MULTI-SITE STUDIES: EXPONENTIALLY MORE WORK AND MORE FUN THAN SINGLE-SITE STUDIES

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INTRODUCTION

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EXPECTATIONS AND AGENDA

- Agenda
  - Review basic definitions
    - Focus on best-practices at each stage of study
    - Site Selection
    - Startup
    - Open and Enrolling – Through Final Data Collection
    - Site Closure
  - Case Study Discussion – Provided examples but let's also talk about challenges you might be having or envision with multi-site studies
- Ask questions!
- Out of Scope
  - Will not focus on FDA-regulated studies
  - Will not focus on DSMBs
  - Will not focus on budget or contracting

- ✓ Learn how to apply best practices in single-site management to multi-site management
- ✓ Identify challenges and techniques for addressing them in multi-site study management

<u>Your Mileage May Vary</u>
Depending on the size of your multi-site study, some of these recommendations not might make sense. Up to you to "fit" the recommendations to your study needs and not necessarily to your budget.

This presentation isn't meant to be exhaustive with processes, steps, or requirements. There are always institutional or study nuances that cannot be addressed or might even contradict what is included.

DEFINITIONS

Just what do these words I keep hearing mean?

DEFINITIONS (1 OF 4)

- Multi-Site: the same research procedures from the same protocol are being conducted at more than one site with each site under the responsibility and control of a local Site Principal Investigator.
- Sometimes **institutions define site as a specific FWA**, regardless of the local Site Principal Investigator
  - This might be ONLY for IRB submission purposes but NOT for how responsibilities are delegated, how study documents are completed, or even how FDA will request things.
- **Site ≠ Physical Location:** often a "site" can have several physical locations where recruitment or research procedures are taking place, even including multiple clinics.
  - Main hospital with satellite sites would generally not be multi-site unless there is a local Site Principal Investigator who has complete responsibility for the activities and participants at that specific site.
- **Cooperative or collaborative studies:** when sites are conducting different parts of a study – these parts could be procedures, interventions, or even data analysis. Generally speaking, these are not considered "multi-site" per NIH rules but there could be institutional or funding nuance.

DEFINITIONS (2 OF 4)

- **Lead Team or Lead Site**: Often used interchangeable but some subtle differences. Sometimes these are two different "groups", sometimes the same.
  - **Lead Team**: Responsible for the overall study at all sites. Generally, a Study Principal Investigator, Project Manager, Regulatory Manager, Data Manager, Biostatistician, etc.
  - **Lead Site:** Responsible for enrolling participants at the same institution as the Lead Team. Might be the same as above but could be different. Will usually also include coordinators. The Study PI might decide that they are too busy and will have a Site PI responsible for local enrollment.
- **Coordinating Team**: Sometimes this is the Lead Team but there also could be a different group that manages the overall study or pieces of the overall study. Could be at same institution as Lead Team but not necessarily. Could be a commercial/industry organization.
- **Data Coordinating Center**: Different group that handles specifically data including the EDC build and queries. Could be at same institution as Lead Team but not necessarily. Could be a commercial/industry organization.
- **Contract Research Organization (CRO):** Most often used with standard industry sponsored studies but other studies could contract pieces of the management or oversight to them. Examples – IQVIA, ICON, Medpace, PPD.
- **Participating Site**: These are the sites where the research procedures happen including recruitment, enrollment, intervention, and data collection.
- **Study Principal Investigator**: The individual who has overall responsibility for all sites and participants.
- **Site Principal Investigator**: The individual who has overall responsibility for one specific site.

DEFINITIONS (3 OF 4)

- **Startup Packet**: the group of documents that a Participating site is sent by the Lead Site, must contain everything they will need to "start up" the study. Sometimes the budget and contract is sent by a different person/group or separately from the study-specific documents like the protocol and consent template.
  - Should have "packets" for all document changes (protocol amendments, consent updates, etc)
- **Essential Documents**: those documents that individually and collectively permit evaluation of the trial conduct and data quality. Together, demonstrate compliance of all involved with protocol, regulatory requirements, and good clinical practice. ICH GCP Section 8 - Addendum
- **Investigator Site File (ISF):** Essential documents about the site, maintenance is the responsibility of the site, site should retain control of original documents but this isn't a rule.
- **Trial Master File (TMF):** Essential documents about all of the sites and overall study management documents, maintenance is the responsibility of the sponsor (Study PI), site-specific documents should be copies.
- **eRegulatory Binder**: Cloud-based system that can contain the TMF, the ISF, the TMF + all ISFs, or some combination of these.
- **Electronic Data Capture (EDC):** Usually a cloud-based system for data capture that all site staff have access to for entering data. Should allow for data quality and monitoring.

DEFINITIONS (4 OF 4)

- **Single IRB review**: required for all multi-site studies with funding from federal agencies who are Common Rule signatories – this is all DHHS organizations which primarily means NIH.
  - Some NIH nuance – only non-exempt human subjects research with multiple sites that are all conducting the same protocol and procedures
- **sIRB/Single IRB vs cIRB/Central IRB**: Essentially interchangeable but:
  - **sIRB** – generally only used when referring to an IRB that is reviewing one study
  - **cIRB** – generally only used when referring to an IRB that reviews a consistent group of studies
    - Example: NCI's Central IRB that reviews all Phase 3 Adult Cooperative Group studies
- **IRB of record:** IRB that is reviewing the study for all sites
- **Reviewing IRB**: IRB that is reviewing the study for all sites (SMART IRB term of choice)
- **Relying IRB**: Each of the site's IRB that has ceded review to a single IRB (SMART IRB term of choice)

DEFINITIONS –*STRUCTURE EXAMPLES*

Example #2

- Study PI at Institution X
  - Enrolling and responsible for participant activity
  - Has team of project, regulatory, data managers
  - All overall activities take place at X and by the Study PI
- Participating Sites with local PIs

Example #1

- Study PI at Institution X
  - No enrollment at X
  - Enrollment at X
- Site PIs at two affiliate locations of Institution X
  - Study PI is not responsible for participants at those sites
- Participating Sites with local PIs
- Coordinating Center at Institution Y
  - Responsible for project management including communication and meetings with sites
  - Responsible for regulatory management including TMF and sIRB submissions
- Not responsible for data or FDA submissions – remains with Study PI at X

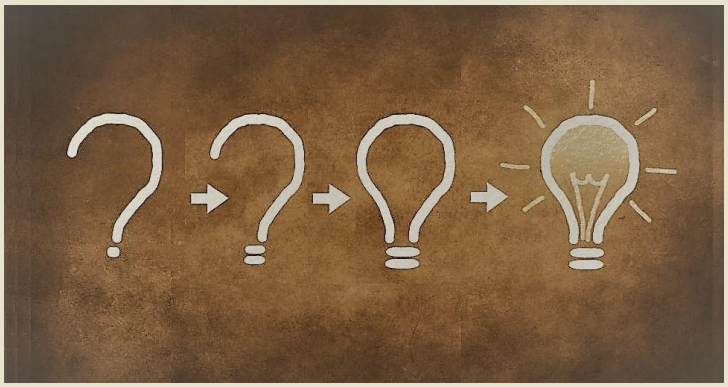
Example #3

- Study PI at Institution X
  - Enrolling and responsible for participant activity at this site
  - Has team of project, regulatory, data managers
  - All overall activities take place at X and by the Study PI
- Participating Sites with local PIs
- Data Coordinating Center at Institution Y
  - Responsible for EDC build, data queries, and quality assurance
- Clinical Coordinating Center at Institution Y
  - Responsible for FDA submissions, TMF, DSMB

Four Basic Activities – Can happen at any number of "sites", at least two but could be more.

- Overall study design and responsibility
- Participant Enrollment and Procedures
- Data Analysis
- Quality Assurance and Safety Monitoring

DEFINITIONS – *OTHER CONFUSING TERMS?*



Are there other words or terms that you've heard that you aren't sure about?

Either about multi-site management or research in general?

FOOD FOR THOUGHT

General recommendations and best practices

GRANT WRITING

- DO NOT put multi-site research into grant without confirming with IRB – might need to submit with grant "letter of support" that IRB will review all sites
- DO NOT put multi-site research into grant without budgeting positions that are solely devoted to site management or at least some significant percentage of time
  - Coordinator should not be expected to project manage
  - Coordinator should not be expected to manage regulatory needs (IRB, documents)
  - Local recruitment and participant activity is a full-time job – do not expect your coordinator to also do two other full-time jobs

SCALE-UPS

- In some cases, a study might be started as a single-site and then scaled-up for additional sites
- Need to be aware that it's not just a one-one ratio in terms of work and budget needs
- Think very carefully about how this will be operationalized – what needs to be changed in procedures or data collection to allow for additional sites

FEASIBILITY – LEAD TEAM

- Before starting any (multi-site) study – during grant writing and study planning – the Lead Team and Study PI should think very carefully about →
  - Staffing resources – is there room in the budget for a project manager, data manager?
  - Staffing resources – if they have time in their own schedule to answer questions (could be many, many more questions than a single-site)
  - Cost – multi-site studies can get very expensive, very fast – each site can increase the cost
    - Lab supplies – blood tubes: purchase for all sites, ship to sites, ship to central lab from sites
    - Drug intervention – shipping to each site, if study drug shipped back to lead team for destruction
  - Monitoring – study will probably require at least some on-site visits, cost of travel + hotel
  - Requirement for research question – does it really need x number of sites/participants?

BEST PRACTICES ARE BEST PRACTICES

Generally – any best practice for a single-site study becomes even more important for multi-site study

Staffing

- Be realistic and honest with how much time actual study procedures take as well as overall management needs
- There is a line between being busy and not meeting deadlines or targets because of overworked staff

Budget/Costs

- Have an actual budget spreadsheet with all line items included including staff time, internal charges or fees, any purchases – all of it
- Each item should come from an actual source of money (future or current)
- If the plan is to apply for a grant to cover something – what happens if grant isn't awarded?

Planning

- Spend time operationalizing the study – figure out how to do all the steps
- Include enough time with buffers for when things need to happen

Meetings and Communications

- Plan for when meetings need to occur, who will attend, how notes will be taken and distributed
- Who is the main point of contact?

SITE SELECTION

How do I pick the right sites to ensure a successful study?

FEASIBILITY –PARTICIPATING SITE

Should be an actual process – NOT just the PI's colleagues from their fellowship program or who they hang out with at national conferences. *THIS HAPPENS ALL THE TIME.*

Process

- Where will you advertise? Think about this as recruitment of sites.
  - List-serve? Known clinicians working in population?
- Before the grant is submitted or after?
- Qualtrics or REDCap to collect data from sites (any online system can work)
  - Easier for sites to submit
  - Easier for Lead Team to review, sort sites

Questions

- # of patients with specific eligibility criteria in specific amount of time
- # of estimated enrollment based on the patient population
- HOW/WHY they picked those numbers
- Expected site challenges
- Staffing plan (ask about number of coordinators, managers, etc and if they will need to hire or not)
- Current standard of care – does it align with study procedures or contradict study intervention?
- Timeline – IRB review, contracting, budgeting, hiring, startup
- Access to systems – does IT block sites, what have they used before?
- Contact information – not just investigator!

FEASIBILITY –PARTICIPATING SITE

Include time for a complete and compliant feasibility process during grant writing, planning, or startup.

Contracting

- Will you require sites to sign a CDA?
  - Confidentiality Disclosure Agreement
- Reach out to contracting group for assistance with this decision/process
- BU: Office of Sponsored Programs or departmental contact
- BMC: Clinical Trials Office

Documents

- What do you need to share with other sites and investigators for them to be able to evaluate the study and if they can participate?
  - 2-3 page study summary
  - Budget estimates or costs
  - Feasibility survey

EVALUATING AND SELECTING SITES

- Have a plan for how sites will be chosen before sending out survey
  - When and how will sites be told they are chosen?
  - Also need to tell sites they are not chosen – be prepared to answer why
- What will be weighted more than others?
  - Example – a site that estimates contracting to take a year might be worth it if they have a very large patient population
- Responsiveness to survey and questions, completeness of information on survey – general vibes – this is most likely how they will perform during the study
  - If a site is disorganized during feasibility or unable to complete something on time without any communication will most likely not be a successful site without significant managing
- Have a plan for when startup will begin and communicate that with sites

STARTUP

Now that I have my sites picked, what do I do? Can I get started?

STARTUP: TWO MAJOR TIME POINTS

Before Sending to Sites

- Build EDC
- Develop CRFs, Surveys
- Develop "Management" template documents like Delegation Logs
- Obtain IRB approval and maybe start sIRB process

After Sending to Sites

- Collect Site Documents like Delegation Log, CVs and Resumes
- Setup recurring meetings for sites
- Answer questions
- Start sIRB process or collect IRB approvals

DO NOT send "startup packets" to sites until EVERYTHING is confirmed and finalized including EDC build, all documents (protocol, consent template, case report forms, surveys). Startup packet should ONLY contain final versions. If you plan on updating or changing things, do not send out startup packets.

BEFORE SENDING TO SITES

- Some of work can be ongoing during feasibility but should absolutely be done before sites are sent the Startup Packet
- Goal is not to send out any corrections, updates, additional documents – ANYTHING ELSE ADDITIONAL OR DIFFERENT – after the Startup Packet goes out.
  - Additions or changes create significant problems – confusing for sites to know which version of documents to use or which procedures are correct, training logs might have to be redone
- DO NOT RUSH PREPARING FOR SENDING EVERYTHING TO SITES

Final Documents	EDC	IRB Approval	Budget and Contract

• IRB-Approved Protocol
• IRB-Approved Consent Template
• IRB-Approved Investigator Brochure
• IRB-Approved Questionnaires and Surveys
• Manual of Procedures
• Lab Manual
• Management Templates
  • Delegation
  • Training
  • Investigator Agreements
	• Sites will need to complete training
	• Have plan for access and training
	• Might require Data Dictionary
	• Provide entire CRF packet so sites can see what they are entering
	• Include Data Entry Schedules
	  • When each form is completed
	  • Expectation for data entry windows
		• All study-wide documents that will require IRB-approval must be approved before sending to sites
		• Provide Approval Memos to sites
			• Have plan for contracting process
			• Usually not sent in Startup Packet or not to same people
			• Site Budget is different than the Study Budget

DEVELOPING CONSENT TEMPLATES

- Use the IRB-approved consent to develop template
- Where local language should be added, delete current information and use [insert here…] instructional text
- Where consent language should not be changed that sites might expect to be able to change, use comments to indicate "Do Not Change"
- Some sIRBs or Study IRBs might require review and approval of the actual template

Changes that sites should be allowed to make to the consent template to align with their IRB required language→

- ❑ Headers and footers
- ❑ How the basic information is displayed (title, IRB info/number, PI name, contact info, etc)
- ❑ HIPAA Authorization and Confidentiality
- ❑ Costs and Payment
- ❑ Genetic Info – GINA
- ❑ Injury Language – as long as the intent remains the same, should align with contract language
- ❑ Disclosure Language

→ Be prepared to have sites request to change other sections – check with Reviewing IRB before allowing. Recommend to confirm with Reviewing IRB about all items above – which they would allow local changes and which they will not.

STARTUP PACKETS

Remember – all document releases to sites should have a "packet" – these procedures should be followed for sending anything to sites.

Process

- How will the packet be sent?
  - Zipped file in email, issues with IT block
  - Uploaded to study website
- Who will it be sent to?
  - Study documents usually sent to team
  - Budget and Contract usually sent to directly to other contact but CC team

Documents for Managing Startup

- Memo which explains steps, requirements, deadlines
- Document checklist to ensure that sites receive all items – require them to sign and return?
- Startup or Site Initiation Checklist

AFTER SENDING TO SITES

Document Collection and Review

- Consent
- Delegation Logs
- Training Logs
- CV/Resumes
- Licensures
- Human Subjects
- GCP (?)

Site Initiation Checklist

- Use this to track the site's progress
- Provide an update checklist to the site periodically with reminders – "please provide an update on when XYZ can be completed"

Budget and Contract

- While this is usually done by a separate team – Lead Team should still keep track of this to understand where things are stuck or to answer questions

AFTER SENDING TO SITES: IRB

sIRB – Lead Team or delegated group/person handles all IRB submissions for the sites

- Depending on sIRB and Lead Team discretion: Example→
  - Advarra has ability for each site to submit their own application under the Study submission
    - Confirm with Advarra analyst if Lead Team requires pre-approval before site is allowed to submit
  - Institutional sIRB, Lead Team would have to submit on sites behalf
- Depending on sIRB, might be additional documents that sites need to complete
  - Could be the site IRB that completes, could be that site study team completes
  - Provide these documents in the Startup Packet

Local IRB Review – Each site is submitting to their own IRB

- Lead Team needs to collect Approval Memos and documentation of what was submitted/approved

DOCUMENTS: REVIEW + COLLECTION

Consents

- Regardless of IRB review process, sites should not be allowed to submit to the IRB without the Lead Team reviewing and approving the local consent.
- Be sure that Startup memo includes contact information for who to send consent to for review.

Licensure

- Recommend that Lead Team complete collection of Licensure for themselves
  - Each state will have system that is publicly available
  - Pulling licenses rather than asking sites to provide ensures that it's consistent and in a complete format
  - Medical clinicians, nurses, pharmacists

Other Documents

- What is plan for how documents will be sent to Lead Team – through email or uploaded to eBinder system? To who?
- What documents need to be JUST collected vs documents that need to be reviewed?
- Delegation
  - Should be reviewed to confirm all tasks are assigned to at least one person
  - Any task requiring licensure or specific training – collection of those documents
- Training – be specific about what needs to be documented and who needs to complete
  - Attendance of Training or SIV
  - Protocol Review
  - Other? EDC, pharmacy specific, procedure specific?

SITE INITIATION CHECKLIST

- Checklist of steps or processes that sites need to have completed prior to being able to open
- Update and provide periodically to sites so that everybody agrees what is completed and what is pending

IRB Approval | Investigator Agreement | Training Meeting - Documentation | Training Documentation | Budget and Contract Signed | EDC Access Confirmed

Other System Access Confirmed | Supplies On Site | Drug On Site | Internal Processes Complete | SIV Complete

TRAINING MEETING – ALL SITES

- Schedule Training Event for all sites to attend
- Confirm with sites which staff are required to attend – PI, Primary Coordinator, Pharmacist, etc
- Provide recordings and slides for those who are required to attend but cannot
- Training documentation must be completed: Lead Team can track who attends live event or require sites to track for themselves
- Depending on number of sites – it's most often more efficient to just schedule for Lead Team's availability and not attempt to schedule for when everybody is available
  - Caveat – may ask each site to provide best day/time for PI and Primary Coordinator but not specific availability
- Don't schedule training too early as site staff might not remember specific things but don't schedule too late so that training holds up sites starting

Background, Rationale, Purpose | Aims, Outcomes, and Objectives | Study Design | Drug Intervention: Treatment Plans, Dosing, Stopping Rules | Other Intervention Procedures or Requirements | Risks and Expected Management

All Visits: Procedures and Assessments | Eligibility Criteria | Enrollment Goals and Expected Rates | Data Entry Expectations | Safety Events and Review Plan | Monitoring

SITE INITIATION VISITS – EACH SITE

- Each site should complete an SIV
- Confirm with sites which staff are required to attend – PI, Primary Coordinator, Pharmacist, etc
- Provide recordings and slides
- Attendance documentation must be completed: Lead Team can track or require sites to track for themselves
- Should provide sites with a list of things that must be completed before an SIV is scheduled
  - Often site IRB approval and budget/contract signed
  - Should be as close to all steps being final as possible
- Should occur after Training Meeting is complete

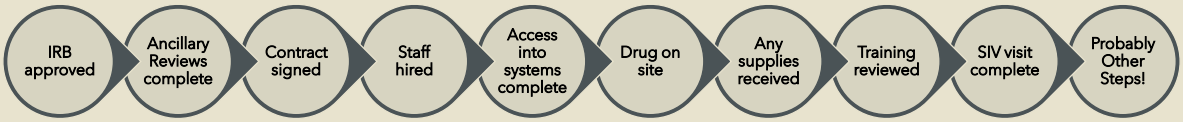
Short Review of what was covered in Training	Site Plans	Checklist Review
• Background, Rationale, Purpose • Aims, Outcomes, Objectives • Study Design • Intervention Details • Risks • Visits and Procedures • Data Entry • Safety Review	• Recruitment • Screening • Retention • Enrollment Goals	• Review each step or process on Checklist and confirm site's progress • If not completed, site should provide plan on how and when will be completed

TRAINING AND SIVS

- Both events should be a "conversation", not just Lead Team presenting information or asking questions
- Expectation should be set that this is site's chance to clarify confusing information or procedures, confirm their understanding
- Use these events to set the stage for sharing and an open flow of communication – this will be extremely important once enrollment starts

SITE OPENING STEPS

- Develop and use Site Initiation Checklist
- Use Site Initiation Visit to confirm all steps are complete
- Use Site Initiation Memos that are signed by Study PI and Site PI to ensure understanding that all steps are complete
- Issue *Green Light Letter* as final step – this is official documentation that site is approved to start enrolling



OPEN AND ENROLLING THROUGH FINAL DATA COLLECTION

My first site is ready to go and start enrolling, what happens now?

REMINDER – STEP-WISE PROCESS

- Not all sites will open at same time – may be months between first and last
- Ensure that Lead Team staffing is prepared to both manage site initiation steps as well as enrollment and recruitment efforts at sites that are open
- Have a plan for sites that may lag significantly far behind other sites in opening
  - At what point are they no longer allowed to work towards opening?
  - Is this built into contract?
  - Has this been explained during feasibility, site selection?

STANDING MEETINGS AND COMMUNICATIONS

- Standing Meetings
  - Will there be meetings that all sites attend?
    - Separate investigator and coordinator/manager meeting?
    - How often? Monthly is great but may not be useful once all sites are active and enrollment is proceeding with no issues
    - What will be discussed?
      - Recruitment strategies, enrollment rates, next steps, regulatory issues or needs
      - Give sites a chance to share successes and challenges
      - Should be two-way communication – not just lead team talking
- Communications
  - About meeting – share agenda before and notes afterwards
  - Newsletters, email blasts – make this make sense for study
  - Have system in place for communications to be shared in a standing manner
  - Can be helpful to be clear in emails to entire group of sites – "save this email in your regulatory binder"

TRACKING

Enrollment Rates and Numbers

- Be able to track rate of enrollment vs a site's stated goal
- Discuss with site if rate isn't meeting expectations
- Challenges – site-specific or study-specific
- May require change at study-level or site may require coaching on recruitment strategies

Data Entry Timeliness

- Requires that Lead Team provided window for data entry
- Discuss with site if not meeting that window consistently

REVIEW OF DATA AND SAFETY EVENTS

- Study PI should be reviewing all safety events in a timely manner
  - Have a consistent plan for adverse events vs serious adverse events vs deaths
  - Make it appropriate for actual study intervention, procedures, risks
    - Example – if primary or secondary outcome is safety or a specific risk, review those in a more timely manner than others
- Most EDC systems have automatic notifications to specific emails based on data entry
  - If yes to XYZ – emails an alert to review data
  - Can send to PI and Lead Team manager or coordinator –whomever needs to review, track review, submit to IRB or other authority
- Automated alerts can be set up for any variable – also can track deviations of specific interest, enrollment, whatever makes sense for study

SAFETY EVENT COMMUNICATIONS

- As part of the DSMP, should have plan for how safety events will be communicated to other sites
  - They may or may need to submit to their own IRBs
    - Prompt reporting vs annual review
  - They may be asked to inquire specifically about event or "be on the watch for"
  - If significant safety event which requires immediate change to procedure or intervention

AMENDMENTS AND CLARIFICATIONS

- Any change to a study document, system, or form should be sent to sites or told has been changed
  - Protocol amendments, with or without consent change
  - Update to questionnaire or survey
  - Changes to case report forms or study database
- Always provide BOTH tracked change and clean versions of documents
  - If not possible to provide tracked change, provide clear summary of change
- Most likely should be in "document release packet"
  - Memo of what is changed, which documents are impacted, next steps, training requirements
  - Mimic "startup packet" – sign off on documents received, zip file or upload to website/system
  - Have plan for how to collect and review anything required from change

SITE CLOSURE

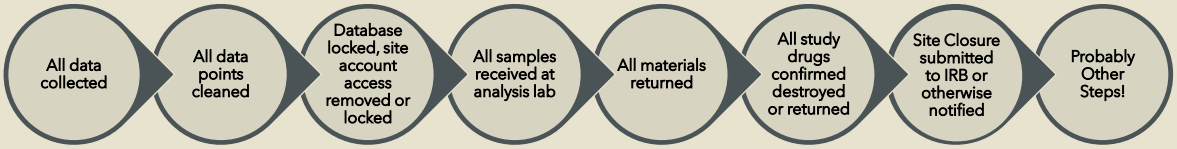
All participants have been enrolled and their last data point has been collected and entered into the IDC, am I done with the sites?

FINAL DATA CLEANING AND QUERIES

- Sites should not be closed until database is clean and all queries answered
  - This might mean that monitor goes out to site to do final visit or last remote visit complete
  - This might mean that data manager has sent all queries within EDC system and all data confirmed as correct and missing data confirmed as missing
- Once sites are closed – no activity should be happening at site

SITE CLOSURE STEPS

- Develop and use Site Closeout Checklist
- Use Site Closeout Visit to confirm all steps are complete
- Use Site Closeout Memos that are signed by Study PI and Site PI to ensure understanding that all steps are complete
- Issue *Red Light Letter* as final step



THANK YOU LETTERS

To Sites

- After all sites are closed, acknowledge the site's contribution
- Does not have to be individual letters to each investigator but one letter that is sent by the Study PI to all Site PIs
- Could contain, as applicable and appropriate
  - Any early results
  - CONSORT diagram breakdown of enrollment
  - Where to find more information
  - Call for manuscript development assistance
  - If sending individual letters, include specifics on local site enrollment and contributions

To Participants

- Planning for this should happen before the study will be closed/final data is collected
- Have a step/step process for how letters will be sent
- Could include individual results or aggregate results
  - *Links go to MRCT for resources and toolkits*
- Letter should be IRB-approved, can use [insert info here] for things like:
  - If randomized, intervention received
  - Total number of participants enrolled
  - Where to find more information, like clinicaltrials.gov postings

  → Check with the Reviewing IRB if they want to review letter before sending

IRB APPROVALS

How does IRB approval work for the study and for each site?

SIRB VS LOCAL IRB REVIEWS

- Confirm the plan for sIRB review during grant submission stage – talk to your IRB before submitting any funding application that will be multi-site and possible require single IRB review.
- If there is no NIH/Common Rule requirement for single IRB review, each site's IRB may review individually. Confirm this with both funding source and your IRB before proceeding.
  - Will still require:
    - Development of consent template for all sites to use
    - System for sharing IRB approval memos and other documentation
    - Submission of all of the same documents to each IRB
- Ensure that site understands their local IRB's requirements if sIRB is used
  - What still needs to be submitted or reported
  - Lead Team should not be responsible for a site's failure to not report appropriately
  - Contract and MOP can be written to state this formally

IRB RESOURCES AND POLICIES

- HRPP 2.5 Multi-Site Research
  - 2.5.1: Options for Review of Multi-Site Research
  - 2.5.2: Establishment of Oversight for Multi-Site Research
    - 2.5.2.1: Investigators at External Sites Relying on the Boston Medical Center and Boston University Medical Campus IRB
    - Investigators at Boston Medical Center or Boston University Medical Campus Relying on an External IRB
  - 2.5.3: Delineation of Oversight Responsibilities
  - 2.5.4: Principal Investigator Reporting Requirements in Multi-Site Research
- If you are planning on having another IRB review – KNOW THEIR POLICIES AND PROCEDURES
  - This includes commercial IRBs like WIRB and Advarra and other institutional IRBs

SMART IRB

Not an IRB – Does not review studies

Learning Center – Investigators
- Videos, Templates, Grant Prep

SMART Talk – Monthly Webinar
- Primarily for IRBs but does provide good context for how institutions approach reviews and the process

SMART IRB's Online Reliance System→
Web-based system that provides a central process for participating institutions and their investigators to request, track, and document study-specific reliance arrangements. Not all institutions will use even if Master Agreement is used.

SMART IRB Agreement →
Master reliance agreement that IRBs and institutions sign – study-specific reliance agreements are still required but the Master Reliance Agreement removes a lot of documentation and negotiation steps.

IRB SUBMISSIONS AFTER APPROVAL

Amendments	Continuing Reviews	Prompt Reporting
• Either provide sIRB approval memo to sites or collect local IRB approval memo	• Allow for enough time to collect and confirm all required information from sites before expiration date • Either provide sIRB approval memo or collect local IRB approval memo	• Have process so that anything requiring prompt reporting at sIRB or Study IRB is actually reported to Lead Team • Write MOP so that any local IRB reporting is the site's responsibility to understand and manage

CHALLENGES IN MULTI-SITE RESEARCH

Case Studies and Scenarios

ELIGIBILITY CONFUSION

- Criteria must be written very, very clearly with no room for interpretation
- If interpretation possible/allowed, state very clearly what that means →
  - "In the clinical judgement of the Site Principal Investigator"
- Ensure open communication from sites on difficulties with eligibility – have system to capture why somebody is not eligible so this can be reviewed
  - Discuss on study-wide meetings with coordinators and/or have CRF to capture and review data periodically

Case Study

- Exclusion criteria: No NSAID in previous 90 days
- Excluded basically EVERYBODY but no site mentioned this specific difficulty for several months
- Huge impact overall enrollment goal targets and rate – study aimed for 100 but only hit 50 before funds ran out
- After this issue was finally raised by one site coordinator, the exclusion criteria was reviewed by medical monitor team and criteria was not actually a safety or outcome based criteria – just a random thing that a non-clinical member of the protocol writing team saw with a similar study that was done many years ago
- Criteria was removed with a protocol amendment

DOCUMENT SHARING AND REVIEWING

- Problems with account set up and management – site staff needs to be tech-savvy
- Version control issues – if one "source of truth" for study-level documents, can help ensure that sites are using correct versions
- What is allowed/expected to be used at BU/BMC

Case Study

- COVID study example, used Box (institutional version, HIPAA compliant)
- Most sites had no issues obtaining access but still required some tech-training
- A few sites needed major tech-training to obtain accounts – several meetings to walkthrough steps together
- One site blocked Box entirely – required approval from IT, provided "security memo" to site on HIPAA compliance
- Developed "map" for account setup, folder system, uploading process → included screenshots

MONITORING AND COMPLIANCE

- Depending on study, may need to complete some level of monitoring
  - On site review of documents, remote access of data integrity between EDC and EMR
- Should be planned for during grant development for budgeting travel and staff
- Included in DSMP with reports submitted to DSMB and IRB as appropriate

Case Study

- Interim monitoring visits completed monthly with similar findings – all related to organization of study files and caseload of research nurse – one monitor
- After third visit, decision made to halt enrollment at site and complete "for cause" review of study with entire Lead Team visiting site (PI, Project Manager, Regulatory Manager, Monitor)
- Discovery that research nurse was not allowing coordinator to complete research procedures – major staffing relationship issues
- Reviewed standard best practices and requirements
- Site was placed on "process improvement plan" with monitoring visits happening much more frequently
- Huge caveat – issues might not have been uncovered in as quick a time period if on-site visits were not happening (pre-COVID and study had budget for on-site monitoring)

DRUG ACCOUNTABILITY

- Keep site contact lists current and ensure that all site staff have the correct contacts as well
- Ensure open-lines of communication and transparency so that all are comfortable with questions and raising concerns

Case Study

- Randomized, blinded study - botanic product in oil solution vs standard saline solution. Site pharmacies received pre-labeled, pre-randomized bottles for dispensing. Blinded site pharmacist calls coordinating center (not Lead Team) to raise concern that blinded product was "switched" in recent batch shipment from compounding pharmacy.
- After consultation with expert in IDS management and approval from Lead Team, CC contacted site pharmacies to conduct "audit" of current, undispensed supply without alerting local study teams. Four of five reported no issues between study drug and placebo. Fifth site (original) reported entire stock was "switched". Fifth site was asked to contact current participants to return drug when complete – Lead PI determined no risk for continuing drug and once returned, allocation status was "corrected" in study database.
- Reported to FDA, study IRB, and local IRB. As no actual harm or adverse event occurred, no further action required except at compounding pharmacy who were required to institute better quality assurance checks.

What else do you think could be difficult with multi-site studies?

Open Discussion

What are the challenges you have had with multi-site studies?

SUMMARY AND WRAP-UP

SINGLE-SITE → MULTI-SITE HOW TO SCALE BEST PRACTICES

Staffing	Meetings and Communications	Documents and Documentation
PI + Coordinator	Standing Meetings	Internal shared folders + Source Documents and CRFs
PI + Coordinator + Data Manager + Project Manager + Regulatory Manager	Standing Meetings for Coordinators + Standing Meetings for Investigators + Newsletter/Memos	EDC + Cloud-based sharing system + Zipped Folders + Templates

Actually works both ways – what is best practice can also be best practice for single-site studies

- Training Meetings and Site Initiation Visits
- Site Initiation Checklists
- Ensuring that "pre-startup" planning is done – cannot emphasize how many challenges and deviations can be prevented with a more intentional planning stage

ADDITIONAL RESOURCES

- SMART IRB Monthly Webinars (Archived Library)
  - 2022 *Single IRB from the Perspective of Research Teams*
- Clinical Research Seminar
  - April 2021 *Experiences with an Investigator-Initiated Clinical Trial During COVID-19: Transitioning from Single- to Multi-center*
- RPN Workshop
  - January 2022 *Cede Review: Navigating the World of Single IRB*
- Slides and Recordings will be made available after today
- CRRO is always available to review more in-depth any of what was discussed today or how to apply the learning to your specific study