Data Monitoring Committees: Best Practices

July 29, 2020

Thomas R. Fleming, Ph.D.
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

ddI Group

600 Blinded

ddC Group

400 ZDV ddI active

200 ZDV ddI placebo

200 ZDV ddC placebo

400 ZDV ddC active
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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:
Primary: Survival  2\textsuperscript{nd}ary: Recurrence-free surv.

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

\[ L = 125, 250, 375, 500 \]
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

\[ \hat{\beta} \]

\[ \ln 0.65 \]

\[ \ln 0.80 \]

\[ \ln 1 = 0 \]

\text{REJECT}\n
\[ H : \beta \geq 0 \]

\[ H : \beta \leq \ln 0.65 \]

\[ H : \beta \leq 0 \]
Cancer Intergroup # 0035: Colon Adjuvant
(1-sided) *O’Brien-Fleming Guideline*: Survival Data

**Spring ‘88**  
Survival: <18 mo med f.u.  
Recurrence: Strong trends

**Fall ‘89**  
Survival: p = .003 < .005  
Recurrence: p = .0001

**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 ‘84 to Fall ‘89**

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<th>301</th>
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<tr>
<td>Fall ‘89</td>
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</tbody>
</table>
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

At risk: 304 for 5-FU+LEV, 315 for Observation
Deaths: 78 for 5-FU+LEV, 114 for Observation

Years from Registration

Percent

0 1 2 3 4

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

Percent

Years from Registration

0 2 4 6 8

At risk

Deaths

7-year estimate

5-FU+LEV 304 121 56%
Observation 315 166 43%

Deaths estimate
Types of Meetings of the Data Monitoring Committee

• Organizational Meeting

• Early Safety/Trial Integrity Reviews

• Formal Interim Analyses
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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- Formal Interim Analyses
Eg. Cancer Intergroup # 0035: Colon Adjuvant

Duke’s C → Observation (327)
Levamisole (328)
5-FU + Levamisole (316)

Follow-up to 500 deaths
Four look O’Brien-Fleming design
≈ every 125 deaths

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
End Stage Renal Disease

Results (Interim at 1/2 planned endpoints)

<table>
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<tr>
<th></th>
<th>n</th>
<th>Death/MI</th>
<th>Death</th>
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<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
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.
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
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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
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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

Outcome: Time to Advanced ARC, AIDS, or Death

Accrual initiation: July 1987
Interim analysis: August 1989

Placebo
ZDV 500 mg (453)
ZDV 1500 mg (457)
Current Concerns: Currentness of DMC Data

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

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<th>P-value vs. placebo</th>
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<td>500 mg (453)</td>
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<td>2.1</td>
<td>.0008</td>
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<tr>
<td>1500 mg (457)</td>
<td>12</td>
<td>3.4</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>17 = 8+9</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)

- **ZDV 500 mg**
- **Placebo**

Time to HIV Progression (months)

- Probability
  - 1.00
  - 0.95
  - 0.90
  - 0.85
  - 0.70

0 4 8 12 16 20 24
Current Concerns: Currentness of DMC Data

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

Probability

Time to HIV Progression (months)

- ZDV 500 mg
- Placebo

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

ddI Group

200

ddC Group

400

ZDV ddI active

ZDV ddI placebo

ZDV ddC placebo

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

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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?
“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>
<thead>
<tr>
<th>NIH Cancer Cooperative Group</th>
<th>NCCTG</th>
<th>SWOG</th>
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<tr>
<td>Interim Data shown only to DMCs:</td>
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<td>NO</td>
</tr>
<tr>
<td>Declining accrual rate</td>
<td>0/10</td>
<td>5/10</td>
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<td>6</td>
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<td>Term early appropriately</td>
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<tr>
<td>Term early inappropriately</td>
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<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>
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

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)
CPCRA #002 Clinical Trial

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
Goal: With 4 analyses, preserve the (1-sided) false positive error rate: 0.025
CPCRA #002 Clinical Trial

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)

* Had 39 vs 19 data been released ⇒ Pre-judgment
“VALUE Trial”
Hypertensive Patients at High Cardiovascular 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>
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<tr>
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<td>178/141; 1.253</td>
<td>841/818; 1.021</td>
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<tr>
<td>M.I.</td>
<td>102/76; 1.332</td>
<td>369/313; 1.171</td>
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<td>Stroke</td>
<td>124/92; 1.338</td>
<td>322/281; 1.138</td>
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<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>
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</table>

*Had May ‘98 data been released ⇒ Misleading Insights*
Maintaining Confidentiality of Emerging Data
“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 CVDeath / Str / MI
At 378 events: 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”
“Data Access Plan”
<table>
<thead>
<tr>
<th></th>
<th>CVD Stroke MI</th>
<th>Overall Deaths CV Total</th>
<th>Stroke MI</th>
<th>D Stroke MI</th>
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<td><strong>Contrave</strong></td>
<td>35</td>
<td>5 5 10</td>
<td>7 24</td>
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<td>59</td>
<td>19 3 22</td>
<td>11 34</td>
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<tr>
<td><strong>HR</strong></td>
<td><strong>0.59</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

✓ **DMC rec:** ‘*Release data to FDA per Data Access Plan*’

**“1st Quadrant”**: Up to 11/23/2013
<table>
<thead>
<tr>
<th></th>
<th>CVD Stroke</th>
<th>Overall Deaths</th>
<th>D Stroke</th>
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<tbody>
<tr>
<td></td>
<td>MI</td>
<td>CV Non-CV</td>
<td>MI</td>
</tr>
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<td>Stroke</td>
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<td>MI</td>
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</table>

**“1st Quadrant”: Up to 11/23/2013**

<p>| | | | |</p>
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<thead>
<tr>
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</table>

✓ DMC rec: ‘Release data to FDA per Data Access Plan’

**“2nd Quadrant”: Between 11/23/2013 and 3/3/2015**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Contrave</td>
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<tr>
<td>HR</td>
<td>1.29</td>
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✓ On 3/3/2015, DMC recommended trial continuation…
<table>
<thead>
<tr>
<th></th>
<th>CVD Stroke</th>
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<tr>
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<tr>
<td>HR</td>
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</table>

**“1st Quadrant”: Up to 11/23/2013**

- **Contrave**: 35, 5, 5, 10, 7, 24, 40
- **Placebo**: 59, 19, 3, 22, 11, 34, 62
- **HR**: 0.59

- **DMC rec**: ‘Release data to FDA per Data Access Plan’

**“2nd Quadrant”: Between 11/23/2013 and 3/3/2015**

- **Contrave**: 55, 12, 21, 33, 15, 31, 74
- **Placebo**: 43, 15, 14, 29, 10, 23, 57
- **HR**: 1.29

- **On 3/3/2015, DMC recommended trial continuation…**
  - That day, sponsor released “1st Quadrant” in Patent Filing
  - **Steering Committee recommends trial termination**
<table>
<thead>
<tr>
<th></th>
<th>CVD</th>
<th>Overall Deaths</th>
<th>D</th>
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<tbody>
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<tr>
<td>Contrave</td>
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*JAMA* 3/8/2016 Final 64%: ‘End of Study’ Results

**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

<table>
<thead>
<tr>
<th></th>
<th>July 1994 SYNTEX #1654</th>
<th>July 1994 CPCRA #023</th>
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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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<td>178</td>
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<tr>
<td>Percent</td>
<td>38.9</td>
<td>49.7</td>
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**OR/2p**

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

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Number & Percent with Confirmed EDSS Progression

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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:
  * Grant, Altman, Babiker, et al. *Health Technology Assessment* 2005

  “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*

• 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)
Canadian Institutes of Health Research
Aspirin +/- Warfarin in Peripheral Arterial Disease

• 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...
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?

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
DMC Access to *Unblinded Efficacy & Safety Data* throughout the clinical trial

Ongoing access to unblinded Efficacy and Safety Data:

- Enables more timely recognition of emerging problems
  ⇒ increases DMC’s ability to protect trial participants

- Enables assessment of safety in a benefit-to-risk context
  
  E.g. An anti-platelet agent may induce major bleeding yet may decrease ischemic events or even mortality

- Facilitates DMC’s ability to identify and assist addressing
  
  ✓ irregularities in trial conduct
  ✓ coding errors in the DMC reports
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**
- **Open Session**
  - Sponsor, Regulators
  - Lead Investigators
- **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

E.g: Fluconazole: Serious Fungal Infections
Proposed Best Practices and Operating Principles

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- Defining the role of the Statistical Data Analysis Center
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
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 (or ISRG), 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
- Confidentiality of emerging data is integral of trial integrity
- 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 / ISRC needs experience, access, and flexibilities
- Regulatory scientists would benefit from direct involvement
CPCRA #007: Study Design

Patient Population

600 Unblinded

ddI

600 Blinded

ddC

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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