Quality Control, Data Collection, and DSMB/IRB Reporting

SCT Pre-Conference Workshop
Essentials of Randomized Clinical Trials

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What is Quality Control?

Quality Control: all process controls and monitoring performed by local staff on a day-to-day basis to maintain data quality

Quality Assurance: involves independent review or auditing of key processes to uncover and remedy problems

Quality Control in all stages of:

Inaccurate data are worse than no data at all


Data Collection


Data Reporting

Quality Control in all stages of:

- Data Collection
- Data Reporting

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What are the Primary Sources of Error in Data Collection Process?

"Oh look, a data trail to follow."

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What are the Primary Sources of Error in the Data Collection Process?

- Missing data – Not assessed, incomplete or irretrievable
- Incorrect data – more difficult to recognize
- Excess variability – can reduce the opportunity to detect real change

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Elements of Data Collection

1. Define Key Variables
2. Design of Forms
3. Standardization and Training
4. Data Acquisition
5. Data Recording / Data Management Systems
6. Study Closeout and Preparation for Analysis

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Elements of Data Collection
#1 Define Key Variables

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Key Variables

WHAT you collect depends upon trial type and outcomes

- At baseline: characteristics of enrolled/non-enrolled participants related to major eligibility requirements
- Primary/Secondary outcome measures
- Variables that might confound/mediate/modify association
- Monitoring adherence to the protocol

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Hint: Think
WHO, What, WHEN, WHERE, HOW

As you define your key variables, consider WHO, WHEN, WHERE, HOW these variables are to be collected

- Is the person doing the data collection blinded to treatment arm? If so, by what mechanism?
- In person, phone, web, etc?
- Time frame?
- If lab or ECG values: central reading center, scanning charts, asking participant?

Hint: Focus on key variables

Only important data should be collected

- As the volume of noncritical data increases, forms become burdensome and complicated leading to confusion
- Example: Clinical care data often not needed as part of trial database

Elements of Data Collection
#2 Design of Forms

What is the purpose of Data Collection Forms?

- To collect complete and accurate data
- To ensure standardization and consistency
- In some cases, to reinforce the protocol

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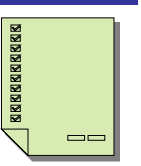
Hints: Design of Forms

- Clean, concise, consistent
- Well-organized with logical flow
- Few “write-in” or “text” answers
- No essay questions!

II-14

Hints: Design of Forms



- Selection of items to be collected
- Timing of visit schedule
- Ordering of Procedures
- *Talk to someone at your institution/company that has done similar research*
- *Use the web – similar studies may have examples on the public side of their web sites*

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Hints: Forms Development

- Preparation of initial versions
- Review by investigators, statisticians, clinic staff, and data management staff
- Pilot-testing
- Debriefing and revamping

Hints: Pilot-Testing Forms

- Mock visits/procedures conducted
- Simulation with practice participants
- Debriefing is essential to improve procedures
- Procedures/forms revised accordingly

Caution: Changes to Study Forms

- Often done early on to improve data collection
- Can be problematic when done repeatedly throughout the trial
  - *Results in multiple versions of data sets*
  - *Can increase risk of errors (clinic, data entry, reporting, analysis)*

EXAMPLE 1: Changes to Study Forms

Troponin results
1 At least 5x upper limit of normal
2 At least 2x upper limit of normal but less than 5x
3 Greater than upper limit of normal but less than 2x
4 Within normal limits

EXAMPLE 1: Changes to Study Forms

Initial Version

Troponin results
1 At least 5x upper limit of normal
2 At least 2x upper limit of normal but less than 5x
3 Greater than upper limit of normal but less than 2x
4 Within normal limits

New Version

Troponin results
1 At least 5x upper limit of normal
2 At least 3x upper limit of normal but less than 5x
3 At least 2x upper limit of normal but less than 3x
4 Greater than upper limit of normal but less than 2x
5 Within normal limits

EXAMPLE 2: Changes to Study Forms

Time to Bed: ☐☐ _A.M. _P.M.

Time Arise: ☐☐ _A.M. _P.M.

Hours of Sleep: ☐ hours

EXAMPLE 2: Changes to Study Forms

Initial Version

Time to Bed: ☐☐ _A.M. _P.M.

Time Arise: ☐☐ _A.M. _P.M.

Hours of Sleep: ☐ hours

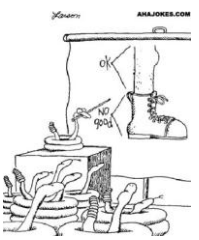
New Version

Time to Bed: ☐☐ (24 hour clock)

Time Arise: ☐☐ (24 hour clock)

Hours of Sleep: ☐ hours

Elements of Data Collection
#3 Standardization and Training



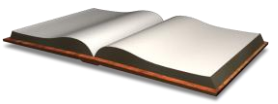
Gary Larson

Standardization & Training: Documents

Study Protocol (high level)

Manual of Procedures (details)

- written prior to and updated during the study
- Standardized procedures
- Clearly written, detailed instructions
- Timely updates and clarifications
- Accessibility is essential



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Standardization & Training: Staff Certification

Training and Certification

- Central, regional, or local (webinar)
- "Train the trainer" model
- Use Audio-visuals
- Certification/recertification to maintain skills

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Standardization and Training: Clinical Site Visits

Quality assurance visit of a clinical trial unit (e.g., clinical centers, coordinating center, central lab, etc.) by a team of experts to observe operations and assess performance

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Elements of Data Collection

#4 Data Acquisition

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How will the data be acquired?

Participant Self-administered?

- Web site
- Mobile device
- Paper Form
  - at home?
  - in clinic?

Staff administered?

- Who is collecting assessment data?
- Expertise?
- Are they Blinded or Unblinded to treatment assignment?

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Hints: Blinded Data Acquisition

Avoid any possibility of assessment bias by requiring assessors to be blinded to treatment assignment

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"In the case of King vs All of His Men I'm decaring a mistrial because of a possible bias by the jury."

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Elements of Data Collection
#5 Data Recording and Data Management Systems

In other words, how will the data get into a central database for reporting and analysis?

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Data Recording

- Traditionally, refers to transcribing information onto case report forms (paper -> database)
- Trend toward direct computer entry with no prior hard copy, with no source document
  Smart Phones, iPads, accelerometers, pedometers, social networks, text messages, smart phones, video game consoles, IRV

- Any approach depends upon well-designed forms/data entry screens

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Types of data entry systems

- Direct by Participant
- Local Staff
  - Data keyed onsite by clinic personnel
  - Potential for quick resolution of data omissions, errors, and inconsistencies
- Central Staff
  - Forms mailed/faxed to sponsor or data coordinating center
  - Data entered by experienced keyers
  - Forms stored centrally.

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Issues with Direct Entry by Participant or Staff

- No source document
- Security Risks
  - Devices could be stolen
  - Not password protected
  - Used in more public settings
  - Cashe
- Who pays for device?
- Who is actually recording/receiving the information?

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Data Recording: acceptable direct data transmissions to/from a participant

- Aggregate data
- Coded answers that do not describe (or contain metadata that describes) health information
- Health information by itself *without any of the 18 Personal Health Identifiers (PHI)*
- Behavioral data
  - Food diaries, exercise logs, your 'MII' in WII
- Transmitted raw data without describing meta data
  - Ex. "120" is not PHI but "Glucose=120" is PHI
- Outward bound messages (e.g., exercise reminders)

Thanks to Scott Rushing, Wake Forest University, for this slide

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Data Management

Design of data management system

- Data entry/editing capability
- Desirable features:
  - Ease of screen set up and use
  - Range, field type, skip pattern checks
  - Query system
  - Ability to accomodate double data entry
- Word processing or spreadsheet software not recommended

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Elements of Data Collection #6 Study Closeout and Preparation for Analysis

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Preparation for Analysis

- Cleaning/editing
  - Inconsistencies
  - Omissions/discrepancies
- Merging records
- Documenting analysis files
  - Definition of variables/cut points
  - Validation of calculated variables
  - Verification of statistical outliers/distribution of data
- Duplicating analyses for key outcomes

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Special notes on study closeout

- Continuous quality control & quality assurance throughout the trial reduces the clean-up job at the end of the study
- Lost-to-Follow-up (National Death Index, web-based searches, paid search firm)
- "Freezing" database at various points of cleanliness
- Public Use Datasets & Data Dictionaries created
- Timing of a "Results Letter" to participants (reveal treatment assignment?)
- Responsibilities to sponsor (i.e., public use datasets, storing study materials)

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Data Safety Monitoring Board (DSMB)
Institutional Review Board (IRB)
Reporting

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What is a DSMB?

Data and Safety Monitoring Boards (DSMBs) are given the responsibility of monitoring the accumulating data.

The DSMB is responsible for assuring that study participants are not exposed to unnecessary or unreasonable risks.

The DSMB is also responsible for assuring that the study is being conducted according to high scientific and ethical standards.

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Why have DSMBs?

- **Protect safety of trial participants**
- Investigators are in a natural conflict of interest
  - Vested in the study
  - They, and their staff, are paid by the study
- Having the DSMB externally review efficacy and safety data protects the credibility of the study and the validity of study results.

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DSMB Principles

Principle 1 - Responsibilities. The primary responsibilities of a DSMB are to safeguard the interests of study patients and to preserve the integrity and credibility of the trial.

Principle 2 – Composition. The DSMB should have multidisciplinary representation, including topic experts from relevant medical specialties and biostatisticians.

Principle 3 - Conflicts. Individuals with important conflicts of interest (financial, intellectual, professional, or regulatory) should not serve on a DSMB.

Principle 4 – Confidentiality Issues. Trial integrity requires DSMB members not to discuss details of meetings elsewhere.

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DSMB Meeting Frequency

Frequency of DSMB meetings depends on disease topic and specific intervention – most meet 1-4 times per year.

Early in the trial, DSMB review will focus more on safety, quality of conduct, and trial integrity rather than on efficacy evaluation.

Single-study DSMBs

Multi-study DSMBs

- Cancer Cooperative Groups
- HIV trial networks

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DSMB Typical Agenda

- Closed executive session
  - Review of agenda, additions to agenda
- Open session with investigators
  - Review current status and conduct of study
  - Accrual update
- Closed session with unblinded investigators
  - Review safety data
  - Review interim analysis (if appropriate)
- Closed executive session
- Open session with investigators
  - Discussion/Recommendations

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DSMB Recommendations

At the conclusion of each meeting, the DSMB makes a recommendation to the sponsor:

- Study should continue without modification
- Study should continue with the following modifications
- Study should be stopped for safety/efficacy/futility

DSMB will also summarize any areas of concern regarding performance and safety.

Soon thereafter, the DSMB chair will provide a written summary of the board's recommendations.

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DSMB Recommendations

Early termination of a trial should be considered if:

- Interim data indicate intervention is harmful
- Significant difference by end of study is probable
- No significant difference by end of study probable
- Severe logistical or data quality problems exist

The DSMB may recommend that the study protocol be terminated, temporarily suspended, or amended.

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Interim Monitoring

The study protocol should include a section describing proposed plan for interim data monitoring.

This plan should detail:

- What data will be monitored?
- The timing of all interim analyses?
- The frequency of data reviews.
- Criteria that will guide early termination

Interim Monitoring

- The decision to stop a trial early is complex, requiring a combination of statistical and clinical judgment.
- Stopping a trial too late means needlessly delaying some participants from receiving the better treatment.
- Stopping a trial to early may fail to persuade others to change practice.
- Statistical methods have been developed for interim monitoring of clinical trials to minimize the role of subjective judgment.

Data Safety Monitoring Boards

Women's Health Initiative (WHI) experience:

Monitoring the randomized trials of the Women's Health Initiative: the experience of the Data and Safety Monitoring Board. Janet Wittes, Elizabeth Barrett-Connor, Eugene Braunwald, Margaret Chesney, Harvey Jay Cohen, David DeMets, Leo Dunn, Johanna Dwyer, Robert P. Heaney, Victor Vogel, LeRoy Walters, and Salim Yusuf. *Clinical Trials, 6 2007; vol. 4: pp. 218 - 234.*

Monitoring and reporting of the Women's Health Initiative randomized hormone therapy trials. Garnet L. Anderson, Charles Kooperberg, Nancy Geller, Jacques E. Rossouw, Mary Pettinger, and Ross L. Prentice. *Clinical Trials, 6 2007; vol. 4: pp. 207 - 217.*

Institutional Review Boards

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Institutional Review Board

Under FDA regulations, an Institutional Review Board is group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

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Institutional Review Board

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research.

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Institutional Review Board

IRB Statistical Reports

- Basic study progress reports
- Recruitment and Monitoring reports
- Safety reports
- Data and Safety Monitoring Board letters / recommendation to continue study

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Institutional Review Board

From the Dept of Health & Human Services:

http://www.hhs.gov/ohrp/

From the Wake Forest IRB:

http://www1.wfubmc.edu/OR/IRB/Policy+Guidelines+and+Regulation.htm

From the FDA:

http://www.fda.gov/oc/ohrt/irbs/faqs.html#IRBOrg

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If there is time…

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Web-based data entry systems

- Flexible
  - Data entry can be local or mix local/central
  - No specific hardware requirements
  - No specific software requirements for internet browser
- Secure link provided
- Data from multiple sources are consolidated on a central server

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Web-based data entry systems

- Security features/protection of human subjects' rights (privacy and confidentiality)
- Controlled Access
- Identification and authentication
  - Requires valid user id and password
  - Password expire every 90 days
  - Automatic logout with inactivity > 30 minutes
  - Specific access rights based on study function

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Web-based data entry systems

- Audit trail
- Each and every access into the system is documented
- Every page that is accessed is documented
- All versions of any record entered are kept and date/time stamped (with user id)
- Virus protection/scanning strategies to monitor and eliminate security threats
- Regular backup for all data
- Database server behind firewall
- Disaster recovery plan

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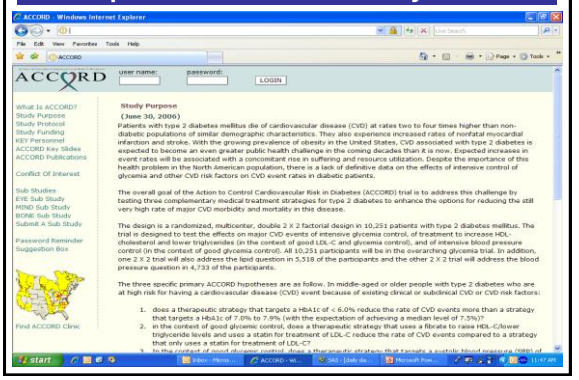
Example of a Multi-center Study web-site



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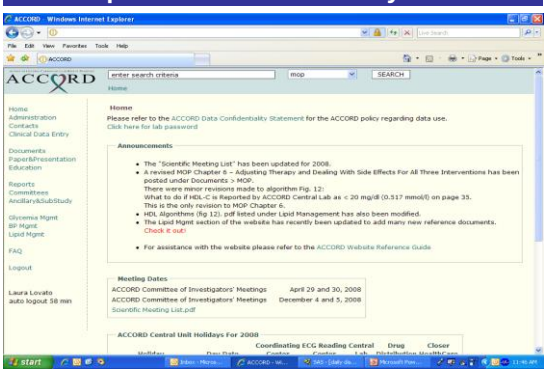

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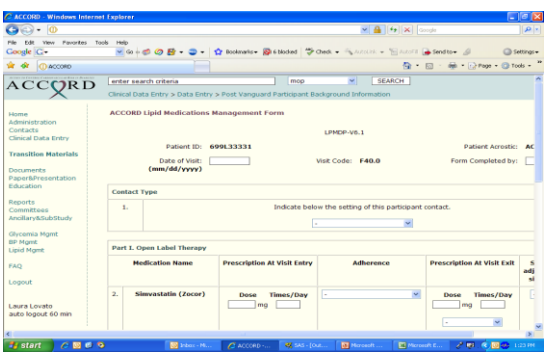
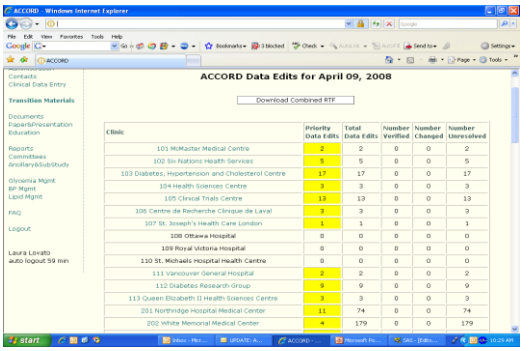


Monitoring Follow-up assessments



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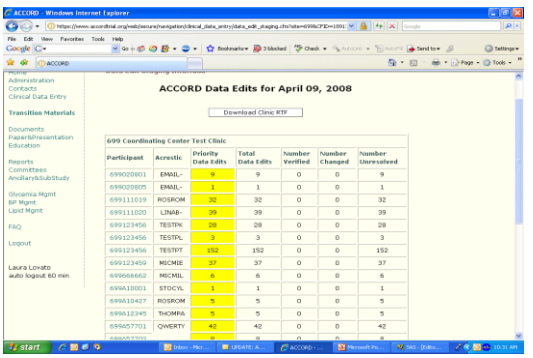

Monitoring Follow-up assessments