

Research Questions, Hypotheses and Predictions

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Learning Objectives

- List the features of a good clinical research question
- Formulate hypotheses
- Make predictions from hypotheses
- Identify key elements of optimal study design
- Give the reasons for performing a pilot study

The Scientific Method





The Scientific Method – *Observation*



The Scientific Method – *Question*

Research Questions

- Goal: Capture the uncertainty about a health problem *that the investigator can resolve*
- No shortage of problems, but defining question takes time
- Challenge is to find an important question that can be answered with a feasible and valid study plan

Research Questions – should be FINER

F
I
N
E
R

Feasible

Interesting

Novel

Ethical

Relevant



Is it Feasible?

- Are there potential mentors and collaborators?
- Is there adequate technical expertise to accurately measure variables?
- Are there an adequate number of subjects available?
 - Sample size calculations (*you need statistician early!*)
- Is the project manageable in scope?
 - Is there adequate time and resources available



Is it Interesting?

- Anticipate the Results before Doing the Study
 - What are all the potential outcomes?
 - What would they mean?
- Is it interesting to you?
 - What would you do next?
- Is it interesting to others?
 - Mentors, colleagues
 - Peer-reviewers for Publication, Study Section



Is it Novel?

- Gain from the experience of others
 - Read the literature
 - Interview mentors, local experts
 - Talk to patients and their families
 - NIH Reporter
- Write a meta-analysis or systemic review in your area of interest
 - [Health Sciences Library Resources](http://projectreporter.nih.gov/reporter.cfm)

A question need not be totally original

- Confirmatory studies may answer:
 - whether a previous observation can be replicated
 - whether the findings in one population also apply to others
 - confirmatory study is particularly useful if it avoids the weaknesses of previous studies

**“Imitation is the sincerest
form of flattery”**





Is it Ethical?

- Can the question be answered without harming the participant?
 - Benefits must outweigh risk
- Is there equipoise?
- Obtain IRB approval before you start your project

Is it Relevant?



- Will the potential results ...
 - guide further research?
 - change clinical management?
 - Influence health policy?
- Consider the logical next step in research? Your career?

PICOT Approach

P Population

- What specific patients population are you interested in?

I Intervention (or exposure)

- What is your investigational intervention or exposure of interest?

C Comparison group

- What is the main alternative to compare with the intervention

O Outcome of interest

- What do you intend to accomplish, measure, improve or affect?

T Time

- What is the appropriate follow-up time to assess outcome?



The Scientific Method – *Hypothesis*

A hypothesis...

- ...is a **preliminary** statement regarding a **mechanistic explanation** for an observation

Preliminary → The answer is not yet known

Mechanistic → Seeks to define cause/effect relationship

Explanatory → Explains how an underlying process mediates an observed effect

The Scientific Method – *Hypothesis*



- A key aspect of the scientific method is to derive predictions from a hypothesis (or hypotheses) about the results of planned experiments and then perform those experiments to see whether results support predictions.

*A well conceived hypothesis is “testable”

Is all scientific research devoted to testing hypotheses?

- Descriptive studies
 - Developing new research methods
 - DNA sequencing
 - Testing toxicity of potential new drugs
 - Prevalence of health conditions
- Qualitative studies
 - Primarily exploratory
 - Assess underlying reasons, opinions, motivations



Is My Hypothesis Correct?

- Hypotheses can be disproven, but never completely proven
- Hypotheses evolve over time as data accrue
- More advanced hypotheses predict data more accurately
- All hypotheses are likely to be disproven (modified) in the future
- Science represents an iterative development of hypotheses, approaching but never achieving truth

Predictions are ...

- Testable propositions that can be accepted or rejected on the basis of empirical observations derived from your study
 - A statement that tells something of a future event



“If I let go of this pen,
it will drop.”

A

Prediction

B

Hypothesis

Prediction or
Hypothesis?

Prediction ...

“This pen will drop.”

Hypotheses ...

This pen will drop because ...

- It is subject to gravity
- Someone tied a string to it
- Invisible demons

*Generally there is prior knowledge to justify a hypothesis; “educated guess”

Prediction or
Hypothesis?

Teenagers who smoke low nicotine cigarettes are less likely to continue smoking as adults compared to teenagers who smoker high nicotine cigarettes.

A

Prediction

B

Hypothesis

Question

Will lowering the nicotine level in cigarettes decrease the number of cigarette smokers?

Hypothesis

There is a level of nicotine in cigarettes that is not additive

Prediction

Teenagers who smoke low nicotine cigarettes are less likely to continue smoking as adults compared to teenagers who smoker high nicotine cigarettes.

Consumption of refined carbohydrates leads to high calorie consumption because of low blood sugar.

Prediction or Hypothesis?

A

Prediction

B

Hypothesis

Question

Are all calories equal?

Hypothesis

Consumption of refined carbohydrates leads to high calorie consumption because of low blood sugar.

Prediction

Consumption of refined carbohydrates leads to high calorie consumption because of low blood sugar.

Importance of Multiple Hypotheses

- Reduce intellectual “bias”
 - Having multiple hypotheses mitigates against becoming too attached to one
- Resist oversimplification
 - Experiments designed to test one hypothesis may result in evidence in support of an unconsidered hypothesis and false conclusions
- Design better experiments
 - Distinguish between or among various hypotheses

Some Predictions/Experiments are Better at Distinguishing among Multiple Hypotheses

- Prior knowledge/observations: Monkeys prefer certain tree types.
- Hypothesis : Monkeys prefer tree types with foliage that provides the best camouflage from predators.
- Hypothesis #2: Monkeys prefer trees that sustains their diet (e.g. specific insects/fruits)
- Hypothesis ##3: Monkeys prefer trees that are more comfortable to sleep in



Some Predictions are Better at Distinguishing among Hypotheses

- Hypotheses :
 - Monkeys prefer tree types with foliage that provides the best camouflage from lions.
 - Monkeys prefer trees with a specific insect/leaf that they like to eat.
 - Monkeys prefer trees that are comfortable to sleep in.
- Potential Predictions- which distinguishes?
 - A. In areas with more better camouflage tree types, monkeys live longer than in areas with more poorer camouflage tree types.
 - B. In areas without lions, monkeys will not show same preference for tree types.



The Scientific Method – *Experiment*

Perform an Experiment

- State the null hypothesis in advance
 - “There is no difference in the calories consumed in people on a diet high in refined carbohydrates and people on a diet low in refined carbohydrates.”
- Identify a primary outcome
 - Avoid indirect measures
- Controls!
 - The experimental arms differ only in the independent variable.

What's a Null Hypothesis?

- Part of the statistical framework to analyze data
- The null hypothesis (H_0) is the converse of the “alternative” hypothesis (H_a)
- “There is no difference or there is no effect.”
- An alternative hypothesis can be supported but never proven
- A null hypothesis can be “falsified” or rejected



Sir Ronald Fisher
1890-1962

Always perform a pilot study

- Are you asking a feasible question?
 - How many of your patients are eligible?
 - How often does your outcome variable occur?
- Do your techniques and methods work?
- Can you analyze the data the way that you thought you could?

Specific Aim

- Exact statements of what you want to do in the proposed project
 - What you need to do to test the hypotheses
 - “Experiment” or study
 - Design and methods
 - An aim has a operational or statistical hypothesis
- Project = 1-2 aims at most
- Grant = 3-5 aims at most

Specific aims direct your grant (and your research project)

- For each aim
 - Experimental design and methods
 - Hypothesis
 - Data and Analysis
 - to test your hypothesis

Conclusions

- Scientific discovery has profoundly changed the practice of medicine
- Understanding hypotheses and study design will enhance your clinical experience
- Choose your research projects and mentors with this in mind