

Clinical Trial Quality-By-Design Case Study – A Small Company Experience

Lynn Seely, MD
Chief Medical Officer
Medivation, Inc.
San Francisco, CA

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Clinical Trial Quality-by-Design

- Objectives: To more effectively and efficiently
 - Protect trial participants
 - Ensure the reliability of study results to benefit future patients
- Systematic, prioritized, risk-based approach to trial design, conduct, and monitoring that is “fit for purpose”

“How can a small company implement quality-by-design?”

Quality-by-Design is Ideal for Small Companies

Small Companies

- Limited resources
 - Money
 - Time
 - People
- Can't do everything so forced to prioritize and focus
- Little tolerance for errors or second chances
 - Have to get it right the first time
- Flexible and agile with rapid decision-making

Quality-by-Design

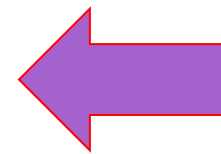
- More efficient and therefore less costly
 - Cornerstone is prioritization and focus
 - Proactive, not reactive
- Real-time risk management and corrective action plans so problems stay small rather than become large and pervasive
- Rapid decision-making and adaptation/adjustments

Quality-By-Design Terminology

Signature Features:

- **Set up in advance and continuous improvement**
- **Effective and efficient**

Pharmaceutical Development	Clinical Trial
Critical Quality Attributes	Critical Success Factors
Process Measures and Controls	Proactive Design, Training and Tracking
Design Space	Risk-Based Targeting
Continuous Improvement	Corrective Action Plans



Critical Success Factors

- Those clinical trial factors most likely to impact patient safety and data reliability
 - Phase 1: Safety monitoring and accuracy of PK timepoints and sample handling
 - Phase 2: Safety monitoring and accurate data collection for biomarker or efficacy endpoint(s)
 - Phase 3: Reliable efficacy endpoint collection; targeted safety monitoring

Critical Success Factors

- Will vary by phase of development, patient population and therapeutic area
 - Phase 3 Prostate Cancer Trial with overall survival as primary endpoint
 - ❖ Enroll the right patients: meet inclusion/exclusion criteria; not so ill that drug has no chance
 - ❖ Keep patients on study drug as long as possible
 - ❖ No patients lost to follow-up
 - Phase 3 Alzheimer's Disease Trial with more subjective outcome measures
 - ❖ Experienced and well-trained raters
 - ❖ Reliable reporters/caregivers
 - ❖ Low discontinuation rate

Key Check Points for Critical Success Factors

- Randomization Authorization Form
 - Requires prior approval by a medical monitor to enroll a trial participant; proactive check for site error
 - Medical monitor checks central labs, ECGs, and information filled out on a brief form
- Contact form: requires contact information for 3 people who will always know the patient's whereabouts
- Track reasons for early discontinuations; medical monitors contact investigators and limit enrollment at sites that are poorly compliant
- Rater qualification and certification

Proactive Design, Training, and Tracking

- Protocol Design
 - “Fit-for-purpose” design: simple elegance
 - Sponsor, key investigators, key study coordinators
- Training
 - Select the right people “fit for purpose”
 - Prioritized training based upon critical success factors
 - Train at central investigators’ meeting and at site initiation visits for later phase trials
 - Monitor training; investigator training; study coordinator training
 - Continues until the trial is over

Monitors and Site Personnel

- Interview, select and train
 - Ensure adequate experience for complexity of trial
 - Personally interview all monitors
 - Select sites; don't outsource that task
- Review trip reports
 - Are action items closed in a timely fashion?
 - Does the PI meet with the monitor?
 - Is there adequate PI oversight?
 - Is the study coordinator experienced and effective?

“If you have adequately trained the right people, quality is usually not an issue”

Data Tracking: A Rich Source of Information About Overall Trial Quality

- Data Tracking is now easy and very do-able with electronic data capture
 - Enrollment rates
 - Timeliness of data entry
 - ❖ Is the site adequately staffed?
 - Timeliness of source data verification
 - ❖ Is the monitor experienced, efficient and organized? Enough time?
 - ❖ Are the site personnel experienced and committed enough to enter high-quality data with organized and adequate source documentation?
 - Listing and patient profile review; overall data quality
 - Number of queries
 - Timeliness of answering queries
 - Adverse event rates
 - Early discontinuation rates

Safety

- Monitoring at site
 - Adequacy of informed consent
 - Investigator oversight and involvement
 - Missed adverse event reporting
 - Adherence to protocol
 - Study drug accountability
- Data Review
 - Timeliness of SAE reporting
 - Outliers for adverse event reporting
 - Responsiveness to AE queries
- Safety Management Committee for signal detection
- Independent Data Monitoring Committee as indicated

Audits

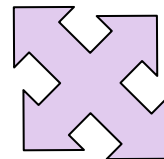
- Quality is an integrated part of study team
 - Trusted advisor; shares responsibility; regularly attends team meetings
 - Audit plan set up at outset but responsive to trial data and realities
- Audits occur early in study
 - To identify gaps/oversights of monitors and study team
 - To identify areas in need of re-training; suboptimal processes
 - At sites in new regions
 - At sites expected to be high enrollers
- Adaptive auditing
 - High enrolling
 - Site/monitor personnel issues
 - Data quality issues

Quality-by-Design: No Silos

Overall Project Team

Site Monitoring
Clinical Operations
Medical Monitors
Data Management
Quality

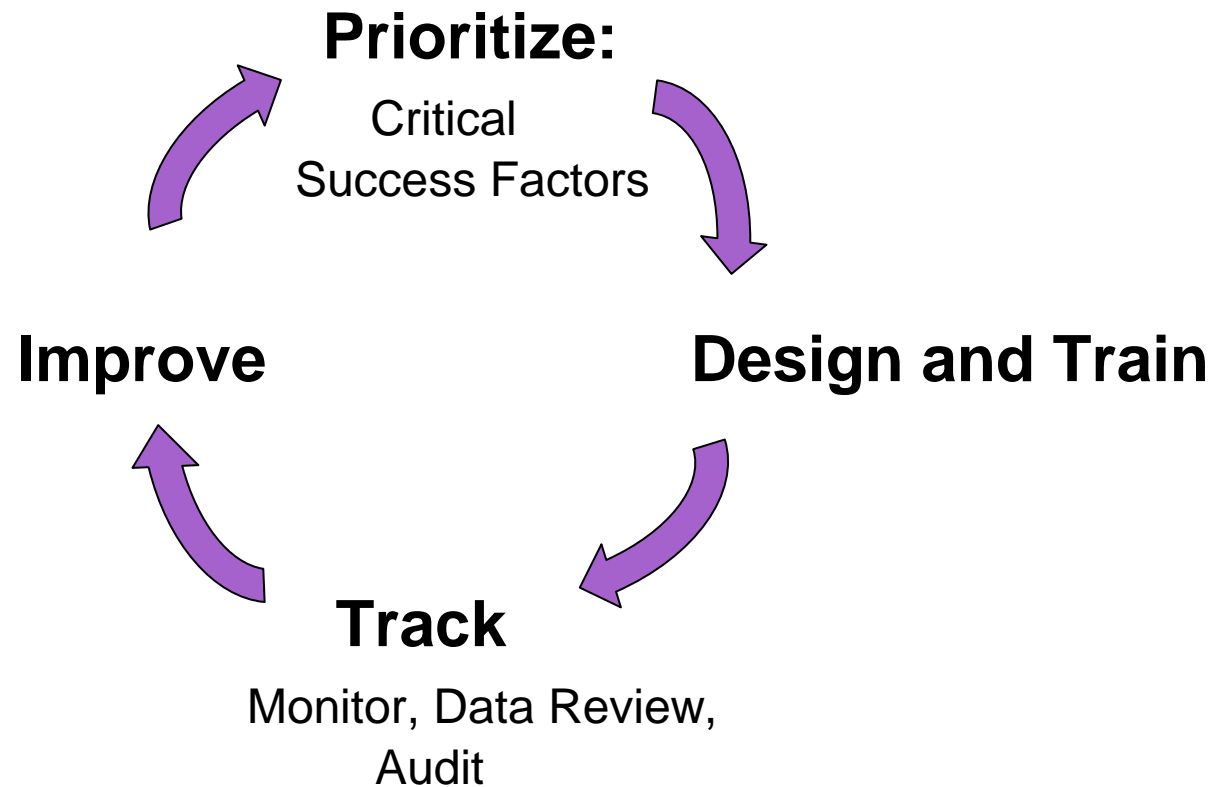
Safety Monitoring
Medical Monitors
Pharmacovigilance
Biometrics



Data Review
Medical Monitors
Data Management
Clinical Operations
Quality

Audits
Quality
Clinical Operations
Medical Monitors

Continuous Improvement



Risk-Based Approach to Quality

- The primary source of data quality occurs at the individual site
 - This is where data are collected, entered, and verified
- All sites are not equal
- Sites are prioritized for level of risk based upon cumulative data
 - Qualification and experience of site personnel (monitor, PI, SC)
 - Enrollment
 - Data timeliness (data entry, source data verification)
 - Adherence to protocol/GCP
 - Data quality and responsiveness to queries

Risk-Based Approach to Quality

- Actions taken to improve quality
 - Direct interaction with monitors
 - Call to investigator by medical monitor
 - Co-monitoring by sponsor; direct interaction with site personnel and monitor
 - Audits
- Monitoring, training, and auditing plans are adapted based upon findings over time
- Currently do not allow less than 100% source data verification of every patient at every site: one size fits all

Challenges

- Risk-based approach to auditing is well-defined by regulators
- Risk-based approach to monitoring is not well-defined
 - Companies don't want to take risk as inadequate monitoring uncovered at an inspection is catastrophic
- Level of required documentation

Potential Solution

- Define a “design space” for clinical trial monitoring
 - Risk-based targeting for monitoring could be defined
 - Sponsor could be allowed to make adjustments to the monitoring and quality management plans “real-time” during the course of the study based upon accumulating data
 - ❖ Increased monitoring at selected sites based upon issues
 - ❖ Decreased monitoring at selected sites based upon data quality
 - ❖ Random monitoring to keep everyone alert
 - ❖ Incentive for sites to do an excellent job

Potential Solution

- Examples
 - Site visits can be discontinued at lower enrolling sites with timely data entry, excellent investigator oversight and high data quality based upon review of eCRF and initial site visit(s).
 - Alternative: 100% SDV can be decreased to key data fields at highly rated sites
 - Every site must have at least one on-site monitoring visit. The number and frequency of subsequent monitoring visits should be determined by:
 - ❖ Enrollment, investigator and coordinator experience, data quality, trial complexity, drug safety
 - ❖ A percentage (10%?) of sites should always be selected at random

Conclusions

- Quality-by-design in clinical trials can be accomplished by companies of all sizes, for each phase of development, and for all therapeutic areas.
- Regulatory guidance is needed to define the “design space” for trial monitoring
 - Allow real-time decision-making by the sponsor during the conduct of the trial based upon accumulating data:
 - “Risk-based Targeted Monitoring”