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FACTORS INFLUENCING AND HINDERING PARTICIPATION IN CLINICAL TRIALS: A COMPREHENSIVE REVIEW

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INTRODUCTION

A clinical medicine trial is a process of exploration that involves testing the safety and efficacy of a new medicine or treatment in mortal subjects. It's an essential step in the development of new specifics, as it allows experimenters to determine whether a new medicine is safe and effective for use in humans. Clinical trials are generally conducted in several phases, each with a specific purpose. Phase I trials are generally the first stage of testing in humans and are designed to determine the safety and tolerability of a new medicine. Phase II trials are designed to estimate the efficacy of the medicine in a small group of cases, while phase III trials are larger, randomized studies that give further definitive substantiation of the medicine's safety and efficacy. Clinical trials are tightly regulated and must adhere to strict ethical and scientific norms to cover the rights and safety of study actors. Actors in clinical trials are levies who have given informed concurrence to share in the study, and they're nearly covered throughout the trial to ensure their safety.

PURPOSE

Clinical trials are systematic and scientific investigations conducted to examine health and disease in individuals. These studies are designed to determine the safety, effectiveness, and potential side effects of medical interventions such as drugs, devices, treatments, or behavioral modifications. Serving as a critical component in advancing medical knowledge, enhancing patient care, and ensuring that new interventions adhere to stringent standards of safety and efficacy, clinical trials encompass various purposes, including:

1. Safety Evaluation
2. Efficacy Assessment
3. Dosage and Administration Studies
4. Comparison with Standard Treatments

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5. Population Variability
6. Regulatory Approval
7. Risk-Benefit Analysis
8. Behavioural Interventions
9. Post-Approval Monitoring

DEFINITIONS

A clinical trial is defined as “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.” Interventions include not only drugs but also, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.[2]

Another definition of drug trial is defined as The term "clinical trial" in the context of a new drug or investigational new drug refers to a systematic examination of such substances in human subjects. The purpose is to generate data related to its:

(i) clinical aspects,

(ii) pharmacological characteristics, including pharmacodynamics and pharmacokinetics, or

(iii) adverse effects.

This is undertaken with the goal of determining the safety, efficacy, or tolerance of the new drug or investigational new drug.

The term "clinical trial protocol" denotes a document encompassing the background, objective, rationale, design, methodology (including aspects of performance, management, conduct, analysis, adverse event handling, withdrawal procedures, statistical considerations, and record-keeping) pertinent to the clinical trial.

A "clinical trial site" is defined as any hospital, institute, or clinical establishment equipped with the necessary facilities to conduct a clinical trial.

[2]https://www.who.int/clinical-trials-registry-platform

HISTORICAL BACKGORUND

Clinical trials have been around since ancient times. Clinical trials are undertaken to advance the development of drugs, devices, or procedures aimed at enhancing human health. These trials primarily serve to ascertain the safety, potential side effects, and suitability for widespread use of the tested substances or interventions.

The history of clinical trials is a fascinating journey that spans over centuries, reflecting the evolution of medical research methodologies, ethical considerations, and regulatory frameworks. The recorded history of clinical trials dates back to as early as 562 BC, with the biblical account in the "Book of Daniel." King Nebuchadnezzar's experiment, though unconventional, marked one of the first instances in the evolution of human species where an open, uncontrolled human experiment influenced a decision about public health.

In 1025 AD, Avicenna's "Canon of Medicine" introduced rules for testing drugs in clinical trials, resembling contemporary approaches. However, these principles were not widely applied at the time. The first planned controlled trial occurred in 1537, conducted accidentally by the renowned surgeon Ambroise Pare during his treatment of battlefield wounded soldiers. It took another two centuries for James Lind to conduct the first controlled clinical trial of the modern era in 1747, focusing on scurvy. Lind's trial laid the foundation for evidence-based medicine and is celebrated annually on May 20 as International Clinical Trials Day.

The 1800s saw the emergence of the placebo effect, with the term "placebo" appearing in medical literature. In 1863, physician Austin Flint conducted the first clinical study comparing a dummy remedy to an active treatment, acknowledging the psychological impact of treatment on patients.

The mid-20th century witnessed significant milestones in clinical trial methodology. In 1943, the Medical Research Council (MRC) conducted the first double-blind controlled trial to investigate the patulin treatment for the common cold. In 1946, the MRC carried out the first randomized controlled trial of streptomycin for pulmonary tuberculosis, introducing randomization and objective measures into trial design.

The ethical and regulatory framework for clinical trials also evolved over time. The Nuremberg Code in 1947 emphasized the voluntariness of informed consent, responding to human abuses during World War II experiments. The thalidomide tragedy in the 1960s led to the 1962 Kefauver-Harris amendments, strengthening federal oversight and requiring informed consent. The Helsinki

Declaration in 1964 and subsequent updates provided ethical guidelines for medical research involving human subjects. The 1974 US National Research Act and the Belmont Report in 1979 further shaped ethics in human experimentation.

In India, the Indian Council of Medical Research (ICMR) has played a important role in the development of medical research since its inception in 1911. The establishment of the Central Ethical Committee in 1996 marked a significant step in addressing ethical issues in biomedical research. Schedule Y of the Drugs and Cosmetics Act in 1988 and its revision in 2005 provided regulatory guidelines for clinical trials in India, aligning with global standards.

As clinical trials continue to advance with novel therapies and technologies, the balance between medical progress and patient safety remains paramount. Ongoing scientific advances will pose new ethical and regulatory challenges, necessitating dynamic updates to the legal framework governing clinical trials.

METHOD OF CONDUCTING CLINICAL TRIALS

Clinical trials are conducted in four phases, each serving a specific purpose and providing valuable information about a new medical intervention. The FDA typically mandates Phase 1, 2, and 3 trials to evaluate whether the drug or device warrants approval for further use. Upon establishing the intervention as safe and effective in the initial phases, the FDA grants approval for clinical application while continuing to monitor its impact.

Each phase serves a specific purpose:

Phase 1 Trial:

Tests experimental drugs or devices on a small group (around 20 to 80 individuals).

Evaluates safety, including any side effects, and determines the appropriate dosage.

Phase 2 Trial:

Involves a larger group (around 100 to 300 individuals) to assess effectiveness.

Gather preliminary data on the intervention's efficacy for a specific disease or condition.

Continues safety assessment, focusing on short-term side effects.

Phase 3 Trial:

Encompasses several hundred to a few thousand participants.

Gather comprehensive data on safety and effectiveness across diverse populations and dosages.

Compares the intervention with other drugs or treatments.

FDA approval is sought based on trial results supporting the intervention's use for a specific health condition.

Phase 4 Trial:

Conducted after FDA approval.

Monitors the intervention's effectiveness and safety in large, diverse populations.

Detects side effects that may become evident over an extended period of use.

It's prominent to note that clinical trials main aim focusing on behaviour change, rather than drugs or medical devices, undergo similar phases, but FDA regulations do not govern behavioural interventions.

ETHICS IN CLINICAL TRIALS:

Ethics in clinical trials is a crucial aspect of ensuring that the research conducted on human subjects is safe, reliable, and respects their rights and dignity. Clinical trials are designed to test the efficacy and safety of new drugs, medical devices, or treatments. Ethical principles guide researchers and institutions in the design, conduct, and reporting of clinical trials.

Here are some key ethical principles that should be considered in clinical trials:

1. Informed Consent: Informed consent is the cornerstone of ethical research. It means that potential participants are fully informed about the study, including its purpose, risks, benefits, and alternatives. Participants should be given sufficient time to decide whether to participate, and their consent should be voluntary and informed.

2. Privacy and Confidentiality: Participants' privacy and confidentiality should be protected during the trial. Participants should be assured that their personal information will not be disclosed without their consent, except as required by law.

3. Risk/Benefit Analysis: Clinical trials must be designed to minimize risks to participants while maximizing potential benefits. The risks and benefits of the study should be carefully assessed, and the risks should be justified by the potential benefits.

4. Respect for Participants: Participants should be treated with respect and dignity. Researchers should ensure that participants are not coerced, intimidated, or manipulated into participating in the study.

5. Ethical Review: All clinical trials must be reviewed by an independent ethical review board (IRB) or ethics committee. The IRB ensures that the study is scientifically valid and that the rights and welfare of participants are protected.

6. Post-Trial Access: Participants should have access to any treatments that were tested in the study after the trial is completed. If the treatment is found to be effective, participants should have access to it as soon as possible.

Ethical considerations are critical trials to ensure that the study is safe, reliable, and respects the rights and dignity of the participants.

CHALLENGES OR MORAL AND LEGAL ISSUES FACED BY ORGANIZATIONS IN CARRYING OUT CLINICAL TRIALS.

In carrying out the clinical trial few challenges are being faced by the organization conducting those trials. It is not only the rules and regulation they have to comply with but also moral issue as well looking at the kind of trial that is to be conducted while people are recruited for the trial to test the efficacy of the drug that has to introduced in the market. Some of those challenges are as follows:

1. Recruiting participants: One of the biggest challenges is recruiting enough participants for the clinical trial. Recruiting can be a lengthy and costly process, and finding the right people who meet the criteria can be difficult.
2. Participant safety: Participant safety is of the utmost importance in clinical trials, and organizations must take all necessary steps to ensure that the participants are not put at

risk during the trial. This includes monitoring for side effects, adverse events, and any other potential risks associated with the treatment or intervention being tested.

3. Regulatory compliance: Clinical trials must comply with strict regulations and guidelines set by regulatory authorities. Failure to comply with these regulations can result in delays or even the termination of the trial.
4. Managing trial data: Clinical trials generate large amounts of data that must be managed effectively to ensure that the results are accurate and reliable. Data must be collected, stored, and analyzed in accordance with strict guidelines to maintain the integrity of the trial.
5. Access to funding: Clinical trials can be expensive, and organizations must have access to adequate funding to cover the costs of the trial. This can be a significant challenge for organizations, particularly those that are not-for-profit or rely on government funding.
6. Ensuring diversity: Clinical trials must be diverse to ensure that the results are applicable to a wide range of people. However, recruiting diverse participants can be challenging, particularly in communities that are underrepresented in clinical trials.

Overall, conducting clinical trials is a complex and challenging process that requires careful planning, execution, and management. Organizations must be prepared to address these challenges in order to ensure the success of the trial and the safety of the participants.

FACTORS FAVORING PARTICIPATION

Although, the risk involve in participating in the trial large number of participate in these trial. Beside the ethical issue in these trial people tend to voluntarily part of the trial. The reason could be personal benefit or influenced by some other methods. Some of the factor favouring the participation of the people have been mentioned below:

1. PERSONAL HEALTH BENEFITS-Potential members are more likely to take part in the event that they are persuaded that the clinical trial yield will advantage them in terms of great wellbeing,assurance from or avoidance of a few disease.The same is genuine for relatives 1 who impact choices on cooperation. On the off chance that they are persuaded that the member will by and by advantage, they regularly energize participation.Free treatment to self or family, torment help for self are a few other illustrations that were too esteemed. Patients with hopeless illnesses or at the terminal arrange of life, select to take part with the trust that the trials may make strides their condition or remedy them. In case of

potential members of a HIV antibody trial, individual assurance from conceivable HIV disease amid and after the trial essentially affected their choices.

2. ALTRUISM- Contributing to the greater good and advancing science and medicine played a part in people's choices to join clinical trials. Wanting to help find a cure or vaccine to stop a disease from spreading was a big reason. Also, wanting to prevent a deadly disease like HIV and make it stoppable were other reason.

3. METHODS OF MOTIVATING PARTICIPANTS- There are various methods of motivating the participants to be part of the trial such as there contribution toward the development will benefit their lives. There are extra perk also offered to participate in the trial apart from the monetary.

4. SOURCE OF EXTRA INCOME- People were more likely to join if they were getting paid. People thought they would get paid or receive gifts and insurance if they took part in a medical study. Also, people who might take part in HIV vaccine tests asked for a guarantee that they or their family would get money or insurance if they died.

5. DETAILED KNOWLEDGE- Multiple studies have shown the importance of informing people in clinical trials about the possible risks involved. People said that knowing whether there was a risk and the medication they were currently taking affected their decisions. This was clear when people wanted more details before they agreed to, for example, give their blood. In HIV vaccine trials, people said they needed to learn more about the HIV vaccine and how it works. They wanted to know how often the HIV vaccine should be given, where to give it, how long it lasts, and how well it works. Using the right words and explaining things clearly was important for telling people about the study.

6. TRUST IN PHYSICIANS- Respondents within the subjective ponders communicated the critical part of family physicians/general professionals (GP) within the clinical trial cooperation - decision-making handle. In comparison to the taught, the uneducated are more slanted to take after their GP's exhortation in connection to clinical trial cooperation

FACTORS SERVING AS BARRIERS TO CLINICAL TRIAL PARTICIPATION

Clinical trial sometimes have to maintain confidentiality of the drug and unavailability of proper information related to the trial and the drug. Safety of the participants and various other factor also serve as a barrier to participation in clinical trials. Some of those factors have been mention below:

1. MISTRUST OF TRIAL ORGANIZATIONS - Participants drew personal conclusions regarding the primary objective of certain trials and expressed a sense of being used as "guinea pigs."

Moreover, participants expressed concerns about the potential administration of placebos, which they believed might not offer any benefits, highlighting mistrust as a significant factor contributing to their reluctance to take part. Conversely, it was noted that family doctors earned the trust of their patients. This trust was apparent as prospective participants expressed a preference for consulting their family doctors for guidance on the safety aspects of participating in clinical trials.

2. CONCERNS ABOUT EFFICACY AND SAFETY OF TRIALS- Prospective participants raised apprehensions regarding safety protocols, potential side effects, and health risks associated with clinical trials. Their unease extended to the untested nature of the proposed therapy. In the context of vaccine trials, individuals expressed worries about the efficacy being unknown and potential long-term adverse effects.
3. DEPENDENCY TRIAL- Participants often relied on guidance from family, friends, or the broader community when deciding to take part in clinical trials. The involvement of a friend, in particular, served as a model, instilling comfort and a sense of solidarity in their decision-making process.
4. LOSS OF CONFIDENTIALITY- Participants expressed apprehensions about privacy protections and highlighted the potential adverse consequences, such as impacts on personal life, marital relationships, insurance, and employment, as reasons for abstaining from clinical trial participation. Participants were concerned that participating in a clinical trial might lead to the disclosure of personal health details, potentially causing harm to them. Consequently, they emphasized the utmost importance of maintaining confidentiality for their personal information.
5. TRIAL BURDEN- This is predominantly linked to the challenges and hardships associated with participating in clinical trials, placing a burden on the subjects. These challenges encompass trial procedures and protocols that can disrupt the normal course of life and inconvenience the participants. For instance, in four studies, respondents mentioned time constraints, travel issues, and the necessity to take additional and unnecessary medications.

On the other hand, trials that were deemed to be more convenient and less disruptive of routine life enhanced participation.[3]

6. PSYCHOLOGICAL REASONS- Mental components impacting subject choices to take part in clinical trials. These components extended from plain fear to fear of injection/stigma/blood tests as well as lack of engagement in participation. Psychological components affecting subject choices to take an interest in clinical trials contributed to the arrangement of this topic. These components extended from plain fear to fear of injection/stigma/blood tests as well as lack of engagement in interest.
7. LANGUAGE-Participants favored the communication of clinical trial data in a basic and clear way. Furthermore, dialect obstructions habitually caused members to have trouble understanding the methods, security, and benefits of the progressing clinical trials, which in this way brought about in disregard and non-participation in clinical trials.

Along with the abovementioned barrier, Unethical clinical trials can also significantly serve as barriers to participation in several ways. Firstly, the historical instances of unethical trials, such as the Tuskegee syphilis study, have led to a deep-seated mistrust of the medical system among certain communities. This mistrust can result in reluctance to participate in clinical trials, particularly among marginalized or vulnerable populations. Secondly, unethical practices, such as non-consensual procedures or withholding treatment, can lead to physical or psychological harm to participants, discouraging others from enrolling. Additionally, unethical behavior can tarnish the reputation of clinical research, making individuals hesitant to engage in trials due to concerns about the safety and integrity of the study. Ensuring ethical conduct in clinical trials is essential not only for the well-being of participants but also to foster trust and confidence in the research process, ultimately reducing barriers to participation.

UNETHICAL CLINICAL DRUG TRIALS IN INDIA:

The issue of unethical and illegal clinical trials in India is a significant concern, drawing attention from both national and international entities. Despite India's appeal for clinical trials due to factors like a diverse population, cost-effectiveness, and supportive government policies, it is imperative to guarantee the ethical conduct of these trials in accordance with legal provisions.

[3] Harris Interactive. Participation in Clinical Trials Lower in Europe and India than in the United States. Harris Interactive studies public perceptions of clinical trialsin six European countries and India. *Healthcare News.* 2005;5

Ethical guidelines and legal regulations governing clinical trials are designed to safeguard participants and ensure the fair and transparent execution of trials. Unfortunately, instances of violations of these guidelines and regulations have occurred, resulting in harm to participants and a decline in public trust. It is crucial for all stakeholders, including pharmaceutical companies, research institutions, regulators, and ethics committees, to uphold ethical standards and adhere to legal requirements. Measures must be implemented to protect participants' rights and safety, maintaining transparency and accountability throughout the trial process.

Raising awareness among the public about clinical trials, their potential benefits and risks, and participants' rights is essential. This approach can foster trust, encourage increased participation in clinical trials, and ensure that participants are well-informed and protected.

Although India holds the potential to become a major contributor to the global clinical trials sector, addressing the issues of unethical and illegal trials is paramount. Upholding integrity and accountability within the sector is crucial for its sustainable and responsible growth.

THERE ARE SOME UNETHICAL CLINICAL TRIALS IN INDIA:

The Swasthya Adhikar Manch case involved allegations of unethical drug trials in the state of Madhya Pradesh, India. In 2013, it was reported that between 2007 and 2010, over 12,000 patients from economically weaker sections of society were enrolled in clinical trials without their informed consent. The trials were conducted by several multinational pharmaceutical companies, including Pfizer, GlaxoSmithKline, and Merck, in collaboration with several Indian hospitals. The patients were reportedly not properly informed about the nature of the drugs they were being given, and some were allegedly given placebos instead of actual drugs.

The Swasthya Adhikar Manch, a coalition of health rights organizations in India, filed a public interest litigation in the Supreme Court of India seeking compensation for the affected patients and a ban on all unethical drug trials in the country. The case eventually led to the formation of new guidelines for clinical trials in India, aimed at protecting the rights of patients and ensuring informed consent.

It's worth noting that this is just one of many instances of unethical drug trials in India and around the world. Such incidents underscore the importance of ethical considerations in medical research and the need for strong regulations to protect vulnerable populations.

Another case **The cervical dysplasia trial** conducted in the 1970s and 1980s by researchers at the Institute for Cytology and Preventive Oncology in New Delhi, India, was a study on women patients who presented with different stages of cervical dysplasia or suspected precancerous lesions of the cervix. The women were not informed that they were participating in a trial, and none of them were asked for consent. The researchers said it was okay to do the study because there was not enough proof that all severe dysplasias turn into cancer. But a big medical journal in North America published a study about cervical cancer. They found that cervical dysplasia can lead to cervical cancer, so all types of dysplasia should be treated. Despite the new information, the researchers from India kept studying the subject. They didn't give the participants any treatment to see how many lesions turned into cancer and how many got better. At the end of the study, 71 women had gotten cancer, and nine of them had cancer that had spread. Sixty-two women only got treated for cancer after it had grown in one area of their body. The argument that started after the research The attention on ethical issues in the 1990s caused the ICMR to make guidelines for biomedical research on people in 2000. The study shows the problems with ethics in medical trials and explains why these trials need strict rules. The rules in Helsinki were not followed in this study because there was no proof that the women were told they might be in a research study.

Furthermore, even though the research in the journal showed that all types of dysplasia needed treatment, the Indian researchers kept doing the study, which goes against the Helsinki Guidelines (1964). These guidelines say that doctors should not do research on people unless they are sure it won't be too risky, and they should stop the research if the risks are greater than the benefits. "Yep, that's right. " In unfair tests, patients may not know or understand that they are part of an experiment and could be taken advantage of by the people running the test. Even when the person knows about the trial, the unequal power between the organizer and the participant still makes it difficult.

The person is weak and can easily be hurt. This is because the person is letting someone else use their life for tests, which might actually make their own life worse. Clinical trials aim to make people healthier without putting their lives at risk or taking advantage of them.

people who are taking part in a trial. It is crucial to make sure that all medical studies are done in a fair and honest way and that all participants agree to take part.

The M4N and G4N trial is an important case in India's history of testing new medicines. The study took place in 1999 at a hospital in Thiruvananthapuram, and was done on 2716 people with oral cancer. The patients were given new drugs, M4N or G4N, instead of the usual treatments like surgery, chemotherapy, and radiation. The goal was to find out if these chemicals could stop the growth of oral cancer.

Even though the people involved agreed to take part, they didn't know they were in a research study or that there were other treatments they could have used. Furthermore, the anti-cancer drug trial was approved by the Indian drug regulator after it had already started, and ethical clearance from the collaborating organization, John Hopkins University, had not been given.

The trial gained attention from the media after a radiotherapist at the center raised concerns about how the trial was being conducted. An investigation was done in India and the US, and they found that only some mistakes in following the rules had happened. The University stopped the main researcher from doing more research on the chemicals. They said any more studies with people must be watched by an experienced University person.

This trial shows how trials are organized in a bad way in India. First, the people in the study didn't know they were in a experiment, so they didn't get the treatment they needed. Furthermore, the trial started without permission, which was against the law according to Section 1. 2 of Schedule Y of the Drugs and Cosmetics Act, 1945. The collaborating organization should have gotten permission from the ethical committee before working together, but they didn't.

However, the M4N and G4N trial shows that clinical trials in India are not done fairly. People in the trials don't know what the study is about, and the people in charge didn't get permission to do the trial. It makes people think about how the place where a trial happens affects the results. For example, in some poor countries there may not be as many rules to follow. Also, some people worry that only rich or certain kinds of people will get approved for the trial.

ROLE OF JUDICIARY

The judiciary has a significant role in overseeing and ensuring the legal and ethical conduct of clinical drug trials. Here is a summary of its role:

- **1. Judicial Review**: People or organizations associated in clinical trials, such as patients, patient advocacy groups, or pharmaceutical companies, can approach the judiciary with

concerns about clinical drug trials. The judiciary can conduct a review to assess the legality, fairness of the trials, ensuring compliance with applicable laws and regulations.

- **2. Protection of Rights:** The judiciary is responsible for protect the rights of individuals participating in clinical trials. If trial participants' rights are violated, the judiciary can provide redress and protect their interests, including issues related to informed consent, patient safety, compensation, and privacy.
- **3. Enforcement of Regulations:** When clinical trials are suspected of violating regulations or ethical norms, the judiciary can take action to enforce existing laws and regulations. This may involve penalizing those responsible for violations and ensuring corrective measures are taken.
- **4. Arbitrating Disputes**: Disputes related to clinical trials can arise between sponsors, investigators, regulatory authorities, and patients. The judiciary can serve as a forum for resolving these disputes and ensuring comformity with the law and ethical standards.
- **5. Public Interest Litigation (PIL)**: Public interest litigations can be filed with the judiciary to highlight issues related to clinical drug trials for public health and safety. PILs can lead to judicial actions or directives for regulatory authorities to investigate and address concerns.
- **6. Transparency and Accountability:** The judiciary can ensure transparency in clinical trials by requiring regulatory authorities to disclose information about ongoing trials and their findings. This transparency is vital for maintaining public trust in the drug development process.
- **7. Compensation and Liability**: If patients in clinical trials suffer harm or injury due to negligence or misconduct, the judiciary can determine liability and order appropriate compensation from pharmaceutical companies, investigators, or regulatory authorities.
- **8. Review of Regulatory Decisions**: The judiciary can review decisions made by regulatory bodies to ensure they comply with the law and public interest. For example, the Central Drugs Standard Control Organization (CDSCO) can be subject to judicial scrutiny.
- **9. Establishing Precedent**: Judicial decisions in clinical trial cases can set important legal precedents, guiding future cases and influencing the development of regulations and best practices in the field.

In summary, the judiciary plays a major role in upholding the legal and ethical standards of clinical drug trials. It ensures that trials respect participants' rights and safety, comply with laws and regulations, and promote public health and justice. The judiciary's involvement acts as a check and balance in the drug development process, fostering trust and accountability.