Data Monitoring Committees Project Expert Meeting

Summary of the Meeting held July 28-29, 2015

DoubleTree by Hilton, Silver Spring, MD

CTTI MISSION: To identify and promote practices that will increase the quality and efficiency of clinical trials

Meeting meeting materials, including agenda, participant list and presentations, are available on the Clinical Trials Transformation Initiative (CTTI) website at: https://ctti-clinicaltrials.org/our-work/ethics-and-human-research-protection/data-monitoring-committees/

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MEETING BACKGROUND

Today, data monitoring committees (DMCs) are used across therapeutic areas and may oversee single trials, groups of related trials, or the entire portfolio of research related to an investigational product. Responsibilities may be limited to analyses of efficacy and safety, or expanded to include review of data quality and other trial operations. As use of DMCs has increased and evolved, critical issues have emerged. The goal of the DMC project is to achieve DMCs composed of qualified members who are convened for appropriate trials and conduct business in a way that is understood by all stakeholders and increases the quality of trial oversight. Project activities have included conducting a survey and set of focus groups to gain a better understanding of the current use and conduct of DMCs, training practices for DMC members, and best practices related to independent DMC use. To consider key themes and possible draft recommendations, 4 work groups were formed: DMC communication, DMC purpose and rationale, organization and formation of DMCs, and DMC training. This expert meeting was convened to review the results of the survey and focus groups and help refine draft recommendations with input from a diverse group of stakeholders.

MEETING OBJECTIVES

- ► Present findings and conclusions from the project survey and focus groups
- ► Share and solicit feedback on findings and proposed DMC recommendations

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MEETING EXECUTIVE SUMMARY

The DMC project convened a meeting involving stakeholders with expertise in this topic on July 28-29, 2015. The participants included approximately 60 representatives from academia, nonprofit organizations, government agencies, institutional review boards (IRBs), industry (including pharmaceutical companies and contract research organizations), professional service organizations, and patient representatives.

The findings of the survey and focus group evidence-gathering activities were presented, along with key themes that emerged from those findings and draft recommendations from the project's 4 work groups. Themes that emerged throughout the meeting included the following:

- DMCs must be composed of qualified individuals who are independent of the sponsor and who have adequate resources and flexibility to perform their duties
- DMCs can take many different forms, so the roles and responsibilities should be flexible, but clearly outlined for each DMC

- Roles and responsibilities should be clearly outlined in a succinct, well-organized, jargon-free, non-legalistic charter that should empower rather than handicap the DMC
- There is a critical need for DMC training and better dissemination of best practices for DMCs
- DMC communication with other stakeholders (e.g., sponsors, regulatory bodies) is complex and should follow guidelines supported by best practices and clearly described in the charter of each DMC in order to maintain DMC independence

Looking ahead, meeting attendees also brainstormed potential barriers to adoption of the recommendations as well as strategies to overcome those barriers. As a next step, the DMC project team will consider the feedback and discussion from the meeting to develop project recommendations, which will be finalized and disseminated via formal CTTI procedures.

MEETING SUMMARY

The meeting began with a presentation that summarized CTTI methodology, challenges facing DMCs, and the objectives of the DMC project. Team members then presented an overview of the project's survey and focus group results, which were used to inform project activities and the development of draft recommendations.

Survey and Focus Group Results

The survey had more than 100 respondents, which included trial sponsors, DMC members, and statistical analysis center (SAC) representatives. The most important DMC activity as ranked by respondents was review of summary safety and efficacy data to make a risk-benefit evaluation. Other activities received an intermediate ranking, and review of individual adverse event reports was ranked as least important. These results were similar when analyzed by type of respondent.

Six focus groups were conducted: DMC members, patient advocates, IRB/US Food and Drug Administration (FDA) representatives, industry sponsors, government sponsors, and SAC representatives. DMC members felt that DMCs should have a limited role in trial design, and that it is important for DMCs to have unblinded efficacy data for all trials they monitor. Some focus group participants expressed that DMCs are overused. Overall, the survey and focus groups revealed that DMCs play a critical role in clinical trials, but there are unresolved issues and remaining gaps in understanding regarding how to determine which trials need a DMC, ensure DMCs are truly independent, ensure enough qualified DMC members are available to meet the growing demand, and compose DMC charters that best reflect DMCs' disparate objectives.

Survey and focus group findings specifically related to (1) DMC communication and (2) DMC member qualification, composition, and training were also reviewed, followed by attendee discussion.

DMC Communication

Sponsors indicated that they have a charter template that is tailored to each trial. DMC members considered charters useful to carry out their responsibilities and appreciate the opportunity to review the charter and provide input. When asked how a DMC charter can be improved, focus group participants indicated that it should not be too short or too long, and statistical analysis plans should remain separate. Furthermore, it should be clear but flexible (i.e., leave room for "judgment calls") relative to DMC decision-making. Charters should pre-specify the contents of the DMC statistical report and detail communication practices between the DMC, SAC, and sponsor. There was high concordance between what elements sponsors and DMC members reported as being contained in DMC contracts, with the exception of pay for unscheduled meetings, pay for work done outside of regular meetings, and Sunshine Act reporting requirements. Regarding statistical reports, DMC members like to see the table shells in advance of the first meeting and be able to request changes. They expressed that there should be flexibility permitted in the SAC analyses, and the statistician should understand the trial protocol and be present at DMC meetings. A proportion of 25% figures/graphics was believed to be ideal for SAC reports. Overall, the findings indicated that DMCs are able to operate independently and with minimal sponsor contact after the charter is finalized. IRBs felt that it was their role to request a DMC, if necessary, but they have no direct communication with DMCs. FDA representatives reported infrequent direct contact with DMCs.

DMC Member Qualification, Composition, and Training

Focus group participants indicated that there are no standard qualifications for DMC members, and this is a problem. DMCs typically have 2 to 6 members, including a statistician, clinicians familiar with the disease being studied, an ethicist (in some cases), researchers with special expertise relevant to the trial, and increasingly, patient advocates. DMC members should have minimal conflict of interest (COI) and/or transparency about their COI, sound judgment, experience on DMCs, and an ability to "play well with others." DMC chairs were identified as serving a pivotal role. They must be able to run a meeting, listen, draw out consensus, and ensure all members are doing their job and being heard. Survey results showed that most DMC members are identified by recommendation or previous experience on DMCs, and they are most often directly contacted by the sponsor to join a DMC. Strikingly, 92% of DMC members reported never receiving formal training to serve on a DMC. According to the survey findings, few sponsors offer or require training. More than half of survey respondents thought DMCs should receive special training for adaptive trial designs. Industry sponsors felt that the government does not have the expertise to develop DMC training, and this would be better accomplished by academia or professional societies. In contrast, government sponsors felt they could have a role in developing training, particularly at the National Institutes of Health (NIH). Suggestions for training included didactic

sessions, interactive sessions (e.g., case studies), and ongoing continuing education. There were also recommendations to develop DMC members through apprenticeships, mentoring, and by allowing non-voting observers during DMC meetings (including closed sessions).

Discussion

In the discussion that followed, meeting attendees noted that there is much variety in how DMCs operate, yet little information on DMC practices is publicly available, likely because DMC confidentiality extends even after trial closure. They identified a need to share best practices for DMCs while balancing requirements for confidentiality. An attendee described success in obtaining sponsor permission to publish a description of DMC activities after trial closure; an agreement for dissemination could also potentially be included in a DMC charter. Other suggestions included using simulated data or examples. Overall, literature describing DMC monitoring and how DMCs reach decisions was felt to be of value and currently lacking.

None of the attendees believed that DMCs should exclude safety monitoring from their remit; however, there is a need to clearly outline which functions will be carried out by a DMC versus a safety monitoring group. The group discussed that a DMC may also monitor multiple trials for the same product, but this can create complexities in decision-making. In these cases, all potential situations should be reviewed with the sponsor for input before monitoring begins.

A concern was raised that there are still sponsors who feel that DMCs should remain blinded to treatment assignment. All attendees agreed that there are no circumstances under which a DMC should remain blinded, as this could create dangerous situations with misinformed decisions. FDA guidelines for DMCs encourage provision of unblinded data but do not require it. Attendees reiterated that safeguards and firewalls should be in place to protect the release of unblinded data, but it should absolutely be provided to the DMC. Statisticians preparing the reports for DMCs should also be unblinded.

Work Group Presentations and Discussion

In a series of sessions, 4 work groups from the DMC project presented their progress to date, including draft recommendations, and requested input from the meeting attendees.

DMC Purpose and Rationale

The DMC Purpose and Rationale work group described challenges in differentiating between DMCs and different oversight committees due to the variety of roles DMCs can serve. The work group has struggled with 2 different viewpoints: some feel that an explicit definition of a DMC is needed that clearly separates it from other oversight committees, whereas others argue that the customization of DMCs is so specific to individual trials that a DMC’s roles, responsibilities, and activities are more effectively addressed in a DMC charter. A majority of meeting attendees were in favor of the latter viewpoint that offered more flexibility in the different formulations of committees that could be considered DMCs.

The work group has started to outline the types of activities that can fall under DMC oversight. They have determined that the roles of executive committees, steering committees, IRBs, endpoint adjudication committees, protocol review committees, and clinical operations activities (e.g., data management, site monitoring) fall outside the scope of a DMC with no overlap. However, safety committees, study quality committees, clinical study oversight committees, or independent safety monitors can potentially have overlapping activities with DMCs.

Data were presented showing that from 2007-2013, 25% of industry-sponsored phase 2 and 3 trials had a DMC compared with 50% of non-industry–sponsored trials. There has been a 2-fold increase in the use of DMCs since the issuance of FDA's DMC guidance. Experts were asked their opinion on whether the existing literature sufficiently describes which trials need DMCs or if more clarity is needed in this area. Attendees suggested providing more guidance on when a DMC is *not* needed. Overall, attendees agreed with the idea that it is not only the nature of the trial that determines the need for a DMC, but whether or not the functions of a DMC are already carried out by another entity. The group could consider developing a list of essential DMC functions, which if not accomplished through another mechanism, would be undertaken by a DMC. Complementary to this could be a list of responsibilities that should not be assigned to a DMC (for example, individual adverse event review).

Attendees discussed the pros and cons of a DMC being involved in the design of a trial. There was agreement that once a DMC has seen unblinded data, they should have no role in designing or redesigning a trial. Some felt that before protocol implementation, DMC members can offer helpful advice in terms of how data are collected or factors that could lead to trial modification or termination. Counterpoints included that protocols already go through a lengthy review process and that involvement in trial design could present potential bias for DMC members. DMCs that monitor an entire program may have also seen unblinded data for a related trial. In summary, there were concerns about having DMCs involved in the early stages of trial design, but attendees also recognized there is an important role for DMCs in reviewing the design before it is final to ensure it can be implemented appropriately and to provide additional expertise for consideration.

Finally, the issue of DMC independence was discussed. The group weighed the merits of considering COI by individual or across the whole DMC. An argument was made that most qualified DMC members will not be completely free from COI, so transparency and balance across the DMC are most important. However, since not all DMC members may be present at every meeting, this balance can be lost, so there is risk to having members with substantial COI. It was noted that academic/intellectual bias can potentially interfere with judgment even more than financial COI. For example, having members from the research team on a DMC is inappropriate. Others cautioned against using too broad a definition of COI—it is not merely a professional belief, but must be strong enough to cause a member to have less interest in maintaining an unbiased view when assessing the scientific validity of the trial. Training to help DMC members compartmentalize their roles could be helpful. The perception of attendance of non-voting members, such as

NIH program officers, was discussed. Overall, clearer definitions are needed about what defines lack of independence.

Organization and Formation of DMCs

Proposed Qualifications of DMC Members

This work group recognized that the identification, selection, and vetting of potential candidates is critical to the functioning of a knowledgeable, responsible, and credible DMC. They drafted recommendations to provide guidelines on best practices in this area. There are currently no standard qualifications for DMC members. With the sum of its members, a DMC should have the expertise and independence necessary to carry out its duties. Members need to understand their roles and responsibilities and have expertise commensurate with the types of decisions they will be making. The group presented recommended qualifying experience by member role. A list of desirable traits for DMC chairs was also presented. The DMC chair must have extensive methodologic knowledge/experience and a range of leadership skills. In the discussion that followed, attendees raised concerns with recommending that DMC members have previous DMC experience. This can be considered preferred, but there should also be a way for new DMC members to serve if they fulfill the other requirements. Training, mentoring, or opportunities to observe could help prepare new members. Attendees also felt the recommendations should be more flexible regarding the number and types of DMC members needed. A DMC should have the fewest members possible to fulfill the necessary expertise; this will be specific to the type of trial and role of the DMC. There was a suggestion for developing "job descriptions" outlining the desired characteristics and responsibilities of each DMC member. It was questioned whether clinicians could be considered as adequately voicing patient interests on a DMC, or whether including patients/advocates is desirable. Several attendees felt strongly that patient advocates offer experience and a unique perspective (on alternative therapies, acceptable risks, etc.) that requires separate representation.

Best practices for vetting of DMC members were discussed. The sponsor and DMC chair should evaluate the potential COI of all members in context and determine whether any actions are needed. Any new potential COI after DMC initiation also needs to be declared and evaluated. Attendees mentioned that serving on another DMC is a potential COI and should be evaluated. The sponsor and DMC chair should also ensure DMC members have a collaborative personality, are willing to commit to review the data and attend the scheduled meetings, and agree to maintain confidentiality.

Proposed DMC Charter Checklist

The DMC charter is a key document that ensures the roles and responsibilities of the DMC are clearly delineated. The charter also outlines DMC procedures and planned communication practices. After reviewing published and unpublished charter templates, the work group developed a comprehensive checklist of potential elements for inclusion in a DMC charter. A key message was that the charter should empower rather than handicap the DMC. There should be a process

for ratifying the charter and also one for version control when changes are made. However, an attendee commented that the charter should not be so specific that frequent changes are needed.

The work group requested feedback on the checklist contents. There was a question regarding whether to include that the DMC should review the primary manuscript before publication to ensure that it accurately reflects the study, but most attendees felt this was the investigators' responsibility and not the DMC's. However, DMCs should review what the primary manuscript says about their process and recommendations. Suggestions were made to include statements about which activities are not being done by the DMC, as well as to more clearly indicate criteria for member dismissal from a DMC in the event that a member is not fulfilling his or her duties.

Communication between DMCs and the FDA and IRBs was also discussed. Some attendees expressed concern that if a sponsor decided not to act on a DMC's decision, regulators would have no knowledge of the disagreement. Conversely, if direct communication by DMCs was encouraged, there were concerns that DMCs may release recommendations to regulatory bodies before allowing time for exchanges with the sponsor. Direct communication between DMCs and IRBs would also be impractical in large multicenter trials. Sponsors are typically already required to submit DMC letters to IRBs. Attendees also recommended that IRBs be notified when a DMC is dissolved.

Concerns were raised over the length of the checklist and that it could encourage more complex and restrictive charters. Attendees agreed that simple, shorter charters that cover basic principles are most effective. The checklist could have an introduction to explain its use or potentially be called a "menu" or "points of consideration" to better indicate that not all items need to be addressed. Alternatively, the group could identify a smaller core set of elements that need to be included in a charter, and clearly mark the rest as optional or dependent on the specific trial.

Communication Between DMCs and Stakeholders

Best practices for communication between DMCs and stakeholders (i.e., sponsor, SAC, steering committee, regulatory bodies) were reviewed. As previously indicated, procedures for communication should be outlined in the charter. DMC–sponsor communication was regarded as most complex. A system is needed for DMCs to request more data without interacting directly with the sponsor; there also must be a system for discussing operational issues. The work group recommended that where possible, the SAC statistician remain the same throughout a trial. The DMC chair is responsible for contacting the SAC statistician when needed. SAC reports can be improved over time by providing feedback. Attendees noted that the reports take time and adequate training to produce. Participants stressed the importance of pre-trial discussions between the sponsor and DMC to provide adequate context and summarize existing knowledge about the intervention being investigated. During the trial, the DMC must strike a delicate balance between communicating queries or decisions to the sponsor while not revealing information

about unblinded data. Decisions should be conveyed with the minimal amount of information necessary to provide clarity. A best practice suggested for DMC open sessions was to have a minimal number of representatives from the sponsor present. There was consensus that it is only appropriate for DMCs to contact the FDA directly after first obtaining permission from the sponsor. Attendees suggested developing best practices for internal communication within the DMC. This would include holding the first or first several meetings in person to establish relationships.

Preparation of DMC Members

This session included panel presentations on DMC training programs from the National Institute of Allergy and Infectious Diseases (NIAID) and Harvard's Multiregional Clinical Trial Center (MRCT). The NIH recently formed a working group to address training and recruitment of DMC members and found that very few training programs exist. Judy Zuckerman presented NIAID's DMC training (https://dsmblearningcenter.niaid.nih.gov). The training arose from a best practices seminar that identified that DMC members were difficult to recruit, and no training was available. They subsequently obtained funding and hired a vendor to help develop computer-based DMC training. A needs assessment, literature review, and semi-structured interviews with DMC chairs were conducted to inform training development. The developers also consulted with subject matter experts at NIAID throughout the process. The training was designed to be broadly applicable across NIH, industry, and academia. Though the target audience is new DMC members, the training may also be useful for project officers, IRBs, and investigators. There are 3 modules that take approximately 1 hour total to complete. They recently published a manuscript about the training to help increase awareness. So far, the number of individuals completing the training is small (16 in 2014). At NIAID, the training is not required to serve on a DMC but is recommended. There are plans to review and update the training annually. They are also considering adding case study examples with facilitated discussion guides that a DMC could use to review with its new members.

The Harvard MRCT Training Program focuses on best practices for trans-national clinical trials; its goal is to build a capacity for DMCs in trials involving the developing world. They worked with pharmaceutical companies to have the training accredited and set up an apprenticeship program to give trainees a pathway to serving on DMCs. The training started as an in-person pre-conference session. From that experience, the curriculum was expanded to cover more fundamentals of clinical research and trial oversight, in addition to topics specific to DMCs. Training sessions are now conducted at sites throughout the world. The trainers research each country's regulatory requirements and partner with a representative from that country to tailor the content. They must also be attuned to cultural differences. Each session includes case studies for discussion. In addition to prospective DMC members, regulators and IRB members have also attended and found the material useful.

Finally, the CTTI work group presented their draft recommendations for DMC training. They recommend a program that includes didactic presentation,

interactive discussion (case studies, review of DMC meeting minutes), and apprenticeship or mentoring. They would like to encourage at least the inclusion of one or more non-voting mentees on each DMC. DMC training could be conducted through a variety of media, such as online, books, courses at professional meetings, or classes at organizations. The group requested feedback on the development of a DMC member database, which could include information on training completed, experience, areas of expertise, and contact information. What organization might be most appropriate to develop and maintain such a database? Additional questions included how to identify new pools of prospective DMC members for training, whether training should be required, and if training should be accredited and by whom.

In the discussion that followed, attendees expressed that potential DMC members should first be experienced clinical trialists, so many felt that clinical fellows do not yet have enough experience. Recruitment of junior members may be more appropriate for lower-risk, smaller studies. The group discussed whether there should be separate training for different audiences, such as patient advocates, clinicians, statisticians, regulators, and IRB members. Training of statisticians was felt to be distinct, and the material is not covered in graduate programs. It was also pointed out that even existing DMC members could benefit from training, since most probably never had any. One approach could be to give pre-tests so that content could be selectively delivered. Specific training for DMC chairs and sponsors was also recommended. The group strongly favored the idea of "toolboxes" that would allow for training customization and would include case studies for discussion. Informal training at a DMC meeting before trial initiation to go over analyses and have briefings on study design and trial- or program-specific information was also viewed as beneficial. Another suggestion was for a DMC chair blog where experiences and best practices could be shared, similar to a blog that exits for IRB chairs. There was consensus that training should not be required, but it should be encouraged, potentially through incentives such as CME credit. Survey respondents indicated that they would like to have training, so individuals may participate if such training is available and advertised. Accreditation was viewed as difficult, but acknowledgment of training could be provided. There may need to be discussions with sponsors about the need for nonvoting members on DMCs and to address concerns related to confidentiality and cost. The group felt that this should not be prohibitive.

Actionable Opportunities for Transformative Change

In the final activity of the meeting, attendees divided into breakout sessions by work group to discuss the recommendations, barriers to change, strategies to overcome those barriers, and ways to facilitate adoption of the recommendations. Work was then presented to the larger group for additional discussion.

DMC Purpose and Rationale

The DMC Purpose and Rationale Work Group used the attendee feedback to create a first draft of their recommendations, as follows:

1. Detailed rationale for having a DMC should be defined in the charter

- Ongoing assessment of risk-benefit profile
- Benefit can be broadly defined (e.g. patient, scientific progress, completion of safety profile)
- Enhancing the credibility of the trial is an acceptable rationale for a DMC
- Responsibilities of the DMC should be directly related to the rationale

2. Expectations of the DMC and sponsor should be detailed in the charter
3. DMCs should always
    - Review the protocol and consent form prior to first patient enrollment
    - Be aware of external information that may affect the risk-benefit profile
    - Assess the continuing scientific validity of the trial (e.g., trial progress, data quality)
    - Assess the initial and continuing ethical acceptability and risk-benefit profile of the study (e.g., consent procedure, aggregate safety data, traditional data monitoring)
4. Adjudication of study endpoints should not be done by the DMC (except in rare circumstances)

In response to the draft recommendations, attendees questioned what information should be considered when DMCs evaluate the risk-benefit profile. The response was that a DMC should use a reasonable person standard in keeping with the principle of respect for persons. There was a suggestion to reword recommendation number 4 to “Ideally, the DMC should not be involved in the conduct of the study."

DMC Training

The training work group summarized the feedback from attendees on the proposed recommendations. The group agreed that there should be a base level of training for everyone with specialized modules based on level of experience. A base training could be required, but there is a need to be mindful of the burden of more comprehensive training. Formalized ongoing training should also be developed to keep stakeholders engaged, and case studies were felt to be the best format. Senior DMC members who are close to retirement could also be a valuable resource for training future DMC members. There were suggestions to provide training on what a DMC report should look like and have a trial orientation session for each DMC when the charter and issues specific to the trial are discussed. DMCs can also consider having a closed session at the beginning of a meeting to review how members understood the data. Increasing participation in DMCs and training will require sponsor engagement, culture change, funding, and incentives. Collaboration among various stakeholders, including CTTI, NIH, FDA, industry, professional societies, nonprofit, and advocacy groups can help to overcome barriers. DMC training could be offered as part of clinical research training workshops or at professional society meetings. Overall, there is a need to increase recognition and raise the profile of DMC service since it is currently not viewed as part of a career path. Actions such as sending a thank you letter to the department chair of a DMC member could be helpful. Though there was agreement that DMC

members should not be coauthors on a publication for a trial, some felt it could be appropriate for DMC members to be recognized in the acknowledgements.

Organization and Formation of DMCs

The group reviewed the feedback received on their recommendations. This included having geographic representation on the DMC reflect anticipated regional differences, differentiating between patients and trained/qualified patient advocates for DMC membership, and having an ethicist member in cases of vulnerable populations or controversial issues per the Belmont Report. Additionally, it is important to consider the overall subject matter expertise of the DMC. The nonvoting apprentice role received broad support. There was a suggestion to collect COI information in a uniform way to ensure transparency with the sponsor, chair, and other DMC members. The group may be able to review existing COI examples and suggest an appropriate vehicle for this. Attendees felt strongly that there should not be a recommendation for the DMC chair to be a clinician, because it depends on the characteristics of the trial and individual.

In terms of the charter recommendations, there should be points to consider rather than a template. Brevity and clarity are preferred; it should not be a long and legalistic document. The goal is to empower the DMC, so the charter should not be restrictive.

DMC Communication

When attendees were asked whether anything had been missed from the Communication work group's recommendations, there was a suggestion to include best practices for communication among the DMC members themselves. This would include not discussing the trial outside of DMC meetings. Attendees also mentioned guidelines for communication between a DMC and a safety review committee, a pharmacovigilance group, or another DMC. Barriers identified to implementation of the proposed recommendations included challenges of delivering negative recommendations to companies, detailed charters and contracts exposing DMC members to liabilities, and DMC members following the charter exactly without enough flexibility. Best practices for how to deliver a decision to the sponsor could be generated. Other ways to facilitate adoption of the proposed recommendations included limiting interaction and sharing of information to discussion between the DMC chair and a predesignated contact at the sponsor, contractual provisions and funding allowing for additional analyses and ad hoc meetings, stating in the charter that the DMC remains committed to the safety of patients, and defining in the charter with whom the major DMC recommendations will be discussed. Additional suggestions included holding DMC meetings at a neutral location rather than the sponsor's offices, having minimal sponsor interactions outside the formal meeting, limiting the open session after meetings, and providing a period for written comments from the sponsor rather than holding a verbal debriefing. Finally, there was agreement that certain DMC meetings should be conducted in-person, such as a formal interim analysis meeting and preferably the first few DMC meetings.

Conclusion and Next Steps

The meeting was closed by thanking the experts for their thoughts and ideas, which will be used to develop recommendations and a plan for a future CTTI implementation project.

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ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to identify and promote practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

For more information, contact the DMC Project Manager Annemarie Forrest at annemarie.forrest@dm.duke.edu or visit http://www.ctti-clinicaltrials.org.

Appendix A. Meeting Agenda

Tuesday, July 28, 2015

8:00 am — **Breakfast (Provided)**

9:00 am — **CTTI Introduction**
Annemarie Forrest (CTTI)

9:10 am — **Issue, Project Overview, and Meeting Objectives**
Dave DeMets (University of Wisconsin)

Session I: — **Presentation of the Survey and Focus Group Results**
Session Facilitator: Jane Perlmutter (Patient Advocate)
Session Objectives:
- Present and discuss findings from the DMC project survey and focus groups

9:30 am — **Introduction to the Project Survey and Focus Groups**
Patrick Archdeacon (FDA)
- Description of survey and focus groups
- DMC purpose, rationale, roles and responsibilities

9:50 am — **DMC Communication Practices Among Key Stakeholders**
Ray Bain (Merck)
- Charter
- Reports to the DMC
- Reports from the DMC

10:10 am — **DMC Composition, Member Qualification and Training**
Jane Perlmutter
- DMC committee composition
- DMC member qualification
- Training DMC members and stakeholders

10:30 am — **Discussion**

11:00 am — **Break**

Session II: — **Data Monitoring Committee Purpose and Rationale**
Session Facilitator: Roger Lewis (Harbor-UCLA Medical Center)
Session Objectives:
- Solicit feedback on the role and function of DMCs and factors that influence their use in clinical trials

- ► Solicit feedback on other types of trial oversight committees, particularly ones whose responsibilities overlap with those of DMCs

11:15 am **DMC Purpose and Rationale**
Roger Lewis

11:20 am **Current Use of DMCs and Other Types of Trial Oversight Committees**
Jonathan Seltzer (ACI Clinical)

11:40 am **Facilitated Discussion**

12:30 pm **Lunch (Provided)**

Session III: **Formation and Organization of Data Monitoring Committees**
Session Facilitator: Ray Bain
Session Objectives:

- ► Solicit feedback on proposed recommendations related to
  - ○ Forming a DMC
    - • Committee qualification
    - • Committee make-up
- ► Operationalization of the DMC
  - ○ Charter preparation and maintenance

1:30 pm **Proposed Recommendations for Formation of DMCs**
John McEachern (Parexel)

1:45 pm **Discussion**

2:15 pm **A Proposed DMC Charter Checklist**
Karim Calis (FDA)

2:30 pm **Discussion**

3:00 pm **Break**

Session IV: **Communication Between the Data Monitoring Committee and Stakeholders**
Session Facilitator: Jason Connor (Berry Consultants)
Session Objectives:

- ► Solicit feedback and develop consensus on proposed recommendations related to
  - ○ Best practices for communication between the Statistical Analysis Center and other stakeholders

- Best practices for communication between DMCs and regulatory bodies
- Best practices for communication between the DMC and sponsor and/or steering committee

3:15 pm **Best Practices for Communication Among DMC Stakeholders**
Jason Connor

3:35 pm **Panel Discussion**
Janet Wittes (Statistics Collaborative, Inc.)
Joseph Heyse (Merck Research Laboratories)
Robert Smith (Brown University)

4:45 pm **Wrap-up**
Dave DeMets

5:00 pm **Dinner Reception**

Wednesday, July 29, 2015

8:30 am **Welcoming Remarks**
Annemarie Forrest

8:35 am **Summary of Day 1**
Dave DeMets (University of Wisconsin)

Session V: **Preparation of Data Monitoring Committee Members**
Session Facilitator: M. Khair ElZarrad (NIH)
Session Objectives:
- ► Solicit feedback and develop consensus on proposed recommendations related to DMC member training

8:45 am **NIAID DMC Training Program**
Judy Zuckerman (NIAID)

9:05 am **MRCT DMC Training Program**
Barbara Bierer (MRCT)

9:25 am **Proposed Recommendations for Training DMC Members**
M. Khair ElZarrad

9:45 am **Discussion**

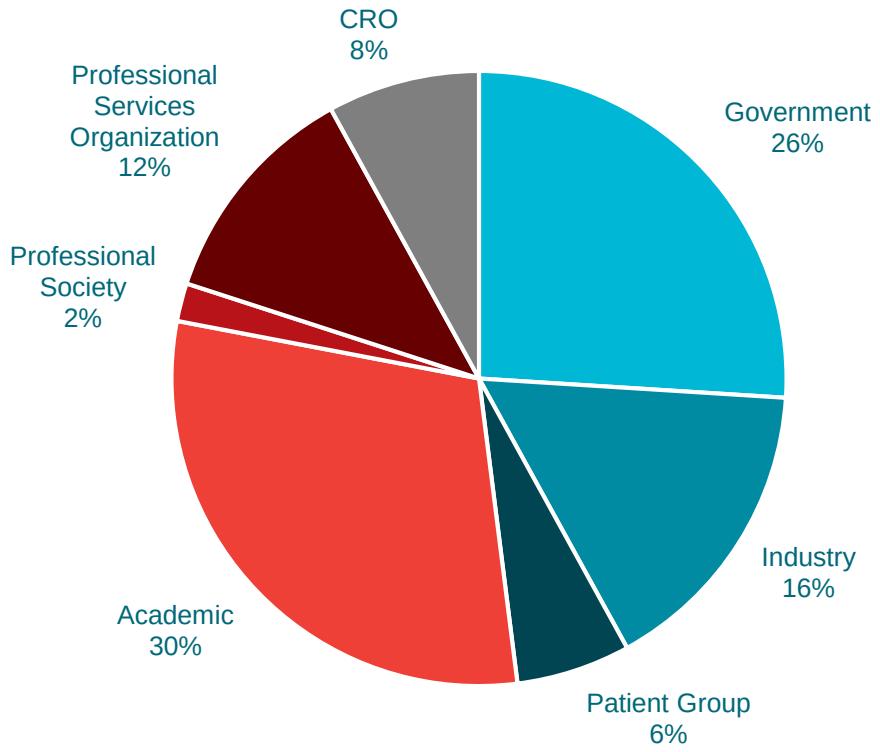
10:15 am **Break**
M. Khair ElZarrad

Session VI:	**Actionable Opportunities for Transformative Change** *Session Facilitator: Karim Calis (FDA)* *Session Objectives:* ► Discuss existing barriers to change and strategies for overcoming those barriers ► Consider ways to facilitate adoption of proposed project recommendations
10:30 am	**Break-Out Group Discussion: Actionable Opportunities for Transformative Change**
12:00 pm	**Working Lunch (Provided)**
12:30 pm	**Report Out and Large Group Discussion: Actionable Opportunities for Transformative Change**
2:00 pm	**Adjourn**

Appendix B. Meeting Participants

Our meeting participants include representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties. Participants are expected to be actively engaged in dialogue both days.

STAKEHOLDERS REPRESENTED



MEETING ATTENDEES

Participant Name	Affiliation
Tomas Andersson	AstraZeneca R&D
Patrick Archdeacon	Food and Drug Administration, CDER
Raymond Bain	Merck & Co., Inc.
Barbara Bierer	Multi-Regional Clinical Trials Center at Harvard
Karim Calis	Food and Drug Administration, CDER
David Chonzi	Genentech
Theodora Cohen	Harvard Clinical Research Institute
John Constant	PRA Health Sciences
Sonia Davis	University of North Carolina
David DeMets	University of Wisconsin-Madison
Matthew Dey	Quintiles
Dennis Dixon	National Institutes of Health, NIAID
Miriam Donohue	Quintiles

Susan Ellenberg	University of Pennsylvania
Mohammed Khair ElZarrad	National Institutes of Health, OK
Marian Fisher	University of Wisconsin-Madison
Elizabeth Frank	Dana Farber Cancer Institute
George Gasparis	The PEER Consulting Group, LLC
Amy Ghelardi	ACI Clinical
David Gordon	National Institutes of Health, NHLBI
John Isidor	Human Subject Protection Consulting, LLC
Jonathan Jarow	Food and Drug Administration, CDER
Hallie Kassan	North Shore-LIJ Health Systems
Karl Kieburtz	University of Rochester
Rene Kubiak	Boehringer Ingelheim
John Kusek	National Institutes of Health, NIDDK
John Lachin	The George Washington University
Roger Lewis	Harbor-UCLA Medical Center
Gary Lin	MIT/JHU Clinical Trials Systems Project
Robert Lindblad	Society of Clinical Trials
John McEachern	PAREXEL International LLC
Wayne Morgan	University of Arizona
Anna Nicholson	National Institutes of Health, NIAMS
Jane Perlmutter	Patient Advocate, Gemini Group
Lynne Quittell	Cystic Fibrosis Foundation-Data Safety Monitoring
Carson Reider	The Ohio State University
Nancy Roach	Fight Colorectal Cancer
Richard Rode	AbbVie
John Schoenfelderr	AbbVie
Suz Schrandt	PCORI
Jonathan Seltzer	ACI Clinical
Pamela Shell	National Institutes of Health, NIMH
Ken Skodacek	Food and Drug Administration, CDRH
Robert Smith	Brown University
Norman Stockbridge	Food and Drug Administration, CDER
Karen Ulisney	Food and Drug Administration, CDRH
Keith Usiskin	Celgene
William Wang	Merck & Co., Inc.
Kimberly Warner	ACI Clinical
Janet Wittes	Statistics Collaborative, Inc.

STAFF

Annemarie Forrest	Clinical Trials Transformation Initiative
Gerrit Hamre	Clinical Trials Transformation Initiative
Clare Matti	Duke Clinical Research Institute
Kimberley Smith	Clinical Trials Transformation Initiative
Gina Uhlenbrauck	Duke Clinical Research Institute