

Data Safety and Monitoring Boards (DSMBs)

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Major Principles of Clinical Trials

- Equipoise
- Randomization
- Intention-to-treat
- Statistical power
- Stopping rules
- Data and safety monitoring



Equipoise

“Substantial scientific uncertainty about which treatments will benefit subjects most, or a lack of consensus in the field that one intervention is superior to another.”

-from NIH human subjects protection training



Intention-to-treat

Design

“... will replace subjects from each arm who drop out prior to completing the full ... treatment course.”

Data Analysis

“For all analyses, we will be using intention-to-treat analysis to reflect real-world conditions.”



Intention-to-treat

Outcomes

“Data from subjects who are non-compliant for more than 20% of the study period will be excluded from data analysis.”

Data Analysis

“The Intent-to-Treat (ITT) Population will include all randomized subjects who took at least one dose of study drug. For analysis of the ITT Population, each subject’s treatment group will be his/her randomized treatment assignment even if the subject did not receive the assigned treatment or did not follow the protocol until completion. All analyses will be conducted using the ITT population unless noted otherwise.”



Stopping Rules

“If there is a trend towards a benefit, but the findings are still not statistically significant after XX subjects have completed treatment, additional subjects may be enrolled as budget allows until statistical significance confirming either the null or alternative hypothesis is achieved.”



Safety Monitoring

“The study will be stopped if any patient is permanently disabled, seriously injured, or dies in a manner that could be consistent with the drug usage. The study will be continued if said patient(s) were taking the placebo or the event is demonstrably unrelated to the subject’s participation in the trial.”



Safety Monitoring

“Since this study is minimal risk, the PI will monitor the study... Blood will be sent to the lab ... to monitor for safety. The PI will review these results ... with the study coordinator. If XX is observed, or YY increases more than Z% from baseline, the subject will be removed from the study and referred to the Primary Care Physician for follow-up”



DSMB 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



Comparison of DSMB with IRB

- Each DSMB member has particular expertise pertinent to the trial being monitored.
- During the conduct of the trial, the DSMB has access to much more information and data than does the IRB.
- In multi-site trials, the DSMB's concern is with the conduct of the *entire* trial while the IRB's concern is with the conduct of the trial at the particular site.
- The DSMB's concern is with the *entire* conduct of the trial, its safety as well as its scientific integrity, while the IRB's concern is predominantly with safety.
- At the end of each of its meetings, the DSMB provides a written report to the IRB.



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 & its 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)



My Experience: Top DSMB Issues

- Recruitment
- Compliance
- Treatment cessations, losses to follow-up, withdrawals
- Power

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



Reasons for Early Termination of a Trial (or an Arm of a Trial)

- Safety (toxicity, SAEs)
- Change in equipoise
- Efficacy (overwhelming benefit)
- Adverse outcomes (Overwhelming and unanticipated)
- Futility
- Inadequate enrollment
- Excessive dropouts and losses to follow-up
- Inadequate compliance
- Inadequate sample size (lack of anticipated statistical power)
- Unanticipated external events (fraud, political upheaval)

