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What Could Possibly Go Wrong?!
Study Start-Up Best Practices
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Presenters

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Workshop Objectives

01	REVIEW	✓ **Understanding** different levels of protocol complexity, including respective study start-up tasks
02	PREVENTION	✓ Create **checklists** and visit **source documents**
03	TROUBLESHOOTING	✓ **What** to do when a problem does occur?
04	IDENTIFY	✓ Case studies: **identifying** best solutions and prevention ideas

Study Start-Up

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Well-Planned

- Feasibility Assessment
- Compliance with GCP
- Data integrity
- Protocol compliance
- Successful enrollment
- Positive relationship with study sponsor

Poorly-Planned

- Budgetary/time/resource constraints overlooked
- Low or no study enrollment
- Protocol deviations
- Poor documentation/audit risk
- Impact patient safety

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What is the worst thing that has happened to you related to study start-up?

The sponsor doesn't respond and goes MIA

Finally completed study start up and they closed enrollment the next day.

Lack of communication from sponsor- requiring modifications/ prolongs start time

opened a study only to have it close to accrual days later

Funding drops

Study not moving forward after most of start up was complete

PI got in over their head.

Major deviations that can't be avoided due to conflicts in protocol

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What is the worst thing that has happened to you related to study start-up?

The sponsor changed the protocol 3 times before our site had a chance to begin enrolling

Realized we had an exclusion criterion without a way to assess it during screening!

Worked on start up for a very complex study. Took months. And IRB review similarly took months bc of the complexity and safety of the study. And when we were ready after countless hours, closed enr

lags and delays, especially when ceding to a different IRB

Poor communication from sponsor

Huge clinic problem identified at SIV, now on hold for months

Startup taking too long due to lack of communication.

Purchasing/contract delays

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What is the worst thing that has happened to you related to study start-up?

Contract was almost scrapped days before intended first patient visit

No patients meeting inclusion criteria at that site.

Consent form taking forever

Failure for paying start up fees after we completed start up

Communication from each coordinator not complete

Sponsors told investigators short timelines on patient submission and review, but then told our team (the coordinators) that the timelines requested by our investigators were not possible.

Central IRB removed site specific language from ICF causing extended delays in approval

Long delays between SIV and site activation.

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What is the worst thing that has happened to you related to study start-up?

miscommunication between irb, sites, and sponsors

ttttt

Na

PI was in over their head & 2/3 clinics dropped out of study.

NA

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Study Start-Up Overview: Levels I and II

Observational and Investigator Initiated Minimal Risk Studies

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Have studies on this been done before? What makes yours different from those? How and why should people care?	Do you have any incentives included in the study? If it is an in-person study, are there travel accommodations to consider? What types of data will you collect and how will you measure that, statistically? Independent vs dependent variables	Initial Submission and responding to any questions or concerns from the IRB.	Study logs, CRF's/checklists External vendor systems (if needed) Vendor system training Internal systems: billing, participant compensation management Supply ordering	Creation of remaining SSU documents e.g. DOA/training logs IRB approval Participant identification & scheduling of Screening Visits

Case Study #1: Recruitment and IRB

- Not enough participants/low retention rate:
  - Alternative recruitment methods
  - How much can you change your protocol to satisfy enrollment needs without wandering too far from the original research question?
    - Age requirements, health status, etc.
    - How does this change the way we analyze the data?
  - Changing inclusion/exclusion criteria
  - Demographic/behavior differences and what is the age cutoff for older vs younger adults?

What could have been done during SSU to avoid this situation?

- Brainstorm possible enrollment alternatives beforehand
  - Include them all in your IRB!
- Community vs. volunteer cohort
  - How would recruitment language and efforts change between different group types?
- Prepare for the worst and hope for the best!

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Well-designed research often fails because of poor subject recruitment and retention procedures, so make this a priority!

Study Start-Up Overview: Level III

Complex Multi-Center Trials (e.g. Industry)

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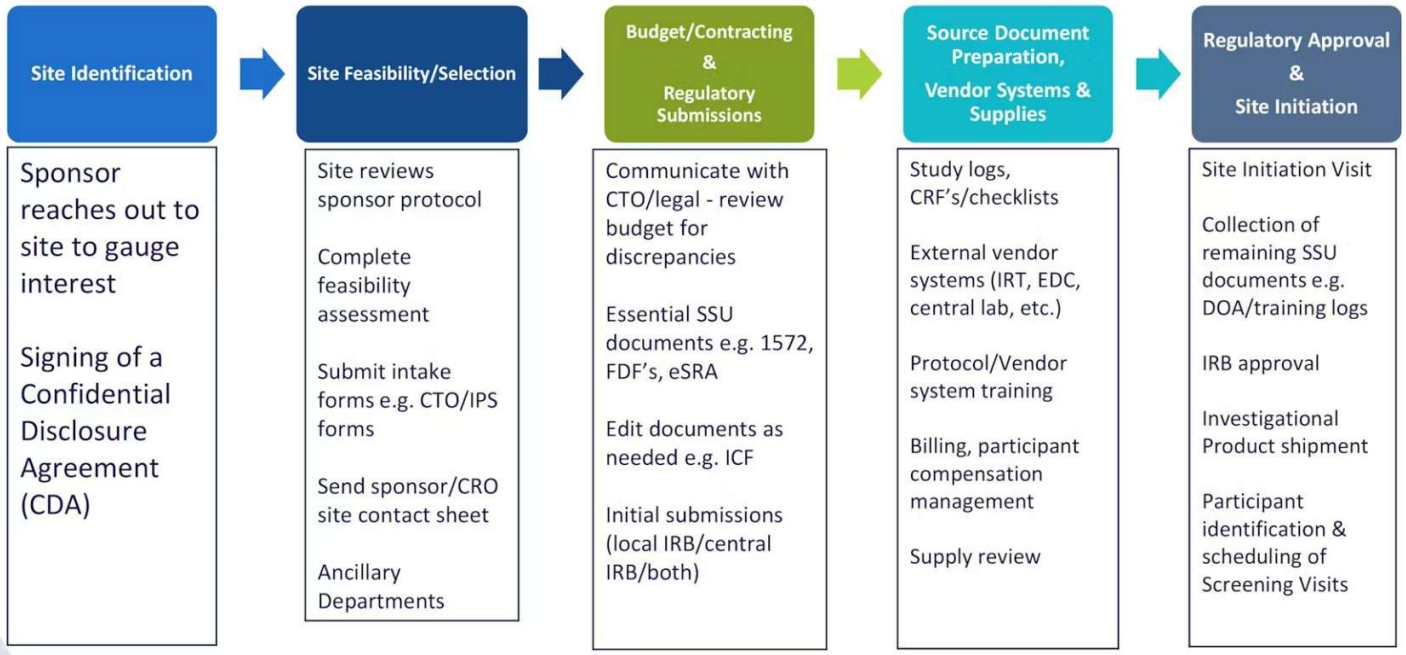

Case Study #2: Feasibility

- Study team was given the green light to proceed from the sponsor in the form of a Site Activation Letter that was issued after full IRB approval was given.
- A short time later the study team receives correspondence from the sponsor that study enrollment has closed.
- The study team has enrolled only one participant into the study since activation but their enrollment target was ten.
- Feasibility and timing estimates were not thoroughly assessed.

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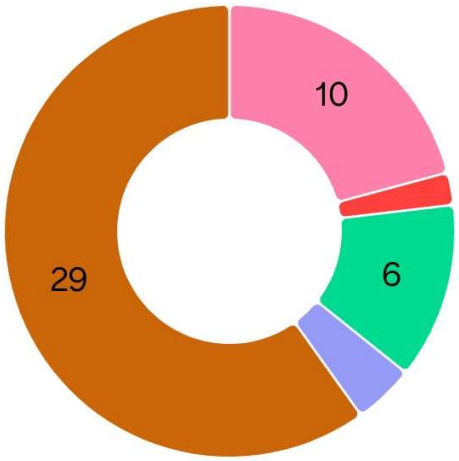
Select what you think is the most common cause for this type of study start up mishap?



0	Lack of communication between the sponsor and the sites budget/contracting team
10	Lack of communication between the sponsor and the study team
1	Lack of communication between the study team and sites budget/contracting team
0	Lack of communication between the study team and the IRB
6	Study team underestimated their start-up timeline
2	Lack of commucation between PI and study team
29	All of the above

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What could have been done during SSU to avoid this situation?

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Questions to ask during Study Start Up

- How much time will it take internally to review and edit the budget/contract?
- How long does the internal legal review take?
- How much time will it take to obtain IRB approval?
  - Are you allowed to submit the IRB application prior to signed contract?
- Do you need to work with any ancillary departments and what are their timelines?
- What is the anticipated date of enrollment of the first subject?
  - Is the study already enrolling?
  - How many sites are already activated?
  - What is the pace of enrollment?
  - When is enrollment scheduled to end?

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If the timeline is not realistic, the study may not be feasible!

Other Considerations…

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- Feasibility doesn't just apply to start up timelines it also applies to almost every aspect of study start up.
- Can we recruit the target patient population?
- Do we have the space to conduct study visits with x, y, z procedures?
- Do we have enough qualified and trained site staff and do staff have the **bandwidth** to conduct the study?

Case Study #3: Site Staff Roles

- The patient has arrived for their study visit but the PI (who is supposed to do a physical exam) is unexpectedly out sick.
- The back-up PI is unavailable.
- The protocol has specific roles for site staff to maintain blinding of treatment assignment.

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Case Study #3: What would you do in this scenario?

Just skip the physical exam that visit

Ask the blinded assessor to do the exam in addition to their own exam

Ask another provider in clinic (not on the study team) who's free to help you out

Have another provider perform the exam and retroactively add them to the delegation log

Ask the patient to come back on another day

What could have been done during SSU to avoid this situation?

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- Have a back-up physical exam assessor trained and listed in the Delegation of Authority log.
- Could the PI have communicated with the study coordinator in advance with the option to reschedule the patient before they come in for their visit?
  - What kinds of communication are there amongst the study team and how flexible are team members?

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If your site has access to additional study staff have a back-up MD, RA or Coordinator available (trained and added to the DOA log) to help in the event of unexpected absences!

Case Study #4: Inadequate Source Documentation

- Participant 005 arrives for their Day 1 visit for an industry drug study. Today they will be receiving study medication for observed dosing.
- All bloodwork apart from a 1 hour post-dose PK sample should be completed prior to drug administration.
- However, the participant was given study drug before any blood work had taken place.

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Case Study #4: What would you do in this scenario?

Skip the lab draws apart from the post dose PK draw

Draw all labs at the post dose PK timepoint

Ask participant if they can return for an unscheduled visit

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Creating Successful Visit Source Documentation

- What tasks need to be done at a study visit and in what order?
- Protocol Assessments Table listing required at each visit (with attention to footnotes)
- Finding important assessment details within the protocol which will impact the timing/processes.
- Is there additional information to be found in related manuals, particularly lab manuals with critical blood processing information?
- Did the sponsor provide eCRF pages in advance?

Example: Visit Checklist

Pre-Visit:

- ☐ MRI scheduled and forms (requisition and NeuroRx study form) sent to MRI
- ☐ Have Covance/LabCorp kits ready (Screening Visit & HIV); check expiration dates
- ☐ PI has ordered ECG and Quantiferon Gold TB testing in EPIC
- ☐ Make sure study tablet is charged and users have access to it

Screen Visit Checklist:

- ☐ Remember to turn on refrigerated centrifuge
- ☐ Review and sign ICF with patient; make a copy for the patient
- ☐ Enter patient's Screening Visit information into IRT system
- ☐ Review Concomitant Medications and Medical History with patient
- ☐ Review Inclusion/ exclusion criteria
- ☐ Columbia-Suicide Severity Rating Scale (use tablet)
- ☐ EDSS form (on tablet)
- ☐ Physical Exam form
- ☐ Collect Vital Signs (inc. height & weight)
- ☐ ECG performed and printed & signed
- ☐ Take patient to lab for blood draw
- ☐ Collect urine (and perform Urine Pregnancy Test if applicable)
- ☐ MRI is completed and passes QC review
- ☐ Make sure Randomization Visit (Day 1) is scheduled within 28 days

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Contact the patient to remind them of their upcoming study visit including time and location. Confirm they know the location and parking situation.

Example: Visit Source Document

Safety[y]																						
Physical examination[h] and vital signs	X	X						X		X		X		X	X	X	X	X	X	X	X	X
Height	X																					
Body weight	X	X						X		X				X		X		X		X	X	X

h Complete physical examination due at screening, baseline, yearly (M12, M24, M36, M48) and at EOS; brief physical examination is sufficient for the rest of the visits (complete and brief physical examinations will include neurological examination and collection of the following vital signs: arterial blood pressure, heart rate, temperature).

Information found deeper in the protocol:

8.2.2 Vital signs

- Body temperature, heart rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with the participant in a supine or sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 heart rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute).

What ended up in the source document:

Patient to rest for at least 5 minutes without distraction; started at: ____:____

Vital Signs taken from R / L arm Sitting ___ Supine ___

Blood Pressures: 1: ____/____ (time: ___:___) 2: ____/____ (time: ___:___)
3: ____/____ (time: ___:___) Average BP: ____/____

Pulse: _____ bpm **Temperature**: ____° C Route: _____ **Weight**: _____ kg

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When creating and/or filling out your source documentation always think of ALCOA-C

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A	**Attributable** It should be obvious who created the record, and when If a record was changed, it should be obvious who made the change, when the change was made, and why
L	**Legible** The research record should be easily read
C	**Contemporaneous** Study evidence/results should be recorded as they are observed All signatures/initials should be attached to a date indicating when the signature was added
O	**Original** Study records should be originals, not copies
A	**Accurate** Study records should have a high level of integrity and honesty to what was truly observed; give a full accounting of the research process Study records should be thorough and correct; work should be double checked for unintentional errors
C	**Complete** Investigators and institutions should maintain adequate, accurate and complete source documents

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If it was not documented, it was not done!

Case Study #5: Vendor Equipment Problems

- The tablet (into which the participant answers questionnaires and study assessments are entered) is not working and you have only 1 tablet on site.
- One of the assessments is a safety questionnaire on suicide ideation and behavior.
- You don't have time to call the help desk and/or they are unable to resolve the issue that day.

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Case Study #5: What would you do in this scenario?

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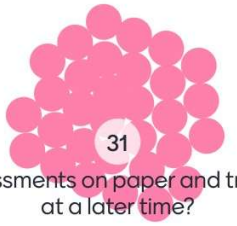
Skip the assessments at the visit.



Do the assessments on paper and transmit data at a later time?

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Ask the patient to return on another day.

Is there a possibility the patient could complete online instead of on the tablet?

What can be done to prevent this situation?

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- Open the tablet the day prior to the study visit and check to see if it's working properly and is sufficiently charged is always a good idea.
- Are new user log-ins working?
- Are there software updates that should be uploaded that you forgot about?

Case Study #6: Site Equipment Malfunction

- You are implementing a study protocol that requires collection of cervical swab samples.
- These samples must be kept in a -20º freezer as soon as collected but there is no -20º freezer on the floor that belongs to your unit.
  - How would you tackle this problem during study start up?

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Case Study #6: ▷How would you tackle this problem during study start up?

Inquire elsewhere at your institution to see if there is a -20 freezer you can use.

I would contact the department that owns the closest freezer to me and see if we can rent space.

Communicating this to the CRA/Sponsor

Are there other's in the department that would be willing to share a small bit of space in their freezer

Ask if the sponsor will provide a -20 to the site.

Get approval from sponsor to transport on dry ice or wet ice.

Feasability questionnaire should cover what equipment is available- so study start up would hypothetically be halted. Or find another clinic which could work in conjunction with yours

Talk to others who may have a freezer on the floor. Consider do you need to cover the cost of storage?

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Case Study #6: ▷How would you tackle this problem during study start up?

Asking what the window of time is

See what other -20 freezers are available that you could use and contact those departments to see if this is feasible.

Make sure any needed equipment that isn't already on site be communicated with the Sponsor

Check with there's one available in another dept/floor/ clinic

Build in the option for dry ice to be made available, or collaborate with the another division that has a -20 and offer to pay for the space

can the specimen be stored in a colder freezer? who else may have a resource you can use temporarily? reach out to colleagues

Ask leadership on the floor if they know of any other trials or services using a -20 in the area. If none available, consider purchasing a small one that could be stored on floor.

Request purchase of freeze from study sponser

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Case Study #6: ▷How would you tackle this problem during study start up?

Make plans to get the sample on a floor that does have a -20 freezer

Identify other resources on campus

Ask Sponsor for a freezer that is compliant or store it in another freezer in different area

Ask sponsor what time window

This is something to ID early on; it may take a while to solve this issue!

Request sponsor provide freezer and build into study start-up. Ensure we have space available and proper location.

I would look into an alternative temp storage option while I searched for an appropriate freezer

Talk to other departments who have freezers and renting space

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Case Study #6: ▷How would you tackle this problem during study start up?

Uiy

Practicing potential difficult situations.

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If it is your first patient's first visit at your site, make sure your study monitor and/or study manager is aware of it so they can help deal with an issue.
Do you have a seasoned co-worker who can be available for help that day as well?

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Wrapping Up: Things to Keep in Mind

- Complexity and Potential Risks of the Study
- Being Proactive and Planning in Advance of Visit Day
- Study Staff Experience
- Creative Problem-Solving
- Keeping up with Protocol Amendments
- Is there a Persistent Problem at your Site? (space availability, staff schedules, etc.)
- Recognizing Protocol Deviation Patterns

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What are some tips and tricks that you have used during study start up to avoid the kinds of issues discussed in this workshop.

LOTS of training and LOTS of documenting

Use study start up check lists

communication and checklists for each process

Having a very brief study startup huddle with just staff, no investigators, to work through just study logistics (who is picking up drug from pharmacy, etc)

Don't be afraid to ask questions about specific, unique scenarios, no matter how unlikely.

Really detailed check lists for each visit

Read the protocol and ALL the supporting documents.

Doing a run through before seeing a participant.

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What are some tips and tricks that you have used during study start up to avoid the kinds of issues discussed in this workshop.

Make sure you have good relationships with others who are helping you run your study, but do not get any reward, so to speak. Be professional and kind. It will help in the long run!

Always doing a "fake participant" or "dress rehearsal" to create as real a scenario as possible so that you're prepared on the day of.

Gantt charts to track things that can happen concurrently

Host a final Study start up meeting just before the study initiation

Have someone look over and verify everything looks correct and having multiple eyes helps

When a protocol is amended, put the protocol version on your updated source document.

DOA and making sure we have the staff we need for each study and transparency

What you noted earlier, great communication with the participant is key as well.

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What are some tips and tricks that you have used during study start up to avoid the kinds of issues discussed in this workshop.

mock visit, a walk through the visits and all the details

Do a mock run-through.

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