



Creating Infrastructure Support for Investigator Initiated Research

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Objectives for this session

- Discuss support activities for investigator initiated FDA regulated research, including tools and templates
- Describe model of support at Mayo Clinic
- Share best practices and lessons learned

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What is Investigator Initiated FDA Regulated Research

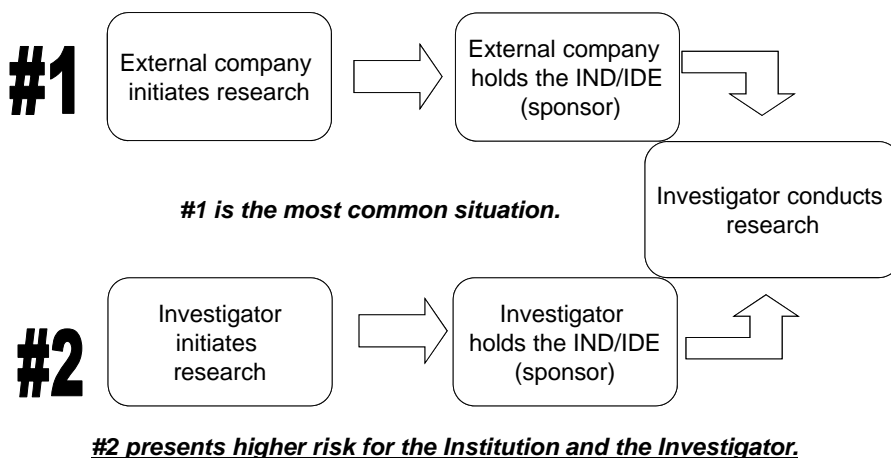
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Examples

- Novel drug (IND- investigational new drug) or device (IDE- investigational device exemption)
- 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

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Two main paths for IND or IDE research



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What is a Sponsor-Investigator?

Investigator conducts the clinical investigation and is responsible to obtain IRB approvals, follow the study protocol, maintain control of investigational product, ensure quality records are complete, file required reports, and oversee the study team.

Regulatory Study Sponsor initiates the investigation and is responsible to obtain FDA approval of the IDE/IND, monitor the collection of quality data, maintain specific records, file required reports, and control distribution of investigational product.

Sponsor-Investigator must meet the responsibilities of both the sponsor and the investigator to ensure the protection of human subjects participating in a clinical investigation.

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Creating infrastructure support.....

- Identification of all Sponsor-Investigators
 - Survey
 - Query IRB system
- Benchmarking w/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

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Mayo Clinic

Support for Investigator Initiated Research

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Mayo Clinic Locations



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Office of Research Regulatory Support

- 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

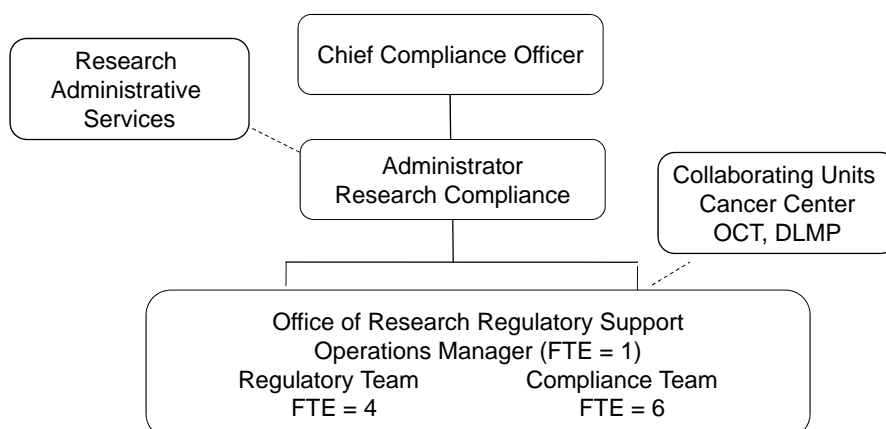
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Office of Research Regulatory Support

- Centralized resource for information, expertise, and support related to the conduct of clinical research from a regulatory and compliance perspective
 - Investigator-initiated Investigational New Drug (INDs) or Investigational Device Exemption (IDEs) submissions
 - ClinicalTrials.gov support
 - Regulatory questions
 - Proactive Review Program

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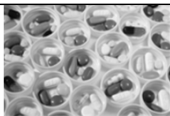
ORRS Organizational Structure



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ORRS Services and Support

IND Applications



Clinicaltrials.gov
oversight



FDA Audit Support



IDE Applications



Proactive Review
Program



Study File Mgmt



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ORRS Services and Support

For Cause Audits



Study Initiation Visit



Consults/Education



Protocol Deviations
Review



Consenting Process
Observations



Tracking Trends



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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

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Office of Research Regulatory Support (ORRS)

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Templates and Forms

IND

IND Application Template

QRG - Using the IND Template

DRUG Protocol Template

IND Annual Report to FDA Template

FDA Communication Log

IDE

IDE Application Template

Investigator Agreement Form Template

QRG - IDE: Mayo PI holds IDE

DEVICE Protocol Template

IDE Annual Report to FDA Template

IDE Device Accountability log

IDE Current Investigator List

FDA Communication Log

FDA Forms

FDA Form 1571 and Instructions

FDA Form 1572

FDA Form 1572 Information Sheet

FDA Form 3674 and Instructions

FDA Form 3500a and Instructions (MedWatch)

Study File Management Forms and References

Study File Management CHECKLISTS for FDA Regulated Studies (Regulatory Binder and Subject Files Checklist)

Study File Management Quick Reference Guide for FDA Regulated Research

Delegation Log

Monitoring Log

Training Log

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Proactive Review Program & Monitoring

- Risk based approach for proactive reviews, includes all Mayo research studies
 - Risk assessment (protocol and study team members) used to select studies for review
- Encompasses sponsor-investigator monitoring
 - Frequency determined by protocol and other factors (S-I and team experience, risk of product, etc.)
- Work with PI/team for process improvements based on findings (quality activities)

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Proactive Review Program & Monitoring

- Regulatory documents/binder review
- Eligibility determinations
- Informed Consent – document and process
- Protocol adherence – are we doing what we said we would do?
- Other assessments of targeted areas

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Monitoring

FDA regulations state that sponsors are responsible for "ensuring proper monitoring" of their investigation(s).
Proper monitoring goes beyond implementing processes to review and correct data errors. It involves regular evaluation of the study conduct and interaction with study team members to help facilitate ongoing study management and compliance with applicable regulations.

NOTE: Recently issued warning letters from the FDA have cited sponsor-investigators for neglecting to fulfill monitoring responsibilities even though they had very acceptable data safety monitoring plans.

Besides Regulatory Compliance, Why Monitor my Study?

Ensure quality and integrity of resulting data to be submitted to the FDA

Assure protection of the rights of human subjects and the safety of all subjects involved in clinical investigations

To support Mayo investigators in upholding their regulatory responsibilities and protecting the welfare of subjects who participate in their studies, trained staff in the Office of Research Regulatory Support conduct regular in-house monitoring of sponsor-investigator initiated studies. This allows concerns to be identified and resolved in a timely manner.

The monitoring plan used by the ORRS follows ICH guidelines for monitoring clinical investigations involving new drugs (including biological products) and devices for human use. Refer to the Study File Management Checklists for documents and records to maintain in your study files so you are always prepared for a monitoring visit.

Sponsor-investigators at Mayo will be contacted by a Specialist to schedule monitoring visits. If you wish to meet with someone prior to that, please see the ORRS Contacts page for the direct phone number where you can reach the Specialist for your department or e-mail the ORRS.

Code of Federal Regulations 21CFR Part 312.50 (Drugs)

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND.....

Code of Federal Regulations 21CFR Part 812.40 (Devices)

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained.....

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Reviews of Consenting Process

- 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 of participants

Education and Consults

- Provide resources for study teams and serve as educators for orientation program and other training sessions
- Provide required training module for sponsor-investigators as per IRB policy
 - Offered on-line
 - Also review educational components “just in time” during initial meetings regarding the planned IND or IDE

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Education and Consults

- Work with CRC Education Group for quarterly “Compliance Corner” Training
 - Identify topics based on identified areas of improvements from proactive reviews, monitoring and for-cause audits
- Communication of findings (general) through presentations to department and other educational initiatives

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Education and Consults

- Building a culture of compliance and trusting environment promotes 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

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For Cause Audits

- Conducted when allegations of suspected or actual noncompliance with federal regulations, state laws, Mayo policies, and/or IRB requirements
- May be referred by IRB, Compliance Office, Participants, Staff, Whistleblower Complaints
- Targeted or full study audit
- Reports and findings are sent back through IRB committee for determination of non-compliance (serious and/or continuing if applicable)

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FDA Inspections – 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)

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FDA Audit Coordination



FDA regulated studies are often subject to audits, so proper preparation and documentation is critical. Adverse audit findings could impact future research at Mayo Clinic and could also lead to limitations on an individual's ability to serve as an investigator in future FDA regulated studies.

Please contact the Mayo Clinic Office of Research Regulatory Support (ORRS) by phone or e-mail as soon as you are contacted by the FDA. The ORRS will help guide you through the audit process and provide tools to make it easier to be audit-ready.

When You Are Contacted by the FDA
Document the details of any contact from the FDA (FDA Contact Name, Phone, Date, who is the PI and the study IRB #) and contact the ORRS as soon as possible either by phone or e-mail. Staff from the regulatory office will help facilitate the process with the FDA.

Once the ORRS is notified of an upcoming FDA audit
You will be contacted by someone from our office to schedule a Pre-Audit Meeting where we will discuss the audit process, identify specific responsibilities for the study team and answer any questions you might have.


When Preparing for an FDA Audit - Use these CHECKLISTS
Organize your study files so documents and records are easy to retrieve during an audit. For additional information, refer to the Study File Management Quick Reference Guide.

Remember that well organized study files will promote self-assuredness as you participate in the audit and will help instill a feeling of confidence for the auditor regarding overall study conduct. Poorly organized study files on the other hand may prompt the auditor to ask more questions, request more files, seek more evidence or even ask to review additional studies.

During the Audit
ORRS staff will assist before, during and after the audit to coordinate logistics, help answer general audit questions and ensure appropriate response and follow-up. Study teams are responsible for providing requested documents and

BEFORE the Audit

The Regulatory Binder and Subject Files are well organized. What else should the study team do to prepare?



Read This Guide!
Tips for a Site Visit

Ensure everyone on the study team who will be participating in the audit reads and understands the material in this Guide.

Here you will find advice on several audit behavior do's and don't's, plus other important considerations to keep in mind when interacting with an auditor. Following the tips you read about in this quick reference

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Study File Management Resources

- Resources for study teams
 - Checklists for FDA and non-FDA regulated study file management
 - Quick Reference guides
 - On-line module and in-person workshop
 - eBinder for ease of maintenance
- Assistance for questions as well as providing tabs to study teams to assist them in organizing study regulatory documents

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- IDE Submissions
- FDA Reporting
- Templates and Forms

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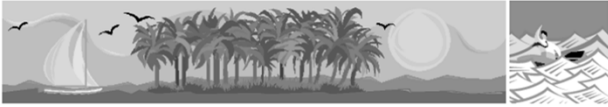
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Study Files

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.

FDA-Regulated DRUG STUDY	FDA-Regulated DEVICE STUDY	NON FDA-Regulated Study
Study File Management Checklist ↗	Study File Management Checklist ↗	Study File Management Checklist ↗
Quick Reference Guide ↗	Quick Reference Guide ↗	Quick Reference Guide ↗

NEW! FOR ELECTRONIC DOCUMENT STORAGE - eBinder Templates are now available for FDA-regulated drug and device studies as well as for non FDA-regulated studies.

Use these templates to set up your system for organizing electronic study files.

STUDY LOG TEMPLATES

Customize these templates for your study and include in the Regulatory Binder.

- [Delegation Log](#) [↗](#)
- [Training Log](#) [↗](#)
- [Monitoring Log](#) [↗](#)
- [FDA Communication Log](#) [↗](#)

Laboratory License and Certification Information

Print and retain CAP and CLIA documents to verify certification

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Regulatory Binder Checklist for FDA-Regulated Studies

Directions: Refer to the Study File Management Guidelines [Quick Reference Guide](#) for detailed information about each section. Please review the Study File Management for Clinical Research [Policy](#) and [Procedure](#) for additional details and information.

IRB number _____ PI name _____

Study title _____

Checklist completed by _____ Date: _____

PI initials indicating that checklist is complete _____ Date: _____

Note: If you are using a Regulatory Binder provided by the sponsor, review the binder to ensure that documents listed in the checklist below are included, but be aware additional documents may be required by sponsor.

Regulatory Binder Checklist				
A. Study Documents				Check one
	Tab or eFolder Label		Documents to include in binder	Yes NA*
1.	Protocol <small>Templates available on ORRS web site.</small>		Include current and all previously IRB approved versions, amendments and/or modifications	<input type="checkbox"/> <input type="checkbox"/>
2.	Informed Consent Form		Include current and all previously IRB approved versions (unsigned)	<input type="checkbox"/> <input type="checkbox"/>
3.	Drug Study	Investigator's Brochure	Include all versions. Alternatively, may include a product/package insert here if there is no IB.	<input type="checkbox"/> <input type="checkbox"/>
	Device Study	Investigational Device Information	Summary document describing the device under study.	<input type="checkbox"/> <input type="checkbox"/>

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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
- Results reporting assistance (direct entry and support for study teams)

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Identifying Applicable Clinical Trials

- Triggers from responses to questions in IRB application once IRB approval is received
- Able to map a subset of the data required in the Clinicaltrials.gov record to our IRB application system. Data is automatically entered in record for study team to 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)

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Results Reporting

- Based on number of trials and efficiency gained with dedicated position, have one FTE for this role (split this between two staff along with other responsibilities)
- Identification of studies needing results posting through our internal system and PRS system
- Senior Regulatory Specialist works with PI and study team to gather information and data, then directly enters results
- Why - savings of Investigator (physician) time

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The screenshot shows the 'Support for ClinicalTrials.gov Study Registration' page. The left sidebar contains navigation links: Home, ASSISTANCE (Study Files, IND Submissions, IDE Submissions, FDA Reporting, Templates and Forms), SERVICES (Monitoring, ClinicalTrials.gov, FDA Audit Coordination), and RESOURCES (Educational Resources, ORRS Contacts, Related Links). The main content area is titled 'Support for ClinicalTrials.gov Study Registration' and features a banner for the Office of Research Regulatory Support (ORRS). Below the banner, there are several sections: 'Registration Requirements' (Assistance with ClinicalTrials.gov, When to Report Results and Adverse Events), 'Online Education: My Learning' (Overview of ClinicalTrials.gov, Registration and Requirements, Short course (10 minutes) through My Learning (LMS), Overview of ClinicalTrials.gov site, Tips on how to enter information into ClinicalTrials.gov), 'Help' (Quick Reference Guide: The following quick reference guides are available for use or printing for future references), 'Basic Assistance with ClinicalTrials.gov' (Information on logging in, locating your study, dosing your study, and releasing a study), 'Tips to Enter Study Information on ClinicalTrials.gov Registration System' (Tips on entering information in certain fields on ClinicalTrials.gov. Answers questions such as: What is a unique protocol ID?), 'Quick Reference Guide: Tips to Specify Arms, Interventions and Outcome Measures' (Includes examples for Entering arms, interventions and outcome measures), 'Determination of Registration Requirements' (Information on what studies are required to be registered on ClinicalTrials.gov, who is responsible, and when to register), and 'Completing FDA Form 3674' (Reference document is intended to help Mayo Clinic investigators when filling out FDA Form 3674 as required; FDA website: www.fda.gov/oc/3674). On the right side, there are 'Access Links' (Log in Screen to ClinicalTrials.gov, First Time users: establish account for ClinicalTrials.gov please email ORRS) and 'Related Links' (NIH ClinicalTrials.gov. registration FAQ's, ICMJE Guidance (Journal Editors)).

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Reportable Events or Protocol Deviations Review Process

- Review submissions timely to provide additional direction to study team; key when a potential PHI disclosure in research
- 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

Study Initiation Visits

- Typically 2-4 hours spent with study team to review overall study and plans for success
 - S-I attends, often for subset of the meeting
- Typical topics covered include: recruitment plans, consent process, study file management, eligibility checklists, AE reporting and study documentation requirements
- Includes documented protocol training for team members and review of delegation log
- Review of sponsor-investigator responsibilities

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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

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CTSA Tools **Investigational Drugs - Devices**

General | IRB | FDA Annual Report | IND/IDE Transfer

IND Number:

Drug Name:

Drug approved for any use: Yes: ☒ No: ☐

FDA Center: CDER ☒ CBER ☐ CDRH ☐

Date Submitted to FDA:

Date Received by FDA:

Effective Date:

IND Status: (per FDA) Pending

Single Patient: Yes: ☐ No: ☒

IND Sponsor (Holder): Mayo Investigator

Training Required: Yes: ☐ No: ☐

Mayo Investigator:

Sponsor Location:

Non-Mayo Investigator:

Drug from Company: Yes: ☒ No: ☐

Company Name:

Any Manufacturing Steps at Mayo: Yes: ☐ No: ☒

Manufacture Location:

FDA Contact:

Phone:

Email:

Other Mayo Research Contact:

Mayo Regulatory Contact:

Notes:

Cancer Center: Yes: ☐ No: ☒

Compounded at Mayo: Yes: ☐ No: ☒

Compounding Location:

Search

Search

Update Reset Search Delete

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Best Practices to consider for Investigator Initiated Research

Points for Consideration

- What is your organization's goal for research?
- Volume of investigator initiated research
- Size and support needed
 - Can support activities be incorporated within another office/team?
- Consider phased in approach
 - What are the critical aspects to provide initially and what can be added next phase

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Key Areas of Support

- Protocol development and writing
- Regulatory writing/documentation and submissions to agency
- Monitoring for participant protections and quality
- Tools and templates, IT system needs
- Education and Training – formal and just in time
- Funding (projects/research and infrastructure support)

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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? Can you implement a phased in approach?
- Determine early what activities are “out of scope”

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More Tips and Lessons Learned

- Consider how you will identify depts. in your institution with investigator initiated activities
 - Survey, work with your IRB, department chairs, research administration, etc.
 - Once identified – how will you address and identify infrastructure support needed?
- Identify key groups to partner with for quality results and improved compliance
 - Research administration, education, study coordinator groups, departments, etc.

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Conclusion

- Consider the following key points when implementing infrastructure and support
 - Importance of setting the right tone and creating a culture of compliance
 - Invest resources to provide services
 - Track findings from audits and monitoring activities with overall goal to improve the research and sustain quality efforts
 - Provide targeted education and training

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Thanks for Your Time and Attention!

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