

Questions, Hypotheses and Predictions

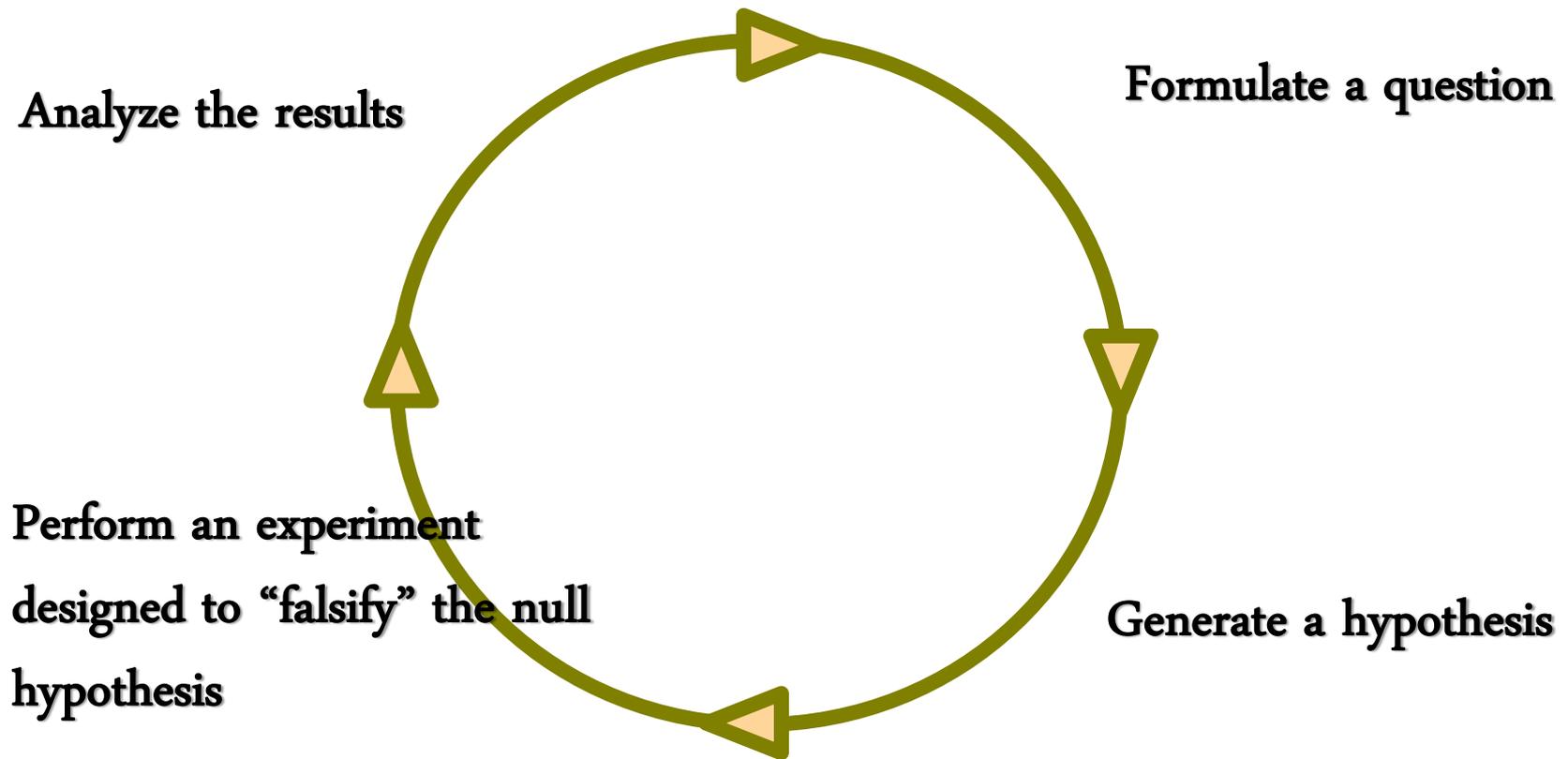
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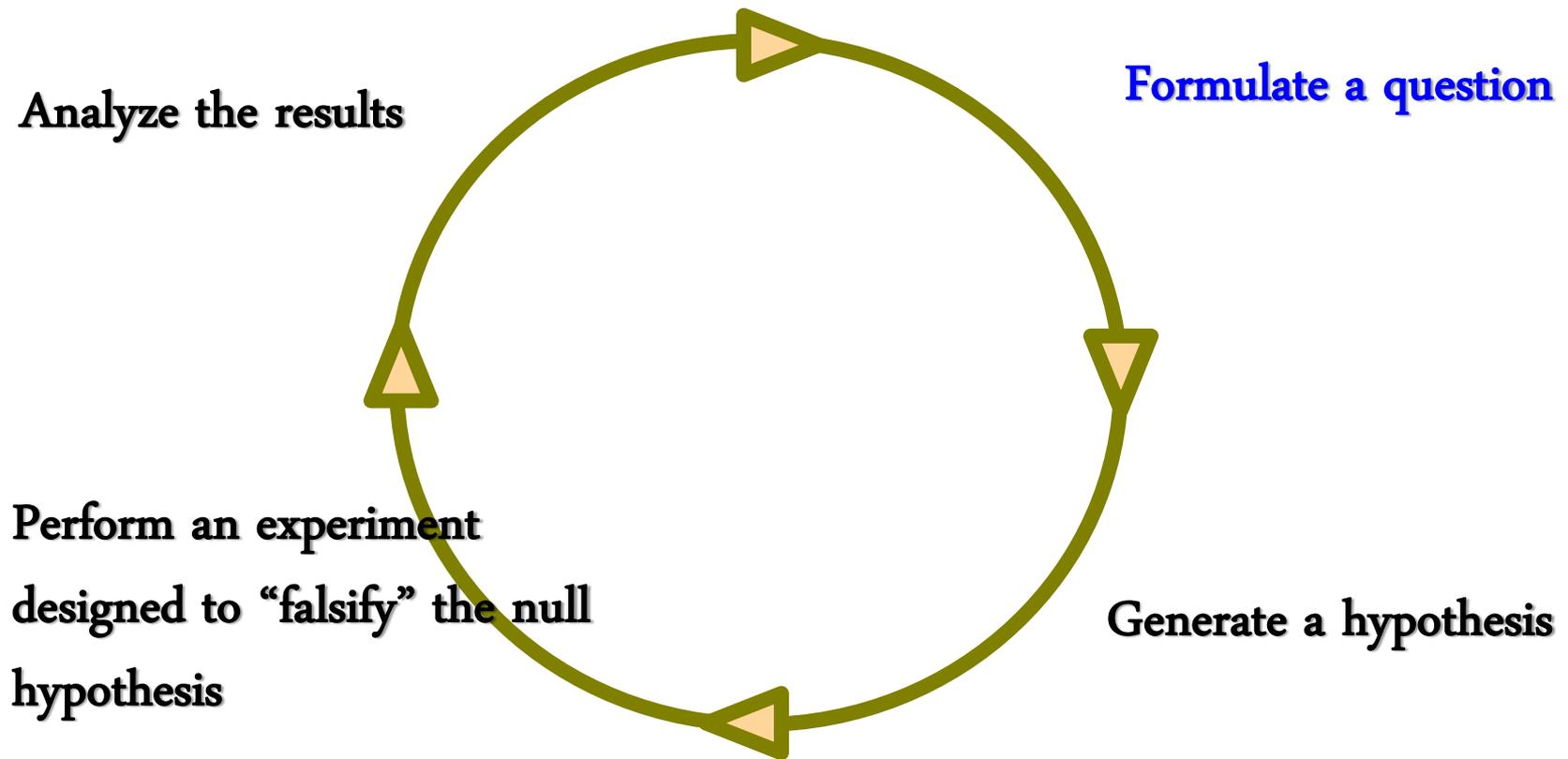
Learning Objectives

- 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



Research Questions

- Capture the uncertainty about a health problem that the investigator can resolve
 - Specific, clear and focused
 - Not a topic
- No shortage of problems
 - But defining the question takes time

Questions

- Should we advise people with diverticulosis not to eat nuts?
- Should anti-motility agents, such as loperamide, not be used to ease symptoms in patients with *C. difficile* infection?

Research Question must be

F

Feasible

I

Interesting

N

Novel

E

Ethical

R

Relevant

Is it Feasible?

- Are there potential mentors and collaborators?
- Is there adequate technical expertise in how the variables are measured?
- Are there an adequate number of subjects?
 - Sample size calculations
- Manageable in scope
 - Time and resources

Is it Interesting?

- Anticipate the Results before Doing the Study
 - What are all the potential outcomes?
 - What would they mean?
 - Example

Is it Interesting?

- Is it interesting to you?
 - Fit for your interest and background
 - What would you do next?
- Is it interesting to others?
 - Mentors
 - Colleagues
 - Peer-reviewed 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.

- 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

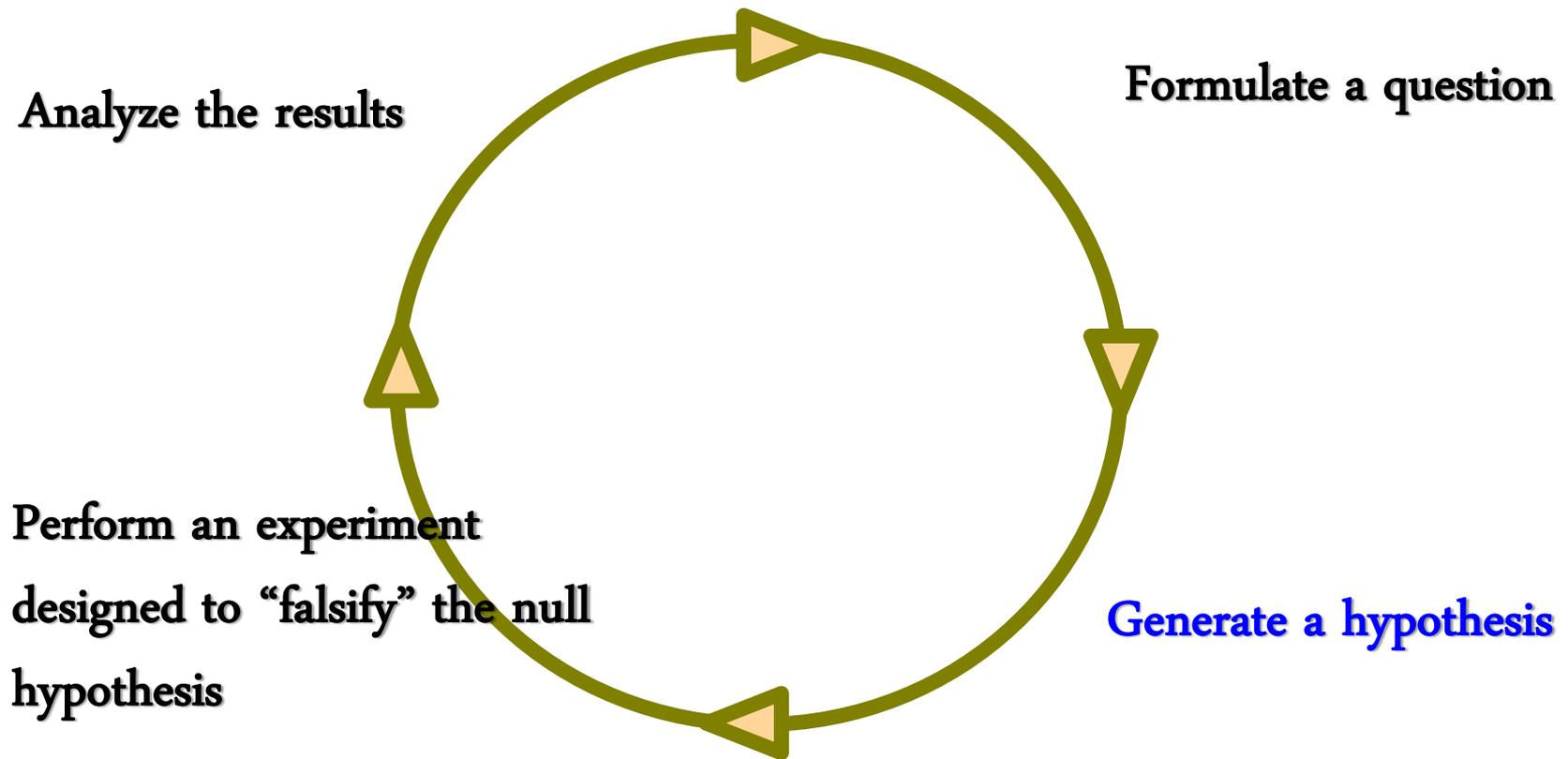
Is it Ethical?

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

Is it Relevant?

- Will it
 - guide further research?
 - logical next step
 - change clinical management?
 - diagnosis, treatment, prevention
 - influence health policy?
 - Clinical or public health guidelines

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A hypothesis...

- ...is a **preliminary** statement regarding a **mechanistic explanation** for an observation
 - Preliminary
 - the answer is not yet known
 - Mechanistic
 - seeks to define a cause/effect relationship
 - Explanatory
 - explains how an underlying process mediates an observed effect
- ...generates predictions that can be tested with experiments

Questions and Hypotheses

- Should we advise people with diverticulosis not to eat nuts?
 - Undigested nut fragments obstruct diverticula leading to diverticulitis.
- Should anti-motility agents, such as loperamide, not be used to ease symptoms in patients with *C. difficile* infection?
 - An anti-motility agent will slow the clearance of *C. difficile* from the colon promoting complications such as toxic megacolon.

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.

Is all scientific research devoted to testing hypotheses?

- No!
- Descriptive studies
 - Developing new research methods
 - DNA sequencing
 - Testing toxicity of potential new drugs
 - Prevalence of health conditions
- Critical for hypothesis driven research

Predictions

- Testable propositions that can be accepted or rejected on the basis of empirical observations derived from your study
 - Specify two or more variables
 - measurable
 - Specify how the variables are related
 - increase
 - decrease

Prediction "Cartoon" Template

Input

Exposure

**Predictor
Variable**

**Independent
Variable**



Output

Disease

**Outcome
Variable**

**Dependent
Variable**

Hypothesis or Prediction?

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

A. Hypothesis

B. Prediction

Prediction vs. Hypothesis

This pen will drop.

This pen will drop because...

- It is subject to the forces of gravity?
- Someone tied a string around the end of it?
- Invisible demons are stealing it away?

- Remember there has to be some prior knowledge to justify the hypotheses

Hypothesis or Prediction?

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

A. Hypothesis

B. Prediction

Question → Hypothesis → Prediction

- Will lowering the nicotine level in cigarettes decrease the number of cigarette smokers?
 - There is a level of nicotine in cigarettes that is not additive.
 - Teenagers who smoke lower nicotine cigarettes are less likely to continue smoking as adults compared to teenagers who smoker higher nicotine cigarettes.

Hypothesis or Prediction?

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

A. Hypothesis

B. Prediction

Question → Hypothesis → Prediction

- Are all calories equal?
 - Consumption of refined carbohydrates leads to high calorie consumption because of low blood sugar.
 - People on a diet high in refined carbohydrates consume more calories than people on a diet low in refined carbohydrates.

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 lions.



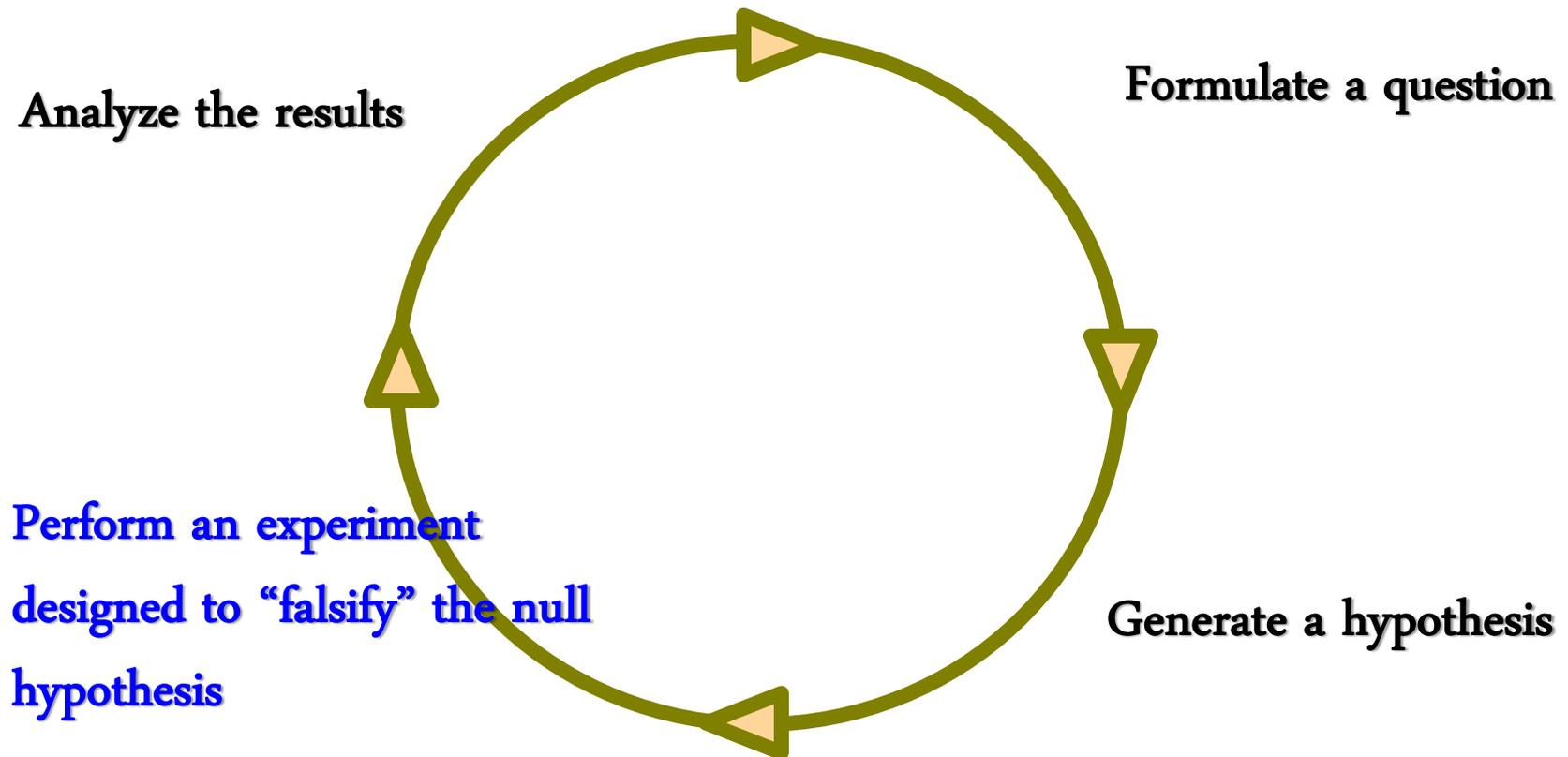
Some Predictions are Better at Distinguishing among Hypotheses

- Hypothesis : Monkeys prefer tree types with foliage that provides the best camouflage from lions.
- What are some other Hypotheses?
 - Monkeys prefer trees with a specific insect/leaf that they like to eat.
 - Monkeys prefer trees that are 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.

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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?



Sir Ronald Fisher
1890-1962

- 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

PICOT Approach

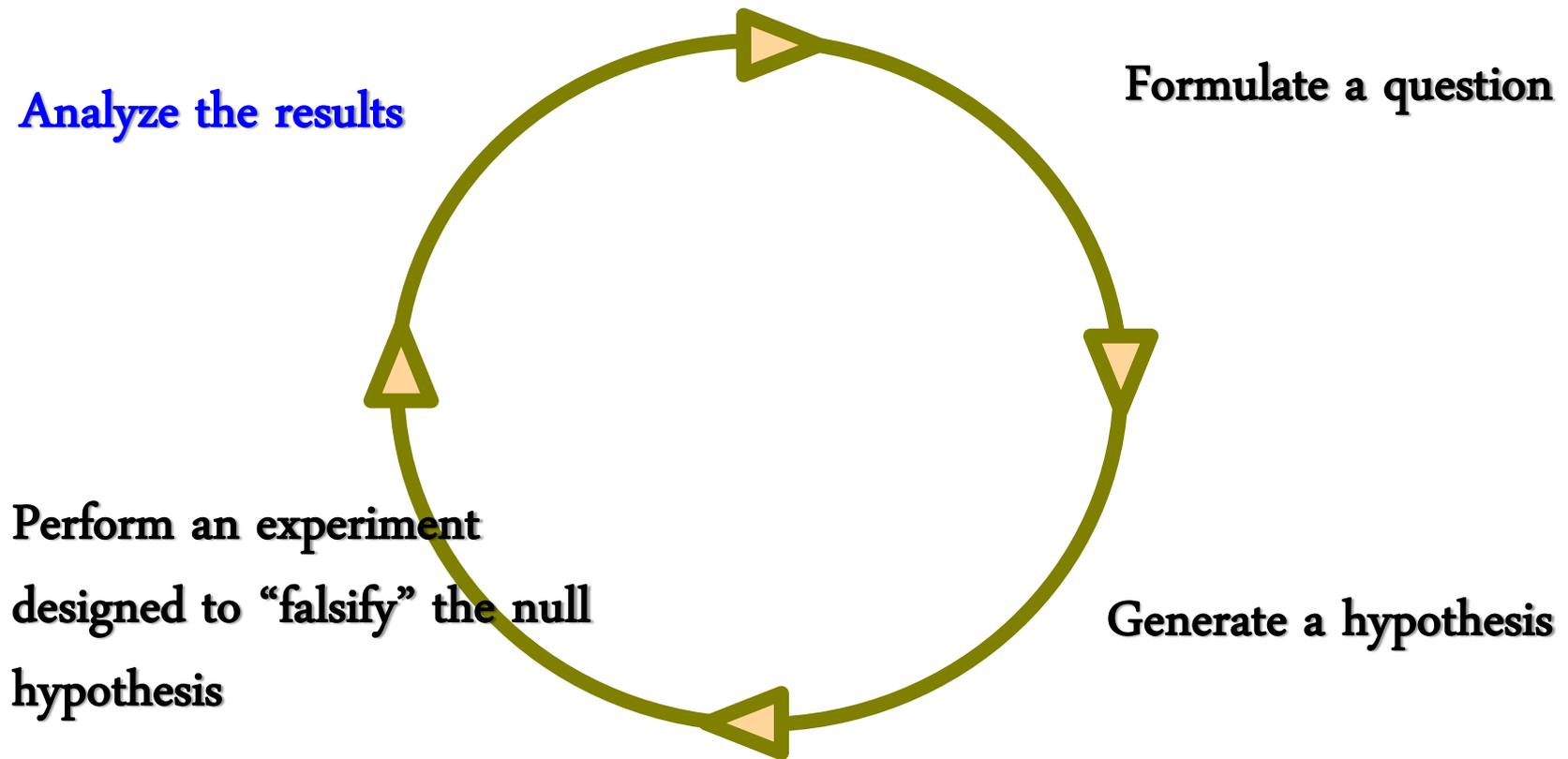
P	Population	<ul style="list-style-type: none">• What specific patients population are you interested in?
I	Intervention (or exposure)	<ul style="list-style-type: none">• What is your investigational intervention or exposure of interest?
C	Comparison group	<ul style="list-style-type: none">• What is the main alternative to compare with the intervention
O	Outcome of interest	<ul style="list-style-type: none">• What do you intend to accomplish, measure, improve or affect?
T	Time	<ul style="list-style-type: none">• What is the appropriate follow-up time to assess outcome?

Brian Haynes R. Forming research questions.
J Clin Epidemiol 2006;59:881-6.

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?

The Scientific Method



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

Homework Assignment:
Review of Specific Aims from
Clinical Research Grants

Will go over on Friday during
my grants talk

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

Bibliography

- Designing Clinical Research, Hulley et al 4th Edition
 - Chapter 2 Conceiving the Research Question
 - Chapter 5 Hypotheses and Underlying Principles
- Ronald Kahn. Picking a Research Question. NEJM, 1994, Vol 33, No. 21 p.1530
- Experimental Design for Biologists, David J. Glass, Cold Spring Harbor Press
- Experimental Design for the Life Sciences, Ruxton and Colegrave, Oxford University Press, Chapter 2

Course Objectives

- ✓ Identify a research question
- Pick a study design
- Collect and manage data
- Analyze data
- Scientific Communication
 - Write an abstract
 - Present a poster
 - Give an oral presentation
 - Publish a paper
 - Prepare a grant
- Identify institutional resources
- Appreciate the ethical, legal and regulatory issues in human subjects research
- Understand the multidisciplinary nature of research
- Recognize career opportunities in clinical and translational research