

# Data Coordinating Centers: Enhancing Quality of Multicenter Clinical Trials



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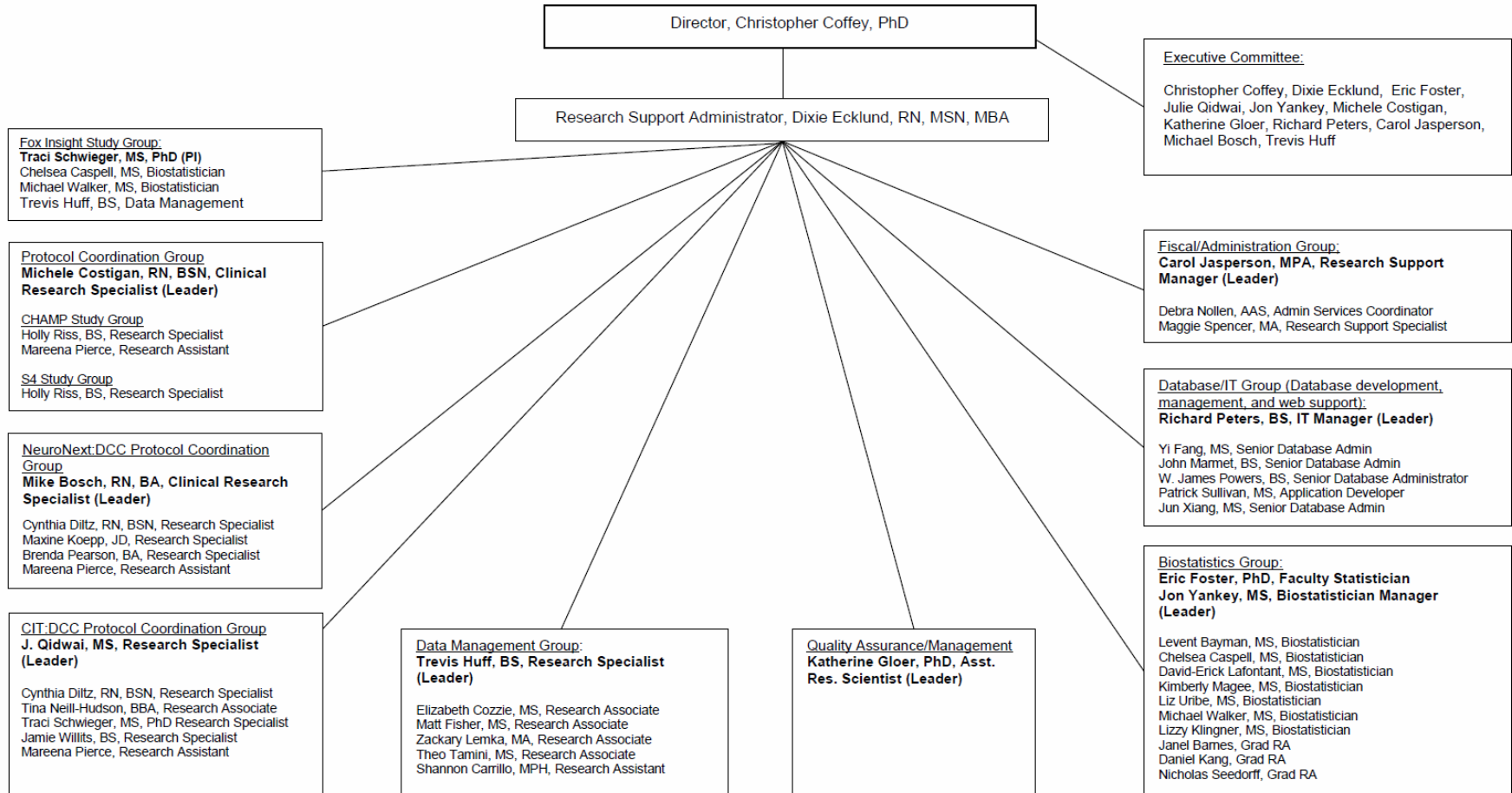
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# ***Multicenter Clinical Trials Require a Team Effort to be Successful***

- Sponsor
- Coordinating Centers
  - Data Coordinating Center (DCC)
  - Clinical Coordinating Center (CCC)
  - Statistical Coordinating Center (SCC)
- Vendors
- Participating Clinical Centers
- Data Safety Monitoring Boards (DSMB)
- Participants!

# What does a Data Coordinating Center look like?

Administrative Organization of the Clinical Trials Statistical Data Management Center (CTSDMC)  
June 2016



# *Teams within Teams*

- *Biostatistics Team*
  - *Team Leader: Jon Yankey*
  - *Fully supports all statistical aspects of clinical trials conducted within the Center.*
    - *Statistical Design*
    - *Protocol Development*
    - *Statistical Analysis Plans*
    - *Report Generation*
    - *Interim Analyses*
    - *Final Analyses*
    - *Clinical Study Reports*



# *Teams within Teams*

- *Protocol Coordination Team*
  - *Team Leaders: Michael Bosch, Michele Costigan, Julie Qidwai*
- *Perform multiple functions in collaboration with all DCC personnel, as well as the PIs, study site personnel, and study sponsors.*
  - *Clinical Expertise*
  - *Manage Sites*
  - *Develop Study Materials*
  - *Maintain Study Supplies*
  - *Manage Site Monitoring Activities*



# *Teams within Teams*

- *Data Management Team*

- *Team Leader: Trevis Huff*

- *Experienced staff members that collaborate with protocol coordination team and database/ software development team to create, test, and validate data entry systems implemented for each protocol.*

- *Technical Coordinators*
- *User's Specifications for Data Entry Systems*
- *Testing Plans for Data Entry Systems*
- *Validate Data Entry Systems*
- *Document Validation*
- *Manage and Resolve Data Queries*



# *Teams within Teams*

- *Database/Software Development Team*
  - *Team Leader: Rick Peters*
- *Develop systems for processing, managing, and analyzing data from multi-center clinical trials.*
  - *Develop Web Applications*
  - *Develop Electronic Data Capture Systems*
  - *Data Storage*
  - *Data Back-up and Recovery*
  - *21 CFR Part 11 Compliance*



# *Teams within Teams*

- *Regulatory Team*

- *Team Leader: Cynthia Diltz*

- *Work with Sponsors to ensure compliance with Good Clinical Practices and all applicable federal guidelines.*

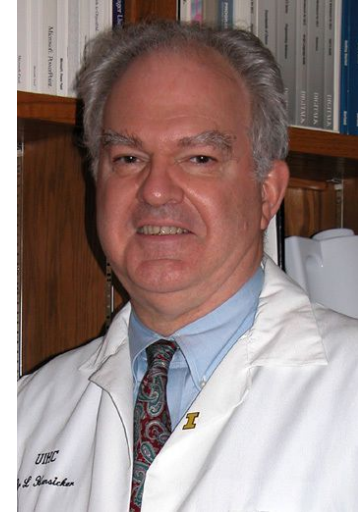
- *Maintain Trials Master Files*
  - *IND Safety Reports*
  - *MedDRA Coding*
  - *FDA Submissions*





# *Teams within Teams*

- *Medical Safety Monitors*
  - *Dr. Lawrence Hunsicker and Dr. Harold Adams*
- *Provide medical expertise to the DCC to evaluate safety, eligibility, deviations, and clinical care questions.*
  - *Aggregate Review of Safety*
  - *Real-time Review of Serious Adverse Events*
  - *Medical Writing*



# *Teams within Teams*

- *Quality Management Team*
  - *Team Leader: Kate Gloer*
- *Ensure that all data management, IT, statistical analysis, regulatory, and administrative support services provided by the Center meet strict quality assurance standards that are founded in Good Clinical Practices and first principles of sound scientific and statistical research.*
  - *Backbone of all processes*
  - *Develop and Monitor SOPs*
  - *Standardize Training/Education*
  - *Develop Center-Wide Metrics to Monitor Quality*
  - *Develop Study-Specific Metrics to Monitor Quality*



# *Teams within Teams*

- *Administrative Team*
  - *Team Leader: Carol Jasperson*
- *Performs day-to-day tasks of managing the fiscal, administrative, and personnel requirements for the Center.*
  - *Develop grant budgets*
  - *Monitor expenditures*
  - *Human Resource functions*
  - *Coordinate Meetings and Travel*



# *What is quality?*

- “Quality means doing it right when no one else is looking.”

*Henry Ford*

# *Why is attention to quality important?*

- Space Shuttle Challenger Explosion – 1986
  - Seven astronauts lost their lives
  - Caused by failure of an O-ring in the solid rocket booster
  - Manufacturer of the O-ring recommended against launch because the cold temperatures on launch day could cause the ring to fail
  - Example of ignoring QA recommendations and not using facts to inform decision-making.<sup>1</sup>

# *Why is attention to quality important?*

- Toyota automobile recall – 2009
  - Approximately 9 million vehicles
  - QA/QC issues with a removable floor mat – accelerators could get stuck and possibly cause a crash (52 deaths)
  - Problems
    - Management ignored input from employees
    - Failure to follow best practices
    - Valuing growth over quality practices.<sup>1</sup>

# *What is clinical trial quality?*

“Quality in clinical trials is defined as the ***absence of errors that matter to decision making*** – that is, errors which have a ***meaningful impact on the safety of trial participants or credibility of the results*** (and thereby the care of future patients).”<sup>2</sup>



# *Why is clinical trial quality important?*

- ***Ethical obligations*** to current and future clinical trial participants
  - Protecting the ***rights and welfare of human subjects*** (Declaration of Helsinki; GCP, regulation)
  - Fundamental principles of ***beneficence, justice, and respect for persons*** (Belmont Report)
- ***Professional obligations*** to the study Sponsor, the public, and the medical and scientific communities
  - Ensuring the ***quality, integrity, completeness, and accuracy of clinical trial data and results***
  - Timely reporting of results.



# *Why is clinical trial quality important?*

- Helps to ensure that investigational drugs, medical devices, or medical procedures are:
  - Safe
  - Effective
  - Have an acceptable risk/benefit ratio
  - Are relatively free of adverse side effects

# *Why is data quality important?*

*Paying attention to data quality helps to ensure that:*

- study data accurately reflect clinical observations and the information collected from study subjects
- data sets for statistical analyses are generated from clean data that are as complete as possible
- there is confidence in the ***primary outcome*** results
- results are ***reproducible*** by others in the scientific research community
- any future studies derived from the study results have a solid foundational basis.

# *Quality requires effort*

“Quality is never an accident. It is always the result of intelligent effort.”

*John Ruskin*

# ***How does the DCC bring quality to clinical trials?***

*Data Coordinating Centers help Clinical Trial Investigators to:*

- follow GCP and principles of sound scientific research
- adhere to Standard Operating Procedures (SOPs)
- collect data accurately and in a usable fashion
- monitor study data and documents for quality and accuracy
- meet defined quality standards or metrics
- ***produce clinical trial results that are more complete, reliable, and reproducible.***

# ***DCC Quality Assurance goals***

- Comprehensive and effective training programs
- Compliance with GCP, regulations, and protocol requirements
- Complete specifications, validation, and testing documentation for database applications and data systems
- Timely, accurate, and complete data collection and electronic data entry
- Proper Adverse Event management and reporting
- Streamlined processes and increased efficiency

# ***What are some challenges investigators face ensuring clinical trial quality?***

- So much work, so little time...
- Deadlines and conflicting priorities
- Resource issues – when it's necessary to prioritize, some things get put on the 'back burner'
- Miscommunication or lack of communication between teams
- Lack of standardized processes and functions
- These challenges can result in:
  - missing the big picture
  - insufficient attention to detail
  - failing to review work for completeness and accuracy.



# *How does the DCC help overcome these challenges?*

- Gain experience/learn from previous studies
- Prioritize study activities (risk-based approach)
- Careful study design
- Set and adhere to clear timelines and milestones
- Encourage collaboration and clear, frequent communication between study team members
- Create ***standardized processes*** and functions

# ***What is clinical trial Quality Control?***

***Quality Control (QC)*** refers to ***day-to-day operational checks and activities*** that ***help to verify*** that clinical trial documents are complete and correct, and that data were generated, collected, handled, analyzed, and reported properly.

- Design CRF templates to accurately collect the correct data for the trial
- Check CRF information against source documentation
- Implement data entry checks and inter-form database queries
- Independently code and compare statistical reports



# *How does the DCC enhance quality of multicenter clinical trials?*

- Standard Operating Procedures (SOPs)
- Personnel training
- Collaborative approach to CRF building
- Clinical study monitoring and audits
- Ongoing data cleaning
- Study closeout activities

# Who oversees clinical trial quality standards?

According to the International Council for Harmonisation:

*"The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s)."*<sup>3</sup>

- **Sponsors** are responsible for selecting and training investigators and monitors, and for monitoring study progress.
- **Investigators** are responsible for implementing and following systems to ensure study quality and integrity.

# *Who enforces and advises on clinical trial quality and safety standards?*

- Sponsor
- Institutional Review Boards (IRBs)
- Regulatory agencies
  - FDA
  - Health Canada
  - European Medicines Agency (EMA)
- Data and Safety Monitoring Boards (DSMBs)
- Medical Safety Monitors

# Following the regulations



# ***What are some important steps that DCC's can take to ensure study quality?***

- Proper informed consent procedures and documentation
- Compliance with the study protocol
- Maintaining adequate and accurate study records
- Data system validation, user access, and security
- Adequate training of study personnel
- Appropriate and timely reporting of adverse events
- Proper investigational product or device accountability and disposition
- Implementing effective corrective actions if deficiencies are discovered

# ***With competing resources, how does the DCC set clinical trial quality assurance priorities?***

- Build a data capture system that collects the data you need (and only the data you need!) to answer the scientific questions
- Adopt a risk-based approach to monitoring
- Maintain randomization and blinding procedures (as applicable to a study)
- Appropriately assess, monitor, and report adverse events
- Identify protocol deviations and implement corrective actions to prevent future deviations
- Be on the lookout for investigator non-compliance, fraudulent data, or unethical study conduct
- Assess compliance with SOPs

# ***What are SOPs and how are they applied?***

SOPs are version-controlled and signature-approved documents that ***describe policies, processes, and procedures for all research areas and study activities.***

- Reviewed and updated every two years, and as needed
- Coordinating Center review and sign-off
- Clinical Site review and sign-off
  - SOPs applicable to their area of work or role on a study or in a network or consortium

# ***What are the key areas of training for clinical trial personnel?***

- Human Subjects Protection (HSP) and research ethics
- Good Clinical Practice (GCP)
- Health Insurance Portability and Accountability Act (HIPAA) – confidentiality
- 21 CFR Part 11 – electronic records; electronic signatures
- Standard Operating Procedures (SOPs)
- Study protocol and proper study conduct
- Specialized research team training (e.g. outcome training)



# ***What are the key areas of training for clinical trial personnel?***

- Adverse Event/Serious Adverse Event reporting
- Protocol deviation discovery and reporting
- Study data system and data entry procedures
- Data collection and data handling
- Investigational product management
- Specimen management

# *How do DCCs ensure ongoing training and performance assessments*

- Participating Clinical Sites
  - Site Initiation Visits or Investigator meetings
  - Ongoing assessments of site performance through onsite monitoring visits
- And
- Scheduled videoconferencing, webinars, teleconferences to review data quality and protocol compliance
- Re-train study personnel, if necessary

# *Why is clinical study monitoring important?*

- Documents study progress (or lack thereof) at the clinical site
- Verifies that the site is using the most recent version of the protocol and study forms
- Verifies that the investigator, site team, and facility are following proper study conduct
- Checks (per the study Monitoring Plan) that clinical data, regulatory documents, and source documents are accurate and complete
- Verifies that the site is properly handling and accounting for specimens and investigational product

# *What is data cleaning?*

- Data cleaning refers to ***activities or data system functions*** that are performed during and after entry of data into the study electronic data capture (EDC) system to ***help to ensure the quality, integrity, completeness, and accuracy of the data.***
- ***Goal of data cleaning:*** Prepare the study database to be locked in anticipation of performing statistical analyses.
- Recommended review article:

*Clinical Data Collection, Cleaning, and Verification in Anticipation of Database Lock: Practices and Recommendations.* V. Pomerantseva and O. Ilicheva, Pharm. Med. 25(4) (2011) 223-233.

# ***What do we mean by data cleaning?***

*Data cleaning is about verifying that study data were:*

- generated properly
- recorded appropriately and accurately at the clinical site
- entered correctly and completely into the study data system
- queried for potential discrepancies or protocol deviations.

*To ensure clean data, it's important to:*

- identify errors and reconcile any discrepancies
- follow up to ensure resolution
- make necessary corrections to study data, and documenting the changes in an audit trail.

# Ongoing data cleaning

*Why is ongoing cleaning important?*

We all know 'that roommate' who leaves the dishes in the sink for weeks at a time. Or who never cleans the fridge.

*Consequences to postponing cleanup...*

- It's harder to clean
- The huge dish pile becomes more daunting by the day, and resistance builds...
- It takes longer than you think it will
- You may discover something alarming
- It's frustrating – for you, and for others
- It can be embarrassing

# *Ongoing data cleaning*

*How does this apply to clinical trial data cleaning?*

- Data may be harder to clean
  - Too long since the data were collected or entered
  - Study Coordinator at site has moved on to another study or left the clinic
- Data cleaning tasks can become more daunting...
  - There can be resistance to the time and effort needed to re-check source documents or subject visit records, or to track down missing data at the clinical site
  - Resources need to be pulled from other aspects of study closeout to attend to data cleaning tasks.

# *Ongoing data cleaning*

- Cleaning can take longer than you think it will
  - Back-and-forth communications between the Coordinating Centers and clinical sites is time consuming
  - Other priorities often take precedence
- You may discover something alarming
  - Errors that could have been corrected early on and affect subject safety/confidentiality or the collection of data for the study endpoints are a major issue



# *Ongoing data cleaning*

- It's frustrating – for you, and for others
  - Everyone is busy during closeout of a study
  - Discovering major (or even minor, but prevalent) errors or issues toward the end of the study or during closeout puts pressure on everyone involved, and taxes the goodwill of collaborators and the study Sponsor.
  - Implementing an amendment to the protocol or changing study procedures based on significant issues discovered early on in the study could have avoided problems down the road.

# *Ongoing data cleaning*

- It's potentially embarrassing (or worse)
  - The reputation of the Principal Investigator, the clinical site, or the Coordinating Centers may be compromised
  - If fraud or other study misconduct is discovered, the repercussions are significant.

# *Ongoing data cleaning*

## *How does a DCC help avoid these problems?*

- Make ongoing data cleaning a priority throughout the study
- Incorporate data cleaning activities and tracking data completeness into designing the study database, developing study monitoring plans, and creating ongoing statistical and data management reports
- Frequently review trackers, data completeness, and data cleaning reports, and follow up until resolution
- Actively communicate between teams and with the clinical sites to emphasize the importance of clean and complete data
- Automate electronic data cleaning processes.

# *What types of reports are useful for data cleaning efforts?*

*Data quality and completeness reports that track:*

- Missing visits
- Incomplete forms
- Unresolved queries
- Data transfers
- Adverse/Serious Adverse Events
- Protocol deviations

# *How does a DCC close out a clinical site?*

- Conduct a study closeout monitoring visit, generate a final monitoring report, and follow up on observations until all are resolved
  - Verify that site regulatory binder is complete
  - Account for missing and incomplete study data or visits
  - Resolve any outstanding adverse events
  - Verify that all protocol deviations have been resolved
  - Complete any necessary data corrections

# *How does the DCC close out a clinical site?*

- Review clinical site data for accuracy and completeness
  - Resolve database queries and data entry checks
  - Run programs to check for duplicate forms and consistency of visit dates
  - Review all data quality and completeness reports, trackers, and tools until data cleaning tasks are complete
- Remove data entry rights and the ability of the site to make data changes, and assign 'View Only' status

## *What needs to be done to close out the study?*

- Decide what types of reports and trackers are needed to follow study closeout progress
- Determine who creates, distributes, and follows up on unresolved items
- Verify that transfers of study data from outside vendors are complete and that the data are reconciled
- Review all study-level data quality and completeness reports, trackers, and tools until data cleaning tasks are complete
- Lock the study data from further changes
- Perform statistical analyses and generate study results

# *What is the end result of all of these DCC activities?*

- Designing clinical trials appropriately leads to answers to important clinical questions.
- Building flexible but complete data collection systems leads to robust data sets.
- Ongoing data management, monitoring, and cleaning activities lead to robust data sets and timely data lock.
- Robust data sets and proper statistical analysis lead to important scientific and clinical findings.
- Publishing important and robust scientific and clinical findings leads to generalizable knowledge that improves the health and care of people with medical conditions.



# Summary

- The need for quality touches all areas of clinical trial research, from initial study design to the publication and submission of the final study results
- Consider up front how quality can be incorporated during each step of clinical trial development
- Create clear, simple, and generalized SOPs
- Establish priorities for areas that will need active quality monitoring and review
- Clean data and monitor study documents throughout the study
- A quality systems approach to clinical trial research helps to ensure that clinical trial results are ***more complete, reliable, and reproducible.***

# *CTSDMC Quality Team*



## *Resources and References Cited*

# *Clinical trial quality guidance*

## **ICH - *International Council for Harmonisation***

- Selected guidelines:
  - ICH E6 – Good Clinical Practice: Consolidated Guidance
  - ICH E8 – General Considerations for Clinical Trials
  - ICH E9 – Statistical Principles for Clinical Trials
  - ICH Q9 – Quality Risk Management
  - ICH Q10 – Pharmaceutical Quality System
- See <http://www.ich.org>

# ***Clinical trial quality and safety guidance***

## ***NIH – National Institutes of Health***

- **NINDS Quality Assurance Guidelines**  
[http://www.ninds.nih.gov/research/clinical\\_research/policies/quality\\_assurance\\_guidelines.htm](http://www.ninds.nih.gov/research/clinical_research/policies/quality_assurance_guidelines.htm)
- **NINDS Guidelines for Data and Safety Monitoring in Clinical Trials**  
[http://www.ninds.nih.gov/research/clinical\\_research/policies/data\\_safety\\_monitoring.htm](http://www.ninds.nih.gov/research/clinical_research/policies/data_safety_monitoring.htm)
- **NIAID Requirements for Clinical Quality Management Plans**  
<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf>

# *Improving clinical trial quality*

- Clinical Trials Transformation Initiative (CTTI)  
QbD (Quality by Design)  
<http://www.ctti-clinicaltrials.org>
- World Health Organization (WHO) Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation, 2002.  
[http://apps.who.int/prequal/info\\_general/documents/gcp/gcp1.pdf](http://apps.who.int/prequal/info_general/documents/gcp/gcp1.pdf)
- University of Wisconsin-Madison Institute for Clinical and Translational Research (ICTR) Study Monitoring Service. <https://ictr.wisc.edu>



# References

1. *Quality Management 2.0 Blog - The Importance of Quality Assurance: Top 3 Quality Failures*. Ashley Osgood, IBS – A Siemens Business, February 23, 2012. <http://info.ibs-us.com/blog/bid/51517> and references within.
2. *CTTI Recommendations on Quality by Design*, 2015 - [http://www.ctti-clinicaltrials.org/files/QbD\\_toolkit](http://www.ctti-clinicaltrials.org/files/QbD_toolkit).
3. *FDA Compliance Program Guidance Manual 7348.801, Chapter 48 – Bioresearch Monitoring*, 2011.
4. *Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance*, International Council for Harmonisation (ICH), 1996.
5. *Guidance for Industry: Computerized Systems used in Clinical Investigations*, US FDA, 2007.
6. *Handbook for Good Clinical Research Practice – Guidance for Implementation*, World Health Organization (WHO), 2002.
7. *Guidance for Industry: Electronic Source Data in Clinical Investigations*, US FDA, 2013.