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**The Johns Hopkins Center for Clinical Trials  
Monitoring treatment effectiveness and safety in  
clinical trials  
19 - 20 June 2003**

*Baltimore  
School of Nursing Auditorium*

**History of treatment effects monitoring**  
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## History of treatment effects monitoring

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## **Treatment effects monitoring**

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An ongoing process of reviewing accumulated outcome data during the trial to assess treatment effects for the purpose of determining whether to allow the trial to continue unaltered.

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## **Names**

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- Data and safety monitoring committee (DSMC); most common
- Data monitoring committee (DMC)
- Independent data monitoring committee (IDMC)
- Safety monitoring committee (SMC)
- Treatment effects monitoring committee (preferred, but not in common usage)
- Ethical committee (uncommon in US; sometimes used in Europe; not recommended)
- Policy Board (not recommended)
- Policy and data monitoring board (not recommended)

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## **Trials requiring monitoring**

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Any trial in which the treatments have the potential for producing an adverse or beneficial treatment effect and where it is possible to detect and act upon such effects during the course of the trial.

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## **"History" of randomized trials**

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- Of recent origin; basically starting in earnest in the 1950s
- USPHS training grants for biostatistics in the 1960s
- Kefauver-Harris Act of 1962
- Evidence-based medicine

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## **"Monitoring": An old concept**

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- Book of Daniel (Ch 1; v 12-15)

Prove thy servants, I beseech thee, ten days; and let them give us pulse to eat, and water to drink. Then let our countenances be looked upon before thee, and the countenance of the children that eat of the portion of the King's meat; and as thou seest, deal with thy servant

## History of treatment effects monitoring

### Monitoring in the "beginning"

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- **Ambroise Paré (1537; on the battlefield)**  
I raised myself very early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by Arquebuses
- **Lind's scurvy trial (1753; on the Salisbury at sea)**  
... the most sudden and visible good effects were perceived from the use of oranges and lemons, one of those who had taken them being at the end of six days fit for duty

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### Factors leading to formalized monitoring

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- Multicenter long-term randomized trials
- Ethical codes (starting with the Nuremberg Code)
- Statistical procedures for "multiple looks"

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### University Group Diabetes Program (UGDP; 1960 - 1981)

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Investigator-initiated, NIH grant supported, multicenter, randomized, placebo-controlled, designed to evaluate the effectiveness of hypoglycemic drug therapy in preventing or delaying vascular complications in type II diabetics

Sample size: 1,027

Centers: 13; 12 clinics and coordinating center

Trts: 5; 2 oral agents; 2 insulin treatments; placebo (double dummy)

## History of treatment effects monitoring

### University Group Diabetes Program (UGDP)

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#### Treatment effects monitoring

- "Looks": Every 6 months based on reports prepared by the CC
- Outcomes monitored: Mortality, cause specific mortality, morbidity, lab results, blood sugar
- Monte Carlo monitoring bound for mortality and for cardiovascular mortality
- Monitoring body: Steering Committee (26 members; director and deputy director of each of 12 centers; 12 clinics and coordinating center)
- Voting re protocol changes: Simple majority of those present
- Decisions: 2
  - Tolbutamide stopped fall 1969
  - Phenformin treatment stopped 1971

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#### Coronary Drug Project (CDP; 1965 - 1980)

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Investigator-initiated, NIH grant supported, multicenter, randomized, placebo-controlled trial designed to evaluate the efficacy of lipid influencing drugs in prolonging life in men with a prior history of myocardial infarction

- Sample size: 8,341
- Trts: 6 (5 test trts and one placebo)
- Centers: 60 (55 clinics; coordinating center, central lab, ECG reading center, drug distribution center, project office)

## History of treatment effects monitoring

### Coronary Drug Project (CDP)

#### Treatment effects monitoring

- "Looks": Every 6 months based on reports prepared by the CC
- Outcomes monitored: Mortality, cause specific mortality, morbidity, lab results, side effects
- Monte Carlo monitoring bounds for mortality and for cardiovascular mortality
- Monitoring body: Data and Safety Monitoring Committee (19 members; all voting); 10 from study including study chair and vice chair and director and deputy director of CC; 9 NIH affiliated including project office and division director of Institute)
- Policy Board: 5 independent; 5 (non-voting) study affiliated (study chair, director of CC, 3 from NIH)
- Recommended stops: 4
  - DT-4 Stop trt of men with FEVBs at BI; change enrollment criteria to exclude such men from enrollment (subgroup recommendation; n = 27) May 1970
  - ESG2 Stop use of ESG2; excess mortality; n = 1,011; May 1970
  - DT-4 Stop use of DT-4; excess mortality; n = 923; Dec 1971
  - ESG1 Stop use of ESG1; excess mortality; n = 882; Mar 1973

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#### **Greenberg Report: Organization, review, and administration of cooperative studies (May 1967; Controlled Clin Trials 1988; 137-148)**

"Organizational components should include: (a) Policy Advisory Board, (b) an Executive Committee, (c) a Coordinating Center, and (d) data-contributing participants"

"The data should be subjected to frequent analysis, including sequential analysis when possible, to assure constant awareness of current status, which is so essential for intelligent direction of the project as it progresses."

"A Policy Board or Advisory Committee of senior scientists, experts in the field of the study but not data-contribution participants in it, is almost essential for a large complex cooperative project. Such a group can review the overall plan, make recommendations on any possible change (including changes in protocol and operating procedures), adjudicate controversies that may develop, and advise the National Heart Institute on such matters as the addition of new participants or the dropping of nonproductive units."

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## History of treatment effects monitoring

### NIH 1979 Clinical Trials Committee

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- Every clinical trial should have provision for data and safety monitoring
- Provision should be approved by IRB
- A multicenter trial should have an independent treatment effects monitoring committee
- Monitoring committee should include clinicians with expertise in disease under study, biostatisticians, and scientists from other pertinent disciplines. Physicians in the study engaged in patient care should be excluded from membership

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### NIH policy for data and safety monitoring (1998)

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It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-sponsored clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants.

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### NIH guidance on reporting to IRBs (1999)

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"Effective July 1, all multi-site trials with data safety monitoring boards are expected to forward summary reports of adverse events to each IRB involved in the study"

"The DSMB's summary report should provide feedback at regular and defined intervals to the IRBs. The Institutes and Centers should assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. For example, after each meeting of the DSMB, the executive secretary should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given day. It should summarize the Board's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform investigators of the study [of] the Board's conclusion with respect to progress or need for modification of the protocol. The investigator is required to transmit the report to the local IRB."

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## History of treatment effects monitoring

### NIH websites re treatment effects monitoring (as of 13 May 2003)

#### **NCI**

All clinical trials supported or performed by NCI require some form of monitoring. The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. Monitoring exists on a continuum from monitoring by the principal investigator/project manager or NCI program staff to a data and safety monitoring board (DSMB).

#### **NHLBI**

When should a DSMB be established? For clinical trials (intervention studies), Data and Safety Monitoring Boards (DSMBs) are established; for observational studies and registries, Observational Study Monitoring Boards (OSMBs) are established. All intervention studies must have ongoing data monitoring. Not all, however, require formal DSMB. If an institution does not appoint a DSMB for intervention study, the data monitoring may be performed, for example, by the investigator, another individual, or by the IRB.

#### **NEI**

... The data and safety monitoring plan may range from the appointment of a Safety Officer to the organization of a formal Data and Safety Monitoring Board (DSMB). Ongoing review of the data by an independent individual or DSMB assures the investigator(s) that the trial can continue without jeopardizing patient safety.

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### Transitions from 1960 to present

- No monitoring to a required activity
- No IRBs to IRBs
- From indifference to assertive activism re monitoring by IRBs
- From investigators to independent body
- From investigator control of monitoring to sponsor control
- Investigator-initiated to sponsor-initiated trials
- No statistical procedure to regimented p-value-based algorithms
- From open to closed meetings
- From competency to objectivity
- From unmasked to masked monitoring
- From unrestricted information flow in CCs to firewalled operations

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## History of treatment effects monitoring

### Forces leading to "independent" monitoring

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- Concern regarding treatment-related feedback bias (Chalmers)
- "Conflicts of interest"
- Celebrated events lacking "independent monitoring"
  - NSABP Lumpectomy trial
  - Tuskegee Syphilis Study
- Marginalization of investigators
- Tyranny of the biostatistician

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### FDA (Draft Guidance for Clinical Trial Sponsors; November 2001)

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All clinical trials require safety monitoring (21 CFR 312.32(c)), but not all trials require monitoring by a formal committee external to the trial organizers and investigators. ... DMCs should be established for controlled trials with mortality or major morbidity as a primary or secondary endpoint. They may also be helpful in settings where trial participants may be at elevated risk of such outcomes even if the study intervention addresses lesser outcomes such as relief of symptoms. Although DMCs may prove valuable in other settings as well, a DMC is not needed or advised for every clinical study.

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### International Conference on Harmonisation (ICH): Statistical principles for clinical trials (1998)

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An IDMC may be established by the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial. The IDMC should have written operating procedures and maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. The independence of the IDMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information.

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## History of treatment effects monitoring

### **JHU IRB policy on treatment effects monitoring**

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**SHPH**

No written policy

**SoM**

No written policy

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\TEMHist\IRBs

## History of treatment effects monitoring

### Readings

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## History of treatment effects monitoring

### Acknowledgements

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Slides set on: [TrialsMeinertsWay.Com](http://TrialsMeinertsWay.Com)

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