

Welcome to the CTTI Data Monitoring Committees Project Expert Meeting

July 28-29, 2015



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Introduction to The Clinical Trials Transformation Initiative

Annemarie Forrest, Project Manager, CTTI

July 28-29, 2015



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REPORT TO THE PRESIDENT
TRANSFORMATION AND OPPORTUNITY:
THE FUTURE OF THE U.S. RESEARCH
ENTERPRISE

Executive Office of the President
President's Council of Advisors on
Science and Technology

NOVEMBER 2012



FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

ENVISIONING A TRANSFORMED
CLINICAL TRIALS ENTERPRISE
IN THE UNITED STATES

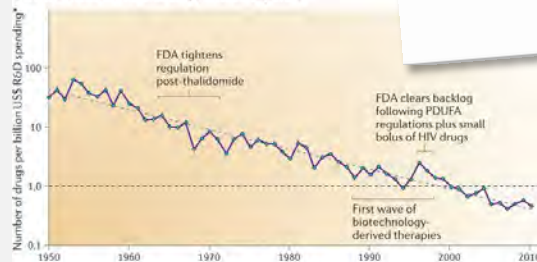
ESTABLISHING AN AGENDA FOR 2020



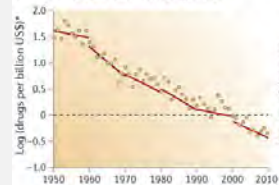
WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

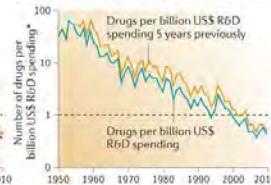
a Overall trend in R&D efficiency (inflation-adjusted)



b Rate of decline over 10-year periods



c Adjusting for 5-year delay in spending impact



Addressing This Need



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

Public-Private Partnership
involving all stakeholders
60+ members

CTTI Organization

Executive Committee (EC)

Provides oversight and strategic direction

Steering Committee (SC)
(member organizations representatives)

Gives input into strategy and project selection
Conducts projects and develops strategies for implementation of project results

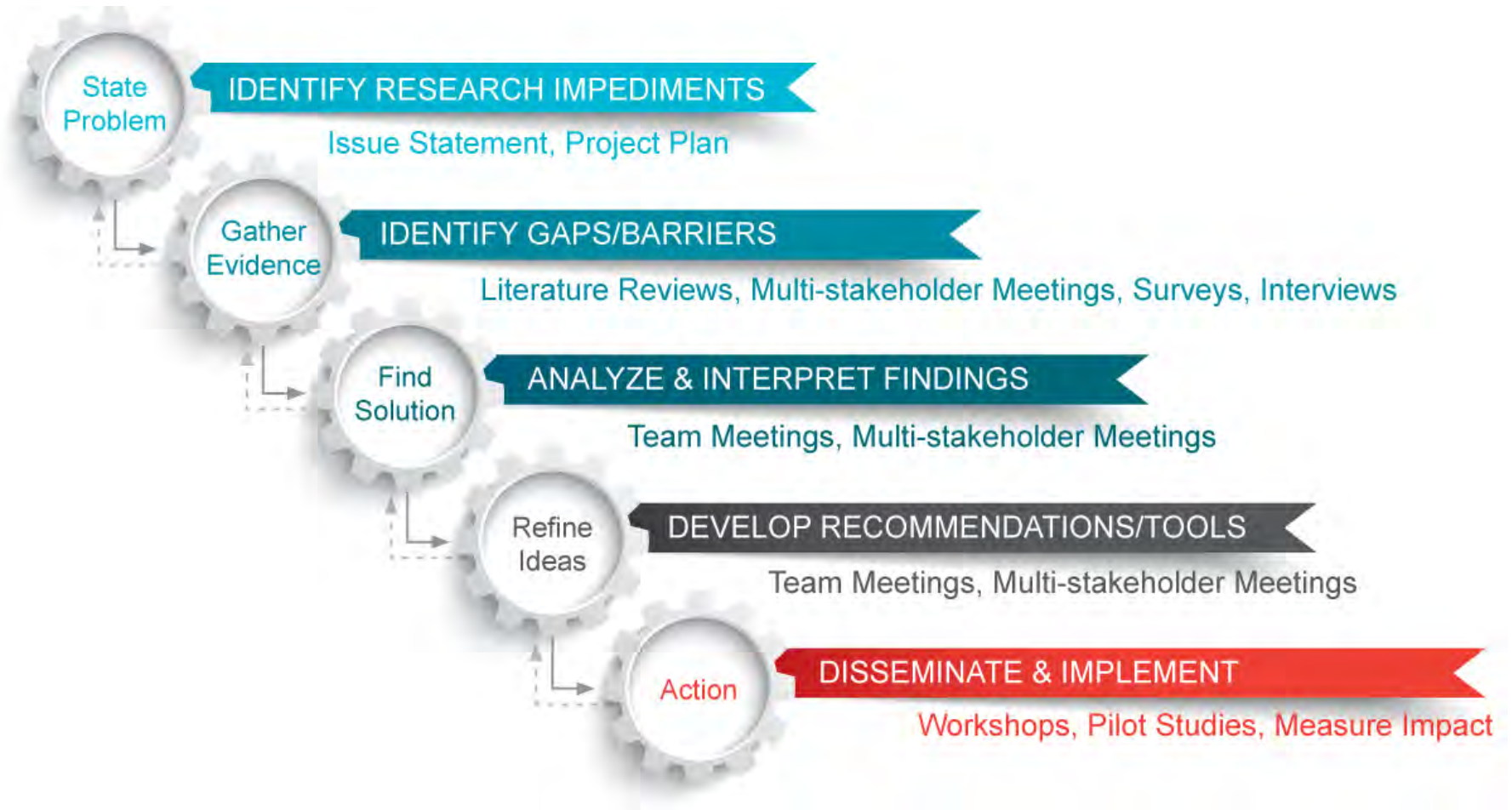
CTTI Staff

Support projects and organization in pursuit of mission

Collaboration Towards Solutions



CTTI Methodology



Portfolio of CTTI Projects

	Investigational Plan	Study Start-up	Study Conduct	Analysis & Dissemination	Specialty Areas
Closed Projects	<ul style="list-style-type: none"> • Large simple trials • Uses of electronic data 	<ul style="list-style-type: none"> • Central IRB • Site metrics • Central IRB advancement • GCP training 	<ul style="list-style-type: none"> • Adverse event reporting • IND safety • Monitoring 		<ul style="list-style-type: none"> • Long-term opioid data
Ongoing Projects	<ul style="list-style-type: none"> • Mobile clinical trials (program) • Patient groups & clinical trials • Pregnancy testing • QbD • Trials based on registries • Uses of electronic data application 	<ul style="list-style-type: none"> • Informed consent • Investigator turnover • Recruitment 	<ul style="list-style-type: none"> • IND safety advancement • Safety case studies 	<ul style="list-style-type: none"> • State of clinical trials • DMCs 	<ul style="list-style-type: none"> • Pediatric antibiotic trials • Streamlining HABP/VABP trials • Unmet need in antibiotic development • ABDD pilot

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Issue, Project Overview and Meeting Objectives

Dave DeMets, University of Wisconsin

July 28, 2015



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CTTI DMC Project Team

Team Leaders

- Patrick Archdeacon (FDA)
- Raymond Bain (Merck)
- Karim Calis (FDA)
- Dave DeMets (Univ. of Wisconsin)
- Jane Perlmutter (Patient Rep)

Team Members

- John Adler (AstraZeneca)
- Mary Kay Ballasiotes (Patient Representative)
- Jason Connor (Berry Consultants)

- Matthew Dey (Quintiles)
- Miriam Donahue (Quintiles)
- Susan Ellenberg (Univ. of Penn.)
- M. Khair Elzarrad (NIH)
- Roger Lewis (UCLA)
- John McEachern (Parexel)
- Michael Pencina (Duke)
- Jonathan Seltzer (APCR)
- Robert Temple (FDA)

CTTI Project Manager

- Annemarie Forrest

Introduction to the CTTI Data Monitoring Committees Project

- ▶ Data Monitoring Committee: An independent group of individuals who review the ongoing conduct of clinical trials to monitor efficacy and patient safety and to ensure the validity and integrity of the trial
 - **Internal:** Individuals who conduct these activities within the sponsor organization
 - **External:** Individuals who conduct these activities outside of the sponsor organization

Evolving role of the DMC...

- The concept of an independent data monitoring committee introduced in 1967 by the Greenberg Report
 - Original charge: monitor conduct and safety of single trial. Trials might be terminated because the intervention's benefit clearly established, because of sufficient evidence of harm, because the trial no longer viable or of interest, or other compelling reason
 - Initially used in large randomized multicenter trials that targeted improved survival or reduced risk of major morbidity
- Today's DMCs take a variety of forms and fill a wide range of roles
 - DMCs may monitor a single trial, groups of trials, or TA portfolio
 - DMCs may be internal or external
 - Use no longer restricted to controlled trials comparing rates of mortality or major morbidity (and NIH and VA, though not FDA, policies may require their use in some additional contexts)
 - Responsibilities may include reviewing data quality and/or trial operations as well as providing ethical oversight

DMC Aliases

- DMC = Data Monitoring Committee
- IDMC = Independent DMC
- DSMB = Data & Safety Monitoring Board
- DSMC = Data & Safety Monitoring Committee
- SMB = Safety Monitoring Board
-

Clarify the roles and functions of DMCs to improve resource allocation

- Evolving roles of DMCs have led to unclear expectations between DMCs and other stakeholders (sponsors, CROs, regulators, investigators, patients)
- The overall increased use of DMCs have resulted in a mismatch between the need for and availability of DMC members
- The new and varying functions of DMCs require clarification of the appropriate training and composition of DMCs
- Lack of plan for preparing next generation of DMC members

Objectives of DMC Project

- Understand the current landscape of DMC use and conduct
- Clarify purpose(s) of DMCs
- Understand best practices for DMCs with regards to:
 - DMC composition
 - DMC Report generation
 - Member qualification and training
- Describe effective communication between DMCs and other trial stakeholders
- Identify strategies for preparing the next generation of DMC members

Project Methodology

Surveys & Interviews

Expert Meeting

Finalize Recommendations

Dissemination & Implementation

Meeting Objectives

Present findings and conclusions from the project survey and focus groups

Share and solicit feedback on proposed recommendations

Ground Rules

- Share the airtime
- Actively participate- success depends on participation, share ideas, ask questions, draw others out
- Different opinions are welcome, but disagree without being disagreeable
- Listen for the future to emerge
- Start and finish on time

Session I: Presentation of the Survey & Focus Group Results

Objective

- Present and discuss findings and conclusions from the project survey and focus groups

Agenda

- Introduction to the Project Survey and Focus Groups
- Data Monitoring Committee Communication Practices Among Key Stakeholders
- Data Monitoring Committee Qualification, Composition and Training

Introduction to the CTTI Data Monitoring Committees Project

Patrick Archdeacon, M.D.
Office of Medical Policy/CDER/FDA

July 28, 2015



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Overview of Presentation

Introduction to the Data Monitoring Committee Project

- Rationale for the project
- Project objectives
- Project methodology
 - Survey
 - Focus groups
 - Expert meeting
- Preliminary findings
 - DMC purpose and scope
 - Gaps and unanswered questions

DMC Project Methodologies

Survey

- to assess current use and conduct of DMCs
- to assess training practices for DMC members

Focus groups

- to provide in-depth understanding of needs and best practices related to DMC use in modern context

Expert meeting (July 2015)

- discuss results of survey and focus groups
- develop preliminary recommendations

Survey Overview

- Question topics developed by work group; refined and survey build by Duke Center for Learning Health Care
- Sent to CTTI members, work group recommended contacts, LinkedIn groups
 - Forwarding allowable
 - No data on how many viewed the invitation to complete the survey
- Respondents were all anonymous
- Open Oct 24, 2014 – December 1, 2014
- Respondents
 - 76 DMC members
 - 52 organizers
 - 15 SAC representatives

DMC Survey

Rank from 1-7 which activities you view as the *most important activity* that DMCs perform

	All Organizers	All DMC Members
To review both summary adverse events and primary outcomes by treatment arm to assess the benefit to risks	2.3	2.2
To review accumulating or summary adverse events by treatment arm	2.9	2.8
To review accumulating or summary adverse event reports overall	3.4	3.7
To increase the integrity of the trial by reviewing, recruitment, adherence to the protocol and quality of data	3.7	3.2
To review individual serious adverse event reports	3.8	4.0
To review individual adverse event reports	5.5	5.4

Average Rank: 1.0  7.0

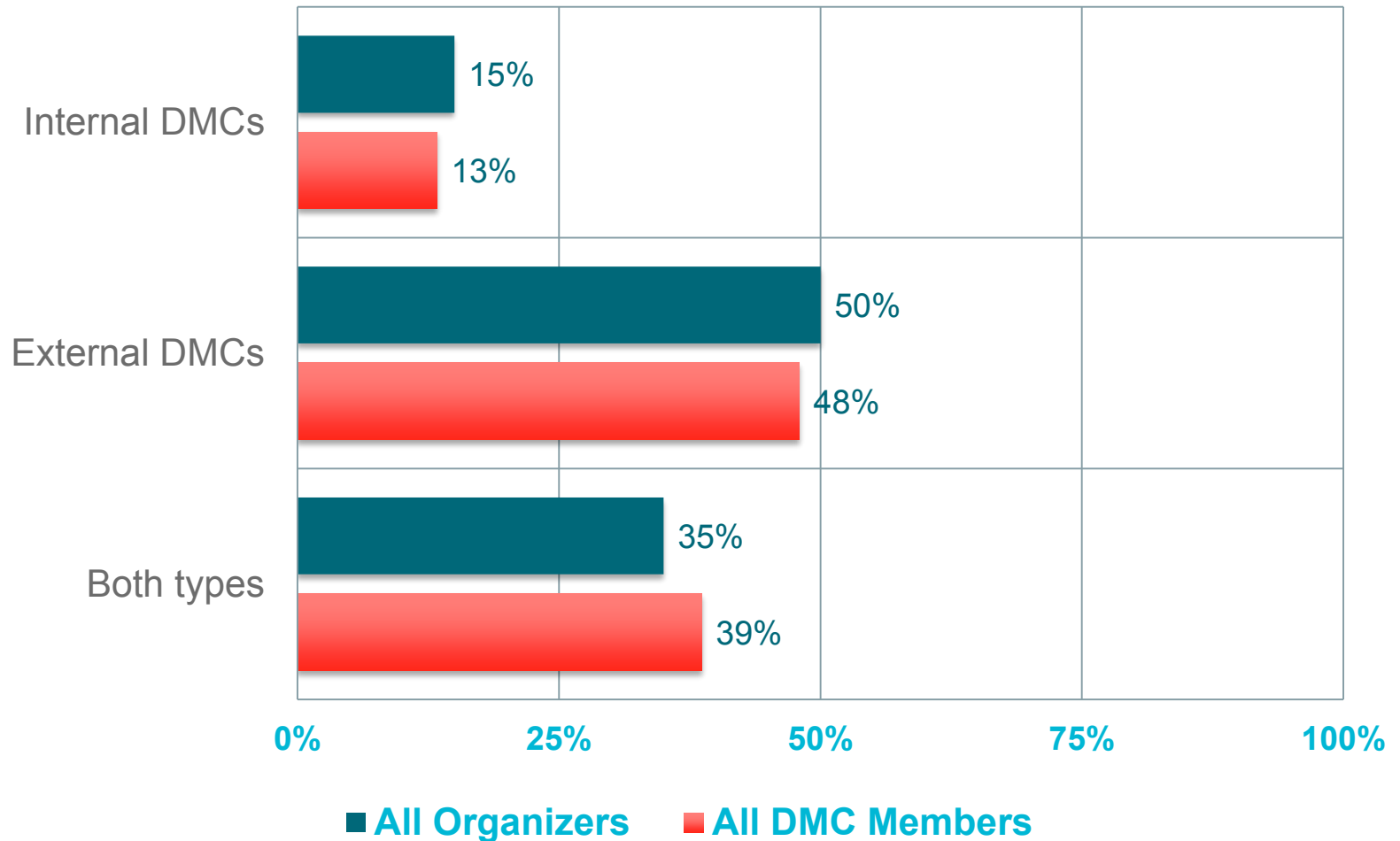
DMC Survey

Rank from 1-7 which activities you view as the *most important activity* that DMCs perform

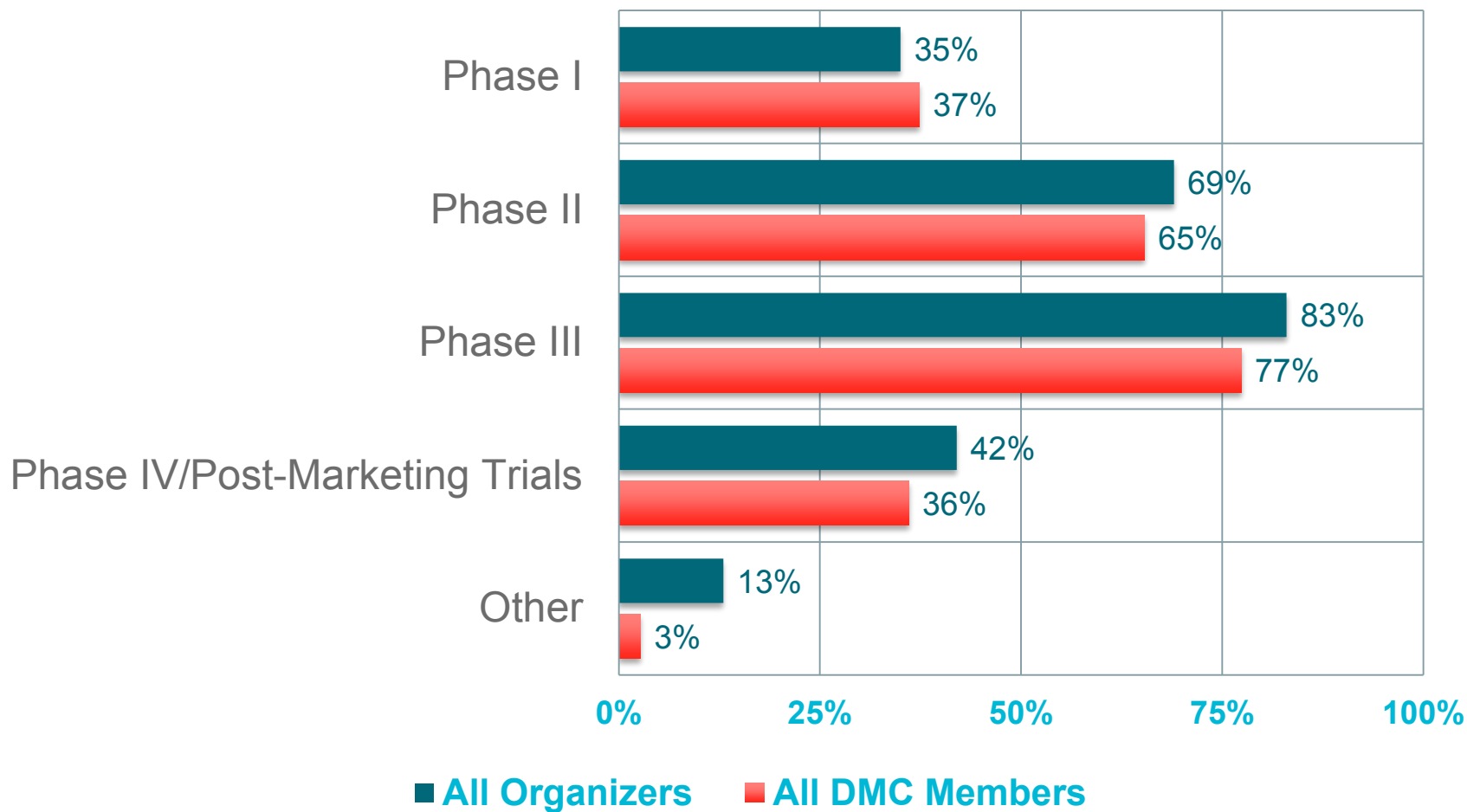
	All Organizers	Academic	ARO/CRO	Govt Sponsors	Industry
To review both summary adverse events and primary outcomes by treatment arm to assess the benefit to risks	2.3	2.9	1.7	2.4	2.2
To review accumulating or summary adverse events by treatment arm	2.9	3.4	3.8	3.2	2.4
To review accumulating or summary adverse event reports overall	3.4	3.3	3.2	3.3	3.4
To increase the integrity of the trial by reviewing, recruitment, adherence to the protocol and quality of data	3.7	3.0	4.2	2.9	4.2
To review individual serious adverse event reports	3.8	3.0	3.5	4.1	3.9
To review individual adverse event reports	5.5	5.4	6.0	5.5	5.3



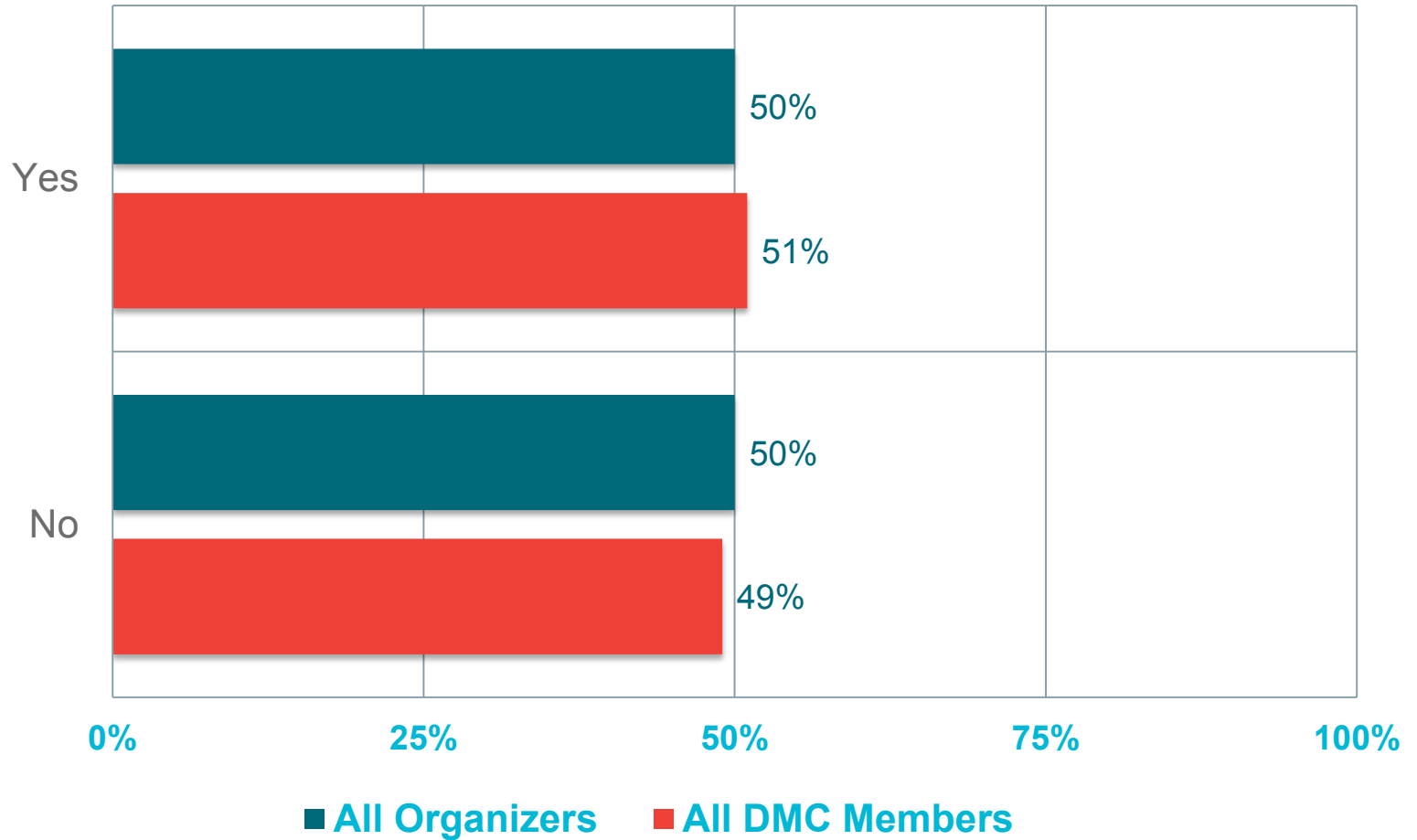
With which type of DMC have you had experience?



Which trial phases do your DMCs review?



Do you interact with or participate in DMCs for adaptive design trials?



Focus Groups Overview

- Question topics developed by work group, based on by preliminary survey data
 - 6 Focus Areas DMC members (10), Pt Advocates (7), IRB/FDA (7), Industry Sponsors (6), Govt/NFP sponsors (6), SACs (6)
- Focus Group participants identified by
 - Self selection via the survey
 - Work group member recommendation
- Focus groups executed by Duke Center for Learning Health Care
 - Held mid-December 2014 through mid-January 2015
- Focus group responses particularly useful for stimulating discussion and thinking within CTTI work group – the samples contained in the following slides are provided not as conclusions but to create threads for today's meeting

DMC Role

DMC Members Focus Group

What is the role of a DMC?

- **The DMC roles should be dictated by a well defined charter.**
- “Heterogeneity of experience and knowledge base of members is the single most important thing for the DMC to function effectively.” Member diversity is important. The standard for being chosen shouldn’t just be that you know someone and they like you.
- It is important for members to have a background in regulatory, statistics, or clinical trial management.
- The role of the chairperson of the committee is critical. He/she has to know the operations and philosophy of the committee.
- The chairperson needs to ensure each member of the committee has a voice and have the ability to pull conversations out of members when meetings are phone calls and not face to face.

DMC Role

DMC Members Focus Group

➤ *What is the DMC's role in regards to trial design?*

- Limited role in trial design, if the DMC becomes too involved they may become vested in the outcome of the trial.
- Committee can make suggestions about protocol that Investigator can consider. If the design is fundamentally problematic or unethical a DMC may be more forceful, but this is rare.

DMC Role

DMC Members Focus Group

➤ *When should DMCs be provided with efficacy data?*

- DMCs should be allowed to review efficacy data for important safety signals.
- Unblinded interim analyses should be identified in the charter and agreed by everyone upfront.
- **It's important to be unmasked to the assignment of treatment and to have the efficacy data for all trials.**
- “DMCs are made up of experts in the field being studied, and if you simply give them A vs. B, you end up with them speculating as to what’s going on, instead of using all of their faculties to evaluate the data.”

DMC Role

FDA/IRB Focus Group

What should be the primary responsibilities of a DMC?

- The primary responsibility of a DMC is to be an independent advisory committee. They can advise to stop a trial for safety reasons, futility, or proven survival or efficacy benefit.
- **“I think DMCs are acting more as DSMBs – doing the detailed analysis of the safety.”**

DMC Role

FDA/IRB Focus Group

▶ *What should be the role of DMCs in detection of unanticipated safety signals?*

- DMCs historically have done pre-specified analyses to see if there are reasons to stop the trial early.
- The DMC makes a recommendation to the sponsor and the sponsor usually updates the protocol accordingly. If there is a recommendation for change that wasn't done, the IRB will ask for justification on why they didn't accept the advice.

▶ *Should recommendations made by the DMC be binding?*

- Historically the DMC has been advisory but it could be more binding if the roles are written that way.

Determining Need for a DMC

FDA/IRB Focus Group

➤ *Do you think DMCs are appropriately, over, or under utilized?*

- DMCs are overused. The number of times a DMC triggers a protocol event is rare and may mean they are being used too often. “We expect all trials to be monitored for safety... but you don’t need a DMC for that.”
- Safety reporting is done through the sponsor; DMCs don’t meet quick enough to catch serious safety events.
- IRBs can feel more comfortable knowing that there is another group (DMC) who is also looking at AEs and safety data, and the onus isn’t on the IRB.

Determining Need for a DMC

Gov/NP Sponsor Focus Group

➤ *How do you determine whether a DMC is needed for a particular trial?*

- The need for DMCs is determined by complexity – complexity of the intervention, risk to patients and vulnerability of the patient population all go into the decision to have a DMC.
- **Multicenter trials and randomized, controlled trials require a DMC. Research networks can have DMCs even if the individual trials do not.**
- A program official or investigator may propose a DMC even though the governing body/institute may not require one.

Determining Need for a DMC

Industry Sponsor Focus Group

➤ *How do you determine whether a DMC is needed for a particular trial?*

- Every study does not need an EXTERNAL independent DMC. Data monitoring, and safety monitoring in particular, is required for most trials and exists internally within the sponsor (like internal safety groups separate from the study teams); although different companies have different policies.
- There are clear cases where independent external DMCs are needed, where no sponsor personnel would be on the committee, even as non-voting members.

DMC Project

Unresolved Issues and Remaining Gaps in Understanding

- *Under which circumstances is DMC review warranted?*
- *Should DMC review be mandatory in certain cases?*
- *Are there factors that influence the decision to use a DMC?*
 - Risk level
 - Trial phase, duration, or complexity
 - Type of study participants
 - Type of study designs or study objectives
 - Type of study endpoints
 - Type of data analysis plan
 - Type of sponsor

DMC Project

Unresolved Issues and Remaining Gaps in Understanding

- ▶ *How do we ensure that DMCs are truly independent?*
 - Do they have a clear and well-articulated charter that contains all of the critical elements (template, checklist)?
 - Can they meet on an ad hoc basis if needed?
 - Do they have adequate resources and accommodations to carry out their duties and fulfill their mission?
 - Are all findings and recommendations of the DMC consistently shared with IRBs and regulatory bodies regardless of the sponsor's opinion or intent in regards to the DMCs advice?

DMC Project

Unresolved Issues and Remaining Gaps in Understanding

- *How do we ensure that there is an adequate number of unbiased, competent, experienced, and well-trained DMC members to meet the growing demand?*
- *If DMCs are created to meet disparate objectives, how can the composition and charter of the DMC best reflect the context of use? Would clarifying such issues lead to better resources allocation and limit unmet expectations?*

DMC Project

Summary

- ▶ ***DMCs play a critical role in clinical trials***
 - monitoring efficacy and patient safety
 - ensuring the validity and integrity of the trial
 - specific roles and functions, however, of DMCs vary according to context
 - greater clarity and communication around uses of DMCs would help limit unmet expectations and improve resource allocation
- ▶ ***Overall, data from the survey and focus groups generally support this assertion***

Thank you.



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Data Monitoring Committee Communication Practices Among Key Stakeholders

Ray Bain, Merck Research Laboratories

July 28, 2015



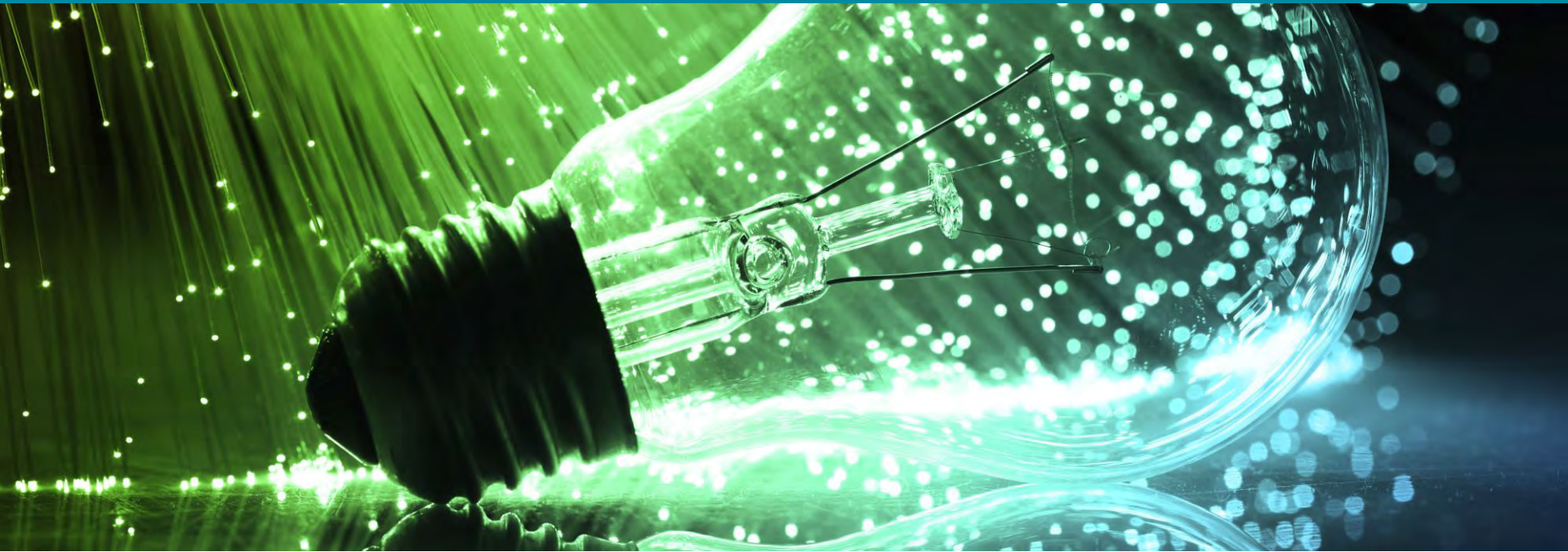
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Project Objective: Communication Practice

- Describe effective communication practices between independent DMCs and trial stakeholders, during all phases of DMC activity including
 - Charter preparation and maintenance
 - Provision of statistical reports to the DMC
 - How and to whom the DMC reports findings under various circumstances
 - How information generated by the DMC is reported to regulatory bodies

Findings: Communication Practice

- Charter preparation and maintenance
 - Contract (including remuneration)
- Provision of statistical reports to the DMC
- DMC report of findings:
 - DMC recommendation
 - Interactions: Sponsor and regulatory agencies



Charter preparation and maintenance

Contract including remuneration

Key Messages:

Charter preparation and maintenance

- Sponsors have SOPs governing conduct of DMCs including a DMC charter template that is tailored to each specific trial
 - Charter authoring originates from multiple sources (e.g. sponsor, SAC)
- DMC charters are considered useful to carry out DMC responsibilities and are approved by the DMC members and/or DMC Chair
 - DMC members have the opportunity to provide input
- Format of meetings is a mix of remote/in-person with frequency of regular (quarterly or semi-annually) plus ad hoc meetings jointly determined by sponsor and DMC
 - DMC has authority to schedule ad hoc meetings

High concurrence on charter items except for the timing of meetings

Charter Item	All Organizers	All Members
Meeting Format	92%	84%
Timing of Meetings	92%	79%
Conflict of interest	88%	90%
Specific Member Responsibilities	88%	81%
Confidentiality	86%	95%
Reporting Instructions after DMC meetings	86%	83%
Outline of data to be reviewed	84%	83%
List of DMC members & contact info including chair	80%	90%
Blinding procedures	78%	76%
Whether additional analyses can be requested by the DMC (in addition to pre-defined analyses in the SAC)	75%	78%
Stat guidelines for early term for benefit/harm/futility	73%	81%

Key Messages: How can the charter be improved

- ▶ “Having <a high quality> one is a good start!”
 - Not too short and not too long; just right
 - Detailed statistical analysis plans remain separate
- ▶ Pre-specify the planned contents of the DMC report
 - Include review of efficacy along with safety
 - Clearly identify items “adaptive by design”
 - Indicate that ad hoc analyses/meetings will be needed
- ▶ Clear (but flexible) about how decisions are made by DMC
 - Leave room for judgment calls
- ▶ Fully address trial blinding
 - If/when trial leadership is notified of aggregate event rates
- ▶ Detail communication practices between DMC/SAC/Sponsor

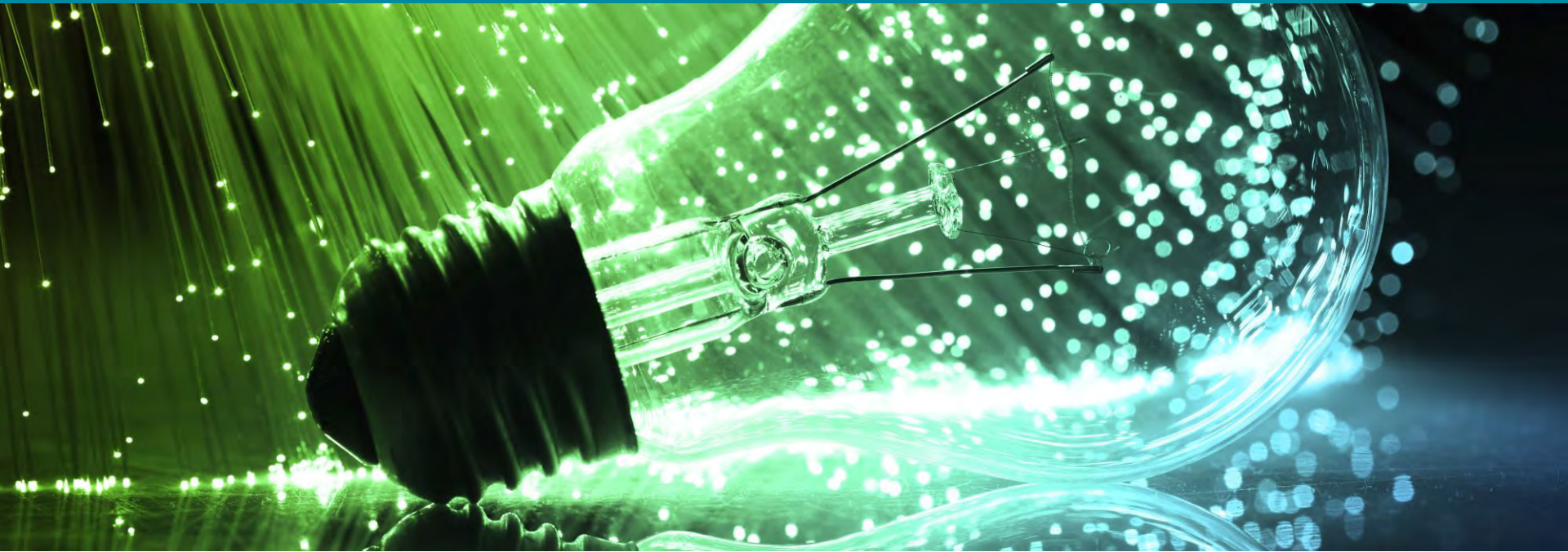
Key Messages:

Contract and Remuneration

- Formal contract between sponsors and DMC members customized specifically for a DMC
- Remuneration is based on per meeting/teleconference rate, or an hourly rate
 - Government sponsors set the remuneration rate while commercial sponsors negotiate with DMC members
- High concurrence between clinical trial organizers and DMC members on contract items (see next slide) except for the following:
 - Pay for unscheduled meetings
 - Pay for work done outside of regular meetings
 - Sunshine act reporting requirements

What does the contract typically contain?

Contract Item	All Organizers	All Members
Confidentiality	94%	95%
Rates	85%	86%
Responsibilities	79%	77%
Conflicts of Interest	79%	88%
Independence from sponsor	70%	66%
Pay for unscheduled mtgs	67%	46%
Intellectual Property	64%	59%
Pay for work done outside of reg. mtgs	61%	43%
Timing and frequency of meetings	58%	61%
Indemnification	58%	63%
Sunshine Act reporting requirements	55%	21%



Provision of statistical reports to DMC

Key Messages:

Provision of statistical reports to DMC

- ▶ DMC members:
 - See table shells in advance of the first interim analysis
 - Have opportunity to suggest changes to table shells
- ▶ SAC-generated interim analysis report:
 - If needed, analyses and/or DMC meetings can change
 - There is flexibility in the content of the DMC analyses
 - Biostatistician with expertise in interim analysis methods who prepared DMC report is present at DMC meetings
- ▶ Sponsor is not aware when changes made to DMC analyses (e.g. additional requested analyses from DMC)

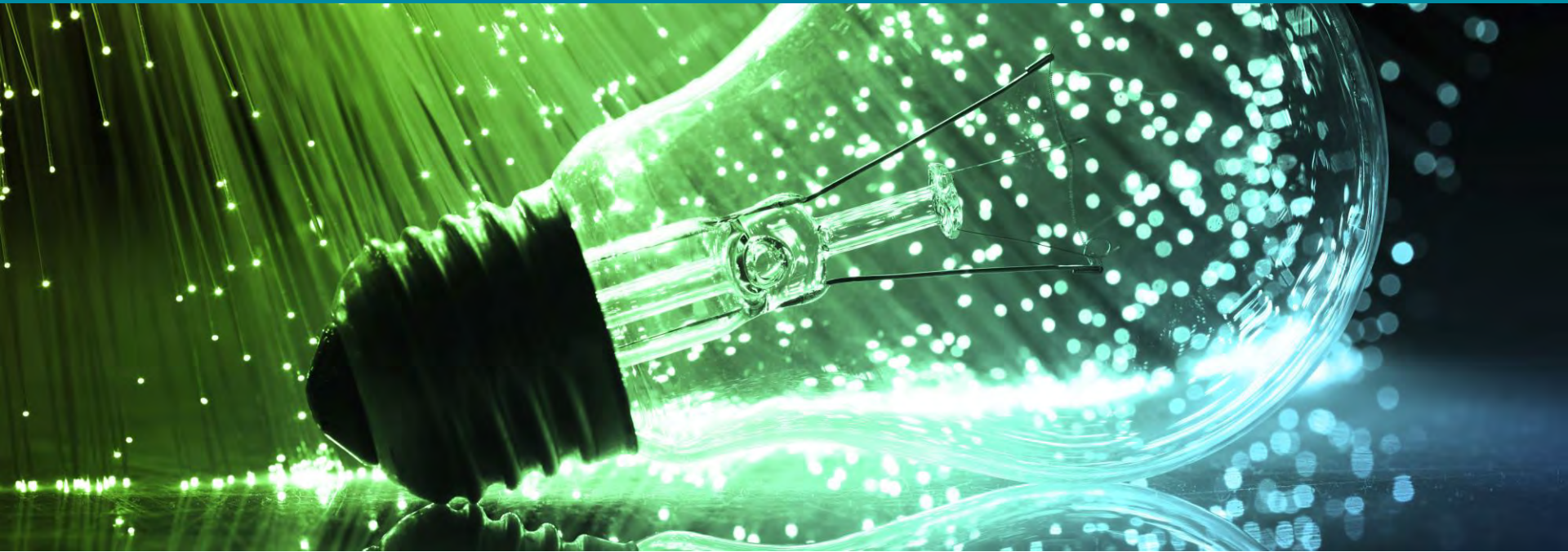
Key Messages:

SAC preparation statistical reports to DMC

➤ Best practices:

- SAC statistician experienced with DMCs and understands the trial's protocol and procedures
- Clearly drafted reports before first meeting allowing DMC members to review and request changes
- Report provides an overview of current study status
- Flexible monitoring rules
- DMC report delivered through a secure system
- Use of figures & graphics

➤ Proportion of an interim analysis report containing graphics (e.g. figures) is 25% or less.



DMC report of findings

Sponsor interactions

Reporting to regulatory bodies

Key Messages:

DMC recommendation & Sponsor interaction

- ▶ DMC have been able to function independently
 - Close communication during charter development; once charter finalized, minimize communication between DMC and sponsor
 - Sponsor contact during DMC meeting open session; more so for industry compared to government sponsors
 - Pressure to make a particular decision not felt and never suffered adverse consequences; pressure if felt is from other DMC members
 - Must maintain charter discipline during “heat of the moment” (e.g. inexperienced chair contacting sponsor)
- ▶ DMC recommendations accepted by the sponsor
 - DMC is advisory (i.e. not expected to make decisions on behalf of sponsor); sponsor makes the actual decision

Key Messages:

DMC and Regulatory/IRB interaction

➤ Request to use a DMC:

- IRB: It's their role to request a DMC, if necessary
- FDA: Rarely request a DMC given already planned

➤ Modify planned DMC:

- IRB and FDA: Will comment on the planned DMC's independence

➤ DMC charter review:

- IRB: No
- FDA: Sometimes, before study initiation

➤ DMC member qualification evaluation: No for IRB & FDA

➤ Direct communication with DMC:

- IRB: No direct; may require documentation of the DMC meetings
- FDA: Infrequent direct; typically when DMC stops trial

Thank you.



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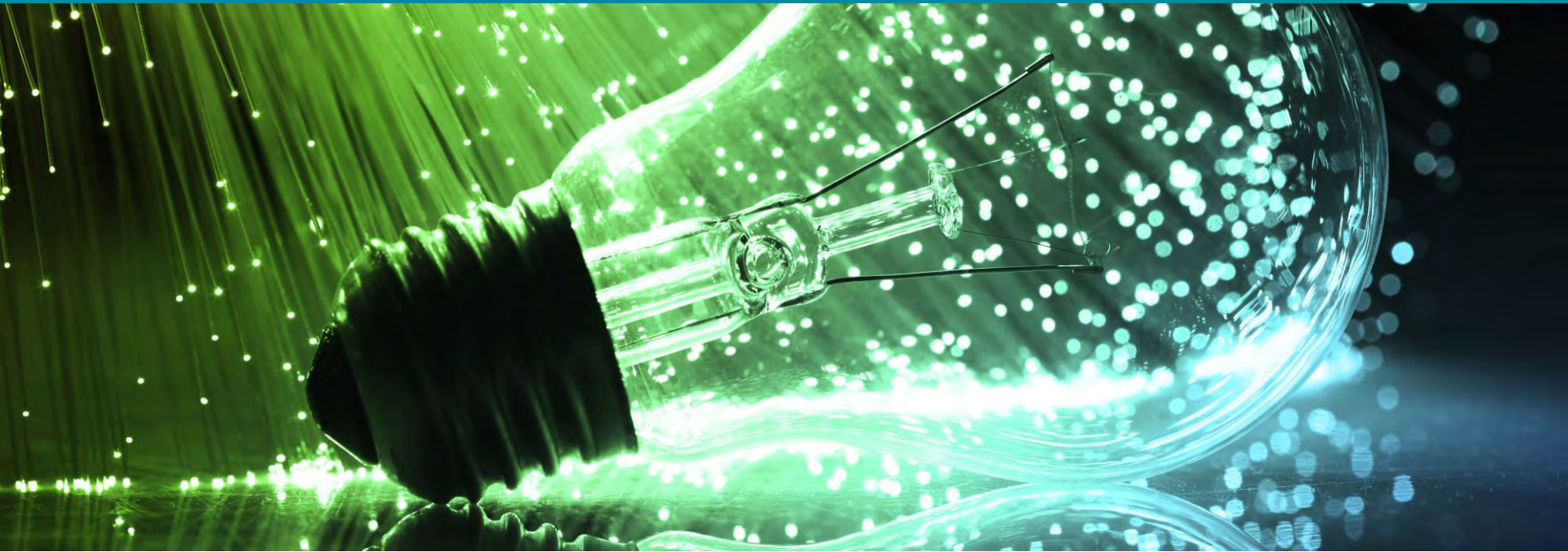
Data Monitoring Committee Qualification, Composition and Training

Jane Perlmutter, Patient Advocate

July 28, 2015



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DMC Membership

Typical Makeup

Qualifications

Identification of Members

Developing the Next Generation Of Members

What is the Typical Make-up of a DMC?

- Two to six members
- Generally includes statistician and clinician familiar with disease
- Sometimes includes ethicist, especially when there are perceived special issues
- Sometimes includes researchers with special expertise relevant to trial
- Increasingly includes patient advocates

DMC Member Qualifications

Category	Special Expertise
Chairperson	Experience as a DMC member Leadership skills
Statistician(s)	Design and conduct of clinical trials Group sequential and adaptive research designs
Clinician(s)	Natural progression of disease Standard treatments and toxicities
Ethicist(s)	Balancing needs of trial patients vs. future patients
Patient Advocate(s)	Patients perspective on benefits vs. risks, Quality of life perspective
Specialist Relevant to Trial	Expertise in potential toxicities Expertise in measurement endpoints

Sample Quote from Focus Groups:

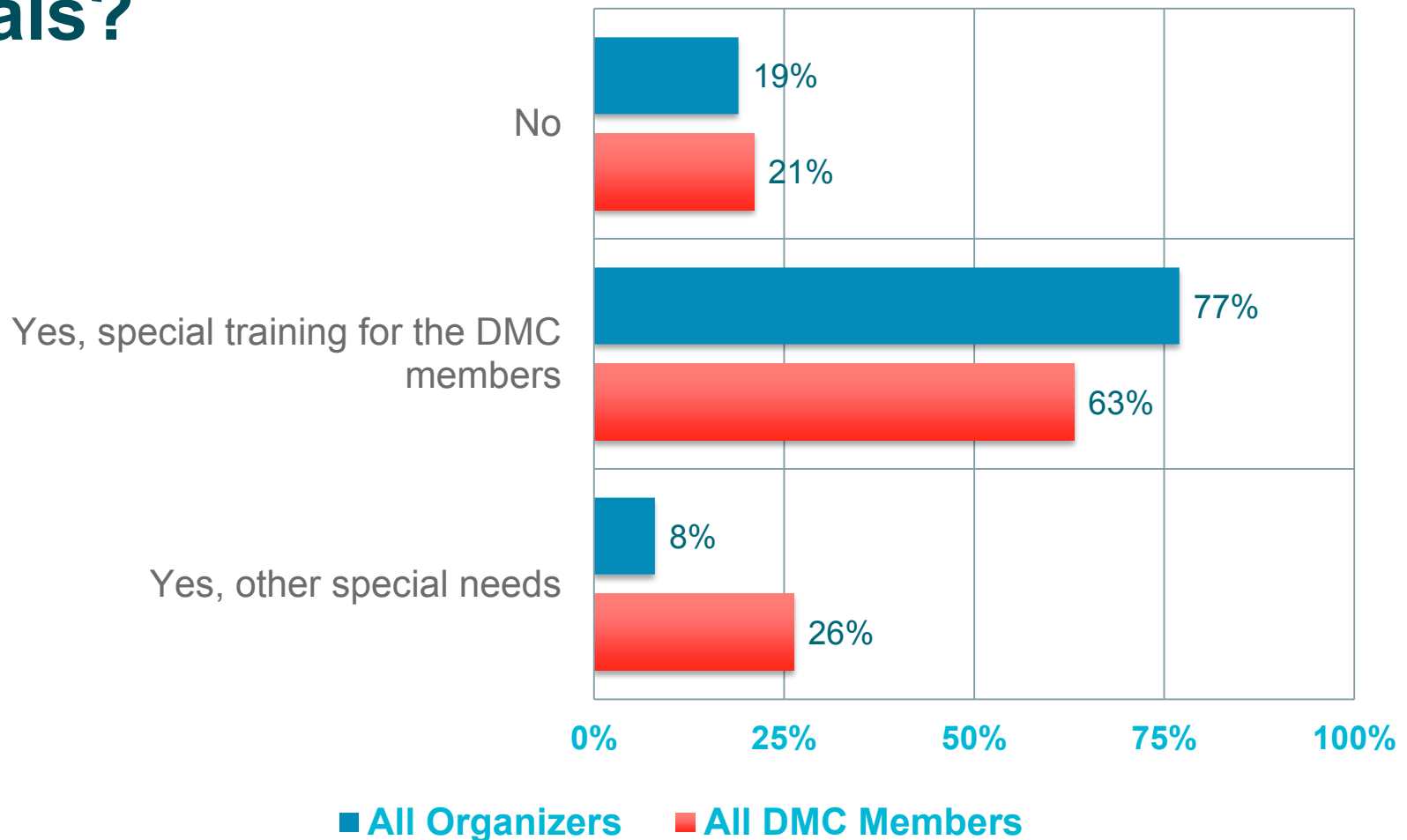
*What Qualifications Do **DMC Members** Need?*

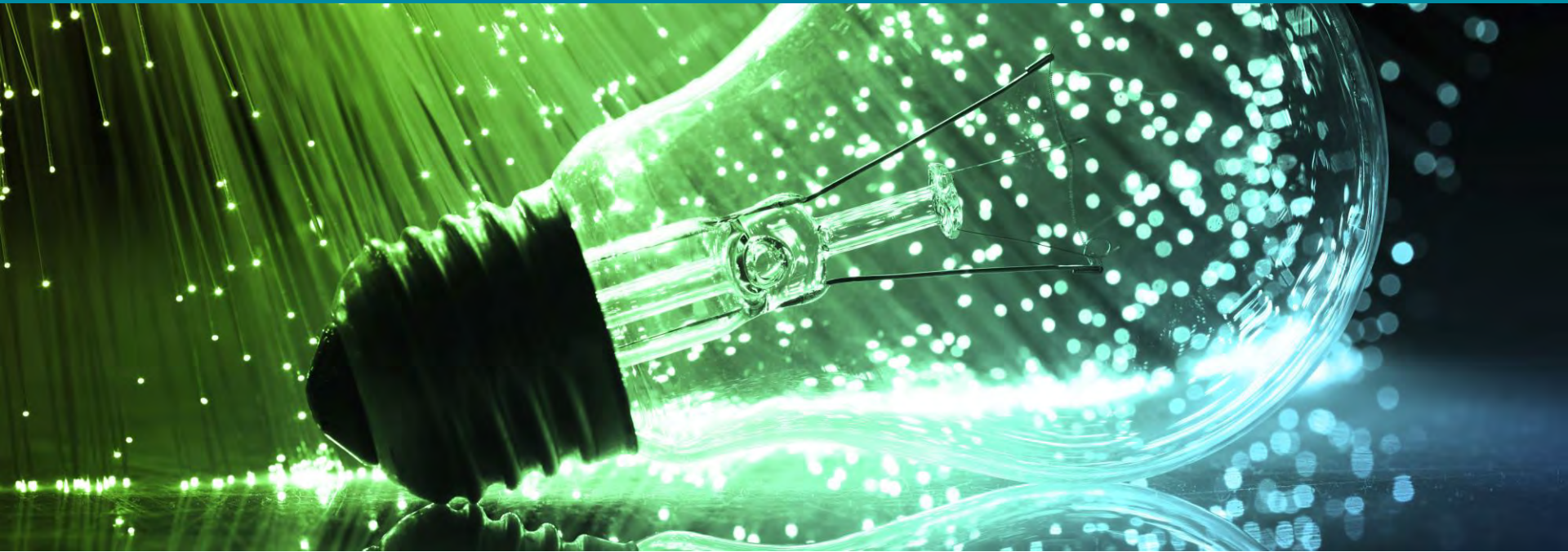
- There are no standard qualifications and that is a problem
- Expertise should be broad enough to cover safety issues that may arise
- Not only should DMC member have disease specific expertise, but also need to understand complex data and challenges of interpretation
- Independence, minimal COIs
 - Regular reporting of COIs
 - Transparency critical
- Experience on DMCs
- Sound judgment and ability to “play well with others”

Sample Quote from Focus Groups: *What Qualifications Do **DMC Chairs** Need?*

- ▶ A key qualification of the DMC chair is experience
- ▶ The chair needs to know how to:
 - Run a meeting
 - Listen
 - Draw out consensus
 - When not to talk
- ▶ Most important qualifications of a DMC chair are:
 - Focus
 - Judgment
 - Experience, not just medical expertise
- ▶ Ensure all member are doing their job and being heard

Do you believe there are special DMC needs in the context of adaptive design trials?



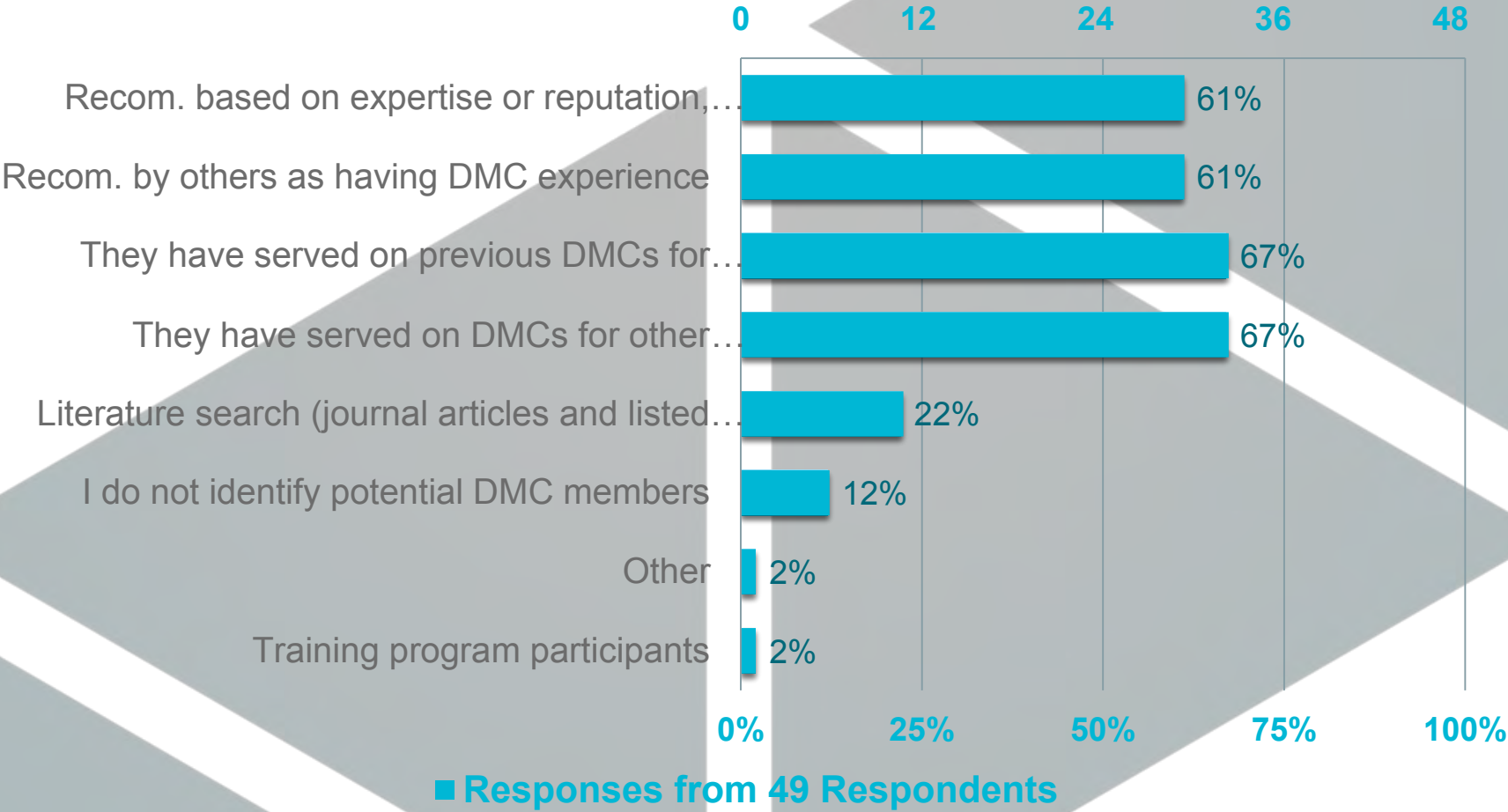


DMC Membership

Identification of Members

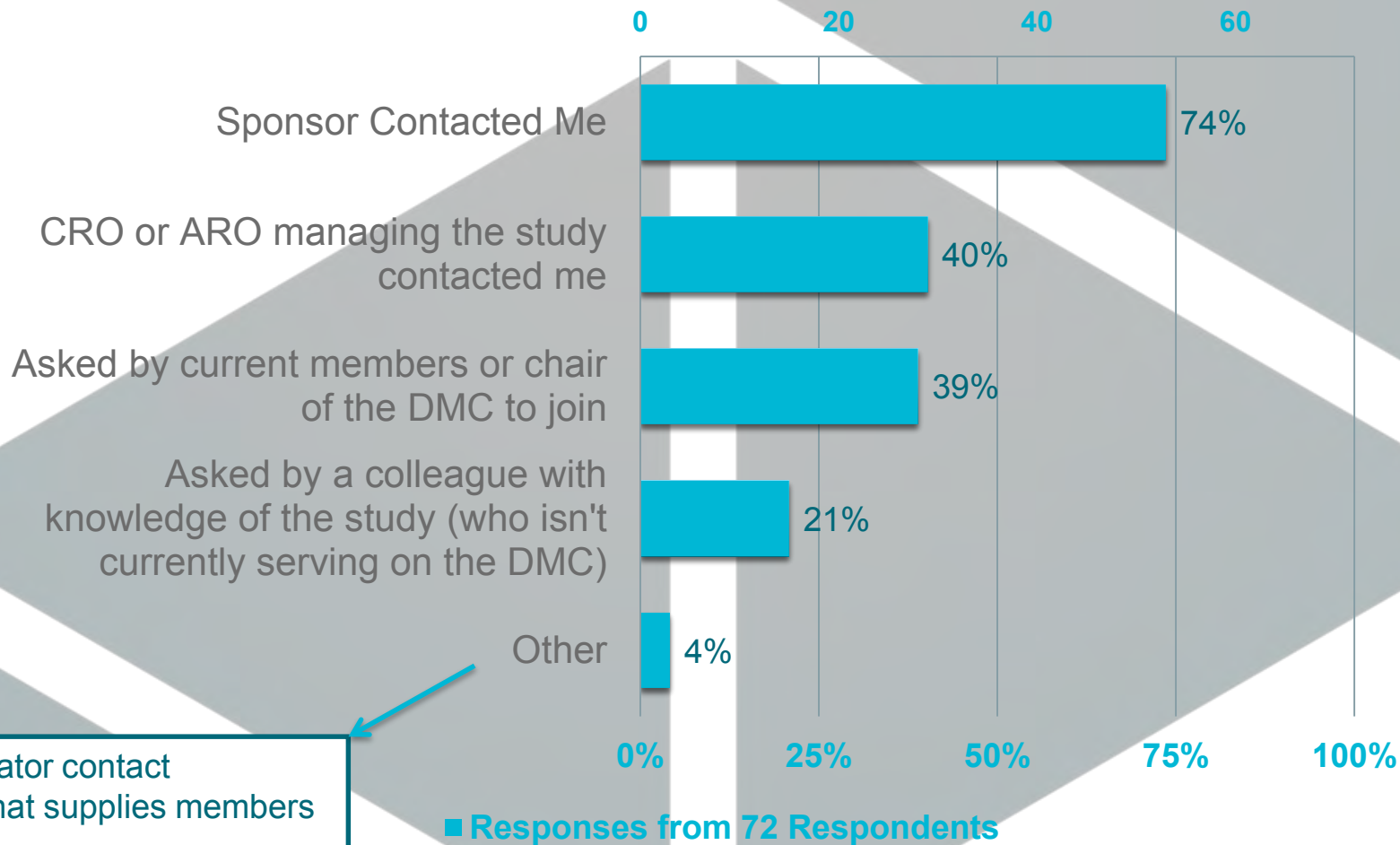
How are DMC Members Identified?

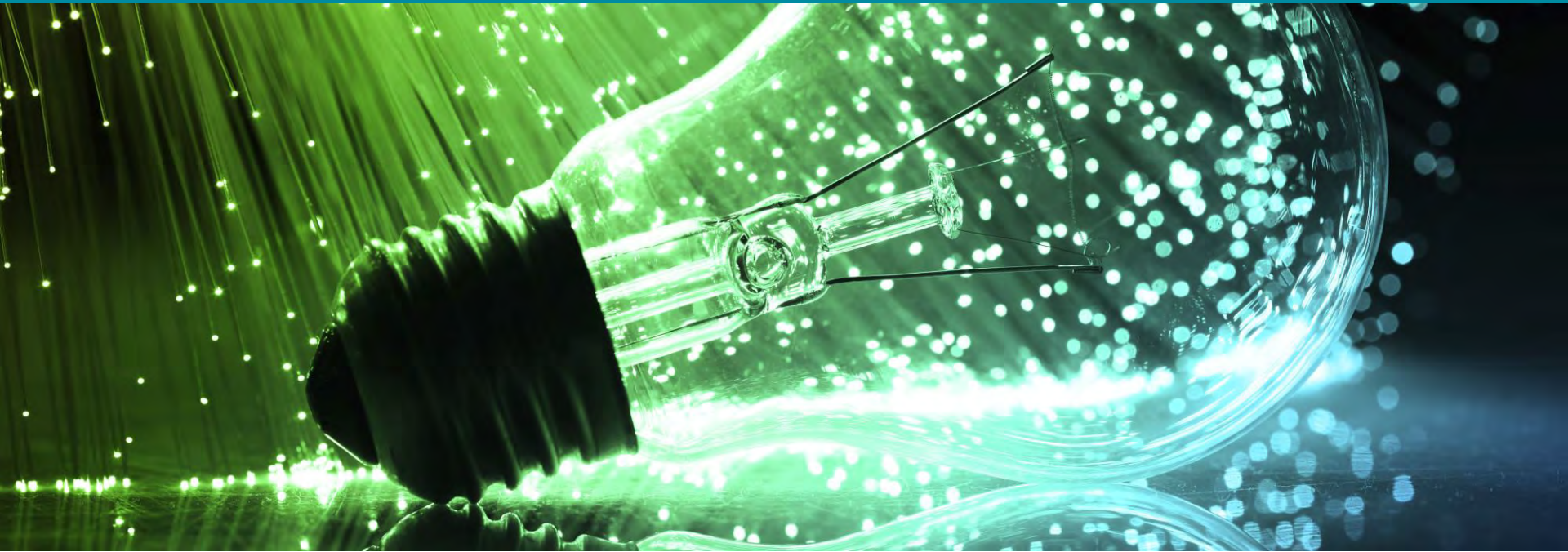
Survey *All Organizers*



How are DMC Members Identified?

Survey *All Members*



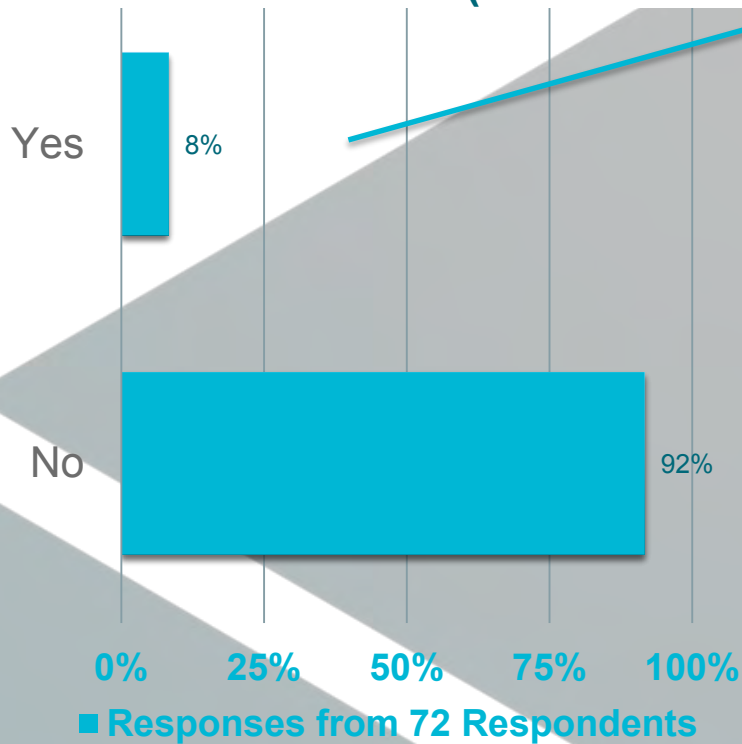


DMC Membership

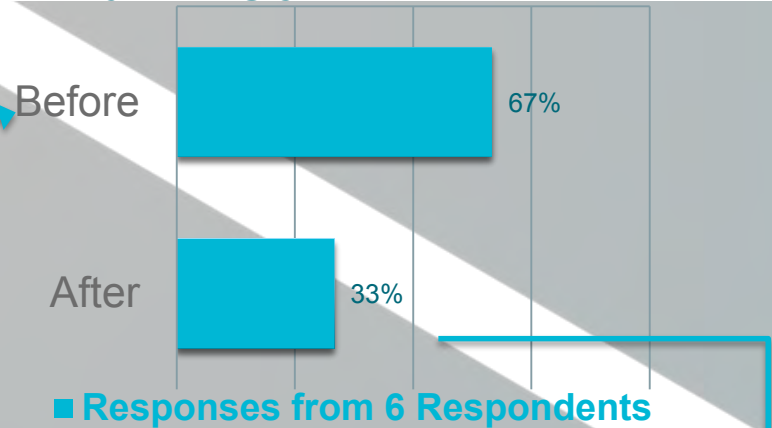
Developing the Next Generation of Members

Are DMC Members Trained? Should they Be?

Have you ever been formally trained to serve on a DMC? (all members)



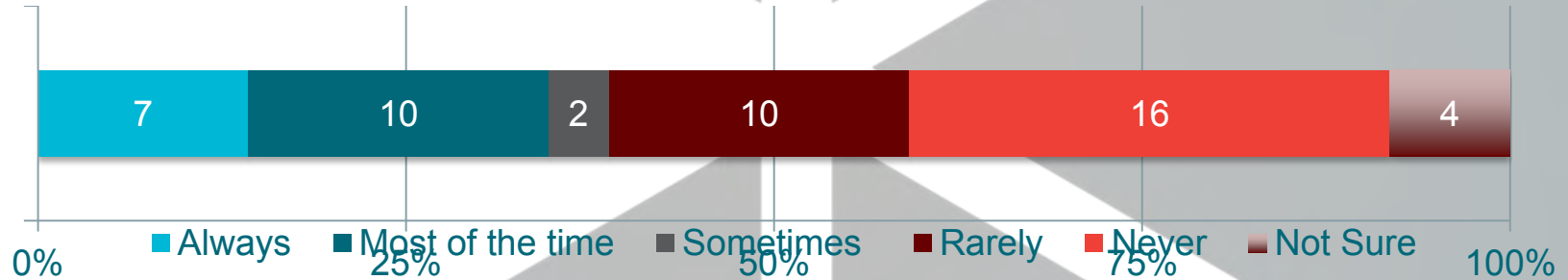
Did the training occur before or after joining your first DMC?



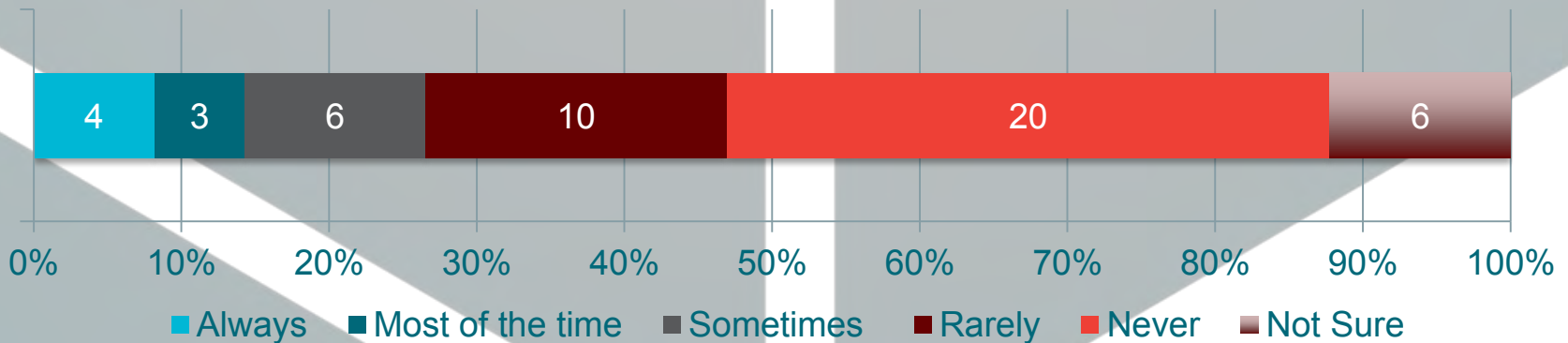
Would you have preferred to have been trained BEFORE serving on a DMC?



Do Sponsors Require Trained DMCs?

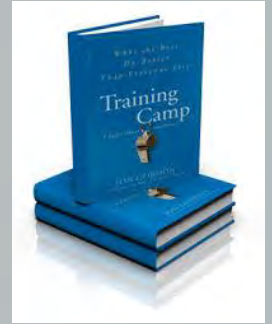


Do Sponsors Offer Training?



What Should be Included In Training?

- Didactic sessions that provide basic information (e.g., regulations, charters, communication expectations)
- Interactive sessions (e.g., discussion of case studies)
- On-going/continuing education (e.g., mentoring)



What Role Should Government Play?

Industry Sponsor Responses

- Government does have knowledge but have been criticized for lack of independence. Academia is where the real expertise is.
- Relevant societies (e.g., SCT) can play a role in training, more so than gov't.

Government/ NP Responses

- “Government would be happy to help develop training sets across the NIH
- A uniform course would help sponsors and investigators to understand what the role of the DMC is.

What Else Should be Done to Prepare the Next Generation of DMC Members?

- ▶ Non-voting observers
- ▶ Apprenticeships
- ▶ Formal mentoring
- ▶ Learn on the job



Thank you.



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Session II: Data Monitoring Committee Purpose and Rationale

Objective

- Solicit feedback on various functions of trial oversight committees including how different committees are differentiated
- Solicit feedback on suggested nomenclature for different types of trial oversight committees

Agenda

- DMC Purpose and Rationale: The Issue
- Proposed Strategies for Differentiating Various Trial Oversight Committees: Naming and Function
- Facilitated discussion

DMC Purpose and Rationale: The Issue

Roger Lewis, MD, PhD

Harbor-UCLA Medical Center

July 28, 2015



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The Issue

- Use of DMCs has increased and evolved over time
- Data from the survey and focus groups generally support the assertion that DMCs play an important role in clinical trials, by monitoring efficacy, safety, and quality of study conduct
- Variability across DMCs in roles and responsibilities may contribute to confusion and unclear expectations among DMCs and other trial stakeholders

Questions for Consideration

- For which types of trials are trial oversight committees warranted?
- What are the disadvantages to having a trial oversight committee?
- What different types of trial oversight committees exist?
- What are the roles, responsibilities and activities of different types of trial oversight committees?
- What terminology should be used to describe different types of trial oversight committees?

Current Use of DMCs and Other Types of Trial Oversight Committees

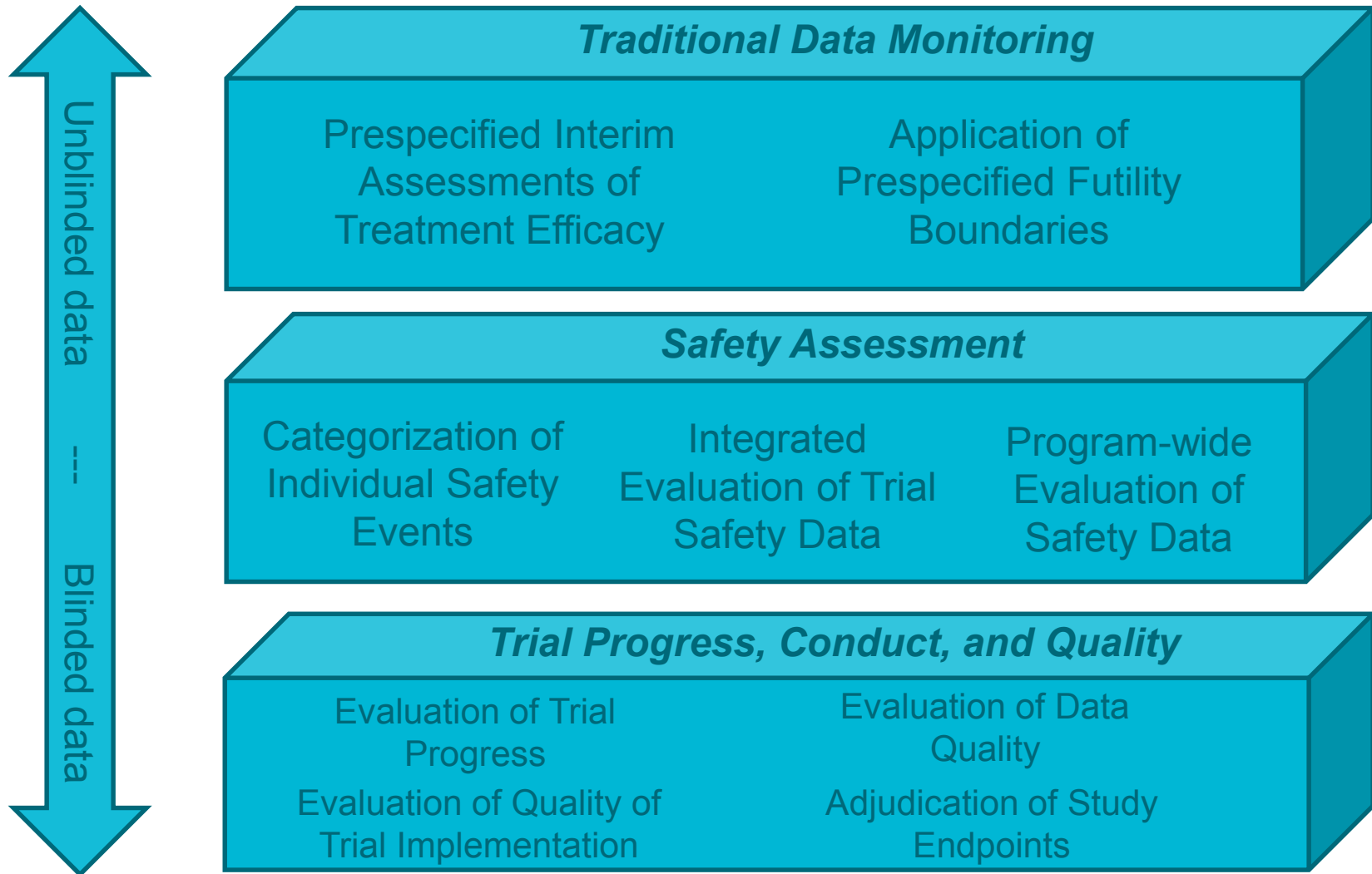
Jonathan Seltzer MD, MBA, MA, FACC,
ACI Clinical

July 28, 2015

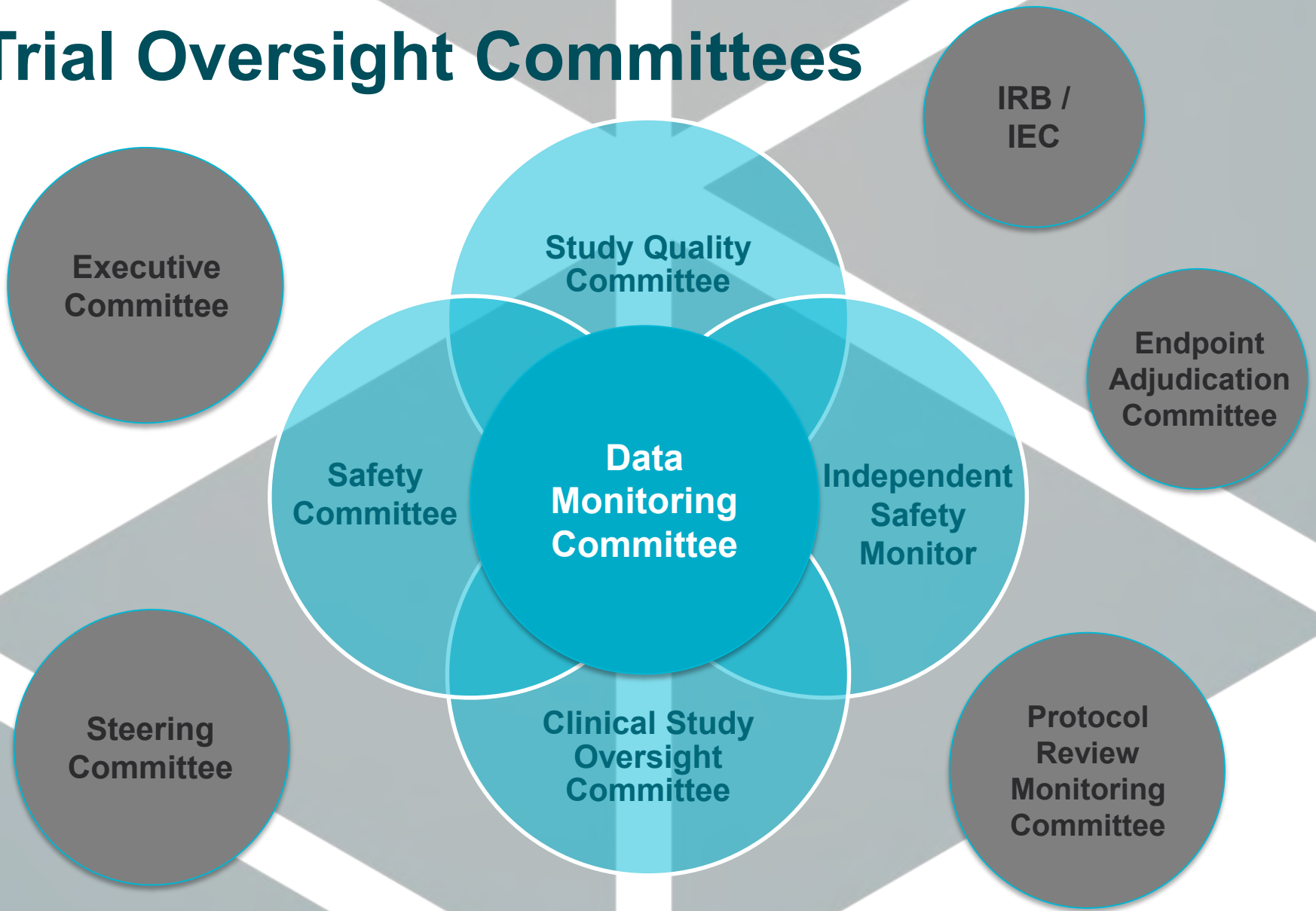


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Activities Required in Trial Oversight



Trial Oversight Committees



DMCs: Clinicaltrials.gov

Prevalence (2007-2013)

- Phase II and Phase III interventional trials
 - 2205 (25%) of the 8823 completed, suspended or terminated industry sponsored trials have had a DMC
 - 2694 (50%) of 5377 completed, suspended or terminated non-industry sponsored trials have had a DMC
- 12% of non-DMC trials were terminated
- 21% of DMC trials were terminated

Approximately 2x increase in use of DMCs since issuance of guidance.

Table 4. Comparison of 2000 versus 2010 literature search.

Journals	2000			2010: All Studies			RR	CI	
	RCT	DMC	%	RCT	DMC	%		5%	95%
High impact	282	70	25	336	175	52	2.0	1.7	2.6
<i>Ann Intern Med</i>	21	5	24	27	10	37	1.6	1	3.7
<i>Arch Intern Med</i>	28	3	11	9	0	0	Unable to calculate; value = 0		
<i>BMJ</i>	34	0	0	50	4	8	Unable to calculate; value = 0		
<i>JAMA</i>	49	12	24	42	26	62	2.6	2	4.4
<i>N Engl J Med</i>	62	22	35	125	88	70	2.0	1	2.8
<i>Lancet</i>	88	28	32	83	47	57	1.8	1	2.5
Therapeutic area	380	49	13	480	147	31	2.4	2	3.2
<i>Cardiology</i>	145	31	21	147	62	42	2.0	1	2.8
<i>Infection</i>	56	10	18	115	37	32	1.8	1	3.4
<i>Oncology</i>	103	8	8	159	43	27	3.5	2	7.1
<i>Psychiatry</i>	76	0	0	59	5	8	Unable to calculate; value = 0		
All	662	119	18	816	322	39	2.1	2	2.6

DMC, data monitoring committee; RCT, randomized controlled trial; RR, ri

What Types of DMCs?

- ▶ Very little information about the rationale and operations of DMCs
 - Clinical Trials DMC is a yes/no field
 - No options for any specificity nor other types of oversight committee
 - 78% compliance
 - Literature rarely, if ever, specifies type or reason for DMC

Defining Domains of Activity

Trial features
Phase
Clinical endpoints
Concern for major AE
Design
Single study vs investigational agent across development program
Required committee expertise
Study population
Statistical
Regulatory
Safety
Patient advocate
Bioethicist
Independence
Charter required
Independence from sponsor
Independence from investigative site
Data reviewed
Summary data by treatment group
Individual adverse events
Patient listings
Interim statistical analysis
Recommendations
Stop due to clinical judgment
Stop due to interim or futility analysis
Modify due to clinical judgment
Sample size modification
Study conduct, overall
Study conduct, site level
Other

Roles and Responsibilities

- ▶ Roles and responsibilities of trial oversight committees may overlap
- ▶ The appropriate committee should be determined by the needs or attributes of individual trials or programs

Session III: Formation and Organization of Data Monitoring Committees

▀ Objectives

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

▀ Agenda

- Proposed recommendations for formation and organization of DMCs
- A proposed DMC charter checklist
- Discussion

Proposed Recommendations for Formation of DMCs

John McEachern, PAREXEL International, LLC

July 28, 2015



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Introduction

- Identification, selection and vetting of potential candidates is critical to the functioning of a knowledgeable, responsible and credible Data Monitoring Committee.
- The purpose of the proposed recommendations is to provide guidelines towards this end, as well as stimulate discussion as to best practices in this area.
- These recommendations won't apply to all cases all of the time—there are always exceptions

Member Qualification

DMC Member Focus Group

▶ What constitutes a qualified DMC?

- **There are no standard qualifications and that is a problem.** We have GCPs for Clinical Investigators and IRB standards to protect human subjects, and no standards for DMCs.
- **Expertise should be broad enough to cover safety issues that arise.** Statistics, ethics, epidemiology, regulatory, clinical trials research, in addition to scientific discipline, across the different members of the DMC.
- We all have a sense of what is good and what isn't but nothing is written. **We need better standards and qualifications.**

DMC Member Preferred Experience and Expertise

- A qualified DMC should be composed of members who have *both* the necessary expertise and independence from the sponsor necessary to execute the DMC's role
- There may be instances when individual members do not meet all of the criteria noted; rather, the whole of the DMC, and the balance of experience and expertise among members, should be considered when convening a DMC

Determining the Need for Specific Roles

- Generally include three to six members
- May include
 - Clinicians
 - Statisticians
 - Ethicist
 - Researchers with special expertise relevant to the trial
 - Patients or patient advocates
- DMC members need to clearly understand their roles and be able to articulate their purpose

DMC Members and the Needs They Serve

Expertise	Need
Clinician	Clinical expertise in area of study always required; clinicians in different specialties may be required for complex studies
Statistician	Expertise in clinical trial design and analysis, including interim analysis, and in appropriate cases adaptive design
Ethicist	When the possibility of difficult decisions arising seems high
Clinical Pharmacologist	Early-phase development
Patient/Advocate	Ensure patient focus and transparency of process, esp. in publically supported trials; trials that include PROs and QoL data; comparative effectiveness trials

Qualifying Experience ¹	Chair	Clinician	Biostat- istician	Patient Advocate	SAC (non- voting)	Other
Prior experience as DMC chair	Preferred	No	No	No	NA	No
Prior DMC Experience	Yes	Preferred	Yes	Preferred	Yes ²	Preferred
Prior clinical trials experience	Yes	Yes	Yes	Preferred	Yes	Preferred
Absence of substantive conflicts of interest	Yes	Yes	Yes	Yes	Yes	Yes

1. Assumptions: 1) Applicable to external data monitoring committees; 2) members do not have regulatory restrictions from participating in a DMC (e.g., serious regulatory sanctions, debarment)
2. Specifically, experience reporting to a DMC

Desirable Attributes of a DMC Chair

- ▶ Methodological knowledge and/or experience
 - Data analysis and statistical methods
 - Clinical research and drug development process
 - Regulatory requirements for clinical trials
 - Drug safety
 - Ethical principles

Desirable Attributes of a DMC Chair

Leadership skills

- Ability to communicate effectively with different stakeholders
- Ability to facilitate effective interaction without being overly directive
- Ability to facilitate communication between all DMC members, particularly those who bring different perspectives
- Ability to build consensus
- Ability to summarize technical discussions
- Organized thinker
- Problem solving skills

Best Practices for Vetting DMC Members

- Sponsor or delegate identifies potential DMC members based on the characteristics and responsibilities of DMC members
- For each potential DMC member, sponsor evaluates independence and potential conflicts of interest (COI)
- DMC Chair (in advance of first DMC meeting) reviews the DMC membership and COI statements
- DMC Chair (at the beginning of each DMC meeting **closed session**) inquires whether any DMC members need to modify their COI statement

Assessing Qualifications/Commitment of DMC Candidates

➤ Sponsor or delegate identifies potential DMC members based on the following characteristics and responsibilities of DMC members :

➤ Characteristics

- Relevant experience and expertise in clinical research
- Prior DMC experience (not a requirement but valuable; identify at least one member with DMC experience)
- Considerate of diverse perspectives
- Collaborative personality

➤ Responsibilities

- Willingness to commit to attend DMC meetings as scheduled
- Commit to review data and apply interpretation and judgment
- Provide advice and guidance to the Sponsor
- Maintain confidentiality of information presented

Review of Conflicts of Interest: Sponsor

- Sponsor evaluates the potential COI of each identified member based on a COI statement
- There are no right or wrong answers to dictate appropriateness to serve on the committee, but instead allows for full disclosure in the selection process
 - Relationships with the sponsor including consulting
 - Relationships with study investigators
 - Intellectual or financial investment in study goals
 - Other DMC memberships related to study goals

Review of Conflicts of Interest: DMC Chair

- ▶ In advance of the first DMC meeting, the DMC Chair:
 - Reviews the proposed DMC membership
 - Reviews the COI statements of each DMC members
 - Interacts with the sponsor to discuss potential actions, if needed (e.g., remove the conflict of interest or cease DMC participation)

Ongoing Evaluation of Conflicts of Interest

- ▶ At the beginning of each DMC meeting closed session, the DMC Chair :
 - Inquires whether any DMC members need to modify their COI statement
 - In the meeting minutes document the inquiry about COI changes
 - In the meeting minutes document any modifications, if needed (e.g., remove the conflict of interest or cease DMC participation)

Thank you.



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A Proposed DMC Charter Checklist

Karim Calis

FDA/CDER
NIH/NICHHD

July 28, 2015



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DMC Charter

- The DMC charter is a key document in which roles and responsibilities of the DMC are established and clearly delineated.
- The charter also outlines and defines
 - the planned communication process and
 - the procedures to be employed by DMC members and relevant stakeholders throughout the course of the study.

DMC Charter

- The charter is a valuable resource that should be used to empower rather than handicap the DMC.
- Above all, it should be an instrument that enhances the independence of the DMC and allows it to fulfill its mission unhindered.

Survey and Focus Groups Findings:

Charter preparation and maintenance

- Sponsors have SOPs governing conduct of DMCs including a DMC charter template that is tailored to each specific trial
 - Charter authoring originates from multiple sources (e.g. sponsor, SAC)
- DMC charters are considered useful to carry out DMC responsibilities and should be reviewed and approved by the DMC members and/or DMC Chair
- Format of meetings is a mixture of remote/in-person with frequency of regular (quarterly or semi-annually) plus ad hoc meetings jointly determined by sponsor and DMC
 - DMC should have authority to schedule ad hoc meetings

Survey and Focus Groups Findings:

Charter preparation and maintenance

- “Having <a high quality> one is a good start!”
 - Not too short and not too long
 - Detailed statistical analysis plans should remain separate
- Should pre-specify the planned contents of the DMC report
 - Include review of efficacy along with safety
 - Clearly identify items “adaptive by design”
 - Indicate that ad hoc analyses/meetings may be needed
- Clearly articulate how decisions are made by the DMC but allow flexibility for judgment calls
- Fully address trial blinding and if/when stakeholders are notified of aggregate event rates
- Detail communication practices between DMC/SAC/Sponsor

Indicators of DMC independence

- Are the interests of the DMC clearly articulated in the charter?
- Is the DMC able to hold ad hoc meetings without triggering speculation or concern on the part of the sponsor or other stakeholders?
- Does the DMC have adequate resources and accommodations to carry out its duties and fulfill its mission?
- Are DMC findings and recommendations consistently shared with IRBs and regulatory bodies regardless of the sponsor's opinion or intent in regards to the DMCs advice?

DMC Charter Checklist

- We present a proposed checklist of critical elements that may be considered in developing a comprehensive charter.
- The checklist was developed by a DMC project work group after a review of DMC charters and various published and unpublished charter templates.

Introduction

- ▶ Title of the trial
- ▶ Study overview, including objectives and proposed interventions (see annex for figure of the clinical trial design)
- ▶ Scope of the charter document

Independence

- It should be explicitly stated in the charter that the DMC must remain independent from the sponsor, and the sponsor must not have undue influence on DMC decision making.
- DMC members must be provided with adequate resources and accommodations to carry out their duties and fulfill their mission without hindrance.

DMC roles and responsibilities

- Broad statement of aims
- Specific role and scope of the DMC

Before the first interim analysis

- DMC role, if any, in the protocol review process
- Description of DMC meetings prior to first interim analysis (see annex for agenda topics)
- Issues specific to the protocol (e.g., participants, intervention, regulatory issues)

DMC Composition

- DMC membership and size (see annex for contact information)
- DMC Chair's role (see annex for Chair checklist)
- DMC member role (see annex: DMC member qualifications and experience)
- SAC role (see annex for SAC statistician responsibilities before, during, and after DMC meetings) including data analysis preparation for DMC review
- Trial sponsor/management group role (including trial statistician) includes 1) making resources available to the DMC to carry out designated functions; 2) creating and maintaining an SAC to receive data from the data management center and prepare reports for the DMC; 3) communicating regulatory information
- Responsibilities of the data management center include 1) collection and monitoring of case report forms; 2) ensuring completeness and accuracy of data; 3) providing analysis data sets to the SAC for creating DMC reports
- Selection and replacement of members

Governance and relationships

- Governance of DMC and other trial committees/stakeholders (see annex for a figure of relationship between DMC and trial committees/stakeholders)
- Address need for a firewall in cases when there is no steering committee or executive committee
- DMC decision making (advisory or executive)
- DMC conflict-of-interest disclosure (see annex for conflict of interest statement) and plan for ongoing evaluation of COI
- Indemnification of DMC members (addressed in DMC member contracts)

Organization of DMC meetings

- Expected frequency of DMC meetings including flexibility to have additional meetings as the DMC or sponsor deems necessary
- Meeting format (face-to-face vs. teleconference)
- Session organization (open and closed sessions) and who may or may not be present

Documentation, confidentiality, & communication

- Material available in closed and open sessions
- Material periodically reported to the DMC
- In double-blind trials, masking of DMC reports
- Documentation of DMC process during and after the trial (see annex, DMC process checklist)
- Documentation of all data sources (see annex, data sources memo)
- Distribution of material to DMC relative to timing of DMC meetings
- Maintaining confidentiality of DMC material (see annex, confidentiality agreement)
- Responsibility for sharing information that is external to the trial
- To whom DMC communicates decisions and recommendations
- Disposing of DMC documents and related material

Decision-making

- When is the DMC quorate for decision-making including allowable delegation of responsibilities
- List of possible DMC actions and recommendations
- Include or provide reference to formal statistical methods for decision-making, and whether these are binding or non-binding
- Specific trial design issue(s) that might influence decision making
- Obtaining input from a DMC member who cannot attend a DMC meeting
- Obtaining consultation from sources outside of the DMC
- Decision-making process within the DMC (voting, consensus)

Reporting

- Drafting of DMC meeting minutes (by whom and how records are maintained)
- Format used to report DMC decisions
- Process by which recommendations are reviewed for accuracy and possible redaction (e.g., unblinding or biasing information)
- Statement regarding how DMC recommendations and sponsor responses are communicated to stakeholders (e.g., IRB, FDA)
- Process to resolve disagreement between the DMC and the sponsor or other stakeholders

After the trial is completed

- Plans for publication of results, including information about the DMC
- Constraints on DMC members in regard to public disclosure of information pertaining to their deliberations even after the trial findings have been disseminated

Annex:

Additional figures and information

- Figure: Clinical trial design
- Figure: Relationship between DMC and trial stakeholders/committees
- Confidentiality Agreement and Conflict of Interest Statement
- DMC interim analysis report (mock of planned tables, listings and figures)
- Details of interim analysis plans (if not in clinical trial protocol or separate statistical analysis plan document)
- DMC Chair checklist
- DMC member qualifications and experience

Annex:

Additional figures and information

- DMC contact information
- Agenda topics for DMC meeting prior to first interim analysis
- Checklist of required DMC documentation during and after trial completion
- Interim analysis data sources memo
- SAC statistician responsibilities before, during, and after the DMC meetings
- Process for executing revisions to charter
- List of abbreviations

Thank you.



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Session IV: Communication Between the Data Monitoring Committee and Stakeholders

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

Agenda

- Presentation of proposed recommendations
- Panel discussion

Best Practices for Communication Among DMC Stakeholders

Jason Connor, Berry Consultants

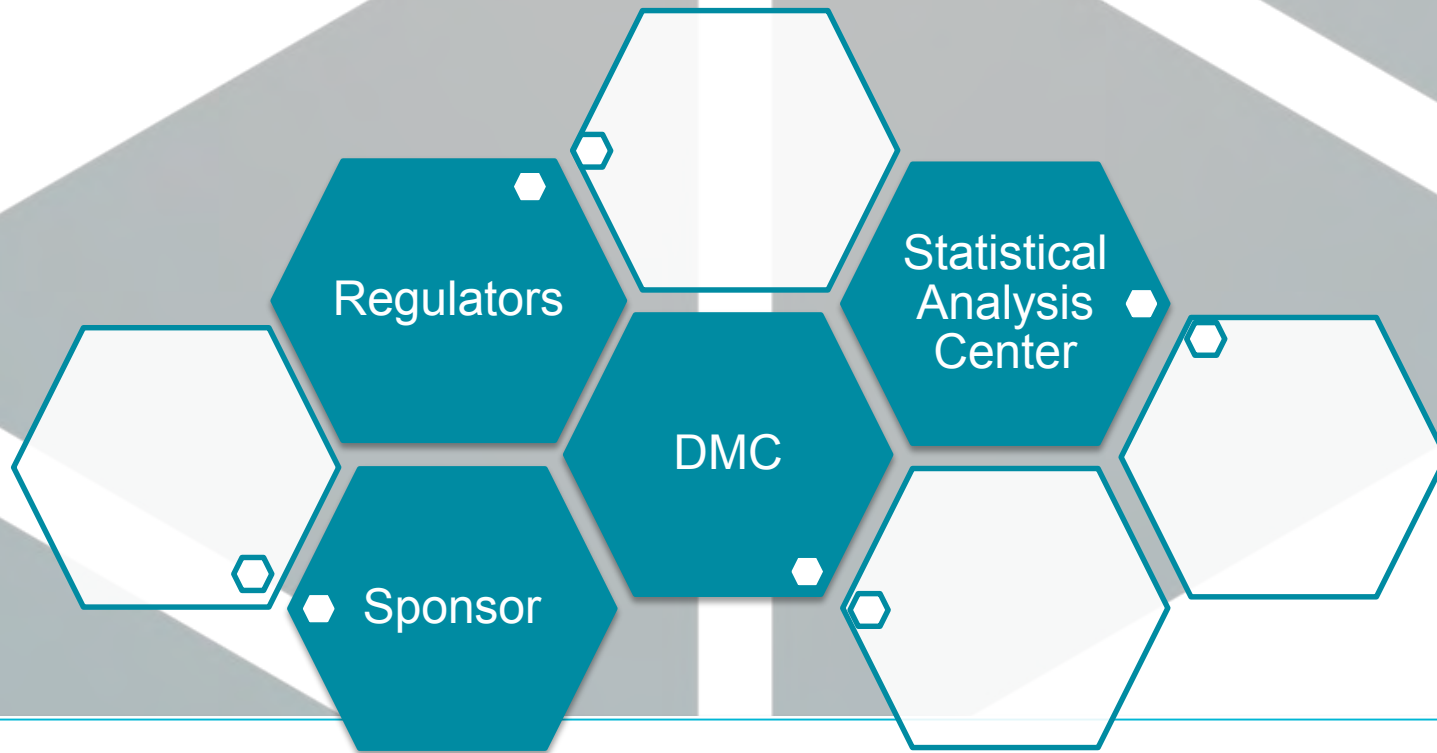
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The Issue

- Communication among all DMC-related stakeholders should be clarified at the time of charter development, and/or convening of the DMC, in order to avoid confusion and to ensure **effective, efficient and appropriate** conduct by all parties **to ensure the integrity of the trial.**



Best Practices for Communication Between the DMC and Sponsor

- The SPONSOR will communicate/provide all pertinent study documents to the DMC
- **Potential DMC members** will **disclose financial interests** prior to selection to the DMC and notify the sponsor of any potential financial conflicts that may arise during the course of the trial
- The **DMC Charter** will detail the operational procedures of the DMC
- The DMC will determine the **need for changes** to the Charter, prepare amendments and provide to the sponsor
- After each meeting, the **DMC will provide the Sponsor and/or Steering Committee with a written report** summarizing its **conclusions** and **recommendations**, which will not include references to unblinded data
- The **DMC will maintain minutes** including a summary of all data reviewed and analyses requested – to be made available to the sponsor and steering committee at the end of the trial

Best Practices for Communication Between the DMC and Sponsor

- The DMC will maintain **full records/minutes** of critical study-related communications among the DMC members and with the sponsor
- The DMC will communicate to the sponsor a **need for additional data review meetings** if necessary to monitor the progress of the trial and safety of the patients
- The DMC Committee will communicate **the need for additional expertise** on the to the sponsor, if necessary
- In the event the DMC is **concerned with safety**, the DMC will notify the sponsor and together they will determine a plan of action
- **Sponsor denial of DMC recommendations** should be communicated to the DMC with explanation

SAC Definitions

- Statistical Analysis Center (SAC) = body that generates and distributes statistical reports to the DMC
 - SAC may also be called Statistical or Data Coordinating Center
 - Some members of the SAC may be blinded, and participate only in open sessions of the DMC
 - The **“Independent Statistician”** is a member(s) of the SAC who
 - is unblinded
 - participates in **closed DMC sessions**
 - presents or supervises presentation of data
 - is **non-voting** participant
 - knows and **understands the study** and the data
 - **Is available** to discuss and communicate about the data and analysis
 - have **access to the full database** and be able to perform additional analyses requested by the DMC without special communication with the trial sponsor or leadership

Best Practices for Communication Between the Sponsor and SAC

- An agreement should be made, along with allocation of additional budget, at the time of DMC formation allowing the SAC to **conduct additional analyses** requested by the DMC **without communication with the sponsor**
- An agreement should be made at the time of DMC formation designating
 - individuals at the sponsor with whom the SAC should communicate when there are sensitive issues
 - topics about which the SAC and sponsor should not communicate at all

Best Practices for Communication Between the DMC and SAC

- Direct contact should be between the DMC chair and the independent statistician at the SAC
- Whenever possible, **one person** should be designated as **the independent statistician** throughout a study, rather than having a different statistician be present from meeting to meeting

Preparation of Statistical Reports for the DMC

- Report length
- Use of figures including Kaplan-Meier plots
- Use of tables based on MedRA classification of events
- Unblinded data
- Both safety and efficacy data
- Provision of routine safety data
- Distribution via cloud-based document sharing

Best Practices for Communication Between DMCs and Regulatory Bodies

- Should the DMC chair have the ability to reach out to the appropriate party at FDA?
- Should standard language be included in the DMC charter that provides consent for the DMC chair to speak with the appropriate regulatory authorities?
- Would working together improve the interpretability of the data by the time it arrives at FDA as an NDA?

Panelists

- ▶ Joseph Heyse, Merck Research Laboratories
- ▶ Robert Smith, Brown University
- ▶ Janet Wittes, Statistics Collaborative, Inc.

Questions for Consideration

- What are best practices for **communication** between
 - The sponsor and the party(ies) who provides statistical reports to the DMC?
 - The sponsor and the DMC?
 - The DMC and the party(ies) who provides statistical reports to the DMC?
 - The DMC and regulatory bodies?
- What are best practices for formatting and **distribution of reports** to the DMC?
- Should **unblinded safety and efficacy data** always be provided to the DMC?

Questions for Consideration

- Have you had experiences where it was necessary or would have been beneficial to **communicate with FDA without sponsor involvement** during the course of the trial?
- Are there certain items that **make a DMC report better** for you as a DMC member? Or easier to read / interpret?
- Are there items that obscure more than they illuminate?
- How would you recommend to **first time DMC members** to learn how to be an effective DMC member?

Thank you.



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Welcome to the CTTI Data Monitoring Committees Project Expert Meeting, Day 2

July 29, 2015



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Session V: Preparation of Data Monitoring Committee Members

Objective

- Solicit feedback and develop consensus on proposed recommendations related to DMC member training

Agenda

- Update on NIH DSMB activities
- NIAID DMC training experience
- MRCT DMC training experience
- Proposed recommendations for preparing new DMC members
- Discussion

Development of Training for Data and Safety Monitoring Board Members

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JULY 29, 2015

JUDY ZUCKERMAN, BSN

DIVISION OF CLINICAL RESEARCH/NIAID

Disclaimer

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The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative, or the National Institute of Allergy and Infectious Diseases.

Learning Objectives

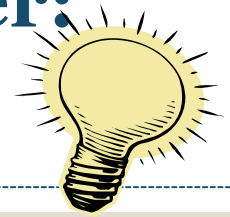
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Participants will be able to:

- Describe how to access NIAID DSMB training
- Identify appropriate audience for NIAID DSMB training



Creating NIAID DSMB Learning Center: Project Inspiration



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“Sharing Best Practices: Data and Safety Monitoring”

Subject Matter Experts (SMEs) from each NIAID Division identified that:

- Qualified DSMB members were difficult to find and recruit.
- No specific knowledge set was identified to qualify as an appropriate DSMB member.
- Training was unavailable.

Creating NIAID DSMB Learning Center: Training Needs Assessment



- NIAID Clinical Research Sub-Committee (NCRS) and the NIAID Executive Committee expressed overwhelming support for CBT for DSMB members
- Funded via Evaluation Set-Aside Funds (Evaluation Express Award \leq \$50,000)
- Primary Objective: To identify learning objectives appropriate for training that would enhance the **NIAID new DSMB members' abilities to** meaningfully contribute to DSMB deliberations

Creating NIAID DSMB Learning Center: Training Needs Assessment

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1. Literature Review

2. Semi-structured interviews

CONSENSUS WITH SUBJECT MATTER EXPERTS

3. Recommendations

- Learning objectives
- Training delivery sequence
- Training delivery methods
- Sample content, assessments, exercises

CONSENSUS WITH SUBJECT MATTER EXPERTS

4. Computer-Based Training

Creating NIAID DSMB Learning Center: Similar Conclusions...

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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

WHAT WE FOUND

... NIH faces challenges in recruiting and training DSMB members.

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.

WHAT WE RECOMMEND

... identify ways to recruit and train new DSMB members.

NIAID DSMB Learning Center: Target Audience

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Primary TNA Objective: To identify learning objectives appropriate for training that would enhance the NIAID new **DSMB members' abilities to meaningfully contribute to DSMB deliberations.**

- Target Audience: New DSMB Members
- Statistical Section is appropriate as a brief overview to the non-statistician DSMB members.
- Other Appropriate Participants: Those who need to understand the roles and responsibilities of DSMBs, such as project officers, IRB members, investigators, etc.

NIAID DSMB Learning Center: Access

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<https://dsmblearningcenter.niaid.nih.gov>



National Institute of Allergy and Infectious Diseases
National Institutes of Health

Sign In

Data Safety Monitoring Board (DSMB) Training

Welcome

NIH Users [Login >](#)

1. Select HHS staff as your Account Type from the dropdown menu. You may log in with the NIH username/password combination that you use to access your NIH desktop computer or the NIH VPN

Non-NIH Users [Login >](#)

OpenID

1. Select Open ID as your Account Type from the dropdown menu
2. Choose your Open ID provider (Google, VeriSign, or PayPal)
3. Log in with your existing username and password or create a new account following the provider's instructions

Research Organizations

Non-NIH users affiliated with an NIH Federated research institution may log in using an existing institution username and password.

1. Select Research Institution as your Account Type from the dropdown menu
2. Choose your research institution and log in using your existing username and password for that institution

More Information

- Visit the [Frequently Asked Questions](#) page
- Contact the [NIAID DSMB Help Desk](#)

3 DSMB Modules

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1. Purpose and objectives
2. Organization and responsibilities
3. Statistical topics



Module 1: Purpose and Objectives

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[Help/Feedback](#)

Identifying DSMB Purpose and Objectives

Module 1

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> 1: Purpose/Objectives

[Purpose of DSMBs](#)
[History of DSMBs](#)
[DSMBs Recommended](#)
[DSMB Role](#)
[Conflicts of Interest](#)
[Module 1: Test](#)

2: Organization/Responsibilities

3: Statistical Topics

[Print Courses](#)

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Module 1: Identifying DSMB Purpose and Objectives

Introduction

At the conclusion of the **Identifying DSMB Purpose and Objectives** module, the participant will be able to:

- Explain the overall purpose of a data safety monitoring board (DSMB).
- Describe the history of DSMBs in government and pharmaceutical sponsored clinical trials.
- Recognize the various types of clinical trials for which the establishment of a DSMB is recommended.
- Describe the scope of a DSMB's authority and its obligations to a trial's sponsors and research participants.
- Explain the importance of having DSMB participants avoid any conflicts of interest.
- Understand the National Institutes of Health's and National Institute of Allergy and Infectious Diseases' policy with respect to DSMBs.

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Module 2: Organization and Responsibilities

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DSMB Organization and Responsibilities: Administrative and Clinical

Module2

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1: Purpose/Objectives

> 2: Organization/Responsibilities

[How DSMBs are Created](#)
[Member Qualifications](#)
[Member Responsibilities](#)
[Confidentiality](#)
[DSMB Charter](#)
[Interim Efficacy & Safety Data](#)
[Importance of Accurate Data](#)
[Types of Meetings](#)
[Interactions](#)
[Module 2 Test](#)

3: Statistical Topics

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Module 2: DSMB Organization and Responsibilities: Administrative and Clinical

Introduction

At the conclusion of the **DSMB Organization and Responsibilities: Administrative and Clinical** module, the participant will be able to:

- Describe how a DSMB is formed.
- Describe the relevant qualifications of DSMB members.
- Explain the confidentiality assurance required of DSMB members.
- Describe the components that should be present in a DSMB charter and the resulting responsibilities of DSMB members.
- Explain the policies and procedures that help ensure that the DSMB has exclusive access to interim efficacy and safety data by study arm.
- Understand the importance of having the PI/sponsor deliver accurate, complete, and up-to-date data presentations to the DSMB.
- Differentiate among the various types of DSMB meetings (e.g., orientation, open/executive, closed/data review, and ad hoc).
- Discuss the topics that should be addressed at the DSMB orientation/initial meeting and the resulting items/decisions that should be agreed upon.
- Understand the different groups with which a DSMB may interact.
- Understand the DSMB members' clinical responsibilities.

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Module 3: Statistical Topics

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Data Safety Monitoring Board (DSMB) Training

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[Help/Feedback](#)

Statistical Topics

Module3

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1: Purpose/Objectives

2: Organization/Responsibilities

> 3: Statistical Topics

Statistical Methods

Sequential Boundaries

Early Unfavorable Trends

Treatment Effects

Multiplicity

Sources of Bias

Module 3: Test

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Module 3: Statistical Topics

Introduction

At the conclusion of the **Statistical Topics** module, the participant will be able to:

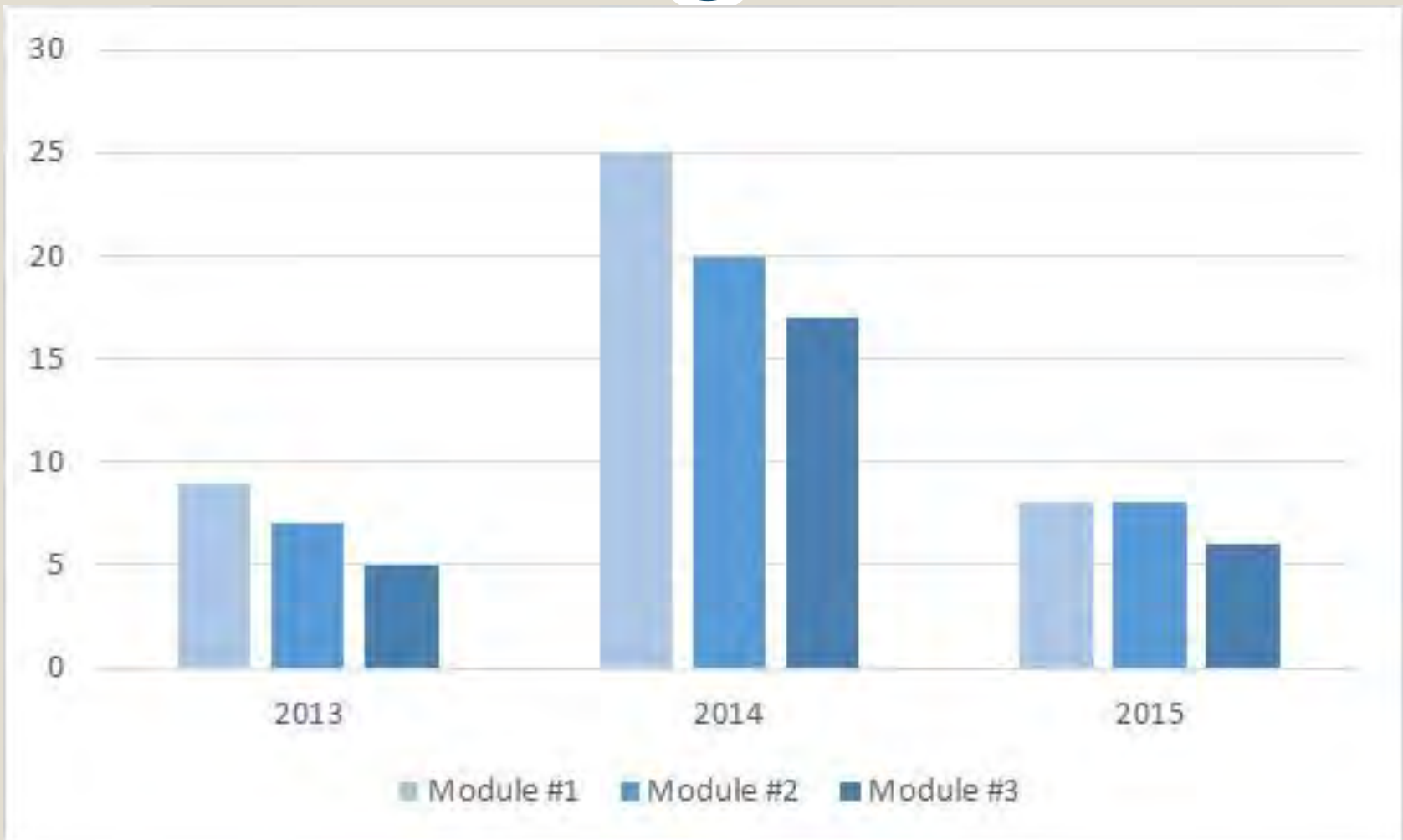
- Understand the statistical procedures that may be presented during a DSMB meeting.
- Explain the general approach to applying stopping rules when performing sequential monitoring of interim data
- List the three criteria that should be considered when early indications of a negative trend in the data raise the question of early trial stoppage
- Differentiate the items that must be considered by a DSMB when making judgments based on short-term versus long-term treatment effects
- Explain the problem when multiple statistical comparisons are made
- Understand the issues associated with bias and identify its possible sources
- Differentiate between clinical significance and statistical significance

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DSMB Course Completions

(9/1/2013 – 6/30/2015)

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Future Considerations for Training Modules

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Ideas to consider:

- Case studies with facilitator discussion
- Links to DSMB presentations
- International topics and translation of modules
- Philosophical and ethical issues
- Cultural and political considerations
- Genetic variation factors
- Advanced level modules for experienced DSMB members

Learning Objectives

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Participants will be able to:

- Describe how to access NIAID DSMB training
<https://dsmblearningcenter.niaid.nih.gov>
- Identify appropriate audience for NIAID DSMB training
 - New or inexperienced DSMB members
 - Other appropriate participants: those who need to understand the roles and responsibilities of DSMBs, such as project officers, IRB members, investigators, etc.

NIAID Subject Matter Experts

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- Kelly Cahill- Division of Clinical Research
- Dennis Dixon- Independent Consultant
- Wendy Fanaroff-Ravick- Division of Microbiology and Infectious Diseases
- Larry Fox- Division of Acquired Immunodeficiency Syndrome
- Joni Love- Division of Microbiology and Infectious Diseases
- James McNamara- Division of Allergy, Immunology and Transplantation
- Barbara van der Schalie- Division of Clinical Research

Training Content References

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- Ellenberg SS, Fleming TR, DeMets DL. *Data monitoring committees in clinical trials: a practical perspective*. John Wiley & Sons, 2003
- FDAnews, *How to create and structure a data monitoring committee: strategies for future trial design*. 2006
- DeMets DL, Furberg DC, Friedman LM. *Data monitoring in clinical trials*. Springer, 2006
- Herson, J. *Data and Safety Monitoring Committees in Clinical Trials*. Taylor & Francis Group, LLC. 2009

Thank You

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National Institute of
Allergy and
Infectious Diseases

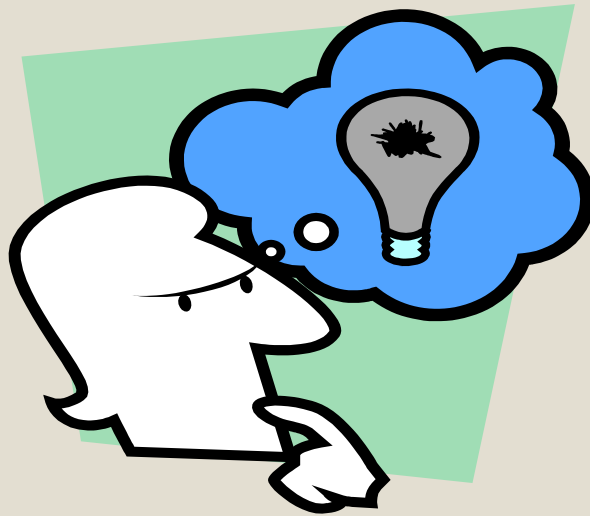
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Questions

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MRCT DMC Training Program

Barbara E. Bierer, MD

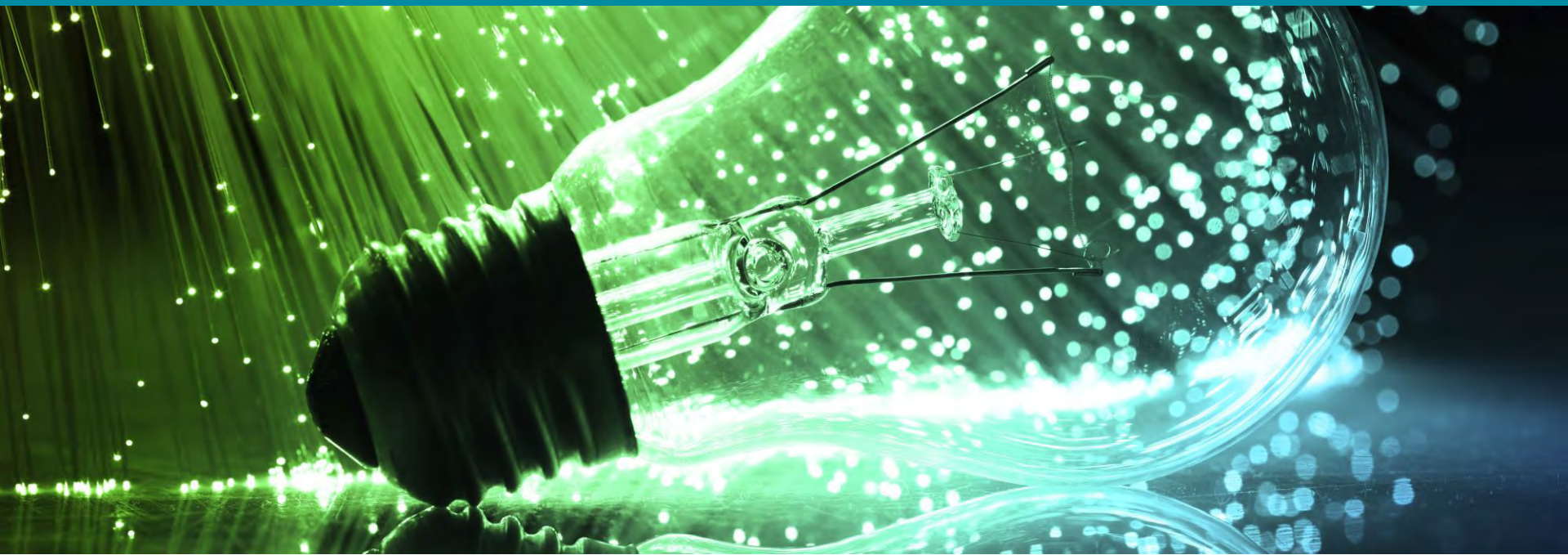
MRCT Center at Harvard and the Brigham and Women's Hospital

July 29, 2015

CTTI Data Monitoring Committees Project



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Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

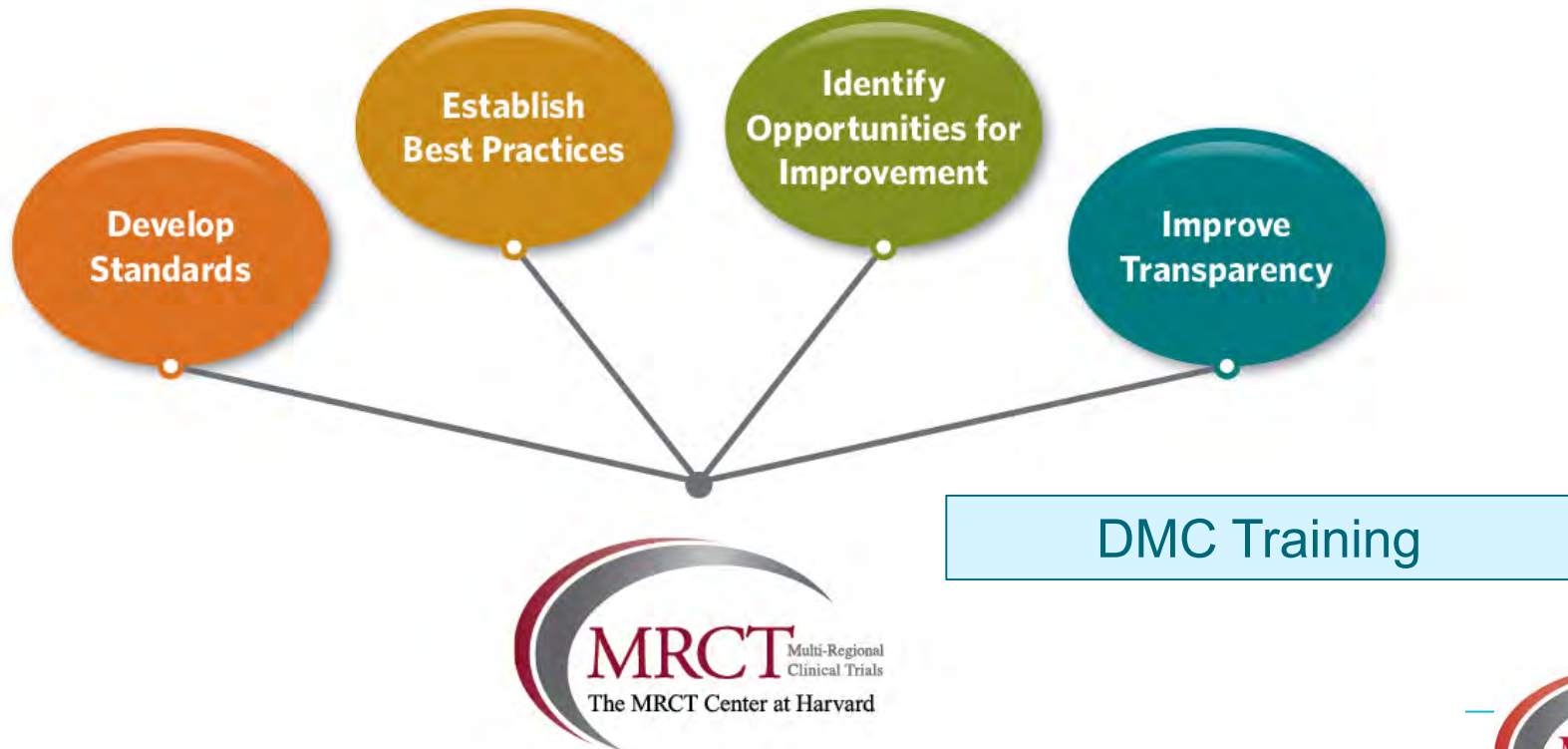
The presenter is an employee of the Brigham and Women's Hospital. Clinical Trials Transformation Initiative has provided travel support for this presentation.

Agenda

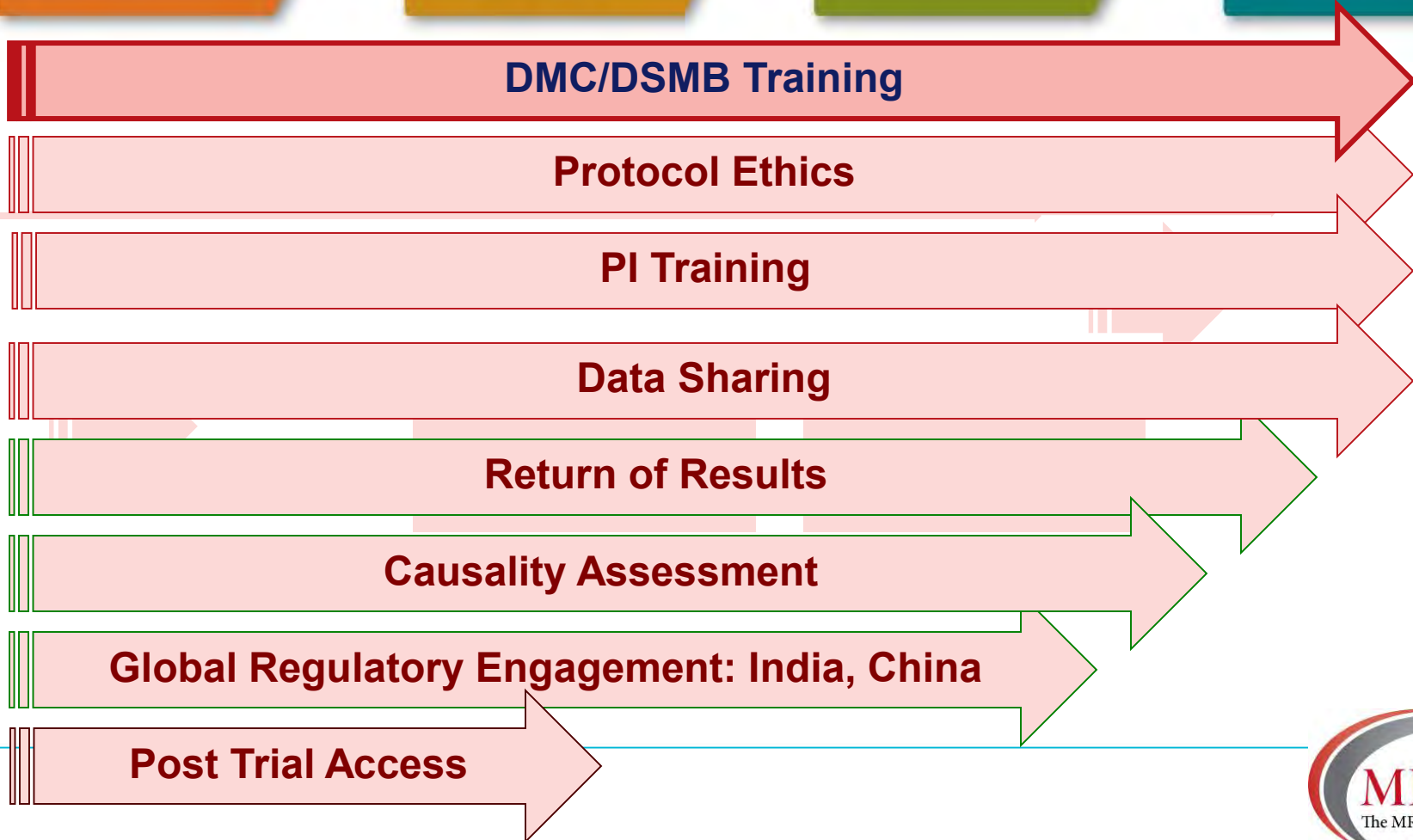
- MRCT Center: Mission and Overview
- Genesis of DMC Project
- Process for Development of DMC Training Materials
- Content of DMC Trainings
- Opportunities for collaboration

MRCT Center: Mission and Overview

The MRCT Center's Purpose is *to improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research.*



Harvard MRCT Project Status



Focus: DMC Capacity in Emerging Countries

Scope:

The U.S. FDA, EMA, ICH, and WHO have offered guidance for the establishment and operation of DMCs by clinical trials. This guidance has not been routinely adopted worldwide.

Opportunity:

Common DMC guidance can be crafted based on the industry's willingness to share information about the operations of their DMCs and their support for such a training program.

Focus: DMC Capacity in Emerging Countries

The goal of the work group is to build the capacity of DMCs (DSMBs), especially those for multi-regional trials that involve the developing world, so that they can effectively monitor the safety and efficacy of clinical trials. A group of DMC experts drafted a role-based, best practices document. The work group also developed and offered regional DSMB trainings to build intellectual infrastructure in places such as India, Korea, and Japan.

MRCT DMC Project

- Identify qualified DMC members from the developing world
- Develop DMC training materials based on industry and NIH standards
- Educate and train DMC members for trials in the developing world
- Apprentice DMC members from emerging markets to serve on boards

MRCT DMC Project

Impact: Increased engagement of experts from emerging world on Data Monitoring Committees for multi-regional trials.

Goals

- To identify, train, recruit experts from emerging regions who have expertise in medicine or statistics, experience in clinical trials, and who would like to serve on Data Monitoring Committees.
- To build capacity in emerging countries

Co-Chairs:

Charles Knirsch (Pfizer)

Joe Massaro (BU)

Barbara Bierer (MRCT, Harvard, BWH)

Susan Ellenberg (Penn)

Sonali Kocchar (Path)

Rebecca Li (MRCT)

John Orloff (Novartis)

Jonathan Selzter (ACI Clinical)

Steve Snapinn (Amgen)

Yoko Tanaka (Lilly)

Janet Wittes (Stat Collab)

Genesis of DMC Project



Building DMC Capacity in Emerging Countries

The goal is to train motivated experienced investigators for DMC membership to increase multinational participation in multi-regional trials. Regulators and industry attend.

Location	Training Partner	Date	Number of Trainees
Boston, USA	Society for Clinical Trials	May 2013	30
Daegu, Korea	DCUMC	October 2013	70
Mumbai, India	ISCR, Amgen	January 2014	50
Tokyo, Japan	JPMA, Lilly	April 2014	150
Shanghai, China	DIA, Amgen	May 2014	20
Bangkok, Thailand	HIV Symposium	January 2015	70

MRCT DMC Learning Objectives

- Understand
 - Purpose of a DSMB
 - Types of clinical trials for which DSMBs should be established
 - Scope of a DSMBs authority and its specific obligations and responsibilities
 - Roles on the DSMB and the specific responsibilities of each role
 - Safety, efficacy, futility in DSMB analysis
 - Specific challenges relating to DSMBs and multi-regional clinical trials
- Experience practical examples with case studies

DMC Training: Content

- Introduction: Harvard DMC Program
- When do you need a DMC?
- Setting the stage: clinical trial study design
- Ethics Committees and DMCs
- DMC Membership and Responsibilities
- US Regulatory Perspective on DMCs
- Ex-US Regulatory Perspective on DMCs
- MRCT Perspectives on DMCs
- Monitoring for Safety & Efficacy
- Monitoring for Futility
- EU Perspectives on DSMBs
- Case Studies / Discussion

MRCT DMC Detailed content

- Types of trial designs, with examples, ending with RCTs
- Overview of drug development
- Overview of oversight of clinical trials
 - IRBs/RECs v DMCs v Clinical endpoint committees and others
- Brief history of DMCs
- When is a DMC required?
- Purpose of a DMC
- Review of regulatory guidances
 - ICH E9 4.5 (interim analysis) and 4.6 (role of the IDMC), FDA

Guidance)

MRCT DMC Responsibilities

- Evaluating accumulating data with regard to efficacy and toxicity
- Recommending termination or continuation of study
- Recommending other study modifications
- Reviewing and approving study protocol
- Assessing study conduct
- Recommending additional analyses

MRCT DMC Reviews:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness;
- Performance of individual centers;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

MRCT DMC Roles and Charter

- Detailed membership and responsibilities of each member
 - Role of the Chair, clinicians, statisticians, epidemiologists, etc
 - Responsibility to review, analyze, question and be diligent
 - Independence
- Charter and elements of charter
- Communication expectations, including confidentiality
- Limitations of DMC authority
- Nature of recommendations (continue as scheduled, early termination, temporary hold for clarification, protocol modification)
- Ensuring integrity of trial

MRCT DMC Meetings

- Open
- Closed
- Ad hoc

Other issues considered:

- Conflicts of interest and management thereof
- DMC member indemnification

MRCT DMC considerations

- Interim “look” for efficacy, safety or futility
- Alpha and alpha spending
- Concerns over early study termination for efficacy (safety, 2^o endpoints etc)
- Strength of data to support early stopping?
- Should DMCs see actual treatment arms or only treatment codes?
 - Arguments in favor of codes: objectivity, confidentiality
 - Arguments for actual treatment
 - safety and efficacy are not symmetric
 - hard to maintain blind without withholding relevant information (e.g., lab tests)
 - places extra burden on DSMB; obstacles, assurance of patient safety
- Should DMCs ever share data?
- Individual DMCs/trial or program-wide DMC?
- DMCs for adaptive trials

MRCT DMC Examples of Case Studies

- Stopping early for futility
 - CONSENSUS II study
- Impact of multi-regional studies and considerations of consistency
 - Ticagrelor vs. Clopidogrel in Patients with Acute Coronary Syndromes (PLATO trial)
 - Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone antagonist (TOPCAT)
- Role of interim monitoring

MRCT Center and CTTI

- Discussion of complementary interests
- Exchange of materials and directives
- Opportunity for robust collaboration

Thank you



Barbara E. Bierer, MD

Faculty Co-Director, Multi-Regional Clinical Trials Center

Professor of Medicine, Harvard Medical School

Division of Global Health Equity

Department of Medicine, Brigham and Women's Hospital

bbierer@partners.org

Preparation of DMC Members

M. Khair ElZarrad, PhD, MPH

NIH Office of Science Policy

July 29, 2015



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Issue

Evidence

Survey and focus group data suggest that DMC training should be defined and made available

Recommendations

Ensure there is an adequate number of unbiased, competent, experienced, and well-trained DMC members to meet the growing demand

DMC Training Program Objectives

- To familiarize participants with the general purpose of DMCs.
- To describe the history of DMCs.
- To broaden the understanding of DMCs by explaining the essential and evolving functions and processes of the DMCs.
- To highlight the importance of independence and confidentiality – the hallmark of DMCs.
- To provide references, examples, tools, and resources for continued education on data and safety monitoring.

Core Curriculum



Didactic

Interactive

Apprenticeship

Didactic Training

- ▶ History and ethical reasons for DMCs
- ▶ Roles and responsibilities
- ▶ Composition
- ▶ Managing COI
- ▶ Meeting format and function
- ▶ Appropriate interaction and communication with other trial stakeholders
- ▶ Recommendations to the sponsor
- ▶ Statistical and philosophical issues
- ▶ Regulatory guidance

Interactive Training

- Case studies; examples may include
 - Assessing possible late treatment effects early
 - Early termination for a major secondary endpoint
 - Conflicting interim results
 - Study termination related to efficacy
- Simulation
 - Review, step-by-step, old DMC meeting minutes or reports to understand how committees made decisions with the information available at the time of the meeting

Apprenticeship/Mentoring

- Establish a process for including junior/inexperienced DMC members in balance with senior/experienced DMC members
- Encourage including at least one mentee (non-voting) on each DMC
- Include statisticians, clinicians, patient advocates and ethicists among mentee pool
- Post-doctoral and clinical fellows interested in clinical trials should be encouraged to participate as mentees on at least one DMC
- Must clarify how the mentor/mentee relationship would function

Training Forum

- Comprehensive training programs may include a variety of different forums, including but not limited to the following:
 - Online
 - Book or other text review
 - Short courses at professional meetings
 - Regular, class-based, training courses at academic and governmental organizations

DMC Member Database

- Would creation of a database of DMC members be valuable? If so, who would maintain?
- Could include:
 - Training completed, including serving as apprentice
 - Experience in clinical trial methods
 - Number of DMCs served, as member/as chair
 - Years served (e.g., 2010-2012)
 - Area of expertise (biostatistician, clinician, etc.)
 - Contact information (if appropriate)

Additional considerations

- Where/how would a new pool of people to train be identified?
 - Medical and post-doctoral fellows
 - Self-selection
 - DMC member or DMC organizer referral
- Should there be policies requiring training? If so, who sets policy?
- Should there be accreditation of training programs? If so, by whom?

Thank you.



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Session VI: Actionable Opportunities for Transformative Change

Objectives

- Discuss existing barriers to change and strategies for overcoming those barriers
- Consider ways to facilitate adoption of proposed project recommendations

Agenda

- Break-Out Group Discussion
- Working Lunch
- Report Out and Large Group Discussion

Breakout Groups

Group	Room	Moderator	Co-Moderator/Notetaker
Purpose & Rationale	Connection 1	Roger Lewis	Jonathan Seltzer
Formation & Organization	Connection 2/3	Ray Bain	Karim Calis
Communication	Leadership	Dave DeMets	Miriam Donahue
Training	Pinnacle Grand	Jane Perlmutter	Khair ElZarrad

Break-out #1
Purpose & Rationale
Leadership

Tomas Andersson
David Chonzi
John Constant
Dennis Dixon
Marian Fisher
Wayne Morgan
Anna Nicholson
Frank Pucino
Carson Reider
Rick Rode
Pam Shell

Break-out #2
Formation & Org.
Collaboration

Theo Cohen
Sonia Davis
George Gasparis
David Gordon
John Lachin
John McEachern
Nancy Roach
John Schoenfelder
Ken Skodacek
Karen Ulisney
Keith Usiskin
Bill Wang

Break-out #3
Communication
Connection II/III

Matt Dey
John Isador
Hallie Kassan
Rene Kubiak
John Kusek
Gary Lin
Claire Matti
Suz Schrandt
Robert Smith
Janet Wittes
Amy Ghelardi

Break-out #4
Training
Connection I

Patrick Archdeacon
Barbara Bierer
Susan Ellenberg
Liz Frank
Lee Grossman
Karl Kieburtz
Robert Lindblad
Lynne Quittell
Norman Stockbridge
Kimberley Warner
Judy Zuckerman

Report Out

- **Purpose & Rationale**
- **Formation & Organization**
- **Communication**
- **Training**

CTTI DMC Project Expert Meeting

DMC Rationale

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Draft recommendations

1. Detailed rationale for having a DMC should be defined in the charter
 1. Ongoing Assessment of Benefit-Risk
 2. Benefit can be broadly defined (e.g. patient, scientific progress, completion of safety profile)
 3. Enhancing the credibility of the trial is an acceptable rationale for a DMC
 4. 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:
 1. Review Protocol and Consent prior to FPI
 2. Be aware of external information which may effect risk-benefit
 3. Assess the continuing scientific validity of the trial (e.g. trial progress, data quality)
 4. Assess the initial and continuing ethical acceptability and benefit-risk 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)

CTTI DMC Project Expert Meeting

Formation and Organization of DMCs

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Feedback to proposed recommendations

- Are there any areas that you believe need to be addressed that have been left out of (or were not adequately addressed in) the recommendations?
 - Geographic representation on DMC to reflect anticipated regional differences (substantial regional heterogeneity)
 - Differentiate between patient and patient advocate
 - need a trained/qualified individual (not just any patient)
 - Life-threatening and chronic, debilitating conditions

Feedback to proposed recommendations

- ▶ Ethicist required per Belmont
 - ▶ Vulnerable populations/controversial issues
- ▶ Non-voting apprentice role
- ▶ Subject matter expertise on DMC
- ▶ Conflict of interest
 - ▶ Full disclosure to sponsor, chair, other DMC members
 - ▶ Ensure transparency
 - ▶ Collect in a uniform manner/include intellectual conflicts

Feedback to proposed recommendations

➤ Charter

- Points to consider rather than template
- Stress brevity and clarity like an SOP
- Goal is to empower DMC
- Should not be long, legalistic
- Should not be restrictive
- Give latitude

Existing barriers to implementing proposed recommendations

Barrier #1

- Identify and prepare qualified DMC members and SAC

CTTI DMC Project Expert Meeting

Group: Communications With Stakeholders

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Feedback to proposed recommendations

- Are there any areas that you believe need to be addressed that have been left out of the recommendations?
- Are there any recommendations that you find objectionable, or would like to see edited?
- Which of the recommendations do you think are most important?

Existing barriers to implementing proposed recommendations

- Knowing the best time to make a major recommendation to the sponsor and how to deliver the message
- Requests for or need to discuss information with the FDA without breaking confidentiality
- Contractual barrier of limiting analyses and meetings without provision for additional requests from the DMC

Existing barriers to implementing proposed recommendations

- Challenges of working with companies and delivering negative recommendations without responding to their pressures
- Detailed charters and contracts for DMC members expose them to liabilities.
- DMC members follow the charter to the letter.

Strategies to facilitate adoption of proposed project recommendations

1. Limit interaction and sharing of information to discussion between DMC Chair and pre-designated contact at the sponsor
2. Contractual provisions for allowing/funding additional analyses and ad hoc meetings available to the DMC and SAC
3. DMC remains committed to the safety of patients and state that in the charter.
4. Define up-front in the charter with whom major recommendations from the DMC will be discussed

CTTI DMC Project Expert Meeting

Training

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Feedback to proposed recommendations

- ▶ Are there any areas that you believe need to be addressed that have been left out of the recommendations?
 - Provide base training for everybody
 - Provide specialized modules for each level of experience
 - Develop formalized ongoing training (keep stakeholders engaged)
 - Case presentation is the best format to keep stakeholders engaged
 - **Provide training on what would a DMC report should look like and how to read the reports. (trained DMC members will push back if the report is inadequate)**
 - Provide a pre-orientation for each DMC
 - Consider having a closed session at the beginning of each call to review how members understood the data.
 - How to get people to training (engage sponsors, **culture change**, allocate funding, provide credit on CVs, motivate people, etc.)
 - Sponsors should expect training from DMC members

Feedback to proposed recommendations

- ▶ Are there any areas that you believe need to be addressed that have been left out of the recommendations?
 - Focus on fellows and beyond. They are one of the most likely group to be interested and have the time
 - Use senior people (close to retirement) as a great resource to train future DMC members

Existing barriers to implementing proposed recommendations

- No incentives for participating on a DMC or to get a DMC training
- No appreciation for DMC service
- Barrier to apprenticeship (lack of time and recognition). Part-time apprenticeship may not be as effective
- DMC service is not viewed as a viable part of a career path
- Need to identify who will take ownership of the process (e.g., CTTI, NIH, FDA, Industry, collaboration)

Strategies to facilitate adoption of proposed project recommendations

1. Develop case-studies to highlight essential issues/problems to better engage trainees
2. Mandate a base training but be mindful of the burden of a more comprehensive training (DMC membership is not a full-time job)
3. Recognize the service on a DMC. Raise the profile of service on a DMC
4. Give serious thoughts to having redundant expertise on a DMC for the purpose of training
5. Include DMC training as a part of clinical research training workshops and courses, and professional society training (SCT course on DMCs). Stakeholders are at those meetings anyway, so training is more accessible
6. Disseminate available training programs to all stakeholders (e.g., training programs, non-profit, advocacy groups)
7. Acknowledge the service on a DMC (NIH sending a “Thank you” letter to the chair of department of a DMC members). Also, list the names of DMC members in reports and publications.

Thank you.



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