Data Monitoring Committees

July 26, 2019

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

ddI Group

600
400
200

ZDV ddI
active

ZDV ddI
placebo

ddC Group

600
200
400

ZDV ddC
placebo

ZDV ddC
active
# CPCRA #007: 5/92 - 5/95

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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

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
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

$L = 125, 250, 375, 500$

O’Brien-Fleming

$Biometrics (1979)$
Monitoring Clinical Trials

• 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

\[ \beta \]

\[ \ln 0.65 \]
\[ \ln 0.80 \]
\[ \ln 1 = 0 \]

\[ H : \beta \geq 0 \]
\[ H : \beta \leq \ln 0.65 \]
\[ H : \beta \leq 0 \]
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**  **Fall ‘89**
Consequences of Fall 1989
Release of Results:

• Immediate re-design of next generation Colon Adjuvant Trial

BEFORE

R  5-FU + Leucovorin
No treatment

AFTER

R  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

At risk
Deaths

5-FU+LEV  304  78
Observation  315  114

Years from Registration
0  1  2  3  4

Percent
100  80  60  40  20  0

1p=0.003
Duke’s C Colon Cancer Overall Survival

Percent

Years from Registration

At risk

Deaths

7-year estimate

5-FU+LEV

Observation

0 2 4 6 8

0 20 40 60 80 100

56%

43%

304 121

315 166
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. . . . . Longer term f.u.
• Exclude “dropouts” . . . . Intent to treat
• Safety only . . . . Safety & Efficacy
Organizational Meeting

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Safety/Trial Integrity Reviews

Eg. Cancer Intergroup # 0035: Colon Adjuvant

Duke’s C \( \Rightarrow \) Observation \( \approx \) every 125 deaths

Levamisole \( \approx \) every 125 deaths

5-FU + Levamisole

Follow-up to 500 deaths

Four look O’Brien-Fleming design

0                       125                     250                     375                     500
Fall ‘84           Spring ‘88                     Fall ‘89

Eg. Cancer Intergroup # 0035: Colon Adjuvant

- Observation (327)
- Levamisole (328)
- 5-FU + Levamisole (316)
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 \( (or \text{ futility}) \)
  - established harm
  - or inability to reliably answer issues the trial was designed to address
**End Stage Renal Disease**

---

**Standard Dose ESA**

**High Dose ESA**

**Results** (Interim at 1/2 planned endpoints)

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<thead>
<tr>
<th></th>
<th>n</th>
<th>Death/MI</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Dose</td>
<td>615</td>
<td>164</td>
<td>160</td>
</tr>
<tr>
<td>High Dose</td>
<td>618</td>
<td>202</td>
<td>195</td>
</tr>
</tbody>
</table>

Death / MI relative risk: 1.30 (0.94, 1.79)

Besarab et al, NEJM 339:584-590, 1998:

“↑ in incidence of thrombosis of vascular access sites”
Symmetric O’Brien-Fleming Group Sequential Boundaries

\[ \hat{\beta} \]

\[ \ln 0.75 \]

\[ \ln 0.866 \]

\[ \ln 1 = 0 \]

REJECT

\[ H : \beta \geq 0 \]

\[ H : \beta \leq \ln 0.75 \]

\[ H : \beta \leq 0 \]

* ESA
Oversight Bodies in Ongoing Clinical Trials: Partnership of Responsibilities

• **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
  - Ongoing monitoring of SUSARs & SAEs

• **Data Monitoring Committees (DMCs)**
  - Sole access during conduct of the clinical trial to:
    - Aggregated efficacy/safety data across the trial
    - Unblinded by treatment group
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
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 Hennekins, JD Neaton, GD Pearson, TLG Andersson, MA Pfeffer, SS Ellenberg

Proposed Best Practices and Operating Principles

• Achieving adequate training/experience in DMC process
• Indemnification
• Currentness of DMC data
• 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
Proposed Best Practices and Operating Principles

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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
  - DMC chairs should 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**
• Currentness of DMC data
• 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
Indemnification of the DMC

• DMC Indemnification
  ✓ Multiple sources of possible liability from clinical 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

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Current Concerns: Currentness of DMC Data

ACTG 019: Asymptomatic HIV+ Patients CD4<500

- Placebo (428)
- ZDV 500 mg (453)
- ZDV 1500 mg (457)

Outcome:
- Time to Advanced ARC, AIDS, or Death

Accrual initiation: July 1987
Interim analysis: August 1989
8/2/89  (Data freeze on 5/10/89)

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<th>Prog</th>
<th>Prog* Rate</th>
<th>P-value vs. placebo</th>
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<tr>
<td>1500 mg (457)</td>
<td>12</td>
<td>3.4</td>
<td>.015</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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<td>.05</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)

Probability

ZDV 500 mg
Placebo

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

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

ACTG 019: HIV Progression

ZDV 500 mg

Placebo

Time to HIV Progression (months)

Probability
Current Concerns: Currentness of DMC Data

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’
CPCRA #007: Study Design

Patient Population

600 Unblinded

ddI Group

600 Blinded

ddC Group

400

ZDV ddI active

200

ZDV ddI placebo

200

ZDV ddC placebo

400

ZDV ddC active
**Issues & Controversies:**
DMC ↔ DMC Data Sharing

**CPCRA #007:**

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<th>ZDV ddI Placebo</th>
<th>ZDV ddC Placebo</th>
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<td>172</td>
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<td>42</td>
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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 NIH Cancer Cooperative Group Studies
Maintaining Confidentiality ⇒ ↓ Pre-judgment ⇒ ↑ Trial Integrity

<table>
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<tr>
<th>NIH Cancer Cooperative Group</th>
<th>NCCTG</th>
<th>SWOG</th>
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<tr>
<td>Declining accrual rate</td>
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<td>5/10</td>
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<tr>
<td>Number closed</td>
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<td>9/10</td>
</tr>
<tr>
<td>Full accrual</td>
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<td>6</td>
</tr>
<tr>
<td>Term early appropriately</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Term early inappropriately</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Completed studies with current results inconsistent with early published results</td>
<td>0/9</td>
<td>2/9</td>
</tr>
</tbody>
</table>
Survival of Patients with Rectal Carcinoma in Control and Irradiated Groups

Princess Margaret Hospital – Toronto Study

# = no. at risk

Survival %

Years

100
90
80
70
60
50
40
30
20
10

1 2 3 4 5 6 7

Control
Irradiated

60
65
Maintaining Confidentiality of Emerging Data from Ongoing Clinical Trials:

- Reduces the Risk of Pre-judgment, correspondingly increasing the ability to achieve:
  - Timely Enrollment
  - Targeted levels of Adherence & Retention
  - Timely Trial Completion with Reliable Results

- Reduces the Risk for Early Release of Misleading Results
- Protects the Flexibility to Modify Trial Design Based on Insights from Emerging External Data
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?
CPCRA #002  HIV Infected Patients who are AZT Intolerant/AZT Failures

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

Outcome:
Survival Time, 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)
* 2.08 1.25 0.88

11/7/91 (66/50)
2.44 2.04 1.41 1.00 0.82

2/13/92 (91/77)
1.75 1.64 1.20 0.89 0.82

8/21/92 (130/130)
1.25 1.00 0.80

2.5 1.7 1.25 1.0 0.8
O’Brien-Fleming Group Sequential Boundary

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

\[ L = 61, 122, 182, 243 \]

O’Brien-Fleming

*Biometrics* (1979)
ddC/ddI: Rate of Progression to AIDS/Death

- 8/29/91 (39/19)
  - 2.08
  - 1.25
  - 0.88

- 11/7/91 (66/50)
  - 2.44
  - 2.04
  - 1.41
  - 1.00
  - 0.82

- 2/13/92 (91/77)
  - 1.75
  - 1.64
  - 1.20
  - 0.89
  - 0.82

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

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>May ’98 to August ‘00 (n = 15,290)</th>
<th>May ’98 to December ’03 (n = 15,245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>178/141; 1.253</td>
<td>841/818; 1.021</td>
</tr>
<tr>
<td>M.I.</td>
<td>102/76; 1.332</td>
<td>369/313; 1.171</td>
</tr>
<tr>
<td>Stroke</td>
<td>124/92; 1.338</td>
<td>322/281; 1.138</td>
</tr>
<tr>
<td>H.F. Hosp</td>
<td>104/112; 0.922</td>
<td>354/400; 0.879</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No data</td>
<td>690/845; 0.811</td>
</tr>
</tbody>
</table>
“LIGH T Trial”

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

Key Design Objectives:  
At 90 events:  \textbf{2.0} Margin for CVDeath / Str / MI  
At 378 events: \textbf{1.4} Margin for CVDeath / Str / MI

…FDA’s Part 15 Open Public Hearing, 8/11/2014…
“Confidentiality of Interim Results in Cardiovascular Outcome Safety Trials”
<table>
<thead>
<tr>
<th>CVD Stroke MI</th>
<th>Overall Deaths CV Non-CV</th>
<th>Total</th>
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</tr>
<tr>
<td>Placebo</td>
<td>59</td>
<td>19</td>
<td>3</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>HR</td>
<td>0.59</td>
<td></td>
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</tr>
</tbody>
</table>

“1st Quadrant”: Up to 11/23/2013

✓ DMC rec: ‘Release data to FDA per Data Access Plan’
<table>
<thead>
<tr>
<th>CVD</th>
<th>Overall Deaths</th>
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<tbody>
<tr>
<td>Stroke</td>
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| “1st Quadrant”: Up to 11/23/2013 |
|-------|---|---|---|---|---|---|---|

|-------|---|---|---|---|---|---|---|

| Contrave | 55 | 12 | 21 | 33 | 15 | 31 | 74 | |
| Placebo | 43 | 15 | 14 | 29 | 10 | 23 | 57 | |
| HR | ≈1.29 | | | | | | ≈1.30 | |

✓ On 3/3/2015, DMC recommended trial continuation…
<table>
<thead>
<tr>
<th></th>
<th>CVD Stroke</th>
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✓ On 3/3/2015, DMC recommended trial continuation… That day, sponsor released “1st Quadrant” in Patent Filing  ⇒ Steering Committee recommends trial termination
### “1st Quadrant”: Up to 11/23/2013

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**HR** 0.59

### JAMA 3/8/2016 Final 64%: ‘End of Study’ Results

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</thead>
<tbody>
<tr>
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<td>26</td>
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<tr>
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</table>

**HR** 0.95

### Key insights:

- Potential unreliability of interim data
- Breaches in confidentiality provide potential for:
  - Dissemination of misleading results
  - Risks to irreversibly bias subsequent trial conduct
“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
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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<tr>
<td></td>
<td>Rx</td>
<td>PLA</td>
</tr>
<tr>
<td>n</td>
<td>486</td>
<td>239</td>
</tr>
<tr>
<td>CMV</td>
<td>76</td>
<td>72</td>
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<tr>
<td>(RR/p)</td>
<td>(0.45 / 0.0001)</td>
<td>(0.87 / 0.60)</td>
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<tr>
<td>Death</td>
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<td>68</td>
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<td>Death</td>
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<td>222</td>
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<td>(RR/p)</td>
<td>0.71 / 0.052</td>
<td>1.27 / 0.34</td>
<td>0.83 / 0.09</td>
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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

<table>
<thead>
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<th>October 1998 EU Trial</th>
<th>October 1998 NA Trial</th>
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<td>Rx</td>
<td>PLA</td>
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<tr>
<td>n</td>
<td>360</td>
<td>358</td>
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<tr>
<td>Number</td>
<td>148</td>
<td>178</td>
</tr>
<tr>
<td>Percent</td>
<td>38.9</td>
<td>49.7</td>
</tr>
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(OR/ 2p) (0.644/ 0.005) (1.027/ 0.90)
## Betaseron in Secondary-Progressive MS Patients

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

Number & Percent with Confirmed EDSS Progression

<table>
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<tr>
<th>Time Period</th>
<th>EU Trial</th>
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<th>NA Trial</th>
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<td>PLA</td>
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<tr>
<td>Percent</td>
<td>38.9</td>
<td>49.7</td>
<td>18.9</td>
<td>18.5</td>
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<td>34.4</td>
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<tr>
<td>(OR/ 2p)</td>
<td>0.644/ 0.005</td>
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<td>1.071/ 0.64</td>
<td></td>
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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?
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)
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…
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
  ...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
• Currentness of DMC data
• 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
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
Proposed Best Practices and Operating Principles

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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 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
- Currentness of DMC data
- 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
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

Clinical guideline committees
Proposed Best Practices and Operating Principles

• Achieving adequate training/experience in DMC process
• Indemnification
• Currentness of DMC data
• 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
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 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
CPCRA #007: Study Design

Patient Population

600 Unblinded

600 Blinded

ddI Group

400

200

ddI active

ddI placebo

ddC Group

200

400

ddC placebo

ddC active
### CPCRA #007:

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