Administration By Humans. Drug Alcohol Depend. 2004;73 (3):279–287. Doi:10.1016/J.Drugalcdep.2003.10.015
[9]. Hengy H, Kolle E-U. Determination Of Gabapentin In Plasma And Urine By High-Performance Liquid Chromatography And Pre-Column Labelling For Ultraviolet Detection. J Chromatogr. 1985;341(2):473–478. Doi:10.1016/S0378-4347(00)84064-5.
[10]. Howland RH. Gabapentin For The Treatment Of Substance Use Disor-Ders. J Psychosoc Nurs Ment Health Serv. 2013;51(12):11–14.Doi:10.3928/02793695-20131120-01
[11]. ICH Harmonized Tripartite Guideline For Good Clinical Practice 'Academy For Clinical Excellence.
[12]. ICH Guideline For Good Clinical Practice: Consolidated Guidance.
[13]. "India: Prime Destination For Unethical Clinical Trials". Common Dreams.
[14]. Magnus L. Nonepileptic Uses Of Gabapentin. Epilepsia. 1999;40(Suppl6):S66–S72; Discussions73-64. Doi:10.1111/J.1528-1157.1999.Tb00936.X
[15]. Paul J, Seib R, Prescott T (Mar 2005). "The Internet And Clinical Trials: Background, Online Resources, Examples And Issues" (Free Full Text). Journal Of Medical Internet Research.
[16]. Pharmabiz.Com, Mumbai (May 2014),ISCR Releases Guide For Clinical Trial Participants On International Clinical Trials Day.
[17]. Rang, HP; Dale, MM; Ritter, JM; Moore, PK (2003). Pharmacology 5 Ed. Edinburgh: Churchill Livingstone.
[18]. Ryback R, Ryback L. Gabapentin For Behavioral Dyscontrol. Am J Psychiatry. 1995;152(9):1399. Doi:10.1176/Ajp.152.9.1399a.
[19]. Raby WN, Coomaraswamy S. Gabapentin Reduces Cocaine Use Among Addicts From A Community Clinic Sample. J Clin Psychiatry.2004;65(1):84–86. Doi:10.4088/Jcp.V65n0114
[20]. Reimann W. Inhibition By GABA, Baclofen And Gabapentin Of Dopa-Mine Release From Rabbit Caudate Nucleus: Are There Common Or Different Sites Of Action? Eur J Pharmacol. 1983;94(3–4):341–344. Doi:10.1016/0014-2999(83)90425-9.
[21]. Schlicker E, Reimann W, Gothert M. Gabapentin Decreases Mono-Amine Release Without Affecting Acetylcholine Release In The Brain. Arzneimittelforschung. 1985;35(9):1347–1349.
[22]. The Lancet (2009). "Phase 0 Trials: A Platform For Drug Development?". The Lancet. 374 (9685): 176–118.
[23]. Vollmer KO, Von Hodenberg A, Kolle EU. Pharmacokinetics And Meta-Bolism Of Gabapentin In Rat, Dog And Man. Arzneimittelforschung.1986;36(5):830–839.
[24]. Walden J, Hesslinger B. Value Of Old And New Anticonvulsants In Treatment Of Psychiatric Diseases. Fortschr Neurol Psychiatr. 1995;63 (8):320–335. Doi:10.1055/S-2007-996633.
[25]. Yang, Z. J., Et Al. (2010). "Motivation For Health Information Seeking And Processing About Clinical Trial Enrollment." Health Communication 25(5): 423-436.
[26]. Zullino DF, Khazaal Y, Hättenschwiler J, Borgeat F, Besson J.Anticonvulsant Drugs In The Treatment Of Substance Withdrawal. Drugs Today. 2004;40(7):603–619. Doi:10.1358/Dot.2004.40.7.850478.