DATA AND SAFETY MONITORING

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Introduction to the Principles and Practice of Clinical Research
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Presentation Outline

- Example – monitoring by independent Data and Safety Monitoring Board
- Data and safety monitoring basics
- Monitoring a small study
- When to use a DSMB

Preventing Mother-Infant HIV Transmission

- Zidovudine 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
Preventing Mother-Infant HIV Transmission

- Powered (80%) to detect a 33% reduction of transmission rate (through 78 weeks of life) relative to projected rate of 30%
- Target N was 748; began April 1991
- Projected accrual to take at least 5 years and 15% dropouts

Preventing Mother-Infant HIV Transmission

- 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

At First Interim Analysis

\[ P = 0.00006 \]
Preventing Mother-Infant HIV Transmission

- DSMB recommended stopping (after careful review of data quality and completeness, toxicity, transmission rates)
- Trial leaders and NIAID agreed
- Zidovudine provided to those in control group
- PHS Guidelines modified

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

Data and Safety Monitoring: What?

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

  Develop specific benchmarks
**Data and Safety Monitoring: What?**

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

**CONSORT Diagram**

- # screened
- # entered
- # ineligible (reasons)
- # refused (reasons)
- # withdrawn (reasons)
- # lost to follow-up
- # discontinued therapy
- # completed
- # analyzed

**Protocol Adherence**

**Missed Visits**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Visit 1</th>
<th>Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td># Expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Missed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Retained</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overdue Forms**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Visit 1</th>
<th>Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td># Expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Complete</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Baseline Characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>% Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median, Min, Max</td>
</tr>
<tr>
<td>Race</td>
<td>% White, % African American</td>
</tr>
<tr>
<td>Stage of Disease</td>
<td>% Early, % Advanced</td>
</tr>
<tr>
<td>Prior Therapy</td>
<td>% None, % Surgery, % Chemo</td>
</tr>
</tbody>
</table>

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

Adverse Event Summaries

Lab Abnormalities and Clinical Signs

- Tables of frequencies, by AE type and severity
  - Include all those treated
  - Sort by body system
  - Count 1st occurrence for each volunteer
  - Summarize across types
Adverse Event Summaries

<table>
<thead>
<tr>
<th>Body System MedDra Term</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe or Worse</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3(30%)</td>
<td>1(10%)</td>
<td>0(0%)</td>
<td>4(40%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1(10%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>1(10%)</td>
</tr>
<tr>
<td>URI</td>
<td>0(0%)</td>
<td>1(10%)</td>
<td>0(0%)</td>
<td>1(10%)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>1(10%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>1(10%)</td>
</tr>
</tbody>
</table>

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

Efficacy Summaries

Summarize study endpoints:
• % treatment success
• Average AUC, antibody response, etc.

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
Why Data and Safety Monitoring Boards?

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

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

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
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

Scope of DSMB Responsibilities

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

Monitoring Recommendations

- Continue Protocol Unmodified
- Modify Protocol
- Terminate Trial
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

Decision Making Process is Complex

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

ALL TRIALS NEED MONITORING BUT NOT ALL TRIALS NEED DSMBS
Data and Safety Monitoring
Regs, Policies, Guidelines

• Regulations NONE
• Policies - NIH
  - All trials need a plan - describe in application (2000 NIH Guide)
  - Phase III trials must use a DSMB (1998 NIH Guide)

Data and Safety Monitoring
Regs, Policies, Guidelines

• Policies - FDA NONE
• Policies - NIAID
  - Clinical Terms of Award
• FDA Guidance on DMCs (2006)

When Are Independent DSMBs Needed?

• Large randomized trials with mortality or major morbidity endpoints
• Trials for which assessment of serious toxicity requires comparison of rates
• Trials of novel, potentially high-risk treatments
**Independent 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

**TRIAL LIFE -- OVERSIGHT**

IRBs and DSMB review the proposed "Data and Safety Monitoring Plan" as part of the initial protocol review.