Data Safety Monitoring Boards: Overview of Structure and Role in Spinal Cord Injury Studies

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This paper provides an overview of the history, composition, organization, responsibilities, and regulatory requirements of Data Safety Monitoring Boards (DSMB), with particular reference to the context of clinical trials in spinal cord injury. It is intended to help potential members of such boards and those undertaking the design of new clinical trials to understand the important role of the DSMB in safeguarding the integrity of complex trials, promoting safety, and countering potential bias. An independent DSMB helps to protect research subjects by providing study oversight and serves as an additional step to assure that clinical trials are performed to existing and appropriate standards. The DSMB must meet on a regular schedule, diligently evaluate all the information it receives, and report in a timely and decisive manner. Members must be free of significant conflicts of interest throughout the study and be adequately trained and experienced to serve their roles within the group. DSMB service can be a valuable learning experience and a gratifying opportunity to participate in advancing medicine and helping to maintain and improve the standards of research. **Key words:** *bias, clinical trials, data monitoring committee, development, patient safety*

Origin of the DSMB

Appropriate monitoring of study quality and participant safety are essential elements of all clinical studies, and responsibility for them should be incorporated into clinical trial design. At the heart of this monitoring is the need to balance potential risk and benefit for the individual and the community. The practical and ethical challenges posed by that need will depend on the nature and complexity of a particular study and its goals, but they are greatest for large, blinded trials with significant, known safety risks and extended recruitment and/or treatment periods.[1,2] Such trials are typically designed to provide at least an interim answer to a question such as, "Is intervention X safe and effective for the treatment of condition Y, such that its benefits outweigh its risks?" The conundrum for those responsible for trial oversight lies in the fact that the answer to the question is usually not possible to assess reliably and with sufficient statistical power until the trial has been completed. That leaves the safety of the participants somewhat open to interpretation, based on necessarily limited historical information, while the trial is going on. It is important to do everything we can to avoid the risk of bias in that interpretation, and the potential for bias should never be underestimated.

Although *all* trials with human subjects must be monitored continuously for safety by those responsible for their performance, that monitoring and its oversight will vary with the stage of development and complexity of the study. For early stage, typically unblinded, studies with small participant numbers, it may be sufficient for a single, qualified "medical monitor" (usually an independent, contracted physician) to provide the oversight. Such a person would be provided safety data at agreed upon intervals as it is entered and reported by the study coordinator/manager, with particular urgency around serious adverse events (SAEs) and their attendant reporting deadlines. However, beginning with large-scale, government-sponsored trials in the 1960s, it has become gradually more standard for studies meeting certain levels of complexity or

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risk to have a dedicated *independent committee* (in addition to or in lieu of an independent medical monitor) to review blinded and unblinded data as they accumulate during the study. Such committees will look particularly for signals that might not be readily apparent to the study team or the medical monitor regarding the performance of the study and for emerging safety and efficacy signals. These committees are often referred to as Data and Safety Monitoring Boards, or DSMBs.

The International Council for Harmonization (ICH) Good Clinical Practice Guidelines define a DSMB as "an independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial."[3] The acronym is sometimes interpreted as "Data Safety Monitoring Board" though, clearly, they are not concerned with the safety of the data but with monitoring the data with particular concern for the safety of the study subjects or participants. The shorter title of Data Monitoring Committee, or DMC, may also be used interchangeably, but DSMB remains the dominant and perhaps preferable term.

Recommendations for the formation and management of DSMBs may be obtained locally, as from the Institutional Review Board, but they may also come from government agencies, such as the US Food and Drug Administration (FDA)[4] and the National Institutes of Health (NIH),[5] from corporate sponsors, or others. For example, the US Department of Defence requires a formal monitoring plan and independent research monitoring for FDA-regulated studies or those with greater than minimal risk[6] while NIH requires a DSMB for "multi-site clinical trials involving interventions that entail potential risk to the participants."[5] The FDA itself does not require the use of a DSMB except in the case of "research in emergency settings in which the informed consent requirement has been excepted."[4] In some cases, individual institutions may charter their own DSMBs for the oversight of academic research, independent of external sponsorship.[7]

Role of the DSMB

The concept of the DSMB is that it will be empowered to monitor the conduct of a trial, first to make sure that it is proceeding according to the approved protocol and then to look for signals in the data stream that raise potential concerns. These will include any evidence that the intervention is unsafe or, at the other extreme, that it is so overwhelmingly effective that it could be unethical to continue the study and withhold its benefits from those outside the treatment group. Meaningful evaluation of the data generally requires it to be unblinded with respect to treatment assignment, which adds to the importance of the DSMB's independence from those sponsoring, managing, and performing the trial (see **Appendix,** Case 1).

Information supplied to the committee must be organized carefully and confidentiality by the clinical research team itself such that only those responsible for holding the randomization codes have access to them. Any information supplied by the DSMB back to the trial staff must also be carefully censored so that it does not risk unblinding the study staff, investigators, or participants.[8] All these considerations mean that the selection and authorization of the DSMB function and its communications are some of the most delicate aspects of clinical trial management. Wherever possible, the written charter supplied to the DSMB from the outset must be designed to manage problems proactively rather than reactively.

When Is a DSMB Required?

Trial safety monitoring should reflect the risks, complexity, and size of the trial. Recognizing that a DSMB (DMC) "adds administrative complexity to a trial and requires additional resources," the FDA Guidance[4] states that:

> …DMCs have generally been established for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome, such as a cardiovascular event or recurrence of cancer. DMCs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity, *but a DMC is not required or recommended for most clinical studies*. DMCs are generally not needed, for example, for trials at early stages of product development. They are also generally not needed for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes. [emphasis added]

A short summary of the Guidance regarding factors to consider with respect to the advisability of incorporating a DSMB includes the following:

- The study might ethically require termination before its planned completion.
- There are a priori reasons for a particular safety concern.
- There is reason to expect serious toxicity with the treatment.
- The study is being performed in a particularly vulnerable population or a population at elevated risk of death while the study addresses a lesser endpoint.
- The study is large, of long duration, and multi-center.

The presence of a DSMB can benefit the sponsors of trials by providing an independent and objective review that can increase the credibility of the study and the decisions made during the trial involving modification of its design, for example, if a protocol revision is necessary. It will also provide them with valuable alternative views and interpretations of data that can be taken into account before such decisions are made. On the other hand, the DSMB is not usually involved in operational aspects of executing the protocol, so that its function of monitoring progress would tend to be similar for a classical randomized controlled trial or for a more innovative adaptive trial design.

As noted previously, individual funding agencies may require a specified level of study safety monitoring, ranging from primary investigator (typically low-risk, investigator-sponsored trials), an independent medical monitor (low to moderate risk), or a DSMB (high-risk and/or complex trials). Guidance and examples can be found on individual government websites. For federally sponsored trials, the requirement for a DSMB may occur as a result of reviewer/program recommendations. The Harvard Catalyst Group has provided a sample algorithm with suggested levels of monitoring.[9]

Specific Issues for the DSMB in Spinal Cord Injury Research

Some issues encountered by a DSMB depend on the nature of the clinical target. There are concerns that affect mortality studies in cancer research that would not be relevant to SCI. Within the field of SCI itself, there are differences between an acute, neuroprotective intervention study and a trial of a chronic intervention aimed at repair. These include the time pressures on enrollment of individuals into an acute study, the uncertainties around acute prognosis, and the simultaneous need for complex medical and surgical care. Yet some considerations would be shared. Both acute and chronic SCI are accompanied by clinical problems and adverse events that may be difficult to assess for treatment-relatedness. Patients experience numerous medical complications in acute SCI.[10] Extensive experience may be needed to interpret these events in the context of the experimental therapeutics (one example being an infusion reaction in acutely injured persons receiving assisted ventilation).

Many clinical outcome measures are partially subjective and show spontaneous variability. There is temporal delay between initiation of an intervention and any expected change in clinical outcome. This limits the ability to perform meaningful ongoing analysis of efficacy or ultimate safety. DSMB tasks are made easier with experience, and fields where trials have been frequently performed will benefit. Larger, late-stage trials have been infrequent in SCI, and there is limited experience on which to draw. SCI is also the target of invasive interventions involving direct manipulation of neural tissue, such as cellular transplants, biomaterial insertion, and placement of electrical stimulators, that require particularly rigorous and long-duration safety evaluation.[11]

Composition of the DSMB

The DSMB should include a relatively small number of individuals who combine between them the range of skills and experience required for evaluation of the study data. Typically, three or five members would provide for sufficient diversity and avoid tied opinions. These may be interested volunteers assembled for a particular trial or be organized as a tailored professional group that specializes in providing such expertise. Ideally, some of the members, particularly the chair, will have DSMB experience. Members may receive compensation, but the compensation must be modest to avoid bias and conflict of interest.

The independence of the group should be assured during the selection process, particularly with respect to any personal financial or

reputational involvement in the research program or with its sponsors. Following standard guidelines for independence such as those of the National Institute for Mental Health, members should not be "collaborators, co-authors, supervisors, mentors or mentees, subordinate of the investigators, or a member of the investigator's institutional department within the last three years."[12] Ideally, members are from a different institution than the investigator or one another. Independence needs to be confirmed and documented with conflict of interest and confidentiality agreements from the beginning and periodically confirmed during the performance of the trial. However, it is important to note that absolute independence is neither possible nor advisable[4] given the interconnectedness of clinical research and the fact that the DSMB is usually appointed by and remunerated through the sponsor.

The skills of individual members of the group should include a knowledge of interpretation of condition-specific outcome measures, good clinical practice, and clinical medicine, particularly familiarity with the tools used to monitor safety, including vital signs, blood and urine tests, and adverse event reporting. Specialist medical knowledge will also be valuable, related both to the study population and to any expected safety concerns with the planned intervention (e.g., if there are expected cardiovascular or neuropsychiatric side effects from a particular drug). Additionally, in the case of SCI, an understanding by at least one member of a DSMB of what would constitute normal neurological recovery or deterioration is essential. Specific expertise may be required depending on the trial, such as surgical, radiological, immunological, or rehabilitative.

Typically, the majority of DSMB members are physicians, but nonphysician members may be sought with expertise in outcome measures or other features relevant to a particular study. Although one typically considers DSMBs for drug, biologics, or device studies, there may be instances in which a DSMB would be beneficial for a rehabilitation study, which would influence the make-up of the DSMB. Those providing medical oversight should be appropriately licensed and credentialed.

Experience with clinical trials and their propensity to generate unexpected events will be valuable on the team, and a member with specific expertise in statistical inference will be essential. Most clinicians and bio-scientists have a working understanding of statistical methods, but they often lack a deeper appreciation for their limitations, especially in the context of ongoing analysis of a data stream. In particular, the impacts of multiple and repeated comparisons are generally poorly taught or understood, beyond a theoretical acquaintance, by most working scientists. This means that a well-trained and experienced statistician, capable of communicating clearly with nonstatisticians on the board, will be a valuable resource within the DSMB. In addition to the technical expertise outlined above, there may be circumstances that call for the inclusion of a trained ethicist or person with "lived experience." Finally, the DSMB is formed from a group of individuals with disparate backgrounds and likely strong opinions, based on their specific expertise, and therefore will require leadership from a chairperson with strong management and diplomatic skills and sufficient seniority to keep the team focused and bring decisions to resolution.

DSMB Charter

Outline templates for DSMB charters are available for adaptation to a new purpose. Most academic institutions and government agencies engaged in funding or regulating clinical research will have experience and particular requirements in this area, as will most industry sponsors. Many elements of the DSMB charter will be generic in nature, such as membership and responsibilities, meeting frequency, materials and format, timeframe for SAE reporting and DSMB response, and timeframe and content of DSMB reports to the investigator or sponsor.

The charter also includes study-specific requirements. "Stopping rules" may need to be defined for the committee before the trial starts. These may be based on a calculation of what would constitute an unacceptable imbalance of adverse events developing between treatment groups or a signal, based on efficacy data, that it would be futile or unethical to continue recruitment with respect to the established goal of the study. The latter is a circumstance more common in mortality studies, for example, in oncology. Although there

may be studies in which the DSMB does not need to consider efficacy signals in its deliberations, efficacy measures in the case of SCI will also usually constitute important safety information relative to the neurological status of the participants. Stopping rules will define the circumstances under which the board would be required to advise the sponsors to suspend or terminate the trial, though the ultimate decision will remain with the sponsors, usually in dialogue with the relevant regulatory body (see **Appendix,** Case 2). They will also often include options for suspension of a part of the trial, such as a particular treatment arm[13] or a change in some aspect of the protocol, such as the recruitment criteria.

Other examples of study-specific charter adaptations are those for trials with more intensive monitoring, such as DSMB review between dose escalation cohorts or, for particularly high-risk trials, between each enrolled participant.

DSMB Responsibilities

The first responsibilities of the DSMB begin before study initiation; these will include review of the DSMB charter, study protocols, investigator brochure, informed consent forms, case report forms, manual of procedures, and other relevant documents. Any updates to these documents, such as protocol amendments, should similarly be made available for DSMB review prior to implementation. This is a critical stage at which recommendations for trial, DSMB charter, and format of DSMB material modifications should be considered and implemented, as needed. Once the study is approved and underway, the DSMB will perform periodic reviews of the accumulating study data, including available demographics; endpoint and safety data; participant recruitment, retention, and compliance; and study conduct information. These data will be reviewed not just for indications of any efficacy and safety concerns but also for quality and adherence to the protocol and good clinical practice and for responsiveness to previous recommendations. In the event of serious complications, the DSMB may request additional data sufficient to understand events in detail and to frame recommendations. The DSMB may also consider external data that may impact the study.

The DSMB charter may specify reporting timelines to the DSMB for SAEs, which may require rapid review by DSMB members. Considering this, as well as other meetings with unplanned or short time frames (e.g. dose escalation, individual participant review), potential DSMB members need to consider their availability prior to committing to serve.

The primary responsibility of the DSMB is to act as an *independent* and *objective* monitor of all aspects of the study, to make sure, as far as possible, that the interests of the participants and the community that they represent are best served by it continuing to move forward as planned or with recommended modifications. At the same time, the DSMB is not empowered to act or interact independently outside its reporting relationship with the study sponsor or sponsor-investigator.

DSMB Meetings

The frequency of DSMB meetings, either in person or remotely, will be defined in the charter but will vary with the characteristics of the trial in question, particularly its overall duration, recruitment rate, and frequency of assessments. Meetings will usually be no less than semi-annual and may be significantly more frequent at the beginning of the study, particularly to assess the quality of data and the appropriateness of the arrangements for providing ongoing material to the board. The frequency may be greater for some types of trials in which a DSMB review may be required prior to dose escalation or in high-risk trials where review may be required after each subject is enrolled, at least in the early stages. The periodic meetings will normally include a closed session, available only to the members of the DSMB; this is particularly important in the case of blinded studies. Open sessions should be held before the closed session in order for the board to obtain current updates from the study staff and clarification of any issues and for the board to provide information to the sponsor's representatives. Such information must be carefully selected so that it does not risk disclosure of confidential DSMB material that could unblind the study. An open session following the meeting may also be included to provide additional feedback, though this may also be provided, for example, via email.

The material for DSMB review should be provided by the contract research organization, study coordinator, principal investigator, or designated statistician with sufficient time for thorough assessment by the DSMB members, usually 1 to 2 weeks before the scheduled meetings. Additional unscheduled meetings may be needed in the event of serious complications that require more timely responses, such as the unexpected death of a trial subject (see **Appendix,** Case 3).

DSMB Reports

A written summary report of findings should be provided by the DSMB chair (after review by all DSMB members) to the investigator or sponsor and Institutional Review Board, ideally within a few days of each meeting. Each report should include a recommendation on whether the study should continue as planned, be modified, or be terminated. As always, the DSMB report should be carefully edited to avoid releasing any information that might compromise the blinding or performance of the trial, unless such a release is deemed to be absolutely required for subject safety. Documents must be managed securely at all levels. The DSMB chair is responsible for recording the closed meeting discussion by the members. The chair will keep these closed session minutes until the end of the study and then provide them to the investigator or sponsor.

Legal Issues

One aspect of DSMB service that may be overlooked is that of legal indemnification.[14] Members of the board may be subject to subsequent lawsuits in cases where a litigant considers the DSMB may have contributed to a safety issue based on the appropriateness of their communications or actions, lack of action, or timeliness of action. There is no clear regulation of this matter, particularly because the government itself is bound by rules that prevent government indemnification. However, the contract between the study sponsors and the members or the overall DSMB contract organization should address this risk to provide legal protection for those serving on the board. Unless they are covered by their home institution, individual members may also wish to carry insurance to protect themselves from possible claims, as unlikely as these may be to succeed if the work is performed with appropriate diligence.[15] However, this does serve to highlight the great seriousness of the obligations undertaken by the DSMB and the importance of maintaining responsible conduct of the highest order.

Despite their contractual obligations to the sponsor, members of a DSMB remain responsible in cases where they become aware of questionable science, ethics, or other legal issues with execution or interpretation of a study in which they are involved. Such an issue can be raised internally to the board and the sponsor but, if not satisfactorily resolved, would have to be reported to the authorities for the case at hand. The most relevant authority would depend on the particular issue involved.

Advances in Safety Monitoring Technology

The reporting sequence from a clinical event through medical record and case report form to the sponsor allows opportunity for errors and delay. Current safety monitoring relies on human filters that include making a diagnosis, recording vital signs, and interpreting laboratory tests. Study personnel must extract this information to case report forms using predetermined descriptors (e.g., fever, headache, rash) that lack qualitative and quantitative granularity and context. The application of machine learning (ML) tools may increase the ability to cluster information and find associations of adverse event terms with more granular data to better appreciate the significance and linkages to other events.[16] Natural language processing (NLP) can be used to interrogate electronic health records with greater efficiency than a human assessor. NLP-detected events can be cross-matched to vital signs and lab tests. ML using NLP can also improve data quality through verification.[17] Platforms such as IQVIA AETracker and others are being developed to enhance pharmacovigilance through adverse event detection and reporting. ML has been used to develop decision-support tools to avoid errors and improve clinical decision-making in medicine.[18] These powerful tools may contribute directly to DSMB function and efficiency in the near future.

Summary

Independent DSMBs help to protect research subjects by providing study oversight, but they also

have a responsibility to the wider community to make sure that clinical trials are performed to existing standards. The DSMB must meet on a regular schedule, diligently evaluate all the information it receives from the study managers, and make sure that it is both timely and adequate to their needs. Members must be free of significant conflicts of interest throughout the study and be adequately trained and experienced to serve their roles within the group. DSMB service can be a valuable learning experience and a gratifying opportunity to participate in advancing medicine and helping to maintain and improve the standards of research. A well-functioning DSMB should be an asset to the credibility of a study, ensuring the safety of participants and ultimately of the community that will benefit from the study findings.

Conflicts of Interest

The authors declare no conflicts of interest.

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APPENDIX

Examples of Anonymized Case Studies

Case study 1: Unblinding of subjects due to elevated lab results

The Data Safety Monitoring Board (DSMB) may wish to request clarification on existing reports or additional information on data presented. If the DSMB members have a concern about adverse events (AE), serious adverse events (SAE), or laboratory data presented with regard to subject safety, the DSMB will evaluate the potential to request an unblinding of subjects enrolled in the study. This request will be made through the unblinded statistician and study team, and the sponsor will not normally be informed of the information produced, unless it becomes necessary. For example, if the DSMB sees there is evidence of a subject safety concern following their unblinded review of the individual subject's data and correlation between the AEs, SAEs, or labs, this will be discussed with the sponsor.

In a Phase 2, Randomized, Double-Blind, Placebo-controlled study to Assess the Efficacy and Safety of Study Drug X in Subjects with Acute Traumatic Cervical Spinal Cord Injury, the DSMB members were concerned with elevated lab results of several subjects. During their review of data listings provided for the scheduled DSMB meeting, it was noted that lab results for 15 of 25 subjects showed increases in their serum electrolyte (sodium and potassium levels) and blood urea nitrogen and creatinine following study visits. Several study investigators had deemed the lab results clinically significant (CS) and several others noted them as not clinically significant (NCS) during their reviews of the lab data. The DSMB was concerned with the reporting of the CS or NCS by the investigators and wanted to further review these data.

During this meeting, the DSMB members felt it was prudent to make the sponsor aware of this concern, and they requested subject treatment assignment information from the unblinded study statistician. During the DSMB closed meeting, the members and the unblinded statistician reviewed the randomization codes for those subjects with the elevated electrolytes and renal panel test levels. This review allowed the DSMB to see whether these 15 study subjects were receiving study investigational product (IP) versus placebo.

Following the review of the subject treatment groups against those subjects with elevated lab results, the DSMB members determined these elevated results were probably related to the study IP and recommended placing the study on hold to the sponsor. These elevated labs were noted to be in direct correlation to the administration of study IP, and the DSMB was concerned with possible kidney injury to the study subjects.

The sponsor, medical monitor, and DSMB met to review these data. It was decided to place study enrollment on hold and to consult a critical care renal expert for an advanced opinion. The renal expert advised that it was indeed likely that the study drug was responsible for the observed abnormal lab tests and that further drug administration could result in permanent kidney injury. At this point, the DSMB advised the sponsor to terminate the study and discussed how the study sites and FDA would be notified of their review and findings.

Case study 2: Unplanned interim analyses and the advisory role of DSMBs

In a randomized, controlled trial involving individuals with chronic spinal cord injury (SCI), the sponsor had included a planned interim analysis regarding the trend for efficacy when approximately two-thirds of the total number of subjects had complete (final evaluation) data from a 6-month follow-up. The endpoint was based on change in an ordinal measure, but the exact percentage of change and the estimated difference between groups used in the underlying power calculations were not made publicly available.

An unplanned interim analysis was conducted, under the sponsor's instruction, when evaluable data were available for less than half of the planned subject number. The analysis did not meet the preestablished futility threshold for the originally planned interim analysis, and only a slight trend in improvement in treated subjects compared to the control group was noted. The DSMB concluded that the safety profile was acceptable and the intervention was well tolerated. They recommended continuing the study, based on the absence of safety concerns, and noted that the unplanned interim analysis was severely underpowered for considerations of efficacy or futility. Nonetheless, the sponsor made the decision to discontinue the trial, based primarily on financial considerations.

The role of DSMBs in planned and unplanned interim analyses:

- Sufficient DSMB clinical and statistical expertise is required to execute this critical external oversight function.
- DSMBs have a role in interim review of safety, study enrollment, protocol compliance, and (when appropriate) efficacy data. In SCI, the neurological evaluations that generally provide efficacy endpoints are also usually relevant to safety, in the sense that these outcomes can worsen as well as improve.
- The simplest results of a planned interim analysis are early stopping of the trial for futility or significant positive results that meet preset criteria or suspension for significant safety concerns.
- A planned interim analysis may also lead to recommendations to modify aspects of study design, such as sample size, to deal with safety concerns or to optimize operations in other ways.
- An unplanned interim analysis is not part of the prespecified trial design and can be triggered by ethical and/or safety concerns, any unanticipated event(s) (e.g., unusually high drop-out rate or unusually low enrollment rate), or at the sponsor's discretion, as in this case.
- Interim analyses are challenging in many ways and generally should be avoided. Every time the data are reviewed, there is a reduction in statistical power and an enhanced likelihood of introducing both type 1 and type 2 errors of interpretation. Further, interim analysis can introduce bias in study oversight.

Case study 3: Case of mortalities in an SCI surgical study

A special DSMB meeting was called to review two sequential mortalities at a single center in a multicenter acute neuroprotection clinical trial of a surgically delivered intervention. The underlying cause of death was deep venous thrombosis (DVT) and pulmonary embolization complicated by respiratory insufficiency that led to multiple ventricular arrhythmias in one subject and by fatal pneumonia in the other. According to the trial-stopping rules, the trial was placed on hold while an investigation of the medical events occurred. At the time of hold, the trial had accrued 13 of a planned 40 subjects across six sites with no prior mortalities.

The DSMB sought to determine if there was a possible relationship between the spinal cord surgical intervention and the deaths. To make this analysis, detailed medical records were requested. In the investigation, some potential risk factors were identified. Firstly, both spinal surgeries associated with mortality had exceeded 10 hours in duration with large blood losses and intraoperative transfusion. One subject was 68 years old and the other was 52. One subject had a history of hypertension and a displaced femur fracture that was fixated in the same surgical session. The other had a high body mass index (BMI) and a smoking history. Neither had received anticoagulation prior to surgery.

After review, the DSMB determined that the deaths were not directly related to the clinical trial intervention but that the affected subjects had DVT risk factors and that failure to provide adequate perioperative anticoagulation could be a contributing factor, as well as age, BMI, and long bone fracture. Recommendations were provided to modify the clinical trial inclusion and exclusion criteria and to add a uniform DVT prophylaxis across the study. These were adopted by the trial steering committee.