Designing Clinical Research Studies: So You Want to Be an Investigator

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On behalf Of
The NASPAG Research Committee

Objectives

– Learn to design a clinical research project using defined steps
– Learn to identify and strengthen a research question
– Know the different forms of research studies
– Practice designing a research project
– Know how to choose collaborators and mentors

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Disclosures

• We have no financial disclosures.
• We don’t plan to discuss off-label use of any medications.
• We are members of the NASPAG Research Committee.

1. Steps to Follow in Designing a Research Project

• Ask the question
• State why it matters
• Set a time frame and structure
• Choose selection criteria & sampling strategy
• Identify Variables
• Know your statistics – sample size, analyses needed

2. Developing the Research Question

• Know the literature
• Know the experts
• Be sure the question is
  – Feasible
  – Novel but pertinent
  – Ethical
The Research Question

• The general question from which the hypothesis will be stated.
• Research question should "pass the FINER test":
  – Feasible
  – Interesting
  – Novel
  – Ethical
  – Relevant


Research Question Development

• Discuss your ideas with potential mentors, including at least one senior researcher.
• Identify a statistician who can discuss feasibility of your proposal with the number of subjects you can reasonably recruit.
• Identify the primary question and THEN secondary questions.

The Research Question

• Ask a question arising from an area of research interest.
• Know the current literature and identify experts in the field.
• Conferences are a great source to identify interests and formulate questions.
• Find a mentor/mentors who has interest in the question.
Is This Question Feasible & Interesting?

- Can I recruit enough subjects?
- Is there enough technical expertise to carry out the study?
- Can I get funding for this idea?
- Is the project achievable in a reasonable amount of time? For a reasonable cost?
- Does this question pique my interest? My colleagues?

Is This Research Novel?

- New finding
- Finding that refutes or confirms a previous finding
- Can lead to changes in diagnosis, treatment, or application of research to patients

Is This Idea Ethical?

- Will need institutional review board approval
- Should respect privacy, give full informed consent, and be free of deception/trickery/undue risk
Is This Proposal Relevant?

- Will findings advance knowledge?
- Will findings change practice or policy?
- How important is the question we want to answer?

Translational Research

- From Bench to Clinical Research = T1: identify both basic scientists & clinical investigators
- From Clinical Research to Larger Populations = T2: identify community collaborators, large clinics, or health plans to expand

Summary

- Start with a simple statement of the research question
- Develop a one page summary outline
- Use the outline to develop the protocol
Study Outline

- Research question
- Significance of the question
- Design of study to test question
- Subject description (inclusion/exclusion, source)
- Variables to measure
- Hypothesis/ null hypothesis

3. Variations on a Theme: Types of Research Studies

- Observational
  - Cross-sectional
  - Cohort
  - Case-Control
  - Nested Case-Control
  - Nested Case-Cohort
  - Case-Crossover
- Intervventional Clinical Trials
  - Randomized Blinded Trial

Observational Studies

- Two primary purposes
  - Descriptive – examining the distributions of predictors and outcomes in a population.
  - Analytic – characterizing associations between these predictor and outcome variables.
- Most are designed to suggest a predictor may cause an outcome, but not every association represents causality.
  - Chance, bias, confounding, cause-effect
Cross-Sectional Studies

• All measurements are made at about the same time with no follow up period.
• Good for examining associations.
• The choice of which variables are labeled predictors and which as outcomes depends on cause-and-effect hypotheses of the investigator rather than study design.
• Constitutional factors (age, race, gender) cannot be altered by other variables and are therefore always predictors.

Cross-Sectional Studies

• Provide information about prevalence (proportion who have a disease or condition at 1 point in time).
• Strengths
  – Fast
  – Inexpensive
• Weaknesses
  – Difficult to establish causality
  – Impractical for rare diseases

Case Series

• In the case of rare disease, a case series is better suited to describing the characteristics of the disease.
• May be preferable to analyzing differences between patients with disease and healthy patients.
• Case-series of 1st 1,000 patients with AIDS
  – 727 homosexual/bisexual males
  – 236 injection drug users
  – Control group was not needed to conclude that these groups were at increased risk.
Example
Cross-Sectional Study
• **Define Objective:** is exposure to movies in which the actors smoke associated with smoking initiation?
• **Define selection criteria/recruit population sample:** random-digit-dial survey of 6522 US children 10-14 yrs.
• **Measure predictor and outcome variables:**
  – Quantified smoking in 532 popular movies.
  – Subjects asked which of 50 randomly selected subset of movies they had seen.

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Example
Cross-Sectional Study
• **Measure predictor and outcome variables:**
  – Covariates – age, race, gender, parent smoking and education, sensation-seeking, self-esteem.
  – Outcome variable – ever tried smoking a cigarette.
• **Results:**
  – Prevalence of smoking varied from 2% in lowest quartile of movie exposure to 22% in highest quartile.
  – After adjusting for all confounders, this difference was statistically significant.

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Cohort Studies
• **Cohort** – a group of subjects, specified at the outset, and followed over time.
• **Prospective cohort study**
  – Cohort assembled at baseline
  – Measure predictor variables and, if appropriate, baseline level of the study outcome
  – Consider storing specimens/images for later analysis
  – Follow the cohort over time, minimizing loss to f/u
  – Measure the outcome variable during f/u
Prospective Cohort Study

• **Strengths:**
  – Allows calculation of **incidence** (number of new cases of a condition occurring over time).
  – Strengthens the process of inferring causality.

• **Weaknesses:**
  – Expensive
  – Require time
  – Causal inference muddied by influences of confounders.

**Example**

Prospective Cohort Study

• **Define selection criteria/assemble cohort:** RNs, aged 25-42, in 11 most populous states in 1976 invited by mail. Those who agreed = cohort (121,700)

• **Measure predictor variables/confounders:** questionnaire about weight, exercise, risk factors

• **Follow-up cohort and measure outcomes:** periodic questionnaires + questions about disease occurrence

• **Results:** heavier women had higher risk of breast cancer after menopause

Retrospective Cohort Study

• Cohort selection and follow-up occurred in the past.

• **Steps:**
  – Identify an existing cohort that has some predictor information already recorded.
  – Assess loss to follow-up that has occurred.
  – Measure the outcome variable(s) that have already occurred.
Retrospective Cohort Study

- Strengths: many of the advantages of prospective cohort study but less costly and time-consuming.
- Weaknesses:
  - Limited control over:
    - Approach to sampling
    - Follow-up of the population
    - Quality of baseline measurements

Example

Retrospective Cohort Study

Do head CTs in childhood increase leukemia/brain tumor risk?

- Identify suitable existing cohort: UK National Health Service Central Registry data, 178,604 children/young adults < 22 with head CT between 1985-2002.
- Collect predictor variable data: reviewed medical records for age, gender, # and type of radiology procedures and estimated radiation dose.
- Collect outcome data:
  - Leukemia at least 2 years after 1st CT
  - Brain tumor at least 5 years after 1st CT

Example

Retrospective Cohort Study

- Results:
  - Childhood CT scans increased risk of both cancers.
  - Increase risk was dose-related.
  - Cumulative doses of 50-60 mGy tripled the risk.
  - However, absolute increase in risk was low i.e. 1 excess case per 10,000 scans.
  - Concluded that CT scan benefits likely outweigh risks but radiation doses should be kept low and alternative procedures uses wherever appropriate.
Case-Control Studies

- Retrospective study design works backwards from outcome to predictor.
- Steps:
  - Define selection criteria and recruit one sample from population of cases and one sample from a population of controls.
  - Measure current values and historical values of predictors.

Case-Control Studies

- Strengths:
  - Inexpensive
  - Efficient for studying rare diseases
- Weaknesses:
  - Cannot provide incidence/prevalence estimates
  - Susceptible to sampling bias
  - Susceptible to measurement bias
- Nested case-control study minimizes both sampling and measurement bias.

Example
Case-Control Study

Does IM vitamin K in newborn period increase childhood cancer risk?

- Selected sample cases: 107 children with leukemia from the German Childhood Cancer Registry.
- Selected controls: 107 children, sex- and DOB- matched, randomly selected from same town as case.

- Measured predictor variables: medical records review for exposure to vitamin K in the newborn period.

- Results:
  - 64% cases and 59% controls received vitamin K
  - Odds Ratio 1.3 (95% CI: 0.7 – 2.3)

von Kries et al.
Nested Case-Control Study

- Case-control study “nested” within a defined cohort.
- Can be retrospective or prospective
- Steps (retrospective):
  - Identify a cohort from the population with previously stored specimens, images, or other data.
  - Measure the outcome variable that distinguishes cases from controls.
  - Measure predictor variables in all cases and in a random sample of controls.

Example

Nested Case-Control Study

Do higher sex hormone levels increase breast cancer risk?

- **Identify a cohort:** Study of Osteoporotic Fractures cohort.
- **Identify cases at the end of follow-up period:** 97 subjects with 1st occurrence breast cancer in 3.2 years of follow-up identified by questionnaires and review of death certificates.
- **Select controls:** random sample of 244 women in cohort without breast cancer.

Example

Nested Case-Control Study

Do higher sex hormone levels increase breast cancer risk?

- **Measure predictors:** levels of sex steroids measured in serum frozen at baseline.
- **Results:** women with high levels of estradiol or testosterone had a threefold increase risk of subsequent breast cancer diagnosis.

Cauley et al.

Cauley et al.
Interventional Clinical Trials

• An intervention is applied and the effect is observed on one or more outcomes.

• Strengths:
  – Able to demonstrate causality.
  – Random assignment minimizes influence of confounding variables.
  – Blinding minimized biased ascertainment of outcomes or predictors.

• Weaknesses:
  – Expensive
  – Time-consuming
  – Address a narrow question
  – Expose participants to potential harm

• Clinical trials are best reserved for relatively mature research questions.

Let’s Design a Study

• General question: What is the normal anti-Mullerian hormone level in childhood, adolescence, and in girls with PCOS?
• Develop a primary question and secondary questions with your group
• Why do these questions matter?
• How will you design the study?
• Who are your subjects?
Designing Your Mock Study

- What will you measure?
- What is your hypothesis?
- What sample size is needed?
- How will you analyze the data?

4. Choosing Mentors & Collaborators

- Qualities of the good mentor
- Finding collaborators
  - Institutional
  - Local
  - Nationally/Internationally
  - Being a collaborator

Types of Mentors

- Refer to the mentoring overview handout, used with permission from Maria Trent
- Traditional
- Peer-mentoring
- E-mentoring
- Project based mentoring
- Team mentoring

Kathy Kram, Community of Mentors Guidelines 2010, Boston University
The Idea of the Developmental Network

- Involves the mentors of previous slide PLUS
- Colleagues
- Family/friends
- Mentees and juniors

Working with Your Mentors

- Regular meeting times
- Informal discussions – live, email, phone
- May need one mentor to learn techniques (labwork, social media), another for statistics, another for clinical study design
- Part of mentoring is learning to write---the grant proposal, the interim reports, the abstracts, the manuscripts

Mentoring Needs of the Successful Researcher

- Learn how to design the accepted abstract poster
- Learn how to give an oral presentation
- Learn how to revise a manuscript with reviewers’ comments
### NASPAG Research Opportunities

- Research Committee – contact Andrea Bonny, Ellen Connor, or Veronica Gomez-Lobo
- Abstract Committee – contact Rebekah Williams or Jennifer Woods
- Mentor Program – contact Veronica Gomez-Lobo
- Fellows research – contact Veronica Gomez-Lobo
Designing Clinical Research

Ellen L. Connor, Andrea E. Bonny

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III. Developing a Research Question:

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IV. Types of Research Studies:

- Observational - descriptive and analytical; characterize associations between predictor and outcomes, but not all associations present causality.
- Cross-sectional – all measurements are made at the same time period with no follow up period; provide information on prevalence (proportion who have a disease or condition at 1 point in time); fast and inexpensive; difficult to establish causality and impractical for rare diseases.
- Case Series – in rare diseases, better suited for describing the disease characteristics.
- Cohort - a group of subjects, specified at the outset, are followed over time; can be prospective or retrospective; allows calculation of incidence (number of new cases of a condition occurring over time); strengthens the process of inferring causality; expensive, require time, causal inference muddied by influences of confounders
- Case-Control - retrospective study design works backwards from outcome to predictor; recruit one sample from population of cases and one sample from a population of controls; measure current values and historical values of predictors; inexpensive and efficient for studying rare diseases; cannot provide incidence/prevalence estimates; susceptible to sampling and measurement bias.
- Interventional Clinical Trials - intervention is applied and the effect is observed on one or more outcomes; able to demonstrate causality; random assignment minimizes influence of confounding variables; blinding minimizes biased ascertainment of outcomes or predictors; expensive, time-consuming, address a narrow question, expose participants to potential harm. Best reserved for relatively mature research questions.

V. Choosing Mentors & Collaborators

- Concept of the Developmental Network
- Part of mentoring is learning to write - the grant proposal, interim reports, research abstracts and presentations, manuscripts.
A Sample Study for Trying Out the Process

- Design a study to compare the efficacy of ethinyl estradiol 30mcg/0.15 desogestrel versus ethinyl estradiol 20mcg/0.3 norgestrel on acne in adolescents girls with moderate to severe acne (comparing 3rd to 2nd generation progestins in moderating acne)
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