Workshop on Clinical Trials

Monitoring Guidelines, Adaptive Methods & Data Monitoring Committees

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University of Washington
Seattle, WA
October 18, 2017
South Africa
Workshop on Clinical Trials

Obtaining insights
to recognize and effectively address scientifically challenging issues in

- Design
- Conduct
- Analysis/Reporting

of clinical trials
Workshop on Clinical Trials
October 16-17: Durban & Johannesburg

- **Design of Clinical Trials**
  - Biomarkers and Replacement Endpoints
  - Designs using Active Controls: Non-inferiority (NI) Trials
  - Monitoring Guidelines & Adaptive Methods

- **Conduct of Clinical Trials**
  - Addressing Missing Data in Clinical Trials
  - Data Monitoring Committees: Current Issues

- **Analysis/Reporting of Clinical Trials**
  - Exploratory Analyses: Why do we need particular caution?
Workshop on Clinical Trials
October 18: HPTN African Regional Meeting

• Design of Clinical Trials
  – *Biomarkers and Replacement Endpoints*
  – *Designs using Active Controls: Non-inferiority (NI) Trials*
  – *Monitoring Guidelines & Adaptive Methods*

• Conduct of Clinical Trials
  – *Addressing Missing Data in Clinical Trials*
  – *Data Monitoring Committees: Current Issues*

• Analysis/Reporting of Clinical Trials
  – *Exploratory Analyses: Why do we need particular caution?*
Workshop on Clinical Trials

• Group Sequential Guidelines
• Adaptive Methods
• Data Monitoring Committees
Coronary Drug Research Project Group

Z Values for Clofibrate - Placebo Differences

Month of Study

Z Value

10 20 30 40 50 60 70 80 90 100
Coronary Drug Research Project Group

Life-table Cumulative Mortality Rates

Cumulative Mortality Rate

Month of Follow-up

Placebo

Clofibrate
Suppose we want to compare the survival of patients randomized to chemotherapy vs observation.

Assume it is planned to accrue patients into the study from 1/1/16 to 1/1/19, with final analysis on 1/1/20.

For each patient,
- *: Date of Randomization
- +: Date of Death
Suppose we want to compare the survival of patients randomized to chemotherapy vs observation.

Assume it is planned to accrue patients into the study from 1/1/16 to 1/1/19, with final analysis on 1/1/20.

For each patient,

* : Date of Randomization
+ : Date of Death
Results of Simulations

LR P-value < 0.05 at 4 years in 31 of 100 studies

LR P-value < 0.05 at 2 years in 27 of 100 studies
Results of Simulations

LR P-value < 0.05 at 4 years in 5 of 100 studies

LR P-value < 0.05 at 2 years in of 100 studies
Results of Simulations

LR P-value < 0.05 at 4 \textit{years} in 5 of 100 studies

LR P-value < 0.05 at 2 \textit{years} in 5 of 100 studies

Were these the same studies?
None of the studies with \( P < 0.05 \) at 2 years had \( P < 0.05 \) at 4 years.
MOS. AFTER START OF RX

100
90
80
70
60
50
40
30
20
10
0

3  6  9  12  15  18

PERCENT SURVIVING

REGIMEN A

LOG-RANK
2-sided
p=0.0030

REGIMEN B

MOS. AFTER START OF RX
RESULTS

The log-rank P value was less than 0.05 at

- The final test; i.e. at 4 years in 5 of 100 studies
- Either the 2- or 4-year test in 10 of 100 studies
- At least 1 of 4 yearly tests in 0 of 100 studies
- At least 1 of 8 semi-annual tests in 0 of 100 studies
- At least 1 of 16 three-month tests in 0 of 100 studies
RESULTS

THE LOG-RANK P VALUE WAS LESS THAN 0.05 AT

The final test; i.e. at 4 years
Either the 2- or 4-year test
At least 1 of 4 yearly tests
At least 1 of 8 semi-annual tests
At least 1 of 16 three-month tests

in 5 of 100 studies
in 10 of 100 studies
in 17 of 100 studies
in  of 100 studies
in  of 100 studies
RESULTS

THE LOG-RANK P VALUE WAS LESS THAN 0.05 AT

The final test; i.e. at 4 years in 5 of 100 studies
Either the 2- or 4-year test in 10 of 100 studies
At least 1 of 4 yearly tests in 17 of 100 studies
At least 1 of 8 semi-annual tests in 21 of 100 studies
At least 1 of 16 three-month tests in 26 of 100 studies
GOAL

Develop a design for repeated data analyses

- which satisfies the ethical need for early termination if initial results are extreme

- while not increasing the chance of false conclusions
(1-sided) false positive error rate: 0.025

At analysis $j$, compute the p value $P_j$
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
Workshop on Clinical Trials

- Group Sequential Guidelines
- Adaptive Methods
- Data Monitoring Committees
The objective of adaptive design usually is to improve flexibility and efficiency by folding the discovery process into confirmatory trials...

“These methods use unblinded data regarding measures of treatment effect to make:

- adaptive selection / modification of treatments,
- adaptive selection of primary endpoints (Bauer and Kohne, 1994),
- adaptive modification of maximal sample size (Proschan and Hunsberger, 1995; Muller and Schafer, 2001; Shi, 2003; Jennison and Turnbull, 2006; Tsiatis and Mehta, 2003),
- adaptive modification of randomization ratios (Berry and Eick, 1994; Yao and Wei, 1996), and
- adaptive enrichment, i.e., adaptive modification of target populations (Freidlin and Simon, 2005; Jiang et al., 2007).”

When conducting discovery or exploratory analyses, it is critical to properly distinguish noise from signal.

Eg: In pursing genetic signatures for enrichment, discovery is performed using a “training data set.” Then confirmation is pursed by evaluating these discoveries in a “validation data set” firewalled away during the discovery process.

When using the same data to generate and then confirm hypotheses, it is critical to address these multiplicity issues…
- to avoid random high bias in estimates of effects and
- to provide an interpretable sampling context for inference (such as p-values).
Adaptive Designs

The objective of adaptive design usually is to improve flexibility and efficiency by folding the discovery process into confirmatory trials...

“These methods use unblinded data regarding measures of treatment effect to make:

- adaptive selection / modification of treatments,
- adaptive selection of primary endpoints (Bauer and Kohne, 1994),
- adaptive modification of maximal sample size (Proschlan and Hunsberger, 1995; Muller and Schafer, 2001; Shi, 2003; Jennison and Turnbull, 2006; Tsiatis and Mehta, 2003),
- adaptive modification of randomization ratios (Berry and Eick, 1994; Yao and Wei, 1996), and
- adaptive enrichment, i.e., adaptive modification of target populations (Freidlin and Simon, 2005; Jiang et al., 2007).”

Efficiency and Interpretability Issues: Standard vs. Adaptive Monitoring Procedures

Illustration: \( \delta = 6\)-week Drop in HAM-D depression Score

\[ \delta = 4, (n_1+n_2 = 267), \text{ vs. } \delta = 2, (n_1+n_2^* \approx 1100) \]

Adaptive Approach: \( n_1 = 200; \quad n_2 = 67 \)

\[ \text{Interim Analysis at } n_1 = 200: \quad \delta = 1.8 \]

Enroll additional \( n_2^* = 900 \)

<table>
<thead>
<tr>
<th>Monitoring Proc:</th>
<th>Standard</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort (i=1, 2)</td>
<td>200</td>
<td>200 (67)</td>
</tr>
<tr>
<td>200</td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td>900</td>
<td></td>
<td>900</td>
</tr>
<tr>
<td>( \hat{\delta}_i )</td>
<td>( \hat{\delta}_i )</td>
<td></td>
</tr>
<tr>
<td>( n_1 ) vs ( \sqrt{n_2 n_2^*} )</td>
<td>.182</td>
<td>.449</td>
</tr>
<tr>
<td>( n_2 ) vs ( \sqrt{n_2 n_2^*} )</td>
<td>.818</td>
<td>.551</td>
</tr>
<tr>
<td>Relative Efficiency</td>
<td>1.0</td>
<td>0.676</td>
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</table>
Key Issues: Outline

- Efficiency
- Interpretability
- Reliability of Interim Results
- Maintaining the Integrity of the Monitoring Process: Scientific and Ethical Considerations
- Conclusions:
  Clinical vs. Statistical Significance
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)

11/7/91 (66/50)

2/13/92 (91/77)

8/21/92 (130/130)
O’Brien-Fleming Group Sequential Boundary

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

$L = 61 \quad 122 \quad 182 \quad 243$

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
Key Issues: Outline

• Efficiency

• Interpretability

• Reliability of Interim Results

• Maintaining the Integrity of the Monitoring Process: Scientific and Ethical Considerations

• Conclusions:
  Clinical vs. Statistical Significance
Key Issues: Outline

- Efficiency
- Interpretability
- Reliability of Interim Results
- Maintaining the Integrity of the Monitoring Process: Scientific and Ethical Considerations
- Conclusions: Clinical vs. Statistical Significance
Primary Goal of Clinical Trials

- Not:
  "To obtain a statistically significant result"
- Rather:
  "To obtain a statistically reliable evaluation regarding whether the experimental intervention is safe and provides clinically meaningful benefit."

Fleming, Statistics in Medicine, 2006

Clinical Significance as well as Statistical Significance
Mehta E.g. \( \delta = 1.8 \)
Adaptive Designs

Proper adaptive procedures:

- should be specified in detail before unblinding the personnel who would implement them
- have the potential for having less favorable operating characteristics than more conventional study designs

- FDA Guidance for Industry on “Adaptive Design Clinical Trials”

Adaptive methods may have:

- reduced efficiency & interpretability (Emerson: Costs of planning to not plan)
- imbalanced weighting of statistical versus clinical significance
- reduced flexibility to address emerging external information if adaptive method provides insights about interim results.

- Tsiatis and Mehta, 2003; Bauer and Posch, 2004; Emerson, 2006;
- Fleming, 2006; Jennison and Turnbull, 2006; Emerson and Fleming (2010);
- Emerson, Levin and Emerson (2011); Levin, Emerson and Emerson (2013)

Preferred role for Adaptive Design may be Exploratory Stages of Development
“Thomas Edison once said, ‘Opportunity is missed by most people because it is dressed in overalls and looks like work.’ In clinical science, it is the steady, incremental steps that are likely to have the greatest impact.”


Workshop on Clinical Trials

- Group Sequential Guidelines
- Adaptive Methods
- Data Monitoring Committees
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
### CPCRA #007: 5/92 - 5/95

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<th>B</th>
<th>p-value</th>
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</tr>
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<td>151</td>
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<td>16</td>
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</tr>
<tr>
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<td>172</td>
<td>168</td>
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<tr>
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<td>28</td>
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<td>37</td>
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</tr>
<tr>
<td></td>
<td>ZDV ddI Active</td>
<td>ZDV ddI Placebo</td>
<td>ZDV ddC Placebo</td>
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<tr>
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<td>55</td>
<td>42</td>
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<td>Death</td>
<td>18</td>
<td>17</td>
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</table>
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
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

\[ \text{R} \leftrightarrow \text{Peptide-T} \]
\[ \begin{array}{c}
\text{Control} \\
\end{array} \]

- 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 \[ R \] 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
Safety/Trial Integrity Reviews

Eg. Cancer Intergroup # 0035: Colon Adjuvant

Duke’s C  R  Observation  (327)
Levamisole  (328)
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Follow-up to 500 deaths
Four look O’Brien-Fleming design
≈ every 125 deaths

0  125  250  375  500
Fall ‘84  Spring ‘88  Fall ‘89
Duke’s C Colon Cancer
Overall Survival

1p=0.003

Years from Registration

Percent

At risk

Deaths

5-FU+LEV
Observation

304 78
315 114
Duke’s C Colon Cancer
Overall Survival

Years from Registration

At risk
Deaths
7-year estimate

5-FU+LEV 304 121 56%
Observation 315 166 43%
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
Workshop on Clinical Trials

Data Monitoring Committees: Promoting Best Practices

October 18, 2017

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
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 Hennekens, 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
• 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
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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

• 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
• Defining the role of the Statistical Data Analysis Center
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)

<table>
<thead>
<tr>
<th>Rx</th>
<th>#</th>
<th>Prog*</th>
<th>Rate</th>
<th>P-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (428)</td>
<td>31</td>
<td>7.5</td>
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</tr>
<tr>
<td>500 mg (453)</td>
<td>8</td>
<td>2.1</td>
<td></td>
<td>.0008</td>
</tr>
<tr>
<td>1500 mg (457)</td>
<td>12</td>
<td>3.4</td>
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<td>.015</td>
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* Failures per 100 person years of follow-up
### 8/16/92 Updated Analysis

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<tr>
<th>Rx</th>
<th>Prog</th>
<th>Prog*</th>
<th>Rate</th>
<th>P-value vs. placebo</th>
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<tr>
<td>Placebo (428)</td>
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<tr>
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<td>1500 mg (457)</td>
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<td>.05</td>
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</table>

* Failures per 100 person years of follow-up

O’Brien-Fleming: .005
ACTG 019: HIV Progression (8/2/89)

Time to HIV Progression (months)

Probability

ZDV 500 mg
Placebo

Current Concerns: Currentness of DMC Data
Current Concerns: Currentness of DMC Data

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

- ZDV 500 mg
- Placebo

Time to HIV Progression (months):
- 0
- 4
- 8
- 12
- 16
- 20
- 24

Probability:
- 0.70
- 0.85
- 0.90
- 0.95
- 1.00
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’*
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
• Defining the role of the Statistical Data Analysis Center
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 Cooperative Group Studies

<table>
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<tr>
<th>NIH Cancer Cooperative Group</th>
<th>NCCTG</th>
<th>SWOG</th>
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<td>Interim Data shown only to DMCs:</td>
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<td><strong>Declining accrual rate</strong></td>
<td>0/10</td>
<td>5/10</td>
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<td>Number closed</td>
<td>9/10</td>
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<td>Term early inappropriately</td>
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<tr>
<td>Completed studies with current results inconsistent with early published results</td>
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<td>2/9</td>
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</table>
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

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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:
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
### “VALUE Trial”

**Hypertensive Patients at High Cardiovascular Risk**

**Events on Valsartan / Amlodipine; Relative Risk**

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<th>Outcome Measure</th>
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<th>May ’98 to December ’03 (n = 15,245)</th>
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<td>Death</td>
<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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<td>322/281; 1.138</td>
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<td>690/845; 0.811</td>
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“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”
<table>
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<tr>
<th></th>
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**“1st Quadrant”: Up to 11/23/2013**

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## Statistics Table

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</table>

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

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

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</table>

**HR** indicates the Hazard Ratio, which measures the relative risk of an event occurring in one group compared to another group.
“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>
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<th>July 1994 CPCRA #023</th>
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<td>72</td>
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<td>(RR/p)</td>
<td>(0.45 /0.0001)</td>
<td>(0.87 / 0.60)</td>
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<tr>
<td>Death</td>
<td>109</td>
<td>68</td>
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<tr>
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<td>(0.71/ 0.052)</td>
<td>(1.27 / 0.34)</td>
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<tr>
<td><strong>(RR/p)</strong></td>
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<td>(0.87 / 0.60)</td>
<td>(0.92 / 0.60)</td>
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<td><strong>Death</strong></td>
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<td>68</td>
<td>58</td>
</tr>
<tr>
<td><strong>(RR/p)</strong></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

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<td>Rx PLA</td>
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<td>360 358</td>
<td>631 308</td>
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<td>Number</td>
<td>148 178</td>
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<td>Percent</td>
<td>38.9 49.7</td>
<td>18.9 18.5</td>
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<td>(OR/2p)</td>
<td>(0.644/0.005)</td>
<td>(1.027/0.90)</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>
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<tr>
<th>Time</th>
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<th>NA Trial</th>
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<tr>
<td></td>
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<td>49.7</td>
<td>18.5</td>
</tr>
</tbody>
</table>

*EU Trial*

*NA Trial*
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...
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
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
• 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

- **Open Session**
  - Sponsor, Regulators
  - Lead Investigators
  - *E.g:* Fluconazole: Serious Fungal Infections

- **Closed Session**
  - Allows for more efficient use of the Open Session
  - Enhances DMC chair leadership of the DMC meeting
Proposed Best Practices and Operating Principles

• Achieving adequate training/experience in DMC process
• Indemnification
• 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
• 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
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

- The SDAC needs experience, access, and flexibilities
- Regulatory scientists would benefit from direct involvement
CPCRA #007: Study Design

Patient Population

ddI Group
- 600 Unblinded
  - 400 ZDV ddI active
  - 200 ZDV ddI placebo

ddC Group
- 600 Blinded
  - 200 ZDV ddC placebo
  - 400 ZDV ddC active
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Workshop on Clinical Trials
October 18: HPTN African Regional Meeting

- Design of Clinical Trials
  - Biomarkers and Replacement Endpoints
  - Designs using Active Controls:
    Non-inferiority (NI) Trials
  - Monitoring Guidelines & Adaptive Methods

- Conduct of Clinical Trials
  - Addressing Missing Data in Clinical Trials
  - Data Monitoring Committees: Current Issues

- Analysis/Reporting of Clinical Trials
  - Exploratory Analyses:
    Why do we need particular caution?
ACKNOWLEDGEMENTS

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