COMMENTARY

Independent Data and Safety Monitoring in Psychiatric Intervention Research

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ABSTRACT

A data and safety monitoring board (DSMB) is a multidisciplinary group of scientists that monitors a randomized clinical trial. Although DSMBs have been used for clinical trials in cardiology, oncology, and infectious disease for decades, it was not until the late 1990s that the National Institute of Mental Health (NIMH) initially required a DSMB for some of its larger trials. The NIMH mandate expanded during the succeeding decade to require DSMBs for many of the clinical trials in psychiatry. In turn, the need for board members has grown quickly. The objective of this commentary is to consider the purpose of a DSMB and to describe its roles, responsibilities, composition, and implementation.

The rationale for a DSMB is to ensure the integrity and validity of the trial and, most importantly, to protect the safety of trial participants. A board conducts comprehensive reviews of accumulating unblinded data for safety and, in some trials, for efficacy. Reviewers examine adverse events and serious adverse events at regular intervals during the course of the trial. In addition, a DSMB monitors recruitment, randomization, retention, adherence, and follow-up in an effort to evaluate the validity of a trial. Because it is unethical to expose a participant to the risks of an experiment that will be unable to answer the scientific question that was postulated, a board should also evaluate the study protocol prior to trial commencement. Ultimately, a DSMB's responsibilities are broader than that of the trial being monitored. It will protect potential study participants and eventually could affect patients seeking clinical treatment for the disorder being studied.

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The randomized clinical trial (RCT) is the standard for treatment evaluation. The science of the RCT design, implementation, and analysis has advanced considerably since the initial psychopharmacology trials of 6 decades ago. The development of ethical standards initially lagged behind the trial methodology. For example, the US Food and Drug Administration (FDA) first required that all study participants provide informed consent in trials included in regulatory submissions in 1962.[1] In 1964, the Declaration of Helsinki set forth ethical principles for human experimentation. Fifteen years later, the Belmont Report outlined the ethical principles that are the basis for the federal regulations for protection of human subjects in the United States.[2]

Independent data and safety monitoring boards (DSMBs) have monitored intervention trials since the 1960s.[3] Trials in cardiology, oncology, and infectious disease were at the forefront of this effort. However, it was not until more recently that DSMBs became widely used in studies of psychiatric interventions. In 1998, the National Institutes of Health (NIH) issued a policy that required DSMBs for "multi-site clinical trials involving interventions that entail potential risk to the participants … The method and degree of monitoring needed is related to the degree of risk involved."[4] The first NIMH DSMB was formed in 1998 to monitor large trials such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D),[5] Clinical Antipsychotic Trials of Intervention Effectiveness for Schizophrenia (CATIE),[6] and Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).[7] There are now 3 independent NIMH-administered DSMBs that monitor the clinical trials funded through contract or cooperative agreement mechanisms. The current NIMH policy, which was issued in 2005 and revised in 2007, specifies "an extramural investigator-initiated NIMH-funded intervention study must establish a data and safety monitoring plan commensurate with the risks, complexity, and nature of the trial."[8] This applies to medication and psychotherapy trials alike. Detailed monitoring plans must be submitted to the NIMH and to the investigator's institutional review board (IRB) as part of the protocol prior to commencing the study. Most of these trials are monitored by study-specific DSMBs, not by a National Institute of Mental Health DSMB.

With the development of the National Institute of Mental Health's DSMB policy came a proliferation of monitoring boards for psychiatric interventions research. This in turn has spurred demand for board members. Undoubtedly, each monitor must be experienced with design and implementation of RCTs and some must have expertise in the disease area of focus or in biostatistics. Yet the objectives of monitoring a trial are quite different from those of designing or implementing a trial. There are unique facets of trial monitoring that are not necessarily learned from trial experience. In fact, some aspects of monitoring are diametrically opposed to standard clinical trial conduct. For instance, the blinding of investigators, raters, and study participants to the randomized treatment assignment serves a critical role in conducting an RCT, reducing the risk of a biased estimate of the treatment effect. Yet unblinded data provide

Clinical Points

- A data and safety monitoring board is not only concerned with participant safety and trial integrity, but ultimately could protect patients seeking treatment for the disorder being studied.
- Placebo adverse event data provide safety monitors with background event rates. Those rates are compared with rates among participants randomized to the investigational agent.

safety monitors with essential information for assessing risk. Although safety monitoring may well seem intuitively obvious to trialists and clinicians alike, DSMB members are seldom trained to monitor. This is unfortunate because lack of understanding of a DSMB's objectives and procedures can adversely impact the quality of monitoring and, in turn, jeopardize the safety of the trial participants and validity of trial results.

The general rationale for a monitoring board is to ensure the integrity and validity of the trial and, most importantly, to monitor the safety of study participants. Comprehensive publications on safety monitoring are available and all DSMB members and aspirants alike are strongly encouraged to read at least 1 of 2 documents prior to monitoring.[3,9] The objective of this commentary is to consider the purpose of a DSMB for psychiatric intervention research in some detail and to describe its roles, responsibilities, composition, and implementation. Monitors of clinical trials in various areas of medicine have some shared and some unique sets of concerns. Monitors of trials in oncology may be more focused on medical deterioration, whereas monitors in psychiatry must be sensitive to psychosis, metabolic syndrome, and suicidal ideation or behavior.

Purpose of a DSMB

Monitoring boards are called independent data and safety monitoring boards, data monitoring committees, safety monitoring boards, and permutations of these words. They monitor the accumulating unblinded data for safety and, in some trials, for efficacy. A DSMB's primary purpose is to protect the safety of RCT participants. This involves comprehensive reviews of adverse events at regular intervals during the course of the study. The board is also expected to protect credibility and validity of the study by monitoring recruitment, randomization, retention, adherence, and follow-up. In addition, a board should facilitate timely dissemination of reliable results to the clinical community.[9]

Oversight Boards for RCTs

There are several types of oversight boards for clinical research, including the institutional review board, a scientific advisory board, and the DSMB. Some trials include an endpoint adjudication committee[10] or site monitoring committee. Each of these serves complementary roles, with some shared responsibility.

When Is a DSMB Needed?

Not all RCTs in psychiatry require a DSMB. One should be used when studying an intervention with prior safety concerns, a fragile population, or a group at risk of serious morbidity or death. Large studies, multisite studies, and studies of long duration should also have a DSMB. However, DSMBs are not mandated by the FDA, except in an emergency research study that has an informed consent waiver. Nevertheless, DSMBs have become a standard component of large industry-funded trials of psychopharmacologic interventions for over a decade. As stated earlier, the NIMH requires DSMBs for all phase 3 clinical trials and for all multisite trials.

DSMB Composition

A DSMB is a multidisciplinary group of scientists that is independent of the investigators, the study, and the sponsor. It must include clinicians in the medical subspecialty studied in the trial and a biostatistician. If necessary, an ethicist, an epidemiologist, a pharmacologist, a toxicologist, or a patient advocate will also be included on a DSMB. The minimum number of members on a board is 3, yet they are often larger. All DSMB members must commit to serve until the trial is completed. In the exceptional case, when a member must resign, the DSMB will decide whether to identify a replacement and, if needed, recommend names to either the study principal investigator or the study sponsor.

Independence

The DSMB must make unbiased, objective recommendations. All members will disclose potential conflicts of interest. Each board member must be independent of the sponsor, with no vested interest in the outcome of the study. Board members must be objective, not influenced by financial or intellectual conflicts, not involved in study design, and neither a study investigator nor affiliated with an organization that is a study site. Members must not have a relationship with a trial investigator that could be perceived as affecting objectivity. The purchase of equity in a pharmaceutical or device company by a DSMB member who has seen relevant confidential, unblinded results is not only inappropriate but a potential violation of security regulations.

An honorarium should be provided to each DSMB member to compensate for the time, expertise and the effort devoted to each meeting.[9] This will reduce the temptation for the study sponsor, study investigator, and DSMB members to trade favors, which could adversely affect objectively. The NIH and foundation grant applications must include a budget line for data preparation and to compensate DSMB members. In an effort to achieve full transparency, each article that reports results from a trial monitored by a DSMB should mention each member in the acknowledgments.[9] In contrast, board members should not be included

as authors of publications that report results of trials that they monitor.

DSMB CHARTER

The purpose of a DSMB charter is to define standard operating procedures for monitoring a particular trial. The board's structure and function is delineated in the charter. The charter also describes the roles and responsibilities of the DSMB, principal investigator, sponsor, and the data management and statistical data analysis centers.

The charter describes the board membership with names and contact information, the timing and purpose of meetings, and procedures to ensure confidentiality. The charter also includes statistical monitoring guidelines, a description of safety analyses, and report templates. If interim efficacy analyses will be conducted, the criteria are delineated in detail. The charter will specify who will prepare, distribute, and maintain the DSMB reports and minutes of the DSMB meetings. An excellent DSMB charter template has been presented elsewhere.[9]

DSMB MEETINGS

Ideally, the first DSMB meeting will take place prior to trial commencement, allowing time for protocol review and planning of monitoring procedures. A DSMB should determine if, on the basis of the protocol, there are undue risks to participant safety or study integrity. It is imperative that the study principal investigator or sponsor allow sufficient time from funding notification to participant enrollment to allow the DSMB to provide feedback on the protocol. If possible, this feedback should be given before the institutional review board (IRB) reviews the protocol to avoid the need for supplementary IRB review and before the first participant is randomized. It is also at the initial meeting that the DSMB charter and DSMB report templates are reviewed and modified as necessary.

The board will monitor study conduct and evaluate whether the ongoing study can answer the research question. It is unethical to expose participants to the risks of an experiment that will be unable to answer scientific questions posed by the investigator. For that reason, participant accrual is routinely reviewed to determine if enrolling the target number of participants appears to be feasible. If the proposed sample size is deemed infeasible, the planned level of statistical power is compromised. The board can recommend changes in recruitment strategies such as advertising more extensively, adding new sites, dropping poor performing sites, or, in extreme cases, terminating the study. Each meeting after the start-up will include open and closed sessions. Often these meetings are conducted by teleconference, but occasional face-to-face meetings prove to be more productive. Minutes must be kept separately for open and closed sessions. The latter are to be archived but not distributed to non-DSMB members until trial completion.

Open Session

Attendance at the open session includes DSMB members, the unblinded statistician, and either the sponsor or the principal investigator along with other trial personnel. The DSMB receives an update on trial progress, including issues such as recruitment and retention. Abbreviated case listings of serious adverse events are described in a blinded fashion. Presentation of primary and secondary efficacy results, even if aggregated, is inappropriate at the open session because, among other reasons, the risk-benefit profile could be inadvertently revealed.

Closed Session

The closed meeting will include only DSMB members and perhaps the unblinded biostatistician. The unblinded DSMB report (described below), in which the actual treatment assignments are identified, not simply masked codes, must be carefully reviewed by each DSMB member prior to the meeting. (The rationale for unblinded reports is discussed below.) Data and safety monitoring board members discuss the report during the closed session. It is during the closed meeting that the board considers recommendation options and voting takes place.

Confidentiality of interim results is critical. Data and safety monitoring board members must not reveal any interim safety or efficacy results to non-board members. Interim analyses must not be used in a way that threatens the scientific integrity of the trial. For instance, unblinded interim results (eg, effect sizes) cannot be used to plan a new study because that could sacrifice the ongoing study for a future, as yet hypothetical, study.[11]

Board Recommendation

The outcome of deliberations at each board meeting is to recommend 1 of the following actions: (1) continue the trial as designed, (2) modify the trial, (3) temporarily suspend recruitment, or (4) terminate the study. The recommendation is advisory and made for the study sponsor, although, in NIH-funded studies, it is typically delivered by way of the study principal investigator. Recommended modifications might involve consent procedures, data management, treatment regimens, inclusion/exclusion criteria, or need for additional sites. The recommendation is based on the consensus of the board. A board's decision should be terse, revealing nothing about interim results (eg, alarming QTc signals) unless absolutely necessary. A common error among board chairs is to refer to specific safety signals that raised questions. Instead, an example of a board's recommendation could read, "After review of the cumulative evidence, the DSMB found no cogent reasons to recommend alteration or termination of the trial."

DSMB REPORT

A DSMB report is issued to the board members in advance of the meeting, allowing ample time for careful review

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(eg, 10–14 days). There are several essential components of a DSMB report. (Each boldface heading that follows, except Unblinded Versus Masked Reports, can be thought of as a separate section of the report.) The report must be based on the most timely data that can be reasonably expected, perhaps data from 4 to 6 weeks prior to the meeting. (The date of data extraction should be clearly indicated throughout the DSMB report.) An evaluation is based on accumulating evidence from 1 *or more* ongoing trials. Although more burdensome, the responsibility for the monitoring of multiple trials of the same intervention provides a greater number of participants exposed to risk of the trials, and, therefore, a better opportunity to detect risks—particularly for rare events. Multiple trials of an intervention would most likely come from an industry-sponsored program such as that of asenapine involving well over a dozen trials.

Synopsis of the Study Design

A brief synopsis of the trial design will present inclusion and exclusion criteria, primary and secondary objectives, outcome measures and assessment schedule, planned sample size, randomization allocation ratio, study drug doses, timing of administration, and duration of treatment. For example, the synopsis might begin by stating, "This is a randomized, double-blind, parallel group study designed to evaluate the efficacy, safety, and tolerability of treatment for 4 weeks, with 2 fixed doses of drug X compared with placebo in acutely manic subjects with bipolar disorder."

Unblinded Versus Masked Reports

The design and implementation of an RCT require blinding of study participants, clinicians, assessors, and other investigators. Blinding is a fundamental characteristic that reduces bias in reporting symptoms, rating illness severity, and determining whether to withdraw a participant from a study. Monitoring, on the other hand, requires that the DSMB have complete access to treatment status. Masked data (eg, treatment A vs treatment B) deny the DSMB the ability to monitor competently, and that limitation, in turn, poses risks to participant safety.[12] For that reason, the DSMB report must identify randomized treatment assignment, not masked codes.[9] (Masked reports are acceptable only if DSMB members are provided the treatment codes in a separate document prior to the review.) Consider, for instance, the difficulty in evaluating a dose-response–associated risk without unblinded information.

There are critics of unblinding who believe that it interferes in the objectivity of the monitor, particularly in highly contentious areas. In such cases, monitors can request to be blinded to the study findings to avoid any potential bias. Yet such an approach fails to differentiate the goals of RCT implementation and the goals of safety monitoring. I believe that blinding handicaps the monitor and, as a result, jeopardizes participant safety.

There is reasonable concern that unblinded results could affect subsequent portions of a trial and that the board is obliged to protect study integrity.[13] However, the DSMB is charged with the responsibility of protecting study participants and ensuring validity and integrity of the trial. This can be accomplished only with full access to treatment assignment. Clearly, study investigators must not have access to interim results before trial completion. Safeguards must be in place to prevent unblinded results from leaking beyond the board and the unblinded statistician. Each DSMB member must sign and strictly adhere to a pledge of confidentiality. Either an independent statistician or an internal study statistician will conduct analyses. If the latter is used, that individual cannot be involved in subsequent decisions to modify the study in any manner.[14]

Participant Accrual and Disposition

The report will describe subject accrual and disposition. Accrual is typically presented in a CONSORT-type flowchart that indicates the number and percentage of patients screened and consented, the number eligible and ineligible, the number randomized to each intervention arm, the number who withdrew from the study and the number who completed, separately for each arm.[15] Recruitment and retention are also presented by site, unless sites are so numerous as to render site-specific rates infeasible or uninterpretable. Attrition can interfere with the goals of a clinical trial by introducing bias into the estimate of the treatment effect and reducing statistical power, feasibility, and generalizability.[16] Furthermore, attrition could be a sign of an intolerable treatment. Therefore, it is for participant safety and study integrity that a board must examine participant retention and reasons for early study termination.

Status of Randomized Subjects

The report should indicate the number and percentage of subjects in each treatment arm who are currently on each treatment, completed treatment, and discontinued during treatment.

Reason for Early Discontinuation

The number and percentage of subjects in each treatment arm who discontinue and the various reasons for discontinuation will be delineated. These reasons include protocol violation, adverse event, insufficient clinical response, study commitment time unacceptable, lost to follow-up, withdrawal of consent, and administrative reason. The latter 2 categories are overly inclusive and tend to be uninformative. Therefore, those categories should be used only when other reasons are inaccessible. The more specific the reasons for discontinuation that are presented, the better it is for trial monitoring.

Baseline Characteristics

Baseline clinical and demographic characteristics are presented stratified by treatment group to allow an evaluation of the extent to which randomization achieved balance between groups. The mean, median, standard deviation, and

sample size are presented for continuous measures, whereas percentages and frequencies are displayed for categorical variables. Box and whisker plots are an especially useful manner of displaying group-specific percentiles (10th, 25th, 50th, 75th, and 90th) for continuous measures.

Protocol Deviations

Data and safety monitoring board reports often include a listing of protocol deviations. For instance, the percentage and number of assessments that took place outside of the permissible window of time (eg, day 14 ± 3 days) might be displayed weekly and in aggregate over time for each treatment group. Likewise, the number of randomized participants who did not meet inclusion criteria or who did not adhere to the assigned study intervention is presented.

Safety

The focus of the review is to monitor comparative safety; therefore, safety is covered extensively in a DSMB report. The frequency (percentage), severity, and "relatedness" of adverse events and serious adverse events are presented separately for each intervention arm, typically using the Medical Dictionary for Regulatory Activities (MedDRA) codes.[17,18] The MedDRA is a standardized medical terminology developed by the International Conference on Harmonisation "to classify adverse event information associated with the use of biopharmaceuticals and other medical products"[17] that has been adopted by the FDA and the European Medicines Agency. (MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations.) The MedDRA codes are readily applicable to studies of psychopharmacologic, psychotherapeutic, and device interventions

"An adverse event is any undesirable experience associated with the use of a medical product in a patient."[19] An adverse event must be reported whether or not it is attributable to the investigational agent. It is the role of a DSMB to use the accumulating evidence to identify a pattern of elevated rates of a particular adverse event associated with an intervention. The term *side effect* is not used because it implies causality, whereas *adverse event* does not.

A *serious adverse event* is defined by the FDA as an event that is life threatening; requires a new or prolonged inpatient hospitalization; results in death, persistent or significant disability, or congenital anomaly; or requires an intervention to prevent 1 of these events.[19] Individual serious adverse event reports should be distributed to DSMB members on an ongoing basis and not accumulate unreported until each DSMB meeting. Serious adverse events are also reported to regulatory agencies and IRBs, as required. However, it is generally only the DSMB that is told of treatment assignment during an ongoing trial. A participant who experiences a serious adverse event should not necessarily be excluded from the trial. Monitors, if asked to mediate such a decision, must examine the serious adverse event with careful consideration of study entry criteria and trial integrity. Clearly, if further participation will most likely result in participant's mortality or irreversible morbidity, termination from the study is critical.

The interpretation of safety results is much enhanced with data from a placebo group because those data, in essence, provide a benchmark—an estimate of background event rates for the patient population (ie, those meeting study inclusion criteria). For example, some participants will contract influenza regardless of randomized treatment assignment. Similarly, falls due to vertigo could very well be a function of age or the illness, or could in fact be due to the investigational intervention. Placebo data allow safety monitors a means by which to disentangle such information.

The comparisons typically involve informal examination of rates of each MedDRA code that was reported. However, some reports present *P* values for group comparisons. Although these are helpful for identification of signals of risk in a voluminous report, a series of multiple *P* values ignores the inflated probability of false-positive results. Therefore, unless bona fide interim analytic approaches are employed (discussed below), *P* values must be interpreted as guides to facilitate safety signal detection, not as definitive inferential results.

Treatment-Emergent Serious Adverse Events

The report will include case listings for each serious adverse event that took place after randomization. Evaluation of serious adverse events should be done with careful consideration of entry criteria. This presentation will include subject identification number, system organ class, MedDRA-preferred term, randomized treatment, treatment at onset of serious adverse event, study days that it commenced and ended, severity, outcome, action, and causality. The latter refers to the site investigator's attribution of whether the randomized treatment was the cause of the serious adverse event. Data and safety monitoring board members must understand that the attribution is not at all definitive due to the wide variability in training and objectivity across investigators.

Shift tables provide a succinct approach that facilitates detection of a pattern of changes from normal to abnormal laboratory values. This approach might be used to detect treatment-emergent metabolic syndrome in a trial of antipsychotics. These tables display a cross-classification of discrete baseline laboratory values (eg, abnormally low, normal, abnormally high) with endpoint (or other post-baseline) values. Operational definitions of "abnormal" must be provided as footnotes in such a display.

Efficacy

In some clinical trials, but only a small minority in psychiatry, comparative efficacy is also examined by the DSMB. In such a case the board considers whether, based on available evidence, potential benefits appear to outweigh risks. What determines whether efficacy must be monitored by a DSMB? If the treatment is being tested to reduce mortality or serious

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morbidity, efficacy monitoring is necessary. For example, a study of an intervention to reduce suicidal ideation and behavior must have a DSMB that monitors efficacy, even if it is conducted as a single-site study. If the board determines that one treatment is noticeably inferior to the other, it has an ethical obligation to terminate the trial. It is only with the inclusion of efficacy analyses that safety risks can be fully put into context. The integration of risk and benefit provides the DSMB an opportunity to tolerate a safety risk that might, in isolation, seem unacceptable.

Results of interim analyses can be used to support early stopping for either efficacy or safety issues. However, multiple testing raises concerns about interim analyses, unless the risk of false-positive results (type I error) is properly controlled. Methods to control type I error are well established.[13] Group sequential methods can be used for repeated, planned, interim tests of the efficacy or safety hypotheses as trial data accumulate and, at the same time, can provide an effective strategy to minimize the risk that DSMB recommendations are based on false-positive or false-negative conclusions.[20] For instance, planned analyses might be conducted after 25% and 50% of the proposed sample size have completed the study. Group sequential boundaries[21] use very stringent stopping rules early in a trial when results are most unstable and imprecise due to the limited number of data points. Stopping criteria become less conservative as the trial progresses and the results tend to fluctuate less. Alternatively, an α spending function approach to group sequential methods has the advantage of not requiring the DSMB (or the investigators) to prespecify the exact number and timing of the interim analyses.[22]

Another approach involves interim futility analyses, which examine conditional statistical power.[23] This approach addresses the following question: On the basis of evidence to date, what is the probability that a true (population) treatment effect would be detected if the trial were to be conducted in full? The risk with such a strategy is premature termination of a trial and, perhaps, termination of the development of an intervention that is based on a false-negative result (type II error). For these reasons, futility analyses typically choose extreme criteria for stopping rules (eg, the trial will terminate early if conditional power is no more than 20%).

DISCUSSION

An independent DSMB is needed for studies of psychiatric interventions with participants at risk of death or serious morbidity, interventions with known safety concerns, multisite studies, trials of long duration, and other criteria, as mandated by NIH and NIMH policies.[4,8] A DSMB monitors clinical trials to protect the safety of RCT participants, the credibility of study, and the validity of study results.

Each DSMB member will review and evaluate the DSMB reports and vote on recommendations. The focus is to scrutinize the comparative safety data by examining the adverse events and serious adverse events. Data from the placebo or other comparator group are invaluable for this purpose because they provide the base rates (ie, levels that might be expected in lieu of the novel intervention). It is essential that DSMB members have access to unblinded data. The monitors are also responsible to assure that the study is well executed such that, if the investigational intervention is superior to the comparator, ideally the results will be known.[24] Therefore, the DSMB also monitors recruitment, retention, and participant disposition. After review of cumulative interim data and consideration of risk and benefits and the scientific integrity of the trial, the board will recommend continuation, modification, temporary suspension of recruitment, or termination of the trial.

Although monitoring primarily involves evaluation of study participants' data, other matters, such as variations in protocol implementation among sites, can reduce the validity of the trial results. Therefore, a DSMB may need to intervene in issues regarding study management and implementation that are critical to the trial. A DSMB may also be called upon for permission to drop a participant who, after being randomized, proves to be ineligible for the trial. For example, a participant's psychotic features might only become apparent 2 weeks into the trial. The DSMB must provide thoughtful guidance that is independent of the study investigator's influence.

It is critical that interim safety and efficacy results remain confidential. An investigator might ask a DSMB to sanction release of interim results to support a subsequent grant application. However, premature dissemination of interim results, even if limited, could impact recruitment, retention, delivery of the intervention, assessments, or other aspects of trial conduct. Release of such information should not take place. Trial integrity is threatened if interim results are made available to anyone beyond the DSMB and the unblinded statistician conducting the analyses.

A DSMB is charged with ensuring the integrity and validity of a study and protecting participants enrolled in a clinical trial. Yet a DSMB's impact extends beyond the trial that is monitored. It will ultimately protect patients with the disorder under study, whether potential study participants or, more broadly, patients eventually seeking clinical care with the intervention being evaluated.

Drug names: asenapine (Saphris).

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