

Clinical Trials

Part 5

Planning Measurements and Monitoring the Study

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As

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Overview

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- I. Determining what data to collect
 - II. Case report form design
 - III. Data capture methods
 - IV. Data quality problems
 - V. Planning quality control
 - VI. Organizational structure of multi-center trials
 - VII. Interim monitoring

How Much Data Do We Need?

- We need to collect everything.
 - You never know what we'll need later.
 - We can get another paper if we add these variables.
 - It helps me understand everything that happened to this patient.
- The collection of completed case report forms for a patient should not be viewed as a medical record.

How Much Data Do We Need?

- Try not to collect any more data than is absolutely necessary to support the study.
- Time spent recording unneeded data can be better utilized recruiting and following study patients and ensuring that quality of important data is high.

What You Shouldn't Do

- VA Cooperative Study #458: National Health Survey of Gulf War Era Veterans and Their Families. Phase III – Physical Examinations
 - Very little time to develop forms
 - No time to pre-test
 - Many revisions to forms during the study
 - Large number of forms/variables
 - Many not directly related to study objectives
 - Many open-ended questions
 - Major stylistic differences across forms
 - Complex forms

What Was The Result?



What Was The Result?

- Site staff overwhelmed
 - Not enough time to examine new subjects
 - Backlog of forms to be sent to Coordinating Center
 - Increased sloppiness/unusable data/missing data
- Coordinating center overwhelmed
 - 6 month backlog of forms waiting to be reviewed
 - Unable to provide feedback on forms problems in a timely manor
 - Increased inability to resolve forms problems

What Was The Result?

- Extra funding needed to increase staffing at sites and at coordinating center
- Less data and more imprecision
 - More difficult to meet study objectives

Selection of Variables

- Collect the following
 - Safety
 - Primary objectives
 - Secondary objectives
 - Administrative (e.g. missing visits)
- What to consider
 - Anticipated high correlation with response variables
 - Another variable already selected that is highly correlated with the variable under consideration

Selection of Variables

- What to consider
 - Anticipated quality (validity and reliability)
 - Will collecting it cause any harm to study patients?
 - Is the cost of measurement commensurate with its anticipated value?
 - VA Cooperative Study #369 – Prevention of ESRD
 - Primary outcome measure: change in GFR or creatinine clearance?

General Organization of Forms

- Sequence related to how patient would typically progress through the study.
- Group variables into forms according to who and where they will be completed.
- Consider how frequently and at which visit they will be used.
- Helpful to create a chart showing which forms should be completed at each visit.

Forms Design Tips

- Each form should be given a number and name. Avoid suggestive names for forms which patients complete, e.g. depression scale.
- Organize subareas/variables on each form to follow a chronological sequence of completion, when possible.
- Organize variables so that direction on form does not change frequently.

Forms Design Tips

- Leave sufficient space for data changes, explanatory comments.
- Each page should have identifier information.
 - (name of study, form number, form name, page number/total number of pages, patient initials, patient study id number, study visit number, visit date, at end of form: signature of person completing form)

Forms Design Tips

- Include definitions where feasible.
- Indicate at beginning of form at which visits it should be completed.
- Clearly indicate skip patterns.
- Identify each subarea/variable with a numeric and/or alphabetic label.
- If possible, avoid open-ended questions.

Example

- VA Cooperative Studies #392, "A Comparison of Subcutaneous and Intravenous administration of Recombinant Human Erythropoietin in Dialysis Patients"
- Major manuscript by Kaufman, Reda, Fye et al NEJM 1998; 339:578-83

Example

- Study Design Summary
 - 24 VAMCs, 208 patients
 - follow-up ave. 42 weeks (26 weeks maintenance)
 - patients randomized to thrice weekly epo by IV or SC administration
 - goal to determine dose needed to maintenance target hct of 30-33%.
 - Substudy to determine pain/discomfort and patient preferences

Example

- Results
 - SC route is 32% more efficient
 - no difference in pain
 - patients tended to prefer IV

Data Capture Systems

- Scanning/facsimile
 - forms are faxed or scanned into a system and then transmitted
 - computer at central site receives images and digitizes them
 - works best on questionnaire type data where boxes or circles are filled in
- Direct Data Capture
 - measuring device is connected directly to a computer
 - limited uses

Data Capture Systems

- Computerized medical records
 - not all types of data needed may be available on the system
 - completeness/validity of data?
 - complexity of writing programs to extract data
 - access
- No system is best for all situations
- Using a variety of approaches in one study is usually not feasible

Measurement Validation

- Bias : How far is your sample estimate from the true value (population parameter)?
- Precision : How variable are the data points upon which the sample estimate is based?

Measurement Validation

- Validity : Are you measuring what you think you are measuring?
 - Internal : findings in the study vs. truth in the study
 - External : truth in the study vs. truth in the universe, generalizability
 - Convergence : the degree to which the measurement agrees with other approaches to measuring the same characteristic
 - Content : a subjective judgment of whether a measurement make sense intuitively

Measurement Validation

- Scaling issues
 - ceiling and floor effects
 - sensitivity to change
- Reliability (reproducibility)
 - within-patient
 - intra-rater
 - inter-rater

Sources of Error

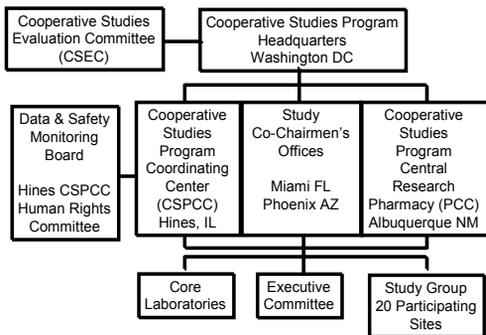
| Source of Error | Characteristics | Examples of strategies to prevent the error |
|--|---------------------|--|
| 1. Inadequacy of the methods or instruments used | Observer Subject | Observer: high accuracy Subject: high accuracy Observer: high accuracy Subject: high accuracy |
| 2. Training and practice of the observer | Observer | Observer: high accuracy Subject: high accuracy |
| 3. Accuracy of the instrument | Instrument | Observer: high accuracy Subject: high accuracy |
| 4. Accuracy of the instrument | Observer | Observer: high accuracy Subject: high accuracy |
| 5. Inadequacy of the instrument | Observer | Observer: high accuracy Subject: high accuracy |
| 6. Blinding | Observer | Observer: high accuracy Subject: high accuracy |
| 7. Calibration of the instrument | Instrument | Observer: high accuracy Subject: high accuracy |

From: Hulley SB, Cummings SR. Planning the measurements: precision and accuracy. In: Designing Clinical Research, eds SB Hulley, SR Cummings, Williams & Wilkins, Baltimore, 1988, p. 38.

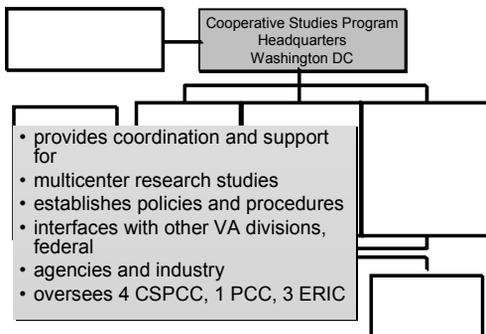
Monitoring/Quality Control Plan

- On-site 100% auditing?
- Random sample of source documents
- Data query reports
- Retesting/Recalibration of instruments
- Periodic retraining
- Statistical analysis of data quality
- DSMB interim monitoring procedure

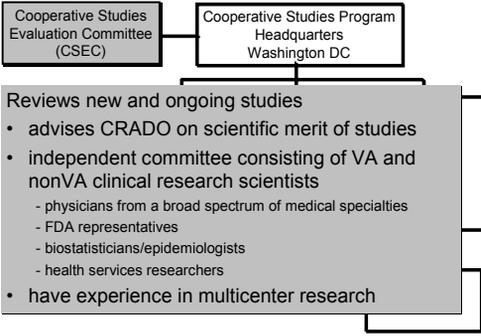
Organizational Structure



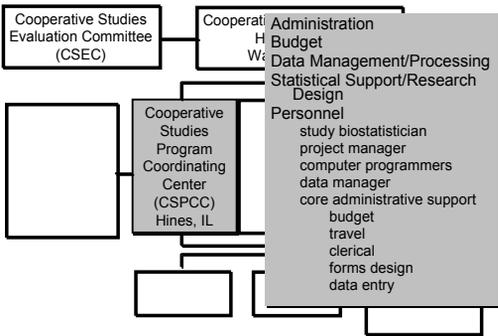
Cooperative Studies Program Central Office



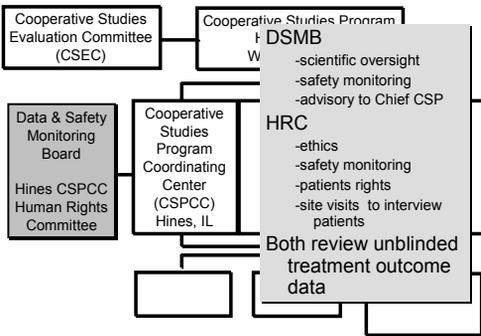
Organizational Structure



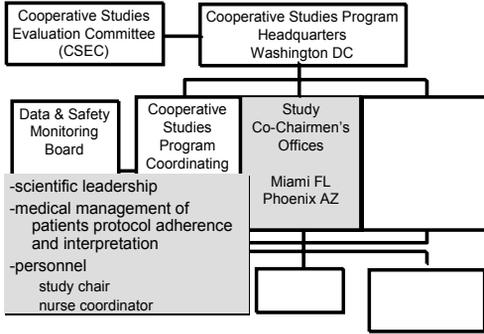
Organizational Structure



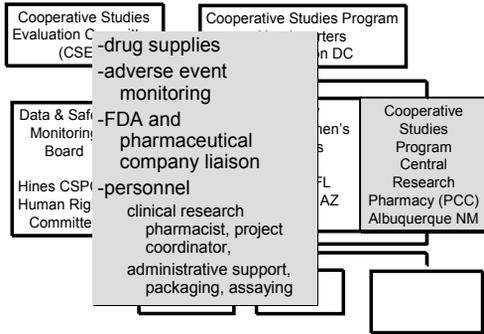
Organizational Structure



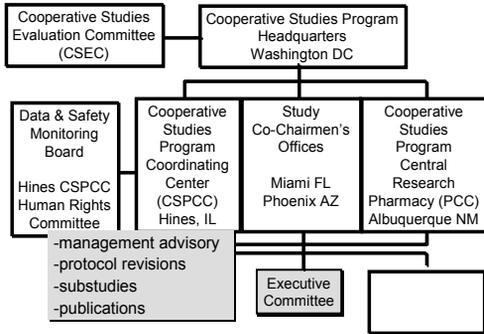
Organizational Structure



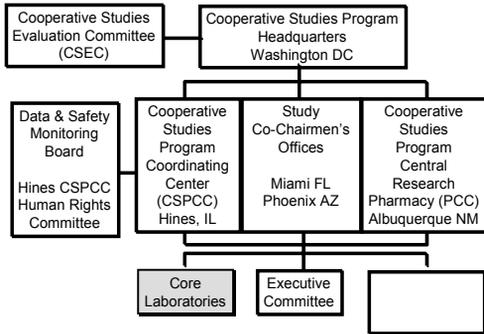
Organizational Structure



Organizational Structure



Organizational Structure



Core Laboratories

- Blood Storage (Boston VA MAVERIC)
- C Peptide (University of Chicago)
- Central Biochemistry (Tufts)
- Cost-Effectiveness (Ann Arbor HSR&D)
- ECG (Tucson VA)
- Endpoints
 - Chair (cardiologist)
 - 5 members (3 cardiologists, 1 neurologist, 1 vascular surgeon)
 - coordinator

Central Laboratories

- Useful for standardizing measurements
- Eliminates one source of variation
- May be needed for the research community to accept study results
- Expensive
 - separate personnel, equipment, shipping
- CSP generally recommends a central laboratory only for the primary endpoint(s) of the study

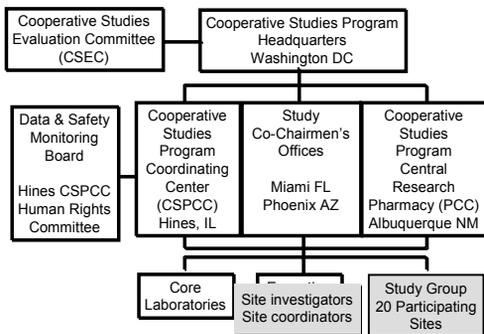
Endpoint Committees

- Useful, perhaps necessary, to validate primary outcome(s) measurement of study (e.g. cause of death, MI, etc.)
- Experts in field, ideally not associated with study
- Ideally, masked to treatment group
- Independent reviews or group consensus

Endpoint Committees

- Define in protocol the composition and functioning of committee, materials they will receive, definitions of endpoints
- Have them periodically review events during course of the study

Organizational Structure



Training/Certification

- Operations manual
 - to detail how protocol is to be conducted
 - to describe day-to-day study operations
 - to define all variables and measurements
 - to specify measurement techniques to be used
- Study kickoff meeting
 - to review protocol
 - to review operations manual
 - to provide hands-on training

Training/Certification

- Study initiation site visits
 - to evaluate ability to conduct the study
- Training tapes

GOOD CLINICAL PRACTICES

- Definition
 - "... all regulations governing the conduct of clinical trials are collectively called GCP.
- Purpose
 - Ensure quality and integrity of data
 - Ensure protection of research subjects

GOOD CLINICAL PRACTICES

- Regulations
 - Legally enforceable requirements
 - 21 CFR Part 50 Informed Consent
 - 21 CFR Part 56 IRBs
 - 21 CFR Part 312 IND Regulations
 - 21 CFR Part 812 Device Regulations
 - 45 CFR Part 46 Vulnerable Populations

INVESTIGATOR FILES

- Adequate and accurate case histories
- Documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced
- Essential documents
 - Study patient records
 - Case report form casebooks/binders
 - Clinic chart for each patient (source documents)
- Regulatory documents, correspondence, etc.

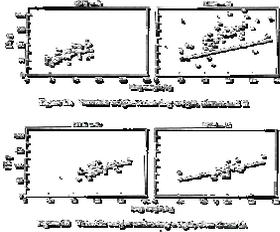
SOURCE DOCUMENTS

- Lab reports
- Study drug dosing records
- Progress notes
 - All scheduled visits
 - Unscheduled visits and phone contacts
 - Completion/non-completion of procedures
 - Adverse events
 - Concomitant medications

SOURCE DOCUMENTS

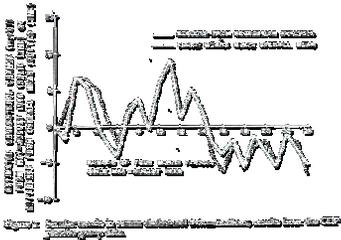
- Common problems with progress notes
 - Inadequate documentation of site investigator's involvement
 - Failure to document consent process

Bias?



Bailey, KR. "Detecting fabrication of data in a multicenter collaborative animal study." *Controlled Clinical Trials*, 12:741-752, 1991.

More Bias?



Canner PL, Krol, WF and Forman, SA. "External quality control programs." *Controlled Clinical Trials*, 4:441-446, 1983.

Interim Monitoring

- Goal 2: to minimize the length of a study when there is little likelihood that a treatment difference will be observed if the study were continued (stochastic curtailment, futility analyses)

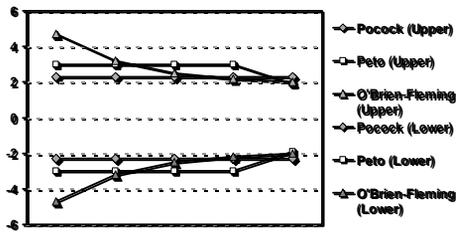
Stopping Rules

- Sequential monitoring
 - Compare treatments as each patient outcome is observed
 - Appropriate only when an outcome can be observed quickly
- Group sequential monitoring
 - Compare treatments after every x time-units or after every x outcomes have been observed

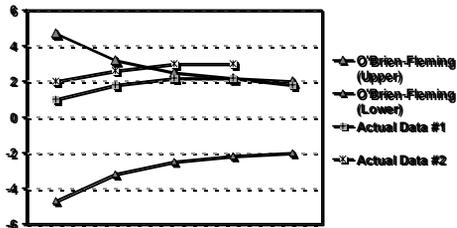
Stopping Rules

- All such procedures adjust the alpha level at each interim look so that the probability of type I error for all looks is no greater than the chosen alpha level for the trial (usually .05)
- Alpha Spending Functions

Types of Group Sequential Procedures



Examples of Interim Monitoring



Decision Based Solely on the Data?

- Beta Block Heart Attack Trial
 - Trial terminated 9 months early
 - Propranolol group had a 26% reduction in mortality compared with control group ($p=.005$)
- Coronary Drug Project
 - Comparison of clofibrate to placebo was significant 3 times during the first 30 months
 - Final mortality results were 25.5% vs 25.4%

Factors to Consider Before Stopping a Trial

- The merits of the treatment
- The availability and usefulness of alternative treatments
- The seriousness of the conditions being treated

Factors to Consider Before Stopping a Trial

- The acceptability of the treatment to patients
 - Their willingness to use it
 - Number of side effects
- The clinical importance of the observed difference
- The consistency of the results with other findings in the trial and with other studies

Futility Analysis

- Comparison of drug A vs. drug B
- Hope to establish that drug B is more effective than standard therapy (drug A)
 - Drug B is considerably more expensive
 - Drug B may produce more side effects
- All patients have been recruited
- ½ of follow-up has been completed

Futility Analysis

- Response rates are 50% for drug A and 52% for drug B
- Is it worth continuing the study?
- Conditional power calculation
- What is the likelihood of showing a significant difference based on the results obtained so far if the study were to continue until its planned end?

Futility Analysis

- If conditional power is low, may decide to stop
- Other factors should be considered
 - Perhaps effect of drug B increases with time?
- Can calculate conditional power assuming the current trends continue or assuming a different trend

Case history: NCI Breast Cancer Cooperative Study Group

1. Cooperative Study of Lumpectomy vs. Mastectomy.
 - Result: Lumpectomy less disfiguring and no difference in survival
2. Pressure to recruit. Study took in only 85 patients in first year. Target sample size 2000.

Case history:
NCI Breast Cancer Cooperative Study Group

3. Reports of fraudulent data.
 - Montreal - 2 sets of data.
 - California - 23 of 29 patients flawed; ineligible patients, nonrandomized, lack of consent or late consent, errors in survival data.
4. Chairman, coordinating center late in reporting to NCI.
 - Were relieved of their duties.

Case history:
NCI Breast Cancer Cooperative Study Group

5. Data had to be re-analyzed by independent statistical group.
6. Many women who had lumpectomies were worried, needlessly.
7. Participating investigators at those centers barred from receiving future NIH support and have damaged their reputations.

Summary

- Maximizing data quality is essential to assure the study can achieve it's objectives
- This can be achieved by
- Careful consideration of what data are needed
- Well-designed case report forms

Summary

- A data entry system which minimizes additional errors being introduced after data collection
- Sufficient training
- Monitoring of data quality throughout study
- Honesty and integrity of investigators and support staff are essential
