Implementing a CAPA Program in a Clinical Quality System – CRO Perspective
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• Review key terms and fundamentals of CAPA
• Review development and implementation of a CAPA program
• Investigate developing thorough and comprehensive understanding of systems/processes
• Application of CAPA to a Clinical QS
• Investigate role of QC, QA and Operations in an effective CAPA program
• Q&A
Overheard at the Water Cooler

- “DB lock is going to be delayed by several days…again!”
- “Don’t worry about catching all of the mistakes – that is what QA/QC is for – you need to worry about getting it done…”
- “The TMF is ‘messed’ up again…I can’t remember the last time we got it right at EOS!”
- “We’re never going to get the subjects/patients we need for this study…”
- “PK shipment was missing samples…I can’t believe it happened again!?”
• **What is Quality in GCP?**
  – Subject Safety
  – Data Integrity and Quality

• **What is Quality in GCP for stakeholders?**
  – Efficient - Timely deliver of service
  – Effective – Recruitment capabilities
  – Science/Medicine – study design
  – Experience/Training – Investigators and study staff
  – Cost
Quality Management System (QMS)

- How do we “operationalize” the controls necessary to meet the main GCP and stakeholder objectives?
- Need a starting point….defining a system for managing quality
• A set of policies, processes and procedures required for planning and execution (production/development/service) in the core business area of an organization. QMS integrates the various internal processes within the organization and intends to provide a process approach for project execution. QMS enables the organizations to identify, measure, control and **improve** the various core business processes that will ultimately lead to **improved** business performance.
Quality in research is comprised of a wide range of elements. Such elements include a scientifically valid protocol, meaningful informed consent, appropriate attention to patient safety, complete and accurate recording of results, proper performance of tests and evaluations, and appropriate record verification and retention. Once a suitable study is designed and thoroughly reviewed, assurance of quality is dependent on the behavior of the clinical investigator, which is affected by training and integrity. Additionally, quality is supported by appropriate monitoring. Monitoring provides a direct assessment of certain aspects of quality, and is a means of highlighting the activities of those responsible for executing the clinical trial.
Fundamentals of CAPA

• From the definition:
  – Continuous Improvement ("We need to get better!")
    • Improve efficiency
    • Improve effectiveness
    • Support scientific innovation
    • Lessons learned
    • Reduce costs
    • Understanding and assessing Risk
• **Definitions**
  – Non-conformance
  – Potential Non-conformance
  – Correction
  – Deviation/variance
  – Corrective Action
  – Preventive Action
• Where do we start?
  – Quality Control
  – Quality Assurance
  – Site Operations
  – Management
    • Management must buy-in
      – Change in culture – blame free atmosphere
      – Empowerment of staff
      – Ownership of systems and processes
      – Quality is everyone’s responsibility
  • Quality Management System (QMS)
Management is committed…

- System/Process understanding
  - What do we do?
  - How do we do it?
  - Resources
  - Controls
  - What do we do well…not well?

- Development and implementation of a CAPA program is facilitated through thorough and comprehensive understanding of S/P
  - Mapping Tool – i.e., Process Mapping
    - “Start with the end in mind”

- Thorough understanding of S/P enables assessment of risk
Clinical System/Processes

- Systems/Processes of the Clinical QS
  - Subject recruitment/medical screening/enrollment
  - Drug Accountability
  - Biosample processing
  - Source/CRF data
  - Monitoring/QC
  - Computer validation
  - Equipment calibration/maintenance
  - Informed Consent
  - Study conduct
  - Sub-contractors
  - Quality Review function
Building Process Knowledge

Input → Process → Output

Resource → Process

Controls → Process

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Input

Resource

Controls

Output
Developing System/Process Knowledge

• Steps involved in the system, process and sub-process
  – Are there too many steps?
    • Gain efficiency
    • Improve effectiveness
  – Are controls adequate?
    • Over-the-top
    • Not enough
  – Staff accountability and responsibility
    • Ownership
Application of CAPA

• Fundamentals of CAPA process (IERAIF)
  – Identification
  – Evaluation
  – Root Cause Analysis/Investigation
  – Action Plan
  – Implementation
  – Follow-up (Effectiveness check)
Tracking tools for IERAIF
- Details
- Rating system (Significant, Minor, other)
- Investigation/RCA
  - Assign responsibility
- Corrective action/Preventive Action
  - Set reasonable dates for completion and implementation
  - Follow-up/Effectiveness, as applicable

Trending and Management Review
Considerations for RCA

- Aim performance improvement at root causes – not symptoms
- RCA must be performed systematically, with conclusions and causes backed up by documented evidence
- Often, more than one potential root cause for an issue
- The analysis must establish all known causal relationships between the root cause(s) and the defined issues.
- Root cause analysis changes “culture” from reactionary to a pro-active problem solving – creating a variability reduction and risk avoidance mindset.
Application of CAPA

- **CAPA Program**
  - Need a “designated” driver
    - Quality Review Function
  - Input into CAPA program
    - Rugged Documentation system for recording, tracking…
  - Feedback mechanism
    - Timely “loop” into process owners
    - Timely completion of corrective action
  - Implementation of preventive measure to eliminate recurrence and/or occurrence
  - Assess effectiveness of corrective and preventive measures
    - Metrics analysis – trending
    - “ISO Thought” – Management Review
Application of CAPA

- **QS change considerations from CAPA**
  - SOP Development, revision and retirement
  - Training
  - Resources
  - Technology
  - Quality Control
  - Audit focus

- **Important notes regarding QS change:**
  - Evolution of the QS should be incremental and step wise.
  - Evaluate and understand risk
Role of QA and QC in CAPA Program

- **Quality Control**
  - Embedded in operations
  - Verification/confirmation of operational activities
  - “Real-time” directed process focus
  - Short feedback-loops – error correction
  - Collection of compliance metrics
  - Issue identification and assignment
  - Effectiveness checks

- **Quality Assurance**
  - Independent of operations
  - Validation of effectiveness of the QS (holistic)
  - “Big Picture” focus – fitness of QS
  - Evolving feedback loop – error prevention
  - Analysis of compliance metrics
  - Issue identification and assignment
  - Follow-up and effectiveness checks
Role of Operations in CAPA Program

• Develop “top to bottom” S/P departmental knowledge
• Foster “blame-free” culture; empower staff
• Quality self-reliance
  – “I don’t worry about mistakes – QA/QC will catch them”
• Partner with QRF
• Conduct thorough and comprehensive investigations/RCAs
• Implement appropriate corrective and preventive (as applicable) action plan
Summary

- Effective and value-added management of quality begins with a well-defined set of policies and procedures
- CAPA program drives continuous improvement
- It begins with Management buy-in and development of thorough and comprehensive understanding of S/P
- QC is an operational activity; QA Independent of operations
- CAPA is fostered in a blame-free environment with timely identification and investigation/RCA of issues
- CAPA is implemented through effective action plans to correct errors, prevent occurrence and reoccurrence – documented tracking and routine management driven follow-up
- Change (continuous improvement) needs to be incremental
Definitions

- **Nonconformance**
  - Non-fulfillment of specified requirements

- **Potential Nonconformance**
  - Trend, emerging issue, or opportunity for improvement that has the potential to adversely affect the quality of a product/service

- **Correction**
  - Action to eliminate a detected nonconformity

- **Deviation/variance**
  - Departure from an approved written procedure
Definitions

- **Corrective Action**
  - *Steps that are taken to remove the causes of an existing nonconformity or undesirable situation.* The corrective action process is designed to prevent the recurrence of nonconformities or undesirable situations. It tries to make sure that existing nonconformities and situations don’t happen again.

- **Preventive Action**
  - *Steps that are taken to remove the causes of potential nonconformities or potential situations that are undesirable.* The preventive action process is designed to prevent the occurrence of nonconformities or situations that do not yet exist. It tries to prevent occurrence by eliminating causes.
References

- ISO 9000:2008
- “Juran’s Quality Handbook”, Godfrey, A.B.
- “The RCA Handbook”, Ammerman, Max
- “Kaizen: The Key to Japanese Success” Imai, Masaki
- “GCP Auditing: Methods and Experiences” 2nd Edition – DGCF
- FDA Concept Paper on GCP Critical Path
Questions