

DATA AND SAFETY MONITORING BOARDS

Dennis O. Dixon, PhD

Biostatistics Research Branch

NIAID

Introduction to the Principles and
Practice of Clinical Research

January 14, 2008



DOD/BRB/NIAID

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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

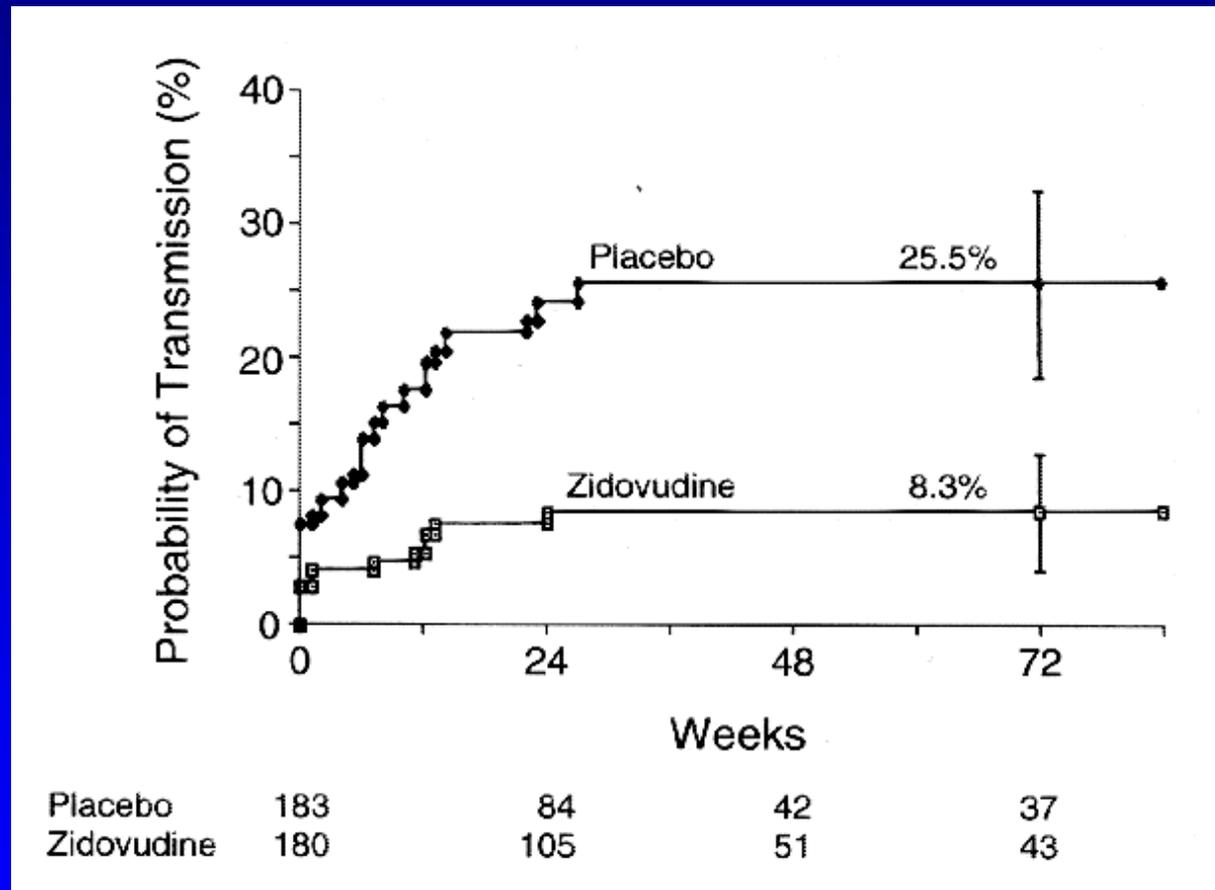
Preventing Mother-Infant HIV Transmission

- * 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)

Data and Safety Monitoring: *Who?*

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

Data and Safety Monitoring: *Who?*

- * Ethics Committee(s)
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DMB, etc)
- * Investigator(s)
- * Safety Monitor

U. Wisconsin CCC Protocol Review and Monitoring System

- * Disease/modality groups are primary
- * Quarterly or semi-annual reports to a central Clinical Trials Monitoring Committee that meets regularly and as needed
- * CTMC monitors compliance with plans
- * CTMC reviews whenever a prespecified AE threshold is reached

ALL TRIALS NEED
MONITORING BUT

NOT ALL TRIALS
NEED DSMBS

A Definition

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

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

Statistical Concern

- * Repeated testing 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
- * Currently, many methods available to permit early stop without increasing error rate

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 given major responsibility

Structure of DSMB 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?

Monitoring Recommendations

- * Continue Protocol Unmodified
- * Modify Protocol
- * Terminate Trial

Decision Making Process is Complex

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

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

Downside of Early Stopping for Efficacy

(ref: Buchanan and Miller)

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

Data and Safety Monitoring Regulations, Guidelines

* NIH Policies

- All trials need a plan - describe in application
- Phase III trials must use a DSMB
- Notify IRBs of DSMB
Recommendations

* FDA Guidance

When Are External DSMBs Needed?

- * 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

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

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