Putting It All Together: Protocol Development and Thought Exercises

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ISPE

Learning Objectives

- To understand the reasons to develop a protocol prior to study conduct
- To gain familiarity with the essential elements of a protocol
- To utilize the concepts taught in the course to develop a research study

Protocol Development

Why Plan a Research Project?

- Avoid unanticipated problems:
  - Improper assignment of subjects to treatments
    - Improper randomization
  - Unexpected variability among subject characteristics:
    - Need for baseline control of confounders
  - Unrealistic schedule for study completion
    - Need for pilot component
  - Inadequate or no data management:
    - Poorly designed case report forms
    - No plan for database creation / management

Planning for the Study

- Consider reviewing study plan via:
  - Medical literature (Has study been done?)
  - Research mentor
  - Colleagues familiar with the research area
  - Research facilitators (Study coordinator)
  - Statistical consultant
  - Colleagues (Is protocol clear?)

Protocol Development Sequence

1. Formulate specific aim(s) and hypotheses
2. Identify appropriate study setting
3. Determine subject eligibility, exclusion criteria
4. Decide upon appropriate study design
5. Determine data variables needed
6. Estimate sample size needed
7. Anticipate limitations → try to mitigate these
8. Write research proposal for review

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Step 1. Formulate Specific Aims

- Important and relevant question:
  - Your experience in the field
  - Interaction with peers, mentor
  - Knowledge of the medical literature
- Begin with the question:
  - "What is the question?"
- Address feasibility
  - Methods, databases
  - Time, resources, funding

Step 1: Formulate Specific Aims

- What do you really want to do? → Objective
- Write out Specific Aims of project
  - For each aim, formulate hypothesis
- Considerations:
  - Feasibility: continuous assessment
  - Review feedback from:
    - Mentor
    - Other researchers, colleagues
    - Self (sleep on it!)

Step 1: Determine Hypotheses

- Hypothesis: prediction of how variables will be associated in statistical analyses
- Can be stated in 2 forms:
  - Null hypothesis (H_0):
    - No difference between 2 study groups
  - Alternative hypothesis (H_a):
    - There is a difference between two groups

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Step 2. Identify Study Setting

- What is best study setting to test hypothesis?
  - Allows aim to be definitively answered
  - Permits all data variables to be collected
  - Feasible
- Examples:
  - Databases
  - Clinic settings

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Step 3. Study Subjects

- Determine eligibility criteria for subjects:
  - Who are subjects of interest?
  - "What is the target population?"
    - Target population = Persons to which study results are to be generalized
- Determine exclusion criteria:
  - Why should certain subjects be excluded?
    - Ethics
    - Safety
    - Avoid biases, confounding

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Step 4. Choose Study Design

Descriptive Studies	Analytic Studies
• Case reports	• Case-control
• Case series	• Retrospective cohort
• Analysis of secular trends	• Prospective cohort
	• Experimental

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Step 5. Determine Data Variables

- Identify variables needed to answer Specific Aim:
  - Exposure: drug treatment, risk factor, disease
  - Main study outcome(s)
    - Appropriate and valid (surrogate vs. clinical)
    - Systematic bias in assessments
    - Cost to measure → feasibility
    - Impact of choice on sample size, analyses
  - Potential confounding variables

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Step 6. Estimate Sample Size

- How many subjects needed to detect difference in outcomes between groups?
- Depends on:
  - Size of the difference (e.g., RR, OR)
  - Type 1 error rate (typically 0.05)
  - Power you seek to detect difference (usually 80%)
  - Ratio of controls:cases or unexposed:exposed
  - Event rate in controls
- Consider biostatistical assistance to calculate
- Sample size programs available

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Step 7: Anticipate Limitations

- All studies have limitations
  - Are results still valid despite these?
- Recognize potential limitations
- Discuss how to mitigate limitations
  - Adjust study design to reduce bias
  - Control for confounders in analyses

Common Study Limitations

- Bias:
  - Systematic difference between groups that leads to over-/under-estimation of measure of association
- Confounding:
  - Knowledge of the disease and pathogenesis is invaluable in anticipating confounding
  - Can be controlled for for in analyses
- Generalizability: representativeness
- Sample size

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Step 8. Write Protocol

- Now write your study protocol!
- Iteration of protocol takes time
- May require many drafts

7 Rules of a Good Protocol

1. Clearly identify your Specific Aims
   - Can have sub-aims or secondary objectives
2. Clearly describe study significance / rationale
   - Why are you doing the study?
   - What do you hope to demonstrate?
   - Why is study important (clinically, biologically, public health significance)?
3. Design study to achieve primary objective
   - Study procedures, study design, statistical analysis

7 Rules of a Good Protocol

4. Ensure consistency from section to section
5. Describe all study details / analyses clearly:
   - Give clear directions for each step of the protocol
   - Consider the relationship of one procedure on another
   - Develop a flow sheet for study day or week
   - State how the data will be handled and analyzed
6. Carefully consider conditions of evaluations:
   - Avoid unnecessary measures (e.g., how often do blood sample need to to taken?)

7 Rules of a Good Protocol

7. Ensure patient safety:
   - For novel compounds, does the toxicology in animals cover the dose and duration in humans?
   - Has the route of dosing been studied in animals?
   - How will subject's safety be evaluated, by whom, how often?
   - How will severe/serious events be evaluated?
   - Define AEs and SAEs and their reporting requirements
   - How will the study be monitored?

Putting It All Together Thought Exercise

Thought Exercise

- You wish to evaluate the risk of acute liver injury assoc. with oral azole antifungals
  - Concern that ketoconazole may be esp. hepatotoxic
- Questions:
  - What study design would you use?
  - What outcomes should be evaluated?
  - What data source to use to answer the aim?
  - What potential effect modifiers, confounders to collect?