IDENTIFYING THE RESEARCH QUESTION

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Introduction to Clinical Research
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OUTLINE

• Formulating the research question
• Finding resources to conduct the study
• Writing a proposal

THE RESEARCH QUESTION

• Fundamental first step in any study
• Need to feel some passion for the research question or path for this research
• First start as a question, then create hypothesis
• Define it before you collect or analyze data
• Time spent up front is an investment that pays dividends
• Confused studies ask confused questions
Research Questions

• Why do these individuals develop multiple sclerosis?
• Can I predict toxicity of this new drug in humans with a mouse model?
• Why don’t smokers engage in proven methods to stop smoking?
• Does the use of this PET scan improve clinical outcomes?

2 x 2

<table>
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<th>Exposure (Treatment)</th>
<th>Outcome (Disease)</th>
<th>Total</th>
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<tbody>
<tr>
<td>Yes</td>
<td>a</td>
<td>b</td>
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<td>No</td>
<td>c</td>
<td>d</td>
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<tr>
<td>Total</td>
<td>a + c</td>
<td>b + d</td>
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Sources of Research Questions

• Clinical experience
• Teaching experience
• Review of medical literature, especially evidence-based syntheses
• Senior mentors, local experts
• Journal clubs
• Scientific meetings
• Application of methods from non-medical fields
• Introduction of new medical technologies
Defining the Research Question

- Get good advice
- Start with the problem
- Consult with experts
- Start creating a research team
- Write it down!

WRITE IT DOWN!

- Use simple declarative statements—avoid compound sentences
- Break it down into its component parts
- Structure of the question will determine structure of the proposal and subsequent publications
- Development of research question, hypothesis and study plan is an iterative process
**SEQUENCE AND CYCLE OF RESEARCH**

1. Choosing the research question
2. Developing the hypothesis/protocol
3. Pretesting and revising the protocol
4. Carrying out the study
5. Analyzing the findings
6. Drawing and disseminating the conclusions

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**Refining the Research Question**

- Literature review
  - PubMed and literature search
  - Systematic reviews (Cochrane Collaboration)
  - Practice guidelines
  - Articles from experts
  - Editorials
  - RFPs or Funding Opportunity Announcements
- Discussion with colleagues and experts
  - Establish relationship with senior mentor
- Secondary analysis of existing data: vital statistics, disease registries, health care system data

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**Examples**

- We propose to test the hypothesis that the incidence of treated ESRD increases with increasing level of diastolic and systolic blood pressure.
- We propose to test the hypothesis that excessive variability in weight is more predictive of future CVD than rate of gain during lifetime or absolute level of weight.
Examples

- We will conduct a randomized trial in 985 consecutive outpatients with clinically suspected deep venous thrombosis to compare the diagnostic value of serial impedance plethysmography and serial compression ultrasonography.

Refining the Question

- Write a short proposal (1-3 pages)
- Outline research objectives
- Create a conceptual model or figure
- Should include:
  - research question and hypothesis
  - specific aims
  - basic plan of conduct
  - shell of main results table

Conceptual Model

- Logically structured representation of the concepts, variables, and relationships involved in a research study with the purpose of clearly identifying what will be explored, examined, measured or described.
Deciding to Proceed

- Are you excited? Are colleagues excited?
- Is it feasible?
- Is it ethical?
- Will the research yield important and new results?
- Will the study get us closer to improving health outcomes? Is there a translational pathway?
- Consider what would be the next steps if the results went one way or the other.

NIH Review Criteria

- Significance
- Investigator
- Innovation
- Approach
- Environment
Common Problems with Research Questions/Study Plans

- Too vague or broad
- Not innovative
- Not feasible
- Too expensive
- Don’t have the skills to carry out the project
- Not ethical
- Low power to find an effect

Solutions: Too Vague

- Write the research question down early on
- Be specific in the study plan about:
  - how participants will be sampled
  - what variables will be measured and how
  - what is the projected difference between groups
- Calculate a sample size
- Construct tables that would be in the paper describing the final results
- Do a pilot of 1 or 2 individuals

Solutions: Not Feasible

- Specify a smaller set of variables
- Narrow the question
- Expand inclusion criteria
- Eliminate exclusion criteria
- Add other sources of subjects (i.e., go from single center to multicenter)
- Lengthen the time frame for entry
- Lengthen the follow-up period
- Use more efficient variables or designs
Solutions: Too Expensive

• Consider less costly study designs and measurement methods
• Scale back on amount of data to be collected or on sample size
  – Large simple study or “practical clinical trials”
• Seek additional financial support
  – break the project down into complementary parts
• Outline the ultimate translational pathway

Solutions: Inadequate Skills

• Consult experts and review the literature for alternative methods
• Learn the skills
• Collaborate with colleagues who have the skills

Solution: Not Relevant or Novel

• Not every research project needs to win a Nobel Prize but you do want to refute or extend previous findings
• Should be a publishable no matter the result
• On the other hand, very innovative projects often not understood
• Convince reviewers what is proposed is the next logical step – address alternatives
Unethical Research Question

• Few people set out to do unethical research (e.g., informed consent)
• Need to heed the advice of institutional review board; obtain ethics consult for “challenging” cases
• Modify the research question or change the protocol to avoid potentially unethical elements
• Research always needs IRB review, even “exempt research”

Perform a Pilot Study

• Test feasibility
  – Recruitment
  – Intervention (reproducibility and complexity)
  – Data collection
  – Equipment
• Refine methods and procedures
• Confirm or revise sample size estimates but not based on effect size found in pilot

Sources of Funding

• NIH
  – RO1, RFA, RFP (Contract), U01 (cooperative agreement)
  – Career Development Award
• Foundation Support
• Disease Specific Organizations
• Institutional Support
• Pharmaceutical Industry Support
  – Investigator Initiative
  – Contract
• Mentors
• Grateful patients
Advice on Writing a Grant Proposal

• Defining the research question is critical first step
• Good idea is necessary but not sufficient
• Have to convince reviewers that you can accomplish the work; feasible project and team with necessary skills
• Know your audience, i.e., match the topic to the funding agency
• Data Sharing

Plan Ahead

• Identify limiting step (ex., subcontract with other organization)
• Create timelines
• Know how you work best

Writing a Grant Proposal
How to Proceed

• Get organized!
• Assemble a team of co-investigators
• Decide on research question; formulate specific aims
• Assign writing tasks, perhaps by section
• Set deadlines for completion of tasks
• Leave adequate time for colleagues to review preliminary drafts
Know Your Audience

- What is the mission of the funding agency? Is it consistent with your project?
- Has the agency funded similar projects in the past?
- Is there a program announcement in this area?
- Talk to previous grantees
- Call the agency or project officer

Know Your Reviewers

- Find out who is on the review group
- Consider a literature search on the reviewers
- Make sure that you deal with questions likely to arise from the reviewers’ previous work

Abstracts

- May be the only part of your application that some review group members read
- Structured format is helpful
- Should clearly convey the rationale, overall goal, and specific aims of this study
- Don’t leave the audience hanging—end with a punch! Indicate implications of the work.
Specific Aims

• Provide framework for rest of grant
• Organize background, previous work and methods by aims

Background

• Explain importance of research topic
• Include estimates of morbidity, mortality and cost due to disease under study
• List unanswered questions
• Set the stage for proposed study

Previous Work

• Describe members of investigative team, their experience and accomplishments
• Detail previous studies by PI and coinvestigators
• End by indicating how previous work demonstrates your ability to complete proposed work
Methods

- Introduction--Describe conceptual model and overall study design, table of contents
- Graphical description of protocol
- Organization--Management of study, especially if multicenter, draw an organizational chart
- Data collection--Include validity of exposure and outcome measures or plans to validate them
- Analysis—restate hypotheses, link to analysis
- Sample size—necessary for EVERY grant
- Limitations—pre-empt the reviewers

Nuts and Bolts

- Follow directions exactly
- Organize application exactly as suggested
- Meet deadlines

Helpful Hints

- Consider the reviewer and make their job easier
- Use formatting to emphasize important points, organization
- Summarize with tables
Aphorisms

• Plan ahead--don’t run out of time
• Be realistic--don’t overpromise
• Address validity of exposure and outcome measures
• Don’t take it personally if you don’t get funded—it’s your job to reapply!

Questions or Comments