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Editorial

The Importance of an Unbiased Safety Review Board in Phase I Clinical Trials

Gerald L. Klein, MD*; Roger Morgan, MD

Department of Pharmacology and Toxicology, The Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA

Corresponding author
Gerald L. Klein, MD
Adjunct Professor, Department of Pharmacology and Toxicology, The Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA;
E-mail: gklein@medsurgpi.com

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Conducting clinical trials is the process that biopharmaceutical companies must use to demonstrate that their product is safe, well-tolerated, and efficacious to obtain marketing approval from the Food and Drug Administration (FDA).[1] Human clinical trials are initiated after preclinical trials have demonstrated sufficient safety data. At that point, the FDA will allow these trials to begin on normal healthy volunteers. However, if the FDA considers the risks too high for these volunteers, the agency will require the specific disease population to be studied. For example, the associated adverse effects of many oncology drugs frequently place them into a riskier category, and ethically it would be inappropriate to expose healthy volunteers to these medications. Since many adverse effects of a drug are not yet known during a Phase I study, they carry an inherent risk to the participants.[2]

To monitor the safety of clinical trials, a safety group such as a Data Safety Monitoring Board (DSMB) is created to provide a continuous review of the study.[3] A DSMB is composed of independent unbiased experienced clinicians who monitor the progress and safety of the trial.[4] Phase I clinical trials often require a pharmacokinetic study which involves sequentially increasing the drug dosage until either a toxic level or a maximum therapeutic level has been achieved. The FDA has not recommended the use of DSMBs in these studies due to their required time, cost, and complexity.[5] So another type of safety group, the Safety Review Committee (SRC), is usually tasked with this role in Phase I clinical trials. These are typically comprised of the principal investigator, the medical monitor, and a third physician of the study sponsor's choosing. However, this group is not independent and may be biased by the nature of their role and relationship with the sponsor.[6,7] In this situation, a conflict of interest may exist. This conflict occurs when a committee member has the possibility of being affected by other conditions that could influence their professional judgment in a patient's welfare or the data integrity of another interest. In this case, they may no longer be impartial and objective.[8] This conflict can be subtle or even occur subconsciously, in a way that undermines their objectivity, impartiality, or integrity. Personal, financial, or other interests of an individual or organization could compromise their ability to act in the best interests of others, or when there is a risk that their actions could be influenced by these conflicting interests.

Conflicts of interest can arise in various contexts, such as research and professional settings. They may be from a personal relationship (a principal investigator's (PI's) relationship with the sponsor), professional relationship (the need for publication), or financial relationship (prolongation of a consulting contract).

Managing conflicts of interest is crucial in maintaining the safety, data integrity, and reliability of the clinical trial. It is typical to establish policies and procedures to identify, disclose, and manage potential conflicts. These measures have typically been included in SRC charters and include recusal from decision-making, disclosure of financial interests, and implementing ethical guidelines to prevent any undue influence or bias. It's important to note that unintentional conflicts of interest may occur if there is an ongoing relationship with the sponsor.

We recommend that the members consist of individuals who have expertise in relevant fields, such as clinical research, biostatistics, pharmacology, and patient safety. The bottom line is that it is important to ensure that the members have no conflicts of interest that could compromise their objectivity.

We, therefore, recommend an unbiased independent "Safety Review Board (SRB)" consisting of an independent medical monitor and two independent clinicians. This SRB, unlike an SRC, would not have the potential built-in bias of having a relationship with the sponsor. This board can quickly review the pharmacokinetic and safety data and, if no worrisome safety events have occurred, they can agree *via* email to advance to the next dosage level. This group can provide an independent evaluation of safety data generated during early clinical trials.

By incorporating diverse perspectives and expertise, the board can critically analyze adverse events and safety concerns, reducing the potential for bias and conflicts of interest that might compromise participant safety. Through vigilant monitoring and analysis of adverse events and other safety data, an unbiased board can swiftly recognize potential risks, allowing for early intervention and the implementation of necessary measures to protect the trial. SRB members should be required to disclose any potential conflicts of interest before participating in board activities. As with SRC members, this includes financial interests, relationships with sponsors or competing companies, and any other factors that could influence their decision-making. Transparent disclosure allows for the identification and management of conflicts, ensuring the board remains unbiased. When there are any questions or concerns, a quick teleconference can take place.

We recommend written procedures that outline the board's responsibilities, processes for data review and analysis, criteria for decision-making, and guidelines for reporting adverse events. Adhering to standardized procedures promotes consistency, transparency, and fairness in the board's activities. By implementing these strategies, organizations can establish and maintain an unbiased SRB, which is essential for protecting the welfare of participants and maintaining the integrity of clinical trials.

The use of the SRB should serve to make Phase I clinical trials safer and reassure the public of the biopharmaceutical company's interest in protecting patient safety and providing objective safety data.

Protection of Participant Welfare

An unbiased SRB ensures the protection and welfare of trial participants. By independently reviewing safety data and adverse events, the committee can detect potential risks and take appropriate measures to mitigate harm. This commitment to participant safety is essential for clinical trials which emphasizes promoting well-being and minimizing harm to patients. The board must be unbiased and only consider the safety data without any prejudicial influences affecting their decision making. This will help to determine that patients are treated appropriately and have an opportunity to gain any benefits or to help in the advancement of medical science.

The independent operation of the SRB is crucial in making freethinking decisions regarding participant safety. It should not be unduly influenced by external pressures, such as sponsors, site management organizations, contract research organizations, or other entities.

The unbiased nature of this decision-making enables the board to prioritize participant safety above all other considerations.

ETHICAL CONSIDERATIONS

The presence of an unbiased SRB underscores the ethical foundation of all clinical research. The board's commitment to participant safety and their objective evaluation of safety data aligns with the spirit and ethical principles of the Helsinki Accords, and World Health Organization (WHO) and will help maintain public trust in the conduct of clinical research.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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