DATA AND SAFETY MONITORING
Acknowledgements

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Presentation Outline

Definition

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
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.
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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
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

Preventing Mother-Infant HIV Transmission (2)

Powered (80%) to detect a 33% reduction of transmission rate (through 78 weeks of baby’s 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 (3)

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

P = 0.00006
Preventing Mother-Infant HIV Transmission (4)

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
Preventing Mother-Infant HIV Transmission (5)

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
CAST

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
CAST (2)

At second look, 48 events

Now expected only 300 events by end of study, so they revised t

Revised information fraction was $t=48/300=.16$

Boundary $\pm 2.98$

Logrank $Z=3.22$

DSMB unblinded and found drugs harmful
CAST (3)

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
Case Studies (4)

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
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)

Investigator(s)

Safety Monitor
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
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
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

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

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?

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

Statistical Concern

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

Actual False Positive Rate Using ±1.96:

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), EP-guided treatment appeared to be harmful and then proved beneficial at end.

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

Futility Monitoring

Studies are sometimes stopped for futility because of:

Poor recruitment

Lower than expected event rate and trial was powered for given percentage reduction

Higher than expected dropout or crossover rates

No effect of treatment on intermediate outcome through which treatment is assumed to work (e.g., HbA1c in diabetes trial)

Poorer than expected treatment effect on primary endpoint?

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)

Futility Monitoring
Want to ask two different questions:

Will end result be null?

Will null result still be meaningful?

Two different tools for the two different questions:

Will end result be null?  Conditional power

Will null result still be meaningful? Unconditional power

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

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

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

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!

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

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

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

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


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)

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

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

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

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

Sample Items Monitored by the DSMB

CONSORT Diagram

Protocol Adherence
Baseline Characteristics

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 adverse event (AE) type and severity

Include all those treated

Sort by body system

Count 1st occurrence for each volunteer

Summarize across types

Adverse Event (AE) Summaries

Efficacy Summaries: If Planned

Summarize study endpoints:

% treatment success

Average area under the curve (AUC), antibody response, etc.

Combined or by group?

Interim futility monitoring

Interim efficacy monitoring

Important to have independent committee

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

Further Reading


Statistical References

Jennison C and Turnbull BW. Group Sequential Methods with Applications to Clinical Trials Chapman & Hall/CRC 2000