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A review on selection of investigator in clinical trials

Jyothi K. Navya*[1], Jogi Prameela[2], V.C.Randeep raj[3]

*[1] Pharm D, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India

[2] Pharm D, Avanthi Institute of Pharmaceutical Sciences, Near Tagarapuvalasa Bridge, Vizayanagaram, Andhra Pradesh, India

[3] Clinical SAS Programmer,Clinosol Research Pvt.Ltd, Visakhapatnam, Andhra Pradesh, India

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Abstract

According to ICH GCP investigator may be considered as a person proficient in education, training, and experience who will take the major restraint for the good conduct of the trial and should satisfy all the requirements described by applicable regulatory authorities and must comply with GCP. Investigators are very much important for the primary conduct of the study, whose primary importance is to conduct research while protecting the rights, safety, and well-being of the participants. Investigators have many important roles in conducting ethical research, taking responsibility for the informed consent process, giving the statement of the investigator, checking of investigational product, reporting adverse events, maintaining accurate records. A selection of the investigator for the conduct of research is a complex process. Investigators should be selected based on their interest and their requirements for education, training, and experience. This can be done by assessing professional competency or through a referral from other investigators or through online databases or by advertising their CV on the internet. In multicenter trials selection is done by querying public and private, using databases, a referral from the clinical research team, performing a publication search. After the recruitment of Investigators, he will continue his activities like signing the investigators' form and perform the informed consent process, and finally enrollment of subjects. The Investigators involved in COVID-19 trials and the study type, recruitment status, purpose of the trial was collected.

Keywords: clinical trials, investigator, selection, Covid-19.

***Corresponding Author**

Jyothi K. Navya

Email: naviyahjyouthi24@gmail.com

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Introduction

The investigator may be considered as a person proficient in education, training, and experience who holds the restraint for the proper conduct of the trial and should satisfy all the qualifications specified by the applicable regulatory requirements, must aware and comply with GCP, applicable regulatory requirements. One of the primary responsibilities of a principal investigator is to conduct research while protecting the rights, safety, and wellbeing of human participants [1].

The principal investigators are carefully selected by proper education, training, experience, and interest in a particular trial. They must have experience in the field of trials related to drugs. The investigators who are rated first are either the members of Research and Development or advisors to the government or members of drug approval advisory panels and should meet requirements according to protocol, SOPs, GCP, and applicable regulatory authorities. In the US and, Europe most of them are experienced in cancer, AIDS, hypertension, metabolic diseases (dyslipidemias), organ transplant, autoimmune diseases (rheumatoid arthritis), sepsis, contrast agents, psychiatric and neurological diseases (dementia, depression, Parkinson's and, Alzheimer's) [2].

Clinical trials will provide huge information to the clinicians scientifically to decide what therapy should be planned in a systematic manner to the patients with

available data. The clinician participating in clinical trials will be benefited from the knowledge and the gained knowledge will provide an impact on care for human participants [3].

This article will describe about the importance of investigator in the clinical trials, who should be selected as an investigator, the process of selecting investigator, documents required for the selection process for the primary conduct of the study and the requirements of the investigator.

1. Importance of Investigator in The Clinical Trial

We will discuss in detail about the investigator importance below. Fig 01: shows the requirements and responsibilities of investigator.

Category	Requirements and Responsibilities
Principal investigator	•Anyone qualified by training to run the trial; a physician or dentist must be listed as a subinvestigator if the principal investigator is not a physician
	•Hire and train qualified individuals to run the trial
Subject safety	•Protect subjects from harm
	•Keep track of drugs and distribute only as specified in the protocol
	•Obtain informed consent
	•Ensure IRB approval
	•Keep careful records and maintain them for as long as the protocol dictates or at least 2 years
Reports	•Progress, safety, financial, and a final report to the study sponsor
	•Adverse events; serious adverse events must be reported immediately
	•Update financial disclosures if any circumstances change during the study
Form 1572	•Strictly adhere to the protocol
	•Directly supervise the study and take responsibility for study staff
	•Inform subjects of experimental nature of the drug products
	•Report adverse events and stay updated on the investigational brochure
	•Maintain records
	•Ensure IRB compliance
FDA inspections	•Ensure all records are complete and easily accessible by FDA
	•Send a written response within 15 business days if any violations are found
How to avoid violations	•Read all communications from the IRB
	•Hire experienced staff and verify their credentials
	•Train staff regularly
	•Check for conflicts of interest/financial disclosures regularly
	•Write efficient protocols or reduce inefficiencies or confusing portions of the protocol
	•Keep regulatory binders up to date and conduct continuing reviews
	•Meet with the team regularly
	•Conduct several dry runs to ensure the study will run smoothly
	•Regularly check data processes

FDA, US Food and Drug Administration; IRB, institutional review board.

FDA, US Food and Drug Administration; IRB, institutional review board.

Fig 01: Investigator responsibilities and requirements

1.1 Conducting ethical research

The investigator should take an ultimate responsibility in conducting the ethical research from the initial design of the protocol itself. In 1979, the Belmont report stated three principles to prevent ethical problems are respect for persons, beneficence and, justice [4]. Investigators will perform ethical research only but even the experts may experience great challenges. This can be avoided by reading protocol and investigator's brochure thoroughly and understanding primary and secondary endpoints [5]. Apart from this investigator should receive adequate education and training on ICH GCP, human subject protection, and biological specimen transportation requirements for the proper conduct of the study. In the site selection process appropriate site and resource selection is the best ethical conduct. In site initiation process selection of Investigators, IRB submission and delegations should be strictly followed for proper ethical conduct and, during the conduct of study following medical care, maintaining compliance, following informed consent process, safety reporting, and investigational product management relays for the ethical conduct of study [6].

1.2 Informed consent process: fig 02

The investigator plays an important role in the informed consent process who is qualified and experienced in understanding the protocol, adverse effects, and potential benefits. Investigators take the responsibility of recruiting the participants after the subjects have been explained about the study, risks and benefits, alternative treatment options. The investigator should give an opportunity for the participants to ask any questions they have and, they can make choices about the treatment. If the trial is randomized controlled, the investigator should explain the treatment allocation to the subjects [6].

After the completion of the explanation, subjects should be provided with an informed consent document. An informed consent document is a document that provides information to the subject so that they can make a decision to participate in the trial voluntarily.

Contents of the informed consent document

1. A sentence that study is research and can participate in the trial voluntarily
2. Purpose, duration of study and procedures should be included
3. Benefits and risks of the study
4. Alternative treatment and procedures [7].

This document needs to be approved by the IRB before the initiation of the trial. This document can be transcribed into local languages. Participants interested in enrollment should be provided with this document so that they can study and discuss it with their family members or relatives. They should be given ample amount of time to ask any questions. After the agreement for their participation, they should sign the current version of the informed consent document [6].

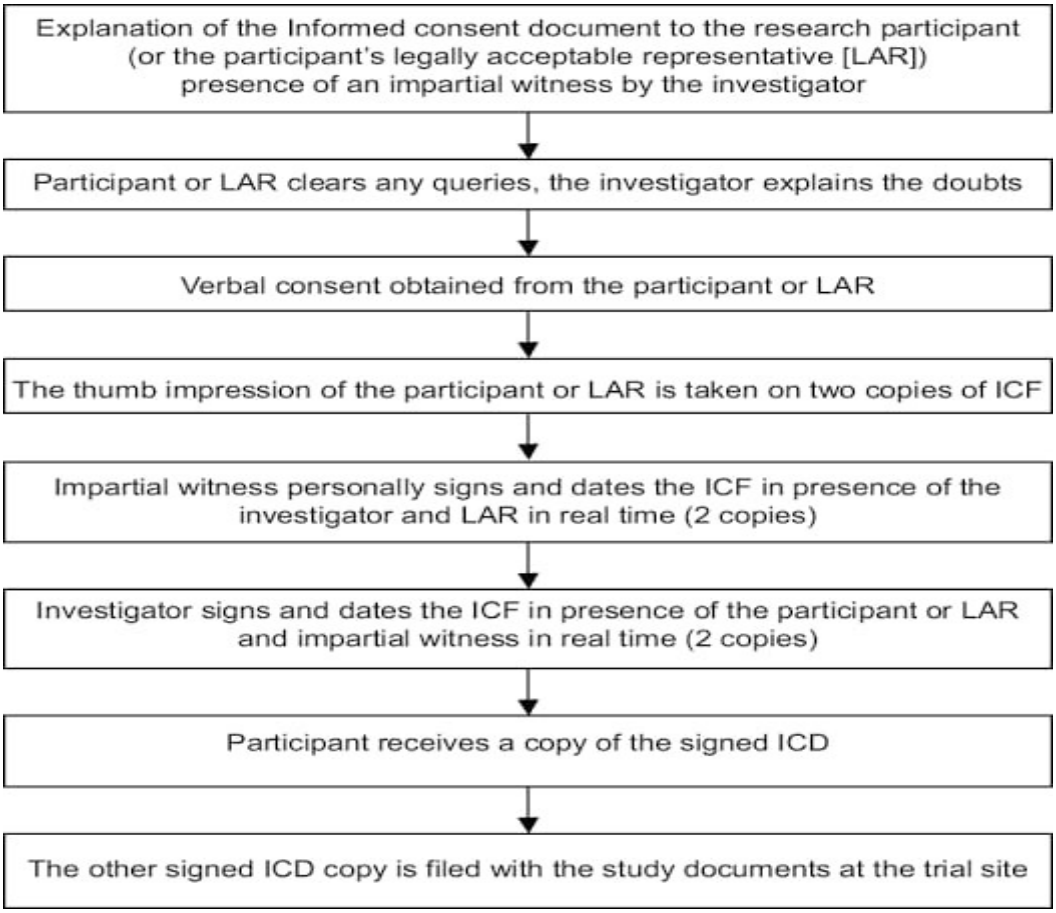

Fig 02: Informed Consent Process

1.3 Oversight of investigational agents

The qualified, experienced, and trained pharmacist or pharmacy technician is responsible for proper handling, administration, storage, and destruction of investigational agents. But the ultimate responsibility of the investigator is the supervision for drug accountability. This process is essential for promoting patient safety through the proper and safe use of the investigational products which is an important aspect of the audit. These audits help to ensure that records are properly maintained or documented. Good communication between pharmacy and research staff helps to ensure proper oversight of investigational agents.

After the investigational product reaches the site, the quantity received, and quantity dispensed should be recorded in the drug accountability report form (DARF) and the amount remained after the trial should send back to the sponsor for destruction. The product should be stored according to the protocol-specific requirements in a secured place at a temperature specified by the sponsor. Individual drug accountability

forms should be kept separate for each agent and each dosage form according to the protocol specifications. If a particular investigational agent is used in more than one protocol, the supply of products should be maintained in individual accountability form [8]. Manufacturing procedure, use of the product, the individually calculated dose administered, time at the administration of dose should also be documented [6].

1.4 Statement of investigator

Before starting a clinical trial, the investigator should sign the statement of investigator form (FDA form 1572) under an investigational new drug application, which means that the investigator should follow all FDA regulations. The principal investigator should have a clear understanding of protocol and potential risk as explained in investigator brochure. If any of the FDA 1572 forms went wrong by the investigator, strict action will be taken on the investigator, resulting in disbarment but can do it by reporting to the sponsor or in case of complications [9]. Section 9 of the FDA Form 1572 will list all the commitments that the investigator should fulfill, if any delegations occur it is the responsibility of the investigator to ensure that all study-related activities are fulfilled.

Section 6 of FDA form 1572, provides the list of all sub investigators and it also contains investigator qualifications and site-specific details [6,13]. According to 21 CFR 312.3(b) when a particular trial is conducted the investigator is the head of that particular trial [10]. FDA guidance document provides the list of all qualified individuals who are directly involved in the conduct of the trial, the qualified individual who wants to perform trial and, clarifies whether he/she is investigator or sub-investigator will be listed on the form 1572 [11].

Form 1572 is not required for investigational devices. In such a case CV, a statement of experience, compliance with the protocol, to supervise the performance of the device on human subjects, the informed consent form should be obtained and documented. The financial disclosure of medical devices should be submitted and updated [12].

1.5 Reporting of adverse events

One of the primary responsibilities of the investigator is reporting adverse events. The adverse events reported during clinical trials should be reported and reviewed regularly in the scheduled meetings. The adverse events that occurred should be identified and action to be taken immediately i.e., dose reduction, dose-escalation, dosage adjustments, changing alternative treatment, etc. The adverse events should be reported to IRB and sponsor within a suitable time. In order to maintain consistency in reporting adverse events and providing a reference for which AEs should be reported, the research site should develop standard operating procedures (SOP) [6]. The investigator should send to the sponsor safety reports, progress reports, and financial disclosure annually during the trial and the final report should be sent at the end [12]. Financial disclosure should be updated to the sponsor for 1 year following the investigation. If the stock is held by his spouse or children financial disclosure should be updated [13]. The procedure for reporting adverse events arising as a result of participation in the trial is shown in Fig 03.

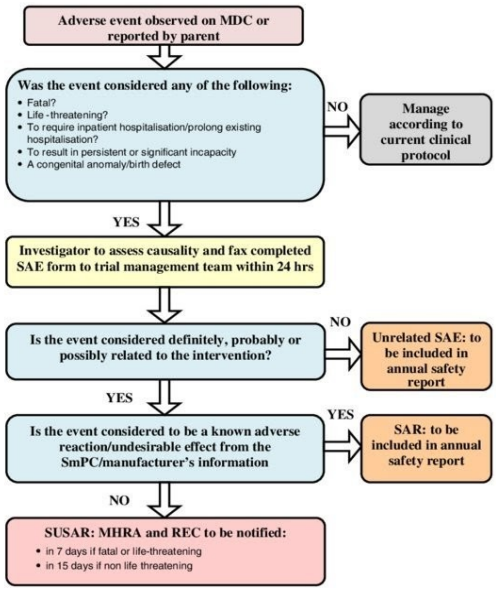

Fig 03: Process of reporting adverse events

1.6 Maintaining adequate records

Record maintenance is also the primary responsibility of the investigator. Record data should be provided with the following details:

1. Information collected should match the patient history and laboratory reports
2. Information about any protocol deviations
3. Information about delayed issues which are not reviewed even after many days

Any protocol deviations identified in records will help to make corrective actions to prevent from developing future mistakes. The research staff could use this as a guide to developing SOP. If any delegations occurred it will be recorded in a delegation log, so effective communication between research staff and investigator tasks assigned to each team will be identified and delegations will be corrected.

For effective communication between investigator and staff routine meetings should be held. Staff can use this

opportunity to raise questions and record actions taken for the concerns. The number of meetings for a trial depends on trial complexity and the participants enrolled. These meetings also provide an opportunity for the investigator to review and report adverse events that are serious and unexpected, and action is taken should be documented in the records and then investigator should provide the signature [6]. The records should be retained for 2 years after the drug is released into the market [10].

2. Selection of Investigator

The investigator should be selected in such a way so that he/ she will help in reducing cost and time in the process of drug exploration, and in the data errors. The criteria for selecting investigators are similar all over the world. He/ she will be selected as an investigator if he/she is medically qualified from the medical council of India, well experienced and trained with publications, strong points in CV and reputation, adequate staff, equipment, laboratory, and facilities according to ICH, GCP. A sponsor should provide training to investigator and trial staff on the use of the investigational product, protocol, and case report form according to GCP, ethical and applicable regulatory authority requirements. For proper selection of investigator several factors should be considered like investigator performance, adequate facilities, closeness to sponsor, quality of staff and study coordinator, managed care affiliation. The person selected should also be experienced in clinical and academic teaching, administrative duties. The knowledge he/she has on a drug obtained through thorough reading is not sufficient, he/she should evaluate the disease process [1,14].

If the clinical trial involves the use of specialized technique, the required investigator should be equipped with the handling of this specialized technique on one hand, and on the other hand, if the trial requires simple technique, protocol, and non-critical participants then the investigator does not need to work in tertiary care units. With CDM, the statistics team as joints experts work together in identifying disease and its therapy [14]. According to Center Watch 2003 report, "200-250 investigators belonging to around 25 hospitals in India are conducting clinical trials and training. From 1995-2001 less than 75 trials were carried out involving 15,000 participants and trials are increasing since 2003 in India. Following should be considered for conducting clinical trials in India by the investigator:

1. Assure that all participants are informed about their rights, safety, wellbeing, benefits and, risks in their native language
2. Get approval from IRB/ IEC
3. Never perform any trial until and unless get approval from USA/EU
4. Avoid recruitment of a large number of participants in a short span
5. Provide treatment to participants even after termination of the trial
6. Establish data monitoring and safety board for large scale studies
7. Provide training for GCP courses, investigator meeting, protocol and, CRF training [2].

2.1 Who should be selected as an investigator?

The physicians who are adequately trained, experienced, knowledgeable in a particular area of settings and interested in conducting clinical trials can be selected as an investigator. He need not require adequate awareness in ICH/GCP training, clinical trials regulations, strong statistical background, knowledge in statistical principles. But a basic study design, ethical issues, regulatory environment understanding is helpful. Apart from this, the physician should be enthusiastic to evaluate the answer to the question. This motivates other physicians to work in clinical trials and will add prestige to your practice or profession. This also helps the investigator to gain experience and recall outcomes which would provide clinicians best data from the available medical literature and decide what treatment plan will work well, thus this is useful in providing evidence-based therapy. The gained knowledge can be exchanged and collaborated for future plans. One of the most important barriers to the participation of the investigator is- it takes a longer time for completion of clinical trials. Like in training supporting staff and conducting meetings, get approval from IRB/IEC for the conduct of the study, perform site visits, completing regulatory and study-related documents, selection of participants and obtaining informed consent, increased hospital visits, attending follow up meeting of IRB/IEC, planning efficient use of study coordinator and staff. Another important barrier for the fresher investigator is experience.

3. Process of Selecting Investigator

A large number of investigators are always required for the conduct of a particular trial. Sponsor and CROs will visit the study sites where are conducted well, but this could not have happened without the investigator. Investigators are recruited through a referral from other

investigators or medical specialty directories or online databases or by advertising their capabilities on the internet or by assessing professional competency.

3.1 Assessing professional competency

With the need for clinical investigators, industries are trying their best for improving the selection process. There are three methods used for assessing professional competency

1. Advanced degree- MS degree
2. Acquiring state licensure to practice medicine
3. Certification from specialty organization [15,16].

Investigators should be certified from the specialized areas than non-investigators. But the experience, knowledge, skills, and competency are not directly transferred to clinical research. The investigators certified in clinical pharmacology are similar to the specialty in clinical research. Weaker practitioners need additional training for identification which would be reflected from certification. Interestingly investigators selected to conduct studies from 1990-1995 are certified in internal medicine rather than clinical pharmacology or clinical research [17]. FDA along with several organizations are looking for providing training to the investigators in GCP for improving the quality of clinical research.

Industry unable to assess the investigator' competency because the investigators recruited for a study, in all likelihood, will never conduct another study. Apart from these investigators are lagging at knowledge according to GCP. This represents huge cost and time loss to the industry. Finding a solution to the investigator's performance is a great challenge in the drug development process [15].

4. Selection in Multi Center Trials

Selection of investigator is the crucial or fundamental process which is a major challenge in the multicenter trial performed by sponsor. Using multiple search activities like querying public and private, using databases, a referral from the clinical research team, performing publication search. After searching, the sponsor shall recruit investigators based upon certain specifications like education, training, experience, and availability. This is done by examining curriculum vitae, medical licensure, investigator facility, and interview the relevant site personnel. This whole process is known as a Pre-study site visit (PSSV) or site qualification visit or pre-trial assessment performed by the monitor and sponsor. After completion of PSSV, investigators are selected based on their suitability to participate in a clinical trial. Then the management staff will either accept or reject the recommendation. An ultimate list of investigators who participate in a particular trial will be obtained after selection by the management staff [18]. To protect the trial process sponsor will continuously recruit additional sites as participant recruitment is not similar at all sites. In a multicenter trial the percentage of recruitment will be shown in the fig 04.

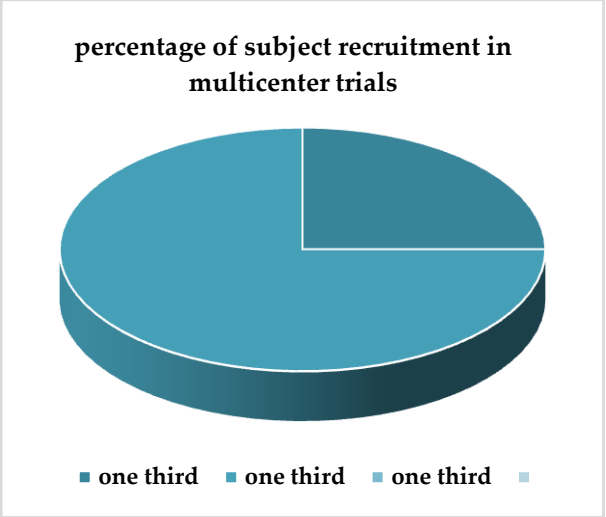

Fig 04: participant recruitment in multicenter trials

5. Documents Required For Selection

Once a potential investigator has been identified, several forms have to be completed or filled.

1. Confidential disclosure agreement(CDA); Form FDA 1572
2. A protocol signature page
3.An investigational drug brochure(IDB)
4. curriculum vitae(CV) of investigator and sub investigator
5.IRB and IEC approval letter
6.laboratory certificates and their normal ranges
7.Financial disclosure statement of principle investigator [3].

6. After The Selection of Investigator

6.1. Signing on the statement of investigation form: An investigator who is running a clinical trial for the study of new drugs must has to file a form. After providing the completed statement of investigator form to the sponsor an investigator can be participated in the investigation.

While conducting a clinical trial, signatures of sponsor and investigator is required to sign the contract which includes (investigator's responsibilities, number of subjects recruited, timelines for recruitment, regulatory requirements which are involved in clinical trials) and its budget (it includes how much was paid by the investigator for study activities) [19].

6.2 Informed Consent Guidelines

Investigator cannot involve a human as subject unless and until he obtains a legally effective informed consent of the subject. Informed consent guidelines must meet the requirements and necessities which are mentioned in 21CFR 50.20 and 50.25a [10,12].

Before initiating the trial, investigator should take an approval letter or opinion from the IRB and IEC for consent process updates and additional requirements like advertisements and mainly for trial protocol and also, he or she should provide a current copy of the investigator's brochure. For review of the subject document's investigator provide all the documents to IRB/IEC, while the trial is taking place [1].

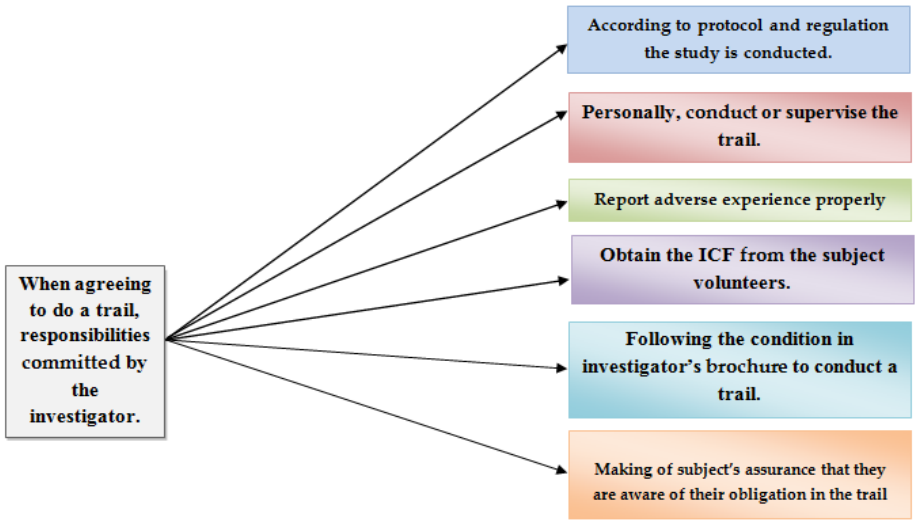

Fig 05: Responsibilities performed by investigator before conducting trial

7. Investigators In Covid-19

The List of investigators (table 1) involved in clinical trials of COVID-19 and their specializations was collected from clinical trial.gov. 122 investigators were involved across all over the world in 98 trials. Along with this study type, the purpose of the study, and the status of recruitment of participants were also collected. Specializations of investigators are as below in fig 05.

Table 01: list of investigators involved in COVID-19 and their countries

Sl .no	Investigator names	Country where trail is conducting
1.	Mariano Duarte	Argentina
2.	Scott A Halperin, Fengcai Zhu Jiangsu, Joanne M angley,	Argentina, Chile, Mexico, Pakistan, Russian federation
3	Craig Anderson	Australia
4	Lorusso	Austria, Belgium, Czechia, Denmark, France, Germany, Greece, Hungary, Italy, Israel, Lithuania, Netherland, Poland, Portugal, Russian federation, spain, Sweden, Switzerland, United Kingdom
5	Henning Bundgaard	Austria, Denmark, Germany, Russian federation, United Kingdom
6	Mahmud Reaz, Wasif Ali Khan, Mostafa Kamal Arefin	Bangladesh
7	Henrique Pott, LEILA KATZ	Brazil
8	Jan Tack, Raf Bisschops	Belgium
9	Luanne Metz, Olivier Beauchet, Scot Simpson	Canada
10	Zhuan Liao	China, Shanghai
11	Fengcai Zhu	China, Jiangsu
12	Steffen Christensen, Thomas Strøm, Bodil S Rasmussen, Klaus T	Denmark

	Kristiansen	
13	Riham H Raafat	Egypt
14	Elisabeth Botelho, Bruno Hoen, Juliette SALLES, Eilie Garrido-Pradalie, Frédéric BLANC, Jean-Claude NGUYEN, Jean-Michel PAWLOTSKY, CLAIRE ROGER, Frédéric Balen, Christelle Vauloup Fellous, Guillaume BONNET	France
15	István Várkonyi	Hungary
16	Brynja Ingadottir	Iceland
17	Rubi Zomer	India- Maharashtra Israel
18	Prasenohadi	Indonesia
19	Aryan MF Jalal	iraq
20	Gian Paolo Rossi, Antonio Carroccio, Luca Rinaldi, LUCREZIA SPADERA, Arianna Di Stadio, Riccardo Colombo	Italy
21	Jihoon Hwang	korea
22	Eric Ochoa-Hein	Mexico
23	Mehwish Iftikhar	Pakistan
24	Belen L Dofitas	Phillipines
25	Hanna Czajka	Poland
26	Dmitriy Pushkar, Sergey Martsevich, Mikhail Loukianov, Andrey Pulin, Elena Pavlikova, Nikita Lomakin, Roman Khokhlov, Mikhail Samsonov, Jean-Francois Rossi	Russian federation
27	Pilar Ruiz-Seco	russian federation, spain
28	Mohammed Al Ghobain	Saudi Arabia
29	Juan F Masa Jiménez, Sebastià Videla Cés, Esteve Fernández Muñoz, Fermín Mayoral-Cleries	spain
30	Gregor Hutter, Miodrag Savic	Switzerland
31	Zafer Sezer, Derya Karasu, Aysel Özdemir, Begum Kara Kaya	Turkey
32	Olga Holubovska	Ukraine
33	Rona Smith, Lars ostergaard, Kenji cunnion, Dell, lucine francis, Molly Rosenberg, Elyse Stock, Eleftherios Mylonakis, Veronique Michaud, Derek W Guillory, Lloyd Tran, Michael Silverstein, Francis J McMahon, Jane O'Halloran, Adam P Bress, Jessica L Schleider, Henna Budhwani, Marci Gluck, Leslie G Biesecker, Monique Ernst, Eliza M Gordon-Lipkin, Joyce Y Chung, Balachundhar Subramaniam, Stephen J Greene, G. Michael Felker.	United States
34	Larissa A Korde	United States, Canada, Puerto Rico
35	Richard Davey	United States, Denmark, Japan, korea, Mexico, Singapore, spain, United Kingdom
36	Matthieu Jabaudon	United States, France, Germany, Spain, Switzerland
37	Faheem Guirgis	United State, Japan, Korea, Mexico, Singapore

38	Larry Corey, Shelly Karuna	United States, Malawi, Peru, South Africa, Zambia, Zimbabwe

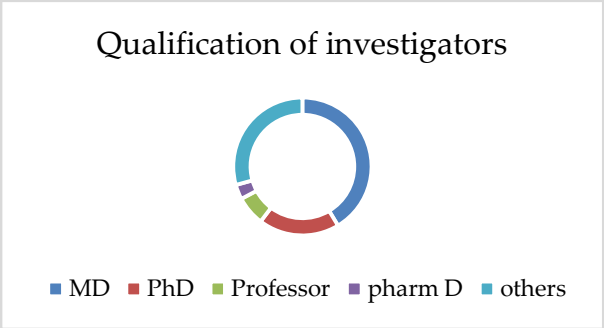

Fig 06: Qualification of investigators

Primary purpose of trials done by investigators is depicted below in figure 6 and study type of trails is shown in the fig 07.

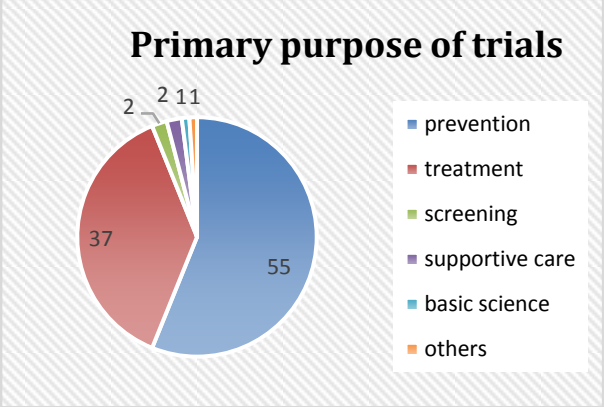

Fig 07: Primary purpose of trials

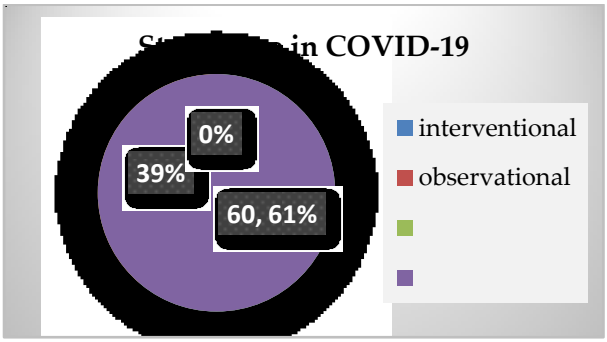

Fig 08: Study type in COVID-19 trails

Status of recruitment in trials is shown below in fig 09

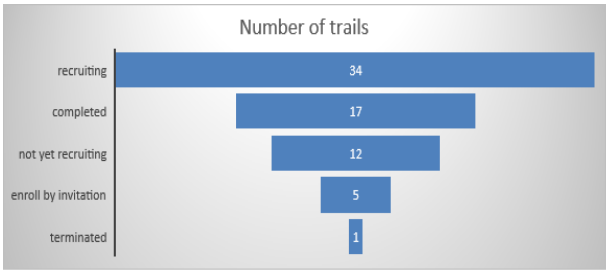

Fig 09: Status of recruitment in trials

Conclusion

Therefore, investigator plays a crucial role in conducting ethical research, recruiting the subject volunteers to fill informed consent process, in reporting adverse events and records maintenance. The investigator maintains professionalism and acts with integrity, contributes the knowledge by protecting human rights and welfare. By standing on good clinical practices, they result in good quality data collection and also makes easier in analyzing process. In now a day's compliance driven environment, selection of Investigator is the most challenging task facing by the clinical research professionals. Hence, they are being responsible for maintaining the public trust. More than 98 clinical trials on covid 19 were listed in the clinical trials.gov of June 2021,122investigators were involved across the world of which 61%are observational Majority of the investigators are from Europe who have pursued MD, following pharm D, PhD, professors and others. Primary purpose of the trials includes 55%for prevention and 37%treatment purpose.34%of the trials are with recruitment status of recruiting.

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