



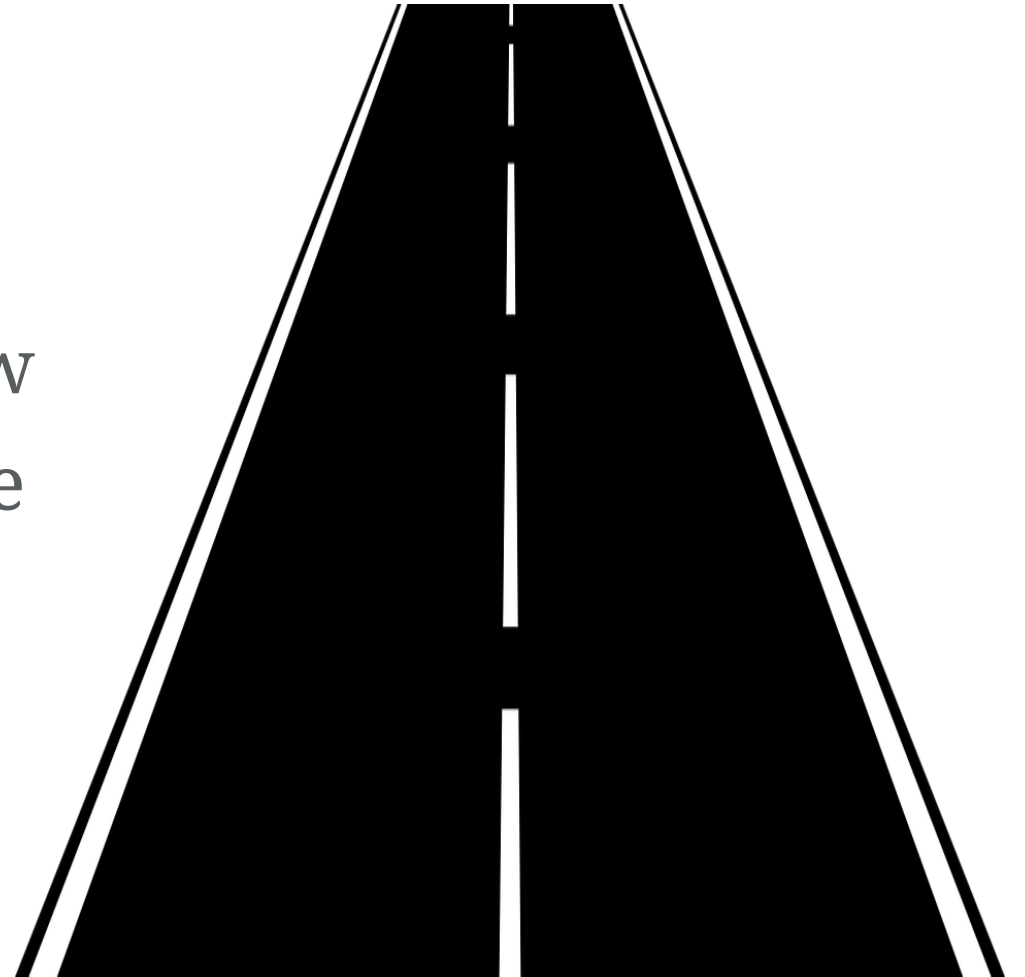
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Transforming your Grant into a Protocol: The *Art* of Protocol Development

February 15, 2024 PRESENTED BY: Bridget Adams, MSHS, CCRA, Manager OCTRI Regulatory Knowledge and Support

Topics We Will Cover

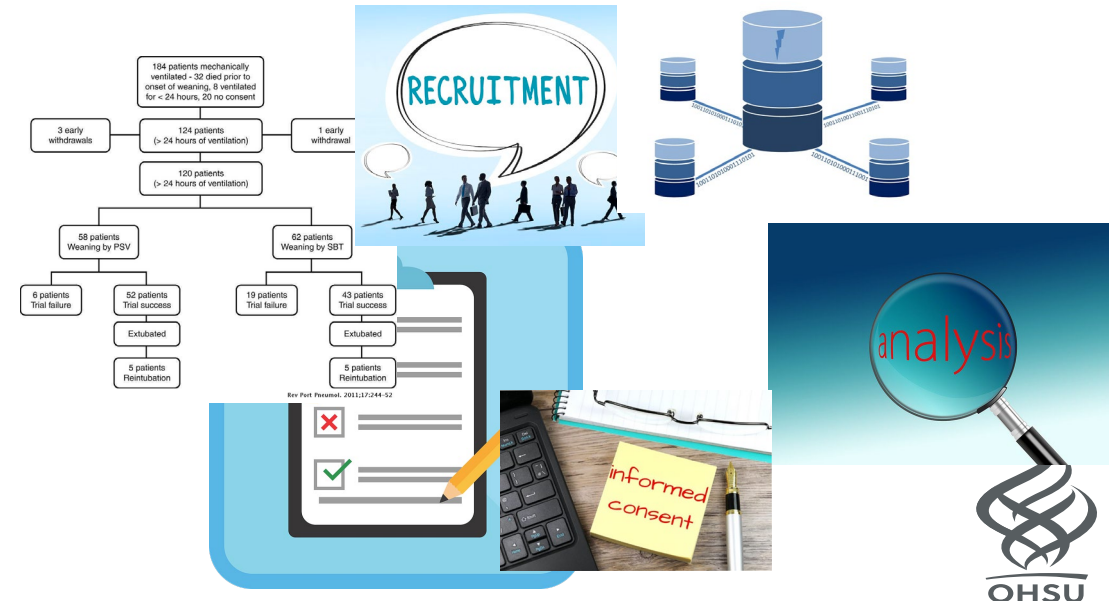
- Difference between grant, protocol, operations manual
- Guidance on when to write a new protocol or revise an existing one
- Required Protocol Elements
- Importance of Good Protocol Development



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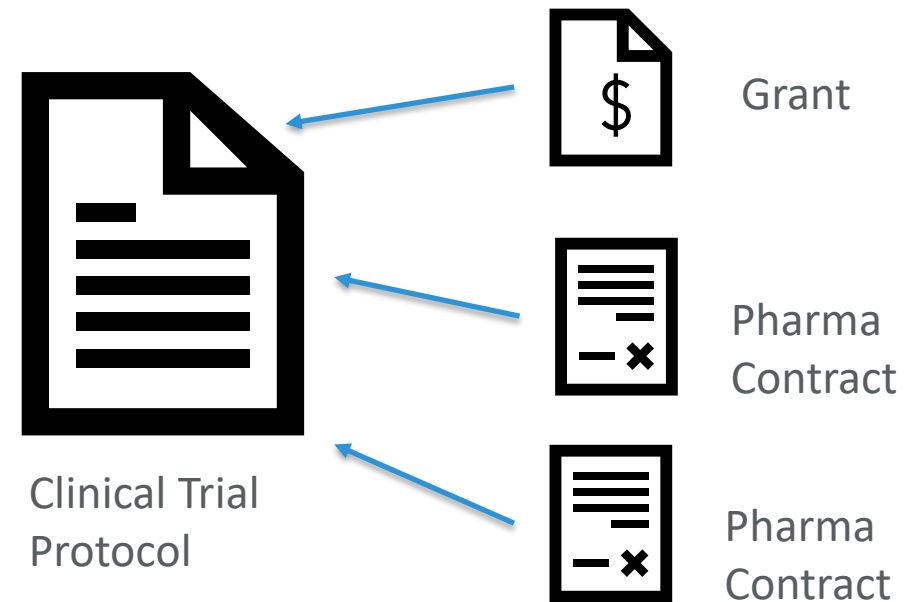
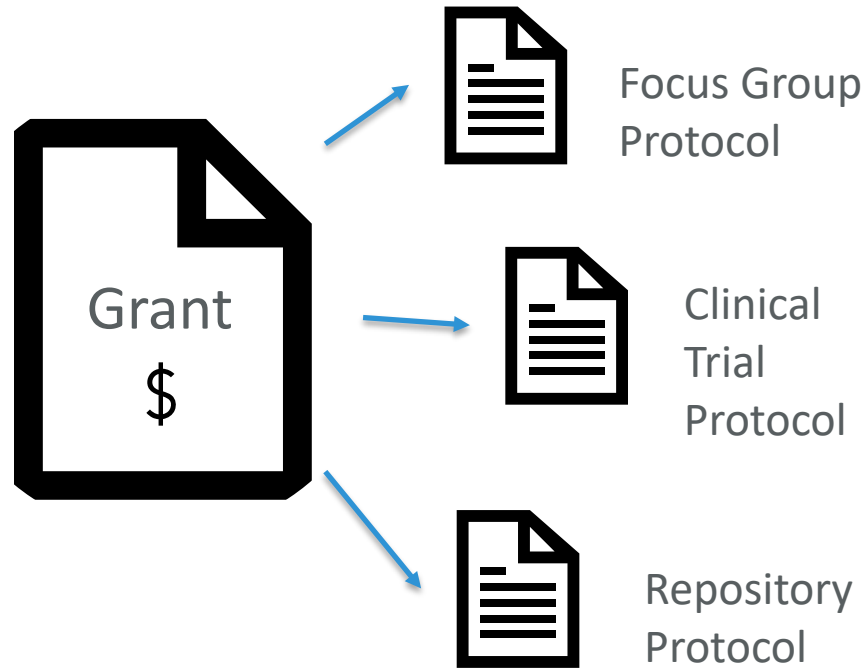
Grant vs. Protocol Goals

- Grant/Proposal:
 - Written to convince reviewers
 - That your project is worthy
 - That you can complete the project
- Protocol
 - Written to explain who, what, where, when, why of your project
 - Must be clear and understandable
 - Detailed – without boxing you in when research meets real world



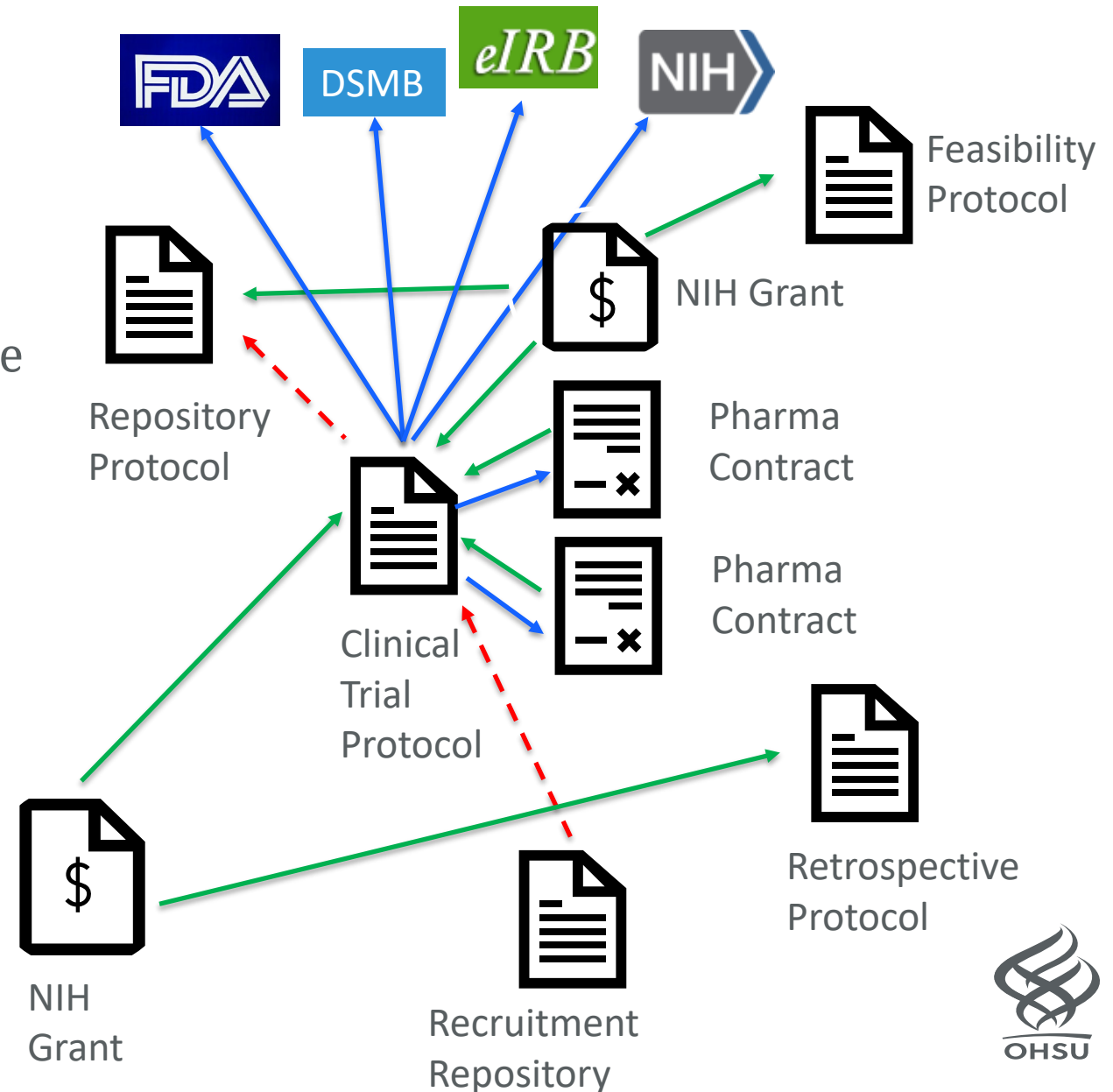
Grants and Protocols

- A grant can include multiple protocols
- A protocol can be funded by multiple grants, foundations and/or pharma contracts



If you want to Combine Grants/Protocols, You Need a Strategy

- Think carefully about:
 - Does it scientifically/operationally make sense
 - How/when you will **share/destroy** information
 - **Regulatory/reporting** obligations
 - **Funding/contractual** obligation
 - See study guide for more info

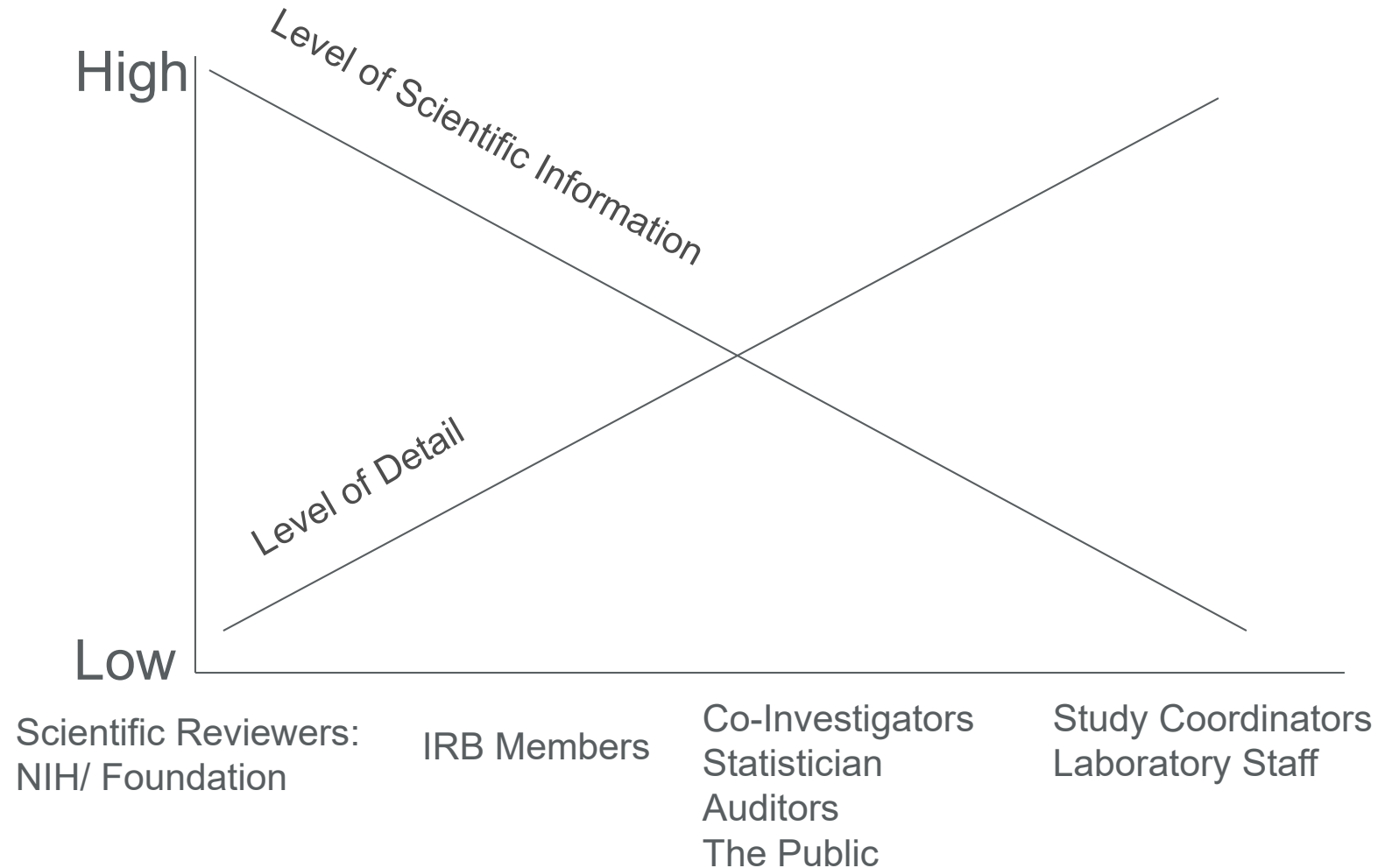


New Protocol or Revise Existing Protocol

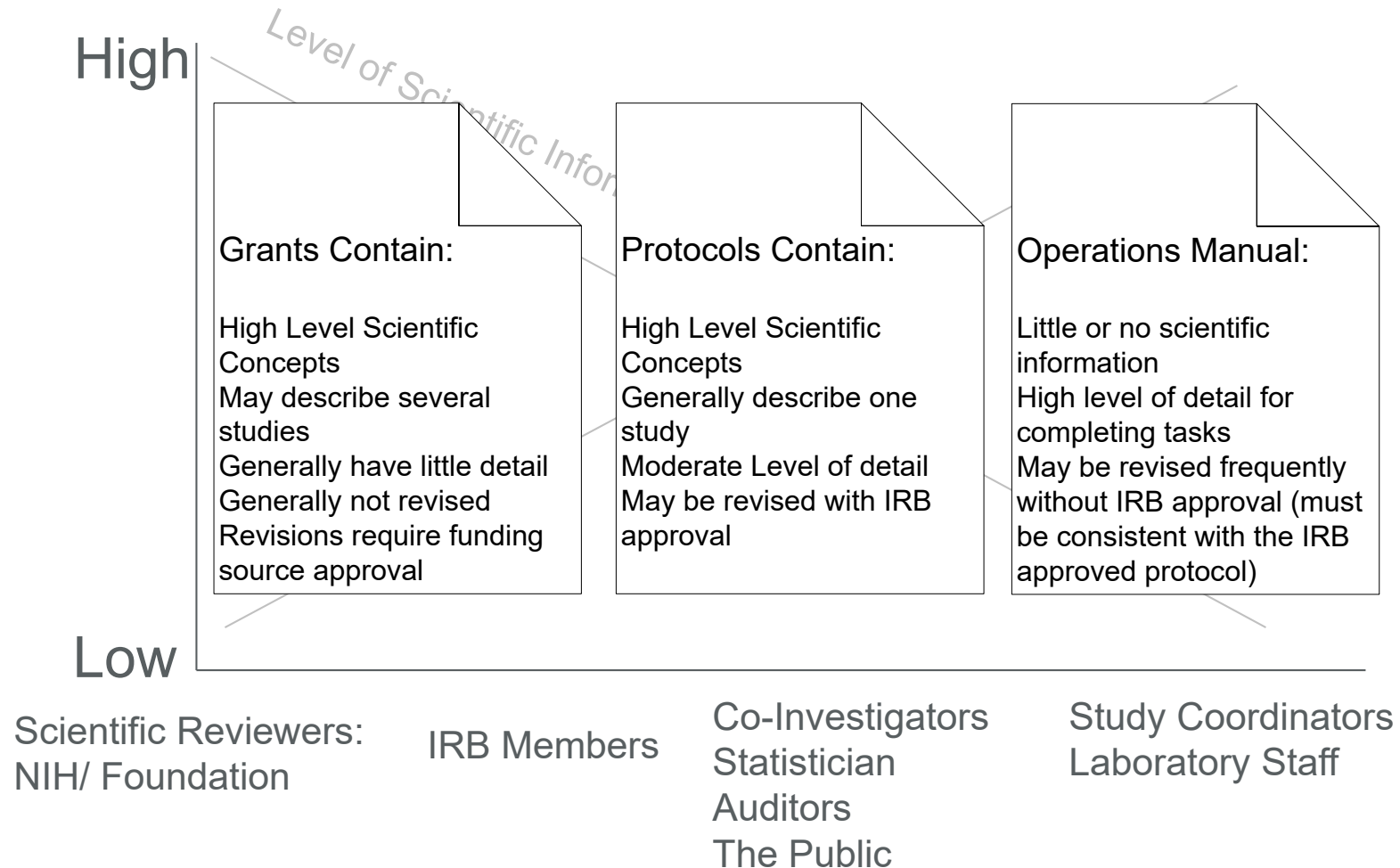


- Consider writing a new protocol when:
 - New patient population
 - Unrelated aims
 - Risk of the new study is greater than the existing protocol
 - e.g. don't add an investigational drug to an observational study
 - Different study design
 - Different regulatory requirements
 - Different contractual requirements
- Consider revising an existing protocol when:
 - Aims of the study and design are the same/similar
 - Population, risks, design are the same
 - Minimal changes are needed
 - Extending the study duration
 - Increasing the number of participants
 - Add a new sub-analysis

Study Documents



Study Documents



Who Reviews the Protocol?

Reviewer	Reason for Review
IRB	Subject protection, compliance with state/federal laws, institutional policies
FDA federal oversight (<i>if applicable</i>)	Protect public health
Study Coordinator/staff (e.g. statistician, nurses, lab, pharmacy, etc.)	Feasibility, operational implementation
Institutional Offices (<i>CRBO, Radiation Safety, Knight CRRC, OCTRI, etc.</i>)	Institutional Offices (<i>CRBO, Radiation Safety, Knight CRRC, OCTRI, etc.</i>) for compliance with state/federal law and institutional policies
<i>The Public (if applicable)</i>	Must upload protocols in clinicaltrials.gov for applicable clinical trials

Protocol Elements

Title

Introduction/Background

Aims/Objectives

Research Methods/
Study Design

Risks/Benefits

Statistical Analysis

Writing the Protocol

- Start with a protocol template
 - OHSU IRB has a template with the required elements and instructions
 - You can use another template/format as long as the necessary content is included
 - If the study is cancer related, investigators must use Knight Cancer Institute Protocol Template



Protocol Development

- Protocol Development is an **Art**
- Balance of scientific ideals and the real world
 - Balance of essential and trivial details
 - Balance of structure and flexibility



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Title



- Give your study a descriptive/meaningful title that is specific, concise, and reflects the content of the study

Example:

“A Study of Mindfulness”

What is wrong with this title?

How would you improve it?

Better title:

“The Effects of Mindfulness-Based Stress Reduction vs. Routine Care”

Best title:

“The Effects of Mindfulness-Based Stress Reduction in Patients with PTSD: A Randomized Controlled Multicenter Trial”



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Introduction, Background, Rationale

- Include brief discussion of important background research and scientific justification.
- State the reason(s) for conducting the study, including relevant information about study population, disease, limitations of existing knowledge.
 - Shouldn't be a copy and paste from your grant.
- Explain why the procedures you propose will answer your research questions.

Aims/Objectives

- Make sure Aims/Objectives are measurable and align with the study duration.
- Write aims with a statement of purpose: “to assess” “to determine” “to compare” “to evaluate”
- Outcome measures should correspond with the study aims and hypotheses.
- Examples:
 - Too Vague – to learn about disease X
 - Better – to determine the risk factors for disease X
- Ensure that the aims in the grant match the aims in the protocol.



Protocol Elements

Title

Introduction/Background

Aims/Objectives

Research
Methods/ Study
Design

Risks/Benefits

Statistical Analysis

Research Methods/Study Design

- Describe the overall approach to the study (ex. prospective/retrospective, observational/interventional, blinded/open label, randomized).
- Describe the different groups, arms, and/or subject population.
 - You may need to describe certain protocol elements for each group/arm
- Study designs that meet the definition of a “clinical trial” may have additional requirements for clinicaltrials.gov registration.
 - See study guide for more information.

Three Little Bears Approach to Protocol Development



- Not too little information
- Not too much
- Just right

Study Population

- # of subjects – what details should you include?
 - # you plan to consent, # needed to complete the study
 - account for screen failures/subject withdrawals
- Inclusion/exclusion criteria - what details should you include?
 - Describe diagnosis and how individuals will be screened for eligibility
 - diagnostic measures used and timing, demographic information
- Inclusion of vulnerable populations (if applicable)
 - What populations and how will they be protected e.g. children, prisoners, decisionally impaired adults, limited English proficiency
- Subject withdrawal criteria – what details should you include?
 - Allowances for temporarily stopping drug/intervention
 - Non-compliance or Safety Issues

Example: Enrollment Criteria too Broad

Study: Blood samples collected to develop a new lab assay

- **Inclusion Criteria**
 - Healthy Subjects
- **Exclusion Criteria**
 - Evidence of infection
 - On medication
 - Medical conditions that may compromise the quality of cells
 - Disorders that may cause problems for the subject

Example: Enrollment Criteria Too Narrow

Study: Evaluating the relationship between hormone levels and PMS symptoms

•Inclusion

- Women between 18 and 30
- PMS symptoms every cycle for at least 1 year
- Normal pap smear within last year
- Regular Menstrual cycles >26 and <32 days

•Exclusion

- Hysterectomy
- Hormonal contraceptives in last 3 months
- History of smoking
- History psychiatric disorder
- History of alcohol/drug abuse
- Use of medications that could affect mood or sleeping
- Abnormal screening blood tests (TSH, LFT, HGB)
- Pregnancy within last year or plan to get pregnant during study
- Use of medications/ alternative treatments for PMS within the last 60 days
- History of insomnia
- History of Migraines

Example: Enrollment Criteria Just Right

Study: Any Clinical Research Study

• Inclusion Criteria

- Characteristics that are relevant to the research question
- Demographic characteristics (e.g. age)
- Clinical characteristics (e.g. diagnosis)
- Geographic characteristics (e.g. Clinic Patients)
- Temporal characteristics (e.g. life expectancy greater than 6 months)
- Vulnerable Populations (if applicable)

• Exclusion Criteria

- Describe subset of population that won't be studied
- Characteristics that make it unethical to withhold treatment
- Subjects at high risk of side effects
- High likelihood of lost to follow-up
- Characteristics that might interfere with the quality of the data

Recruitment Methods

- Describe when, where, and how potential participants will be identified and recruited
 - Describe advertising materials
 - Describe identifiable information you will need to use/collect prior to consent
 - (e.g. email addresses, phone #s, etc.)
 - Describe how you will identify potential participants
 - Describe how/when you will approach/recruit potential participants
- All recruitment materials require IRB approval prior to use
- We recommend you plan to use a variety of recruitment methods



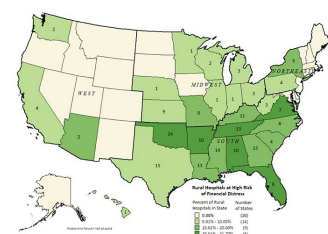
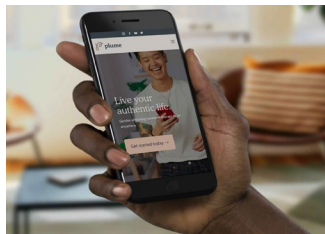
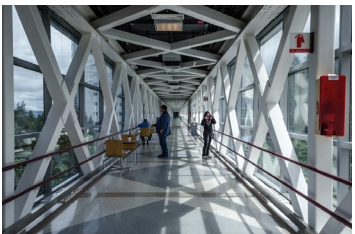
Consent Process

- Describe how you will obtain and document consent
 - Where, when and how you will consent
 - Using eConsent?
 - Include the platform and process you plan to use
 - Steps to minimize coercion/undue influence
 - How you will ensure participant understanding
- Special Considerations: Describe how you will consent participants with limited English proficiency, children/parents/ decisionally impaired adults, emergency research
 - See study guide for links to quick guides for these issues



Study Setting

- Sites/locations where your research team will conduct the study
 - Specify activities occurring at OHSU vs. other locations (ex. VA)
 - Specify where activities will occur and where data/\$/samples originate
 - outside lab, samples from another institution, patient's home, telehealth
 - IRBs involved (Single IRB)
 - Multi-site studies have additional considerations
 - Clarify what activities are performed at OHSU or by OHSU personnel
 - Need to consider how each site will satisfy IRB review requirements
 - If OHSU is the coordinating center there is additional information required
- May want to move activities that may vary from site to site to an supplement (e.g. recruitment, consent, local data handling)



Procedures and Interventions

- Describe research procedures so they can be performed consistently
- Common medical procedures may not need a lot of detail
- State if any procedures are considered standard of care
- Measures and assessments
 - Procedures for physical exams, vital signs, handling samples
 - Procedures when intervention is temporarily stopped or a participant withdraws from the research study
- Data and Specimen banking (if applicable)
 - Indicate whether specimens may be used for future genetic research
- A schedule of events is often very helpful

Schedule of Events

Procedure	Screening Visit	Visit 1 7 days +/- 2 days	Visit 2 30 days +/- 5 days
Consent	X		
Medical Hx	X		
Vital Signs ¹	X	X	X
Chest X-Ray ²	X		
Randomization		X	

1 – BP, HR, Respiration taken after patient sits for 10 minutes

2 – Prior Chest X-Ray can be used if completed within 6 months of randomization

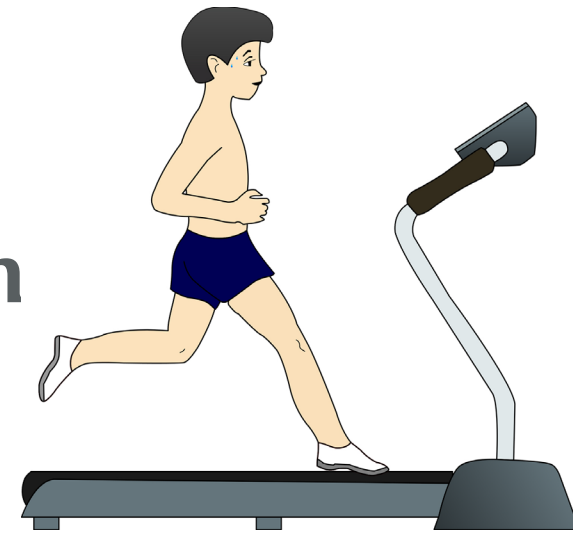
Examples of Procedure Descriptions:

- Timing of procedures
 - Too specific: at 0800, day 7
 - Not specific enough: Subjects will return for a follow-up visit
 - Just right: day 7 +/- 3 days
- Include acceptable ranges
 - Lab values (LFT < 2x normal)
 - Blood volumes (up to 25 mls, approximately 25 mls)
- State when procedures are optional
 - Chest x-ray if not completed within last 6 months, or chest x-ray may be done at the investigators discretion

Example: Procedure Detail

Study evaluating a new pacemaker algorithm

- Too Little Detail:
 - Treadmill test
- Too Much Detail:
 - The treadmill will be calibrated before each treadmill test. Then the cardiac lab nurse (Nancy) will instruct the subject on the treadmill test, ask the subject if they have to go to the bathroom before they begin, carefully clean the skin with alcohol and possibly shave the skin before placing the electrodes (if subject sensitive to alcohol, water may be used)
 - This information would be better in the Operations Manual
- Just Right:
 - Subject will have a Bruce Protocol Stress Test



Example: Proposal states “Frequent blood draws”

A observational study of reproductive hormone patterns in over 24 hours at different points in the menstrual cycle. What is an idea study design?

Ideal Design:
Blood draw every
5 mins for 24
hours

How would you modify?

Option 1
Inpatient Visit Blood draw
every 30 minutes for 12
hours then every 2 hours
for next 12

Option 2
Outpatient Visit Blood
Draw every 30 minutes for
12 hours

Option 3
Subject obtains saliva
samples at home for 24
hours

Final Design:
**Balances scientific ideals with
real world considerations**
Blood or Saliva Samples every 30
minutes for 4 hour outpatient visit
subject collects saliva samples at
home every 2 hours for 12 hours
and first thing the following AM



Risks and Benefits

- List reasonable foreseeable risks, discomforts, hazards, or inconveniences related to participation
 - Include probability, magnitude, duration and reversibility
- List risks for interventions and procedures
- List potential benefits to participants
 - Include probability, magnitude and duration
 - State if study won't have direct participant benefits
 - Participant compensation isn't considered a benefit

Example: Risks

- Risks
 - Too Little Detail: No known risks
 - Too Much Detail: List every adverse event that a study subject encountered in previous studies without regard to relatedness or population
 - Just Right: Pick a cut-off for all study intervention and procedure related risks and be consistent

Safety Assessments/Protection from Risks

- Safety Assessments/Protection from risks
 - Identify procedures conducted for safety
 - Determine how you will recognize, document, and report adverse events
- Stopping Rules/Criteria
 - Don't make them overly strict
 - Too Strict: If an Serious Adverse Event Occurs
 - Just right: Based on statistical and clinical context of your study

Privacy, Confidentiality and Data Security

- Describe steps taken to protect privacy during all phases of the study
 - Steps to secure data and specimens during storage use and transfer
- IRB has a [Security and Confidentiality Protocol checklist](#)

! Common Error – stating data will be de-identified when it includes HIPAA identifiers (e.g. visit dates)

Take the [Recognizing Coded and De-identified Data](#) short training



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Statistical Analysis Plan (SAP)

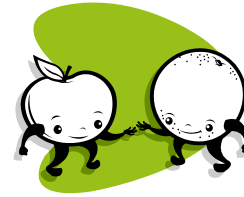
- A well defined SAP is essential for improving the validity and generalizability of clinical trials and other specific research.
- What does a good SAP include?
 - Endpoints (clearly indicate primary, secondary)
 - Method of analysis
 - Monitoring, interim/integrated analysis strategy
 - Comparisons and significance levels (predefined)
 - Exploratory data analyses
 - Get IRB approval for changes
 - Must be kept up to date (clinicaltrials.gov, publication) see study guide for more information

Conducting the Protocol for Compliance

- Once the study has IRB approval the study team is expected to adhere to the protocol without deviations (unless necessary for the safety of the subject)
 - 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
 - Delegate study tasks to qualified individuals (e.g. physical exams delegated to MD, FNP, PA)
 - Supervise the conduct of delegated activities

Protocol Modifications

- Submit a revised protocol to the IRB to address new information or address implementation/recruitment problems
- Strive to minimize modifications so that data remains “poolable”
 - Don’t want to compare apples and oranges
- Maintain consistency within and between the protocol, consent, and procedure manuals



Protocol Best Practices



- Write to your audience – if there is jargon define it
- Describe what you are going to do, not everything you might ever do
- Beware the “copy and paste” from other protocols
- Use boilerplate language when available
- Make it easy for reviewers, coordinators, auditors, others to understand
- Submitting a clearly written, consistent protocol will shorten your IRB review time
- Conduct a feasibility analysis

Your Protocol may be Publicly Available

- Some major journals (e.g. Lancet, Annals of Internal Medicine) require submission of the protocol and post them with the trial manuscripts.
- All studies that are required to submit results to clinicaltrials.gov must include a protocol/statistical analysis plan at time of results posting



Keep your protocol up to date and tidy.

Consider results reporting when deciding to revise or submit a new protocol to the IRB



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Thank You