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Systematic Review

A comparison of regulatory approval of clinical trial protocol with different countries

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ABSTRACT

In present scenario, different countries must follow different regulatory requirements for protocol approval process of new drug application. Present study, we studied the regulatory requirements, timelines of approval and guidelines according to central drug standard control organization (CDSCO), therapeutic goods administration (TGA), food and drug administration (FDA) and European medical agency (EMA). The objective was to compare the regulatory approval of clinical trial protocol process. A comparative observational study was undertaken among the clinical trials and regulatory bodies of India (CDSCO), Australia (TGA), US (USFDA), Europe (EMA). The study specified various regulatory guidelines and safety requirements for conduct and inspection of clinical trial. Clinical trial protocol guidelines the essential documents are determined, and various timelines are being identified. And compared with the fees with other countries. Indian payments were compared with other countries. Timelines with safety reporting were compared with other 3 countries (Europe, Australia and US). The regulatory guidelines in the clinical trial different between countries. There is different timelines and requirements of clinical trial application approval process for each regulatory body. This study methodology has enabled comparisons to be made both within agencies and between different authorities and has identified differences in the timelines that applications spend in different stages of the review.

Keywords: RA guidelines and requirements, FDA, TGA, EMA, CDSCO, Clinical trial approval process, Timelines and requirements of CTA

INTRODUCTION

Indian drug regulatory system is CDSCO regulatory authority responsible for the clinical research trial (CTs) for the approval process and inspections. To regulating sale and importation the drugs in CTs were responsible for the India drug controller general of India (DCGI) heads CDSCO. The CDSCO is also responsible for the granting clinical trial protocol permission regulating the export, importation of drugs, sale and for use in human trials. CDSCO is responsible for conducting CT studies, established in standard drugs, approving new medicines, assessing the quality of import and exported drugs, manufacturing, distribution of medicines and coordinating the state licensing authorities were regulates the sale.[1]

In India, each state's drugs control authority has given rights to DCGI apart from CDSCO approval. So in India has been center of conducting various multicenter trials and is also essential for CTs conducted in India should as per the ICH-GCP (international conference of harmonization-good clinical practices guidelines) follow the recently amended new CTs rules and regulations of the drug, cosmetic act. In today's turbulent scenario in the pharmaceutical industry have good knowledge.[2]

DCGI review of the applications for the new investigational drugs and new CTs, global CTs and post marketing trials phases I-IV. CDSCO has nightly calendar days to require to evaluate the application for the drugs developed outside India and in India it requires 30 days for medicine manufactured, researched and discovered.[3]

It is based on some of the following evaluation conditions like the evaluating of the risk versus benefit to the study subjects, change in live therapeutic option, unfulfilled drugs need in the country, it requires safety investigational tests and in post marketing additional information needed before marketing full inclusion in packages insert a applicant (sponsor) is responsible for financial settlements fee to the regulatory agencies like DCGI to submit a CT application.[4]

It is required to conduct a CT are investigator brochure, protocol, case report form, informed consent document, clinical trial agreement, source document, regulatory approval, insurance statement, EC notification and investigational product document. So, the primary responsibilities of the ethics committee relates to continue and protect the rights, safety and welfare of all trial subjects, mostly these who in exposed population in multispectral, representing a mixed gender and age composition activities should be independent EC. The Indian council of medical research CT registry in India (clinical trial registry in India) CTRI in academic trials including clinical trials to register is compulsory for all subjects. Frequently occurring clinical trials reviews may provide monitoring and internal audit reports to EC as part of its quality assurance system, investigators provide periodic study progress reports. If it's available the audits certify and it may be issued.[5]

In Australian department of health, TGA is a part of the health products regulation group (HPRG) and TGA is responsible for clinical subjects and trial approvals, oversight and inspections and also regulates the supply, import and export, produce, advertising of therapeutic goods, prescription medicines, vaccines, medical device. TGA manages Australian register of therapeutic goods (ARTG) for all therapeutic goods for human use in CT.[6]

TGA has double-tiered system including supportive drugs and regulations of drugs to assess the. quality, safety and efficacy of the product higher hazard chances of drugs must be registered on ARTG. Low risk elements make restricted claims can be grouped on the ARTG which contains pre-approved is lower chances of risk.[6] Clinical trial notification or clinical trial scheme are essential to registered or tabulate medicines are used in conditions of the clinical trials. In the national declaration of national health and medical research council (NHMRC) verify human research ethics committee's (HREC) should arrange particular guidelines in the clinical studies so for this there is no official equipments.[7]

In European union there are two regulatory steps which is approved from the market where as human trial application were approved at state level and market authorization were approved at both the member state and centralized level.[8,9]

In US and Europe, report highlights particular points in terms of authors, investigators and readers reporting of risk management plans (RMPs) and serious adverse event reports, EC review books focus are on clinical study registration, clinical studies can be recorded through web based data entry system called PRS. It is a process for entering. Protocol data using the PRS can be used and viewed on the website. US based drug companies data to be entered include descriptive information, enrolled information location, contact information and delegate information this information widely available to the public and search criteria such as company, site, drug name, infection and delegating user friendly.[8,9,10]

In the world, US considered most demanding medicine. In various countries for marketing authorization is single regulatory approval is applicable currently in different countries have to fallow different regulatory requirements for approval of new medicine may be US has world's most requirements standard for approving new medicines.[13] Objectives of study was to compare the regulatory approval of CT protocol process namely CDSCO, TGA, EMA and FDA and highlight the importance of clinical trial regulatory approval timelines. The purpose of the study is to compare the regulatory. Approval process of CT protocols, modalities in India and other countries. By this study we came to know that how Indian CT protocol approvals differ from other country's regulatory approvals and the timelines followed by different CT regulatory approvals.

METHODS

In this study, a methodology-based WHO regulation and CDSCO and DCGI present guidelines are followed and based on research articles, research journals, countries legal website and scientific publications have provided a basis for detailed analysis of timelines for CT review and approval of four regulatory authorities. This research showed that the various timelines and requirements of CT approval process of CT regulatory guidelines of India compared with Europe, US and Australia. Timelines of CT approval process and its requirements in India were compared with other respective countries.

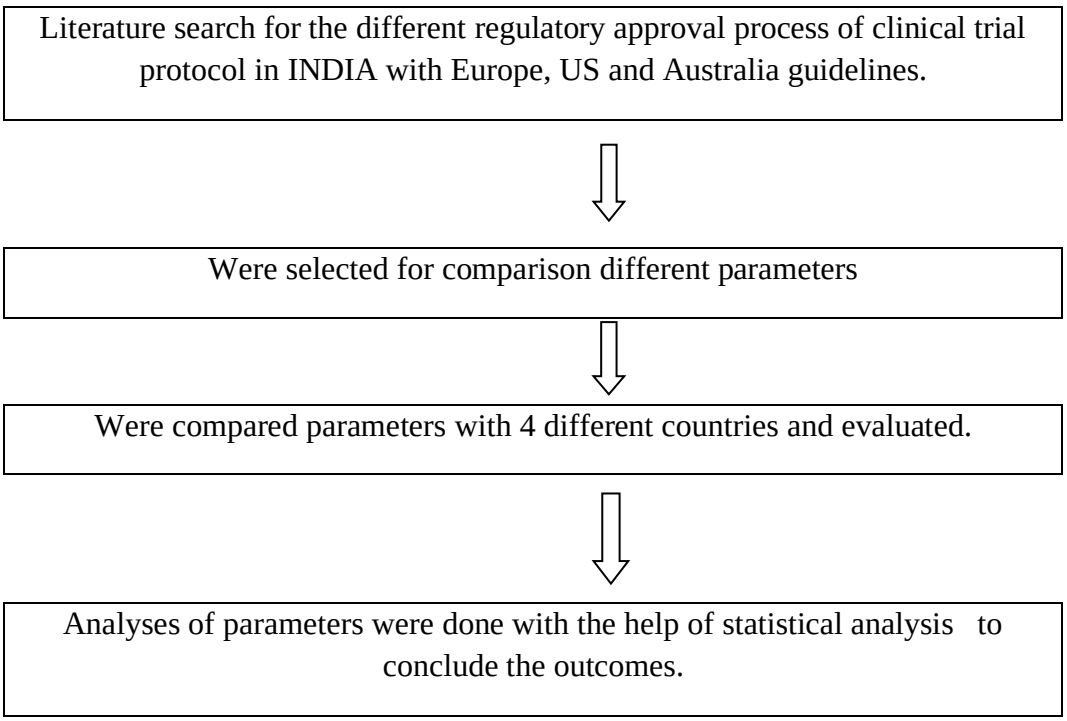

Figure 1: Litrature.

RESULTS

Effective regulation of medicines/devices requires a different of functions, guidelines including evaluating the safety and efficacy data from CT and licensing and inspecting manufacturing facilities and distribution channels.

The reason for this study was to comprehend and look at the international clinical trial regulatory guidelines with the Indian clinical trial regulatory guidelines for protocol approval, furthermore to survey and study similitudes and contrasts between guideline in the other countries. Clinical trial regulatory guidelines for protocol approval are expressed in a clear way then rules of every nation trial approval guideline are represent in the Table 1. The duration of study was 5 months and the outcomes acquired are as per the Table 1.

Table 1: Comparison of Indian clinical trial protocol approval process with other counties.

S. no.	Parameters	India	Europe	Australia	United States
1.	Clinical trial or study application language in all respective countries	English	English	English	English
2.	Submission of essential documents for protocol approval	Dossiers, ICF, IB, CRF, CTA, diagrammatic flow chart for protocol.	Dossiers, ICF, IB, CRF, CTA, diagrammatic flow chart for protocol.	Dossiers, ICF, IB, CRF, CTA, diagrammatic flow chart for protocol.	Dossiers, ICF, IB, CRF, CTA, diagrammatic flow chart for protocol.
3.	Authority for clinical trial registration in the respective countries	CTRI	EUDRACT	ANZCTR or ICMJE	NHMRC (USA)
4.	Access for registration of trial in Respective registry	http://CTRI.nic.in	www.clinicaltrials, register.eu	http://www.anzctr.org.au/BasicSearch.aspx	ClinicalTrials.gov, run by the (USNLM)

Continued.

S. no.	Parameters	India	Europe	Australia	United States
5.	Types of clinical trial registration methods	One-time registration process	Multiple registration process like national (one-member state); mutual recognition (at least two member states); centralised (European community) decentralised (at least two member states)	Multiple registration process	One-time registration process
6.	Payment methods for clinical trial registration	There is no payment required for registering CTs	There is no payment required for registering CTs	Payment required for registering CTs	There is no payment required for registering CTs
7.	The form of presentation documents for clinical trial	PAPER	e-CTD	e-CTD and PAPER	e-CTD and PAPER
8.	Regulatory agencies and regulatory authority bodies in respective countries	DCGI CDSCO	National health agencies; EMEA; CHMP	TGA; ARTG; NHMRC (AU)	USFDA
9.	Regulatory authority fees for Protocol approval in specific countries	Required	Required	Required	Not required
Regulatory authority fees for respective countries according to clinical trial phases					
10	Phase I	3,00,000	2,84,116	57,748.31	If relevant
	Phase II	2,00,000	20,890	7,12,539.60	If relevant
	Phase III	2,00,000	20,890	7,12,539.60	If relevant
	Phase IV	2,00,000	27,800	If relevant	70,480
11.	Regulatory authority and ethics committee reviews conducted at same time of trial submission in all respective countries	Both reviews conducted in same time	Both reviews conducted in same time	Both reviews conducted in same time	Both reviews conducted in same time
Clinical trial application regulatory approval timelines					
12.	Regulatory review timelines of clinical trial protocol in respective countries	45 days	45 days	CTN-scheme on weekly basis; CTX-scheme 30 to 50 days; review depending on the level of review TGA +20 days	Within 30 calendar days of receipt of the original IND
	Institutional ethics committee review timelines of clinical trial protocol in respective countries	Four (4) to eight (8) weeks.	76 days+50 days for advanced therapies or biologics	Timeline varies by institution (earlier notification)	Maintains its own procedures and processes for review. No statement
13.	At the time of protocol submission required the process validation	Required	Required	Required	Not required
14.	Ethics committee duration of renewal registration	5 years	4 years	3 years	3 years
15.	Ethics committee fees for protocol approval process	Required	Required	Required	Required

Continued.

S. no.	Parameters	India	Europe	Australia	United States
16.	Regulatory guidelines Followed in clinical trials	New drugs and clinical trial rules, ICMR guidelines, Indian GCP.	ICH-GCP; CTFG rules; EUDRALEX rules; EudraCT rules	ICH-GCP; NHMRC guidelines; TGR rules; ACTH guidelines	US-ICH-GCPs FD and Cact rules OGCP
17.	Initial Reporting of SAE Timelines in specified countries	24 hours	As soon as possible no before 7 calendar days	Within 24 hours and in any case no later than 72 hours	As soon as possible no later than 7 calendar days
18.	SAE due analysis reporting timelines in above mentioned countries	14 working Calendar days	Fallowed by as complete a report as possible before 8 additional calendar days	15 days	15 days
19.	Ethics committee approval is mandatory in all respective countries	Mandatory	Mandatory	Mandatory	Mandatory
20.	Regulatory authority fees for protocol approval in specific countries	Required	Required	Required	Not required
21.	Number copies required protocol submission application	4 copies like 2 hard copies 2 soft copies	2 copies both e-CTD and PAPER	2 copies both e-CTD and PAPER	2 copies both e-CTD and PAPER
22.	Regulatory authority bodies and EC reviews conducted at the time of trial submission yes/no	Yes	Yes	Yes	Yes
23.	Post approval changes in respective countries	Post approval changes like major; moderate	Post differences in the sanctioned drug: IA type; IB type; II type	Post approval changes like major; moderate	Post approval changes in the approved drug: minor; moderate; major
24.	Parallel regulatory and ethical review permitted in respective countries yes/no	Yes	Yes	Yes	Yes

DISCUSSION

This study is first of this kind, where the guidelines of different countries in CT protocol approval process compared with Indian regulatory system. A similar study conducted by Kumar which mainly focused/compared on regulatory approval guidelines for protocol approval in USA and India. In our study we compared four different countries regulatory guidelines, we added 2 more countries like Australia & Europe and find the necessities protocol approval in clinical trials.1 This study also highlights the timelines and guidelines of protocol approval process in clinical trial.

In discussion part we find out some main characteristics or parameters, these parameters are discussed one by one.

Protocol approval process

Indian Regulatory Guidelines compared with four different countries and find out some major parameters in Protocol Approval Process and listed in result part and similar study conducted by Snehal.W. shows some timelines of clinical trial protocol approval and we find out some similarities and Differences in each country Regulatory Guidelines. Based on legal websites and guidelines.[2]

Indian timelines are compared with USA, Australia and Europe and find out the varies in protocol approval process like regulatory review and CTA application are mainly focused on this study.

Institutional ethics committee approval process

The ethics committee timelines find out and compared with respective countries. Some variations are concluded and mentioned above Table 1. A similar study conducted by Evangeline, in their study also mentioned variations of timelines for ethics committee approval India and European ethics committees are clearly mentioned specific timelines but US and Australians regulatory body of EC maintains its own procedures.[1]

In this study differentiated some specific parameters like parallel regulatory review, ethical review, languages of study application and copies of documents during the submission of application these all parameters are find out and a similar study conducted by Yadav in their study also find out above mentioned parameters and differentiated each country. Yadav compared only in 3 different countries in our study we compared one more country guideline like Australia all variations in parameters are listed above table.[7]

In this study we observed that differences and similarities in agencies and registration process of CT protocol and trial registration process. A similar study conducted by Jawahar based these parameters in different countries and we also find out variations that parameters according to Indian regulatory guidelines of present scenario. In the protocol approval process mainly clinical trial registration process and post approval changes also essential for protocol approval, we find out these parameters in our study.[6] Namely India and US are one regulatory agency and both Europe and Australia having multiple regulatory agencies. All the agencies' details are clearly notified in above mentioned in results table. these agencies are required for both countries and take main lead in CT protocol approval process.[16] Regulatory registration process differentiated in times registered, in India and US having one-time registration method and both Europe and Australia having multiple registrations process and post approval changes also compared and these are same in INDIA, US and Australia differ in Europe.[7]

A study conducted by Surabi specified each trial SAE data records are to be reported within period of regulatory timelines and up-to-date. This study observed that the quality of trial needs to be improved in clinical trial reporting but in this study additionally highlights for quality control measures and reporting time frame in initial SAE and due analysis reporting timelines compare to other Indian timelines are accurate and speed in process.[5]

Indian new CT rules are differentiated in CT phase's fees accordingly on duration and requirements of trial and study fees. Indian ethics committee renewal extended two years other countries are fallow old guidelines and timelines fallowed in renewal of ethics committee.[17] Accordingly Indian CDSCO regulatory guidelines mentioned ethics committee approval is mandatory for new clinical trial study approval process in our study compared with fallowing countries other countries fallow these method according their own guidelines like Australia follow TGA guidelines, US follow FDA guidelines and Europe follow EMA guidelines in registration of IRB and approval process.

CONCLUSION

The study specifies various regulatory guidelines requirement for CT protocols. This study has only evaluated Indian regulatory body with other countries regulatory guidelines. This study does not include any information related to quality of the regulatory approval process. Each regulatory body has stringent guidelines while approval of CT protocols with significant regulatory approval guidelines have seen. This study method has enabled comparison to be made both within the regulatory guidelines and also identified differences of each trial protocol approval regulatory guidelines. CDSCO has made drastic changes through exceptional improvement in its guidelines whenever required and made stringent. Relatively CDSCO rules have guaranteed that trial units in India are consistent with administrative norms and can fulfil adequate guidelines of value in their lead of trials. In USA regulatory approval process is faster before thirty calendar days of receipt of the original IND than the other country regulatory bodies. There are certain aspects that were not survey within the space of thesis. The study did not focus on the SAE regulatory guidelines. This study concludes that submission of essential documents for protocol approval to/from regulatory body to institutional ethics committee approval.

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