Research Compliance and Quality Assurance - Why, What & How?

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Disclaimer

For the purposes of this presentation, “Research Compliance” pertains to Human Subject Research Compliance

Objectives

- Understand the importance of research compliance oversight at an academic institution.
- Identify the elements of compliance, research compliance and quality assurance.
- Recognize how research compliance protects subjects, Principal Investigators, their research teams and the University.
- Become aware of the consequences of not having a well functioning research compliance team.

WHY
Do We Need Research Compliance?

Manage and reduce compliance risks to:

- Ensure continuous federal and industry funding for clinical research
- Reduce liability
- Ensure public trust
- Ensure quality of publications
- Demonstrate to regulators (FDA, OHRP, NIH, DOD, etc.) that the University takes compliance seriously

WHAT
Are The Elements Of (Research) Compliance?

General Elements:

- Structure of compliance leadership and involvement of senior leadership
- Training and education
- Clearly defined responsibilities, accountabilities and roles
- Strong and clear lines of communication
- Constant evaluation if system works
- Risk evaluation and mitigation strategies and processes

WHAT
Are The Elements Of (Research) Compliance?

General Elements cont:

- ☑ Correction and Prevention – CAPA (Corrective and Preventive Action)
- ☑ Enforcement and disciplinary actions
- ☑ Policies and Procedures – Written Standards
- ✔ Compliance Committees (IRB, COI, SNCC, etc.)
- ✔ Quality Systems
- ✔ Hotline: CaneWatch – anonymous reporting; Whistleblower Protection Statement https://umshare.miami.edu/web/wda/policieshr/WhistleblowerProtectionStatement.pdf

WHAT
Are The Elements Of (Research) Compliance?

General Elements cont:

- ✔ Customer Service
- ✔ Mission and vision, defining organizational compliance culture
- ✔ Defined scope

Symbol key:

- ✔ Existing
- ☑ In process or existing but insufficient
- ⛔ Not existing

Research Compliance and Quality Assurance

Introduction:

- Part of the research compliance structure within the Office of the VPR (Vice Provost for Research) with a direct reporting line to the VPR
- Part of the overall institutional compliance structure at the university (Chief Compliance Officer)
- University-wide functions
- Independent from operational functions
- Independent from IRB and HSRO
- Collegial instead of policing approach

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How does RCQA operate?

1. Risk Management Approach

Definition of Risk:

The combination of the probability of an event and its consequences. (ISO/IEC Guide 73)

Process:

Identification, analysis and mitigation of research related

Determine highest risk areas and prioritize accordingly. For example: risks to patients/subjects, risks to PI/Sponsor-Investigator, financial risks to Institution, reputational risks to Institution, etc.

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How does RCQA operate?

2. Quality Management (QM) Approach

A holistic approach that views continuous improvement in all aspects of an organization as an ongoing process.

The objective is long-term success rather than short term goals.

QM includes a customer service focus and involvement of key stakeholders throughout the process of program implementation.

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How does RCQA operate?

Quality Management Approach (cont.)

The following QM principles are included in our strategic planning:

- Involvement and commitment of University leadership.
- Process management: written processes are established and their effectiveness and outcomes are measured.
- Customer approach: *everyone* involved in research is a customer. The involvement of PIs and research teams in this process will be fostered.
- Information and feedback: clear communication lines between RCQA and University leadership and the research community are being established and maintained. A process of constant feedback is promoted.
- Education and training: The research community at the University is offered all necessary training related to research compliance.

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RCQA provides the following services:

a) Audits
b) Voluntary assessments
c) Preparation of Principal Investigators (PIs) and study teams for external federal audits
d) Assistance for PIs and study teams during external federal audits
e) Assistance with responses to federal agencies (Form FDA 483, EMA audit reports, NIH audit reports, etc.)
f) Corrective And Preventive Action (CAPA) system
g) Clinical Trial Disclosure Compliance System
h) Research related education and training

Research Compliance and Quality Assurance

a) Audits:

- Systematic and independent examination of the trial related activities and documents.
- Snapshot in time of a subset of subjects.
- Determine whether the trial related activities were conducted and data recorded accurately, analyzed and appropriately reported according to:
  - Protocol
  - SOPs
  - GCPs
  - All applicable regulatory requirements (FDA, ICH-GCP, OHRP, NIH, DOS, state and local laws)
- Audit report is created and written PI response is required.
- Audit activities are NOT subject to FDA audits.

Auditor:

- Plans, communicates and conducts audits and proposes corrective and preventive actions as applicable.

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a) Audits cont.

Types of QA audits:

Directed: For cause audits, directed by the Institutional Official (IO) based on identified concerns about compliance (allegations, complaints, hotline).

Routine – risk based selection: sponsor-investigators, PI-initiated studies, storing/dispensing investigational products on site, high-risk studies. Investigators who are: working outside their area of specialty, oversee a high number of studies, have a history of non-compliance or who have never been audited before

Focused: follow-up audits, follow-up on Corrective and Preventive Action (CAPA) plans.

Investigator requested: audits requested by Principal Investigator.

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b) Voluntary Assessments

- Requested by PIs and/or study teams, center directors
- Review and assessments of systems and processes
- Gap analysis:
  - Identify topic/process for gap analysis
  - Identify current status
  - Identify desired/required status
  - Identify gap between current and desired/required status
  - Determine how to reach desired/required status (SWOT analysis – Strengths, Weakness, Opportunities, Threats)
- Follow-up actions as needed

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c) Preparation of Principal Investigators (PIs) and study teams for external federal audits:

- Upon notification of external federal audits, the QA team prepares the PI and research team 1) regarding communication/interaction with the FDA, NIH, EMA; 2) for the inspection process, discussing “Do’s and Don'ts,” etc.

d) Assistance for PIs and study teams during external federal audits

- The QA team is present at the beginning of the audit, during interviews, at debriefings, at the exit interview.
- The QA team acts as institutional representatives and communicates closely with UM leadership during an external audit.

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e) Assistance with responses to federal agencies: Form FDA 483, Untitled Letters, Warning Letters, EMA audit reports, NIH audit reports, etc.

- The QA team works with the PI and institution on responses to audit reports from federal agencies
- Responses are usually done within a CAPA format
- UM leadership committee must agree to the final response for FDA and EMA audits (NIH audit responses as applicable)

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f) Corrective And Preventive Action (CAPA) system (in implementation stage)

Corrective Action

- Action to eliminate detected non-compliance/nonconformity (=non fulfillment of a requirement), in addition to addressing systemic problems

Preventive Action

- Action to eliminate the cause of non-compliance /nonconformity to prevent **recurrence**
- Must be instituted **systemically**
- Should be instituted as a prophylactic measure to prevent **occurrence** (importance of risk assessments)

Not every deviation/non-compliance requires a CAPA plan

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f) Corrective And Preventive Action (CAPA) system (in implementation stage)

Goals:

- Creation and maintenance of policies and SOPs for internal CAPA system
- University-wide workshops/training sessions for faculty and research staff
- Creation of a university-wide system/database for CAPA plan tracking/metrics
- Training and assistance/support for UM research teams in regards to creation, revision and closure of CAPAs
- CAPA plans are created as necessary in response to internal and external audits; IO/IRB request, etc.
- University-wide process for CAPA auditing, monitoring (as applicable), effectiveness checks (revisions), assessments and closure

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g) Clinical Trial Disclosure Compliance System

- What is Clinical Trial Disclosure?
  - The act of making clinical trial information (protocol registration and protocol results) known and/or available publicly.
- How is Disclosure achieved?
  - ClinicalTrials.gov as a registry databank.
    - Operated by the National Library of Medicine (NLM)
    - Can be searched in real time to find enrolling/completed studies
    - Created to increase research transparency and to help people find trials

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g) Clinical Trial Disclosure Compliance System

Regulations and Requirements that affect Clinical Trial Disclosure

- FDAMA Section 113 (1997): Mandates registration of trials for serious and life-threatening diseases or conditions.
- ICMJE (2004): Encourage journal editors to require that all clinical trials be entered in a public registry before the start of participant enrollment, as a condition of consideration for publication.
- FDAAA Section 801 (2007): Expands registry and adds results reporting requirements.
- CMS Medicare National Coverage Determination (NCD) for Routine Costs in Clinical Trials; effective January 1, 2014

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g) Clinical Trial Disclosure Compliance System

- **Awareness**
  - ListServ emails, Grand Round discussions, targeting those most affected
- **Training**
  - Robust planned training, Q & A Sessions
- **Administrative Oversight**
  - Policy creation, identifying needed process improvements, implementing technology to facilitate compliance, tracking legal and/or clinical research guidances and requirements
- **Support**
  - SOP templates, interactive tools to help determine if proposed study meets the requirements for registration, readily available FAQ document, links to educational material, helpful hints documents, courtesy notifications and reminders of upcoming tasks, Peer Coaching to increase internal capabilities to comply with Clinical Trial Disclosure
- **Compliance**
  - Audit Clinical Trial Disclosure tasks, produce and analyze metrics and quality of submissions, evaluate and report on trends and identify areas for improvements

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h) Research Compliance related education and training

- Live education and training provided via scheduled classes and available also for individual research teams, divisions and departments
- Training examples: Preparing for an FDA Audit, Responding to FDA Observations/FDA Form 483 and Warning Letters, The Audit Process, Introduction and Overview of Clinical Trial Disclosure, Protocol Registration on ClinicalTrials.gov, Result Reporting on ClinicalTrials.gov, Managing your record on ClinicalTrials.gov, Is Your Protocol Registration Ready, etc.
- New training starting in Fall 2014: Discussion and Analysis of FDA Warning Letters; Research Compliance and ICH-GCP; Criminal Investigations in Human Subject Research; etc.

CEUs are provided for nurses, social-workers and psychologists. Attendance certificates are provided to obtain education credits with research related professional organizations such as ACRP Association of Clinical Research Professionals) and SOCRA (Society of Clinical Research Associates).

HOW
To Achieve Research Compliance?

Research Compliance is *everybody's* responsibility

Awareness building with:

Education and Training: overall research and compliance related education is important, but not sufficient; departmental hands-on competency training must be implemented; coaching and mentoring; adequate job descriptions

Internal Controls: University-wide controls such as IRB, COI, RCQA, monitoring for IND/IDE holders are present; in addition, departmental controls must be implemented: internal quality control conducted by study team members with the help of simple tools (see slide "compliance tools");

Risk assessments: determine highest risks to subjects, PIs and the university and prioritize those risks

Gap analysis: determine actual status of research related processes by conducting a review (should be independent, according to size of operations), determine desired status and fill/restore the gap.

Compliance Tools

Deming Cycle

Compliance Tools

Deming Cycle – PDCA or PDSA

- **PLAN:** Design or revise processes to improve results
- **DO:** Implement and measure
- **CHECK/STUDY:** Assess the measurements and monitor, evaluate the processes and outcomes against objectives and report the results
- **ACT:** Decide on changes needed to improve processes and apply actions to the outcome for necessary improvement. Review all steps - Plan, Do, Check, Act - and modify the process to improve as necessary.
- Additional Steps: Observe → Plan → Do → Check → Adjust

Compliance Culture

Character is doing the right thing when nobody's looking. There are too many people who think that the only thing that's right is to get by, and the only thing that's wrong is to get caught.

J. C. Watts

Compliance Culture
How To Overcome Potential Barriers

- All organizations/universities have a “compliance culture” – where do we stand?
- Good “intentions” are not enough and not getting caught is not a sign of a compliant organization
- Compliance must be objective and measurable – with a formal, systematic and nonthreatening approach. It is not about getting caught, but rather how we remediate and learn from problems.

Compliance Culture
How To Overcome Potential Barriers

- PIs and research team members must be:
  - able to get regulatory advice from within the organization (IRB, HSRO, RCQA, CRORS. ORA, etc.)
  - willing to inform management of problems and report violations to management without fear of sanctions – how do we treat whistleblowers?
  - able to trust management that they care
  - aware that unethical behavior is punished at all levels → consequences

Managing Ethics and Legal Compliance: What works and what hurts, Trevino et al, 41 California Management Review, No. 2 1999.
AND
The Culture of Compliance *By* Lori A. Richards , *Director, Office of Compliance Inspections and Examinations, U.S. Securities and Exchange Commission*
http://www.sec.gov/news/speech/spch042303lar.htm

How
Does Research Compliance Help/Protect?

a) Audits – assessments of individual studies, processes and procedures; provides a status update to PIs and research teams

b) Voluntary assessments – assessments of processes and procedures; status update is provided

c) Preparation of Principal Investigators (PIs) and study teams for external federal audits – PIs and study teams are prepared to deal with external auditors; all records will be available and potential issues might be discovered prior to the external audit

d) Assistance for PIs and study teams during external federal audits – enables a smooth audit process; audit might be completed earlier

e) Assistance with responses to federal agencies (Form FDA 483, EMA audit reports, NIH audit reports, etc.) – well prepared response might help avoiding further actions from the federal agencies

How
Does Research Compliance Help/Protect?

f) Corrective And Preventive Action (CAPA) system – ensures that university researchers and senior leadership are aware of promised actions to federal agencies, those actions are tracked and monitored to ensure they are completed/implemented.

g) Clinical Trial Disclosure System (CTD) – ensures that University researchers are compliant with the applicable regulations and requirements associated with CTD. Provides training, support and timely reminders to ensure compliance.

h) Research related education and training – provides basic knowledge for PI and research teams. Ongoing training assists PIs and teams to remain up-to-date with Federal regulations and guidelines. Demonstrates to regulators that the University takes compliance seriously.

What
Are Consequences of Not Having a Compliance Program?

- Increased institutional risks
  - Risk to subject safety and/or rights
  - Principal Investigators, research teams, the University
- Potential fines and penalties
  - Form FDA 483, Untitled Letters, Warning Letters, Disqualification
  - CTD fines
  - Criminal investigations
- Negative publicity and reputation
  - Dr. Robert Fiddes conducted research fraud, endangered subjects and data falsification – sentenced to prison and lost medical license

    http://www.nytimes.com/1999/05/17/business/a-doctor-s-drug-trials-turn-into-fraud.html
  - Coast IRB shut down as result of a Federal sting operation

    http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm136673.htm
- Suspension of and decrease in federal awards and funding

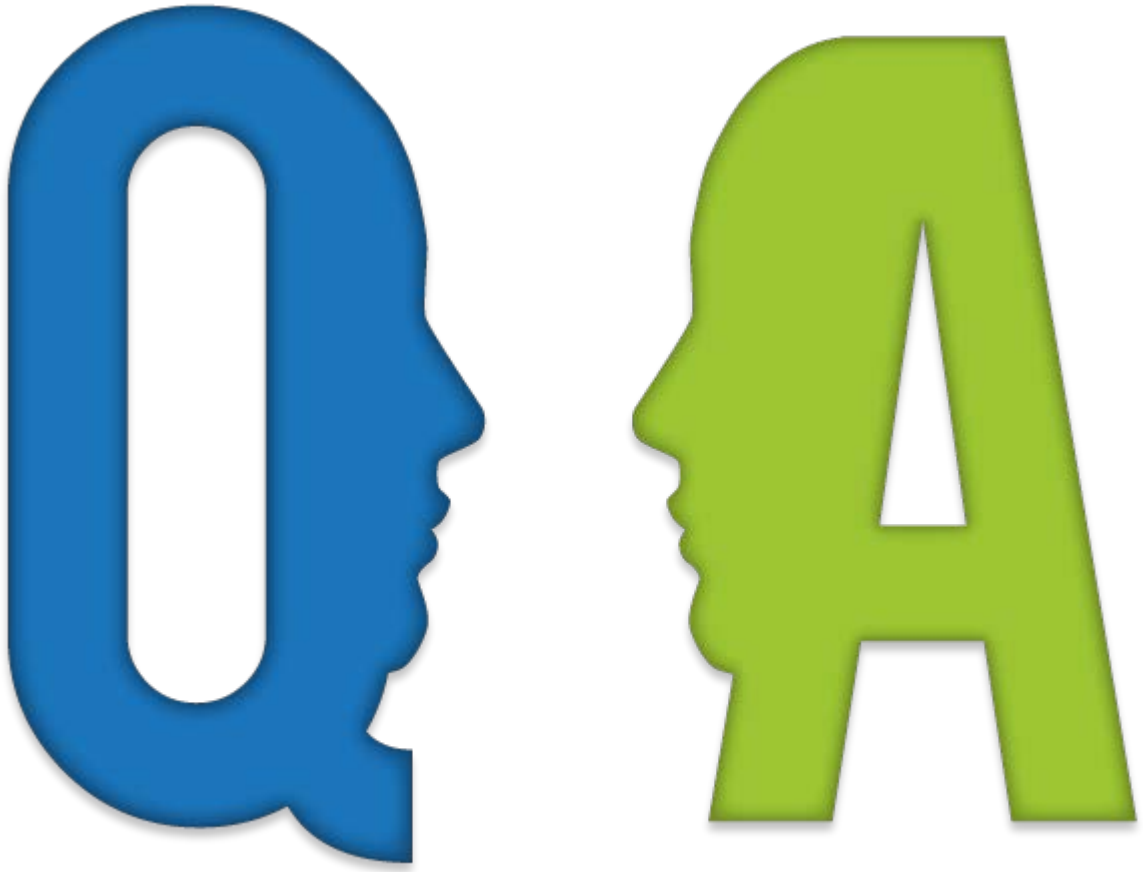
How? → Building Alliances

Building Alliances between all involved parties by:

- Moving away from Silo-Approach
- Learning from each other
- Embracing errors → learn → move on
- Sharing of pertinent information such as: internal audit findings, external audit findings, form FDA 483 and Warning Letters (all anonymously) to correct and/or avoid systemic issues
- Strongly incentivizing greater/more PI participation in training with their study team
- Enlist top performing study teams to discuss best practices and motivate others
- Encouraging senior management, division and departmental leaders to publicly reinforce UM's commitment to research compliance and excellence.

Why? → It is the right thing to do!


Thank
you!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