Data Monitoring Committees

July 28, 2016

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University of Washington

Fleming TR et. al. “Maintaining Confidentiality of Interim Data to Enhance Trial Integrity & Credibility”. Clinical Trials 2008; 5: 157-167
Mission of the DMC
CPCRA #007: Study Design

Patient Population

600 Unblinded

600 Blinded

ddI Group

600

400 ZDV ddI active

200 ZDV ddI placebo

ddC Group

600

200 ZDV ddC placebo

400 ZDV ddC active
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<th>DATE</th>
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<td>ZDV (ddC)</td>
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<td>42</td>
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<td>Death</td>
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<tr>
<td>n</td>
<td>337</td>
<td>172</td>
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<tr>
<td>Prog/Death</td>
<td>55</td>
<td>42</td>
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<td>Death</td>
<td>18</td>
<td>17</td>
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<tr>
<td>All Events</td>
<td>92</td>
<td>73</td>
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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

While a DMC is reviewing data from ongoing clinical trials, to achieve this 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 composition and functioning
Some Fundamental Principles (re. DMC composition & functioning)

- 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.
Evolution of DMCs: Brief History

- Greenberg Report to NIH in 1967 (Ref: CCT 1988)
  …Develop a mechanism to terminate early if:
  ✓ Question has been answered
  ✓ Trial can’t achieve its goals
  …Guided by recommendations of outside consultants
  …Motivated development of statistical guidelines…

- Use in NIH-sponsor Cancer trials in late 70’s-early 80’s

- Increased use in Industry Trials since 1990
  ✓ Value of independent monitoring is recognized
  ✓ Creation of NIH & Regulatory DMC Guidelines
An Illustrative Experience: Cancer Intergroup #0035 Colon Adjuvant

Duke’s C

- Observation (327)
- Levamisole (328)
- 5-FU + Levamisole (316)

Outcome:
Survival Time, Time to Recurrence

Follow-up to 500 deaths
Four look O’Brien-Fleming design
... one every 125 deaths
O’Brien-Fleming Boundary

Goal: With 4 analyses, preserve the (1-sided) false positive error rate: 0.025

O’Brien-Fleming Biometrics (1979)
How the O'Brien-Fleming guideline works:
Arriving at recommendations about early termination of clinical trials

- that establish benefit
- that rule out benefit
- that establish harm
Symmetric O’Brien-Fleming Group Sequential Boundaries

\[ ln(0.65) \]

\[ ln(0.80) \]

\[ ln(1) = 0 \]

\( \hat{\beta} \)

**REJECT**

\( H : \beta \geq 0 \)

\( H : \beta \leq ln(0.65) \)

\( H : \beta \leq 0 \)
**Cancer Intergroup # 0035: Colon Adjuvant**

*(1-sided) O’Brien-Fleming Guideline: Survival Data*

- **Spring ‘88**: Survival: <18 mo med f.u. \( p = .0015 \)
  - Recurrence: Strong trends \( p = .005 \)

- **Summer ‘88**: FDA/NCI Confidential Review
  - … 1 day later, results publicly revealed

- **Summer ‘89**: Article in Science, Vince DeVita
  - Former NCI Director challenges DMC

- **Fall ‘89**: Survival: \( p = .003 < .005 \)
  - Recurrence: \( p = .0001 \)

---

0 125 250 375 500

Fall ‘84 Spring ‘88 Summer ‘88 Fall ‘89
Consequences of Fall 1989
Release of Results:

- Immediate re-design of next generation Colon Adjuvant Trial

BEFORE

5-FU + Leucovorin
No treatment

AFTER

5-FU + Leucovorin
5-FU + Levamisole

- 1990 FDA Approval of Levamisole NDA

Follow-up continued through March, 1993
Median follow-up increased from 3 years to > 6 years
Duke’s C Colon Cancer Overall Survival

Years from Registration

At risk

Deaths

5-FU+LEV

Observation

1p=0.003

0                    1                    2                    3                    4
Duke’s C Colon Cancer
Overall Survival

p=0.001

Years from Registration

Percent

At risk
Deaths
7-year estimate

5-FU+LEV
Observation

304
315
121
166
56%
43%
Types of Meetings of the Data Monitoring Committee

- Organizational Meeting
- Early Safety/Trial Integrity Reviews
- Formal Interim Analyses
Organizational Meeting

Data Monitoring Committee:

- **Ethically & Scientifically Supportive of:**
  - Study Objectives & Design
    - incl. specified endpoints & monitoring guidelines

- Refine the draft of the DMC Charter

- Endorse & Refine the Content and Format for Open and Closed Reports

- Confidence in Procedures for Capturing Relevant Information of High Quality
Supportive of Study Design
(Advisory Capacity to Sponsor/Investigators)

Illustrations:

1991 NIMH:
HIV-infected Patients with Cognitive Impairment

- X-over at 6 mo.
- Exclude “dropouts”
- Safety only
- Longer term f.u.
- Intent to treat
- Safety & Efficacy
Organizational Meeting

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Types of Meetings of the Data Monitoring Committee

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Eg. Cancer Intergroup # 0035: Colon Adjuvant

Duke’s C \( \xrightarrow{R} \) Observation (327)

Levamisole (328)

5-FU + Levamisole (316)

Follow-up to 500 deaths

Four look O’Brien-Fleming design

\( \approx \) every 125 deaths

0 \( \uparrow \) 125 \( \uparrow \) 250 \( \uparrow \) 375 \( \uparrow \) 500

Fall ‘84 Spring ‘88 Fall ‘89
Safety/Trial Integrity Reviews

• Patient Safety Data
• Accrual rates
• Treatment balance
• Eligibility violations
• Adherence to treatment
• Pooled event rates
• Completeness of follow-up
Types of Meetings of the Data Monitoring Committee

- Organizational Meeting
- Early Safety/Trial Integrity Reviews
- Formal Interim Analyses
Formal Interim Analyses

- **Trial Continuation** with recommendations to address ethical, safety or trial integrity issues

- **Trial Termination** due to:
  - benefit
  - lack of benefit (or *futility*)
  - established harm
  - or inability to reliably answer issues the trial was designed to address
DMCs and other Oversight Bodies: Relative Responsibilities and Relationships

- **Sponsors, Investigators, Care Givers**
  - Decision making responsibilities for design, conduct, & analysis of the trial
  - Primary patient care responsibilities

- **Institutional Review Boards & Regulatory Authorities**
  - Approval of Ethics/Science of the Trial Design
  - Real time Monitoring of SUSARs & SAEs

- **Data Monitoring Committees**
  - Sole access during conduct of the clinical trial to:
    - Aggregated efficacy/safety data across the trial
    - Unblinded by treatment group
An Opinion:

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

...The Emergence of Some Common Myths can adversely impact DMC Independence...
A Dozen Common ‘Myths’ that can Adversely Impact DMC Independence

- DMCs procedures must rigidly follow the DMC Charter
- DMCs use ‘stopping rules’, not ‘monitoring guidelines’
- The # & timing of DMC meetings are fixed in advance
- Content of DMC reports is rigidly pre-specified
- The DMC chair & statistician needn’t have DMC experience
- DMC meetings always should begin with an **Open** Session
- The sponsor or CRO should lead the DMC **Open** Session
- DMC members are consultants for the trial’s sponsor
- DMC members should indemnify the trial’s sponsor & CRO
- Currentness of DMC reports is based on passive procedures
- DMCs should review ‘blinded’ efficacy and safety data
- DMCs ‘vote’ when developing their recommendations
Addressing Threats to the Independence of DMCs: An Outline of Topics to be Discussed

- DMC Meeting Format
- DMC Charter
- Currentness of DMC Data
- Training & Experience in the DMC Process
- Maintaining Confidentiality of Interim Data
- Blinding DMC Members
- DMC Member Contracts & Conflict of Interest
- Avoiding Conflict of Interest
- Indemnification of the DMC
- Conclusion: What should be done?
DMC Meeting Format, as evolved in the 1980s:

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

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

- **Closed Session**
  - E.g: Fluconazole: Serious Fungal Infections
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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 has lead responsibility to finalize the DMC Charter
Current Concerns: DMC Charter

• DMC Charters should be a set of guidelines and principles, not a legal contract; they are getting longer…

• Sponsor’s control: ‘limit # of looks at outcome data’, saying ‘don’t spend any alpha’, ‘just review safety’, etc.

• Some sponsors budget for fixed number of meetings, & don’t allow flexibility in format/content of DMC reports

• Some refer to voting rather than consensus development

• Sponsor compulsion about documentation, rather than empowering the DMC regarding its main mission
  — Frequent updated and signed CVs
  — Constantly changing the DMC Charter
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ACTG 019: Asymptomatic HIV+ Patients
CD4<500

Outcome:
Time to Advanced ARC, AIDS, or Death

Accrual initiation    July 1987
Interim analysis     August 1989
Current Concerns: Currentness of DMC Data

8/2/89  (Data freeze on 5/10/89)

<table>
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<tr>
<th>Rx</th>
<th>#</th>
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<th>P-value vs. placebo</th>
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<td>31</td>
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<tr>
<td>500 mg (453)</td>
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<td>.0008</td>
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<td>1500 mg (457)</td>
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* Failures per 100 person years of follow-up
### Current Concerns: Currentness of DMC Data

**8/16/92 Updated Analysis**

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<th>Rx</th>
<th>Prog*</th>
<th>Rate</th>
<th>P-value vs. placebo</th>
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<tbody>
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<td>38 = 31+7</td>
<td>7.6</td>
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</tr>
<tr>
<td>500 mg (453)</td>
<td>17 = 8+9</td>
<td>3.6</td>
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<td>1500 mg (457)</td>
<td>19 = 12+7</td>
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* Failures per 100 person years of follow-up

O’Brien-Fleming: .005
Current Concerns: Currentness of DMC Data

ACTG 019: HIV Progression (8/2/89)

---

Time to HIV Progression (months)

- ZDV 500 mg
- Placebo

---

Currentness of DMC Data

ACTG 019: HIV Progression (8/2/89)
Current Concerns: Currentness of DMC Data

ACTG 019: HIV Progression (8/16/89)

Time to HIV Progression (months)

Probability

- ZDV 500 mg
- Placebo

[Graph depicting the probability of HIV progression over time for ZDV 500 mg and placebo groups.]
In typical trials with duration 18 months to 4 years:

- **‘Clinical Cut Date’** → DMC Meeting: 6 to 9 weeks
  5-6 weeks: Accuracy/Currentness issues

- **‘Data Lock Date’** → DMC Meeting: about 3 weeks
  2 weeks: Analysis/Report generation
  1 week: Reports to DMC for their review

- Also SAE data & non-validated key endpoint data should be current to the **‘Data Lock Date’**
Data Monitoring Committees

July 28, 2016

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Current Concerns: Expertise in DMC Processes

• DMC chairs
  — 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 and finalizing the DMC Recommendations & DMC 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
Addressing Threats to the Independence of DMCs:
An Outline of Topics to be Discussed

• DMC Meeting Format
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• Conclusion: What should be done?
Some Important Questions Regarding Early Release of Interim Data

Will early release of interim data increase enthusiasm of participating investigators?

Will early release of data provide more timely access to reliable insights?

Will Release of Data from a Concurrent Companion Trial render other Trials Non-influential?
Confidentiality of Interim Data

DAMOCLES*: The current prevailing view is that the trial investigators should not see the unblinded interim results, and the argument that releasing interim results would aid enthusiasm and accrual is false.

* The United Kingdom NHS Health Technology Assessment Program commissioned the ‘Data Monitoring Committees: Lessons, Ethics, Statistics Study Group’ (DAMOCLES):
  — to investigate existing processes of monitoring accumulating data
  — to identify ways of improving the DMC process.

Grant, Altman, Babiker, et al. Health Technology Assessment 2005
Evidence from Cooperative Group Studies

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<th>Cooperative Group DMCs</th>
<th>NCCTG</th>
<th>SWOG</th>
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<td>5/10</td>
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<td>Full accrual</td>
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<tr>
<td>Term early inappropriately</td>
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<td>published results</td>
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Survival of Patients with Rectal Carcinoma in Control and Irradiated Groups

Princess Margaret Hospital − Toronto Study

# = no. at risk
Enhancing Trial Integrity
By Preventing Breaches in Confidentiality

- Reduce Risk of Pre-judgment
- Reduce Risk of Declining Enrollment
- Reduce Risk of Altered Adherence
- Maintain Commitment to Capturing Outcome Data and Maintain Integrity of Subsequent Data Evaluation
- Protect Flexibility to Modify Trial Design Based on Insights from Emerging External Data
- Reduce Risk of Early Release of Misleading Results
Some Important Questions
Regarding Early Release of Interim Data

Will early release of interim data increase enthusiasm of participating investigators?

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Will Release of Data from a Concurrent Companion Trial render other Trials Non-influential?
CPCRA #002  HIV Infected Patients who are AZT Intolerant/AZT Failures

Dideoxyinosine (DDI) (230)
Dideoxycytidine (DDC) (237)

Outcome:
Time to AIDS/Death

Enrollment: 12/90 - 9/91

DMC Efficacy Interim Analyses:
Approximately at increments of 60 events
(Protocol: Follow-up until 243 events)
ddC/ddI: Rate of Progression to AIDS/Death

8/29/91 (39/19)
(8/29/91 (39/19)

11/7/91 (66/50)
(11/7/91 (66/50)

2/13/92 (91/77)
(2/13/92 (91/77)

8/21/92 (130/130)
(8/21/92 (130/130)

2.08 1.25 0.88
2.44 2.04 1.41 1.00 0.82
1.75 1.64 1.20 0.89 0.82
1.25 1.00 0.80

2.5 1.7 1.25 1.0 0.8
Goal: With 4 analyses, preserve the (1-sided) false positive error rate: 0.025
ddC/ddI: Rate of Progression to AIDS/Death

8/29/91
(39/19)

11/7/91
(66/50)

2/13/92
(91/77)

8/21/92
(130/130)

2.08 1.25 0.88

2.44 2.04 1.41 1.00 0.82

1.75 1.64 1.20 0.89 0.82

1.25 1.00 0.80

2.5 1.7 1.25 1.0 0.8
### “VALUE Trial”

**Hypertensive Patients at High Cardiovascular Risk**

Events on Valsartan / Amlodipine; Relative Risk

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<th>May ’98 to December ’03 (n = 15,245)</th>
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<td>178/141; 1.253</td>
<td>841/818; 1.021</td>
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<td>M.I.</td>
<td>102/76; 1.332</td>
<td>369/313; 1.171</td>
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<tr>
<td>Stroke</td>
<td>124/92; 1.338</td>
<td>322/281; 1.138</td>
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<tr>
<td>H.F. Hosp</td>
<td>104/112; 0.922</td>
<td>354/400; 0.879</td>
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<tr>
<td>Diabetes</td>
<td>No data</td>
<td>690/845; 0.811</td>
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</table>
“LIGHT Trial”

Naltrexone SR/Bupropion SR: “Contrave”
CV risks in Overweight/Obese Subjects With CV Risk Factors

Key Design Objectives:
At 90 events: **2.0** Margin for CVD/S/MI
At 378 events: **1.4** Margin for CVD/S/MI

…FDA’s Part 15 Open Public Hearing, 8/11/2014…
“Confidentiality of Interim Results in Cardiovascular Outcome Safety Trials”
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“1<sup>st</sup> Quadrant”: Up to 11/23/2013

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“It isn’t so much
The Things we Don’t Know
That get us into Trouble.
It’s the Things we Know
That Aren’t So.”

Artemus Ward


Fleming TR et. al. “Maintaining Confidentiality of Interim Data to Enhance Trial Integrity & Credibility”. Clinical Trials 2008; 5: 157-167
Some Important Questions
Regarding Early Release of Interim Data

Will early release of interim data increase enthusiasm of participating investigators?

Will early release of data provide more timely access to reliable insights?

Will Release of Data from a Concurrent Companion Trial render other Trials Non-influential?
Release of Data from a Concurrent Companion Trial

CPCRA 023 Trial: April 1993 – July 1995

Oral Gancyclovir: Prevention of CMV Symptoms

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<th>July 1994 CPCRA #023</th>
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## Release of Data from a Concurrent Companion Trial

### CPCRA 023 Trial: April 1993 – July 1995

**Oral Gancyclovir: Prevention of CMV Symptoms**

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## Betaseron in Secondary-Progressive MS Patients

Berlex North America (NA) Trial: 2/96 - 2/00

Number & Percent with Confirmed EDSS Progression

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(OR/ 2p) (0.644/ 0.005) (1.027/ 0.90)
## Betaseron in Secondary-Progressive MS Patients

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Regarding Early Release of Interim Data

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Will Release of Data from a Concurrent Companion Trial render other Trials Non-influential?
Opposing Views

- Lilford et. al.: “Why should data arising in a trial be secret... setting up a system that perpetuates ignorance violates Kant’s injunction that people should not be used as a mere ends to a mean.”

- Fleming et. al.: “This opinion does not recognize that clinical trials must be conducted in a manner to address both collective and individual ethics. Addressing collective ethics includes achieving the goal of a timely and reliable evaluation of the overall benefits and risks of an intervention for the benefit of all patients. Furthermore, many patients join clinical trials in part due to altruistic interests in achieving this same goal, so failure to maintain trial integrity violates individual as well as collective ethics.”

...the second principle of clinical equipoise...
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
• Anand, Wittes, Yusef, et. al. “What information should a sponsor of a randomized trial receive during its conduct?”

• Survey of “experienced clinical trialists”:
  “Do you think that in a large randomized clinical trial, in which there is an independent DMC, made up of reputable clinical trialists and biostatisticians who carefully monitor the trial, interim data such as conditional power should be given to the sponsor when requested?”

  Response: Yes: No: (EU, US, Australia, Canada)
Anand, Wittes, Yusef, et. al. “What information should a sponsor of a randomized trial receive during its conduct?”

Survey of “experienced clinical trialists”:

“Do you think that in a large randomized clinical trial, in which there is an independent DMC, made up of reputable clinical trialists and biostatisticians who carefully monitor the trial, interim data such as conditional power should be given to the sponsor when requested?”

Response: Yes: 0  No: 28  (EU, US, Australia, Canada)
Current Concerns: Confidentiality of Interim Data

Another Illustration:

- Potential Registration Endpoint:
  e.g. ‘Validated’ Biomarker or Symptom Measure
- Clinical Endpoint of Principal Interest:
  e.g. Overall Survival (OS)
  …For subsequent labeling or other regulatory authority…

Approach to maintain integrity of Overall Survival data:
When data on the ‘Registration Endpoint’ are complete, and if the monitoring boundary for OS is not crossed:
- Release data on the Registration Endpoint
- Maintain confidentiality of OS data until the boundary is crossed or target # of events is achieved
Current Concerns: Sponsor Access to Pooled Data

- Availability of Interim Safety and Efficacy Data on a “Need to Know Basis”
  
  E.g:  
  - Medical Monitors for Reporting SUSARs & SAEs
  - Caregivers in Unblinded Trials
  - Pooled data to modify sample size

- Open access (e.g., in DMC Open Reports) to pooled data on efficacy and safety measures readily may provide insights into treatment effects
DMC Open Report: An Outline

- Enrollment rate, by time and by institution
- Baseline characteristics
- Eligibility violations
- Adherence to randomized study medications
- Retention rates
- Currentness of data capture & adjudication of key events

...All information is pooled across treatment groups...

N.B.: The DMC Open Report does NOT provide safety or efficacy data, even pooled by treatment regimen
DMC Closed Report: An Outline

• Repeat of the DMC Open Report information, in greater detail by treatment group
• Analyses of primary and secondary efficacy endpoints
• Analyses of lab values, including basic summaries and longitudinal analyses
• Analyses of adverse events and overall safety data

…The DMC is provided information to allow unblinded review by treatment groups…
Addressing Threats to the Independence of DMCs: An Outline of Topics to be Discussed

- DMC Meeting Format
- DMC Charter
- Currentness of DMC Data
- Training & Experience in the DMC Process
- Maintaining Confidentiality of Interim Data
- Blinding DMC Members
- DMC Member Contracts & Conflict of Interest
- Avoiding Conflict of Interest
- Indemnification of the DMC
- Conclusion: What should be done?
Current Concerns: Blinding DMC Members

E.g: DAIDS Therapeutic DMC

-'86-'06 About 50 clinical trials
-'86-'88 DMC Blinded:
  Safety (A/B); Efficacy (X/Y)
-'88-Present DMC Unblinded

DMC Unblinding facilitated the
Timely/Efficient detection of:

✓ risk/benefit issues
✓ trial integrity issues
Current Concerns: Blinding DMC Members

Eg: Cardiology Pre-Trial Organizational Meeting

➢ Blind

- leaks: Data falls in wrong hands
- leaks: By DMC Membership
- overreaction to something “not real”

➢ Don’t Blind

- Timely & informed integration of complex patterns
  …including risk (A/B) / benefit (X/Y)
- Earlier detection of something “real” using evidence that does exist
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
  …DMC recommended continuation

- Emergency DMC Meeting:
  - 33 vs. 9 sudden deaths;
  - 56 vs. 22 overall deaths
  …DMC recommended immediate termination
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Current Concerns: DMC Contracts and COI

• To avoid creating unnecessary Conflicts of Interest, (e.g., re. developing treatment guidelines, serving on FDA ACs)
  
  …DMC members do not work for the sponsor…

DMC members should be engaged by an entity that is independent from the trial sponsor

• DMC member contracts are becoming very long and legal looking – very one sided – should be simple without needing a lawyer to review – should cover:

  – Confidentiality
  – Intellectual Property
  – Consulting Rate
  – Indemnification
Addressing Threats to the Independence of DMCs: An Outline of Topics to be Discussed

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Current Concerns: Avoiding Conflicts of Interest

• To further avoid creating unnecessary Conflicts of Interest:

  ✓ DMC members should not socialize with the sponsor or study investigators, (e.g., pre meeting dinners)
    ─ “loose lips” and “body language”

  ✓ DMC meetings should not be in resorts or exotic locations
    ─ Chicago O’Hare Hilton is good enough
      – perception of independence
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Current Concerns: Indemnification of the DMC

- **DMC Indemnification**
  - Sponsors/CROs often propose the DMC insure them
  - DMCs cannot function if worried about litigation

- **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
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What Should Be Done?

• Turn the tide on making the DMC process more complicated than it needs to be…
  Implementing rigid and legalistic procedures isn’t consistent with the proper objective of protecting the integrity of independent oversight

• Training, training, training…
  ✓ Textbooks, articles, courses etc.
  ✓ Apprentice approach to train future DMC members

  ➢ *DMC chairs* and *DMC statisticians*
  ➢ Sponsors & their designated ‘*DMC Meeting Coordinators*’
  ➢ *Statistical Data Analysis Centers* supporting DMCs
  ➢ *Regulators*…Seek opportunities for membership on DMCs
What Should Be Done?

• Implement Creative Approaches & Current Best Practices
  – Consider beginning DMC meetings with Closed Sessions
  – The DMC Chair should lead the DMC Open Sessions
  – When possible, have independent entities engage DMC members
  – Reduce Conflict of Interest when planning meeting venues/events
  – DMC members should have proper indemnification
  – Active (not passive) approaches are needed for data capture and adjudication to ensure currentness to the ‘clinical cut date’
  – The DMC should be unblinded in its review of Closed Reports
  – DMC Recommendations: ‘consensus development’, not ‘voting’
  – Regulators should ensure confidentiality of interim data on primary endpoints if obtained from ongoing clinical trials
  – Regulators should provide co-leadership in ensuring necessary steps are taken to protect DMC independence.
CPCRA #007: Study Design

Patient Population

ddI Group
600
400
200
ZDV ddI active
ZDV ddI placebo

ddC Group
600
200
400
ZDV ddC placebo
ZDV ddC active
### Issues & Controversies: DMC ↔ DMC Data Sharing

#### CPCRA #007:

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- **n**: Number of participants
- **Prog/Death**: Progesterone/Death events
- **Death**: Death events
- **All Events**: Total events
**Issues & Controversies:**

**DMC ↔ DMC Data Sharing**

**CPCRA #007:**

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