

UPenn Conference on Statistical Issues in Clinical Trials

DMCs: Promoting Best Practices to Address Emerging Challenges

April 19, 2017

Thomas R. Fleming, Ph.D.
Professor, Dept. of Biostatistics
University of Washington

Fleming TR et. al. “Data monitoring committees: Promoting best practices to address emerging challenges”, *Clinical Trials* 2017

Context for this Presentation

- An expert panel of representatives from academia, industry and government sponsors, and regulatory agencies met in June 2015 to discuss ongoing and emerging challenges potentially threatening DMC's independence and effectiveness
- A position paper was published in 2017 in *Clinical Trials* to summarize these discussions and to offer the authors' recommendations to improve the DMC process
- The authors of the *Clinical Trials* article:
TR Fleming, DL DeMets, MT Roe, J Wittes, KA Carim, AN Vora, A Meisel, RP Bain, MA Konstam, MJ Pencina, DJ Gordon, KW Mahaffey, CH Hennekens, JD Neaton, GD Pearson, TLG Andersson, MA Pfeffer, SS Ellenberg

Mission of the DMC

- To Safeguard the Interests
of the Study Participants
- To Preserve Trial Integrity and Credibility
to enable the clinical trial to provide
timely and reliable insights
to the broader clinical community

Some Fundamental Principles in Achieving the DMC Mission

To assist the DMC in achieving its Mission,
procedures are needed...

- To reduce pre-judgment of interim data
 - ⇒ *Maintaining confidentiality of interim data*

- To guide the interpretation of interim data
 - ⇒ Group sequential monitoring boundaries
 - ⇒ Unbiased judgment
 - ... *Well-informed*
 - ... *Independent*

... Motivates fundamental principles
for DMC functioning and composition...

Some Fundamental Principles

- DMC should have *Sole Access* to interim results on relative efficacy & relative safety of interventions
- DMC should have *Multidisciplinary* representation having experience in the DMC process
- DMC should be *Independent* with freedom from apparent significant conflicts of interest ... financial, professional, regulatory

Summary:

An Opinion: The DMC process
for monitoring randomized clinical trials
is *not* better than it was 10 years ago !

In particular, ongoing and emerging challenges
threaten the DMC's *independence* and effectiveness...

Best practices and operating principles
for effective functioning of DMCs
have been proposed to address these challenges

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
 - ✓ DMC meeting format
 - ✓ Creating an effective DMC Charter
 - ✓ DMC recommendations through consensus, not by voting
 - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center
- Better integration of regulatory authorities in DMC process

Proposed Best Practices and Operating Principles

- **Achieving adequate training/experience in DMC process**
- Indemnification
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
 - ✓ DMC meeting format
 - ✓ Creating an effective DMC Charter
 - ✓ DMC recommendations through consensus, not by voting
 - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center
- Better integration of regulatory authorities in DMC process

Current Concerns: Expertise in DMC Processes

- DMC chairs and members
 - Only 8% of DMC members had training in DMC processes
 - ...nearly all indicated prior training would have been valuable
 - Some DMC chairs don't realize they should take leadership:
 - ...in planning the DMC meeting,
 - ...in the conduct of the DMC **Open** as well as **Closed** Session,
 - ...in developing DMC Recommendations & Meeting Minutes
 - Rather than simply asking if anyone identified “any problems”, the DMC chair should ensure the DMC is led through the key findings in the DMC **Closed** Report
- DMC Administrative Support Staff & the DMC Independent Statistician:
 - Should have meaningful expertise in DMC procedures obtained through proper training and previous experiences

Adequate Training/Experience in DMC Process

- Training options for those involved in the DMC process should be more widely developed and used
 - *DMC members, esp DMC chairs and DMC statisticians*
 - Sponsors & their designated '*DMC Meeting Coordinators*'
 - *Statistical Data Analysis Centers* supporting DMCs
- ✓ Didactic Instructions
 - Formal curriculum with textbooks, articles, web-based lectures, interactive courses, etc.
- ✓ Apprenticeship model for initial DMC service to provide real-world experiences

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- **Indemnification**
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
 - ✓ DMC meeting format
 - ✓ Creating an effective DMC Charter
 - ✓ DMC recommendations through consensus, not by voting
 - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center
- Better integration of regulatory authorities in DMC process

Indemnification of the DMC

- DMC Indemnification
 - ✓ Multiple sources of possible liability from clin trial stakeholders
 - ✓ Sponsors/CROs often propose DMC members insure them
 - ✓ DMC concern about litigation could influence their performance
- DeMets et. al.; *Clinical Trials* 2004; 1: 525–531
 - ✓ Recommendations for indemnification of DMC members
 - ✓ DMC coverage without escape clauses: e.g., “negligence”
vs. “willful misconduct or fraudulent acts”
- Tereskerz 2010; *Accountability in Research*
 - ✓ Recommendation for legislation requiring all sponsors:
 - To indemnify DMC members, and
 - To empower them to select and retain
their own independent counsel

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- **Addressing confidentiality issues**
- Implementing procedures to enhance DMC independence
 - ✓ DMC meeting format
 - ✓ Creating an effective DMC Charter
 - ✓ DMC recommendations through consensus, not by voting
 - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center
- Better integration of regulatory authorities in DMC process

Confidentiality of Interim Data

- DAMOCLES:

“There is near unanimity

*that the interim data and the deliberations of the DMC
should be absolutely confidential...*

...Breaches of confidentiality

are to be treated extremely seriously”

- Formal statements of concordance have been issued by
NIH, WHO, EMA and FDA*

*Fleming et al. Maintaining confidentiality of interim data to enhance trial integrity and credibility. *Clinical Trials* 2008; 5: 157–167

Current Concerns: Blinding DMC Members?

E.g.: The CAST Trial

- DMC blinded through X/Y coding
for: Class IC antiarrhythmics vs. placebo
- First DMC Meeting:
 - *19* vs. *3* sudden deaths
 - ...The “blinded” DMC recommended continuation
- Emergency DMC Meeting:
 - *33* vs. *9* sudden deaths;
 - *56* vs. *22* overall deaths
 - ...DMC recommended immediate termination

Addressing Confidentiality Issues

- Preserving confidentiality of interim clinical trial data is essential to trial integrity by reducing risks of prejudgments
- DMC review of *'unblinded'* efficacy as well as safety data throughout the trial facilitates timely/efficient detection of:
 - ✓ benefit/risk issues
 - ✓ trial integrity issues
- In rare settings in which the DMC believes the sponsor's dissemination or lack of dissemination of information has led to serious scientific or ethical concerns, some type of mediation process could be useful

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Addressing confidentiality issues
- **Implement procedures to enhance DMC independence**
 - ✓ DMC meeting format
 - ✓ Creating an effective DMC Charter
 - ✓ DMC recommendations through consensus, not by voting
 - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center
- Better integration of regulatory authorities in DMC process

DMC Meeting Format

DMC Meeting Format, as evolved in the 1980s:

- **Closed Session**

- **Open Session** { Sponsor, Regulators
Lead Investigators

- **Closed Session**

E.g: Fluconazole: Serious Fungal Infections

- ✓ Preserves confidentiality
while maximizing opportunities for interaction
- ✓ Allows for more efficient use of the Open Session
- ✓ Enhances DMC chair leadership of the DMC meeting

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Addressing confidentiality issues
- **Implement procedures to enhance DMC independence**
 - ✓ DMC meeting format
 - ✓ **Creating an effective DMC Charter**
 - ✓ **DMC recommendations through consensus, not voting**
 - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center
- Better integration of regulatory authorities in DMC process

DMC Charter

- Primary Responsibilities of the DMC
- Membership of the DMC
- Timing and Purpose of the DMC Meetings
- Procedures to Maintain Confidentiality
 - ✓ **Open** and **Closed** Sessions
 - ✓ **Open** and **Closed** Reports
 - ✓ **Open** and **Closed** Session Minutes
 - ✓ DMC Recommendations to the Steering Committee
- Statistical Monitoring Guidelines

The DMC shares responsibility to finalize the DMC Charter

Creating an Effective DMC Charter: Avoid Rigid Procedures

- DMC Charters should articulate *principles* that provide *guidance* to the DMC process rather than providing a *rigid set of requirements* ...
DMCs need flexibility to deal with unexpected challenges
- Sponsor's should avoid excess control: such as '*limiting # of looks at outcome data*', or saying '*just review safety data to avoid spending alpha*', etc.
- Budgets should allow flexibility in meeting frequency and in the format/content of DMC reports
- DMC Recommendations through *consensus*, not *voting*
- Proper focus: empowering the DMC regarding its mission rather than a compulsion about documentation

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
 - ✓ DMC meeting format
 - ✓ Creating an effective DMC Charter
 - ✓ DMC recommendations through consensus, not by voting
 - ✓ **DMC contracting process**
- Defining the role of the Statistical Data Analysis Center
- Better integration of regulatory authorities in DMC process

DMC Contracting Process and COI

- Real/Perceived Conflicts of Interest should be identified and procedures should be followed to avoid creating them
 - Criteria for achieving independence of DMC members
 - Selection of venues for meetings, avoiding pre-meeting dinners
 - Rather than using generic consulting agreements, develop “independent scientist” agreements to engage DMC members...
that recognize DMC members as independent scientists having primary focus to protect patient safety and trial integrity
 - If possible, ‘independent entity’ should engage DMC members, such as academic leadership of study steering committee

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
 - ✓ DMC meeting format
 - ✓ Creating an effective DMC Charter
 - ✓ DMC recommendations through consensus, not by voting
 - ✓ DMC contracting process
- **Defining the role of the Statistical Data Analysis Center**
- Better integration of regulatory authorities in DMC process

Defining the Role of the Statistical Data Analysis Center

- The DMC relies on the DMC Open and Closed Reports, generated by independent statistician at the SDAC, for timely & accurate data on efficacy, safety, & quality of trial conduct
- The independent statistician at the SDAC should have *sufficient depth of knowledge* about the study at hand and *experience with trials* in general to ensure the DMC has access to timely, reliable, and readily interpretable insights about emerging evidence in the clinical trial
- DMC Reports should be thoughtfully developed concise documents, with optimally informative figures and tables
- The SDAC independent statistician should routinely have access to all unblinded efficacy and safety data...
...permission from the sponsor should not be required to address DMC requests for additional information

Proposed Best Practices and Operating Principles

- Achieving adequate training/experience in DMC process
- Indemnification
- Addressing confidentiality issues
- Implementing procedures to enhance DMC independence
 - ✓ DMC meeting format
 - ✓ Creating an effective DMC Charter
 - ✓ DMC recommendations through consensus, not by voting
 - ✓ DMC contracting process
- Defining the role of the Statistical Data Analysis Center
- **Better integration of regulatory authorities
in the DMC process**

Integration of Regulatory Authorities in the DMC Process

- Regulatory authorities have developed guidelines that provide an important set of principles for the DMC process
- Additional regulatory guidance would be useful to address emerging challenges to DMC independence & effectiveness
- To enhance the regulators' understanding about DMC process and hence, their ability to provide effective advice, regulatory authorities may benefit from
 - direct experience in the DMC process including through observing or serving on DMCs...(ideally in specialty areas unrelated to their review function)

Proposed Best Practices and Operating Principles for Effective Functioning of Contemporary DMCs

- DMC chairs and members need better training opportunities
- DMC members should be protected against legal liability
- DMCs should review *'unblinded'* efficacy and safety data
- Overly rigid procedures can compromise DMC independence
 - ✓ DMC Charters: providing principles to guide DMC process, rather than listing a rigid set of requirements
 - ✓ Developing DMC recommendations: consensus, not voting
 - ✓ Beginning DMC meeting with Closed Session may enhance independence and establish the DMC Chair's leadership
 - ✓ DMC contracts should recognize DMC as independent scientists
- The SDAC needs experience, access, and flexibilities
- Regulatory scientists would benefit from direct involvement

