Class Objectives

- Learn how to evaluate protocol feasibility
- Learn how to identify what you need to do as a study coordinator to get a study up and running here at OHSU and keep it running smoothly

“Protocol” Documents

- Grants Contain:
  - High Level Scientific Concepts
  - May describe several studies
  - Generally little detail
  - Generally not revised
  - Revisions require funding source approval

- Protocols Contain:
  - High Level Scientific Concepts
  - Generally describe one study
  - Moderate Level of detail
  - May be revised with IRB approval

- Operations Manual:
  - Little or no scientific information
  - High level of detail for completing tasks
  - May be revised frequently without IRB approval (must be consistent with the IRB approved protocol)
Who Evaluates the Protocol?

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Reason for Review</th>
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<tbody>
<tr>
<td>IRB</td>
<td>Subject protection</td>
</tr>
<tr>
<td>Funding agency (NIH, private foundation)</td>
<td>Funding agency</td>
</tr>
<tr>
<td>FDA federal oversight (if applicable)</td>
<td>Protect public health</td>
</tr>
<tr>
<td>Investigator</td>
<td>Scientific interest, feasibility</td>
</tr>
<tr>
<td>Study Coordinator</td>
<td>Feasibility, operational implementation</td>
</tr>
<tr>
<td>Institutional (if applicable)</td>
<td>EX: OCTRI or Knight Clinical Trials Office</td>
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Coordinator Protocol Review

- Learn the protocol requirements
- IRB application
- Write the consent
- Operational Implementation
  - Develop study checklists and data collection forms (i.e. DCFs or CRFs)
  - Plan study workflow
- Feasibility

Protocol Analysis

Redesign or Decline Study

Study Information → Feasibility → Conduct Research → Evaluate

Budget → Operational
Protocol Analysis

Who?
What?
Where?
When?
How?
Why?

Feasibility Analysis

“No idea is so outlandish that it should not be considered with a searching but at the same time a steady eye.” – Winston Churchill

Why should we do a feasibility analysis?

• 2011 paper published about research at OHSU found that 31% of studies at OHSU enroll 0 or 1 subject
  - Cost to institution = $1 Million annually
  - Underperforming studies slow down the entire research system
  - Increases the risks of bad science

Initial Feasibility Analysis

Initial Feasibility
• People (Who?)
• Time (When?)
• Protocol Requirements (What? and How?)

People
• Subjects
  – Do you have the subjects at OHSU?
  – Is the subject burden reasonable?
• Research Staff
  – Do you have enough staff to take on the study?
  – If not, can you afford to hire and train someone?
• Investigators
  – Do the investigators have the proper training?
  – Does the PI have access to the subjects?

Time
• Time to conduct the research
  – Need to make sure PI has time to supervise the study
  – Don’t want to take on the study if a PI is leaving OHSU before the end of the study
• Time to enroll subjects
  – Average 4 months from IRB submission to contract execution
  – Don’t take on studies if enrollment is expected to close within 8 months (if you have the subjects!)
Protocol Requirements

• Do you have the required equipment? Can you use it at OHSU?
• Does the OHSU Standard of Care (SOC) match the protocol requirements and what the sponsor is willing to pay?
• Does the sponsor’s subject injury position conflict with OHSU’s?
• Do we do the required labs/tests here?

Identification of Standard of Care

• SOC varies among institutions so an OHSU PI or MD co-investigator makes determination (not the sponsor!)
• Not always obvious in the protocol
• Not always obvious to the MD
• Work with the CRBO if you have questions

Industry Sponsors/CROs

• Have you done studies with this sponsor/CRO in the past?
• How did it go? Were there contract problems?
  – Ask around if you don’t have experience with the sponsor or CRO
How do I conduct a feasibility analysis?

Feasibility checklist on OCTRI website
- [http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/forms.cfm](http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/forms.cfm)
  - Modify the form to meet your needs.

Feasibility checklist on Knight website
(Toolkits: Initial Submission - 2. Feasibility)
  - Modify the tools to meet your needs

Feasibility Scenarios

Operational Analysis
“Proper preparation prevents poor performance”
- Charlie Batch
Operational Analysis of a Protocol

• More detailed than the initial feasibility analysis
• Ask what, who, where, when, how, and why for every procedure listed in the protocol
• Also same questions for study management activities that aren’t listed in the protocol (DSMP activities, data entry)
• In the end you should have a road map for conducting the study

Asking the questions
Identification of Labs

Protocol states 20 mls of blood drawn at visit 2
• Why are you drawing the sample?
• What tubes do you need to draw?
• Where is supply of tubes?
• What is the minimum amount of blood needed?
• Does the sample need to be on ice?
• Will sample be processed at OHSU or a central lab?
• Does it need to be shipped that day?

Asking the questions
Identification of Unspecified Procedures

Procedures required for safe conduct of a study aren’t always listed in the protocol
• Example: the protocol states a ‘Dexa Scan will be completed at Visit 3’
• What is a potential unspecified procedure for a Dexa Scan?
Asking the questions: 
**Identification of Safety Procedures**

- Safety Assessments
  - Which procedures are conducted for safety monitoring?
    - Are labs/procedures tied to safety endpoints?
  - Are there any special precautions for specific side effects, if required?

Asking the questions: 
**Adverse Event Management**

Adverse Experiences (AEs)
- What are the expected adverse events?
- Who will likely be the first study team member to learn of AEs? To whom do they report them?
- What documentation is required and where will it be kept?
- What criteria are you using to grade severity?
- What criteria are you using to grade relatedness?
- How long do I follow AEs?
  - After AE, usually follow until event is resolved
  - UPS that occur within 30 days of last study intervention/subject discontinuation must be reported to the OHSU IRB

Asking the questions: 
**Subject Discontinuation/Stopping Rules**

Subject Discontinuation criteria
- How many subjects do you expect to drop out/or be withdrawn?
- What study procedures need to be done?
- Will you need to replace these subjects?

Stopping rules/criteria
- What is your review/communication process to make sure you follow your plan?
Where else should I look for information?

- OHSU IRB Initial Review Questionnaire (IRQ)
- Investigator Drug Brochure (IDB)
- Investigator Device Brochure (IDB)
- Laboratory/Operations Manual
- Standard Operating Procedures (SOPs)
- Grant/Contract

Initial Review Questionnaire (IRQ)/Local Context supplement

Look in IRQ or Local Context Supplement for information that may not be in the protocol:

- Approved research staff
- Funding information, budget details
- # of subjects at OHSU
- Recruiting and consenting procedures
  
  + eCRIS: contains useful study information

What is in Investigator drug/device manual?

<table>
<thead>
<tr>
<th>IDB (investigational drug brochure)</th>
<th>IDB (investigational device brochure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains information on drug agent</td>
<td>Contains device information</td>
</tr>
<tr>
<td>Study results to date</td>
<td>Implant or compatibility or programming requirements</td>
</tr>
<tr>
<td>All known AEs and risks, listed by body system</td>
<td>Calibration requirements</td>
</tr>
<tr>
<td>Detailed information on dosing</td>
<td></td>
</tr>
</tbody>
</table>
What is in a Lab/Operations Manual?

May be referred to by other names.
Can include detailed information on almost anything
• Lab processing
• Shipping instructions
• Case Report Form (CRF) completion
• Patient flow during a visit (e.g. call ahead to see if X-ray is backed up before you head down there with a patient)
• Calling and paying for a taxi
• Many, many other details

What will I find in policies and SOPs?

• Institutional Policies (OHSU): describe how hospital systems interact with research systems at OHSU
• Departmental SOPs: describe who, what, where, when, and how of research activities are conducted in a specific unit/department.
  – How to obtain/verify informed consent
  – Drug accountability

If you have local SOPs and policies, you will be held to them in an audit. Know them and use them.

What will I find in the Grant/Contract?

• Number of subjects in contract—what is the maximum # of subjects you can enroll?
• How and when do we get paid?
• How do we terminate the contract?
• Term of the contract/grant?
• Reporting Requirements to the sponsor
• Contracts must be signed by the appropriate OHSU institutional signatory (not the PI or Department) before the study can begin
Implementing A Research Protocol

**Check Institutional Approvals**
- eCRIS – Visit Schedule General Information smart form (not an “institutional approval” but should match contract)
- Personnel
- IRB-approved documents.
- Regulatory binder updates
- Working with a sponsor? Are your essential documents in? Are all current documents approved?
- Non-English speaking patients/materials

**Review Protocol (Operational/Project management perspective)**
- Tool: Protocol Review Checklist or Study Start-up Task List
- Intention of developing protocol SOP/checklists
  - Who, What, When, Where, Why, and How
  - Example: PI initiated study looking at attitudes towards new ultrasound machine through brief patient survey. Intent to enroll 140 pregnant women ages 18-35 at 9-28 weeks, receiving routine ultrasound at OHSU. Exclusion criteria: unable to provide informed consent.
Implementing A Research Protocol

• What Institutional resources do I need?
  – eCRIS
  – Research Rates (hospital services charged to the study account)
  – Industrial Account number
  – Interpreter services
  – Research store
  – Research pharmacy
  – Impacted departments/research groups
  – OCTRI, PCRO, WHRU, Knight Cancer Institute

Implementing A Research Protocol

What are my equipment and supply needs?
• Labs (shippers, tubes, spot cards, orders, lab slips, etc.)
• Document storage (folders, binders, etc.)
• Study equipment (Sponsor or Hospital)
• CRFs (Sponsor or Department Template)
• Questionnaires/Validated Instruments
  – Directions for administration and scoring
  – Contact for re-order

Implementing A Research Protocol

• What are my administrative needs?
  – Contact or process for patient reimbursement
  – Study alias for ordering supplies and shipping
  – Study tracking (enrollment, AIMS, labs)
  – Study ID and labelling
  – Templates (Fax, common communication)
  – Lab sheets/Downtime forms
  – Reporting process
  – Tracking study goal/AIMS
  – Managing training, competencies, and certifications
  – Managing equipment
Implementing A Research Protocol

Do I have what I need for my recruitment plan?
- IRB approved flyers/advertising
- IRB approved phone scripts/appointment reminder cards
- Direction and maps
- Medical records release forms
- Referral process in place
- Permission to Contact Form
- Screening checklists
- Consent process
- Translated documents/short forms

Putting it into action!

1. Break-down visit 1 from protocol
2. Answer who, what, where, when, why, and how for procedures
3. Make a “To Do List”
Protocol Implementation

• Hurry-up, Wait, Go, Wait!

Training

• Verify study staff have training on Core Competencies
  – (see OHSU Clinical Research Coordinator Required training Checklist [http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/templates-checklists.cfm](http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/templates-checklists.cfm))
  • EPIC access/training, as required
  • eCRIS training, as required
  • EDC/RedCap/Data management

Training

• Staff protocol training
  – Make sure study staff read and understand the protocol
  – Have study staff acknowledge their roles in the study
  – Make sure study staff know how to identify and report deviations
  – Document that training was completed!
**Workflow planning**

- Workflow planning is a balance between *critical steps* and *Dependencies*.
- What are the critical steps for a study activity?
  - Example: Enrollment 1) Review clinic schedule 2) Identify eligible patient 3) call and screen for eligibility 4) Invite for study visit if preliminarily eligible 5) Consent for participation
- What are these critical steps dependent on?
  - Example: 1) IRB approval/WOA for recruitment plan 2) Appropriate training and access to EPIC for study staff 3) Database or log for screening 4) IRB approved Screening Script 5) Eligibility/Screening form 6) staff/process for scheduling 7) Availability of space

**Workflow Planning**

- Workflow planning will need to accommodate changes in:
  - Protocol
  - Enrollment timeline
  - Institutional changes
  - Study staff
  - Data storage/reporting
- Reconciles protocol requirements with practical constraints of human subjects research.
- An essential component in documenting and evaluating study processes.

**Common Workflow Problems**

Don’t account for all the critical steps and/or dependencies related to study activities
- *Don’t forget regulatory/contractual timelines!*

Leads to:
- Enrollment issues
- Regulatory / Non-Compliance Issues (Protocol Deviations, adverse events)
- Patient safety concerns
- Poor data integrity
Avoiding Poor Workflow Planning

• Understand the protocol and institution you are working within
  – Examples: Scheduling, office space, shipping deadlines, CRBO updates, etc.
• Understand your patient population:
  – Illness, mobility, socio-economic concerns, mental health, availability,
    familiarity with institution or research process, motivation for participation,
    language, etc.
• Establish workflow processes that work for your team
  – Ask for what you need – PI, Sponsor, Institution, Study subjects!
  – Be adaptive
• Have a documented workflow process and communicate changes in
  systematic way.

OHSU Tools and Forms

Knight: toolkits on OHSU Bridge

OCTRI: list of research-related forms and templates:
• [http://www.ohsu.edu/xid/research/centers-institutes/octri/resources/policies-forms/forms.cfm](http://www.ohsu.edu/xid/research/centers-institutes/octri/resources/policies-forms/forms.cfm)
  Including: EPIC access, Research Rates, CRBO forms
• Research Subject Preconsent Study Status form
  [http://www.ohsu.edu/xid/research/about/integrity/crbo/](http://www.ohsu.edu/xid/research/about/integrity/crbo/)
• It is necessary to have the research association set prior to scheduling the
  patient’s first research appointment. Studies that are in eCRIS will have
  research associations automatically added to Epic when study staff add a
  consenting subject to eCRIS.

OHSU Tools and Resources

• Use of Research Devices and Equipment
  – Must be inspected by Clinical Technology Services if the
    device/equipment was not purchased by OHSU
• Computers
  – If the sponsor provides you with a computer for the study
    (not purchased through OHSU) it must be inspected by ITG
OHSU Tools and Policies

• Subject Injury
  – If a subject is injured during an industry sponsored clinical trial and the PI feels it is related to the study drug/device/intervention or study procedures
  – Follow the Research Subject Injury Reporting Policy available on the CRBO website
  – Notify the sponsor, CTO contracting, IRB analyst, and CRBO as soon as you become aware of the injury
  – You will be asked to provide injury and patient information to comply with billing and contracting requirements

OHSU Tools and Forms

Follow OHSU research and hospital policies:
• IRB Policies: [http://www.ohsu.edu/xd/about/services/integrity/policies/](http://www.ohsu.edu/xd/about/services/integrity/policies/)
• OHSU Research Policies and Guidance: [http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/index.cfm](http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/index.cfm)
• Knight SOPS and policies on Bridge: [https://bridge.ohsu.edu/research/knight/policies/SitePages/Home.aspx](https://bridge.ohsu.edu/research/knight/policies/SitePages/Home.aspx)
• Clinical Research Billing office forms and policies: [http://www.ohsu.edu/xd/research/about/integrity/crbo/forms-and-policies.cfm](http://www.ohsu.edu/xd/research/about/integrity/crbo/forms-and-policies.cfm)

Conducting the Protocol

After study has IRB approval, the study team is expected to adhere to the protocol without deviations – unless it is for the safety of the subject
Prediction is very difficult, especially if it's about the future.

Niels Bohr

Protocol Analysis

Redesign or Decline Study

Study Information

Feasibility

Budget

Operational

Conduct Research

Evaluate!

Evaluate! Re-evaluate

• Once your studies are up and going, put in place a plan to evaluate the recruitment and study conduct (every 3-6 months)
• If enrollment isn’t going well ask yourself why? Is there anything you can do?
• If you are having a lot of protocol deviations and you won’t meet your endpoints look at your operational analysis to see if there is something you can change
• If you don’t think you can turn the study around as designed the PI should consider stopping it.
Revising the Protocol

• Protocol Modifications
  – An amendment/modification can be submitted for IRB approval to address new information/difficulties
  – Strive to minimize modifications so that data remains “poolable” by completing a good analysis
    • Don’t want to compare apples and oranges
  – Maintain consistency within and between the protocol, consent, and procedure manuals (avoids confusion)

Protocol Revisions, cont.

• Modifications
  – You may want to re-analyze your protocol if there are significant changes before you submit the modification to the IRB but you should always analyze new procedures before implementation
    • Feasibility
    • Location/Scheduling
    • Training
    • Budget

Stopping a Study

• If you determine you won’t be able to address the recruitment or other problems and want to stop the study:
  • Industry sponsored
    – PI must notify the sponsor in writing
    – Let the Clinical Trials Office and SPA know
  • NIH sponsored research
    – PI should contact program officer to look at options (Your PI should have a plan, e.g. adding sites, protocol modifications)
    – Notify RGC
  • Submit modification to change study status in eIRB
What about budget feasibility?

- Budget Development Training available
- Research Administration Training and Education (RATE)
- [http://www.ohsu.edu/xd/research/administration/training-and-education-rate/classes-workshops/index.cfm](http://www.ohsu.edu/xd/research/administration/training-and-education-rate/classes-workshops/index.cfm)