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Review Article

Enhancing Safety Monitoring in Clinical Trials: Leveraging Innovative Methods

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ABSTRACT

Monitoring patient safety during clinical trials is a critical component throughout the drug development life-cycle. It is imperative for pharmaceutical sponsors to engage in proactive and cooperative efforts with all relevant parties to establish a methodical approach to safety monitoring. The regulatory environment has changed, resulting in more demands for risk assessment, mitigation, and management plans. There will be an increased need for more thorough and creative methods that use quantitative techniques to gather data from all sources, from the discovery and pre-clinical through the clinical and post-approval stages, as the industry moves from passive to active safety surveillance activities. Statistical techniques, particularly those built upon the Bayesian framework, are crucial instruments for assisting in giving the safety monitoring procedure objectivity and rigor[1].

INTRODUCTION

Pharmacovigilance has been defined by WHO (2002) as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine or vaccine-related problem. The information generated by pharmacovigilance is useful in educating doctors about ADR and in the official regulations of drug use. Its main purpose is to reduce the risk of drug-related harm to the patient. It has an important role in the rational use of medicines as it provides the basis for assessing the safety of medicines[2].

The activities involved in pharmacovigilance are Post-marketing surveillance and other methods of ADR monitoring such as voluntary reporting by doctors, prescription event monitoring, computerized medical record linkage and other cohort / case-control studies. Dissemination of ADR data through 'drug alerts', 'medical letters', and advisories sent to doctors by pharmaceuticals and regulatory agencies[3].Changes in labelling of medicines indicating restrictions in use or statuary

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warnings, precautions, or even drug withdrawal, by the regulatory decision-making authority. The goal of the safety monitoring is to ensure that the benefits of the use of medicine outweigh the risks and thus safeguard the health of the Indian population[4].

The objective of safety monitoring is to monitor Adverse Drug Reactions (ADRs) in the Indian population. Also to create awareness amongst healthcare professionals about the importance of ADR reporting in India and monitor the benefit-risk profile of medicines by generating independent, evidence-based recommendations on the safety of medicines[5].

CLINICAL TRIALS:

It is a prospective ethically designed investigation of human subjects to objectively discover/verify/compare the results of two or more therapeutic measures (drugs). Depending on the objective of the study, a clinical trial may be conducted in healthy volunteers or patient volunteers. Healthy volunteers may be used to determine pharmacokinetic parameters, tolerability, safety for certain types of drugs (e.g., Hypoglycemia, hypnotic, diuretics) even efficacy. For the majority of drugs (e.g., anti-epileptic, anti-inflammatory, anti-tubercular etc.) therapeutic efficacy can only be assessed in patients[6].

The clinical studies are conventionally divided into 4 phases;

1. Phase 1 (Human pharmacology and safety)
2. Phase 2 (Therapeutic exploration and dose ranging)
3. Phase 3 (Therapeutic confirmation/comparison)
4. Phase 4 (Post-marketing surveillance/studies)

Each year, the 'International Clinical Trials Day' is celebrated around the world on the 20th of May to celebrate the day that James Lind started his famous trials on the 20th of May 1747[7].

The difficulties in conducting clinical research are not limited to a single nation, so in order to promote better clinical research that is pertinent to patients' needs worldwide, transnational communication on clinical trials needs to be invited and coordinated by a transnational organization. Phase II trials, which represent the initial round of testing on human subjects, are the norm for human pharmacology trials. Phase II - IV clinical trials can also have components of human pharmacology, but these studies are usually conducted on small populations of healthy humans to specifically determine a drug's toxicity, absorption, distribution, metabolism, excretion, duration of action, drug-to-drug interaction and drug-to-food interaction[8].

MATERIALS AND METHODS

A drug under development by a German company was tested in 2006 in a commercial phase I unit in Landon. The pre-clinical data including high-dosing studies in primates −did not indicate any safety concerns, but the test drug was targeting the immune system, which should have raised concerns. But in this first-into-human trial, six healthy volunteers were simultaneously dosed with the test drug and within a minute they all experienced systemic inflammatory response[9]. All suffered from multiple organ failure and required machine support. Fortunately, everyone recovered or recovered with sequelae after weeks of hospital care. The review of the incident revealed that the sponsor and the commercial phase I unit provider had followed all regulations at the time with respect to pre-clinical testing misconduct was identified that could have caused the event. The event triggered much press coverage and eventually also led to a new regulation in Europe for the conduct of phase I trials[10].

In last 10 years (2011-2020), 4506 participants have died during clinical trials. It takes 10-15 years and around 1 billion to develop one successful drug. Unto 90% of drug candidates fail in clinical

trials. In India, in Hyderabad, Bangalore clinical trials are mainly done.

SAFETY MONITORING IN CLINICAL TRIALS

Monitoring patient safety during clinical trials is a critical component throughout the drug development life cycle. It is imperative for pharmaceutical sponsors to engage in proactive and cooperative efforts with all stockholders to guarantee a methodical approach to safety monitoring[11]. Given that clinical trials include human subjects, defined protocols must be followed to safeguard the participants' safety, rights, and general well-being.[12].

These standards include:

- The International Conference on Harmonization Good Clinical Practice (ICH - GCP) guidelines.
- International Ethical Guidelines for Biomedical Research Involving Human Subject Issued by the Council for International Organizations of Medical Science (CIOMS).
- The ethical Principles set forth in the declaration of Helsinki

STAKEHOLDERS IN SAFETY MONITORING

1. SPONSOR

Protocol

The clinical trial protocol is created by the trial's sponsors, which are typically pharmaceutical corporations. The trial population and its specific inclusion and exclusion criteria, the rationale for the experiment, the administration of the investigation's medicines, trial protocols, data gathering standards, endpoints, and sample size are all covered in detail in the protocol. The policy also specifies how safety reports should be made, particularly how quickly major adverse events must be reported.. The Informed Consent Form (ICF) is used to disclose current information about the investigation drug and about the procedures, risks and benefits for subjects who participate in the clinical trial. Informed consent is a vital part of the research process. Sponsors are in charge of establishing and maintaining clinical databases for the trial's data collection in addition to the protocol and ICF. The sponsor creates Case Report Forms (CRF) as a means of gathering data. Rather of using the more conventional paper-based approach, these solutions are increasingly dependent on electronic data gathering modules via the internet.. With access to all accumulating data, sponsors are mandated to report key safety information to all stakeholders in a timely fashion[13].

2. SUBJECTS:

[11] The informed consent must be given freely, without coercion and must be based on a clear understanding of what participation involves. By giving consent, subjects permit the investigators to collect health information and body measurements as per the protocol. While subjects are encouraged to follow the protocol to trial completion, they can withdraw at any time[14]. They do not need to give a reason for withdrawing consent. In a phase I clinical trial, when the drug is first used in humans, healthy volunteers are compensated for their time and willingness to be exposed to unknown risks. Later phase trials are mostly conducted in patients with the disease of interest, and payments to these subjects for participation are contentious. The main concern is the payment could be coercive or serve as undue inducement leading to impaired judgment on trial participation[15].

3. INVESTIGATORS

Those with the necessary qualifications, expertise, and training to administer medical care to trial participants are known as investigators. To guarantee that individuals are able to make an educated choice, investigators find possible subjects and inform them about the experiment. It is expected of the investigators to provide care in accordance with the protocol treatment plan during

the trial[16]. They keep track of, assess, monitor, and record every side effect of the treatment, including any reported adverse events. Any concerns that endanger the security and welfare of the trial participants must be reported to the sponsor and their institutional review boards. In the end, the conduct of the clinical trial and the security of the patients in their care rest on the shoulders of the investigators[17].

4. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The Institutional Review Board (IRB), also known as the ethics committee, is charged with protecting the rights and welfare of human subjects recruited to participate in research protocols conducted under the auspices of the institution to which the IRB is affiliated. The IRB reviews all clinical trial protocols involving human subjects that the particular institution is involved with and has the authority to approve, disapprove or require modifications to the protocols[11]. IRBs bear further the responsibility of reviewing ongoing research to ensure continued diligence that subjects are not placed at undue risk and that they give unconcerned, informed consent to their participation. The training and education of investigators at the institution who participate in clinical research is also a responsibility of the IRB. Members of an IRB generally come from a wide range of scientific disciplines and from outside academic communities in which research is being conducted[18].

5. DATA AND SAFETY MONITORING BOARD(DSMB)

Chartered for one or more clinical trials, the Data and Safety Monitoring Board (DSMB), also known as the Data Monitoring Committee (DMC), is an expert committee operating independently of the sponsor. The DSMB's mandate is to periodically assess the growing body of data from the clinical trial in order to guarantee the ongoing safety of both enrolled participants and those who have not yet registered. The clinical equipoise at the start of the study may no longer be justified if the DSMB reviews efficacy data at certain interim points to determine whether there is overwhelming evidence of efficacy or not[19]. The DSMB also bears the additional duty of providing the sponsor with advice regarding the trial's ongoing validity and scientific worth. A formal DSMB is not necessary for all clinical trials. DSMBs are most common in double-blind randomized phase 3 trials. Members of the DSMB typically include clinical trial experts, including physicians with the appropriate speciality, at least one bio-statistician and possibly person(s) from other disciplines, such as biomedical ethics, basic science/pharmacology or law[20].

The purpose of DSMB is to Protect the safety of the trial participants, identify high rates of ineligibility determined after randomization, and Identify protocol violations under suggested changes to the protocol. Also, DSMB identifies unexpectedly high dropout rates that threaten the trial's ability to produce credible results and ensure the credibility of the study and validity of study results and advises the sponsor regarding the continuing safety of trial subjects[21]. Responsibilities of DSMB include Interim monitoring, Monitoring of effectiveness, Monitoring of safety, Monitoring of study conduct, Considerations of external data, Studies of less serious outcomes, DSMB will recommend early termination based on positive results, only when the data are truly compelling and the risk of false positive conclusion is acceptably low. The second type of consideration is whether the hypothesized benefit is likely to be achieved. If the interim data suggests that the new product is of no benefits i.e., there is no trend, indicating superiority of the new product, a DSMB may consider whether continuing of the study is futile and we recommend early termination on this basis[22].If the subject who are given the

investigational intervention (drug) are found to be at higher risk of the outcome of interest (for example: Mortality, disease may recommend early termination on safety ground. However, there are some false conclusions that there is an adverse effect. Hence it is appropriate to demand, less rigorous proof of harm to justify early termination.DSMB will review data related to the conduct of the study[23].

Rates of recruitment, ineligibility, noncompliance, protocol violations and dropouts. Completeness and timeliness of data Degree of concordance between site evaluation of events and centralized review. 'The DSMB may issue recommendations to the sponsor regarding trial conduct when concerns arise that some aspects of the trial conduct may threaten the safety of participants (or) the integrity of the study'. In some cases, particularly when unexpected safety issues arise in plated studies, the sponsor may bring external data to the attention of the DSMB. Then the DSMB may be asked to consider the impact of external information on the study, being monitored. Such data may lead to recommendations like: termination of the study (or) one (or) more study arms (or) changes to the consent from (or) investigator brochure, (or) letters from the sponsor to study participants describing the new results[24].

These studies are generally short term, evaluating treatments effect over periods of a few days to a few months. DSMB have not been commonly established for such short-term studies. Early termination for effectiveness is rarely appropriate in one study, except for ethical reasons. In such a case, an outcome group to monitor data regularly is probably warranted. DSMB are not usually warranted in early studies, such as phase-1 (or) early phase-2 studies (or) pilot/feasible studies, but formal monitoring groups may be used for certain types of early clinical studies. While these formal monitoring groups will often consist of individual internal to the sponsor, and/or investigators, a DSMB overseeing safety may be considered when risk to a participant appears unusually high. Ex: with novel approaches to treating a disease condition[25].

Fundamental responsibility of a DSMB is to make recommendations to the sponsor concerning the continuation of the study. The DSMB recommendations after an interim review may be Studied to continue as design, Study continuation with major (or) minor modifications, Study termination, Temporary suspension of enrolment and/or study intervention until some uncertainty is resolved, Both a written recommendation and oral communication with opportunity for questions and discussions are advised[26].

The DSMB should keep minute of all meetings. The DSMB should divine meetings of confidential data (usually unblinded compared to data). After each meeting, the DSMB should issue a written report to the sponsor based on the meeting minutes. This report should include sufficient information to explain the rationale for any recommended changes. If no changes are recommended, the report may be as simple as the DSMB recommends that the study continue as designed. DSMB meetings will be held at least annually (or) as required by the timings of the protocol. The DSMB will review the status of the trial including toxicity, efficacy outcomes and next formal monitoring data as specified in the protocol[27].

The review of each trial includes three parts:

i. The first is an open session in which the principal investigator may be present to clarify the status of the status of the study.

ii. Second is it closed session limited to DSMB members and study statisticians and, the statistician presents the outcome results.

iii. Third is a closed session in which the DSMB members discuss outcome results and develop recommendations[28].

REGULATORY AUTHORITIES

In the US, prior to the initiation of a first in human clinical trial, pharmaceutical sponsors must submit an Investigation New Drug (IND) application to the FDA as required by law. The FDA reviews the IND (typically within 30 calendar days) for safety to ensure that research subjects will not be subjected to unreasonable risk. In 2010, the FDA issued guidance to sponsors and investigators on safety reporting requirements for human drug and biological products that are being investigated under an IND and for drugs that are the subjects of bio-availability and bio-equivalence studies that are exempt from the IND requirements. The guidance provided the agency's expectations for timely review, evaluation and submission of relevant and useful safety information and implemented internationally harmonized definitions and reporting standards. The European Medicines Agency (EMA) is the European Union's FDA equivalent. The agency has several scientific committees that carry out the evaluation of applications from pharmaceutical companies. In other parts of the world, regulatory authorities will have similar mandates, but may operate under different local laws and regulations[29].

MEDICAL COMMUNITY AND PATIENTS

Clinical trials generate data that contribute to the body of knowledge about the treatment and the disease that benefit the broader medical community and, ultimately, the patients. Safety information of one product may be informative to other practitioners using a similar class of agents. In 1997, the US Congress passed the Food and Drug Modernization Act (FDAMA), requiring clinical trial registration. ClinicalTrials.gov was created as a result. The website was further expanded in 2007 after the Congress passed the Food and Drug Administration Amendments Act (FDAAA), which required more types of trials to be registered. In September 2008, as required by FDAAA 801, ClinicalTrials.gov began allowing sponsors and principal investigators to submit the results of clinical studies. Submission of adverse event information was optional when the results database was released and became required in September 2009. The mandatory requirement on clinical trial registration and the disclosure of trial results are significant achievements in advancing science and increasing transparency in clinical research[30].

AGGREGATION OF SAFETY DATA DURING CLINICAL DEVELOPMENT

Aggregating safety data across clinical trials during drug development is important because trials are generally designed to focus on determining how well the drug works. The safety data collected and aggregated across multiple trials as the drug is developed allows the sponsor, investigators and regulatory agencies to monitor the aggregate safety profile of experimental medicines as they're developed. Decisions based on aggregate safety assessment during development of the medicine can be made throughout the medicine's development and it sets up the sponsor and regulators well for assessing the medicine's safety after the drug is approved[31].

Safety monitoring in different phases of clinical trials:

Phase 1: Experimental drug in a small group of people (20-80) to evaluate its safety, determine a safe dosing range, identify side effects.

Phase 2: Experimental (study) drug is given to a large number of people (100-300) to see its effectiveness and further evaluate safety.

Phase 3: Experimental drug is given to a large group of people (1000-3000) to confirm its effectiveness, monitor side effects, and collect information for safety.

Phase 4: Post marketing studies, gives additional information includes drug risk benefits, and optimal use. For drugs being studies under Investigational New Drug Application [INDA],

the FDA published a regulation, establishing a new safety reporting paradigm. According to this clinical investigator and sponsor have to be more responsible in reporting and analysis of serious, unexpected events that might be caused by drug[11].

COMMUNICATING SAFETY INFORMATION AMONG STAKEHOLDERS

In order to guarantee subject safety in clinical trials, prompt communication between the many stakeholders is essential. The Protocol (which includes the ICF) lays out the specifics of assessments as well as the frequency and duration of follow-up. Furthermore, to guarantee a methodical approach to safety surveillance and monitoring, the majority of pharmaceutical sponsors have Standard Operating Procedures (SOP) in place for gathering, processing, reviewing, evaluating, reporting, and communicating cumulative safety data. The clinical trial investigators report safety information, such as adverse events and laboratory results, to a sponsor. The quarterly update of the Investigators Brochure (IB) is another means of disseminating the evolving safety information[32]. The goal of safety monitoring in clinical trial is to identify, evaluate, minimize and appropriately manage risks.

STATISTICAL METHODS IN SAFETY MONITORING

I. Methods for Single Arm Trials.
II. Methods for Randomized, Control Trials
III. A Hypothetical Clinical Trials[33]

CONCLUSION

Monitoring patient safety during clinical trials is a critical component throughout the drug development life cycle. It is imperative for pharmaceutical sponsors to engage in proactive and cooperative efforts with all relevant parties to establish a methodical approach to safety monitoring. The regulatory environment has changed, resulting in more demands for risk assessment, mitigation, and management plans. We have covered the statistical techniques that can be used to watch ongoing clinical trials without blinding or with blinding. Because of its shortcomings in incorporating the "current" information of the safety profile into the decision-making process, we suggest using the Bayesian approach as the analytical framework for safety monitoring. Bayesian methods have an important advantage, as safety signals identified in clinical trials may be limited. The globalization of clinical trials has posed additional challenges. A great deal of coordination is required of sponsors to ensure timely communication of new safety findings among all stakeholders in all regions. Innovative statistical methods can be applied to increase the efficiency in reviewing a large volume of safety data, to identify safety trends and to establish prospective monitoring guidelines, as described in this article.

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Moreover, such a transformation from passive to active surveillance would demand novel approaches employing quantitative methodologies across the entire development chain of drugs. The author acknowledges the fact that there is a need

for stronger, deeper ways for the surveillance of safety – with data from a broad variety of sources and from discovery throughout the post-approval period.This is because of the fact that statistical methods, especially those that fall under the purview of the Bayesian framework, contribute toward making practices of safety monitoring objective and rigorous. In safety evaluation, these methodologies also not only contribute to efficiency but to a more systematic and analytical approach in data interpretation of data generated all along the life cycle of the drug in development. The contributing author recognizes that statistical tools can be instrumental in providing a structure and an evidence-based foundation for monitoring activities dealing with safety that are part of the clinical trial management process. These are considered activities important enough to drive continuous improvement and innovation.

Conflict of interest

The authors declare that they have no conflict of interest.

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