DATA AND SAFETY MONITORING

Dennis O. Dixon, PhD
Biostatistics Research Branch
NIAID
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

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

- Probability of transmission (%)
- 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

<table>
<thead>
<tr>
<th></th>
<th># screened</th>
<th># entered</th>
<th># ineligible (reasons)</th>
<th># refused (reasons)</th>
<th># withdrawn (reasons)</th>
<th># lost to follow-up</th>
<th># discontinued therapy</th>
<th># completed</th>
</tr>
</thead>
</table>

Protocol Adherence

Missed Visits

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Visit 1</th>
<th>...</th>
<th>Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td># Expected</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td># Missed</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>% Retained</td>
<td>...</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>...</th>
<th>Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td># Expected</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td># Received</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>% Complete</td>
<td>...</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</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe or Worse</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>1(10%)</td>
<td>1(10%)</td>
<td>0(0%)</td>
<td>4(40%)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1(10%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>1(10%)</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 DSMBs review the proposed "Data and Safety Monitoring Plan" as part of the initial protocol review.