Data and Safety Monitoring Boards (DSMBs)

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Underlying Principles

- Group of experts *external* to the trial & *independent* of the sponsor

- Responsibility to monitor the conduct of the trial & review accumulating trial data

- Sponsor & investigators delineate the specific charge(s) to the DSMB

- Makes recommendations to the sponsor & investigators regarding the conduct of the trial (including a possible recommendation for early termination)
Three Major Monitoring Charges to DSMB

- Safety
- Efficacy (including interim analyses & group sequential monitoring)
- Assumptions underlying sample size calculation
DSMB Recommendations at Each Meeting

- Continue as is
- Continue, but with modification
- Stop temporarily until certain conditions are met
- Terminate
Advantages to Sponsor

- Eliminates potential conflicts of interest
- Strengthens scientific integrity & credibility of the trial
- Provides a sounding board & expertise to deal with knotty problems that arise during the conduct of the trial
- Can alert the sponsor to emerging problems during the course of the trial
- Can support the sponsor in making tough, sometimes unpleasant decisions (‘hatchet man’ role)
- Can aid & support the sponsor in dealing with the FDA
Disadvantages to Sponsor

- Additional cost & administrative burden
- Perceived sense of loss of control & authority
- Added possibility of breach of confidentiality & information leakage
- Potential for a contentious relationship to develop between sponsor & DSMB members
Sponsor’s Responsibilities to DSMB

• Strict maintenance of ‘hands off’ policy
• Charter: articulate (in detail & in writing) the charge to the DSMB & the DSMB operating guidelines
• Convene DSMB meeting *before* trial commences to review protocol, charge, operating guidelines, table shells for DSMB perusal
• Provide the DSMB with all the information requested for DSMB members to discharge their duties properly
• After trial concludes, keep DSMB informed as to what is being done with the data collected & the trial findings
• (?) Indemnify DSMB members should the DSMB be sued
DSMB Members’ Responsibilities to Sponsor

• Avoid any & all potential conflicts of interest
• Maintain strict confidentiality of trial information
• Maintain objectivity
• Avoid emotional involvement & personality clashes
• Insofar as possible, participate actively in all teleconferences & in-person meetings
• Keep accurate minutes of all teleconferences & in-person meetings
Membership on DSMB

- Minimum of three members; no maximum number
- One member must be a biostatistician
- Other members to represent relevant clinical and/or basic science disciplines
- Often useful to have an ethicist or patient ombudsman member
- Previous DSMB experience desirable, but not necessary
Pre-DSMB Meeting/Teleconference

• Distribute tables & report of trial progress
• Sample contents:
  – Narrative: Executive Summary
  – Screening, enrollment, randomizations
  – Baseline comparability
  – Follow-up status
  – Compliance
  – Protocol violations
  – Safety: Deaths, Serious Adverse Events, other adverse events
  – Laboratory findings
  – Outcome findings: primary, secondary, tertiary
Structure of DSMB Meeting/Teleconference

• Open session (All)

• Closed session (DSMB & statisticians)

• Executive session (DSMB only)

• Recommendations (DSMB & PI)
Contents of DSMB Open Session

• Administrative issues (including funding)
• Equipoise – risk/benefit alterations
• Proposed protocol & informed consent modifications
• Emerging evidence external to the trial relevant to the continuing conduct of the trial & informed consent
• Subject recruitment & accrual
• Site performance; probationary measures for poorly performing sites
• New ancillary studies
Contents of DSMB Closed Session

- Baseline comparability
- Compliance
- Protocol violations
- Unblindings, withdrawals, treatment cessations, losses to follow-up
- Serious Adverse Events (SAEs) & deaths, including scenarios
- Other adverse events
- Laboratory & clinical findings
- Outcomes: primary, secondary, tertiary
- Interim efficacy analyses (if relevant)
- Ancillary studies
- Emerging issues
Early Stopping of a Clinical Trial
Early Stopping of a Trial
Inadequate Enrollment

MY EXPERIENCE

– Cardiovascular trial within the VA Cooperative Studies Program

– Phase III therapeutic trial for squamous cell cancer of the head & neck
Early Stopping of a Trial
More than Anticipated Enrollment

MY EXPERIENCE

- IVGG in treatment of Kawasaki Disease
Early Stopping of a Trial
Inadequate Frequency of Primary Outcome Events

**MY EXPERIENCE**

– Cardiovascular component of Physicians Health Study (PHS)
Early Stopping of a Trial
Poor Compliance

MY EXPERIENCE

– Oral contraceptives vs. foam contraception and adverse effects
Early Stopping of a Trial
Safety – Change in Equipoise

**MY EXPERIENCE**

– Stroke Prevention in Atrial Fibrillation I (SPAF I)
Early Stopping of a Trial
Lack of Efficacy/Futility

MY EXPERIENCE

– Regeneron trial for treatment of Amyotrophic Lateral Sclerosis

– Phase III therapeutic trial for squamous cell cancer of the head & neck
Early Stopping of a Trial
Efficacy

Interim Analysis
Early Stopping of a Trial

Two extremes in data analysis:

– Fixed sample size – conduct single analysis at the completion of data collection

– Fully sequential – conduct analysis continuously, after completion of each observation
**Interim Analysis:**

**Effect of Repeated Testing**

<table>
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<tr>
<th>No. of tests at 5% level</th>
<th>Overall significance level</th>
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<tr>
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<tr>
<td>2</td>
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<td>10</td>
<td>0.19</td>
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<td>20</td>
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Assuming tests are performed after equal increments of information. *Data Monitoring Committees in Clinical Trials. Ellenberg, Fleming, DeMets. 2003*
Early Stopping of a Trial

Evolution of sequential analysis:
- 1947 – Wald’s fully sequential design
- 1960 – Armitage’s closed sequential design
- 1983 – Whitehead’s triangular sequential design

1970’s & 1980’s – Group Sequential Designs
Early Stopping of a Trial

Group Sequential Designs:
- O’Brien – Fleming
- Lan - DeMets (alpha spending function)
- Haybittle – Peto
- Pocock
# Summary of Findings from Formal Interim Analysis of the BCPT

<table>
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<tr>
<th>Date of ERSMAC Review and Formal Interim Analysis</th>
<th>Number of Invasive Breast Cancers</th>
<th>P-value for difference between Treatment Groups at Interim Analysis</th>
<th>P-value for Monitoring Boundary at Interim Analysis</th>
<th>Interim Monitoring Boundary Crossed</th>
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<td>March 1995</td>
<td>Placebo Group = 44, Tamoxifen Group = 27</td>
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