Objectives

• Describe the organizational structure of Mayo Clinic Research Compliance Office program and staff as well as the activities and resources provided

• Show tools, templates and resources created for regulatory infrastructure support

• Discuss audit and monitoring findings, and share ideas to improve compliance within research based on tracking these trends
Importance of Research Compliance

- Research is an essential component of mission
- Rules/demands may be viewed as in conflict with other activities (clinical care)
- Highly complex, often with many sets of rules applicable to a single activity
How Complex is Research Compliance?

- NIH Grants Policy Statement (terms and conditions of NIH awards)
- Human subject protection regulations
- FDA drug/device study regulations (for sponsors and investigators)
- Animal use regulations
- Medicare clinical trial billing rules

Historical Research Compliance Activities

- No dedicated Research Compliance staff; no one primarily responsible for helping to identify and address compliance issues
- Often little oversight/visibility
- Reactive and sporadic
- Fragmented
Current Research Compliance Office Initiatives

• Dedicated staff and resources that are primarily responsible for helping to identify and address compliance issues
• High level of oversight/visibility
• Proactive and preventive
• Coordinated

Goals of Research Compliance

• Assure integrity in research
• Comply with applicable laws
• Protect research subjects
• Avoid financial penalties
• Proactively manage risk
Research Compliance Subcommittee
Membership

- Physician investigators and scientists representing clinical and basic science
- Vice Chairs of Research Administration – sites and shared services as well as admin/managers from quality office, sponsored projects
- Chair of Research Finance
- Research Compliance Officer

Research Compliance Subcommittee
Reporting

Mayo Clinic Compliance and Enterprise Risk Management Committee

Mayo Clinic Research Committee

Mayo Clinic Research Compliance Subcommittee
Involvement of Research Compliance Officer and RC Subcommittee

- Work with process owners to develop action plans
- Help to identify resources
- Oversee implementation of action plans
- Assist with development of educational materials

What goes to RC Subcommittee

- More complex issues that require extensive evaluation and action plans benefit from RCS input
- Issues that can be addressed between the process owner and the Research Compliance Office staff are not necessarily taken to the subcommittee
Research Compliance is a Shared Responsibility

• Leadership and Management provide the direction and resources
• Research Compliance Officer identifies and assesses compliance issues, then works with process owners to minimize compliance risk
• Research community works within the rules, and helps us identify compliance gaps

Activities and Role of Research Compliance Officer

• Oversee and coordinate compliance-related initiatives related to research
• Risk assessment and prioritization for development of annual plan
• Develop and coordinate educational materials
• Serve as Regulatory Service Line leader within research administration
Activities and Role of Research Compliance Officer

• Work proactively with research investigators and administrative staff to develop effective approaches to complying with rules and regulations

• Administrator for Office of Research Regulatory Support (ORRS) and IRB Regulatory Compliance Unit (IRCU) staff

Office of Research Regulatory Support

• Provide assistance to all Mayo Clinic investigators working on FDA regulated research involving drugs, biologics, devices or other test articles.

• Centralized resource for information, expertise, and support related to the conduct of clinical research under investigator-initiated Investigational New Drug (INDs) or Investigational Device Exemption (IDEs).
Why was the ORRS created?

• Failure to comply with FDA regulations can result in the following:
  • Risk to human subjects
  • FDA audit findings
  • Publicly released warning letters
  • Negative reflection of research at Mayo Clinic
  • Monetary fines
  • Withholding of federal funding

Two main paths for IND or IDE research

#1
External company initiates research

#1 is the most common situation.

#2
Investigator initiates research

#2 presents higher risk for the Institution and the Investigator.
Examples of Investigator Initiated FDA Regulated Research

• Novel drug or device
• Marketed drug being researched for a non-approved indication (new route, new patient population, new dose, etc.)
• Marketed/cleared device being researched for a new indication
• Conducting research on the use of a product as a drug or device

ORRS Infrastructure Support at Mayo Clinic

<table>
<thead>
<tr>
<th>CREATION</th>
<th>FUNDING</th>
<th>REPORTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiated by CTSA grant, Research and Compliance Leadership</td>
<td>Funding through institutional research funds</td>
<td>Report through Compliance</td>
</tr>
<tr>
<td>Approval by Research Committee and MC Administrative Team</td>
<td>Separate from research funding</td>
<td>&quot;Dotted line&quot; to Research Administration</td>
</tr>
</tbody>
</table>
ORRS Services and Support

IND Applications

IDE Applications

Clinicaltrials.gov oversight

FDA Audit Support

Monitoring Sponsor-Investigator Studies

Study File Mgmt

Assistance for IND/IDE applications

- Consultation
- Templates and Quick Reference Guides
- Communication and correspondence with FDA as needed
- Pre-IND or IDE meeting assistance
- Maintenance:
  - Annual Report reminders
  - Safety reporting assistance
Monitoring Sponsor-Investigator Studies

• Frequency of visits determined by protocol and needs
• Work with study teams for improvements based on findings
  • Additional training on identified topics
  • Communication of findings (general) through presentations to department and educational initiatives
Monitoring Sponsor-Investigator Studies

- For 2014, working on risk based approach to monitoring
  - Risk assessment of protocol and study team members
  - Decision of full study monitoring vs. targeted monitoring
  - Also evaluating the use of self-monitoring with targeted follow up audits

FDA Audit – Centralized Coordination

- Pre audit meetings with PI/research team
- Notification of areas involved
- Just in time training to prepare for upcoming audit
- Assistance provided to study teams during the audit from first phone call through written response (if needed)
Study File Management Resources

- Resources for study teams
- Checklists for FDA and non-FDA regulated study file management
- Quick Reference guides
- On-line module
- eBinder development
- Assistance for questions as well as providing tabs to study teams to assist them in organizing study regulatory documents
Organized and Complete Study Files are the Key to Smooth Sailing versus Sinking in Papers!

Throughout the course of a clinical research investigation, multiple documents and records are generated relating to the study and its participants. To ensure a well-managed study that can be readily verified as compliant with applicable regulations, these study and subject files must be complete, accurate, traceable and retrievable in a timely and efficient manner.

Using a 3-ring binder with labeled tabs to divide sections is the standard for organizing study documents. Understanding what should go into the Regulatory Binder and keeping it updated as study activities proceed is an excellent way to remain confident that you are accounting for required documentation and maintaining an audit-ready study.

For your FDA Regulated studies, contact the ORRS for binders, dividers and pre-labeled tabs to organize your study documents and records.

STUDY FILE ORGANIZATION - Helpful Tools and Tips

Use the Checklists and Quick Reference Guides in the table below to help you determine which documents to maintain in the regulatory binder and subject files for each study.

<table>
<thead>
<tr>
<th>Regulatory Binder Checklist</th>
<th>Yes</th>
<th>N/A*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol + Templates available on CDRH web site.</td>
<td>Include current and all previously IRB approved versions, amendments and/or modifications</td>
<td></td>
</tr>
<tr>
<td>Informed Consent Form</td>
<td>Include current and all previously IRB approved versions (unsigned)</td>
<td></td>
</tr>
<tr>
<td>Investigator’s Brochure</td>
<td>Include all versions. Alternatively, may include a product/package insert if there is no IB.</td>
<td></td>
</tr>
<tr>
<td>Investigational Device Information</td>
<td>Summary document describing the device under study.</td>
<td></td>
</tr>
<tr>
<td>FDA Form 1572 (Statement of Investigator)</td>
<td>Include all versions</td>
<td></td>
</tr>
</tbody>
</table>

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Oversight of ClinicalTrials.gov process

- Protocol Registration System (PRS) administrator part of the ORRS team
- Resources for study teams
  - Quick Reference guides
  - On-line module
  - Classroom training
- Assistance for questions on registration process
- Initiated in 2012: Results reporting assistance (direct entry and support for study teams)

Identifying Applicable Clinical Trials

- Triggers off responses to questions in IRB application once IRB approval is received
- Able to map approximately 1/3 of the data required in the PRS record to our IRB application system. Data is automatically entered in record for study team to then complete
- Email sent to PI/SC to finish the registration of the study if they have an account, or to set up account to complete the registration (through system and PRS administrator)
Results Reporting

• Previous Practice
  • Notify responsible party (investigator) of requirements to post results
  • Send reminders at regular intervals
  • Offer information, training guides and links via our internal website
  • Investigators responsible to post results and adverse event information

Results Reporting

• Previous Practice effects
  • Complaints from investigators regarding time required for entering results
  • Investigators called with numerous questions about the system and unsure what was needed for entering results
  • Frustrations were numerous and escalated to leadership
Results Reporting

• Pilot project
  • Identified studies needing results posting and contacted investigators for willingness to participate
  • Senior Regulatory Specialist worked with team to gather information and data, then entered results
  • Tracked pertinent resources (people, FTE, data access, etc) needed for results reporting

Results Reporting

• Research and Compliance Leadership reviewed pilot data and discussed need for additional FTE support
  • Based on number of trials and efficiency gained with dedicated position, hired 1 FTE for this role (split this between 2 staff along with other responsibilities)
  • Why - worth future savings of Investigator (physician) time
Other Key Components

- Tracking all Mayo Clinic sponsor-investigator INDs or IDEs
  - Database to maintain pertinent information
  - Notification to sponsor-investigators when annual reports due to FDA
    - Email reminder sent with annual report template for S-I to complete
  - Ability to run reports
IRB Compliance & Regulatory Unit

• Goal is to ensure compliance and integrity in research.
• Support the protection of human subjects in research by ensuring compliance with Federal, State, and Institutional guidelines.
• Staff work in partnership with Mayo Clinic Office for Human Research Protection, the Institutional Review Board (IRB), Research Administration, and the research community.

IRB Compliance Activities/Initiatives

- For Cause Audits
- Protocol Deviations Review
- Proactive Reviews Initiative
- Consenting Process Reviews
- Consults/Education
- Tracking Trends
For Cause Audits

- Conducted when allegations of suspected or actual noncompliance with federal regulations, state laws, Mayo policies, and/or IRB requirements with respect to human subject

- Directed by:
  - Institutional Review Board and/or Chairs
  - IRB Medical Director
  - Research Compliance Office
  - Participants, Staff, Whistleblower Complaints
  - Claims of Subject Injury

Definitions

- **Allegation of Noncompliance**: An unproven assertion of noncompliance.

- **Noncompliance**: Failure to comply with federal regulations, state laws, Mayo Clinic policies or procedures, and/or the policies, requirements or determinations of the Institutional Review Board, or provisions of the approved research study.
Example of notification from IRB member

For Cause Audits
- May be targeted reviews (consent, eligibility, PI oversight) or full study review
- Reports and findings are sent back through IRB committee for determination
  - Non-compliance
  - Serious and/or continuing non-compliance
Definitions

• **Serious Noncompliance**: An action or omission taken by an Investigator that any other reasonable Investigator would have foreseen as compromising the rights and welfare of a participant or compromises the integrity of the study data. The following events will in most cases be considered Serious Noncompliance:
  - The conduct of any non-exempt research involving human subjects without IRB review and approval.
  - Enrollment of any human subject in a research study involving greater than minimal risk without informed consent.
  - Implementation of substantive modifications involving possible risks to human subjects or others without IRB review and approval.
Definitions

- **Continuing Noncompliance**: A pattern of repeated actions or omissions taken by an Investigator that indicates a deficiency in the ability or willingness of an Investigator to comply with Federal regulations, Mayo Clinic IRB Policy, or determinations or requirements of the Mayo Clinic IRB.
Proactive Reviews

• Randomly select studies and conduct a proactive review of the study and the associated documents
  • Regulatory documents/binder review
  • Eligibility determinations
  • Protocol adherence – are we doing what we said we would do?
  • Other assessments of targeted areas

Reportable Events or Protocol Deviations Review Process

• Review submissions “just in time” to provide additional direction to study team
• Deviations happen in research: determinations as to whether need to be reported immediately or at time of continuing review w/study team
  • More tips and training have been added to assist study teams to make this decision
• Leads to awareness of non-compliance in an expedited fashion
Consenting Process Reviews

- Randomly select studies and conduct an observation of the consenting process
  - Ask permission of potential participants
  - Partner with the Research Subject Advocate in conducting these reviews
  - Feedback provided to study team after the consenting session
  - Surveys and questions of participants

Consults and informal education

- Building culture of compliance and trusting environment lends toward calls for help and advice versus fear
- Assist study teams with questions about protocol deviations/violations, reporting requirements and creating processes for compliance within their study team activities
- Work with Office of Research Education for training and education for study coordinators and investigators
Creating infrastructure support…..moving from reactive to proactive

- Identification of all Sponsor-Investigators
- Survey
- Query our electronic IRB system
- Benchmarking with other institutions who offer similar support
- Creation of Templates, Forms, Database, Educational Modules, Training of Staff

Feasible

- Hire "great staff"
- Communicate
  - relevant presentations, newsletters, emails
- Build Trust
  - perceptive about customer environment and needs
  - "creating the culture of compliance"

Challenging

Lessons Learned – Tips to create support

- Set the tone and culture of the group.
  - Supportive and not punitive
  - What is the focus? How will findings be received?
- Identify how much FTE will be needed. What services are you planning to provide? Will a "phased in" approach be used?
- Determine early what activities are “out of scope”
More Tips and Lessons Learned

• Consider how you will identify risk areas in your institution?
  • Survey, work with your IRB, department chairs, research administration, etc.
  • Once identified – how will you address and track mitigation activities?

• Identify key departments or areas to partner with for results and improve compliance
  • Research admin and education, Study Coordinator Groups, etc.

Results from Monitoring and Auditing

Track to proactively make improvements
Examples of Common Deficiencies

• Failure to follow the protocol or investigational plan & protocol deviations
  • Violation of inclusion/exclusion criteria
  • Failure to perform required tests

• Failure to maintain adequate or accurate case histories
  • Missing source documents
  • Inaccurate or incomplete source docs

Examples of Common Deficiencies

• Inadequate subject protection, such as informed consent issues
  • Signed the wrong or non-approved consent
  • Missing consent or consented after study procedures
  • Re-consenting issues

• Lack of IRB approval or communication
  • For consent, protocol changes, etc.)
Failure to follow protocol and regulations

- Corrective Action: Ensure protocol is being followed and documentation maintained
- Preventative Measures:
  - Well written protocols (offer template)
  - Use of eligibility checklists
  - Standardize documentation practices with the use of guides or checklists
  - Training study team (and PI) on protocol and regulations

Investigator Oversight

- Corrective Action: Ensure PI oversight and involvement in the study
- Preventative Measures:
  - Study team meetings – discuss protocol requirements, updates, changes, (document the meetings!)
  - Delegate tasks and follow up they are done (by PI and supervisor)
  - Delegation log on file and up to date?
Obtaining Informed Consent

• Corrective Action: Ensure appropriate staff obtain informed consent as required by the protocol and/or sponsor

• Preventative Measures:
  • Create an SOP and train staff on the process
  • Follow flow sheet to ensure consent completed prior to study procedures
  • Partner with IRB for clear direction on re-consenting needs

Partnering activities to decrease risk

• Study Coordination Quality Management System
  • Oversight group to review process & changes
  • Documents for activities and work of study coordination as well as process flows
    • Pre-approval
    • Post-approval regulatory
    • Post-approval finance
    • Subject management
    • Scheduling and ordering
Partnering activities to decrease risk

• Office of Research Education
  • CRC quarterly forums – “Compliance Corner” initiative for 2014 - topics include
    • Adverse event reporting
    • Consent and re-consenting
    • Delegation and investigator oversight
    • Documentation of eligibility requirements

Partnering activities to decrease risk

• Research Finance
  • Compliance and quality team oversee policy adherence and conduct monitoring and audits for financial compliance
  • Code and Coverage Analysis office and post award billing group

• Comprehensive Research Management System Executive Team
  • Issues brought forward for review and applying systems approach to address
Conclusion

• Consider the following key points to move from Reactive to Proactive…
  • Importance of setting the right tone and creating a culture of compliance
  • Invest resources to provide support
  • Track findings from audits and monitoring activities with overall goal to improve and make changes
  • Provide targeted education and training

Thanks for Your Time and Attention!

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