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

No. of tests at 5% level	Overall significance level
1	0.05
2	0.08
5	0.15
10	0.19
20	0.25

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

Date of ERSMAC Review and Formal Interim Analysis	Number of Invasive Breast Cancers		P-value for difference between Treatment Groups at Interim Analysis	P-value for Monitoring Boundary at Interim Analysis	Interim Monitoring Boundary Crossed
	Placebo Group	Tamoxifen Group			
March 1995	44	27	0.028	0.00013	No
April 1996	89	45	0.000090	0.00015	Yes
March 1997	124	65	0.000011	0.00016	Yes
March 1998	154	85	0.000006	0.00017	Yes