Reasoning and General Guidelines for Data Monitoring Committees

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1. Inspiration and Resources
   a. Poll audience
      i. Has anyone reported to a DMC before? If so, how many?
      ii. Has anyone sat on a DMC before?
   b. The idea of DMCs comes up often. Do we always need one? Why would we/wouldn’t we need one?
   e. DMC ‘Training’ Video: https://videos.ictr.wisc.edu/DMCTraining/story.html
   g. Regarding the naming conventions
      i. DMC = Data Monitoring Committee
      ii. DSMB = Data and Safety Monitoring Board
      iii. DSMC = Data and Safety Monitoring Committee
      iv. They are all synonymous
2. A DMC is an independent group of experts (and potentially patient representative[s]), appointed by a sponsor/investigator to review accumulating **clinical trial data** on a regular basis
   a. They are not legally required for any/all studies; exception: studies in emergency settings with waiver of informed consent
   b. Usually comprised of three to five members; may be more in several situations

3. Why are DMCs used?
   a. Ethical – monitor patient safety
      i. Monitor for harm or for efficacy
      ii. It is unethical to withhold potentially efficacious treatments from patients (or to prolong the study if there is clear benefit)
      iii. It is unethical to subject patients to undue risks of study involvement if there is clearly harm or if treatments are futile early on
      iv. It is unethical to continue studies that are failing for other reasons (logistical, etc.) such that they will not be able to address initial question
   b. Scientific – monitor study conduct and ensure sound design, operation, analyses
      i. Independent party that can identify sources of bias and/or protect against operational biases
      ii. Diverse, expert panel allows for another layer of review to ensure appropriate (sound) methods
   c. Economical – monitor trial progress to ensure time/effort/money/resources are not wasted
5. History
         i. NHI (precursor to NHLBI) convened committee to review conduct of clinical trials
         ii. Greenberg Report published in 1988 in Controlled Clinical Trials
         iii. Idea: “mechanism must be developed for early termination if unusual circumstances dictate that...a study should not be continued” ...“on recommendation of consultants”
         iv. BUT those involved in the design and conduct a trial may not be fully objective in “reviewing interim data for emerging concerns”
   b. Coronary Drug Project (CDP) = one example trial in which precursor to DMC involved
      i. 53 sites, five treatment groups, >8K participants
      ii. CDP became prototype for many other institutes/centers/studies
      iii. Published in 1981
   c. DHHS in 2000: all trials must have a monitoring plan (may or may not include DMC and may or may not “live” in the study protocol)
   d. NIH policy (1998): all sponsored trials must have a monitoring system (may include safety, efficacy, validity) and a DMC often mandated for phase III trials
   e. FDA DMC Guidelines (2006):
      i. Not binding recommendations
      ii. DMC only required per FDA for one type of trial: emergency setting and waiver of informed consent
   f. Increased use in 1990s due to International Conference on Harmonization (ICH) efforts/documents (https://www.ich.org/products/guidelines.html); increased collaboration between industry/NIH/FDA
   g. Today – many variations of DMCs: some are merited, others are superfluous
7. **Determining Need for DMC**
   a. *Usually* for large, randomized, multisite studies in which outcome is **time-to-death** or **major adverse health outcome** (cardiovascular, recurrence of cancer, etc.)
   b. Generally **not needed** at **early** stages of intervention development
   c. Generally **not needed** for trials with “**lesser**” outcomes (e.g., relief of symptoms) unless population studied is at elevated risk for more severe outcomes
   d. **FDA guidance recommends considering** a DMC when:
      i. Study result may be such that highly favorable or unfavorable results (or even futility) at an interim analysis might ethically require termination of the study early
      ii. Predetermined reasons for safety concerns (e.g., invasive procedure)
      iii. Possibility of toxicity/severe side effects
      iv. Fragile population (children, pregnant women, elderly, terminally ill, etc.)
      v. Large, long duration, multicenter studies
      vi. **NOTE:** it also needs to be **practical**

8. **Membership** *(usually at least three people: two clinical members + one biostatistician)*
   a. Clinical expert in relevant field(s)
   b. Biostatistician
   c. Basic scientist
   d. Regulatory specialists
   e. Ethicist
   f. Patient representative
   g. NO conflicts of interest: financial, clinical involvement, intellectual investment
9. **DMC Review Process**
   a. Beginning to end of study
   b. The DMC Reviews...
      i. Design/initial protocol
      ii. Data quality/timeliness/completeness
      iii. Adherence to protocol – procedures, clinic visits, treatment allocation
      iv. Early data summarizations: baseline characteristics, comparability of groups, design assumptions, etc.
      v. Interim analysis results – evaluate risk/benefit profile
   c. Meeting schedule = study/DMC dependent
      i. Pre-study initiation
      ii. Interim trial fractions (e.g., 25%, 50%, 75%, 100%)
      iii. Usually at least once/year
      iv. As needed; may require ad hoc meetings
      v. Flexibility = key
   d. **Meeting format** – usually dictated by a charter (important, living document that guides DMC procedures; plan of operations for DMC)
      i. **Open session**: all parties involved present (site, CRO, sponsor, DMC, reporting statistician); review data in aggregate
      ii. **Closed session**: just DMC + unblinded statistician; review unblinded data by study arm
      iii. **Executive session**: DMC only
      iv. **Debrief session**: involves sponsor/team representative(s) + DMC
      v. Minutes/recommendations communicated after meeting in writing
   e. **Recommendations the DMC generally makes**...
      i. **Continue as planned** with no modifications – most common
      ii. **Continue as planned** with protocol modifications – less common
      iii. **Termination of the study** – usually guided by pre-specified stopping rules (there are separate, statistical methods that are often used here) – least common
      iv. These are recommendations, not decisions

10. **Reasons for Early Termination**
   a. Unequivocal evidence of treatment benefit or harm (group sequential methods, stopping bounds, spending functions)
   b. Unexpected, unacceptable side effects
   c. No emerging trends/ no reasonable chance of demonstrating benefit (futility; conditional power)
   d. Overall progress/conduct of trial – not enough patients at a sufficient rate, lack of compliance in large numbers, poor follow-up, poor data quality
   e. Based on external information – other studies answer questions, other studies or data illustrate risks
   f. Caution – do not use statistical tools as “law”; they are tools (i.e., guidelines)
11. Topics for Further Discussion
   a. Training issues
      i. An MD, MS, or PhD is not enough: must have more than “classical” training
      ii. Also true for sponsor/PI/funder other study team members and DMC members
          – DMC chair = vital in taking ownership and dictating the demands/needs of DMC
      iii. “Apprenticeship” model – this seems like a good idea in my opinion
   b. On reporting
      i. Report and charter are living documents, subject to change per needs of DMC
      ii. Concise reporting
      iii. Be thoughtful, anticipate questions
      iv. Will need to involve a clinical expert and/or obtain feedback from DMC regarding needs
      v. Unblinded data in closed report (include codes ‘A’ or ‘B’ in case the report is sent to the wrong person/people, but reporting statistician should have these codes available during the meeting)
      vi. Open report and closed report do not need to overlap so much
      vii. May not always be appropriate to report aggregate event rates to sponsor or investigators
      viii. Should highlight/report new findings since last time
      ix. Always include protocol synopsis
      x. Number pages, number tables, make it simple, report denominators
      xi. Allow ample time to review reports (at least a week?) – allow for walking through report as a team and generate/pose questions in advance of meeting
   c. DMC Myths (DeMets)
      i. DMCs should be blinded
      ii. DMCs meetings must be held precisely as scheduled and be limited in number
      iii. Review must be on clean, adjudicated data only
      iv. DMC reports can be pre-programmed
      v. Each AE/SAE must be reviewed by DMC
Examples (see online video)

- Example: ddI/ddC Trial (HIV network trial)
  - AIDS/death = primary outcome
  - ddI approved while trial in process
  - Early trend of ddI efficacy when compared to ddC, but due to large error bounds, decided to continue

**Relative Risk of ddC/ddI (on a log scale)**


- DMC needs to be flexible; meeting schedule adapted according to results and need
- Final results:
Early findings can be unreliable; importance of restricting interim results to DMC may be relevant as well here

Ultimate conclusion: “neither drug very good”

### ddl/ddC Final Results

<table>
<thead>
<tr>
<th></th>
<th>ddl (N=230)</th>
<th></th>
<th>ddc (N=237)</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS or death</td>
<td>157</td>
<td>93.3</td>
<td>152</td>
<td>87.7</td>
<td>0.56</td>
</tr>
<tr>
<td>Death</td>
<td>100</td>
<td>42.8</td>
<td>88</td>
<td>35.1</td>
<td>0.09</td>
</tr>
<tr>
<td>ΔCD4+ count at 2 months</td>
<td>+8.6</td>
<td></td>
<td>+5.9</td>
<td></td>
<td>0.009</td>
</tr>
</tbody>
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*per ICC person years*

“zacitabine was found to be as efficacious as didanosine… neither treatment offered substantial long-term benefit.”
Another Example: INSIGHT SMART trial
- Another HIV treatment trial in 2001
- ART = antiretroviral treatment: side effects, difficulty with adherence; concerns re: HIV drug resistance; “drug holiday”

SMART Study Design

Participants with CD4 > 350

n = 3000

Virologic Suppression (VS) Strategy
[Use ART to maintain viral load as low as possible throughout follow-up]

Drug Conservation (DC) Strategy
[Stop or defer ART until CD4 < 250; then episodic ART based on CD4 cell count to increase counts to > 350]


- Primary endpoint = AIDS or death; secondary composite endpoints (major cardiovascular endpoints, renal events, etc.)
Secondary Outcome: Major CVD or Metabolic Disease

**Outcome:**
- Cirrhosis
- CAD (requiring surgery)
- Myocardial infarction
- Stroke
- Kidney failure

**Justification:**
- Composite outcome:
  - expected ART toxicities
  - occur with a similar incidence as AIDS events
  - more serious than most AIDS events

- DMC: NIH appointed (10-12 members)
  - Interim review at least one time per year
  - Clinical endpoints reviewed for safety, clear evidence of benefit, clear evidence of harm too
  - Futility as well
  - “Clear and substantial evidence of benefit or harm”

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**January 2006 DSMB Call**

**Enrollment**

**Clinical Endpoints**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Second.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>159 (5800 PY)</td>
</tr>
<tr>
<td>Rates</td>
<td></td>
</tr>
<tr>
<td>DC</td>
<td>3.6</td>
</tr>
<tr>
<td>VS</td>
<td>1.7</td>
</tr>
<tr>
<td>HR</td>
<td>2.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.5 – 3.0</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>
DMC recommends to STOP enrollment
- Additional follow-up will unlikely demonstrate superiority of DC arm
- Re-design if can find an ethical/safe way to conduct or stop study
- Ultimately, after much back-and-forth, enrollment was halted and letter to investigators and participants (2+ times risk of events in DC group)
- Stopping occurred after just 20% of information planned (roughly 20% of patients/events)
Interim Monitoring: O’Brien Fleming Boundaries For The Primary Endpoint By Cut Date

SMART Primary and Supportive Endpoint Results

<table>
<thead>
<tr>
<th></th>
<th>DC Group</th>
<th></th>
<th>VS Group</th>
<th></th>
<th>HR (DC/VS)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>Rate</td>
<td></td>
<td>[95% CI]</td>
<td></td>
</tr>
<tr>
<td>AIDS or death (primary endpoint)</td>
<td>120</td>
<td>3.3</td>
<td>47</td>
<td>1.3</td>
<td>2.6 [1.9, 3.7]</td>
<td>&lt;0.001</td>
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<tr>
<td>Death</td>
<td>55</td>
<td>1.5</td>
<td>30</td>
<td>0.8</td>
<td>1.8 [1.2-2.9]</td>
<td>0.007</td>
</tr>
<tr>
<td>CVD, Renal, Liver</td>
<td>65</td>
<td>1.8</td>
<td>39</td>
<td>1.1</td>
<td>1.7 [1.1, 2.5]</td>
<td>0.009</td>
</tr>
<tr>
<td>- CVD</td>
<td>48</td>
<td>1.3</td>
<td>31</td>
<td>0.8</td>
<td>1.6 [1.0, 2.5]</td>
<td>0.05</td>
</tr>
<tr>
<td>- Renal</td>
<td>9</td>
<td>0.2</td>
<td>2</td>
<td>0.1</td>
<td>4.5 [1.0, 20.9]</td>
<td>0.05</td>
</tr>
<tr>
<td>- Liver</td>
<td>10</td>
<td>0.3</td>
<td>7</td>
<td>0.2</td>
<td>1.4 [0.6, 3.8]</td>
<td>0.46</td>
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