Building Quality into Clinical Trials

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Cincinnati Children’s Gamble Program for Clinical Studies
Objectives

- Identify strategies for developing a Quality Management Plan (QMP)
- Identify components of a QMP
- Review the implementation and evaluation process of a QMP.
Cincinnati Children’s Hospital Medical Center
Infectious Diseases Clinical Research

The Gamble Program for Clinical Studies

- Outpatient
- Inpatient
- Community
- Multicenter studies

Funding:
- Industry
- NIH / Governmental
- NIAID / DMID / VTEU

Epidemiology and Surveillance Research Program

- ED / Outpatient
- Inpatient
- Community
- Multicenter

Funding Sources:
- Centers for Disease Control (NVSN)
- Industry
National Institutes of Health
Vaccine Treatment & Evaluation Units

Group Health Cooperative
Children’s Hospital Medical Center
University of Maryland
Vanderbilt University
Duke University
Emory University
University of Iowa
Baylor College of Medicine
Saint Louis University
Vaccine Treatment & Evaluation Units

- Established in 1962
- Resource for conducting clinical trials of vaccines and treatments for infectious diseases
- Key role to develop new and improved vaccines and therapies
Roles of the DMID VTEU’s

- Testing Novel Vaccines
- Developing Combination Vaccines
- Testing Novel Delivery Systems
  - Nasal spray vaccines
  - Edible Vaccines
  - Transdermal Vaccines
Roles of the DMID VTEU’s

Strengthening the Nation's Biodefense

- Smallpox: explored the best way to use existing supplies of Dryvax smallpox vaccine to protect military and civilian populations
Areas of Research Interest

- Respiratory Diseases
- Diarrheal Diseases
- Bacterial Infections
- Agents of Bioterrorism
- Sexually Transmitted Infections

Bonus Question: What is the image above?
Answer: Bacillus Anthracis
My Introduction to Quality Management

Musical Chairs
Evolution of A Comprehensive Quality Management Plan

Our Progression

**Prior to 2005**
Basic QA tools with rotating responsibilities

**2005**
First QMP developed by departmental committee

**2007**
All VTEU sites required to have CQMP Plan
Followed template provided by NIH
Quality Manager oversight
What is Quality Management?

An overall system for oversight of the conduct of clinical research

Ensures that data collected are accurate and complete.

Ensures the rights and safety of participants in clinical research are protected

Encompasses both Quality Control (QC) and Quality Assurance (QA) activities
Purpose of Quality Management

- Facilitate planning for protocol implementation
- Assure compliance with regulations and requirements
- Identify areas in need of corrective action
- Verify the accuracy of data
- Assure readiness for external monitoring and auditing
Components of a Quality Management Plan

- Formal written document detailing QMP
- Process
- Scope and Frequency of Activities
- Responsibility of staff and involvement
- Ongoing QM Plan Maintenance
- Documentation of Education and Training
- Process for Review and Trend Analysis
Gamble Program for Clinical Studies
Overview of Quality Management Program Structure
(Based on NIH / DMID Guidelines)

Director
Clinical Research Manager

Quality Manager

Ensures Training of Qualified Staff

Oversight of QC Activities
Assign to Designated QC study personnel

Oversight of QA Activities
Assign to Designated QA study personnel

Review of Regulatory Files
Assign to Designated Regulatory Review study personnel

Review of Data / Web Reports Monitor Reports
Quality Manager and designated study personnel

Oversight of QC / QA of Research Specimen and Investigational Product
Designated lab and pharmacy personnel
Why Have a QM Program?

Isn’t that why we have monitors?

Isn’t that why the data center generates queries?

Isn’t that why CCHMC has ORCRA review our studies?
Why Have a QM Program?

• Answer: QM is a proactive method to identify and address issues before they become critical.

“Understanding the causes for the rapid sinking of the Titanic is necessary to prevent similar accidents in the future.”

Vicki Bassett
Mistakes Happen
QM is Critical During Peak Enrollment Periods

- Protocols and consents were created and IRB applications were submitted in record time for 8 H1N1 Studies.

- Recruitment and study coordinators responded to approximately 10,500 calls generated by media coverage and general interest over 4 months with calls continuing in response to mass publicity regarding H1N1.

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<th>Target Enrollment</th>
<th>Approximate # telephone Screens</th>
<th>Total # Screened</th>
<th>Number Enrolled</th>
<th>Visits Completed</th>
<th>Vaccines Randomized &amp; Administered</th>
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Getting Started - Important First Steps

- Communicating the need for a formal structure
- Education regarding the value of QM
- Developing your team
- Determining your Key Quality Indicators
Staff Attitudes towards QA/QC

Survey Section I - QA Questions

- I would like to receive data regarding QA/QC trends.
- I have received adequate QA/QC training.
- I do not receive enough feedback about QA/QC reviews.
- I believe the purpose of QA/QC activities is being achieved.
- I am aware of the key quality indicators that are reviewed for QA/QC.
- Communication regarding QA/QC activities is adequate.
- There has been a reduction in errors because of QA/QC.
- QA/QC activities have had a positive impact on monitor visits.
- The current QA/QC process is confusing.
- The current QA/QC process is too time-consuming.
- I actively participate in QA/QC activities.
- QA/QC is important to my position.
- QA/QC is important to my department.
- The QA/QC system in my department is clearly defined.
- I understand the purpose and scope of quality assurance and quality control activities.
Define Key Quality Indicators

- Scheduled Tests/Procedures
- Missed Visits, Follow-up, Tests, Procedures
- Study/Clinical Endpoints Verification
- Adverse Event Identification and Reporting
- Serious Adverse Event Identification and Reporting
- Treatment/Study Discontinuation
- Specimen Storage, Management
- Electronic Data Entry
- Data Anomalies Report
- Missing forms and Values reports
Types of QM Reviews
Quality Control

- Ongoing, daily process of checking records for completion and logic
  - Concurrent
  - Involves 100% review of records
  - Includes documentation and observation of work processes
Quality Control (QC) Activities

- Performed by qualified designated personnel
- Ongoing at each clinic visit
- 100% review of informed consent and eligibility criteria
- Complete QC Audit tool for each subject record
- Data entry with ongoing QC
- Return completed tools to coordinator for corrections
- Results entered onto spreadsheet
- Quality Manager reviews findings and meets with study staff to discuss trends, issues, and resolutions
- Quality Manager reports findings in monthly report to Director and Clinical Manager
# Sample QC Tool

**QC Chart Audit Worksheet**

<table>
<thead>
<tr>
<th>CCHMC Gamble Program For Clinical Studies</th>
<th>Cincinnati Children’s Hospital</th>
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<tbody>
<tr>
<td><strong>Quality Control Notes</strong></td>
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</table>

Protocol #: _______________  PID #: _____  Reviewer Name: _______  Date Reviewed: ___________

Documents requiring action (check all that apply):

- [ ] Inc/Exc criteria  
- [ ] Informed consent form  
- [ ] HIV consent form (if indicated)  
- [ ] Visit 1  
- [ ] Visit 2  
- [ ] Visit 3  
- [ ] Visit 4  
- [ ] Visit 5  
- [ ] Visit 6  
- [ ] Visit 7  
- [ ] Supplemental visit  
- [ ] Lab tests  
- [ ] Concomitant Medications  
- [ ] Adverse Events  
- [ ] Serious Adverse Event  
- [ ] Memory Aid/Diary Card 1  
- [ ] Memory Aid/Diary Card 2  
- [ ] Pregnancy Test log  
- [ ] Other

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Quality Assurance

- Retrospective sampling of “key quality indicators” to identify trends
  - Systematic, comprehensive review of all components of total work effort
    - Assess accuracy of data
    - Adherence to GCP
      - Includes clinical, sample / specimen collection and investigational product
Quality Assurance (QA) Activities

- Performed by qualified designated personnel
- First 10 charts and minimum of 10% of total enrolled for each study
- Complete QA audit tool
- Return to study coordinators for review and corrections
- Results entered into spreadsheet
- QM meets with coordinator/pharmacy for review and to confirm resolution
- QM meets with staff to discuss trends, issues, and resolutions
- QM reports findings in monthly report to Director and Clinic Manager
Web-based QA Audit tool
QA Trends Report Screenshot

QA Chart Audit: REDCap

Date Enrolled

Were there any new consent forms required, and if so were all forms present, correct, and properly documented?

- Yes
- No errors
- No

Were there any errors/issues with the eligibility criteria and its documentation since enrollment?

- Yes
- No

Were there any errors/issues with error corrections?

Staff Attitudes Towards Web-based QA

Survey Section II - REDCap Questions

- I would prefer to use web-based QA/QC tools in REDCap.
- I would prefer to use paper QA/QC tools.
- I have received training in the use of REDCap.
- REDCap is easy to navigate.
- I would be comfortable using QA/QC tools in REDCap.

Colors represent:
- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

Cincinnati Children's
QA Trends Report Screenshot

Number of Visits Reviewed: 67
Total Number of Errors Resolved: 3
Total Number of Errors Discovered: 48
# errors for internal processes: 10
Total # of VTEU/ Key Quality Errors Discovered: 36
# errors documenting protocol deviations: 0
# product administration/ documentation errors: 0
# delegation log deviations: 3
# missing signature errors: 0
# data entry out of window errors: 2
# of CRF/ eCRF discrepancies: 3
# of missing/ incorrect data errors: 5
# of AE/SAE errors: 12
# of improper error correction: 1
# of eligibility errors: 8
# of consent errors: 1

13-0034 Totals: 0 10 20 30 40 50 60 70 80
12-0023 Totals: 0 10 20 30 40 50 60 70 80

Total Number of Errors Discovered
Total Number of Errors Resolved
Number of Visits Reviewed
Total # of VTEU/ Key Quality Errors Discovered
# errors documenting protocol deviations
# product administration/ documentation errors
# delegation log deviations
# missing signature errors
# data entry out of window errors
# of CRF/ eCRF discrepancies
# of missing/ incorrect data errors
# of AE/SAE errors
# of improper error correction
# of eligibility errors
# of consent errors

13-0034 Totals: 0 10 20 30 40 50 60 70 80
12-0023 Totals: 0 10 20 30 40 50 60 70 80
Trend Analysis

- 4 month period of time
- 10% of charts for 11 studies were reviewed
- Total 433 charts reviewed
- Assessed the following Key Quality Indicators:
  - No significant trends in the following categories: Consent Process; Eligibility Criteria; AE/SAEs; Visit Schedule Compliance; Product Administration; or Specimen Collection.
  - Trends related to data collection/electronic data entry.
  - 82% of all inaccuracies occurred in the categories and were resolved during the QA process.
QC versus QA

QUALITY CONTROL
• Done in “real” time
• Focuses on review of data collection forms
• Does not ensure quality-exposes lack of quality

QUALITY ASSURANCE
• Retrospective review on monthly basis
• Encompasses all aspects of study management
• Corrective Action Plans to ensure quality
Review of Regulatory Files (Binder)

- Performed by Quality Manager (or designee) at study start-up, annually, and as needed
  - Complete regulatory review tool
  - Review Tool returned to coordinator for corrections
  - Quality Manager meets with staff to discuss trends, issues, and resolutions
  - Quality manager reports findings & actions in monthly report to Director and Clinic Manager
Monthly Review of Data and Monitor Reports

- Performed by Quality Manager or Designee
- Web Reports
  - Data Queries
  - Manual Queries
  - SAE report
  - Missing forms
  - GT Collection & Future Use Data Discrepancies
  - Visit Schedule Compliance
  - Protocol Deviations
- Monitor Reports
  - Coordinators submit electronic copies of all reports to Quality Manager for review
Research Laboratory and Pharmacy Activities

Performed by designated lab and pharmacy personnel

- QC: Complete QC checks
- QA Review
- Submit monthly reports to Quality Manager
- Monthly meetings with Quality Manager
Departmental education and training records are maintained by individuals and the departmental Education Coordinator

- **Required Education and Training:**
  - Hospital Orientation
  - CCHMC Clinical Research Professionals Training
  - CITI / GCP Training
  - NIH / DMID and Other Regulatory Training

- **Continuing Education and Training**
  - NIH / DMID Training (per NIH requirements)
  - Departmental competencies
  - Monthly research professionals meetings
  - Annual CCHMC research symposiums
  - Protocol-specific training
QM Oversight of Multi-Center Studies

- Quality Manager provides oversight of subcontractor’s quality management activities
  - Reviews and approves sites QMP prior to submission to sponsor
  - Reviews sites monthly QM reports
  - Participates in monitor de-briefing and QM reviews
  - Resource for site quality management activities
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<tr>
<td><strong>From:</strong></td>
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<tr>
<td><strong>Description of Event:</strong></td>
<td><em>Brief description of what occurred</em></td>
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<tr>
<td><strong>Problem Identification:</strong></td>
<td><em>Provide description of all areas affected and how the problem was discovered</em></td>
</tr>
<tr>
<td><strong>Reason for Noncompliance:</strong></td>
<td><em>Provide summary of weaknesses/failures in systems</em></td>
</tr>
<tr>
<td><strong>Corrective Plan:</strong></td>
<td><em>Describe details regarding the plan to resolve issue and prevent future occurrences, include references to any SOPs, institutional or departmental policies, etc.</em></td>
</tr>
</tbody>
</table>
Corrective Actions

STAFF RE-EDUCATION IS CRITICAL
Maintenance of the QM Plan

- Quality Manager is responsible for:
  - Reviewing sponsor websites for QM updates and making revisions to plan as needed
  - Reviewing QM plan annually and updating as needed
  - Reviewing sub-contractor plan annually or more frequently as needed
  - Maintaining copies of all QM review records electronically
  - Submitting plan updates to sponsors for approval
  - Communication and Oversight of all QMP Activities
BENEFITS OF QUALITY MANAGEMENT
Benefits of Quality Management

- Involvement of all study personnel leads to increased compliance to protocols
- Creates an environment of teamwork
- Decreases number of monitor findings
- Decreases number of electronic data queries
- Enhances identification and resolution of data errors prior to data entry
Prepares for unexpected FDA Audit
QMP = Peace of Mind
Questions