WHO Blueprint Workshop on Clinical Trial Design

The “Master Protocol”: Protecting the Integrity of Clinical Trials Conducted in Public Health Emergences

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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>
<thead>
<tr>
<th>NIH Cancer Cooperative Group</th>
<th>NCCTG</th>
<th>SWOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interim Data shown only to DMCs:</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Declining accrual rate</td>
<td>0/10</td>
<td>5/10</td>
</tr>
<tr>
<td>Number closed</td>
<td>9/10</td>
<td>9/10</td>
</tr>
<tr>
<td>Full accrual</td>
<td>8</td>
<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>
Enhancing Trial Integrity
By Preventing Breaches in Confidentiality

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
  ✓ Continued Commitment to Capturing Outcome Data
  ✓ Timely Trial Completion with Reliable Results

• Reduces the Risk for Early Release of Potentially Misleading Results
Maintaining Confidentiality of Emerging 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

Interest in ‘Positive’ Results in Clinical Trials

- **Industry Sponsors**
  - Company profits, ↑ value of stock options, promotion

- **Government Sponsors**
  - Claims of success in advancing health care
  - Leverage for ↑ in federal funding

- **Journal Editors** (Publication bias)

- **Academic Investigators / Caregivers**
  - Increased ability to publish results
    - ↑ professional stature, earlier promotion, ↑ salary
  - Desire to offer more therapeutic options to patients

Result: *Wide Spread & Significant Conflicts of Interest*
Coronary Drug Research Project Group

Life-table Cumulative Mortality Rates

Cumulative Mortality Rate

Month of Follow-up

Placebo

Clofibrate
## “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>

*Had May ‘98 data been released ⇒ Pre-judgment*
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 CVDDeath / Str / MI
At 378 events: 1.4 Margin for CVDDeath / 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></th>
<th>CVD Stroke</th>
<th>Overall Deaths</th>
<th>D Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI</td>
<td>CV Non-CV Total</td>
<td>MI</td>
</tr>
<tr>
<td>Contrave</td>
<td>35</td>
<td>5 5 10</td>
<td>7 24</td>
</tr>
<tr>
<td>Placebo</td>
<td>59</td>
<td>19 3 22</td>
<td>11 34</td>
</tr>
<tr>
<td>HR</td>
<td><strong>0.59</strong></td>
<td></td>
<td></td>
</tr>
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</table>

**“1st Quadrant”: Up to 11/23/2013**

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

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

- **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
## 1st Quadrant: Up to 11/23/2013

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<tr>
<td>Contrave</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>59</td>
<td>19</td>
</tr>
<tr>
<td>HR</td>
<td>0.59</td>
<td>0.64</td>
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## JAMA 3/8/2016 Final 64%: ‘End of Study’ Results

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<td>Stroke CV Non-CV Total Stroke MI Stroke MI</td>
<td></td>
</tr>
<tr>
<td>Contrave</td>
<td>119</td>
<td>26</td>
</tr>
<tr>
<td>Placebo</td>
<td>124</td>
<td>42</td>
</tr>
<tr>
<td>HR</td>
<td>0.95</td>
<td>1.02</td>
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### Key insights:

- Potential unreliability of interim data
- Breaches in confidentiality provide potential for:
  - Dissemination of potentially misleading unreliable results
  - Risks to irreversibly bias subsequent trial conduct
ddC/ddI: Rate of Progression to AIDS/Death

Had 39 vs 19 data been released ⇒ Pre-judgment
Some Scientific & Ethical Considerations

Maintaining Confidentiality:

\[ \downarrow \text{Risk of Pre-judgment} \Rightarrow \uparrow \text{Trial Integrity} \]

2\textsuperscript{nd} principle of clinical equipoise:

“Anything that jeopardizes the trial’s ability to disturb the initial state of equipoise is to be avoided”

⇒ Inconclusive evolving evidence, when an outbreak wanes, should remain confidential to allow continuation at next outbreak