

# The Art of Protocol Development

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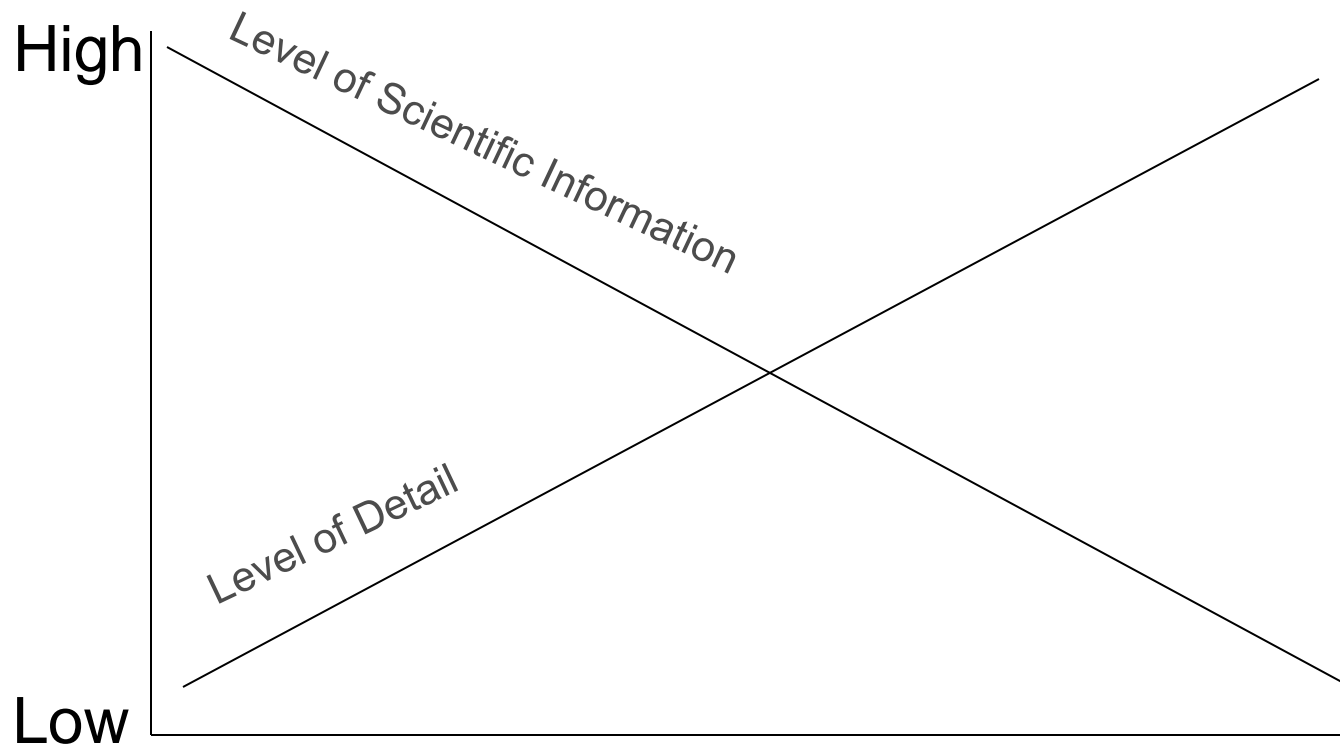
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OREGON CLINICAL + TRANSLATIONAL RESEARCH INSTITUTE



# “Protocol” Documents



Scientific Reviewers:  
NIH/ Foundation

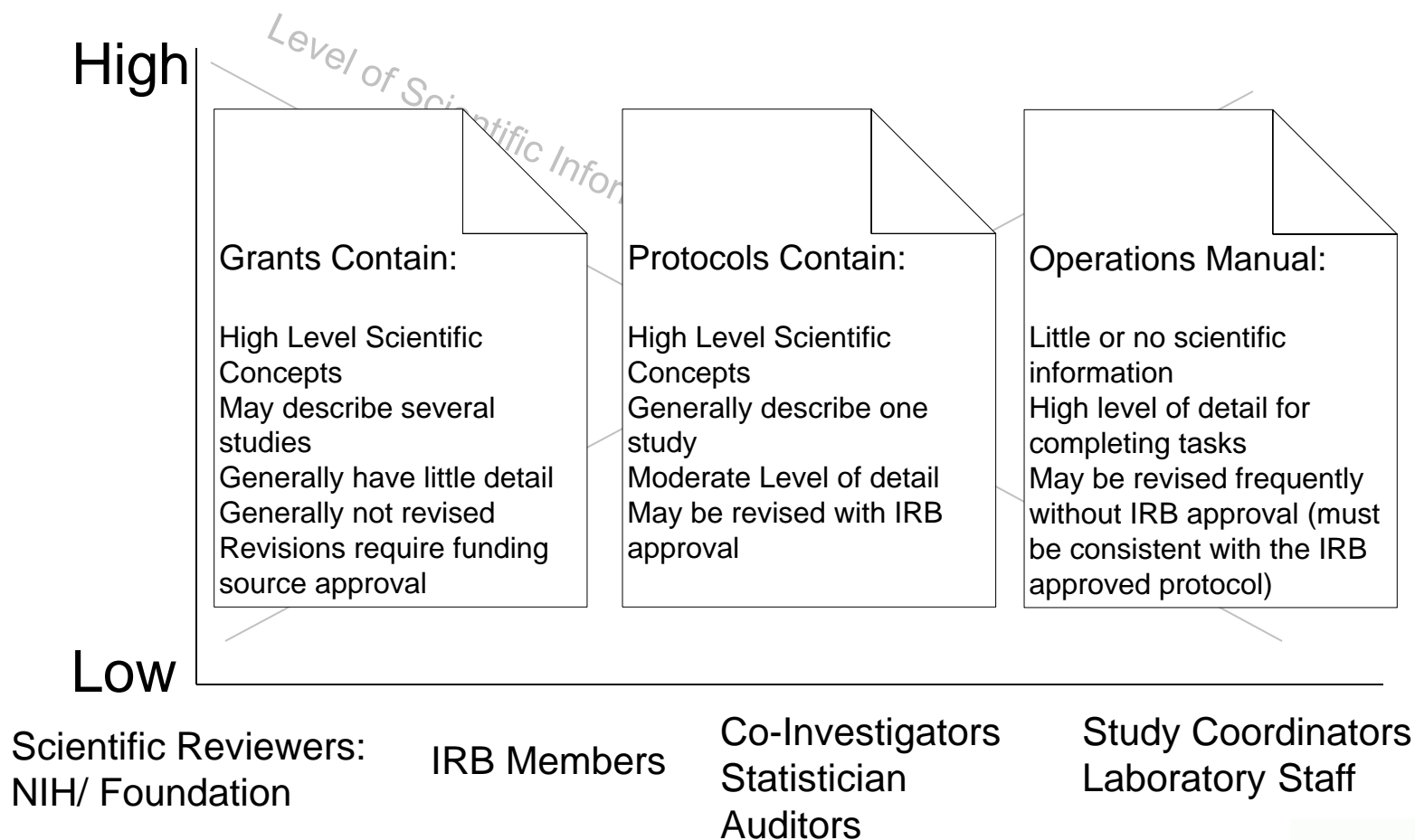
IRB Members

Co-Investigators  
Statistician  
Auditors

Study Coordinators  
Laboratory Staff



# “Protocol” Documents



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



# Required Protocol Elements

- Title
- Introduction, background, rational, literature review
- Purpose(s), Objective(s)
- Research Methods/ Study design
  - Subjects (#, inclusion/exclusion, withdrawal criteria, recruitment, consent)
  - Setting
  - Study procedures
  - Drug/ Device/ Interventions
  - Stopping Rules
  - Duration
  - Endpoints
  - Safety Assessments
- Risks
- Statistical Analysis



- **Study Population**

- # of subjects
  - Distinguish between the # you plan to consent and the # needed to complete the research procedures
    - account for screen failures/subject withdrawals
- Inclusion/exclusion criteria
  - Describe how individuals will be screened for eligibility
    - diagnostic measures used, demographic information
- Inclusion of vulnerable populations (if applicable)
  - You may not include vulnerable populations unless you include this in your protocol
- Individual subject withdrawal criteria
  - Allowances for temporarily stopping drug/intervention
  - Non-compliance



## Study: Blood samples for 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



## Study: 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 of psychiatric dis order
- 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 OMS within 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 materials that will be used to recruit participants

- **Consent Process**

- Describe how you will obtain and document consent
  - Where, when and how the consent process will take place
  - How you will ensure ongoing consent
  - Steps to minimize coercion/undue influence
  - How you will ensure participant understanding
  - How you will consent non-English speaking participants
  - Any requested modifications to the consent process (emergency research, information sheets)
  - Assent and parental involvement
  - Decisionally impaired adults



- **Setting**
  - Sites and locations where your research team will conduct the study
    - Specify activities occurring at OHSU and those occurring at other locations (VA)
    - If there are other sites/IRBs involved specify this in the protocol (are you using an outside lab, recruiting from a non-OHSU clinic, samples from another institution)
- **Duration** (individual subjects and study)



- **Description of study procedures/interventions**
  - Research procedures described in detail so they can be performed consistently
  - Common medical procedures may have no detail to allow for appropriate variation among clinicians (if scientifically acceptable)
  - Measures and assessments
    - procedures for carrying out physical exams, vital signs, handling samples if it is essential to the data collection
    - Procedures that will be followed when a participant withdraws from the research study
    - Indicate if you plan to share results with participants
  - Data and Specimen banking (if applicable)
    - Indicate whether specimens may be used for future genetic research



- **Description of procedures/interventions examples:**
  - 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



## 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)
- Just Right:
  - Subject will have a Bruce Protocol Stress Test



# Example: Proposal states “Frequent blood draws”

**Ideal Design:**  
Blood draw every  
5 mins for 24  
hours

**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 the reasonable foreseeable risks, discomforts, hazards, or inconveniences to the participants related to their participation
- Include the probability, magnitude and duration and reversibility of the risks
- List risks for interventions and procedures
- Indicate risks to embryo or fetus
- List potential benefits to participants, include probability, magnitude and duration





- **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
    - (e.g. intervention/procedure related AEs experienced by  $\geq 5\%$  of the study subjects in previous studies)



- **Privacy, Confidentiality, and Data Security**
  - 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



- **Safety Assessments/Protection from risks**
  - Identify procedures conducted for safety
  - Adverse event recognition, documentation, and reporting requirements
    - May not be specifically stated in the protocol
- **Stopping Rules/Criteria**
  - Don't make them overly strict (e.g. the study will be stopped if a serious adverse event occurs)
  - Think ahead – what should you do if an SAE occurs



- **Endpoints should be**
  - Measurable
    - Measures should be as objective as possible to avoid bias
  - Feasible
    - Do you have equipment, subjects, etc.



- **Why do we care?**
  - If you have too much detail then you will have a lot of protocol deviations to report to the IRB
  - If you have too little detail you won't be able to implement your protocol or analyze your data
  - A well written protocol protects health and safety of research participants



# Conducting the Protocol for Compliance

- **Once the study has IRB approval the study team is expected to adhere to the protocol without deviations**
  - 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

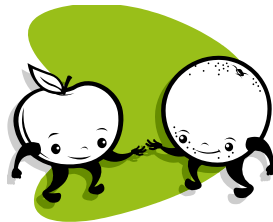


- **Include contingency plans to handle:**
  - Unexpected situations (as much as possible)
  - New information
  - Issues that arise during protocol implementation
  - Exclude subjects with a high risk of study related adverse events (if appropriate)
  - Include expected risks in protocol and consent
    - If it isn't in the protocol and/or consent it is reportable
    - Define events that you won't report



- **Protocol Modifications**

- An amendment/modification can be submitted for IRB approval once the study has been initiated to address new information/difficulties
- 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