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CURRENT LAWS GOVERNING COMPARATIVE STUDIES AND CLINICAL TRIALS IN INDIA, THE UNITED STATES, EUROPE, AND SINGAPORE

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ABSTRACT: Clinical trials (CTs) are carried out to investigate novel, patient-acceptable, and more effective interventional procedures. Specific regulatory criteria for conducting CTs are recommended by the country's drug regulatory authority, and these guidelines are followed when conducting CTs. The USFDA oversees regulating CTs in the USA in accordance with the Federal Food, Drug, and Cosmetic Act's 21 Code of Federal Regulations, Part 312 (CFR). According to the GCP Directive 2005/28/EC of the 8 April 2005 and the CT Directive 2001/20/EC of the European Parliament and of the Council of the 4 April 2001, they are under the control of the European Commission and EMA in the EU. Both the ICMR and the CDSCO (Schedule Y, D&C Act) have control over the Ethical Guidelines for Biomedical Research on Human Subjects. The European Commission's objective of promoting an environment that is suitable to CTs within the EU is to be realised with the help of the Clinical Trials Regulation (CTR) (No. 536/2014). All interventional CTs involving medicines for human use that are done in the EU going forward must comply with the CTR legislation. It strives to harmonise submission and evaluation procedures, raise overall safety standards, and enhance cooperation and transparency within and among Member States. Compared to India and Singapore, the USA and Europe have a greater success rate for CTs, which may be attributable to highly competent researchers, a quick regulatory approval process, and eager subject volunteers. Also, several case studies pertaining to the CTs are carried out in these nations.

INTRODUCTION: Finding a medication molecule that is therapeutically effective in managing and treating a disease state is just one aspect of the complex process of discovering new drugs.

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Typically, new insights into a disease process that enable investigators to build a pharmaceutical to prevent or oppose the effects of the disease lead to the discovery of new drugs by researchers [1].

The identification of drug candidates, as well as their synthesis, characterization, screening, and therapeutic efficacy testing, are all components of the drug development process. Following clinical trials, the process of developing a medicine will begin when a molecule produces outcomes that are satisfactory in these studies. The process of drug development and discovery has shown the

tremendous expenses of R&D and clinical trials given in **Fig. 1**. A single new drug molecule must undergo nearly 12 to 15 years of development from the time it is discovered to the point where it is sold to patients [2].

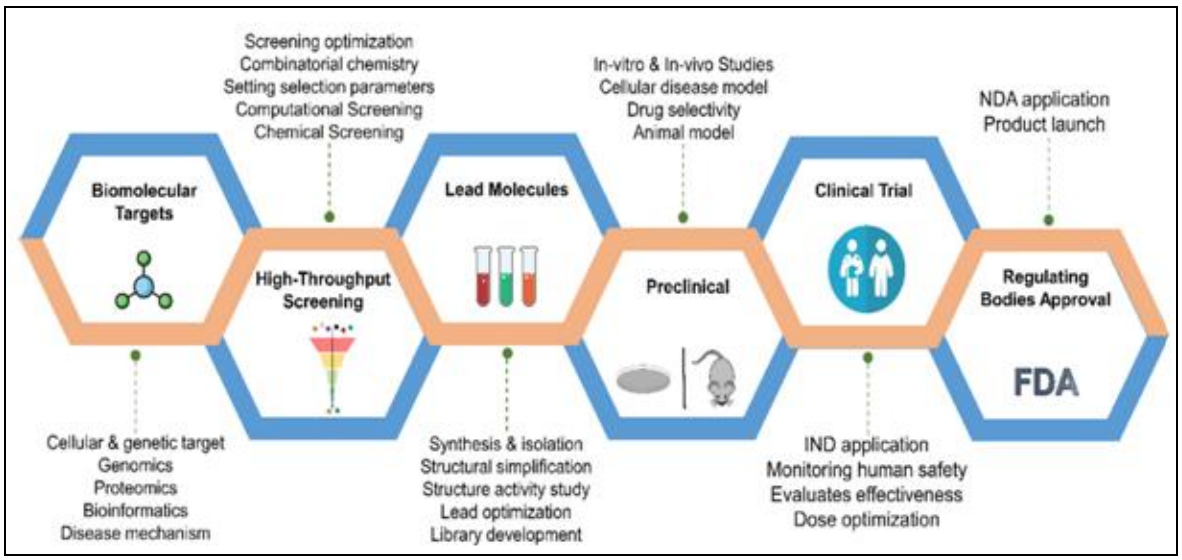

FIG. 1: DRUG DEVELOPMENT AND DISCOVERY PROCESS

The procedure contains several steps, including;

1. Target identification is the first step in the process of choosing physiologically relevant targets for a certain illness state.
2. Hit compound identification by high-throughput compound library screening.
3. Lead identification and lead optimization, which aims to enhance the selectivity, potency, and ADME characteristics of the hit compounds.
4. Preclinical research, where the enhanced drugs are analysed in animal models to ascertain their pharmacokinetic properties and medicinal benefits potential.
5. Regulatory approval comes after clinical studies, in which drug candidates are examined for safety and effectiveness in four stages on humans. A medicine is then made available for use in clinical trials when a regulatory body approves its commercialization for molecules with favourable pharmacokinetic properties, therapeutic efficacy, potency, and few side effects [3].

Clinical Trials: A clinical trial is a prospective biomedical or behavioural research study that uses human participants to answer specific questions about biomedical or behavioural therapies (vaccines, drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

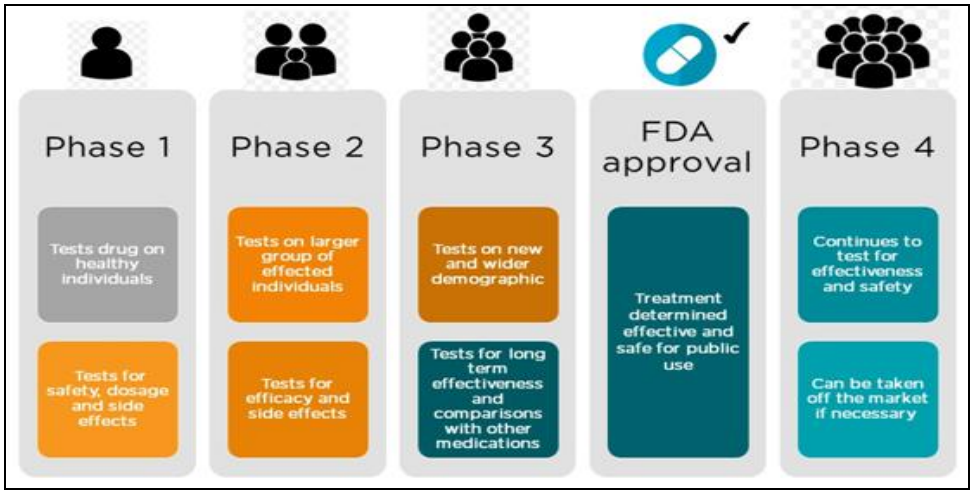

FIG. 2: PHASES OF CLINICAL TRIALS

The effectiveness, efficacy, and safety of cutting-edge biological or behavioural interventions are assessed through clinical studies given in **Fig. 2**. Research using human subjects to create or evaluate clinical laboratory tests (such imaging or molecular diagnostic tests) may be classified as a clinical trial if the subject will utilise the test to make medical decisions or if the test itself imposes more than minimum risk on the subject [4].

Preclinical Studies: To ensure that their techniques (such as a drug, treatment, preventative measure, or diagnostic) are not dangerous to people, researchers conduct comprehensive preclinical studies in the lab prior to starting a clinical trial. Toxicology is used to quantify the degree of injury. Preclinical studies don't use human subjects for the research. Instead, before being tested on humans, new medications, and treatments—as well as the techniques to administer them—are first examined in cells, animals, or both. Preclinical research typically does not take up much space. Researchers evaluate their preclinical testing results and choose whether to move forward with human testing. Phase I is where the possible medical treatment is tried on humans for the first time after appearing to be safe in cells or animals [5].

Phase I Clinical Trials: An investigational therapy is first administered to people during phase I clinical trials. Instead of determining how beneficial the medicine may be in treating a particular ailment, these trials are concerned with making sure that it is safe to use in individuals.

A small, tightly supervised group of healthy volunteers participates in this research trial on a regular basis. Volunteers who have the condition may take part in circumstances where it is severe or life-threatening. Increasing dosages of the experimental medicine are administered during Phase I studies so that researchers can monitor the body's reaction, particularly how the drug is absorbed, how long it stays in the blood stream, and which dosage levels are secure and well tolerated [6].

Phase II Trials: In the event that Phase I investigations reveal the product to be safe, Phase II trials may start. Depending on the product, hundreds of volunteers receive the treatment during Phase II of a clinical trial. The investigation into safety in the second stage is still ongoing, but efficiency is the main concern. Usually, it takes years or even months to conduct these investigations. Phase II trials often pay less because participation takes place over shorter periods of time than Phase 1 trials do. Phase II trials typically pay between a few hundred dollars and several thousand [7].

Phase III Clinical Trials: Clinical trials undertaken in Phase III are significantly larger than those done in Phase I or Phase II. Numerous locations throughout the world regularly host these studies, which enlist hundreds or even thousands of people. Before receiving approval for widespread use, treatments that performed well in phase II undergo further, more thorough evaluation.

Doctors contrast the novel treatment with the most effective current treatment (also called the "standard treatment"). The study team can then ask for Food and Drug Administration (FDA) approval to make the medication generally accessible after these lengthy trials, which might last for many years if the data demonstrate that the treatment is effective [8].

Phase IV Clinical Trials: Post-authorization safety studies are another name for phase IV clinical trials (PASS). This is done after the new medication has been given regulatory approval and is regularly applied in a clinical environment. It evaluates the medication's long-term side effects and its practical efficacy.

The drug is still being examined for negative effects that were not noticeable in Phase III after the FDA has given the medication its approval and placing it on the market. This phase investigates the overall quality of life that the medicine has improved in a large number of patients [9].

Clinical Trials Methodology: The United States has the United States Food and Drug Administration (USFDA), Europe has the European Medicine Agency (EMA) and European Commission (EC), India has the Central Drugs Standard Control Organization (CDSCO), and Singapore has the Health Science Authority shown in **Fig. 3**.

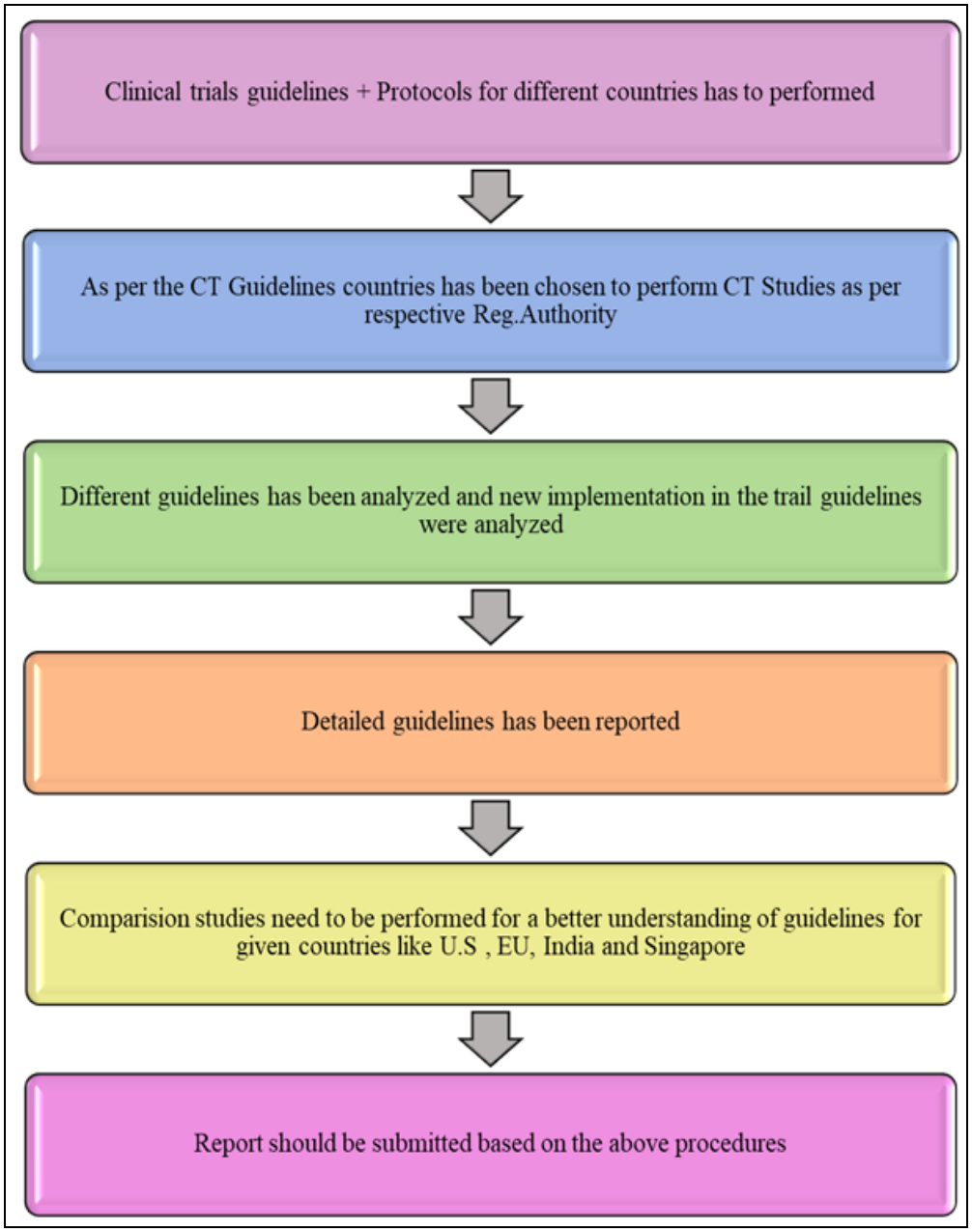

FIG. 3: CLINICAL TRIAL GUIDELINES PROTOCOL

Clinical Study Paperwork Requested by ICH-GCP:

Prior to the Start of the Clinical Trial:

- Researcher's brochure a compilation of clinical and non-clinical data related to the investigational product(s) that will be used in the research on the investigational product(s) in human subjects.
- A protocol was a document that describes the objectives, methodology, design, and structural elements of a study. Additionally, it contains specific reporting methods for technical, laboratory, medical, and safety issues. Though they might also be found in other articles that the protocol refers to, the background and justification for the study were often provided in the protocol as well.
- Case Report Forms (CRFs): A printed, electronic, or optical record aimed to document all the protocol-intended particulars on each trial subject to be submitted to the sponsor.
- Informed Consent Forms (ICFs): A document that defines research participants' rights and provides details on the study's objective, duration, risks, potential advantages, required steps, and key contacts.

- Institutional Review Board's formal endorsement (IRB).
- Blinded trial decoding processes.
- Reports about the beginning of trials [10].

Throughout the Trial:

- Investigator's Brochure Updates.
- Modifications to the protocol, CRF, or ICF that have received IRB/IEC approval.
- Signed ICFs.
- Reports on Visit Monitoring.
- Subject enrolment and screening log.
- A list of any bodily fluids or tissues that were saved. The clinical study report with the trial's results and an interpretation of them, the end trial close-out overseeing report, and the investigator's final report to the IRB/IEC were among the records that must be kept [10].

Fundamentals of all Medical Research:

- Human subjects in medical research must abide by acknowledged scientific standards.
- Every research protocol must have a detailed description of the design and procedures in a research study implicating human subjects.
- Facts on financing, sponsors, investigators, institutional affiliations, and payments for research study participants must be included in the protocol.
- Before registering the first subject, each CT should be listed in a public database.
- To get clearance for the start of the CT, the study protocol should be presented to the ethical committee.
- The study proposal should be forwarded to the ethical committee for approval before the CT may begin since human subject's medical research can only be conducted if the benefit outweighs the danger.

Clinical Trials in India: Clinical research was currently governed by Schedule Y of the 1945 Drug & Cosmetics Rules. After the D&C act was revised in 2005 to bring the Indian laws into compliance with generally accepted definitions and practises, the schedule Y underwent a significant modification. The adjustments included,

- Definitions for Phase I–IV studies underwent revisions, which abolished the Phase lag.
- Sponsors' and investigators' roles are crystal clear.
- Requirements for notifying protocol changes.

In India, standards were set by the CDSCO, a part of the Ministry of Health and Family Welfare (MoH and FW), to certify the safety, efficacy, and calibre of drugs, cosmetics, diagnostics, and technology. The Poisons Act of 1919, Pharmacy Act of 1948, Drug and Magic Remedies (Objectionable Advertisement) Act of 1954, Narcotic Drugs and Psychotropic Substances Act of 1985, Insecticide Act of 1968, Medicinal and Toilet preparation (Excise duties) Act of 1956, and The Drug (Price Control) Order of 1995 (under the Essential Commodities Act) were additional Statutes and Ministries that regulate various aspects of drugs [11]. Pharmaceuticals may be produced, distributed, and sold in India in accordance with the Factories Act of 1948, the Trade and Merchandise Marks Act of 1958, the Indian Patent Act of 1970, the Industries (Development and Regulation) Act of 1951, and other legislation [12]. The Drugs & Cosmetics Act (D & C Act) in India defines clinical trials as "Systematic study of new drugs in human subject(s) to generate data for discovery and/or verification of the clinical, pharmacological (including pharmacodynamics and pharmacokinetics) and/or adverse effects with the aim of determining safety and/or efficacy of the new drugs." Clinical trials must be conducted in India starting with Phase I for new drug compounds found there, and data must be provided in accordance with the requirements given in **Fig. 4**.

For new medicinal compounds discovered in nations other than India, however, Phase I data from the other country will be necessary and must be supplied with the application. When Phase I data generated external of India was filed to the licencing authorities, permission may be granted to conduct Phase I studies again, Phase II trials, and finally Phase III trials concurrently with other

international trials for that medication. Phase III studies must be finished in India before the drug can be approved for sale there. In order to conduct a clinical trial in India, a sponsor was required to submit Form 44, an application for clearance to start a particular phase of the research, along with the required documentation mentioned in Schedule Y of the D & C Act of 1940 and its implementing rules. Using Form 44, a clinical study application was filed along with supporting documentation that includes details on chemicals and medicines, animal pharmacology, toxicology, and clinical pharmacology [13]. The investigator's undertaking, the informed consent form, the case report form, and other trial-related papers must all be presented for approval. It was indeed necessary to mention the trial's regulatory status in other countries. An IEC composed of representatives from each participating site must examine and approve the trial protocol. For biologicals, distinct chemistry and pharmaceutical information requirements have been developed, but other requirements, such as those for conducting clinical trials, have not changed from Schedule Y of the D & C Act of 1945. The CDSCO has made a checklist available for the conduct of phase I, phase II, and phase II clinical trials. If direct permission was granted, it will likely take 8 to 12 weeks for the study's conduct to be approved. The IND committee will assess the applications, which could take anywhere between 12 and 24 weeks whether it was a brand-new treatment or the first time it has been tested on humans. On the basis of this judgement, the DCGI office might approve (with or without specific procedural alterations) [14].

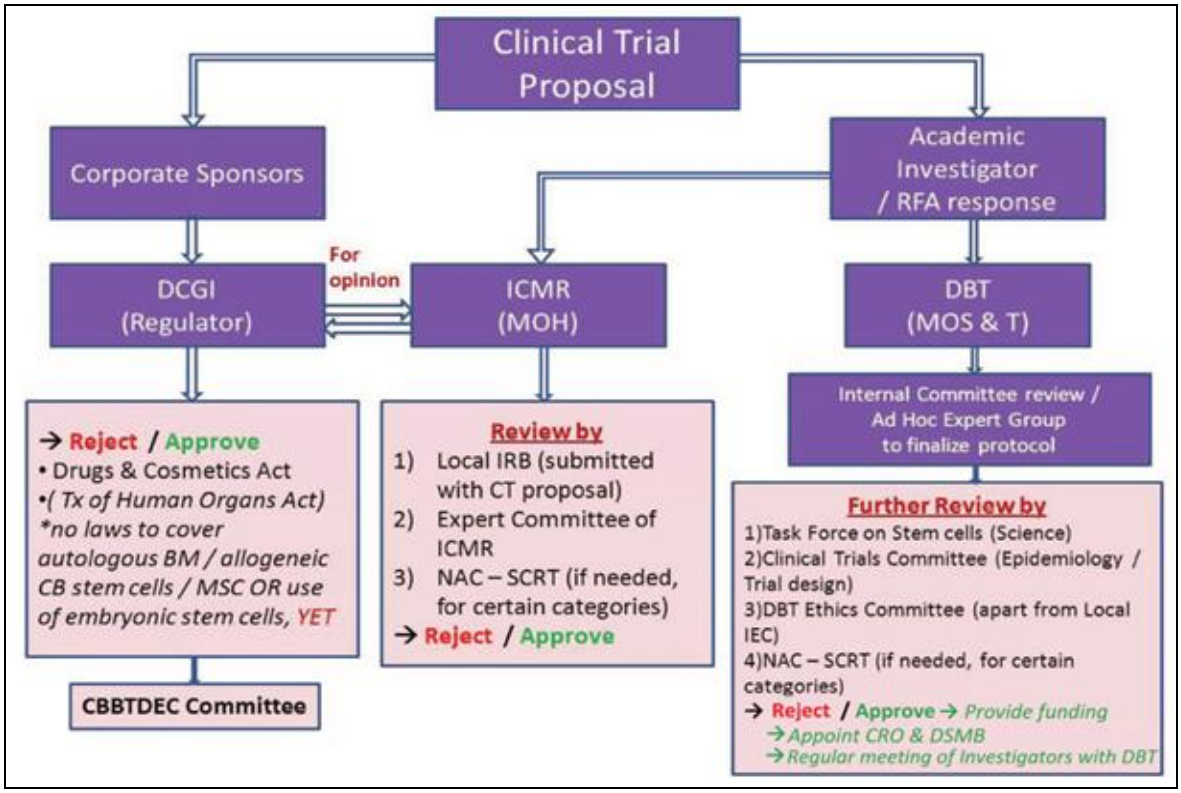

FIG. 4: INDIA'S CURRENT SYSTEM FOR APPROVING CLINICAL TRIALS

Clinical Trials in the US:

Carrying out Clinical Research in the United States:

- An application for an investigational new drug (IND) was frequently submitted to propose clinical research of an unlicenced medication or an established medicine for a new usage or in a new population of patients.
- If the test product contains a novel chemical entity, involves a radioactively tagged medicinal product, or was cytotoxic, an IND was also required to conduct a bioavailability or bioequivalence (BA/BE) research.
- An IND application receives a response from the US FDA within 30 days.

- If the FDA has any questions, the sponsor will need to address them and won't be able to begin the study until the FDA has given them permission in writing.
- If the institutional review board (IRB) permission was in place and the sponsor waits the required 30 days without hearing back from the FDA, they can start the clinical research programme stated in the IND on the 31st day [15].

FDA Amendment Act of 2007, Section 801 was the statute that oversees this in the US (FDAAA Section 801). The law uses the ClinicalTrials.gov database, sometimes known as CT.gov or ClinicalTrials.gov informally, and was controlled by the FDA [16]. It was also handled by the US National Library of Medicine. This database was available to all clinical trials, independent of their origin nation, clinical phase, or sponsor, although being limited by law to clinical studies carried out in the US. When sponsors opt to use this database as their global, all-encompassing "Disclosure" platform, they should keep in mind that all registered studies, including for those that do not fall under FDAAA Section 801, were expected to release results. The database, which provides registration information on 173,199 studies taking place in 187 different countries, was the most popular source for clinical trials disclosure (August 2014) [17]. Any pertinent clinical research that was commenced or initiated in the US after September 2007 or as a part of a US regulatory submission should be registered. Phases 2, 3, and 4 of clinical studies in both adults and children were available. Applies to adult and paediatric Phase II, III, and IV clinical investigations. Show summary results for: Products that have been approved.

The product's FDA approval status affects when summary results from finished clinical studies will be disclosed:

- Authorized product and authorised use/indication: 12 months from the conclusion of the trial.
- New item with novel use or indication: 30 days after approval.
- 30 days following the acceptance, denial, or withdrawal of the application for the approved product and any new use or indication [18].

Recent FDA Guidance Documents:

- Application of Clinical Holds in Response to Clinical Investigator Misconduct (Final, Sept. 04).
- Studies involving biological and pharmaceutical products were exempt from IRB regulations (Final, Jan. 06).
- 5 Info Sheets for Clinical Researchers, IRBs, and Sponsors (IRB inspections, medical device trials, waiver of IRB review) (Jan. 06).
- Utilizing the Multicenter Clinical Trials Centralized IRB Review Process (Final, Mar. 06).
- Setting Up and Running Clinical Trial Data Monitoring Committees (Final, Mar. 06).
- In accordance with 21 CFR 50.24, emergency research was exempt from informed consent requirements (Draft, Aug. 06).
- 21 CFR 50.54 Procedures for FDA Referrals: Additional Protections for Children in Clinical Investigations (Final, Dec. 06).
- Adverse event monitoring improves the protection of human subjects (Draft, Apr. 07).
- Computer-assisted clinical trials (Final, May 07).
- Guarding the safety, rights, and welfare of subjects in the study: Investigators' Supervising Duties (Draft, June 2007) [19].

Adverse event reporting guidelines in draught and it should be noted in every report to an IRB because an incidence was "unanticipated" and poses a "problem" for study. Reports that have not been assessed for their applicability to the study shouldn't be submitted to the IRB (even if the event was unpredicted, it cannot be determined whether each individual AE was unexpected risk if considered in isolation). It was necessary to compile reports that explain how certain details might affect the IRB's evaluation of the study, necessitate protocol modifications, or demand that the permission form be changed.

Only report the following for unforeseen issues that were also negative medication experiences: Any adverse event (AE) that, even without analysis, was a serious one that was uncommon without drug exposure (e.g., hepatic necrosis, agranulocytosis, *etc*.) Numerous unanticipated AEs that, upon investigation, turn out to be a pattern and have an impact on the individuals' rights and welfare Anomalies projected to occur more frequently or severely than anticipated any additional adverse event that would warrant changing the investigator's protocol, permission form, or IRB action [23].

Supportive Regulatory Framework for Generic Products:

- The generics sector and the ensuing rivalry with their brand-name counterparts were supported by the Hatch-Waxman Act of 1984.
- Nine out of ten prescriptions written in the United States today were for generic drugs, because to faster processes and lower sponsor costs.
- The 505(j)-approval process was used for generic drugs.
- BA/BE studies can be carried out using unapproved variations of approved pharmaceutical drugs without submitting an IND [21 CFR 320.31(b) and (d)].
- A mixture of the 505(b)(1) NDA (New Drug Application) for full applications and the 505(j) ANDA (Abbreviated New Drug Application), the 505(b)(2) NDA was also available.

Some data required for NDA approval may come from studies that weren't conducted by or for the applicant, in accordance with the provisions of 505(b) (2). As a result, the cost to the sponsor has greatly decreased, and there was now a possibility for a speedier route to pharmaceutical approval shown in **Fig. 5** [15].

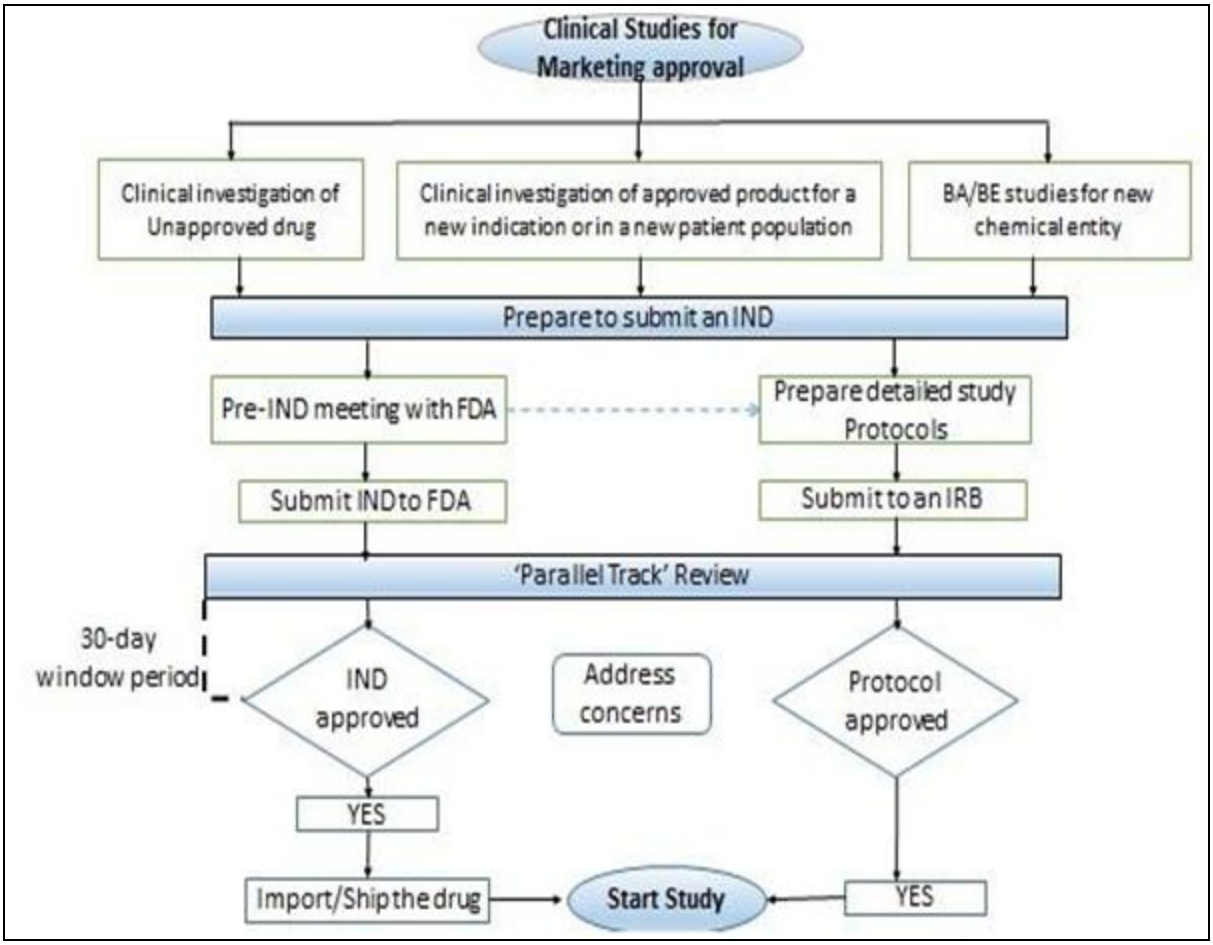

FIG. 5: AN OUTLINE OF HOW CLINICAL TRIALS FOR MARKETING AUTHORIZATION WERE CONDUCTED IN THE UNITED STATES

General Requirements: Personnel; Facility and equipment; QC (Quality Control) function; Control of components, containers, and closures, Laboratory controls, Manufacturing and records, Packaging, labelling, and distributing, Record keeping and Attend the meeting.

FDA's GMP Expectations for Phase I and First-in-Man Clinical Trials require an exhaustive and meticulous examination of the manufacturing environment (including the equipment, process, product environment, materials, and personnel) to identify potential risks.

Personnel:

- Professionals have the necessary education, training, or experience to carry out the task at hand.
- Must be acquainted with QC principles and appropriate procedures for adhering to the legal provision of CGMP and must possess the necessary experience to generate the phase 1 experimental drug.

QC Qualification:

- Examine and discharge components.
- Examining and approving production processes, test processes, and test criteria.
- Investigate faults and start corrective steps before releasing or rejecting each batch following a cumulative review.

Facility and Equipment:

- Enough room, a sanitary setting, and suitable construction.
- Proper ventilation, lighting, and heating.
- Proper plumbing, cleaning, and sanitation.
- All machinery utilised in the manufacturing of Phase 1 drug products shall be maintained in good working order, identified, calibrated, and cleaned in line with the applicable documented protocols.
- Identified and recorded in production records.
- Made of materials that won't contaminate, react with, contribute to, or absorb the product.
- Each piece of machinery used to make Phase 1 medicinal products must adhere to these specifications.

Unique Manufacturing Circumstances:

- Facilities for many products.
- Items created using biology or biotechnology.
- Processing done in an aseptic manner.

To learn how to conduct a thorough and methodical assessment of the manufacturing environment, join the FDA's "GMP Expectations for Phase I and First-in-Man Clinical Trials" lecture. Additionally, the seminar will direct you in taking the proper steps both before and during manufacture to remove or reduce any potential risks and preserve the quality of the phase 1 investigational medicine [20].

Clinical Trials in Europe:
Principal Elements of the European Union (EU) Clinical Trials Regulation:

- The idea of preface of a patient's "once-only" authorization for usage of their data, biological samples, and tissues solely for ongoing medical studies after the trial itself, with the patient's freedom to retract consent at any point of time. This concept must be applied consistently across the EU General Data Protection Regulation and EU Clinical Trials Regulation as well as in all nations since some legislations, such as ethical approval, will come under the purview of diverse nationalised authorities.
- Full publication of all studies, without regard to their outcomes, on a single website, ensuring great transparency of clinical trial data.
- Simplifying the application process and imposing rigorous deadlines for Member State approval.
- Establishing a single data submission site to ease the administrative load placed on researchers, especially those involved in clinical studies involving multiple countries.
- Opinions must now be delivered by new legally mandated deadlines. the establishment of an EU

database that lists each clinical study (while maintaining the role of ethical committees).

- At the EU level, the term "ultra-rare diseases" was initially defined as a political classification.

The new Regulation has important consequences for medical oncologists, and ESMO was working to ensure that they were aware of them. In conjunction with the Clinical Academic Cancer Research Form (CAREFOR) and EU Cooperative Research Groups, ESMO will monitor how the EU Clinical Trials Regulation was being implemented and afford productive criticism and suggestions to the appropriate organisations in charge of coordinating its implementation across the European Union. Collaboration between European Society for Medical Oncology (ESMO), European Organization for Research and Treatment of cancer (EORTC), and European Association for Cancer Research (EACR) led to the creation of CAREFOR. A position paper published by CAREFOR in 2017 addressed the issue of "Safeguarding the Future of Independent, Academic Clinical Cancer Research in Europe for the Benefit of Patients." The study describes CAREFOR's mission to safeguard and advance academic clinical cancer research across Europe. The best practises for cooperation between European academic cooperative groups and business were highlighted in a report published by CAREFOR in 2020 titled Current models, issues, and work handled amongst European industry and academic cooperative groups. To support its members and enhance patient outcomes, ESMO was still working on policies that will encourage cancer research in Europe [21].

All interventional clinical trials involving human pharmaceuticals were governed by the new EU CTR Regulation. Through the implementation of the CTR in early 2022, the European Commission prospects to enhance the conditions for clinical trials in the EU. It aims to foster cooperation and transparency between and within Member States in addition to increase overall safety regulations by consolidating all submission and evaluation processes underneath one roof. It also seeks to streamline and accelerate clinical studies carried out within the EU in order to speed the accessibility of new therapeutic approaches and maintain the EU's appeal to clinical trial sponsors. This study, which also seeks to prepare you for business, examines the primary difficulties you can run into when researching the new Clinical Trials Regulation. The cost and complexity of producing pharmaceutical items were influenced by the differences in national regulatory rules for clinical trial clearance amidst EU member states.

The EU CTR attempts to lessen some of this intricacy by creating universal criteria for clinical trial licencing, evaluation, and monitoring throughout all EU member states. The way clinical trial proposals were handled has changed significantly, even though this was still a laudable undertaking. Therefore, companies must make all necessary preparations for the adoption of the Clinical Trials Regulation while keeping operational concerns in mind.

A Regulation as Opposed to a Directive: Prior to 2004, clinical trial protocols and regulations were progressed at the level of Member States, which resulted in major variations among EU member states. The approval of the Directive in May 2004 marked a significant advancement in the standardisation of clinical trial protocols and criteria. Clinical trials use under the Directive was still incredibly dispersed, nonetheless. Clinical studies that involve multiple Member States must submit separate applications to each country (for now).

- 2001/20/EC Regulation
- Article 536 of Regulation (EU) 2014

Significant Modifications made to the EU's New Clinical Trials Regulation Include:

Clinical Trials Registry & Information System for EU (CTIS): By allowing clinical trial applications to be submitted through a single system and streamlining the entire application process, the CTR launches the CTIS portal. For instance, sponsors submitting applications to several MSCs at once can use this strategy to submit a single application to all nations. The trial, sponsor, and product information in Part I of the application will also be subject to a combined evaluation by all MSCs under CTR, and a single verdict will be rendered in this regard [22].

A Clinical Trial Database Called Clinical Trials Information System: The European Medicines Agency (EMA) already has established and made available a number of training programmes for different user groups to help businesses in developing for the adoption of CTIS. Additionally, the EMA website offers complete training tools. In our upcoming blog, we'll discuss this topic.

The CTIS system updates the application process and gives the general public access to more data. By allowing the public access to documents submitted to the site, the EMA for instance, promotes the transparency of clinical trial information.

Application Submission for Clinical Trials Under the Clinical Trials Regulation: In the initial year of operation, prior to the requirement that submissions under the EU CTR become necessary, sponsors will be able to choose whether to submit new trials under the current Directive (2001/20/EC) / EU CTR. Additionally, the EU CTR will permit sponsors to use the CTIS to file a unified system CTA to Ethics Committees (ECs) and Competent Authorities (CAs) for all EU states intended to take part in a particular study (CTIS). There were two steps to the application process:

- Part I: Scientific evaluations were coordinated by a reporting member state (RMS)
- Part II: Assessment of individual member states

Clinical Trials in Multiple Countries under the New Regulation: The eligible member countries collaborate to complete the Part 1 evaluation while conducting global clinical trials. The study plan determines which member state the reporting member state belongs to. The review report for Part 1 was produced in collaboration with this member state by the reviewing committees of all the other participating member-states. Every single member-state evaluates Part 2 on a particular basis. Consequently, part 1 permission may be obtained by all interested member states. Part 2 permission was required for all the member state's facilities connected to the problem [23].

The process for Medical Ethics Review: The EU will have uniform maximum review times for clinical trials. As a result, simultaneous recruitment can start at all participating nations' sites. In the European Union, all study-related paperwork, including protocols, must be submitted centrally and online. To achieve this goal, a website and database were now being built by the EMA.

Reporting on Safety: Instead of per study, safety reports will be evaluated individually for each product. As a result, safety reporting for each investigational medicine will be the responsibility of each EU member state. You must transmit SUSARs straight away to the EudraVigilance database as a sponsor [24].

Making the Transition to Ongoing Clinical Trials: Within three years of the new EU CTR's deployment, all ongoing clinical trials must be transitioned to it under a clinical trial strategic plan.

The harmonisation or standardisation of documents like the investigator brochure, protocol, and investigational medicinal product dossier across the EU was also required prior to transition.

Reduced Flexibility for Substantial Modifications: There will be little room for manoeuvre for the EU CTR to accept substantial modifications (SMs).

The updated procedure provides for the granting of substantial modifications within 94 days, during which time no more SMs may be submitted. It emphasises the significance of Member State selection and the related submissions process as it relates to the accession of EU member states.

Benefits of the Clinical Trials Regulation: We may anticipate the Clinical Trial Regulation having major benefits, even though adjusting to these changes may need some effort shown in **Fig. 6**.

The Clinical Trials Regulation's overarching purpose was to prevent duplicating clinical trials or avoid repeating failed trials while fostering innovation and research [25]. These were some of the primary advantages of the regulation:

1. Harmonization of Clinical Trials in the EU
2. Trial data publication & Transparency
3. Transparency for laypersons.

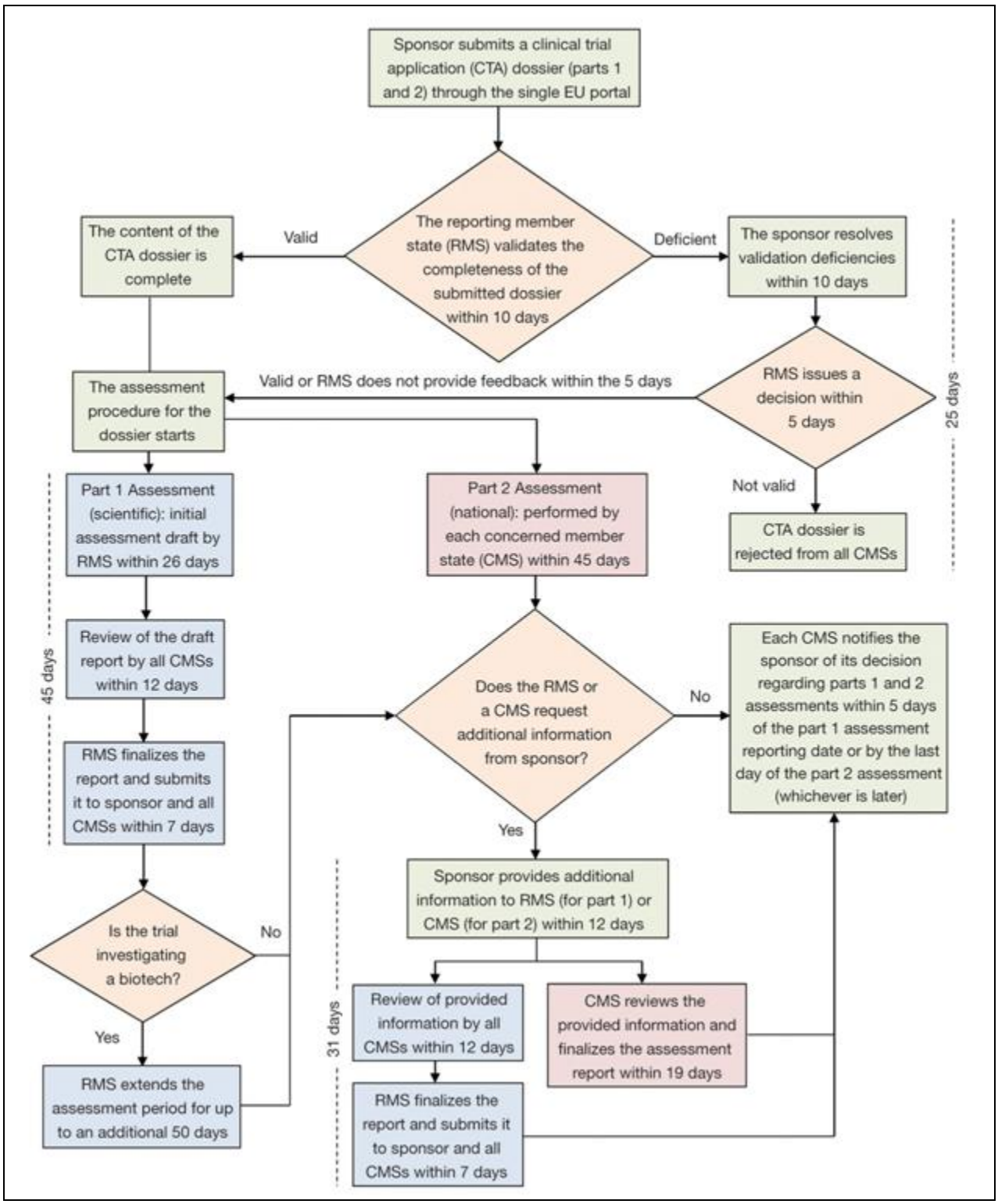

FIG. 6: EU CLINICAL TRIALS REGULATION PROCESS

Clinical Trials in Singapore: The Medicines (CT) Regulations and Health Items (CT) Regulations accordingly, direct in what way clinical trials were conducted for therapeutic products and pharmaceuticals. The regulations provide that one of three submission procedures must be used by clinical trial sponsors to provide HSA with information about their studies:

- ✓ Clinical Trial Authorization (CTA) for testing medicinal items in human trials.

- ✓ Clinical Trial Notification (CTN) - for clinical trials involving medicinal goods with label approval.
- ✓ The Clinical Trial Certificate (CTC), which was required for clinical studies of pharmaceutical goods [26].

Regulatory Requirements for Clinical Trials: CTA or receipt of CTN were prerequisites for clinical trials of therapeutic items before the experiment was initiated or carried out (such as pharmaceutical medicines and biologics). A CTC was required prior to the beginning or completion of a clinical study for a biological product, such as a tissue, cell, or a complementary health product, or gene therapy product.

Regulations (Clinical Trials) for the Health and Therapeutic Products (Clinical Studies) Conducting clinical trials requires adherence to ICH E6 Good Clinical Practice regulations as well as guidelines for biological products shown in **Table 1** [27].

TABLE 1: DOCUMENTS NEEDED FOR DIFFERENT CATEGORIES

S. no.	Documents	Clinical Trial Authorization (CTA)	Clinical Trial Notification (CTN)	Clinical Trial Certificate (CTC)
1	Protocol for medical trials	✔	✔	✔
2	Form of Informed Consent (English)	✔	✔	✔
3	Researcher's Brochure	✔	–	✔
4	Where appropriate, a list of overseas trial locations	✔	✔	✔
5	CV of the principal investigator	✔	✔	✔
6	Certificate for Good Manufacturing Practices (GMP)	✔	✕	✔
7	Investigational Product research batches' Certificates of Analysis (COA)	✔	✕	✔
8	Information about chemistry, manufacturing, and control (CMC), as requested by HAS	✔	✕	✔
9	IRB Approval Letter for Approved Product Label	✕	✔	✕
10	Protocol for medical trials	✕	✔	✕

Regulations Governing Therapeutic Product First-in-Human (FIH) Studies: Prior to starting the FIH trial in Singapore, the medicinal product does not need to be authorised in other nations. The sponsored applicant, like with other clinical trials, must be a business that was duly registered in the country. Companies seeking information on clinical and non-clinical needs should allude to the pertinent ICH recommendations and regulations established by the key agencies (FDA, EMA) [28].

Process of Approval:

- Information on whether a medicine falls within the CTA or CTN category was provided in a guidance document.
- The sponsor was mandated to file the clinical trial form to HSA (Health Science Authority) after it has been recognized that a clinical trial on a pharmaceutical product or products must comply with the standards of the CTN or CTA.
- Clinical studies for pharmaceuticals, including items used in tissue, cell, and gene therapy, as well as supplementary health goods were governed by the Medicines Act and the Regulations for Medicines (CTs). CTC was required before carrying out such clinical trials, must be issued by HSA.
- In Singapore, the sponsors should be a duly incorporated company with an Accounting and Corporate Regulatory Authority (ACRA) registration. The sponsor must employ the Pharmaceutical Regulatory Information System (PRISM) to electronically submit the clinical trial application to HSA.
- The clinical trial application might be filed simultaneously to the pertinent IRB and HSA for clinical investigations necessitating a CTA or CTC. Only when the IRB has granted this approval should clinical trials that need HSA's clearance for CTN be filed.

- Subsequent submissions to HSA during a clinical study, such as reports on significant modifications, grave violations, and trial progress, may be required. If nothing else, use PRISM to make any additional HSA contributions.
- When the sponsor receives HSA permission, the trial may begin.
- For a CTA or CTN, the HSA's approval of the clinical trial or acceptance of the notification was active for the trial period. The time between the start and finish of the clinical trial was included in its length shown in **Fig. 7**.

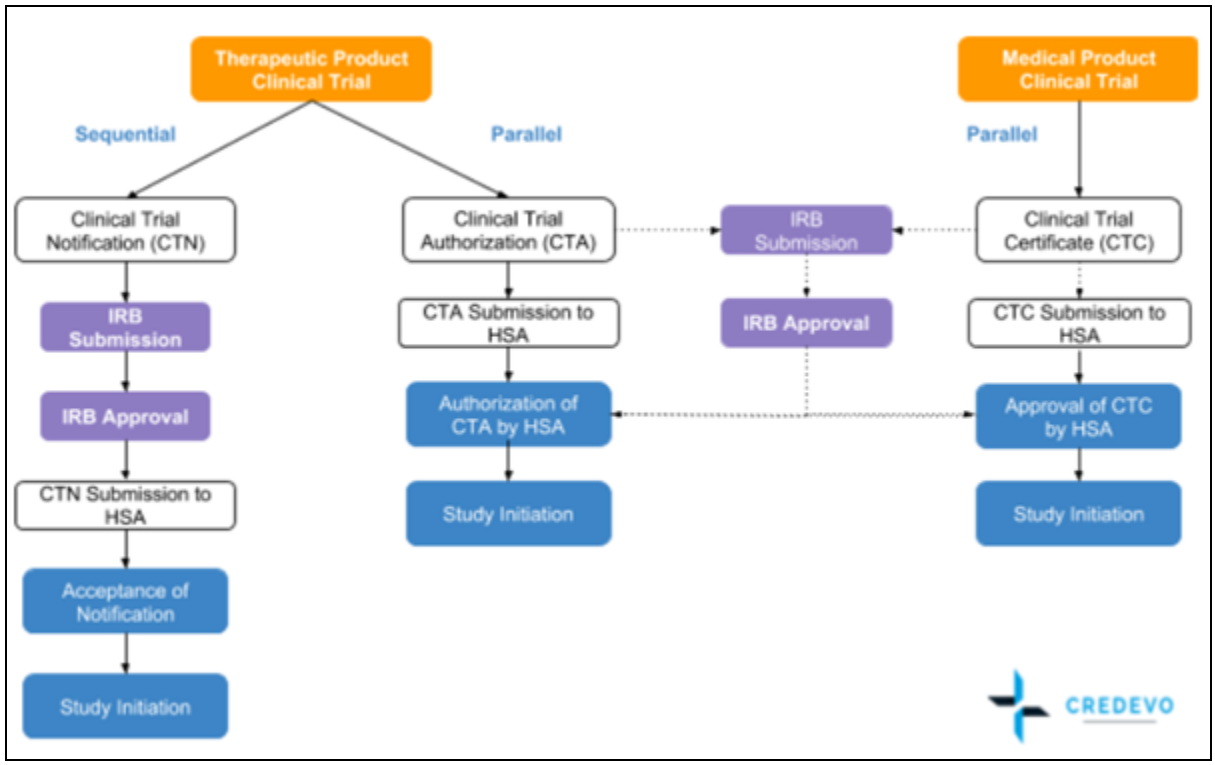

FIG. 7: PROCEDURAL FLOW

Duration of Approval: Depending on what category the trial falls under, the timetable changes.

- Clinical Trial Certificate (CTC) - 30 Working Days.
- Clinical Trial Notification (CTN) - 5 Working Days.
- Clinical Trial Authorization (CTA) - 30 Working Days.

It takes roughly 15 days for CTA Clinical studies in phase 1 that just aim to assess bioavailability, bioequivalence, drug-drug interaction or food effect [29].

A Regulatory Fee: For the time being, there were no fees associated with submitting a clinical trial submission to HSA.

Import and Export Permits:

- The Medicines (Medicinal Products as Clinical Research Materials), Health Products (Therapeutic Products as Clinical Research Materials), and Health Products (Medical Devices) Regulations, correspondingly govern the import and delivery of medicinal products, therapeutic products, and medical devices for clinical trials in Singapore.
- In compliance with these guidelines, HSA must be notified (Clinical Research Material Notification - CRM) beforehand importing CRM made in another country or supplying CRM made locally by a local producer. Local producers, importers, CRM suppliers, and clinical trial sponsors must also follow the rules as they pertain to their respective roles.

- Sponsors of controlled clinical trials should send the CRM notice along with the CTA/CTN/CTC submission form.

- The local manufacturer or importer might need to get sponsorship from sponsors of clinical studies which was not governed by HSA guidelines in order to submit the CRM notification.

- HSA does not require an export licence in order to ship biological samples abroad for analysis [30].

Singapore's Guidelines for Conducting Clinical Trials:

Singapore GCP Regulations: As of right moment, clinical trial conduct in Singapore was not officially governed by GCP. When conducting trials, researchers adhere to the Medicines (CTs) Regulations. The reference standards have been the ICH Guideline for GCP. The Medicines (CT) regulation must also be followed for CTs to be done in Singapore. There were some differences between International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) and Singapore Guidelines for Good Clinical Practice (SGGCP). For instance, in ICH-GCP guidelines, the IRB approves CT applications, whereas in SGGCP, the MCRC reviews CTC applications in place of the IRB. The goal of the SGGCP guidelines was to guarantee that CTs in Singapore were performed in accordance with generally recognised ethical and scientific standards. These regulations, which were adapted from ICH E6 regulations, were put into effect in 1998 and updated on October 1, 1999 [31].

Medical Clinical Research Committee (MCRC): The Ministry of Health set up the MCRC to examine requests for conducting clinical trials on pharmaceuticals in Singapore. MCRC upholds the welfare and rights of each trial participant in compliance with the principles articulated in the Declaration of Helsinki. This committee's responsibility includes ensuring that clinical research was conducted in compliance with Singapore GCP standards. Other activities include developing SOPs, keeping written records of their operations, and ensuring compliance with Singapore GCP Guidelines and the Medicines (CT) Regulations.

Compensation Rule in Singapore: Compensation for participants injured during clinical trials was not specifically regulated in Singapore. Information on compensation should be included in the certificate issued by the governing bodies for the start of the CT. Participants were compensated in accordance with their informed permission, which details the compensation for all types of injury [32]. The comparison of clinical trial guidelines in India, USA, Europe, and Singapore were given in **Table 2**.

TABLE 2: COMPARISON OF CLINICAL TRIAL GUIDELINES IN INDIA, USA, EUROPE AND SINGAPORE

Parameters	India	USA	Europe	Singapore
Regulatory authorities	CDSCO	USFDA	EMA (European Medicine Agency)	HSA
Application for a clinical study	Form 44 was a request for permission to begin a clinical trial	Investigational new drug application (INDA).	Investigational medicinal product dossier (IMPD)	Clinical trial certification application
Fee for Application	Fees were required in Phases I, II, and III, which were $50,000, $25,000, and $25,000, respectively	No fee.	Minor fees vary by member state	No fee was required for this application
Format for submitting an application	Form 44 must be submitted in accordance with national guidelines	Common technical document (CTD) formats, U.S format	CTD format	CTC form according to national format
The deadline for approval	16- 18 weeks	30 days	60 days	Minimum 6 months
Independent ethics committee / Institutional review board (IRB) (IEC)	The clearance of the DCGI (Drug Controller General of India) and the Ethics committee was needed	An institutional review board as well as approval from the Centre for Drug Evaluation and Research (CDER) were required	The approval of the ethics committee was required. CMS-appointed or authorised ECs (Concerned Member States)	IRB/IEC and MCRC approval required

Regulations	The D&C Act, 1945 amended the Schedule Y to the D&C Act, 1940	The following federal requirements must be followed: 21 CFR Part 312, 50, 54, 56	Clinical Trial Directive (2001/20/EC) and Good Clinical Trial Directive (2005/28/EC)	Medicines Act and Medicine (CT) Regulations
Compensation	According to 122 DAB rule	Informed consent-based compensation Parts 50 and 54 of the 21st CFR	Separate "Certificate of patient insurance" was required, as indicated in the procedure and also in the informed consent	Compensation mentioned in CTC and informed consent form
GCP Standards	Indian GCP	ICH GCP	ICH GCP	SGGCP
Storage of documents	After completion, the records will be kept for three years	Time to keep records was two years	Patient identification codes must be updated till 15 years after the CT completion	Till 6 years after completion of trial
Reporting Adverse Events	Any injury or death caused by a clinical study must be reported to the DCGI within 24 hours	A potentially fatal adverse event was reported to the FDA within seven days	Sponsor reports a serious adverse reaction within 7-15 days	Sponsor reports a serious adverse reaction within 7 calendar days
Forms are necessary	Form 44	FDA forms 1571, 1572, 3454, and 3455 were necessary	Clinical trial application form	Clinical trial certification form

CONCLUSION: The identical CTs were regularly conducted across numerous nations. Every CT ought to be registered with a Common International Clinical Trial Organization, according to the recommendation. In addition to reducing duplication in the way CTs were performed, this would also benefit patients from many nationalities by saving them time, money, effort, and discomfort. Regulated countries like the US and the EU have more solid regulations than semi-regulated countries like Singapore and India. CTs were subject to severe rules set by government agencies in the USA. The USA would soon demand that IND applications be submitted in the eCTD format, speeding up the approval process.

Data relevant to CTs was also kept online. IMPD applications and other data pertaining to CTs must be submitted in CTD and eCTD formats, respectively, in Europe where CTs were governed by the EC and EMA. The conduct of the CTs was governed by ICH-GCP guidelines in the USA and Europe. India and Singapore, two nations with a limited regulatory framework, either have fully developed CT rules or adhere to internationally recognized norms. It takes longer to get permission to start the CTs because the CTD format for submitting CT applications in both countries was still not authorized. CTs were performed in these nations in accordance with local laws. Additionally, there were some issues with using the ICH-GCP standards to do the CTs. These aspects help explain why clinical trials in the EU were more effective than those in Singapore and India. The identical CTs were regularly conducted across numerous nations. Every CT ought to be registered with a Common International Clinical Trial Organization, according to the recommendation. In addition to reducing duplication in the way CTs were performed, this would also benefit patients from many nationalities by saving them time, money, effort, and discomfort.

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