QC

QUALITY CONTROL IN CLINICAL STUDIES
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Outline

I. Need for Quality Control
II. Quality Control of Clinical Procedures
III. Identifying Appropriate Data for Quality Control
IV. Study Procedures for Quality Control
V. Data Editing
VI. Bias Resulting from Poor Quality Control
I. Need for Quality Control

A. To assure quality of data and avoid systematic bias or random error leading to erroneous or uninterpretable results

Bias: Any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth
B. Missing data
1. Can be disastrous if affects large proportion of measurements
2. If missing in non-random way (and almost always is) leads to bias in results
3. Often biases toward null but not always
4. Examples: self-report of disease status, income, pulmonary function test, treadmill exercise tolerance testing
5. Best way to deal with missing data is to prevent them from occurring
C. Inaccurate or imprecise data

1. Often remain undiscovered, especially if measurements made by more than one person

2. Typically due to inappropriate technique (poor calibration, biased interrogation, rushed or sloppy measures), often distributed randomly with regard to participant characteristics
3. Less often but more concerning are systematic differences in measurement techniques associated with participant characteristics: obese or unfit persons allowed to hold hand rails in exercise testing; persons with emphysema permitted to shorten exhalation time in spirometry testing
II. Quality Control of Clinical Procedures

A. Steps that precede study

1. Develop manual of operations
   a. Clear operational definitions of eligibility, recruitment, measurement procedures
   b. Standardized instruments and forms
   c. Approaches to analyzing data

2. Train and certify research team

3. Establish procedures for monitoring data quality
Formal Certification Procedures

1. Determine during planning phase which components of study require certification
   Include not only examination procedures but also interviewing, data entry procedures, consenting and randomization, interventions, blood collection and processing

2. Certification form that is kept on file

3. Certification checklist
### LIFE Components Requiring Certification

<table>
<thead>
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<th>Component</th>
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<tr>
<td>Short Physical Performance Battery</td>
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<tr>
<td>Blood Pressure</td>
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<tr>
<td>Weight, Height</td>
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<td>Waist Circumference</td>
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<td>400 m walk test</td>
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<td>Medication Inventory</td>
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<td>Grip Strength</td>
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<td>Blouse/Shirt Test</td>
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<td>Lateral Mobility Task (WFU)</td>
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<td>Cognitive Tests (WFU and Stanford)</td>
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<td>Blood Collection</td>
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<td>Blood Processing</td>
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<td>Interviewing (HRQL and MMSE)</td>
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<td>CHAMPS</td>
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<td>Behavioral Run-in Administration and Assessment</td>
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<td>Physical Activity Intervention</td>
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<td>Successful Aging Intervention</td>
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<td>Program Coordinator</td>
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Note that for all components, the following tasks must be completed:
1. Attendance at the LIFE centralized training session or training by someone certified in the measurement/procedure;
2. Required reading: Manual of Procedures Chapters 1 (Protocol) and 24 (Quality Control);
3. Plus additional items listed on the certification forms (Appendix A).
Certification/Recertification (example)
Seated Blood Pressure

_________________________________      __ __ __
Name

Staff ID

1. Attendance at central training session ___________ or
   Date
   Local training by a staff member certified in the procedure.

   Date       ___________________________________________________________________
   Name of Trainer

Description of local training:

___________________________________________________________________________

1. Become familiar study website.
2. Required Reading
   Chapter 1, Protocol
   Chapter 4, General Procedures
   Chapter 6, Screening
   Chapter 8, Follow-up Visits
   Chapter 16, Physical Measures
   Chapter 24, Quality Control

4. Conduct 3 blood pressures, record on the Blood Pressure, Radial Pulse & Weight Form.
   Trainer uses and completes the Seated BP Certification Checklist during observation of the
   procedure.

5. Date of Certification ______________________________

___________________________________________________________________________

Signature of Program Coordinator   Date   Signature of Principal Investigator   Date
Certification/Recertification Checklist (example)
Seated Blood Pressure

_________________________________ __ __ __Name

During Procedure:
1. Keeps participant warm, relaxed and comfortable
2. Discourages participant from talking except to voice discomfort or confusion about instructions

Observes the Following Procedural Steps:
1. Assembles proper materials and equipment: standard mercury sphygmomanometer, 4 cuff sizes, measuring tape, cosmetic marking pencil
2. Greets participant and reviews purpose, time requirement and procedure.
3. Seats participant in proper position - both feet flat on floor, right forearm resting on table
4. Determines appropriate cuff size by following protocol for measurement of arm circumference. Measures length of arm from acromion to olecranon process, marks midpoint on arm. Measures arm circumference at mid-point, determines cuff size from MOP chart
5. Records arm circumference, cuff size and arm measured on data form
6. Measures and records radial pulse
7. Places cuff properly with center of bladder over the brachial artery and cuff at the level of participant's heart
8. Palpates brachial artery and estimates MIP
9. Confirms participant is relaxed and comfortable and reminds of the need to be seated quietly for 5 minutes prior to the measurement
10. Observes the 5 minutes of relaxed sitting
11. Obtains 2 blood pressure measures with a 30 second interval between end of first reading and beginning of second reading
12. Records both BP readings correctly on the data forms
13. Communicates appropriately with participant regarding a normal or an alert BP

Comments:__________________________________________________________________________

Observer:__________________________________________ Date Observed:______________
B. Steps during study

1. Conduct quality control procedures on regular schedule throughout the study
2. Provide steady and visible leadership
3. Hold regular staff meetings
4. Reward staff for finding quality control "opportunities"
5. Avoid casting blame which encourages staff to hide errors
6. Maintain minimum schedule of performances of procedures (e.g., at least once per week) to maintain certification
7. Recertify research team periodically
8. Tabulate measures by technicians, compare variability, means
III. Identifying appropriate data for quality control

A. Cost of controlling everything is prohibitive

B. May need less attention in blinded, randomized clinical trials as random errors should be distributed evenly between treatment groups

C. Focus on patient safety factors, key exposure variables, and outcome measures
1. Patient safety
   a. Consent forms and consent process
   b. Integrity of randomization scheme
   c. Effects and side-effects of treatment (blood pressure in antihypertensive trial, coagulation measures in anticoagulation trial, etc.)
   d. Drug administration (correct drug and dosage, correct code on participant bottle)
2. Major risk factors such as smoking, alcohol intake, cholesterol level

3. Subclinical or clinical disease assessments
   a. Ultrasound measurements of atherosclerosis: central reading, blinded to participant characteristics, duplicate measures to assess inter- and intra-reader reproducibility
b. Tissue diagnosis of cancer: duplicate readings of all or sample of pathology specimens

IV. Study Procedures for Quality Control

A. Spot checks or repeats of interviews, exam findings, etc.

B. Repeat of tests (EKGs, laboratory tests)
   1. Same reader or lab blinded to subject
   2. Different readers or labs
C. Check forms for omissions or major errors while subject still in clinic
   1. No errors or transpositions of ID number
   2. ID number, name code, study name on each page
   3. No missing entries or faulty skip patterns
   4. Entries legible
   5. Values of key variables within permissible range
   6. Values of key variables are consistent with each other: hysterectomy or estrogen use in men
B. Program computer to flag missing or out-of-range values

C. Ensure accuracy of participant ID number with check digit or duplicate entry

D. Enter data in duplicate or check accuracy of entry by hand in random sample
E. Examine frequency distributions periodically to identify aberrant values or less than expected degree of variability.

F. Credos

1. Quality control problems will occur.
   a. Have a system in place that will identify them
   b. Fix them as early as possible

2. Data which are collected without any ongoing quality checks are best left uncollected.
V. Data editing

A. Should be completed prior to data analysis, though often errors crop up only once data begin to be used

B. Internal consistency and validity checks should be developed
   1. Detect recording, coding, entry errors (prostate problems in women)
   2. Identify inappropriate codes
C. Types of errors

1. Non-normative (clearly wrong) errors—usually easy to detect
   a. Inconsistent or illegal codes
      (for yes/no or 0/1 data, sex = 3; death = 4, etc.)
b. Missing values (find out why missing-- must have ongoing editing of forms, best done immediately after completion while participant still available)

c. Outliers-- plot and examine (see below)

2. Normative errors
   a. Data entry, transcription errors
   b. Extremely difficult to detect
      1. Check each value with data form or record
2. Enter data twice and compare files—unlikely to make same data entry error twice
3. Take random sample and verify with data form or record

D. Identification of outliers
   1. Widely differing values for one or a few individuals requires scrutinizing data to be sure no coding, data entry or recording errors occurred
2. Outlier test (Tukey)
   a. Rank data, divide into percentiles (quartiles)
   b. Identify 25th, 75th percentiles, difference between them (interquartile range)
   c. Define upper limit as 75th percentile plus interquartile range
   d. Define lower limit as 25th percentile minus interquartile range
   e. Reanalyze without outliers, report both
3. Easier to exclude data if reason for extreme value is known
4. Prudent judgment should prevail

VI. Bias in Clinical Trials: Special Issues in QC
A. Minimal requirements for a bias-free RCT
   1. Establish comparable study groups which are free of selection bias
2. Use standard treatment procedures which are reproducible

3. Develop data collection schedule where probability of observing an event, given that it has occurred, is the same for all patients

B. Standardization as a means of bias control
   1. Manual of operations
   2. Description of treatment procedure
   3. Standard definitions
4. Standard equipment
5. Standardized data forms with check lists

C. Checks for bias
   1. Periodic checks on baseline comparability of study groups
   2. Breakdowns in the random allocation process
   3. Differential rate of treatment refusals
   4. Differential rate of dropouts
   5. Unnecessary unmasking
6. Questionnaire to check on efficacy of masking at end of study
7. Protocol violations which are differential by treatment group
8. Differences in variance of readings by treatment group

D. "Correction" for bias
   1. No method of adjustment available
   2. Early detection important
   3. Purging of data may be necessary
4. Stopping of trial may be necessary
5. Reporting in publications is essential

E. Don’t rush into field work (observational studies and RCT’s).

Take adequate time to plan QC activities and to properly train staff.