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Presenting Risks and Benefits: Helping the Data Monitoring Committee Do Its Job

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Data monitoring committees (DMCs), or data and safety monitoring boards, protect clinical trial participants by conducting benefit–risk assessments during the course of a clinical trial. These evaluations may be improved by broader access to data and more effective analyses and presentation. Data monitoring committees should have access to all data, including efficacy data, at each interim review. The DMC reports should include graphical presentations that summarize benefits and harms in efficient ways. Benefit–risk assessments should include summaries that are consistent with the intention-to-treat principle and have a pragmatic focus. This article provides examples of graphical summaries that integrate benefits and harms, and proposes that such summaries become standard in DMC reports.

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Monitoring the welfare of clinical trial participants during the course of the trial is an ethical imperative. Data monitoring committees (DMCs), also known as data safety monitoring boards, play an essential role, particularly for trials involving high-risk populations or potentially harmful interventions (1). The DMC, generally comprising medical and statistical experts with experience in clinical trials, protects trial participants by ensuring that they are not unduly or unfairly at risk for harm and that the scientific integrity of the trial is maintained.

The DMC meets periodically to review reports, produced by a statistical data analysis center (SDAC), that summarize important interim data. The DMC is in a unique position: It is the only entity with access to data by unblinded treatment assignment, effectively keeping trial sponsors and study staff blinded to trial results to avoid operational bias and to retain trial integrity. Independence of the DMC is essential to ensure unbiased assessment of accumulating trial data.

After each meeting, the DMC issues a recommendation to continue the trial as is, continue with modifications, or terminate the trial. The DMC's recommendations are based on careful benefit–risk assessments (2), the quality of trial conduct, and potentially relevant information outside the trial, in accordance with protocol-defined guidelines for stopping or amending the trial. Recommendations for modification or termination may be based on achievement of a definitive result of the treatment comparison, evidence that risks to participants probably outweigh the potential benefits (3), or the likelihood that the trial will not meet its objectives.

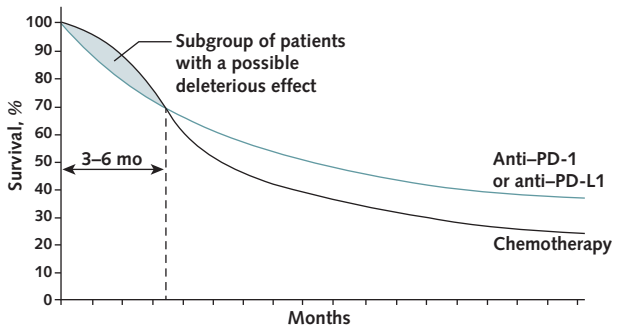
Increased access to important data and improved interim data analyses and presentation may help facilitate informed DMC benefit–risk assessments. Graphical summaries that integrate and summarize benefits and harms are proposed as standard summaries in SDAC reports.

Access to Data

Many members of the clinical trial community regard the DMC's charge as the assessment of participant safety, unless the trial protocol specifically calls for interim efficacy analyses. Data monitoring committees generally receive access to any interim safety data deemed necessary for a robust assessment of safety. However, safety assessments need context. To fulfill its mandate to protect trial participants, the DMC needs timely access to all relevant information, including efficacy data. Access to efficacy data allows the DMC to evaluate equipoise for continued random assignment and follow-up of trial participants, and may reduce the likelihood of a trial being stopped because of safety signals that might be outweighed by potential benefits. On the other hand, it may increase the likelihood of a trial being discontinued on the basis of emerging safety signals when a new treatment seems to have little or no efficacy. For example, studies of the effect of immune checkpoint inhibitors on advanced-stage cancer have shown that a subset of patients may have "hyperprogression," leading to decreased survival relative to control participants during early follow-up (4). Here, survival is providing information about toxicity and efficacy. The DMC would need full access to the survival data for comprehensive benefit–risk assessments (Figure 1).

Trial sponsors are sometimes reluctant to provide DMCs with access to interim efficacy data, possibly because of concerns that it might affect their control of the type I error rate. A common perception among trial sponsors is that any look at efficacy data, regardless of whether a sequential plan is in place permitting early termination for efficacy, requires an adjustment to the significance level used to test the primary efficacy end points at the final analysis. This perception has contributed to the reluctance to share efficacy data with DMCs, especially for trials with many scheduled safety assessments. In principle, the type I error at an interim analysis can occur only if a claim of efficacy has been made. If efficacy is not to be tested, a practical solution that addresses the type I error concern and allows for DMC functionality is to "spend" a minuscule amount of the type 1 error, such as 0.0001, each time efficacy data are reviewed. A prespecified sequential plan should be implemented if there is a chance that a review of effi-

Figure 1. Differences in survival patterns over time.



In phase 3 trials comparing immune checkpoint inhibitors with cytotoxic agents, a phenomenon may be observed whereby survival, an efficacy end point, is lower in the immunotherapy groups in the early stages of the trial (such as the first 3 to 6 mo after treatment initiation [*dashed line*]), suggesting an early toxicity signal (4). PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand-1. (Reproduced from Champiat and colleagues [4] with permission from Springer Nature.)

cacy data would motivate the DMC to recommend early termination for efficacy.

ANALYSES AND DATA PRESENTATION

DMC Report Quality

A DMC report is often a voluminous, difficult-to-digest compendium of poorly integrated tables and listings, limiting the DMC's ability to develop a coherent understanding of the data and benefit–risk profile of the interventions (5, 6). Well-organized reports and increased use of graphics, augmented with listings and tables, enhance the DMC's understanding of the comprehensive effects on trial participants. To foster efficient, informed decision making, reports should be streamlined, concise documents that display important data in optimally informative ways (7). To provide such reports, the SDAC needs statistical, technical, and communication skills; clinical knowledge; and an appreciation of the clinical perspective to provide valid analyses that accurately convey the messages from the data. Because reports are generally constructed by biostatisticians, careful review by clinicians before distribution may be considered to ensure that the report anticipates and addresses questions and concerns from a clinical perspective.

Graphical Summaries That Integrate Benefits and Harms

Historically, DMC benefit–risk assessments primarily have been unstructured, with DMC members informally interpreting and weighing the benefits and harms of the interventions on the basis of their expertise and experience. Thoughtful integration and presentation of benefits and harms may provide structure to these evaluations and will help facilitate DMC benefit–risk assessments. Graphical displays may help elucidate the "big picture" and more comprehensively convey the intervention's effects on trial participants.

Forest Plots That Summarize the Effects on Important Outcomes

Forest plots depicting the results of several important outcomes in a single figure are useful in presenting an overall view of benefits and harms. Presentation of risk differences is important, because the integrated interpretation of relative risks for several outcomes is challenging when outcomes have very different baseline risks. For example, suppose the relative risk is 2 for each of 2 outcomes of similar importance, with each outcome favoring different interventions. One may be tempted to conclude that the interventions produce similar yield. If one of the outcomes is much more common than the other, the similarity in relative risks does not give the full picture. A doubling of 10% risk has very different implications than a doubling of 0.5% risk.

Consider the comparison between vorapaxar, an antithrombotic therapy, and placebo (both with a background of standard of care) for secondary prevention of cardiovascular events, as reported in the TRA 2°P–TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) trial (8). In this study, the risk for intracranial hemorrhage associated with vorapaxar was substantially higher in trial participants with a history of stroke, and no evidence of efficacy was seen within this subgroup. Vorapaxar thus was contraindicated in these patients given its suboptimal benefit–risk profile. The contraindication was extended to patients with a history of transient ischemic attack because of the clinical challenges in distinguishing them from patients with a history of stroke.

The benefit–risk profile for vorapaxar was favorable for trial participants without previous stroke or transient ischemic attack (**Figure 2**). The risk difference per 10 000 patient-years for cardiovascular death, myocardial infarction, or stroke events favored vorapaxar (−68 [95% CI, −99 to −37]). However, no clear difference was seen between vorapaxar and placebo in the risk for severe bleeding events according to the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) classification system (risk difference per 10 000 patient years, 4 [CI, −8 to 15]).

Summaries Synthesizing Benefits and Harms Within Patients

Typical analyses of clinical trials involve intervention comparisons for each outcome. Outcome-specific results are then combined in some way as part of a global benefit–risk assessment. Such approaches do not account for associations between outcomes, and interpretation of outcome-specific results may be challenging because of competing risks. Further, efficacy and safety outcomes often are analyzed in different populations. Efficacy analyses typically include all randomly assigned trial participants according to the intention-to-treat (ITT) principle, whereas safety analyses typically focus on the subgroup of trial participants who received the intervention. Therefore, the popula-

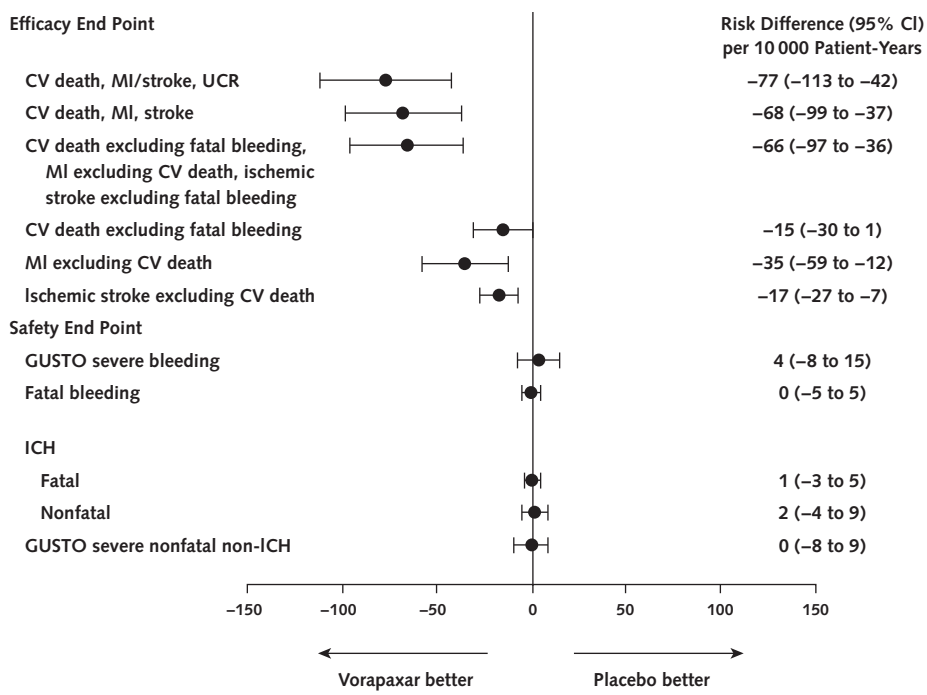
tion to which the results generally apply is unclear. The desirability of outcome ranking (DOOR) approach (9–11) addresses these limitations through use of an ordinal composite outcome that more comprehensively conveys the joint efficacy and safety effects as experienced by the trial participants.

For example, suppose that a trial compares interventions A and B for the treatment of methicillin-resistant *Staphylococcus aureus* bloodstream infections in hospitalized adults. Major efficacy outcomes of interest are survival; treatment success (survival with resolution of symptoms); and a safety outcome, acute kidney injury (AKI). An ordinal benefit–risk DOOR outcome for a study evaluating treatment for this disease is constructed by using mutually exclusive categories, from most to least desirable, as follows (12): treatment success without AKI, treatment success with AKI, treatment failure without AKI, treatment failure and AKI, and death. A sixth category—randomly assigned, results pending—would be used for randomized trial participants who are being followed but for whom outcomes have yet to be observed.

A visual summary of the results may be used to evaluate a synthesized global patient response. The DOOR plot (**Figure 3**) provides a visual comparison of interventions A and B with respect to the DOOR (13). The DOOR plot is easy to understand and can convey information that separate analyses of each outcome cannot (such as cumulative effects on individual trial participants or correlations between efficacy and safety critical for identifying subgroups of trial participants with particularly poor outcomes), providing the DMC with an important summary and contrast of the global effects on trial participants. Rank-based (9, 14–16) and score-based methods, such as partial credit (10), are available to compare interventions with respect to DOOR-like outcomes.

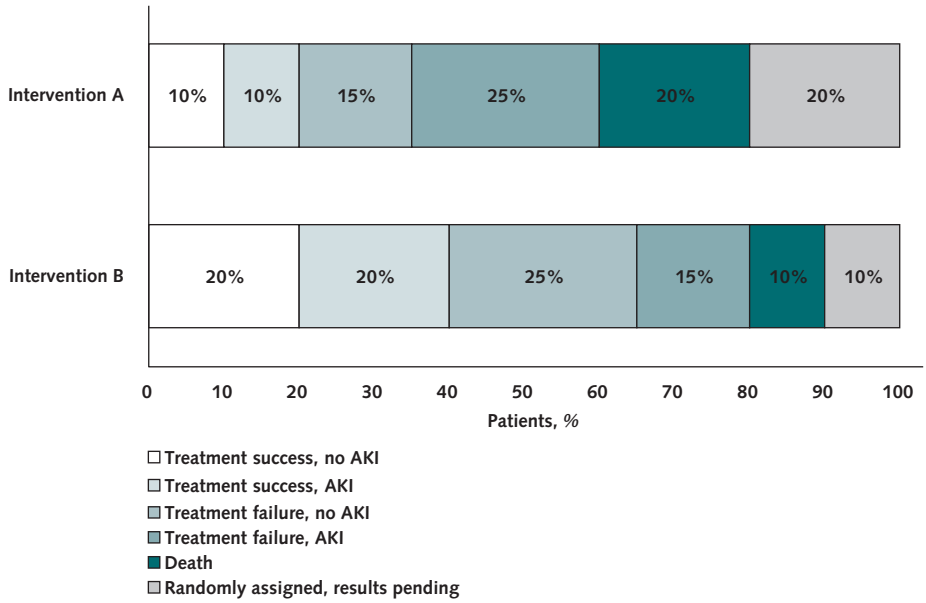
A lasagna plot that provides an individual patient–level summary of a synthesized global outcome over the course of the trial may be used for trials evaluating interventions to treat chronic diseases. Consider a randomized trial comparing treatments A and B. Responses of the trial participants within each visit interval are categorized into 1 of 6 mutually exclusive categories on the basis of events that occur in that time window: benefit without the adverse events (AEs) of interest, benefit with the AEs of interest, neither benefit nor the AEs of interest, no benefit but AEs of interest, withdrawal from the trial, or administrative censoring due to the interim assessment. The responses of trial participants are displayed over time in 2 panels (for participants who have completed the study and those who remain in follow-up), by treatment group (**Figure 4**). The horizontal axis represents time beginning at randomization, whereas trial participants are strategically

Figure 2. Forest plot displaying 95% CI estimates of the risk differences per 10 000 patient-years for important outcomes of the TRA 2°P–TIMI 50 trial.



Analyses are restricted to trial participants without a history of stroke or transient ischemic attack and are based on the intention-to-treat population for efficacy end points and the as-treated population for safety end points. CV = cardiovascular; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (classification system for severe bleeding events); ICH = intracranial hemorrhage; MI = myocardial infarction; TRA 2°P–TIMI 50 = Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events; UCR = urgent coronary revascularization.

Figure 3. DOOR plot, by treatment.



Responses of trial participants are grouped into 6 mutually exclusive categories: treatment success, no AKI; treatment success, AKI; treatment failure, no AKI; treatment failure, AKI; death; and randomly assigned, results pending. The proportion of trial participants assigned to intervention A in each category is 10%, 10%, 15%, 25%, 20%, and 20%, respectively. The proportion assigned to intervention B in each category is 20%, 20%, 25%, 15%, 10%, and 10%, respectively. AKI = acute kidney injury; DOOR = desirability of outcome ranking.

stacked on the vertical axis to help elucidate signals. The plot conveys the relative timing and duration of benefits and AEs, and the timing of study withdrawal for each trial participant, by treatment group. Important signals that may be discerned from this plot include the following: A greater proportion of trial participants in group A withdrew from the study (black); a greater proportion in group B achieved sustained benefit (consistent green); group A displays more toxicity earlier than later, potentially indicating developing tolerance; and group B displays less toxicity early than later, potentially indicating delayed or cumulative toxicity.

ITT: A Pragmatic Focus

Traditional review of clinical trial data involves separate analyses of efficacy and safety. Safety typically is assessed in a population in accordance with an "on-treatment" principle, focusing on an explanatory evaluation of the biological effects of an intervention. Efficacy primarily is assessed according to the ITT principle, focusing on the effectiveness of the strategy used to apply the intervention.

Although DMCs may be interested in on-treatment analyses of safety data, these analyses may be misleading by ignoring the reasons trial participants stop treatment. This creates a selection bias, with analysis restricted to trial participants during periods when they are tolerating therapy, leading to biased estimates of risks (17). On-treatment analyses ending 14 days after treatment cessation led rofecoxib (Vioxx [Merck]) study investigators to underestimate the risks for harm, which were uncovered only with subsequent ITT analyses including events after treatment discontinuation (18). Only ITT analyses preserve the benefits provided by randomization, regardless of whether an end point is characterized as one of efficacy or safety.

Data monitoring committees oversee the welfare of *all* trial participants at *all* points in the trial. Thus, DMC reports should provide efficacy and safety analyses in the ITT population (19). Outcomes and events that occur after an intervention is withdrawn should be included in data summaries. These events are considered downstream consequences of the initial intervention assignment that affect trial participants in the context of the trial, and are attributed to the strategy of intervention application. The benefit–risk profile of an intervention within the context of the trial and potential future use in clinical practice encompasses therapeutic management after intervention withdrawal.

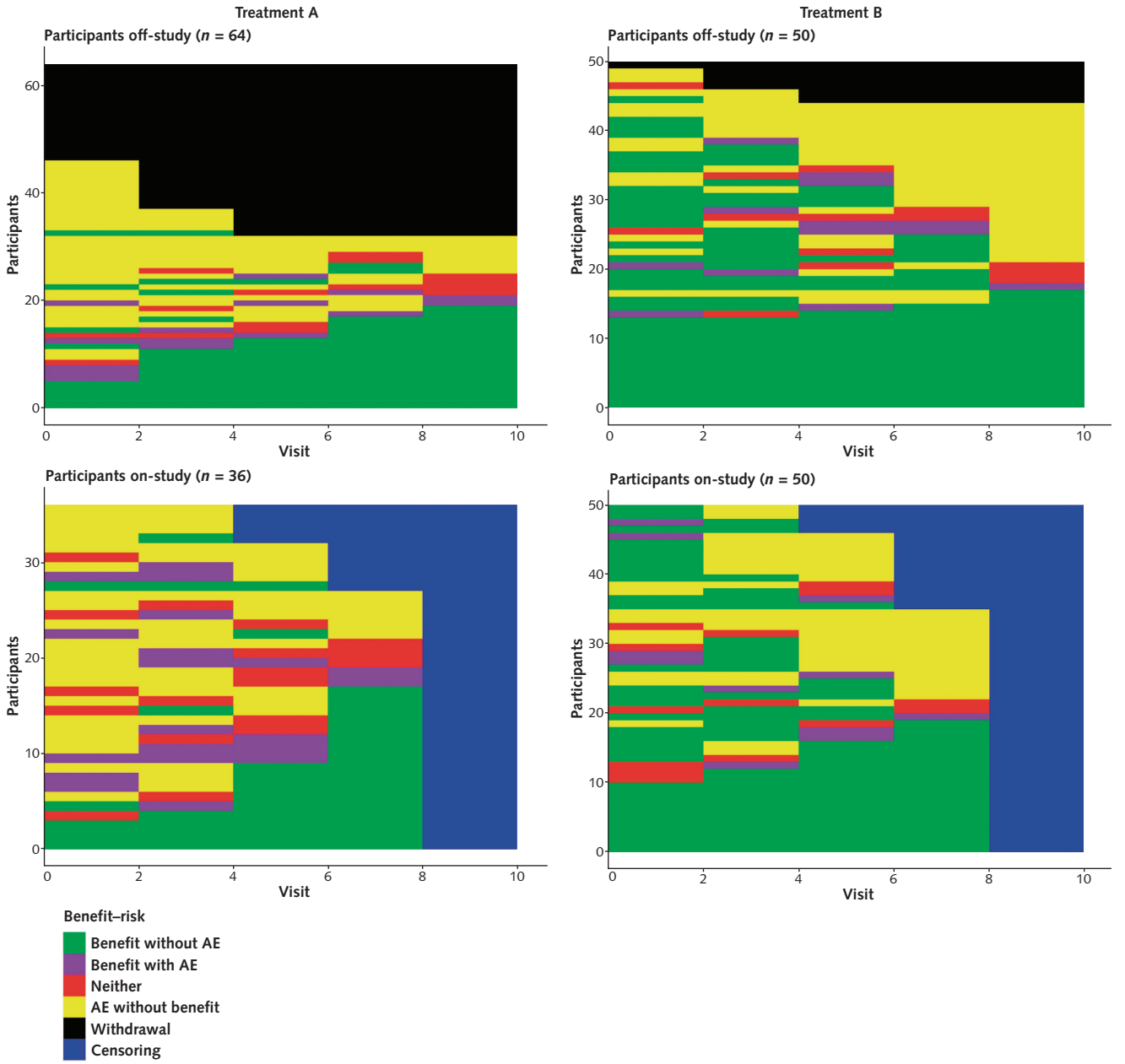
The DMC assessment of causality is distinct from the adjudicated relationship between an intervention and an event. Suppose a randomized trial is comparing 2 interventions, A and B. Further suppose that a trial participant assigned to the A group discontinues intervention A and begins a new intervention, C. The participant then has an AE, adjudicated as related to C but not A. This may lead some to believe that safety is not an issue, because A was not implicated in adjudication. Now suppose 10 additional trial participants discontinue A, begin C, and have the AE. Again, adjudication links the relationship to C but not A. Suppose no such events occur in the B group. In this case, the events are causally associated with the assignment of A; the adjudicated relationship results are less relevant to the

DMC determination, which will recognize that the safety of trial participants assigned to group A is very different from that of participants assigned to B. Data monitoring committees must evaluate whether random assignment to group A is still appropriate. This causality assessment is conducted by contrasting randomized interventions using the ITT population.

SUMMARY

Data monitoring committees play a critical role in ensuring the welfare of trial participants by conducting benefit–risk assessments using interim trial data. The DMC's role is unique because it is the only entity with access to data by unblinded treatment assignment, required for comprehensive understanding of emerging

Figure 4. Lasagna plot providing a benefit–risk summary over time, by treatment, for a trial comparing treatments A and B.



Responses of the trial participants within each visit interval are categorized into 1 of 6 mutually exclusive categories: benefit without the AEs of interest, benefit with the AEs of interest, neither benefit nor the AEs of interest, no benefit but AEs of interest, withdrawal from the trial, and administrative censoring due to the interim assessment. The responses of trial participants are displayed over time in 2 panels (for participants who are off-study vs. on-study), by treatment group. The horizontal axis represents visit number, where randomization is visit 0. Responses within a visit interval are illustrated as starting at the previous visit. For example, participants who discontinued treatment between visit 0 and visit 2 are shown as discontinuing at visit 0. AE = adverse event.

treatment effects. To conduct fully informed benefit–risk assessments, DMCs must have access to all data. Access to safety data is often limited. We encourage the practice of providing all DMCs access to all interim data, including efficacy data, at each review. Doing so will enable DMCs to make more comprehensive benefit–risk assessments in the interest of protecting trial participants.

The typical SDAC report often is a voluminous collection of tables that are difficult to digest. In their reporting, SDACs should place more emphasis on graphical presentations that summarize treatment signals in efficient, transparent, and user-friendly ways, and less on detailed tables and listings.

The DMC benefit–risk assessment frequently is unstructured. The SDAC report should integrate benefits and harms in visual summaries to aid DMC evaluations. We propose that graphical summaries that integrate benefits and harms, such as forest and DOOR plots, become a standard component of SDAC reports. Forest plots provide an efficient summary of the intervention effects on each outcome, whereas DOOR plots summarize the total effects on trial participants. These summaries will enable DMCs to more readily identify signals and to make determinations more systematically and transparently.

Data monitoring committees oversee the welfare of all trial participants and may be interested in all outcomes for trial participants throughout the trial, regardless of treatment status. On-treatment analyses do not fully convey the experiences of trial participants during a trial and thus may not fully convey treatment signals. Benefit–risk and safety assessments by DMCs should include summaries that are consistent with the ITT principle and have a pragmatic focus.

To provide the proposed graphical summaries, SDACs will need to invest resources in the short term to retool and develop integrated data displays, including data visualizations. These costs are small in relation to the costs of a trial and, more important, to the costs of incompletely informed DMC recommendations. Once programming tools are developed, they will be reusable and can be amortized over the cost of future trials, as with other technologic improvements.

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