National Institute of Allergy and Infectious Diseases

Know Before You Go: Conducting International Studies

Objectives

After this presentation, attendees will be able to:

- Understand the importance of regulations for conducting studies globally and with NIH support including concerns related to risk mitigation
- Describe how to assess the adequacy and needs of an international study site
- Explain how to determine the readiness of a site to begin a study
- Describe ways to ensure appropriate implementation and oversight of the conduct of the study

Background

- NIAID DIR and DCR conduct studies both domestically (at the CC and collaboratively with other institutions) and globally.
- Currently OCRPRO oversees/ helps with approximately 22 active studies and 23 studies pending closure in 13 different countries, not including US sites.
- Office of Clinical Research Policy and Regulatory Operations (OCRPRO) provides support DIR Investigators.
  - Regulatory Affairs (IND management)
  - Safety Oversight
  - **Clinical Trials Management**
  - Protocol Navigation/ Protocol Development

Areas to be covered

- Regulations and Policies
- Protocol and Consent Considerations
- Pre-Site Assessment
- Considerations/ Challenges
- Preparedness
- Implementation and Oversight

HRPP Policy & Guidelines

700 Series:

International Research Requirement

Know the requirements:
HRPP Policy & Guidelines: 700 Series-International Research Requirements

- Human subjects research conducted by NIH Investigators is subject to federal law, regulations and policy, including NIH policy, regardless of whether the research is conducted domestically or internationally.
- A foreign institution, must hold an active FWA and an IRB/ EC registered with OHRP that will be reviewing the protocol/ consent.
  - Be sure to check they have an active FWA and correct IRB is linked to the FWA
  - The institution has to file their own and to be done online.

Know the requirements:
HRPP Policy & Guidelines: 700 Series-International Research Requirements

Non-Exempt Human Subjects in a Foreign Country

- Must be approved by an in-country IRB or EC **prior to receiving final approval by the NIH IRB,** when it is the Reviewing IRB.
  - If reviewed and approved by an external U.S.-based IRB prior to in country IRB/EC approval, NIH research may not begin until approval from the in-country IRB or EC.
  - If no in-country IRB/EC, NIH research may not begin until the U.S. based reviewing IRB requirements for local context review has been met.
- When the NIH IRB is the Reviewing IRB, and no in-country IRB/EC, NIH IRB will require a written assessment of the research for its consistency with foreign country laws and regulations, or local customs and culture, by an individual with appropriate expertise in the foreign country's culture, who is independent of the research team.

Know the requirements:
HRPP Policy & Guidelines: 700 Series-International Research Requirements

If conducted or supported by NIH Intramural Program

- But NIH is not engaged in the human subjects research,
  - NIH IRB is NOT required to review, but in-country IRB/EC review and approval is still required
  - In-country IRB must be registered with OHRP and conduct its review compliant with 45 CFR 46 or has equivalent procedures consistent with 45 CFR 46.101(h)

Know the requirements:
HRPP Policy & Guidelines: 700 Series-International Research Requirements

NIH Principal Investigator (PI) and Investigator Responsibilities

- Must comply with:
  - Federal law, regulations, and policy, including NIH policy, regardless of whether the research is conducted domestically or internationally.
  - All applicable foreign country laws and regulations;
  - The requirements of the in-country IRB/EC so long as the requirements are no less restrictive than, and not counter to this policy; and
  - The requirements of the U.S.-based Reviewing IRB.

Know the requirements:
HRPP Policy & Guidelines: 700 Series-International Research Requirements

NIH (PI) and Investigator Responsibilities (cont.)

If the study of test articles (e.g., drugs, biologics, nutritional products or devices) are involved, and the test articles will be shipped from the United States to the foreign site, the NIH PI must:

- Comply with FDA regulations for shipping test articles internationally;
- Comply with applicable NIH requirements (e.g., pharmacy, CC Office of Research Support and Compliance (ORSC));
- Comply with in-country regulatory requirements, approvals for test articles, and any necessary import requirements; and
- Provide written documentation from the foreign site indicating all necessary approvals for use of a test article under the local laws have been obtained to the NIH IRB.

Know the requirements:
HRPP Policy & Guidelines: 700 Series-International Research Requirements

NIH (PI) and Investigator Responsibilities (cont.)

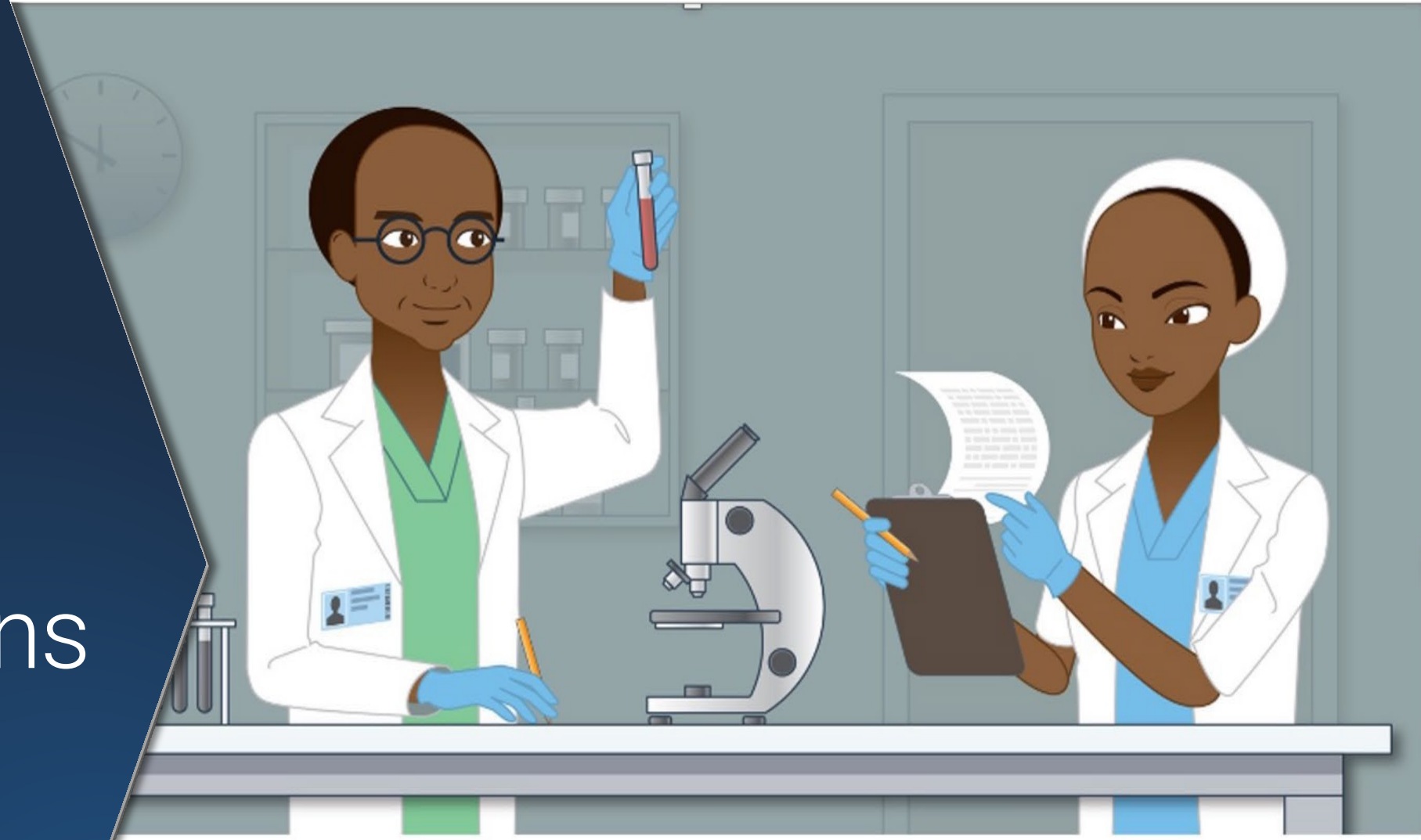
- The NIH IRB will not approve research occurring in a foreign country has been previously disapproved by, or otherwise conflicts with the determinations of, the in-country IRB/EC.
- If previously approved by the NIH IRB and a later determination by the in-country IRB/EC disapproves the research, notify the US-based IRB promptly.
- NIH IRB approval will be rescinded.
- NIH PI must submit the following items to the NIH IRB (including certified/back- translations)
  - Local context not described in protocol including:
    - Description of In-country laws, regulations, customs
    - Whether review is necessary by any other in-country entities
  - Documentation of in-country IRB/EC determinations and approvals
  - Any other materials needed by NIH IRB to complete its review

Regulatory Approvals and Oversight

Identifying the Regulatory Requirements

1. Identify the regulatory authority/agency.
2. Determine if an application is required.
3. Establish in-country working relationships.
4. Initiate communication.
5. Identify application requirements.
6. Timelines for Submission and Approvals.
7. Don’t forget to post the study on ClinicalTrials.gov and any other required registries.

Protocol and Informed Consent Considerations



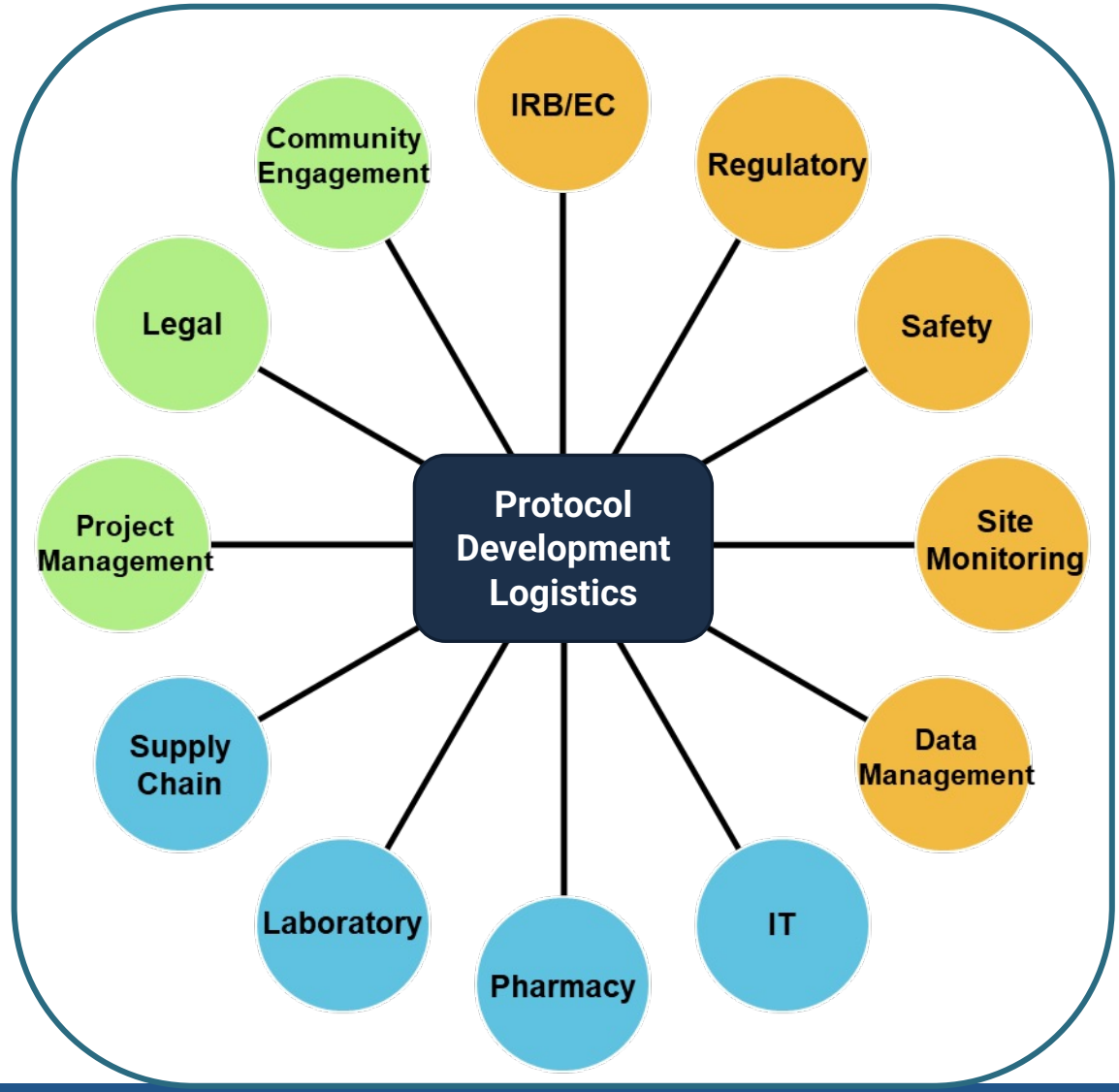
s a clinical research study?

esearch study helps doctors test new ways to treat a disease. One way to do this is by studying new drugs, to
could be used as medicines. In a study, the drugs are 'experimental,' which means they have not been proven
That is why studies are needed to find out if new drugs are safe and work in people.

here today to hear about a clinical research study that we are inviting you to participate in.

Complexity of Protocol Development Logistics

Concept:
- Hypothesis
- Endpoints
- Design
- Statistics



Clinical Research Protocol

Key:
- Infrastructure
- Site
- Oversight

Logistics and Operations

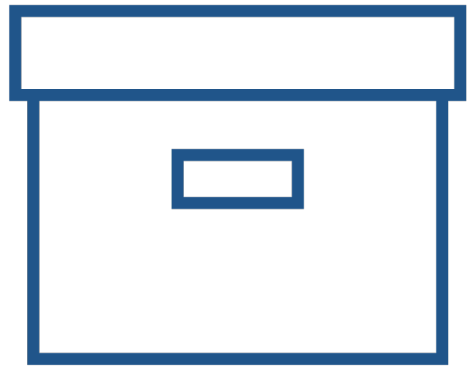
- **Study design and evaluations impact the logistical complexity.**
  - The Schedule of Activities determines timing and involvement of additional departments.
- **Requirements for site operations based on research plan in protocol:**
  - Laboratory
    - Phlebotomy
    - Lab testing capabilities
    - Storage
  - Pharmacy
    - Investigational/study agent storage requirements
    - Preparation
    - Time restrictions for delivery to participant
  - Research site/facility/staff
    - Ensure what is delineated in the protocol can be done on-site

Considerations for Logistics and Operations

- Consider resource limitations at anticipated sites.
- Focus on evaluations to achieve your endpoints.
- Incorporate good planning and involvement of key personnel at early stages of protocol development.
- Coordinate the logistics to meet reasonable timelines.

Data Management Considerations

- **Provide details on what, how, and when data will be captured and by whom.**
- **Describe responsibilities for data management and record keeping, including retention of source documents.**
- **Considerations:**
  - Which data are important for answering the research question(s)?
  - How and when will information be captured?
  - Where are the data maintained?
  - Who will be checking the data frequently to ensure quality, both at the site and for the overall study?
  - Is the data management system compliant with applicable regulations?
  - **Keep in mind:** Focus on collecting the essential data to reach the desired endpoint

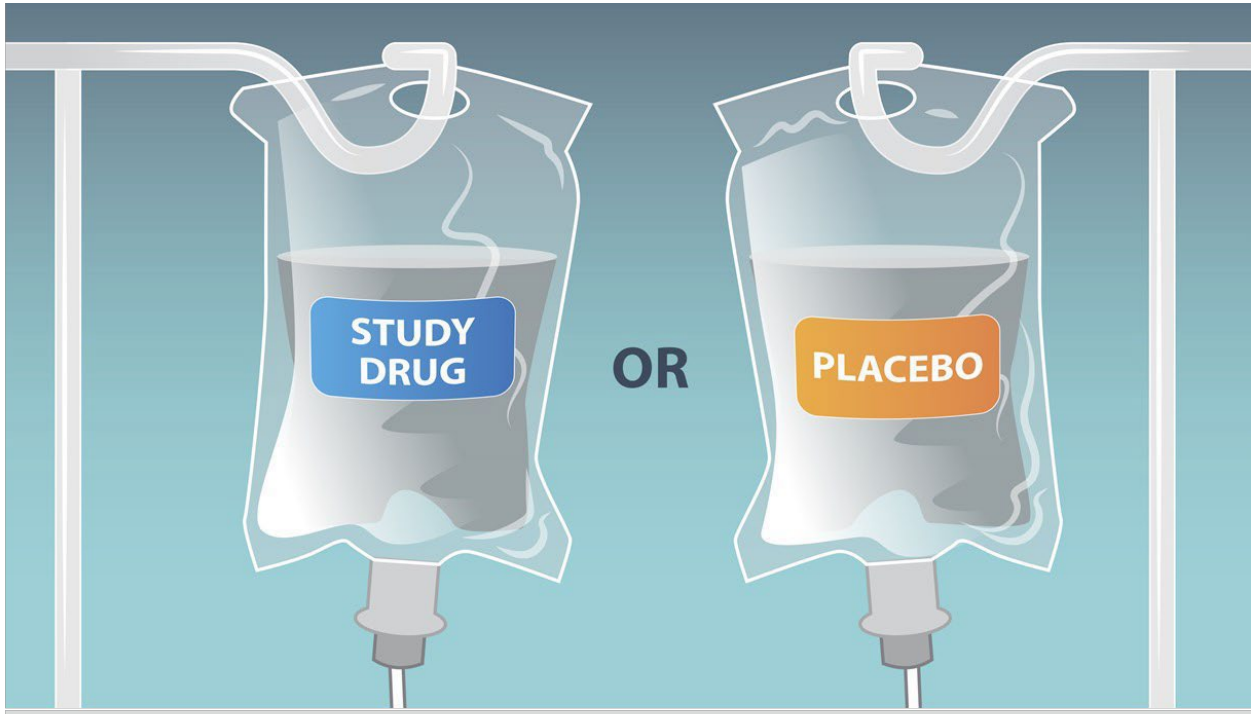


Informed Consent Considerations

- What languages will it need to be translated into?
  - Who will do those translations
  - Back translations
- What is consider the legal age of an adult?
- Legally Authorized Representative
    - Difference between law and common “law”
- Do they have any laws regarding emancipation of a minor?
  - Minor, who is a parent
  - Minor, who is married

Informed Consent and Flipbooks

- Consider using flipbooks to augment the informed consent process discussion.
- Research concepts may be new to the population being enrolled.
  - Relay complex research themes using illustrations and short, simple text
  - Incorporate local context and community opinions
  - Translate into the local language
  - Note: Obtain approvals for the site-specific flipbooks



What drug is being studied?

We are studying a drug called ST-1017. This drug has been studied in animals and in a small number of people. We hope that ST-1017 will help get rid of the Jumba virus that is left inside the body. It is given as an infusion. This means it is given through a plastic tube that is put into a vein in the arm. To find out if ST-1017 (the study drug) works, we need to compare it to something that does not have the drug in it. So some people on this study will get a solution called a placebo. The placebo is a liquid that looks like the study drug but does not have the drug in it. Using a placebo is common in research studies. The placebo is also given as an infusion.

Site Feasibility

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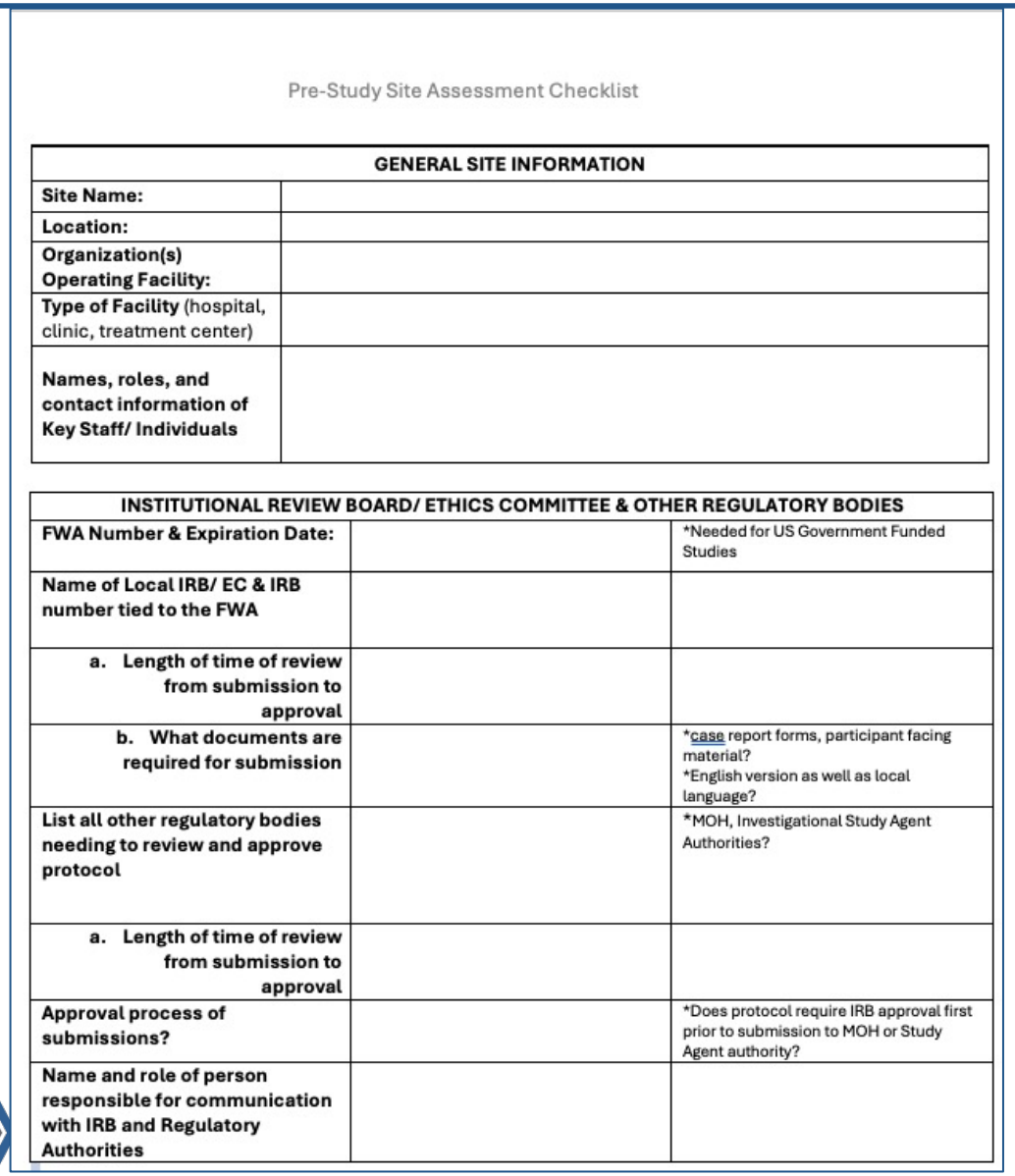
Site Feasibility



Pre-Study Site Assessment Checklist

GENERAL SITE INFORMATION	
Site Name:	
Location:	
Organization(s) Operating Facility:	
Type of Facility (hospital, clinic, treatment center)	
Names, roles, and contact information of Key Staff/ Individuals	

INSTITUTIONAL REVIEW BOARD/ ETHICS COMMITTEE & OTHER REGULATORY BODIES		
FWA Number & Expiration Date:		*Needed for US Government Funded Studies
Name of Local IRB/ EC & IRB number tied to the FWA		
a. Length of time of review from submission to approval		
b. What documents are required for submission		*case report forms, participant facing material? *English version as well as local language?
List all other regulatory bodies needing to review and approve protocol		*MOH, Investigational Study Agent Authorities?
a. Length of time of review from submission to approval		
Approval process of submissions?		*Does protocol require IRB approval first prior to submission to MOH or Study Agent authority?
Name and role of person responsible for communication with IRB and Regulatory Authorities		

- Begin site identification:
  - Contact sites and assess their ability to conduct the study
  - Visit sites
- Complete the pre-study site assessment visit checklist.

Pre-Study Site Assessment Activities

- Ensure interested investigators can conduct research
  - E.g., qualified, research experience, training, etc.
- Identify applicable regulations and approving bodies for research at a given site
- Assess site capacity/setup and visit the site/tour facilities
  - Power supply
  - Water supply
  - Internet connectivity
- Clinical areas-
  - Room to consent,
  - Exam rooms with necessary equipment
  - Phlebotomy area
- Pharmacy
  - Location and space
  - Secure
  - Power Supply
  - Equipment (Freezers, Refrigerators, Preparation hoods, UPS, Computers)

Pre-Study Site Assessment Activities

- Identify whether a local/central lab is needed for sample processing or storage
  - Power and water supply
  - Secured area
  - Pertinent equipment to run study tests
  - Refrigerators, freezers, UPS, adequate storage of supplies and specimens
- Identify access to a site's medical record systems
- Identify a site's database capabilities
- Determine if any protocol-specific equipment will be needed at a given site
  - E.g., MRI, CT scans, X-ray, etc.
- Complete facility qualification

Final Selection of Site

Sponsor/ NIH Investigator Team review of PSSAV outcomes:

- Consider summary of visit and findings noted
- Mitigate any risks noted so the sponsor can determine if a site will be selected to perform the study
- Develop an appropriate timeline for study implementation with following considerations
  - What needs to be completed at the site, brought in to bring site up to level to conduct the study?
  - Supplies needed at site
  - Determine the timing for site/country representatives to obtain regulatory and Institutional Review Board (IRB) approvals
  - Need for import license for study agent.
  - Training of site study staff

Considerations & Challenges

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Best Practice to Enhance Collaboration

- Communication
- Transparency
- Respect & Trust
- Commitment and Coordination
- Strategy
- Contributions
- Cultural Awareness & Sensitivity

Best Practice to Enhance Collaboration

- Consider the impact of your partners' (and your own!) culture:
  - Values, beliefs, perceptions, traditions, and practices
  - Words, gestures, expressions
    - E.g., what one says may mean something entirely different (and unintended) to a partner from a different country, culture, and/or background
- Understand similarities and differences without judgment
  - Improves relationships by informing proper etiquette
    - E.g., what is proper or not in different situations can impact the progress, decisions and outcomes of a partnership's efforts

Potential Barrier to Overcome

- Technology Challenges
- Communication Barriers
- Cultural Differences
- Difference in Standard of Care
- Education & Training
- Geographic Locations/ Infrastructure
- Financial Constraints

Preparedness

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Protocol Activation Checklist

Example of a part of Protocol Activation Checklist

Tunda Regional Hospital (Maniema Province)		
Protocol	**Status:**	**Comments:**
*Protocol version and date approved		
*Protocol Consent and Assents approved		
*Screening Consent and Assents approved		
*Flip book approved		
*Translations completed (with certifications if needed)		Swahili, Lingala, Tetela and French
Regulatory	**Status:**	**Comments:**
* Delegation Logs		
* CV (Signed and dated) for all key staff		
* Medical License		
* Signed Investigator agreement on file		
* Completed training logs for regulatory binder		
*Regulatory binder created		
*INRB CRC Scientific review and approval completed.		
*IRB/EC DRC submission		
*IRB/EC DRC approval		
*Clinical Trial Insurance		
*No Fault Insurance		
*ACOREP (formerly DPM) submission		
*ACOREP (formerly DPM) approval completed		
* Submission of final approved protocol to DSMB (approval not required for study start)		
*Federal Wide Assurance (FWA)		
Training	**Status:**	**Comments:**
* Protocol Training Logs		
* Pharmacy Training Logs		
*GCP training logs		
* Imaging Device/Photo Guidelines Training Logs		
* Laboratory Training Logs (GLP training logs)		
* Clinical Management Training Log		
* Valid GCP certificate / GCLP		
Data Management	**Status:**	**Comments:**

Categories for Protocol Activation Checklist

1	**Principal Investigators**	**Status:**	**Comments:**
2	**Name of PI:**		
5	**Study Coordinator**	**Status:**	**Comments:**
7	**Laboratory Manager/Director**	**Status:**	**Comments:**
8	**Pharmacist(s)**	**Status:**	**Comments:**
9	**Protocol**	**Status:**	**Comments:**
10	**Regulatory**	**Status:**	**Comments:**
11	**Training**	**Status:**	**Comments:**
12	**Data Management**	**Status:**	**Comments:**
13	**Laboratory**	**Status:**	**Comments:**
14	**Site Operations**	**Status:**	**Comments:**
15	**Cold-Chain Supply**	**Status:**	**Comments:**
16	**Psycho-Social**	**Status:**	**Comments:**
17	**SMC**	**Status:**	**Comments:**
18	**Pharmacovigilence (Safety)**	**Status:**	**Comments:**
19	**Pharmacy**	**Status:**	**Comments:**
20	**Clinical Management**	**Status:**	**Comments:**
21	**Site Activation**	**Status:**	**Comments:**
22	* Site Activation		SIV and Site Activation Letter issued by US Monitoring Team on 10/7. Site open for enrollment on 10/8.
23			
24	**LEGEND**		
25	Verified completed/available/will not hold up study start		
26	At ICC/In progress		
27	Pending		
28	Waived/not required for site activation		
29	Unknown	?	

Preparing for Study Start

- Submission to all various regulatory authorities and written approvals in hand
  - Be very careful of version control
- Development of Case Report Forms whether paper or electronic
  - Needs to be completed and signed off by PI prior to study implementation
- Study Manuals
  - Manual of Operations (MOPS)
  - Communication Plans
  - Statistical Analysis Plan
- Standard Operating Procedures (SOPs)
- Delegation logs
- Site Regulatory Binder
- Pharmacy accountability logs
- Ensuring all supplies are shipped to site
- Obtaining any necessary import licenses for study product

Preparing for the Study Start - Training

- Ensuring all key staff have had ICH GCP training or provide the necessary training
- Protocol Overview Training
  - Background of study design
  - Subject recruitment process
  - Inclusion/exclusion criteria
  - Study procedures
  - Consent process
  - Document, recording and reporting of events (AEs/ SAEs)
  - CRF completion

Protocol Implementation & Oversight

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During Study Implementation

- Ensure there is a communication plan in place between staff on the ground and NIH staff
  - Weekly calls with leadership and team leads (Pharmacy, laboratory, key clinical staff)
- QC/QA Plan written and implemented
  - Quality Control checks done by study staff in real time to quickly identify and resolve issues.
  - Help provide checklists for study binder, participant records/ data, and pharmacy
  - Monitoring plan for the frequency of monitoring visit, what will be reviewed during those visits.
    - Can be done remotely with ability view source documents. Need on site monitoring as well.
- Planned trips to the site to work with the staff, reviewing how enrollment is preceding, quality of the data, and provide any necessary training.
- Ensuring annual IRB review of the protocol occurs.
- With any amendments, ensure protocols and consents align and all approvals are received before implementation.

References and Links

- https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-700Series-InternationalResearchRequirements
- Federalwide Assurance
- https://clinregs.niaid.nih.gov
- https://nih.sharepoint.com/sites/NIAID-DCR/OCRPRO/SitePages/Home.aspx
- https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf
- Pending publication: Global Clinical Research Educational Modules through the Frederick National Laboratory public website

Questions and Answers

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Thank You