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Beyond the IDMC:
The Value of Safety Review Committees

Continuous monitoring of safety and efficacy data in clinical trials is a fundamental component of modern clinical research. Because monitoring is complex and involves multiple stakeholders, including investigators, sponsors, contract research organisations (CROs) and other vendors, a structured and collaborative oversight process is essential to ensure timely identification and management of safety signals. Safety and efficacy review committees provide such oversight, ensuring objectivity and maintaining the scientific integrity of the clinical trial. Several types of such committees exist, with the Independent Data Monitoring Committee (IDMC), also known as the Data and Safety Monitoring Board (DSMB), being the most commonly used. The requirements for and management of IDMCs are well described in the literature; however, one type of review committee, the Safety Review Committee (SRC), has received comparatively little attention in the medical and scientific community. In this paper, we discuss key aspects of SRC composition and management.

Continuous monitoring of safety and efficacy, together with periodic risk-benefit assessments, has become an essential component of modern drug development.[1] Various entities contribute to this oversight, the most widely recognised being independent data monitoring committees (IDMCs, also known as data and safety monitoring boards [DSMBs]). These entities review accumulating safety and efficacy data at predefined intervals throughout product development to provide recommendations to the sponsor on whether a trial should continue, be modified, or be stopped.[2,3]

In the past, drug approvals have relied on phase 2 and 3 pivotal trials. These are trials where IDMCs are typically used; however, an increasing number of recent drug approvals, particularly in oncology, are based on early-phase dose-escalation or expansion cohort clinical trials (phase 1 or 1/2). Between 2012 and 2023, these designs supported U.S. Food and Drug Administration (FDA) approval for 46 indications across 36 targeted anticancer drugs.[4] For example, avapritinib, designed to treat gastrointestinal stromal tumours in patients harbouring PDGFRA exon 18 mutations, received approval in 2020 based on the results of the phase 1 NAVIGATOR trial, which enrolled 43 participants with the mutation. Similarly, avelumab, an immunotherapy drug, was approved in 2017 for treatment of metastatic Merkel cell carcinoma based on a phase 2 single-arm trial with 88 participants previously treated with chemotherapy.[5–7]

Phase 1 and 2 clinical trials generally enrol small numbers of participants and have limited treatment exposure and overall duration. Under these limited conditions, the use of an IDMC may be impractical. Instead, a safety review committee (SRC) can provide an efficient and proportionate mechanism for dose-escalation decisions and ongoing safety oversight.[8]

SRCs are already established in early-phase clinical trials (phase 1 and early phase 2), especially in dose-escalation or first-in-human (FIH) trials.[9] Their main goal is to review accumulating safety, tolerability and sometimes pharmacokinetic (PK) data between cohorts or dosing levels. The SRC determines whether it is safe to proceed to the next dose level, continue at the current dose, or pause the clinical trial.[10,11]

Two fundamental questions are how to distinguish between an IDMC and an SRC and whether these committees truly serve distinct functions (Table 1). Definitions provide a useful starting point, yet they reveal an important gap since multiple definitions can exist for an IDMC. For example, the FDA defines an IDMC as 'a group of individuals with relevant expertise that reviews accumulating data on a regular basis from one or more clinical trials and recommends to the sponsor whether to continue, modify, or stop a trial or trials. A clinical trial DMC is established by the sponsor but should be independent of the sponsor and the trial conduct'.[3] By contrast, no widely accepted definition exists for an SRC. Our suggestion for formally defining an SRC is 'a group of sponsor representatives, investigator representatives and independent members as appropriate, who are responsible for reviewing ongoing safety data, including dose-limiting toxicities (DLTs), in early-phase trials to ensure participant safety and guide decisions on dose escalation and cohort progression.' At first glance, these definitions of IDMC and SRC appear similar; however, the key distinctions lie in independence of the members and the committee's purpose. While the members of the IDMC are external to the clinical trial under review, an SRC includes individuals actively involved in the trial. The difference is critical: the IDMC provides impartial oversight to trial participant safety and trial integrity, while the SRC focuses on ongoing monitoring and rapid response within the context of trial operations, with the added benefit of offering objective viewpoints.

Unlike IDMCs, SRCs contain study investigators and sponsor representatives. A typical SRC may include personnel such as the sponsor's medical monitor, a clinical pharmacologist and investigators from enrolling sites. The CRO medical monitor may also participate, as they can provide a broader view of the aggregate trial data. Enrolling sites are generally defined as those with at least one participant entered in the trial, regardless of the participant's current status, be it screening, treatment, follow-up, or discontinuation. Investigators from enrolling sites provide valuable clinical insight and firsthand knowledge of their trial participants' conditions and the trial conduct at their site. However, investigators' inclusion in an SRC raises concerns regarding independence and potential bias, which may affect the interpretation of safety data or decisions. To strengthen objectivity and credibility, one or two independent members external to the trial should be included. Such members enhance the integrity of safety oversight and the transparency of SRC decisions. Another reason to include an independent expert is that investigators and sponsor representatives may have limited experience in interpreting novel toxicities or rare adverse events; therefore, consultation with an external expert should be considered.

When selecting members for an SRC, the criteria should proceed as with IDMCs. For example, identify and manage potential conflicts of interest among SRC members, including independent ones. Another limitation to consider when including investigators from enrolling sites is the potential instability of committee composition. Early in the trial, the number of enrolling sites and eligible investigators may

be small, reducing diversity of opinion and possibly the quality of recommendations. Conversely, in large multicentre studies, inclusion of too many site investigators can create logistical challenges for organising SRC meetings and issuing timely recommendations. To mitigate these challenges, investigators who serve on the SRC should be preselected regardless of their sites' enrolment status in trials with more than 10 sites. In smaller trials, the traditional approach of including investigators from enrolling sites remains feasible and should be continued.

In summary, an optimal SRC might include the sponsor's medical monitor (or clinical lead) and a pharmacovigilance specialist, the CRO's medical monitor (if applicable), and, depending on the size of the trial, either a limited number of selected site investigators (for larger multi-site trials) or representatives from all enrolling sites (for smaller trials with fewer than 10 sites). Ideally, one or two independent members not directly involved in the trial and external to the sponsor should be included to enhance objective oversight. A biostatistician may be invited to advise, particularly in trials employing complex statistical methods, but should serve in a non-decision-making capacity.

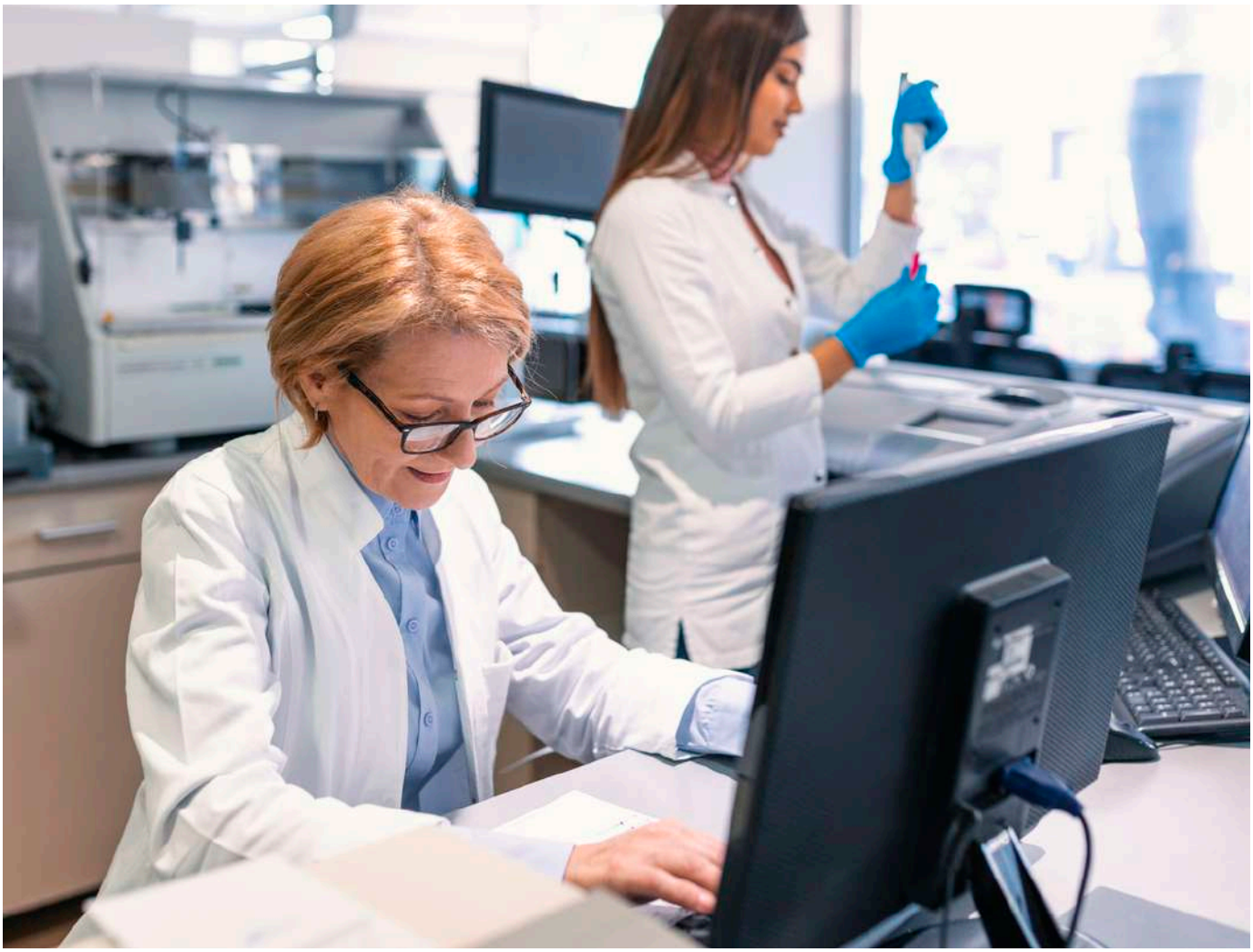
Developing a Charter for any type of review committee is a key element of trial governance as the Charter formally defines the committee's roles, responsibilities, membership and operational procedures. A Charter provides consistency, transparency and accountability in safety oversight and serves as a formal reference for regulatory authorities and ethics committees.[12] However, developing an SRC Charter for early-phase clinical trials poses several challenges. Defining the committee's scope and authority can be difficult, particularly regarding dose escalation, protocol modifications, or trial suspension, especially once investigators and sponsor representatives have overlapping duties or potential conflicts of interest. Unlike an IDMC Charter, conflict of interest management depends on the composition of the SRC and is different for investigators and independent members. The Charter should also define triggers that will result in meetings – such as trial milestones, safety events, time/enrolment-based points, dose escalation criteria and stopping rules, workflow for preparing data review packages, meeting logistics and the decision documentation process.

SRC meetings typically convene after the completion of specific study milestones, such as the enrolment or dosing of a cohort. In trials employing a traditional 3 + 3 dose-escalation design, SRC

meetings are best scheduled on an event-driven basis. For example, an optimal time for the SRC meeting to convene would be after completion of the dose limiting toxicity (DLT) observation period, which is typically 21 to 28 days following administration of the investigational product to the last participant in that cohort for each cohort, once all safety data have been verified and summarised.[13,14] However, the exact timing of the SRC meeting may vary depending on the drug's PK properties and required washout period. By that time, all relevant safety, tolerability and PK data (if applicable) should be verified, summarised and available for review. If a DLT is observed before cohort completion, an ad hoc SRC meeting may be called to determine whether to expand the cohort or suspend escalation. Meeting logistics should allow for rapid review, ideally within 72 hours of data availability and conducted via teleconference. In addition to event-driven reviews, periodic summary meetings are recommended to ensure continuous oversight of cumulative safety and PK data.[15] Although the optimal frequency is not prescribed by regulatory guidance, a best-practice recommendation is to convene periodic summary meetings at predefined intervals,

	IDMC	**SRC**
Typical phase of drug development	Late phase (IIb–III, large pivotal trials)	Early phase (I–IIa)
Result	Ongoing benefit–risk assessment, with the potential to recommend trial modification or termination for efficacy or safety reasons.	Immediate safety and dose-escalation decisions
Frequency	Periodic (e.g., quarterly or semi-annually) and/or triggered by pre-defined number of trial-specific events	Possibly after each cohort or dose step, plus additional periodic reviews at pre-defined time intervals
Composition	Independent experts	Investigators, the sponsor, optional: independent member(s)
Independence	Completely independent of the sponsor and the trial for which the IDMC was established	Not independent (composed only of the sponsor representative and investigators) or semi-independent if includes one or several independent members
Data to be reviewed	Blinded and unblinded cumulative, aggregated safety and/or efficacy data in a form of tables, listings, and figures at predefined intervals	Unblinded, real-time, participant-level safety and tolerability data (e.g., extended narratives, laboratory and pharmacokinetic data)
Decisions/recommendations	Independent recommendations to the sponsor on whether to continue, modify, or stop the trial	Operational decisions on dose or cohort modification, implemented immediately following SRC deliberation

Table 1. Key Distinctions Between IDMC and SRC, The table summarizes the key distinctions between IDMCs and SRCs, highlighting that the SRC's unblinded, investigator-inclusive composition allows for real-time operational decisions essential to early-phase dose-escalation studies.



about every three to six months, depending on the indication, study complexity and rate of enrolment. These periodic meetings provide an opportunity to evaluate emerging safety trends and PK profiles across cohorts, complementing cohort-specific SRC reviews. However, in early-phase, dose-escalation trials, escalation decisions should rely primarily on cohort-specific SRC evaluations following completion of each DLT observation period.

Probably the central point of any SRC's purpose is how the data will be presented and managed for the review. In general, an SRC reviews unblinded safety data, including adverse events (AEs), serious adverse events (SAEs), clinical laboratory results, vital signs, electrocardiograms (ECGs), PK findings and relevant imaging data when supported by pharmacodynamic (PD) findings. The presented data's scope and level of detail are determined by the study design and trial indication. Before the study begins, the sponsor should define the input from the CRO medical monitor and specify it in the SRC Charter. Data visualisation tools, such as graphical patient profiles, time-series plots of key laboratory parameters and trend analyses of AE onset and resolution can enhance interpretation and facilitate focused discussion. Unlike traditional statistical outputs for IDMC that are primarily based on aggregated tables, figures and listings, SRC reviews require participant-level data. For each participant, detailed case narratives, participant profiles and chronological presentations of safety parameters enable the committee to assess causality, emerging safety patterns and dose tolerability on an individual basis. This granular approach assists in real-time evaluation of potential DLTs and supports data-driven decisions on whether to escalate, de-escalate, or suspend dosing in treatment. This is particularly true for phase 1, 3+3 or adaptive dose escalation designs, if the SRC is convened once 3 patients in a cohort are enrolled and treated. In such a situation, the SRC will review and discuss each trial participant separately by using an extended patient narrative for optimal data presentation.

Data files prepared for SRC review undergo standard data-cleaning procedures conducted by the data management and clinical teams. Because reviews are performed while the trial is ongoing, the data may not have the completeness or verification level of a finalised study database. The SRC coordinator distributes the unblinded review package to all committee members in accordance with the procedures outlined in the SRC Charter.

Because the SRC reviews unblinded data and its membership includes the study investigators, discussions are conducted as open sessions with full access to treatment assignments and all available safety information. Decisions made at the conclusion of SRC meetings are typically final, allowing immediate implementation of recommendations regarding dose, cohort, or protocol modifications. This process enables rapid turnaround, minimising delays in study conduct while maintaining a robust safety oversight process. In contrast to IDMCs, which operate under a partially blinded model and issue formal recommendations following closed-session review and discussion, the SRC functions as an operational safety body embedded within the sponsor–investigator framework. All SRC discussions, decisions and supporting data are documented in real time to ensure transparency, traceability and compliance with regulatory expectations for ongoing safety review.

Ultimately, the effectiveness of an SRC depends on the clarity of its Charter, the precision and timeliness of its data flow, its members' cohesion as a committee and the efficiency of its deliberations. When these components function cohesively, an SRC provides a powerful mechanism for real-time safety oversight, bridging scientific rigor and operational agility in early-phase drug development.

Conclusion

Safety Review Committees (SRCs) represent a critical component of early-phase clinical research governance. As the landscape of drug development evolves toward accelerated, adaptive and first-in-human (FIH) designs, the need for scientifically rigorous safety oversight becomes increasingly evident. Unlike independent data monitoring committees (IDMCs), which monitor the safety of trial participants through independent oversight, SRCs enable real-time, data-driven decision-making within the operational context of early-phase studies. Their unblinded review of patient-level data allows for timely identification of emerging safety signals and supports dose modification strategies.

Establishing an effective SRC requires careful planning of its composition, procedures and data management practices. The development of an SRC Charter, clearly defining the committee's mandate, responsibilities and decision-making processes is essential to ensure consistency and transparency. Incorporating independent experts enhances objectivity and mitigates potential bias from sponsor or investigator representatives. Standardised data visualisation tools and validated workflows further improve interpretability and expedite review timelines.

As early-phase trials increasingly provide pivotal evidence for regulatory approvals, the role of SRCs will continue to expand in scope and importance. Future guidance from regulators and professional bodies would help harmonise SRC implementation across therapeutic areas, study designs and across the healthcare industry.

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