How to Analyze and Implement a Research Protocol

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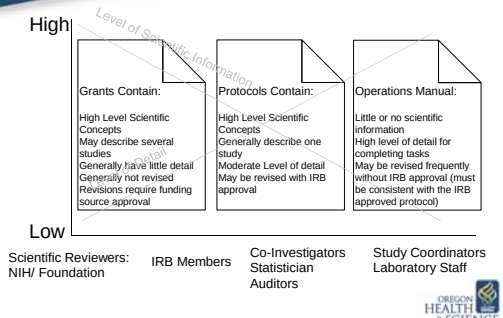
Class Objectives

- 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 –



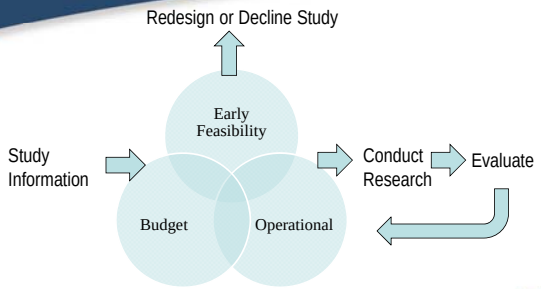
Who Evaluates the Protocol?

- IRB: Subject Protection
- Funding agency (NIH, Foundation): $, Science
- Federal Oversight (FDA) if applicable: Protect Public Health
- Investigator: Feasibility, Scientific Interest
- Study Coordinator: Feasibility, Operational Implementation

Coordinator Protocol Review

- Learn the protocol requirements
- IRB application
- Write the consent
- Operational Implementation
  - Develop study checklists and data collection forms
  - Plan study workflow
- Feasibility

Protocol Analysis



Protocol Analysis

- Feasibility Analysis
- Operational Analysis
- Budget 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

Feasibility Analysis

- 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
- *Kitterman, D.R., Cheng, S.K., Dilts, D.M., & Orwoll, E.S (2011) The Prevalence and Economic Impact of Low-Enrolling Clinical Studies at an Academic Medical Center. Academic Medicine, Vol. 86(11), pp.1-7*

Early 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 the PI has the 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 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

- Standard of care varies from institution to institution 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 available on the OCTRI website
  - http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/forms.cfm
  - You can modify the form to meet your needs.

Feasibility Scenarios

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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 ask these 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

Example Asking the questions: Identification of Labs

- Protocol states 20 mls of blood will be drawn at visit 2
  - Why are you drawing the sample?
  - What tubes do you need to draw?
  - What is the minimum amount of blood needed?
  - Does the sample need to be on ice?
  - Will the sample be processed at OHSU or at 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
  - 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 an adverse event - 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/Device Brochure
- Laboratory/Operations Manual
- Standard Operating Procedures (SOPs)
- Grant/Contract

What is in the Initial Review Questionnaire (IRQ)?

- IRQ information that may not be in the protocol:
  - Approved research staff
  - Funding information
  - # of subjects at OHSU
  - Recruiting and consenting procedures

What is in the IDB/ Device Manual?

- The IDB (investigational drug brochure) contains information on the drug
- Study results to date
- All known adverse events and risks by body system
- Detailed information for the investigator on dosing
- Device Manual will include implant/compatibility/programming requirements
- Device Manual will include any calibration requirements

What is in a Lab/Operations Manual?

- Maybe known by other names
- Could include detailed information on almost anything
  - Lab processing
  - Case Report Form 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 describe how the hospital systems interact with the research systems at OHSU
- Departmental SOPs – describe who, what, where, when and how of research activities are conducted in a specific Unit/Department.
  - Obtaining/verifying informed consent
  - Drug accountability
- If you have SOPs you will be held to them in an audit so know them and follow 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

Where Do I Start?

"Adventure is just bad planning" – Roald Amundsen

Implementing A Research Protocol

- **Check Institutional Approvals**
  - IRQ
  - Number of subjects you should request in the IRQ/ protocol is study dependent
    - Expected rate of attrition
    - Screen failure rate
    - Numbers need to be reasonable and consistent with the protocol and contract (when applicable)
  - 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

Implementing A Research Protocol

- **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)
  - CRBO status change form
  - Industrial Account number
  - Interpreter services
  - Research store
  - Research pharmacy
  - Impacted departments/research groups
  - OCTRI, PCRO, WHRU, Knight Cancer Institute

Implementing A Research Protocol

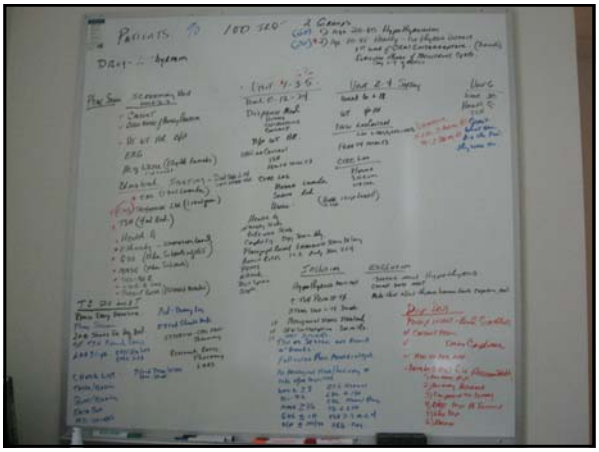
- **What are my equipment and supply needs?**
  - Labs (shippers, tubes, spot cards, MD orders, lab slips, etc.)
  - Document storage (folders, binders, etc.)
  - Study equipment (Sponsor or Hospital)
  - CRFs (Sponsor or Department Template)
  - Questionnaires/Validated Instruments
    - Directions 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
  - Templates for communicating with study subjects
  - 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)
- 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!
  - Tool (sign-in sheet template - http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/templates-checklists.cfm)

Work-flow 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

Work-flow 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

- OCTRI has compiled a list of research related forms and templates that may be useful for you:
- http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/forms.cfm

Including: EPIC access, Research Rates, CRBO forms

- Research Admission - request form available at http://www.ohsu.edu/research/crp/docs/researchFYI.doc
- Research Outpatient Appointment Scheduling Request http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/ohsu-research-policies.cfm?WT_rank=1
  - It is necessary to have the research association set prior to scheduling the patient's ***first*** research appointment

OHSU Tools and Resources.

- Use of Research Devices and Equipment
  - http://ozone.ohsu.edu/clinicalengineering/eqpPolicies.cfm
  - 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 Forms

- Follow OHSU Research and Hospital Policies:
  - IRB 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

Conducting the Protocol

- Once the 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

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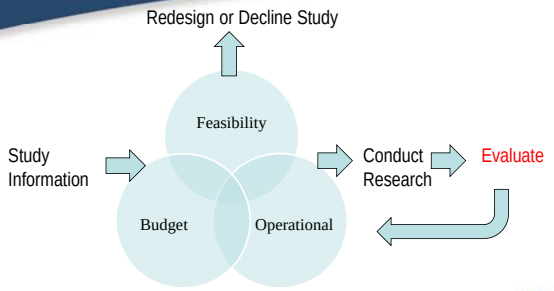
Knight Cancer Institute at Oregon Health & Science University

OCTRI Oregon Clinical & Translational Research Institute

Prediction is very difficult, especially if it's about the future.

Niels Bohr

Protocol Analysis



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 the 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