


DATA AND SAFETY MONITORING

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Presentation Outline

- Introduction
- Examples – monitoring by independent Data and Safety Monitoring Board (DSMB)
- Data and safety monitoring basics
- When to use a DSMB
- Monitoring without a formal DSMB
- Sample items for monitoring
- Summary

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Fundamental Concept: Caution

- In a randomized clinical trial studying the safety/efficacy of a new drug, you don't want to wait until the end of the trial before you consider whether
 - Something fundamentally went wrong with the conduct of the trial
 - The new drug has unexpected harms
 - There was convincing evidence of efficacy much earlier than expected

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Fundamental Concept: Integrity

- Looking at data multiple times, i.e. doing a formal statistical test to compare treatment arms, increases your chance of having a false positive result
- Data monitoring plans are a fundamental part of the trial design/protocol
 - Special methods are used in the statistical analysis to maintain the desired false positive (type I error) rate
- DSMBs will require scientific expertise to know what questions to ask and how to interpret the study data with right amount of caution

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Fundamental Concept: Objectivity

- One way to help ensure the group charged with monitoring the clinical trial can do their job of evaluating safety and integrity of the trial they should have
 - No vested interest in the trial outcome
 - No relationship with study investigators
 - Sufficient clinical expertise and scientific expertise, including understanding of clinical trial design, conduct and data-analytic issues

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A Definition

A **data and safety monitoring board (DSMB)** is a group of independent experts that reviews the ongoing conduct and evolving data of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial.

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Note on terminology

- FDA and European boards called DSMC
- NIH generally uses DSMB

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Example 1. ACTG 076: Preventing Mother-Infant HIV Transmission

- Zidovudine (AZT) able to slow progression of HIV in adults with advanced disease
- AIDS Clinical Trials Group Protocol 076 designed to assess both safety and efficacy of Zidovudine in preventing transmission of HIV from infected (not advanced) women to their babies
 - NEJM 1994; **331**, 1173-1180

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ACTG 076: Ethical Considerations

- If partway thru trial determine AZT prevents vertical transmission, must stop and give to all mothers in trial (individual ethics)
- Don't want to stop before convincing medical community that AZT prevents vertical transmission

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ACTG 076: Study Design

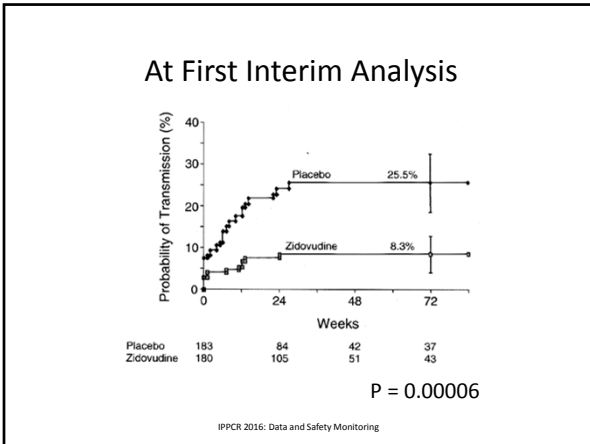
- Powered (80%) to detect a 33% reduction of transmission rate (through 78 weeks of baby's life) relative to projected rate of 30%
- Target sample size (N) was 748
- Accrual began April 1991
- Projected accrual to take at least 5 years, planned for 15% dropouts

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ACTG 076: Monitoring

- DSMB met twice a year to monitor safety
- Efficacy reviews planned after each 1/3 of projected infant infections
- 1st efficacy review took place in February 1994, based on mothers enrolled up to December 1993 and their babies

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Interim Analysis Considerations

– At time of DSMB meeting 46 babies w/unknown HIV status

- Concern: might stop because met stopping criteria, but when 46 infants pending are evaluated, evidence could weaken
- Conditional power can be used for this: Given results in 363 babies, and making different assumptions about the 46 pending, examine probability that test statistic still meets stopping criteria

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Outcomes After 1st Interim Review

- DSMB recommended stopping (after careful review of data quality and completeness, toxicity, transmission rates)
- Trial leaders and NIH agreed
- Zidovudine provided to those in control group
- United States Public Health Service (USPHS) national guidelines modified

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Example 2: CAST

- Cardiac Arrhythmia Suppression Trial (CAST) was designed to evaluate hypothesis of whether suppressing ventricular arrhythmias in patients with recent MI reduced sudden death and mortality
 - Compared 3 active drugs known to suppress arrhythmias with placebo: encainide, flecainide, and moricizine
 - Designed to randomize 4000 patients with 90% power to detect a reduction in sudden death with a 0.05 one-tailed significance level

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CAST: First DSMB Meeting

- DSMB met for first time in March 1987 to review the protocol
- Made recommendation that the one-tailed 0.025 alpha level be used to test for treatment benefit, reducing power to 85%.
 - DSMB argument: one or two-tailed test should not influence the strength of evidence (ie. 1.96 critical value)
 - Very rare to see one-sided 0.05 level tests unless early phase and doing 90% (not 95%) confidence intervals
- **Lesson Learned:** important to have first meeting before study starts to make sure DSMB and investigators agree with scientific design and what will be monitored
 - Two groups need to get along, trust each other, and work together through length of trial

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CAST: DSMB 1st data look

- In Cardiac Arrhythmia Suppression Trial (CAST) (NEJM 1989; 321, 406-412), DSMB chose to be blinded
 - At first look, had 22 of 425 expected events by trial's end; (22/425=.052 = 5% of expected information)
 - Stopping Boundary at first look: 3.22, logrank Z=3.43
 - But boundary not in place at first look
 - Good because actual score at 1st look after pending events adjudicated was 22-10
 - DSMB remained blinded

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CAST: DSMB 2nd look

- At second look, 48 events
- Now expected only 300 events by end of study, so 48 represented a higher percent of total events
- Revised information fraction was $t=48/300=.16$
- Boundary ± 2.98
- Logrank $Z=3.22$
- DSMB unblinded and found drugs harmful

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Further investigation

- Verified treatment labels correct and chemically analyzed random sample of medications
- Looked for baseline imbalances of key variables & did analyses adjusting for baseline imbalances
- Looked at results by subgroup to see if harm confined to certain patients
- Looked at secondary endpoints (like total mortality) to see if consistent
- Checked if harm confined to specific drugs

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Trial Outcomes

- Harm seemed to be confined to encainide and flecainide
- Overall score: 35-13
- Encainide or flecainide versus placebo: 33-9
- "CAST I" stopped in April, 1989
- "CAST II" stopped in July 1991, also for lack of benefit and possible harm

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CAST: Lessons learned

- DSMBs and trial data management system must be in place early on.
 - Negative trend apparent after only 5% of data in, convincing at 15%.
- DSMB and investigators must be able to act/respond quickly
- DSMB/investigators must be ready to make contingency plans

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One other lesson demonstrated (if not learned)

- The ability of the DSMB to do their job can be compromised if they are masked
- Human nature: tend to believe an early trend is in favor of new treatment
 - Require less evidence to prove harm vs benefit
- Masked analyses can be inefficient and error prone.

Fundamental concept: competency

Ref: Meinert, Curtis L. "Masked Monitoring in Clinical Trials—Blind Stupidity?." *New England Journal of Medicine* 338.19 (1998): 1381-1382.

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Data and Safety Monitoring: *Why?*

- To identify any safety problem rapidly
- To identify logistical problems
- To evaluate continued feasibility of trial
- To determine if trial objectives have been met and trial may be terminated early

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Data and Safety Monitoring:
What?

- Logistics
 - Enrollment
 - Baseline Data, Comparability
 - Protocol Compliance
 - Specimen Collection
 - Data Quality

Develop specific benchmarks

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Data and Safety Monitoring:
What?

- Outcomes
 - Adverse Events
 - Interim Variables
 - Response Variables (Endpoints)

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Data and Safety Monitoring:
Who?

- Ethics Committee(s)
- Sponsor
- Regulatory Agencies
- Data and Safety Monitoring Board
(DSMB, DSMC, DMC, External DMB, etc)
- Investigator(s)
- Safety Monitor

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Data and Safety Monitoring Board's Purpose Drives Structure

Recall DSMB's purpose is

- To ensure regular and systematic interim monitoring
- To provide an objective assessment of the interim data
- To protect confidentiality of interim treatment comparisons

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Generally Accepted Principles

- Certain types of trials should have formal DSMBs
- DSMBs should be multidisciplinary
- A charter should describe the operations and procedures of a committee
- DSMB members should be free of conflicts of interest
- Interim data should be considered highly confidential

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Confidentiality of Interim Results

- Interim comparative data generally considered highly confidential, because
- Knowledge of interim data could affect
 - Patient entry
 - Patient care
 - Patient assessment
 - Sponsor action
- When knowledge of interim data potentially could influence trial conduct, interpretation of results could be muddied

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An *Independent* DSMB Is One in Which No Member Has

- Any basis for preferring the outcome to be in one or the other direction
- Any ability to influence the trial conduct in a role other than that of DSMB member

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Establishing a Committee

- Generally appointed by study sponsor
- Made up of
 - Clinicians (appropriate specialty)
 - Statisticians
 - Others as needed (e.g., bioethicist, subject advocate)
 - Executive Secretary
- Membership should be acceptable to trial leadership: DSMB as any version given major responsibility
- Independent of protocol team
 - May or may not be independent of study sponsor

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Structure of Meetings

- Open Session
 - Process data
 - Attended by investigator(s), sponsor representative, data site representatives
- Closed Session
 - Interim and outcome data, adverse events by group
 - Attended by data presenter; any others?
- Executive Session
 - “Private” DSMB member discussion
 - Any other attendees?

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Scope of DSMB Responsibilities

- Evaluating accumulating data with regard to toxicity, and potentially efficacy and/or futility
- Recommending termination or continuation of study
- Recommending other study modifications
- Reviewing study protocol
- Assessing study conduct
- Recommending additional analyses

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Statistical Considerations

- Repeated testing for efficacy over time inflates Type I (false positive) error rate if no adjustment made
- In “early days” of clinical trials, not uncommon to stop study as soon as p-value reached magic level of 0.05
 - Better statistical methods now exist to ensure more valid monitoring structure
- Currently, many methods available to permit monitoring and potential to stop early for efficacy without increasing error rate
- Monitoring plan should be laid out in protocol or a Statistical Analysis Plan and reviewed by DSMB before study begins
 - Situations can arise that require unplanned monitoring

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Actual False Positive Rate Using ± 1.96 :

# Looks	Equally-Spaced	Worst-Case Spacing
1	.05	.05
2	.08	.10
3	.11	.15
4	.13	.19
5	.14	.24
6	.15	.28
7	.17	.32
8	.18	.37
9	.19	.41
10	.19	.45

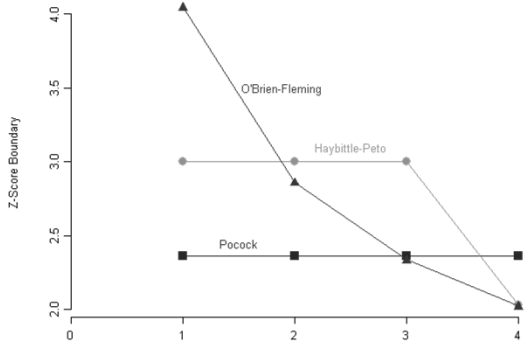
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Efficacy and Boundaries

- Several examples of early results reversing by end of trial
 - In the Coronary Drug Project (CDP), the z-score reached -1.96 three times and ended up about 0
 - In the Multicenter Unsustained Tachycardia Trial (MUSTT), treatment of arrhythmia guided by electrophysiological testing appeared to be harmful and then proved beneficial at end

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Comparison of Boundaries for 4-Look Trial

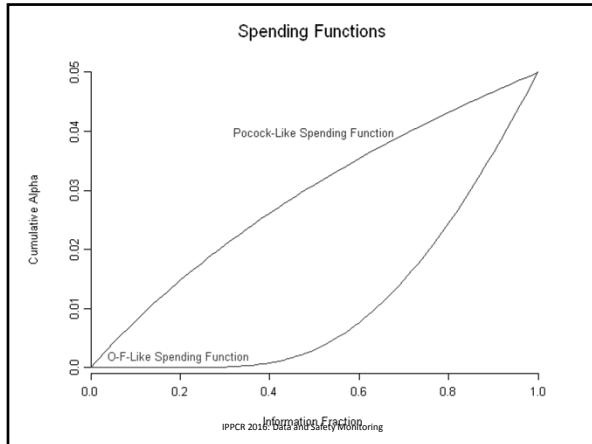


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Common Efficacy Monitoring Approach

- Lan-DeMets (Biometrika 1983; **70**, 659-63) spending function approach:
 - Don't need equal amounts of information between successive looks
 - Don't even need to pre-specify number or timing of looks
- Instead you specify a spending function $\alpha^*(t)$ telling how much alpha you will spend by information fraction t.
 - Example information fraction: current # events/N

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Futility Monitoring

- Studies are sometimes stopped for futility because of:
 - 1) Poor recruitment
 - 2) Lower than expected event rate and trial was powered for given percentage reduction
 - 3) Higher than expected dropout or crossover rates
 - 4) No effect of treatment on intermediate outcome through which treatment is assumed to work (e.g., HbA1c in diabetes trial)
 - 5) **Poorer than expected treatment effect on primary endpoint?**

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Futility Monitoring

- Reason 5 is very different from the others
 - If everything else (recruitment, dropout, effect on surrogate, crossover, etc.) is okay, then
 - Power to detect originally hypothesized treatment effect is still high
 - A small treatment effect answers the question
 - If continuation is ethical, may want to continue to prove that treatment doesn't work (especially if treatment is in widespread use and disease not too serious—glucosamine/chondroitin for arthritis)

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Futility Monitoring

- Want to ask two different questions:
 - 1) Will end result be null?
 - 2) Will null result still be meaningful?
- Two different tools for the two different questions:
 - 1) Will end result be null? *Conditional power*
 - 2) Will null result still be meaningful? *Unconditional power*

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Futility Monitoring

- *Unconditional power*: Had we known prior to trial what we know now about dropout, crossover, control event rate, achievable sample size, what would power have been to detect hypothesized treatment effect?
 - Don't need to see the results by arm
- *Conditional Power*: Knowing the above **and taking into account current results**, what is probability of getting a significant result at end?
 - Need to take into account current results

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Monitoring Recommendations

- Continue protocol unmodified
- Continue and modify protocol
- Study be terminated
- Sponsor makes final decision regarding termination, usually will follow recommendation of DSMB
 - At NIH: Institute director usually makes final decision, but almost always follows recommendation of DSMB

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DSMB May Recommend Stopping If



- A safety issue has emerged
- The trial has already demonstrated efficacy
- Interim results preclude a positive finding
- Operational difficulties are insurmountable
- External information undercuts the scientific rationale for the trial

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Decision Making Process is Complex

- Internal consistency
- External consistency
- Benefit/risk balance
- Current vs. future patients
- Clinical and public health impact
- Statistical issues

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Individual versus Collective Ethics

- Must balance individual & collective ethics
 - *Individual ethics*: primary concern is about welfare of patients in trial
 - Waiting too long to stop jeopardizes their welfare
 - *Collective ethics*: must also be concerned about how trial results affect future patients
 - Stopping too soon may not convince medical community)
- Decisions often difficult!

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Downside of Early Stopping for Efficacy

- Early stopping handicaps safety analysis
- Monitoring safety and efficacy are inherently different
- Clinical trials address relative effects much better than absolute ones

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Example 3: Male Circumcision to Prevent HIV Acquisition

- Phase III controlled trials began at about the same time in South Africa, Kenya, and Uganda
- Designs similar
- South African trial reported clear evidence of efficacy in July 2005
- NIH DSMB recommended continuing other trials in August 2005, June 2006, stopping in December 2006

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ALL TRIALS NEED
MONITORING BUT
NOT ALL TRIALS NEED
DSMBS



Data and Safety Monitoring Regulations, Policies, Guidelines (1)

- Policies - NIH
 - All trials need a monitoring plan, need to describe in application for funding
 - Independent DSMB required for all multicenter Phase III trials since 1979
 - Notify IRBs of DSMB Recommendations
 - Policies across NIH vary

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Data and Safety Monitoring Regulations, Policies, Guidelines (2)

- NIH policy
 - <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>
 - Type of monitoring commensurate with risks, trial size and complexity
 - Part of Clinical Terms of Award
- FDA Policies – NONE
- FDA Guidance on Data Safety Monitoring Committees (2006)

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HHS Office of Inspector General Review

- HHS Office of Inspector General conducted a review of NIH DSMBs to identify whether DSMBs of NIH sponsored trials met with NIH guidelines and whether any challenges to DSMB effectiveness existed
- In June 2013 issued report
 - <http://oig.hhs.gov/oei/reports/oei-12-11-00070.pdf>

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HHS Office of Inspector General Review: Results

Main findings:

- 1) Generally NIH DSMBs met guidance
- 2) Some issues exist:
 - 1) IC participation in closed DSMB meetings diminishes the appearance of independence;
 - 2) Not all Institutes and Centers (IC) policies reference DSMB access to unmasked data;
 - 3) NIH faces challenges in recruiting and training DSMB members.

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HHS Office of Inspector General Review: Recommendations

NIH should

- (1) Direct ICs to articulate the circumstances in which IC staff should participate in DSMB meetings.
- (2) Direct ICs to explicitly reference DSMB access to unmasked data in their DSMB policies.
- (3) Identify ways to recruit and train new DSMB members.

NIH concurred with all three recommendations.

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Formal Study Monitoring

- ANY clinical research study involving more than minimal risk to volunteers
 - Does not have to be a “clinical trial” nor a randomized study
 - Data quality and safety monitored

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When Are Independent/External DSMBs Needed?

- Large randomized trials with mortality or major morbidity endpoints
 - Trial has implications for clinical practice/ public health
- Trials for which assessment of serious toxicity requires comparison of rates
- Trials of novel, potentially high-risk treatments
- Highly vulnerable patient population

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External DSMBs Generally Not Needed for

- Single-arm trials
- Early phase trials
- Short-term trials of treatments to relieve common symptoms
- Any trial for which there is no ethically compelling need to monitor the interim comparisons of safety or efficacy

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Are There Disadvantages to Having a DSMB?

- YES!
 - Increases complexity of trial management
 - Increases costs
- If the ethical imperatives discussed earlier are not applicable, other (simpler) monitoring approaches are usually acceptable

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Independent DSMBs are Not the Only Form of Monitoring

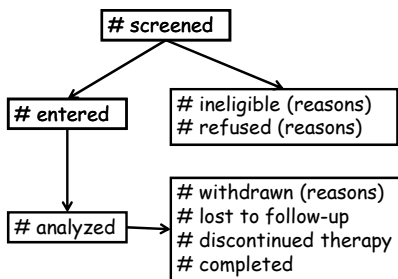
- Independent monitor for minimal risk studies
- Safety Monitoring committees take many forms
 - Protocol Team
 - Independent Safety Monitoring Committee (SMC)
 - IRB
 - DSMB

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Sample Items Monitored by the DSMB

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CONSORT Diagram



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Protocol Adherence

Missed Visits

	Baseline	Visit 1	...	Last Visit
# Expected			...	
# Missed			...	
% Retained			...	

Overdue Forms

	Baseline	Visit 1	...	Last Visit
# Expected			...	
# Received			...	
% Complete			...	

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Baseline Characteristics

Gender	% Female
Age	Median, Min, Max
Race	% White, % African American
Stage of Disease	% Early, % Advanced
Prior Therapy	% None, % Surgery, % Chemo

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Serious Adverse Events

Line Listing showing

- Event
- Study entry, treatment start dates
- Event start, stop dates, final resolution
- Relationship to research procedures
- Other relevant patient characteristics

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Adverse Event Summaries

Lab Abnormalities and Clinical Signs

Tables of frequencies, by adverse event (AE) type and severity Include all those treated

- Sort by body system
- Count 1st occurrence for each volunteer
- Severity of an event summarized by highest grade individual experienced for that event
- Summarize across types

Fundamental Concept: data summaries help identify trends not apparent in line listing

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Adverse Event (AE) Summaries

Body System MedDra Term	Mild	Moderate	Severe or Worse	Total
INFECTIONS				
INFESTATIONS	3(30%)	1(10%)	0(0%)	4(40%)
Gastroenteritis	1(10%)	0(0%)	0(0%)	1(10%)
Sinusitis	1(10%)	0(0%)	0(0%)	1(10%)
Upper Respiratory Infection (URI)	0(0%)	1(10%)	0(0%)	1(10%)
Viral infection	1(10%)	0(0%)	0(0%)	1(10%)

Table: Frequencies (relative frequencies) of adverse events among 10 subjects treated

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Efficacy Summaries: If Planned

Summarize study endpoints:

- % treatment success
- Average area under the curve (AUC), antibody response, etc.
- Combined or by group?
 - Keep report masked, but not DSMB
- Interim futility monitoring
- Interim efficacy monitoring
 - Important to have independent committee

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DSMB Report

Fundamental Concept: Make it as easy as possible for DSMB to do their job

- DSMB report should be provided to the DSMB in enough time for review prior to the meeting
- Report should include a concise (1-2 page) summary of protocol design, including planned N, # of arms, and endpoints
- Should include a clearly written executive summary
- Tables/figures should be concise and easy to understand

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Summary

- DSMBs have a difficult job balancing:
 - Individual ethics (most important)
 - Collective ethics
- Interim monitoring of efficacy requires formal monitoring plan to prevent inflation of false-positive rate, need monitoring boundaries
- Sometimes want to stop for futility
- Stopping decisions almost always based on statistical and extra-statistical considerations
- DSMBs make recommendations, final decisions rest with trial and sponsor leadership

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Further Reading

- Data Monitoring Committees in Clinical Trials: A Practical Perspective by Susan S. Ellenberg, Thomas R. Fleming and David L. DeMets (Wiley Series in Statistics in Practice, 2002)
- Data Monitoring in Clinical Trials: A Case Studies Approach, Editors: David L. DeMets, Curt D. Furberg, Lawrence M. Friedman (Springer 2005)
- Friedman, Furberg, DeMets. Fundamentals of Clinical Trials, 4th Edition (Springer 2010)

Statistical References

- Jennison C and Turnbull BW. Group Sequential Methods with Applications to Clinical Trials Chapman & Hall/CRC 2000
- Statistical Monitoring of Clinical Trials: A Unified Approach (Statistics for Biology and Health) by Michael A. Proschan, K. K. Gordon Lan and Janet Turk Wittes (Springer, 2010)

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Questions?

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