Study Startup and Initiation – The Agony and the Ecstasy

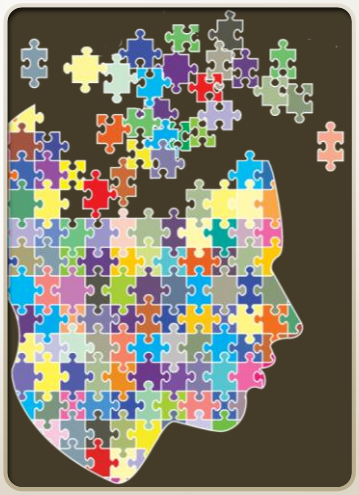
Rana Leed, MPH

Human Research Education Manager, CRRO

Learning Objectives Study Startup and Initiation

Summarize known challenges and best practices for efficient and successful study startup

Identify institutional resources available for study startup processes and requirements



Setting Ground Rules

- Discussion assumes that the protocol is already written – either by external or internal investigator
- Protocol could mean "INSPIR application" (that's your "study plan") or an actual protocol
- Presentation will make specific references to steps or processes that might only be relevant to
  - Industry sponsored studies
  - Externally-managed multi-site research
  - Studies with a drug or device intervention

  But → Many of the steps or processes are applicable to all types of studies
- Discussion is more of a thought-exercise rather than proscriptive
  - Study startup is not a once-size-fits-all – important to make decisions and plan according to the study needs, team needs, specific to the each study

Happy to answer questions during and after presentation about applicability to your specific study

<u>The Agony and the Ecstasy</u>
Study startup, study initiation –
Certainly not an exact science, maybe more like an art?

Presenter Background and Story – Study Startup Expertise

Study Startup – Relevant to all studies

- IRB submission and approval
- Development essential documents –

  Participants
  - Case Report Forms – data collection forms – data entry/collection system
  - Source documentation
- Developing essential documents –

  Regulatory
  - IRB approvals
  - Study team training
  - Delegation log
- Communication planning

- Training for all staff, all roles
  - Protocol and general
  - Having training doesn't mean someone is automatically competent
    - Practice and mentoring still needed
  - Assessment of competencies to do delegated tasks
- Dry Runs
  - Ensure adherence to regulations and policies
  - Establish best practices
  - Ensure consistency in processes and data collection

Study Startup – Interfacing/Interactions

- Study staff role is sometimes just to move all processes forward on multiple fronts, simultaneously. Reliant on other groups/entities to approve or manage things
- Internal and external entities -- some depending on type of study and source of funding
  - Industry sponsor or Lead Team at another academic medical organization
  - Investigational Pharmacy Services (IPS)
  - IRB
  - Grants office:
    - BMC Clinical Trials Office (CTO)
    - BU Office of Sponsored Programs (OSP)
  - Clinical Engineering for investigational AC or battery-powered device
  - BU or BMC Communications for advertisements
  - Nursing department/sign-off training
  - GCRU
  - Radiology
  - Laboratory services
  - Velos set-up (CTO)

- Important to remember that you represent ONE study
- There are always competing interests and timelines
- Allow people the grace and patience to complete their job
- Start processes early

Industry-Sponsored + Externally Funded Specific Steps

The next several slides pertain most specifically to those studies that are sponsored by business and industry or those that have some source of external funding and are initiated by somebody outside of BU/BMC

Primary Examples

- Clinical trial from Pfizer with an investigational new drug
- Multi-site study funded by the NIH but the Lead PI and team is at an external institution

Feasibility Assessment

- Assessment Points
- Study design
- Ability to recruit sufficient number of eligible subjects – set goal
- Staff time requirements and budget
  - Investigator, coordinator, whole team
- Lab tests and procedures
  - Able to do and have the space to do
- Space and equipment
  - Study files and binders
  - Special equipment needed
  - Office space
  - Refrigerator or freezer space
- Operationalization of protocol

ICH GCP 4.2 Adequate Resources

- 4.2.1 The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
- 4.2.2 The investigator should have sufficient time to properly conduct and complete the trial
- 4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities… to conduct the trial properly and safely.

Best Practice – all studies can benefit from this process

- Applies to all studies – industry sponsor, multi-site investigator initiated, local investigator initiated
- Either assessing your own site, a sponsor assessing your site, you assessing another site

Next Steps: Site Selected

- Clock has started ticking – timeline usually provided during site selection process – meet those goals – or communicate that goals have changed!

- Priorities:
  - Negotiating contract - Clinical Trial Agreement (CTA) or other agreement
  - Negotiating budget
  - IRB submission
  - Operationalize the study
  - All must be approved or completed prior to first participant enrolled – sometimes before first participant can be screened

Budget and Contract Process

- All studies with external funding – sponsored, NIH, multi-site, etc
- Depending on who is "receiving" the funds – different departments will handle process and negotiations
  - BU Office of Sponsored Programs (OSP)
  - BMC Clinical Trial Office (CTO): Required if interfacing with any BMC clinical services
- Budget finalization in relation to IRB submissions
  - Dependent on study – neither are required to come first
    - Industry sponsored study – probably fine to submit to IRB without final budget but should check with OSP or CTO
    - Investigator-initiated – dependent on funding source – does funder require IRB approval to release funds? Expecting budget cuts to impact study plan or procedures?
- RPN Workshops
  - Clinical Research Budgets – The Fundamentals (March 2021)
  - Clinical Research Budgets – Advanced Topics (May 2021)

Budget Questions

- Primarily industry sponsored studies but also some multi-site studies
- Does the budget include direct line-items for:
  - Staffing
  - Study start-up activities
  - Supplies
  - Institutional charges: IRB, IPS, GCRU
  - Participant reimbursement or compensation
  - Recruitment efforts
- Payment milestones
  - Per participant – at what timepoints
  - Per data collected –at what timepoints
  - Other milestones
- Non-refundable or required payments regardless of milestones
- If you are able to see the budget during feasibility – should assess all of the above at that point

General Startup and Initiation Steps

The rest of the slides are all relevant to any number of studies – regardless of sponsor, funding, design or type

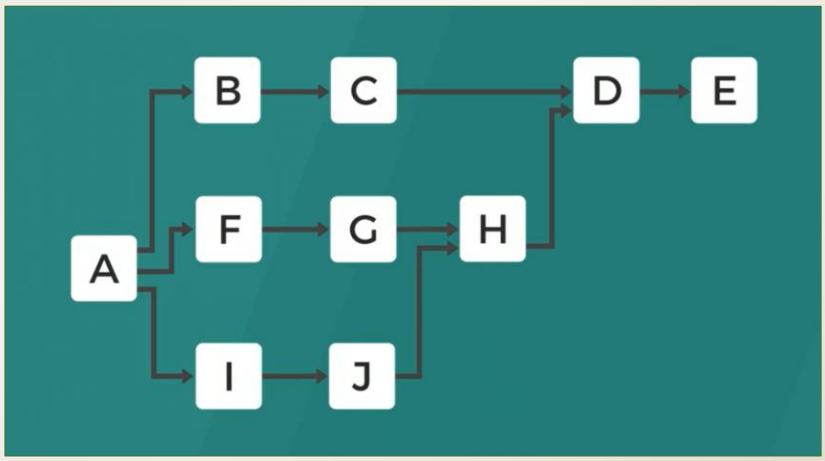
Primary Examples

- Clinical trial from Pfizer with an investigational new drug
- Multi-site study funded by the NIH but the main PI is at an external institution
- Single-site study funded by the PI's department here internally
- Observational or interventional studies
- Data collection or specimen collection studies

All studies should have some amount of planning prior to "opening"

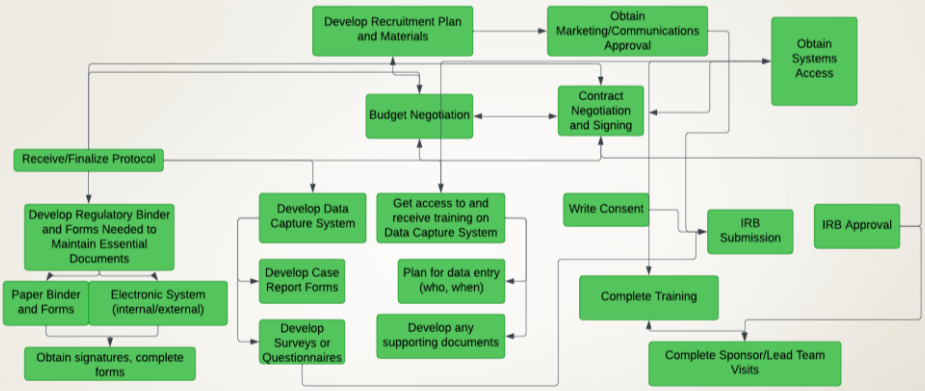
Planning Importance – when study "hits your desk"

- Develop calendar for all associated steps (plan both submission and estimated approval dates)
  - IRB approval, budget approval, contract approval…
  - Study document development – consent, recruitment materials, forms, logs, binders
  - Systems access and approval
  - Training
- Plan for adjustments
  - Allow for "wiggle room"
  - Update calendar as needed
  - Communicate those updates as needed
- Develop Tracking System
  - Document status of each process – what is needed, next steps
    - Think proactively - getting signatures, PI availability, avoid getting "stuck"
  - Track status of all documents - keep tabs on progress, documents received versus outstanding, adhere to timeline/due dates



Parallel and Circular Processing – Account for →

- Several initiatives occurring at same time with different deadlines/timelines and different needs
- Some initiatives may start, then stop, then start again
- Some processes or steps might need to be repeated if changes occur based on a different process or step
- Some processes can be initiated (contract, budget, IRB) but will take time before final approval



This is only a few of the steps – it's already very messy and those arrows are going every which way.

- ✓ Not all steps will apply and some of those steps can be done out of order. Take the time in the beginning to plan this out for your specific study and specific needs.
- ✓ What can you do right away so you can move on to other steps?
- ✓ What will take a long time so it needs done right away?
- ✓ What are the steps that you can't complete until most other steps are complete?

Decide and document →Who, What, How, When

Study Preparation during Initiation (1 of 2)

- While working through contract, budget, and IRB approval →
- Logistics – Operationalize the Study
  - Where is the study taking place?
  - Inpatient? Outpatient?
  - Map out study visits and what study staff needed for each (MD, RN, CRC)
- Establish study timeline/processes with necessary departments
  - Pharmacy
  - GCRU
  - Laboratories
  - Radiology
- Determine what study specific training needs to take place
- Efficient methods of communication, providing updates, triaging questions/concerns
  - Ensure ongoing conversation throughout study with team and necessary departments

Study Preparation during Initiation (2 of 2)

- Trainings must take place prior to staff working on study
  - Institutional requirements (human subjects, GCP, SOP…)
  - Protocol-specific training
  - Role-specific training
  - Document training for all staff: CRRO documentation tools for training logs
- Schedule presentations for key departments and clinicians:
  - Ensure they are aware of study timeline and their responsibilities
  - Ensure that referral systems are set up
- Standardize study procedures/data collection
- Develop SOPs, MOPs, checklists, templates, logs, etc

Operationalize the protocol

What is needed to complete study?

- Clinic space
- Procedure rooms
- Staffing
- Blood draws/laboratory processing
- Radiological imaging
- Source document creation
- Regulatory documents and binder
- Access into systems (internal or external)
- Training

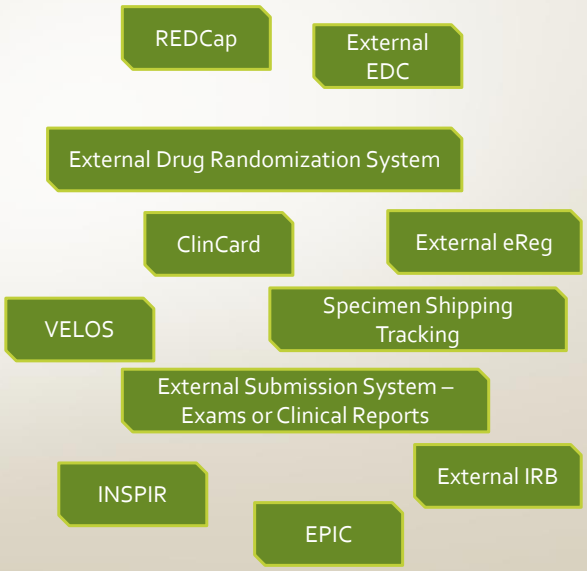
What processes need to be developed?

- Who, what, when, where, how
- Recruitment/screening
- Consent
- Study procedures
- AE monitoring/reporting
- Deviation monitoring/reporting
- Data collection
- Quality monitoring

Spend time reading the protocol – even if you wrote the protocol. How will you ACTUALLY do the thing that the protocol says?

Systems Access, Training, Completing

- What are the systems that will need to be used?
- How long will it take to get access to those systems?
- Who needs access to those systems?
- What training is required for those systems?
- What training would be useful for those systems?
- Where will you document that training?
- Are there manuals that can be reviewed?
- Is the system something that needs to be monitored or updated as participants are enrolled or visits occur? Who will do that?



Supplies Purchasing and Receiving

- What do you need to complete the study and visits?
  - Procedural or clinical equipment
  - Three-ring binders
  - Blood tubes or other specimen collection items
- How will you purchase? Who is paying for?
- Who will receive – shipping address and person to receive
- Where will you store those supplies?
- How much should you order at once, what has expiration dates?
- How will you balance having enough on hand for enrollment but not too many if your goals aren't met?
- What labeling do you need for those supplies so it doesn't get used by others or lost?

Develop Recruitment and Enrollment Plan

- Develop advertising materials
  - For participants (obtain communications approval, submit to IRB)
  - For clinicians (materials don't need submitted to IRB, plan does)
- Identify potential barriers or challenges and plan how to address
  - Competing studies, long visits, difficult procedures, location issues
- Identify possible successes and plan how to address
  - If your recruitment plan is amazing and works right away – do you have the staffing, resources, time to enroll more than a few participants at a time?
- Plan: How, When, Who, Where → Submit to IRB
  - Identify potential participants
  - Screen potential participants
  - Obtain informed consent

IRB Submission Planning

Review all documents needed for submission

- This is just an example – might have more!
- Protocol
- Consent Form
- Investigator brochure or package insert (if applicable)
- Questionnaires or surveys
- All participant-facing materials
  - Recruitment and advertisement
  - Intervention-related materials
  - Visit-related materials (maps, reminder letters, calendars)

Check for completion

- All documents uploaded
  - Only correct, most updated version
- All staff added
- All questions answered in full

Request a CRRO pre-review consultation

Essential Documents – Developing and Maintaining

- These are just some of what are considered Essential Research Documents – SOP and ICH has more extensive list. Specific studies might have more than what is listed.
  - ICH GCP Guidance, Section 8: Essential Documents for the Conduct of a Clinical Trial
  - SOP: Essential Documents
- Track status of documents and completed processes
- Save and document all/significant items
- Paper, electronic, cloud-based, hybrid – depending on study
- Generally, participant files and regulatory files are not kept in same paper binder
- Somebody should be delegated the responsibility of these files (maintaining and reviewing)
- Obviously not all of these will be available during startup – but plan should be in place for collecting and maintaining. Have binders set up and ready to go.

Regulatory Files → General Study Files

- Informed consent and HIPAA Authorization - blank
- Case Report Forms and Source Documents including Questionnaires or Surveys – blank
- Protocol, MOP, study-specific SOP, IB
- IRB submissions and approvals (Initial, amendments, continuing reviews, prompt reporting/RENIs)
- Deviations, Adverse Events, Safety Events
  - Reports to IRB/others, logs
- Communications to sponsor, lead team
- Team member documentation
  - Delegation of Authority log
  - Training log and certificates if applicable
  - CV and resumes
  - Licensure
- Participant Logs (Screening, Enrollment, Randomization, etc)

Participant Files → Specific to an Individual

- Informed consents and HIPAA Authorizations – signed
- Case Report Forms and Source Documents – completed
  - Includes questionnaires and surveys
- Shipping documentation
  - To participant, to sponsor, to lab, to etc
- Communications to participant
  - Letters, emails, telephone calls

Site Initiation Visit (SIV)

- Usually only done with multi-site industry sponsors or NIH-funded studies
- Ensure understanding of protocol and responsibilities
- Ensure necessary resources are available
- Ensures all training is complete

Recommend doing an SIV regardless of funding/sponsor status →

All studies will benefit from "all hands on deck" planning and confirming meeting

Discussion points

- Protocol purpose, design, procedures
- Reporting
- Intervention (drugs, devices, other); storage, instructions, processes, accounting
- Inclusion/exclusion criteria
- Recruitment/screening/enrollment
- Informed Consent
- Randomization processes
- Withdrawal processes
- Case report form completion and data entry
- Source documentation completion and filing
- Adverse Event and Deviation monitoring, assessing, reporting
- Compliance
- Quality management
- "Trial walk-through"
- Review of site regulatory files

Dry Runs – Making Time to Save Time

- Perform all study procedures without a "real" participant
- Start as early in the process as possible and go the whole way through final data collection
- Provides opportunity to identify – Examples →
  - Challenges with physical location
  - Better understanding of time spent on each activity
  - Clarity on staffing needs for each activity
- Go through all physical steps and locations – Examples →
  - If participants will be told to visit phlebotomy after the consenting visit and to them come back for the rest of the visit – plan that walk out and figure out how long that could take
  - If you need to get sponsored-provided equipment from your office to the clinic – plan that out, which elevator is best, which routes to avoid
  - If using sponsor-provided platform for randomization – ask for test usage and see if you can get on from different computer stations

Dry Runs – Establish visit flow and identify challenges

- How long will the visit take?
- In what order are the procedures done?
- What needs prepped before the visit – how long does that take?
- What is the follow up after the visit – how long does that take?
- Who needs to be available (MD, RN, CRC)?
- What is the equipment needed, ancillary services, etc?
- What is the data that is collected as part of the visit – are there forms for this ready?

➢ Based on these dry runs – can develop checklist of what happens at each visit
  - Should include who performed the procedure, who was present – including signature lines if applicable/relevant
  - Doesn't necessarily mean what happens literally during the visit with the participant – can also include the pre and post work that is done
    - Examples -- order placed and signed, data entry, specimen shipped

Dry Runs – Recommendations

- Do more than one dry run – at different times of day or on different days
- Do with different people leading or present
- Include everything – don't make any assumptions about how you think something should or could happen – things change and different staff or participants have their own specific needs
  - ✓ Reviewing medical records
  - ✓ Phone screening
  - ✓ Consenting
  - ✓ All visits
  - ✓ Data entry
  - ✓ Specimen preparing and shipping
  - ✓ Randomization
  - ✓ Working with Investigational Pharmacy

Communication Plan

- Plan an efficient method of communication, providing updates, triaging questions/concerns
  - Think big and small (internal and external)
    - Who is in charge of communicating with sponsor or lead team?
      - Sending regulatory documents vs setting up monitoring visits
    - How will adverse events and deviations be communicated to PI for assessment?
    - How will coordinators communicate screening status of individuals or upcoming visits?
  - Be literal – have a document that includes contact information and outlines processes
    - Sometimes it makes sense to ask people "what is the best way to contact you in an emergency or if the response can wait a day or two?"
    - Example:
      - PI: list email, cell phone, pager
        - If suspected Serious Adverse Event – send text? Or is email sufficient because they check often?

Standing Meetings

- Set to occur on regular basis
- Are not routinely canceled
- Have set, recurring agendas
  - Recruiting and enrollment, enrolled participants and upcoming visits, adverse events, deviations, upcoming IRB submissions, planned amendments, staff time off, etc
  - Use agendas to take notes - maintain as part of study documentation
- Discuss successes and problems or issues
- Involve primary team members, can involve others as needed on rotating or as needed basis
- Should occur fairly often during startup planning/initiation and can occur less often as enrollment and study procedures become routine
- Should not occur less than monthly

Develop Repeatable Processes and Forms

Processes are often repeatable, duplicatable across studies
- ★ Less effort each time you implement - expectation setting, understandable process
- ★ Provides "selling point" for industry sponsored studies and multi-site studies during site selection processes
- ★ Success often has trickle-down/across benefits - models good practices for other teams

Documents are often repeatable, duplicatable across studies
- ★ Templates for logs, checklists, MOPs

Identification of protocol "pain points", often similar across studies
- ★ Ask for clarification from sponsor or lead team before enrollment starts
- ★ Work with clinical care team early in process to prevent pain points

Processes, documents, pain points are often similar across studies within divisions or groups
- ★ Don't work in a silo – if you are struggling, others might be struggling too
- ★ Reach out to colleagues

Next time – work smarter, not harder

BMC Clinical Trial Office (CTO) – *Key Highlights*

- Research fee schedule pricing for participant care costs for all studies using BMC space, services, items, or interventions
- Setting up a study in Velos and Epic helps to reduce billing errors
- ClinCard management which is the BMC preferred method for programmatic and research participant reimbursements
- Pre and post award financial support of industry sponsored clinical trials
  - Reach out as soon as there is a CDA to sign

➢ BMC Clinical Trials Office
➢ CTO@bmc.org
➢ CDA/NDA Intake Form
➢ CTO Services Intake Form

BMC Research Operations

BMC Clinical Research Network (CRN) – *Key Highlights*

- Developing community driven approaches to research awareness and engagement
- Provides direct study team support for institutional prioritized, population health driven protocols, with under-resourced PIs
- Drives change around quality improvement initiatives for BMC and BU study teams

➢ CRN@bmc.org

Investigational Pharmacy Services (IPS) – *Key Highlights*

Role of IPS

- Provide support for all clinical drug studies conducted at BU/BMC
- Responsible for the receipt, storage, accountability, dispensing and disposition of all research-related drug products
- Ensure the investigational products are used appropriately to maximize study human subject protection
- Ensure compliance with applicable regulatory and protocol requirements regarding the use of investigational products

Services Offered

- Study Start-Up and Close-Out
- Inventory Control and Storage
- Dispensing and Accountability
- Assist with database maintenance (Vestigo, EPIC)
- Regulatory Documentation
- Randomization and Blinding
- Compounding/Repackaging (if feasible)
- Collaborating with monitors and auditors for site and remote visits including tours for SIVs

Submit Protocol Planning Worksheet along with protocol, investigator brochure, pharmacy manual – will kickoff planning discussion and budget agreement drafting → Under Forms on CTO website

General Clinical Research Unit (GCRU) – *Key Highlights*

- Located on the 8th floor of the Evans Building and beyond through its additional outreach services "GCRU Without Walls"
- Provides experienced research staff (RNs, research assistants, phlebotomists) to conduct research activities in clinical settings
- Works with the Research Navigator Team to provide implementation support
- Complete form to conduct study at the GCRU (current fee schedule available)

Clinical Data Warehouse (CDW)

- Centralized resource to access patient-level and population-level data for research
  - Simple Counts: aggregate counts for study planning, feasibility analysis, grant submission
  - Recruitment: from EMR, can pull basic info for those who might be eligible
  - Data extracts: from EMR, can pull all required study variables instead of manual chart review
  - Linked data extracts: can link EMR, community health center data, claims data, and other data sources
  - Custom reports: recurring data extractions, automatic prospective reports, patient snapshots
- Submit a Request
- Contact CDW

Standard Operating Procedures

- Cross-institutional collaboration between Boston University Medical Campus and Boston Medical Center
- Effective January 1st, 2023
- Found within INSPIR help menu

- Set of written instructions that document routine activity followed by an organization to comply with regulations
- Form an integral part of a successful quality system as it provides individuals with the information to perform a job properly, and facilitates consistency in the quality and integrity of work performed
- Guidance on how to complete some of the daily activities of a research team and also address overarching structural activities

- The SOPs will specifically guide clinical research studies that target BMC patients, use BMC patient data, or utilize BMC facilities and/or services.
  - BMC patient: any individual with a clinical encounter generating a BMC-specific medical record
  - BMC patient data: patient data that is derived from BMC medical records and/or systems
  - BMC facilities: clinical or non-clinical space owned or operated by BMC
  - BMC services: a unit or group operated or managed primarily by BMC staff

Recommendation

- SOPs provide excellent guidance for studies that are outside of the scope and can be followed/used for any study

Standard Operating Procedures

- Highlights for Startup and Initiation
  - Essential Research Documents
  - Delegation of Authority and Responsibilities
  - Research Team Competency
  - Really – all of them!
- Clinical Research Seminar: November 2022
  - BMC Clinical Research Standard Operating Procedures Implementation
- Clinical Research Times
  - December 2022 Feature Article: Spotlight on SOPs - A Bright New Future
  - Monthly starting January 2023, Spotlight on SOP section

Adverse Event Monitoring, Assessing, and Reporting
Case Report Form Completion
Delegation of Authority and Responsibilities
Essential Research Documents
External Audit Preparation
Informed Consent Process
Institutional Research Policies and Guidance Documents
Participant Withdrawal
Protocol Deviation Reporting
Quality Management
Research Team Competency
Research Training
Site Monitoring Visits
SOP Management
Subject Recruitment

Key Takeaways and Highlights

- Study startup and initiation can take a while – use this time to set yourself up for success – sometimes rushing just means delays after enrollment starts
- Communicate during startup on timelines, expectations, next steps
  - Research team (PI, Co-I, coordinators, etc)
  - Internal and external groups and stakeholders – even if you aren't expecting or need a response
- Reach out early in process to the groups who you'll need to interact with throughout study
- Start building and submitting intake forms to build in systems early
  - CTO, VELOS, ClinCard, IPS, CDW, GCRU, REDCap…probably many others!

Additional Resources and Training

- BMC Research Operations
- Request CRRO consultation for implementation planning
- Clinical Research Seminars: Upcoming and Previous
- RPN Workshops: Upcoming and Previous
- Clinical Research Times – monthly newsletter

Questions and Answers

Was there anything that you struggle with or have questions about that I didn't mention? What did I miss?

Do you have any recommendations for startup planning? What has worked well for you?

If we did this talk again, what information should I include?

Put your thoughts in the chat or unmute! Let's talk!