

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**DATA AND SAFETY MONITORING
BOARDS IN NIH CLINICAL
TRIALS: MEETING GUIDANCE,
BUT FACING SOME ISSUES**



Daniel R. Levinson
Inspector General

June 2013
OEI-12-11-00070

EXECUTIVE SUMMARY: DATA AND SAFETY MONITORING BOARDS IN NIH CLINICAL TRIALS: MEETING GUIDANCE, BUT FACING SOME ISSUES OEI-12-11-00070

WHY WE DID THIS STUDY

A Data and Safety Monitoring Board (DSMB) is a committee of experts responsible for reviewing clinical trial data on an ongoing basis to ensure the safety of study subjects and validity and integrity of the data. Members should be independent, with no vested interest in a specific treatment. A DSMB reviews evidence of adverse events and interim treatment outcomes to recommend whether trials should be continued, altered, or terminated. To do so, a DSMB must have access to “unmasked” data during the course of a trial, meaning that members know which subjects are in which treatment group. This study seeks to determine the extent to which DSMBs met National Institutes of Health (NIH) guidance, identify any challenges to DSMB effectiveness, and contribute to the Office of Inspector General’s body of work concerning clinical trials and human subject protections.

HOW WE DID THIS STUDY

We reviewed the extent to which DSMBs met NIH guidance and identified any challenges to their effectiveness. According to general NIH guidance, DSMBs (which are composed of relevant experts) should meet regularly to review interim trial data and make recommendations concerning the trials’ continuation or termination. Our findings are based on the population of 44 NIH-funded Phase III multi-site clinical trials completed in 2009 and 2010 that entailed potential risk. We reviewed NIH guidance and DSMB policies; documentation regarding DSMB meetings, including membership rosters and recommendations; surveyed DSMB members and principal investigators; and interviewed NIH staff and DSMB stakeholders.

WHAT WE FOUND

DSMBs met general NIH guidance. They met regularly, and 91 percent of meetings resulted in a recommendation to NIH. DSMB members represented multiple disciplines and had significant experience. Most DSMB members identified themselves as either clinicians or as clinical trial experts. However, DSMBs face some issues. NIH participation in closed DSMB meetings diminishes the appearance of independence; not all Institutes and Centers (IC) policies reference DSMB access to unmasked data; and NIH faces challenges in recruiting and training DSMB members.

WHAT WE RECOMMEND

NIH should (1) direct ICs to articulate the circumstances in which IC staff should participate in DSMB meetings, (2) direct ICs to explicitly reference DSMB access to unmasked data in their DSMB policies, and (3) identify ways to recruit and train new DSMB members. NIH concurred with all three recommendations.

TABLE OF CONTENTS

Objectives	1
Background.....	1
Methodology.....	4
Findings.....	7
DSMBs are meeting NIH guidance in their roles as trial monitors	7
DSMBs face some issues that may affect their ability to fulfill their roles	9
Conclusion and Recommendations.....	12
Agency Comments and Office of Inspector General Response.....	13
Appendix: Agency Comments	14
Acknowledgments.....	17

OBJECTIVES

1. To determine the extent to which Data and Safety Monitoring Boards (DSMBs) met National Institutes of Health (NIH) guidance in carrying out their responsibilities to monitor trials.
2. To identify any challenges to DSMB effectiveness.

BACKGROUND

Clinical trials test experimental drugs, devices, and treatments to determine whether they are safe and effective. DSMBs are advisory committees of experts responsible for reviewing ongoing trial data. They play a unique role in ensuring the safety of human subjects enrolled in trials. They also play a critical role in ensuring the merit of these trials.¹ To carry out these functions, DSMBs must have direct access to “unmasked” data during the course of a trial, meaning that members know which subjects are in which treatment group—something the researchers and subjects themselves do not generally know. NIH requires DSMBs to monitor all Phase III multi-site trials that entail potential risk.²

DSMBs serve as independent bodies of experts that have no vested interest in a specific treatment. DSMBs approach trial monitoring with uncertainty regarding whether the intervention or drug being tested will be superior to existing treatments or at all effective until proven otherwise.³ DSMBs review evidence of study-related adverse events and interim treatment outcomes to recommend whether trials should be continued, altered, or terminated. This study seeks to explain the important role that DSMBs play in NIH-sponsored research involving human subjects, and to contribute to the Office of Inspector General’s (OIG) significant body of work concerning clinical trials and human subject protections.

NIH

NIH is the largest source of funding for medical research in the world; it had a budget of \$30.9 billion in fiscal year (FY) 2012.⁴ NIH comprises the Office of the Director and 27 Institutes and Centers (IC), each with a specific research agenda.

¹ NIH, *Policy for Data and Safety Monitoring*, 1998. Accessed at <http://grants.nih.gov> on January 15, 2013.

² Ibid.

³ This approach is known as practicing “clinical equipoise.”

⁴ NIH, *Operating Plan-Budget Mechanism*. Accessed at <http://officeofbudget.od.nih.gov> on December 18, 2012.

Clinical Trials

A clinical trial is a controlled study to determine whether an experimental drug, treatment, or device is safe and effective. Drugs, treatments, and devices generally undergo three phases of clinical trials. Phase III trials typically involve several hundred to several thousand human subjects. These trials are used to confirm the effectiveness of a treatment, monitor its side effects, compare it to commonly used treatments, and collect information on safe usage. Phase III clinical trials also typically involve multiple trial sites where human subjects receive an experimental intervention.⁵ All multi-site clinical trials involving interventions that pose potential risk to the participants require a DSMB.⁶

Grantees, principal investigators, and DSMBs are involved in Phase III NIH clinical trials. A grantee is an organization or individual awarded a grant or cooperative agreement by NIH. The grantee is accountable for the use of funds and for the performance of the clinical trial. Grantees typically include academic centers or pharmaceutical and device companies. To direct the trial, a grantee designates a principal investigator who is accountable to the grantee and NIH for the trial's proper conduct.⁷

A DSMB is a group of individuals with pertinent expertise that regularly reviews accumulating data from one or more ongoing clinical trials. A DSMB functions as a monitor of the trial to ensure the safety of study subjects and validity and integrity of the data. Independence is critical for DSMBs. Without independence, their recommendations could be biased, and the ability of the DSMB to fulfill its mission would be compromised. DSMBs make recommendations to NIH, Institutional Review Boards (IRBs), and/or the principal investigator regarding continuing, altering, suspending, or terminating a trial.^{8,9} For instance, a DSMB may recommend terminating a trial if the results are so overwhelmingly positive or negative that the ultimate conclusion can be readily predicted or if the trial appears futile (e.g., no difference emerged between the treatment groups).

DSMBs meet in open and closed sessions. They generally first meet in an open session attended by voting DSMB members, IC staff, principal

⁵ NIH, *Glossary*. Accessed at <http://grants.nih.gov> on January 15, 2013.

⁶ NIH, *Policy for Data and Safety Monitoring*, 1998. Accessed at <http://grants.nih.gov> on January 15, 2013.

⁷ NIH, *Glossary*. Accessed at <http://grants.nih.gov> on January 15, 2013.

⁸ An IRB is a committee set up to ensure the protection of the rights and welfare of human subjects. Each clinical trial must be covered by an IRB. IRBs are typically site-specific.

⁹ NIH, *Policy for Data and Safety Monitoring*, 1998. Accessed at <http://grants.nih.gov> on January 15, 2013.

investigators, and industry representatives.¹⁰ During an open session, principal investigators or their designee(s) typically provide an update on trial progress and answer questions. Following the open session, the DSMB convenes a closed session to review emerging trial data (including potentially unmasked data). Closed sessions are attended by voting DSMB members and sometimes by study statisticians and other IC staff.¹¹ These closed meetings also include a review and discussions of adverse events, participant risk versus benefits, and trial sites.

NIH DSMBs

Potential grantees who apply for funding must submit a clinical trial protocol, which is a detailed study plan that includes the objectives, methodology, and statistical plan for the trial. The protocol must include a data and safety monitoring plan (DSM plan). For multi-site Phase III clinical trials that involve risk to participants, the plan must involve a DSMB.¹²

NIH allows ICs flexibility in implementing the DSMB guidance for data and safety monitoring. Each IC should have its own DSMB policy. However, NIH does specify responsibilities related to DSMB composition, reporting, and conflict of interest.¹³

Composition. DSMBs should consist of experts in all scientific disciplines needed to interpret the trial data and ensure patient safety. They may include clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study.¹⁴ ICs are responsible for ensuring that DSMB members have the appropriate expertise required for each specific trial.¹⁵

Reporting Recommendations. A DSMB must make recommendations to the IC after each meeting concerning the continuation or conclusion of the trial. The IC should review all recommendations and ensure that they are addressed and shared with the principal investigator and the IRB.¹⁶

Conflict of Interest. To preserve the group's independence, individual DSMB members should not be associated with the trial, meaning that they should have no financial or professional interests in the trial. ICs should

¹⁰ NIH, *Policy for Data and Safety Monitoring*, 1998. Open sessions can be public or private, as decided by the IC. Accessed at <http://grants.nih.gov> on January 15, 2013.

¹¹ Ibid.

¹² Ibid.

¹³ NIH, *Glossary*. Accessed at <http://grants.nih.gov> on January 15, 2013.

¹⁴ NIH, *Policy for Data and Safety Monitoring*, 1998. Accessed at <http://grants.nih.gov> on January 15, 2013.

¹⁵ Ibid.

¹⁶ Ibid.

evaluate whether the potential DSMB members have conflicts of interest with or financial stakes in the research outcomes; when conflicts exist, ICs must have policies for managing them in a reasonable manner.¹⁷ Although it is not explicitly required, ICs may require that DSMB members disclose a conflict or sign a document maintaining that they are free of any conflict of interest.

Related Reports

In 1998, OIG issued a series of reports on IRBs.¹⁸ This report is a follow-up on the recommendations from that series regarding the use of DSMBs. OIG recommended that NIH and the Food and Drug Administration (FDA) define the types of trials for which DSMBs would be required and set forth requirements for the composition of DSMBs.¹⁹ In response, NIH required DSMBs for all Phase III multi-site trials and published guidance about their composition.²⁰ FDA released nonbinding recommendations regarding the use of DSMBs. Like NIH, FDA defines a DSMB as a group of individuals with pertinent experience that reviews accumulating data from one or more ongoing clinical trials. FDA allows trial sponsors to determine when a DSMB may be useful for study monitoring.²¹

METHODOLOGY

This study reviewed the extent to which DSMBs for NIH-funded Phase III multi-site clinical trials met NIH guidance. The findings are based on data collected on the population of Phase III multi-site clinical trials completed in 2009 and 2010 that entailed potential risk. NIH identified a total of 44 trials funded by 10 ICs that met these criteria.

We used several data sources to answer our study objectives: (1) NIH guidance and IC DSMB policies; (2) DSM plans; (3) documentation regarding DSMB meetings, including membership rosters and recommendations; (4) a survey of DSMB members, (5) a survey of principal investigators; (6) structured interviews with staff from the 10 ICs; and (7) interviews with DSMB stakeholders. These sources are described below.

¹⁷ Ibid.

¹⁸ OIG, *Institutional Review Boards: Their Role in Approved Research*, OEI-01-97-00190, June 1998; *Institutional Review Boards: Promising Approaches*, OEI-01-97-00191, June 1998; *Institutional Review Boards: The Emergence of Independent Boards*, OEI-01-97-00193, June 1998; *Institutional Review Boards: A Time for Reform*, OEI-01-97-00193, June 1998.

¹⁹ OIG, *Institutional Review Boards: A Time for Reform*, OEI-01-97-00193, June 1998.

²⁰ NIH, *Policy for Data and Safety Monitoring*, 1998. Accessed at <http://grants.nih.gov> on January 15, 2013.

²¹ FDA, *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Monitoring Committees*, 2006. Accessed at www.fda.gov on March 7, 2013.

NIH Guidance and IC Policies

We reviewed NIH's 1998 *Policy for Data and Safety Monitoring* to assess NIH guidance on DSMBs. Because each IC has flexibility in implementing this guidance as appropriate for its specific clinical research activities, we also reviewed the 10 ICs' DSMB policies.

DSM Plans

We collected DSM plans from ICs for each of the 44 clinical trials. From these we gathered information about the DSMBs' composition and the frequency of their meetings.

Documentation Regarding DSMB Meetings

We received documentation regarding closed DSMB meetings for 39 of the 44 trials in our population (a total of 399 meetings).²² For each closed meeting, we received meeting attendance records, a summary of the meeting (including any minutes), and DSMB recommendations.

Survey of DSMB Members

In April 2012, we surveyed DSMB members about their experiences on DSMBs and whether they had enough information to make recommendations. We identified 322 DSMB members through the DSMB membership rosters provided by NIH for our population of 44 studies. Of the 322, we ultimately surveyed 251.²³ We made up to three attempts to elicit responses and ultimately received 180, 72-percent response rate.

Survey of Principal Investigators

In November 2012, we surveyed principal investigators about their perceptions regarding the representation of scientific disciplines on DSMBs and their overall experiences with DSMBs. NIH provided us a list of all 91 principal investigators associated with our population of 44 trials (some trials had multiple investigators). Of the 91, we ultimately surveyed 69 principal investigators.²⁴ We made up to three attempts to elicit responses and ultimately received 30, 43-percent response rate. Given this response rate, our results may not reflect the opinions of all the principal investigators associated with the 44 clinical trials in our population.

²² One IC accounted for the five trials for which we did not receive meeting minutes. This IC stated that it does not receive DSMB meeting documentation.

²³ Thirty-five email addresses were no longer active; 21 DSMB members were listed more than once; 5 DSMB members were deceased; and 3 individuals stated that they did not serve on a DSMB and were incorrectly identified.

²⁴ Seventeen email addresses were no longer active; four individuals confirmed they were not the principal investigator for the trial; and one principal investigator was deceased.

Structured Interviews With NIH Staff

We interviewed staff from the 10 ICs associated with 2009 and 2010 trials. We asked IC staff about their oversight of DSMBs, including any training provided to members and the recruitment process. We also asked about the IC staff's review of DSM plans and DSMB recommendations.

Interviews With Stakeholders

We interviewed 11 experts with DSMB experience either as DSMB members (e.g., biostatistician, clinician) or a principal investigator. These experts were not directly associated with any trials in our population and were identified through research and individual recommendations. Conversations focused on the independence of DSMBs, DSMB members' access to unmasked data, and recruitment and training of DSMB members.

Limitations

Given our response rates and the possibility that nonresponding DSMB members or principal investigators may have responded differently to our questions than responders, our results may not reflect the opinions of all DSMB members or principal investigators associated with the 44 clinical trials in our population. Also, given that responses were anonymous, we are unable to determine the specific trials with which respondents are associated.

Standards

This study was conducted in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

FINDINGS

DSMBs are meeting NIH guidance in their roles as trial monitors

According to NIH guidance, DSMBs should meet regularly to review interim trial data and make recommendations to ICs concerning the continuation or conclusion of the trial. DSMBs should be composed of experts in all scientific disciplines needed to interpret the data and ensure patient safety. For NIH trials completed in 2009 and 2010, we found that DSMBs met this general guidance.

DSMBs met regularly and made recommendations about the continuation of the trials

Clinical trials span many years; therefore the DSMBs must meet over many years. The 39 trials for which we had meeting records met for 4.5 years on average, ranging from 21 months to 8.5 years. Almost all members reported that their DSMBs met frequently enough to fulfill their mission. Most DSMBs met semiannually (45 percent) or annually (42 percent). The remainder met quarterly.

DSMBs' initial meetings were usually in person, but over half of the subsequent 360 meetings were by teleconference. IC staff reported that meeting via teleconference reduced the burdens of time and travel.

At the conclusion of closed sessions, DSMB members vote on recommendations regarding trial continuation. Making such recommendations is a primary responsibility of the DSMB. The great majority of meetings (91 percent, 365 of 399) resulted in recommendations.²⁵ According to meeting records we reviewed, the DSMBs recommended stopping seven trials. Four of these recommendations were based on findings that the treatments under study were ineffective; the other three were based on findings that the trials could not accrue enough subjects in the allotted time to yield useful results. All seven trials were subsequently terminated.

The great majority of DSMB recommendations were to continue the studies with no changes; 20 percent of the recommendations were to continue the studies with changes. Recommended changes included pretrial changes to the protocol, altering the informed consent form or process, changing enrollment, or changing treatment.

²⁵ Those that did not were often the final meetings at the close of the trial or a specific meeting solely on enrollment updates or a protocol modification.

DSMB members represented multiple disciplines and have significant experience with DSMBs

The effectiveness of a DSMB depends in large part on the strengths of its members. Members volunteer their expertise and time to ensure trial integrity and patient safety. According to IC staff and DSMB stakeholders, DSMB members are experienced professionals respected in their scientific fields.

The DSM plans and DSMB policies we reviewed generally called for members from the disciplines necessary to carry out the task of a DSMB. On the basis of our review of the DSMB rosters, DSMBs met this general requirement. DSMBs were composed of clinicians, clinical trial experts, biostatisticians, bioethicists, and patient advocates. On average, each DSMB had seven members. Membership ranged from 4 to 11 per trial.

More than two-thirds of DSMB members identified themselves as either clinicians knowledgeable about the disease and/or treatment relevant to the trial or as clinical trial experts. The vast majority of DSMB members and principal investigators reported that these disciplines were adequately represented on DSMBs. DSMB members and principal investigators also reported that biostatisticians were adequately represented.

Bioethicists may be warranted on some DSMBs to provide bioethical perspectives on the progress of trials. However, one-third of DSMB members and principal investigators reported that bioethicists were underrepresented. Bioethicists were the least represented discipline of those members we surveyed (15 of 180). Staff from two ICs said that bioethicists are especially difficult to recruit to DSMBs given their limited experience with clinical trials.

Seventy-five percent of DSMB members reported that they had served on more than one DSMB. On average, they reported serving on five DSMBs throughout their careers. Twenty-six of thirty principal investigators surveyed reported that the DSMB members had enough experience to fulfill their roles.

Standing DSMBs may account for the large percentage of individuals serving on multiple DSMBs. A standing DSMB is one that meets for a number of different trials within the same IC in which the same disease or treatment is being studied. Eight of the ten ICs use standing DSMBs for some or all of their trials. Staff stated that the main advantage to using standing DSMBs is having a ready-made, experienced pool of members familiar with the roles and responsibilities of a DSMB.

DSMBs face some issues that may affect their ability to fulfill their roles

DSMBs met NIH's general guidance by having relevant experts who met regularly to offer recommendations to NIH. To fulfill their roles, however, DSMBs must also maintain their independence, be assured access to unmasked data, and have a qualified pool of experts from which to recruit DSMB members. DSMBs face issues in all three of these areas.

IC participation in closed DSMB meetings diminishes the appearance of independence

According to NIH, ideally, individuals are in no way associated with the trials they monitor.²⁶ Association with a trial could take many forms. For instance, DSMB members could have conflicts of interest, meaning personal or financial stakes in the outcome of a trial. However, we found that conflict-of-interest paperwork was generally submitted to ICs, as required.

Additionally, IC staff have interests in the trials because the ICs fund the trials. Staff from 9 of the 10 ICs attended closed DSMB meetings at which interim data were reviewed. DSMBs generate recommendations regarding trial continuation from the interim data review.

We did not assess whether any DSMB recommendations were subject to bias. However, the extent to which IC staff participated in closed meetings diminishes the appearance of independence. Half (15 of 30) of principal investigators responded that IC staff should not participate in closed DSMB meetings. Six of the eleven expert stakeholders expressed concern about the extent to which ICs participate in closed DSMB meetings. One stakeholder said that such participation hindered independence. Another referred to IC participation as a “delicate balance” between the IC obtaining information and the DSMB maintaining independence.

A few DSMB members and principal investigators did not agree that their DSMBs maintained their independence from NIH. Specifically, 14 (of 180) DSMB members and 3 (of 30) principal investigators did not believe that DSMBs maintained their independence.

On the other hand, IC staff, most DSMB members, and most principal investigators agreed that DSMBs maintained their independence from NIH. In fact, one DSMB member noted that the IC's participation in the DSMB was important to help the DSMB make informed decisions; a

²⁶ NIH, *Policy for Data and Safety Monitoring*, 1998. Accessed at <http://grants.nih.gov> on January 15, 2013.

stakeholder noted that the DSMBs benefit from the closer relationship the ICs have with the principal investigators. Others also cited the importance of having an IC staff attend closed meetings to serve as an executive secretary, thereby facilitating note taking, scheduling, and other related functions.

IC staff involvement in DSMB meetings is addressed in each IC's DSMB policy. However, the policies did not always clearly restrict participation in closed meetings or define the role of IC staff in closed meetings. For example, one IC policy appears to include no restrictions, stating that "during closed sessions of the DSMB meetings only DSMB members and IC program staff may attend." Another policy states that "closed sessions will be restricted to voting and ad hoc members ... and IC staff as appropriate." In a third example, the policy is clearer, restricting IC staff participation in closed session (when unmasked data would be discussed) to the IC executive secretary and statistician.

Not all IC policies reference DSMB access to unmasked data

DSMBs are typically the only clinical trial oversight entity with direct access to unmasked data during the course of the trial, meaning that members know who is in the control group versus the treatment group. Many experts and almost all principal investigators agreed that to fulfill their roles, DSMB members must have access to these data if they request them.²⁷

Only 4 of 10 IC policies referenced DSMB access to unmasked data. One IC policy makes clear that members should "review masked or unmasked data as needed and appropriate." In another example, the policy is very clear regarding members' access to unmasked data and states that "the DSMB decides in their first meeting if DSMB members will be unmasked. If the DSMB decides to remain masked, they should consider assigning one DSMB member to be unmasked to treatment assignment." The remaining six IC policies were silent on the issue of DSMB member access to unmasked data.

A small number of DSMB members (17 of 180) did not believe they had access to unmasked data. Additionally, DSMBs for 14 of 39 trials reviewed only masked data at each meeting.²⁸ We do not know whether they requested unmasked data.

²⁷ One expert argues that monitoring a trial without access to unmasked data "denies the monitors the key information they need to perform in a competent fashion, and incompetent monitoring poses a risk to research subjects." (Curtis Meinert, "Masked Monitoring In Clinical Trials: Blind Stupidity?" *The New England Journal of Medicine*. 338, 19. May 7, 1998.)

²⁸ This analysis is based on the 39 trials for which we have meeting minutes.

ICs face challenges in recruiting and training DSMB members

The participation of experienced professionals is essential to ensure that DSMBs are effective, and ICs must maintain a pool of qualified individuals from which to recruit and train new members. According to staff from all 10 ICs, however, recruiting is a challenge. Membership in a DSMB is a voluntary commitment that lasts many years, with little reimbursement. Some DSMB members noted the onerous nature of the conflict-of-interest disclosures. For example, former collaborations with the study sponsor can be considered a disqualifying conflict. Furthermore, the ICs noted that bioethicists can be challenging to recruit, especially because they lack clinical trial experience.

The ICs reported facing challenges in recruiting DSMB members despite the prestige associated with serving on an NIH-sponsored trial DSMB. The ICs touted the qualifications of their DSMB members as representing the best of the best, and the DSMB members cited their DSMB service as not only professionally satisfying but also as an important way to contribute to scientific advancement.

ICs benefit from the depth of experience of their DSMB members. However, sustaining that level of experience is a challenge for the ICs because those with the most experience eventually retire. We found that 9 of 10 ICs do not offer any formal training to DSMB members and, in fact, ICs and stakeholders noted that the best form of training is on-the-job experience. ICs offer informal training such as online reading materials and a review of the DSM plan during the first meeting. Many DSMB members responding to our survey noted that formal training would have benefitted them most only at the outset of their DSMB experiences to create a common understanding of the role of a DSMB.

CONCLUSION AND RECOMMENDATIONS

DSMBs play a critical role in ensuring the safety of human subjects and the merit of clinical trials. They fulfill their mission to monitor trials by making use of the significant strengths of their members' experience. However, DSMBs face three issues that could compromise their effectiveness. The first lies in ensuring their independence—and appearance of independence. The second lies in ensuring their access to unmasked data. The third lies in maintaining a pool of qualified individuals to serve on DSMBs. We recommend that NIH:

Direct ICs To Articulate the Circumstances Under Which IC Staff Participate in Closed Meetings

The extent of IC staff involvement in closed DSMB meetings and the lack of clarity concerning the ICs' expected roles in meetings could diminish the appearance of independence. ICs should clearly describe the circumstances in which it is appropriate for specified IC staff to attend closed DSMB meetings, and the role of these staff during the meetings. For instance, IC policies could outline that IC executive secretaries will attend closed meetings to take minutes and provide appropriate followup. IC policies provide an appropriate platform to set these expectations.

Direct ICs To Explicitly Reference DSMB Access to Unmasked Data in Their DSMB Policies

DSMB members may not always have access to unmasked trial data. The ability of DSMBs to monitor trial progress and ensure the safety of patients may be compromised without access to unmasked data. ICs should ensure that DSMB members have access by directing ICs to reference this access in their DSMB policies.

Identify Ways To Recruit and Train New DSMB Members

According to staff from all 10 ICs, recruiting is a challenge. In addition, 9 of 10 ICs do not offer any formal training to DSMB members. Experienced professionals are essential to ensure that DSMBs are effective.

To help recruit and train new DSMB members, NIH could create a forum for DSMB issues to be shared and discussed across ICs. A forum in which IC staff can discuss challenges and solutions—such as how to address recruitment issues, including the underrepresentation of bioethicists—could be highly beneficial for the effective use of DSMBs. An online forum is one option for ICs to share information and network. NIH could also sponsor an in-person or Webinar conference.

In addition, NIH could create a pool of potential DSMB members by expanding each DSMBs' membership to include one nonvoting member who has not previously (or recently) served on a DSMB.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

NIH concurred with all three of OIG's recommendations. NIH stated that it is organizing a trans-NIH working group to review the report and to ensure that ICs' DSMB policies and practices are optimal.

Although NIH agreed with our first recommendation, it did not find that the presence of IC staff constituted a conflict of interest. However, we found that the presence of IC staff at closed DSMB meetings did create the appearance of a conflict of interest for at least some DSMB members, principal investigators, and stakeholders. NIH did state that IC policies should make staff roles and responsibilities transparent; clarify why their participation does not affect the independence of DSMB-decision making; and delineate instances in which the program staff take on additional roles that would constitute a conflict of interest.

In response to our second recommendation, NIH specified that all IC policies should state that DSMBs have access to unmasked data.

In response to our third recommendation, NIH stated that ICs are actively exploring ways to enlarge their pools of experts and ensuring that DSMB service is appropriately credited and recognized.

APPENDIX A

Agency Comments



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

TO: Daniel Levinson
Inspector General

FROM: Director, NIH

DATE: **MAY - 6 2013**

SUBJECT: NIH Comments on the Draft Office of Inspector General Report, *Data and Safety Monitoring Boards in NIH Clinical Trials: Meeting Guidance But Facing Some Issues* (OEI-12-11-00070)

Attached are the National Institutes of Health's comments on the draft OIG report, *Data and Safety Monitoring Boards in NIH Clinical Trials: Meeting Guidance But Facing Some Issues* (OEI-12-11-00070).

We appreciate the opportunity to review and comment on this important topic. Should you have questions or concerns regarding the NIH comments, please contact Meredith Stein in the Office of Management Assessment at 301-402-8482.

/s/ Francis S. Collins, M.D., Ph.D.

Francis S. Collins, M.D., Ph.D.

Attachments:
NIH General Comments
NIH Technical Comments
on Draft Report OEI-12-11-00070

APPENDIX A

Agency Comments (cont.)

GENERAL COMMENTS OF THE NATIONAL INSTITUTES OF HEALTH ON THE OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT ENTITLED, DATA AND SAFETY MONITORING BOARDS IN NIH CLINICAL TRIALS: MEETING GUIDANCE BUT FACING SOME ISSUES (OEI-12-11-00070)

The National Institutes of Health (NIH) appreciates the review conducted by the OIG and the opportunity to provide comments on this draft report. Data and Safety Monitoring Boards (DSMBs) play a critical role in helping to ensure the safety and integrity of clinical trials funded by the NIH. As a result of this OIG report, the Office of the Director will be organizing a trans-NIH working group to review the report and to ensure that our Institute and Centers' (ICs') DSMB policies and practices are optimal.

NIH policy for data and safety monitoring of clinical trials was issued in 1998 and 2000, see <http://grants.nih.gov/grants/guide/notice-files/not98-084.html> and <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>. The policy defines the principles of trial monitoring and outlines when monitoring should take the form of a DSMB. It calls on each IC to establish a system for the appropriate monitoring of the clinical trials they support and to be responsible for oversight of the monitoring activities. It provides flexibility to the ICs in how monitoring is implemented (e.g., it may be delegated to grantees and contractors) and how oversight of monitoring activities is performed. It also outlines key elements that should be part of an IC's policies.

We were gratified with the OIG's overall findings that the IC policies, procedures, and practices align well with the NIH policy and guidance; that IC policies address the important issues related to monitoring clinical trial data and ensuring the safety of human participants in clinical trials; and that individuals serving on NIH DSMBs have the necessary expertise, experience, and background to perform their monitoring function.

OIG Recommendation: Direct ICs to articulate the circumstances under which IC staff participate in closed meetings.

NIH Response: The NIH concurs with the OIG's finding that all IC DSMB policies should articulate the circumstances, if any, under which NIH staff participation in DSMB meetings is appropriate and necessary and should state explicitly that DSMB members have access to unmasked data. We appreciate the attention the OIG has given to each of these issues, and we plan to take steps to ensure that they are addressed.

Specifically, we agree that NIH staff participation in DSMB meetings should be articulated in IC policies and should delineate whether program staff who have stewardship responsibilities for the trial, and staff who provide logistical support for the operation of the DSMB meetings, should participate in open, closed, or executive sessions. With regard to concerns about the participation of program staff, we believe that these are based on a misunderstanding of their stewardship role and responsibility. Because program staff are responsible for the stewardship of the research within their portfolios, most ICs allow them to be present during both open and closed sessions of the DSMB. Stewardship responsibilities do not constitute an inherent conflict of interest. Program staff do not have a financial stake in the trials they are overseeing and they are insulated from professional conflicts because their performance is not evaluated on the

APPENDIX A

Agency Comments (cont.)

GENERAL COMMENTS OF THE NATIONAL INSTITUTES OF HEALTH ON THE OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT ENTITLED, *DATA AND SAFETY MONITORING BOARDS IN NIH CLINICAL TRIALS: MEETING GUIDANCE BUT FACING SOME ISSUES (OEI-12-11-00070)*

outcome of the trial, i.e., whether it results in positive or negative findings. Their interests are completely aligned with the DSMB's interests, namely ensuring the safety and integrity of the trial. We do agree, however, that IC policies should make staff roles and responsibilities transparent; clarify why their participation does not affect the independence of DSMB decision-making; and delineate instances when the program staff takes on additional roles, such as coauthorship, that would constitute a conflict of interest.

OIG Recommendation: Direct ICs to explicitly reference DSMB access to unblinded data in their DSMB policies.

NIH Response: The NIH is in concurrence that DSMB access to unmasked data is fundamentally necessary for carrying out its monitoring responsibilities and that all IC policies should state that DSMBs have access to unmasked data. Although four IC policies currently do not address this point explicitly, in practice, all ICs do provide their DSMBs with access to unmasked data. At the same time, it is important to note that there are differing views among DSMB experts about the benefits and risks of routine review of unmasked interim data, and DSMBs vary in how they choose to handle this matter. Some DSMBs prefer to review unmasked data only if a serious safety issue arises or only when study outcomes achieve statistical significance. Others may decide that regular review of unmasked data is necessary given the nature and risks associated with the trial.

OIG Recommendation: Identify ways to recruit and train new DSMB members.

NIH Response: The NIH concurs with the OIG that maintaining a robust pool of experts qualified to serve on DSMBs is a critical issue. Indeed, it is difficult to overstate the importance of increasing the number of DSMB candidates available and that more can be done to develop the pipeline of qualified DSMB candidates and to recruit additional members. The ICs are actively exploring ways to enlarge their pools of experts and to ensure that DSMB service is appropriately credited and recognized.

ACKNOWLEDGMENTS

This report was prepared under the direction of Joyce Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office and Russell Hereford, Deputy Regional Inspector General.

Anne Gavin served as the team leader for this study. Amy Glynn served as the lead analyst. Other principal Office of Evaluation and Inspections staff from the Boston regional office who contributed to the report include Shreya Patel; central office staff who contributed include Debra Roush, Talisha Searcy, Jacquelyn Towns, and Sherri Weinstein.

Office of Inspector General

<http://oig.hhs.gov>

The mission of the Office of Inspector General (OIG), as mandated by Public Law 95-452, as amended, is to protect the integrity of the Department of Health and Human Services (HHS) programs, as well as the health and welfare of beneficiaries served by those programs. This statutory mission is carried out through a nationwide network of audits, investigations, and inspections conducted by the following operating components:

Office of Audit Services

The Office of Audit Services (OAS) provides auditing services for HHS, either by conducting audits with its own audit resources or by overseeing audit work done by others. Audits examine the performance of HHS programs and/or its grantees and contractors in carrying out their respective responsibilities and are intended to provide independent assessments of HHS programs and operations. These assessments help reduce waste, abuse, and mismanagement and promote economy and efficiency throughout HHS.

Office of Evaluation and Inspections

The Office of Evaluation and Inspections (OEI) conducts national evaluations to provide HHS, Congress, and the public with timely, useful, and reliable information on significant issues. These evaluations focus on preventing fraud, waste, or abuse and promoting economy, efficiency, and effectiveness of departmental programs. To promote impact, OEI reports also present practical recommendations for improving program operations.

Office of Investigations

The Office of Investigations (OI) conducts criminal, civil, and administrative investigations of fraud and misconduct related to HHS programs, operations, and beneficiaries. With investigators working in all 50 States and the District of Columbia, OI utilizes its resources by actively coordinating with the Department of Justice and other Federal, State, and local law enforcement authorities. The investigative efforts of OI often lead to criminal convictions, administrative sanctions, and/or civil monetary penalties.

Office of Counsel to the Inspector General

The Office of Counsel to the Inspector General (OCIG) provides general legal services to OIG, rendering advice and opinions on HHS programs and operations and providing all legal support for OIG's internal operations. OCIG represents OIG in all civil and administrative fraud and abuse cases involving HHS programs, including False Claims Act, program exclusion, and civil monetary penalty cases. In connection with these cases, OCIG also negotiates and monitors corporate integrity agreements. OCIG renders advisory opinions, issues compliance program guidance, publishes fraud alerts, and provides other guidance to the health care industry concerning the anti-kickback statute and other OIG enforcement authorities.