LET'S STUDY ANTIMICROBIAL STEWARDSHIP

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SHEA ANTIMICROBIAL STEWARDSHIP RESEARCH WORKSHOP

NOVEMBER 29, 2016; SAN DIEGO, CA

Duke University School of Medicine

Duke Center for Antimicrobial Stewardship and Infection Prevention

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Disclosures

Grants: CDC, CDC Foundation, AHRQ

Royalties: UpToDate, Inc.

Honoraria: SHEA (Merck grant to SHEA)

Majority of these slides are borrowed.

Objective: Review Study Designs

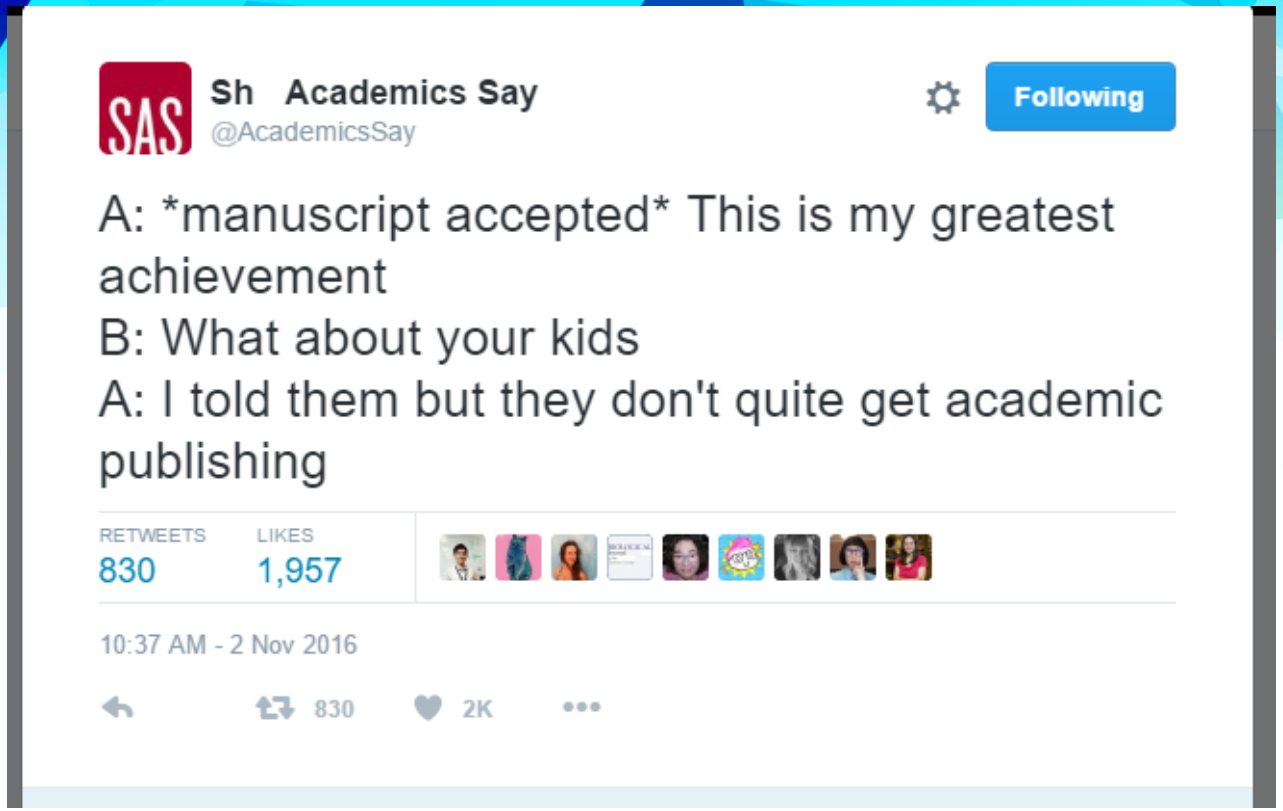
Grades: How do studies get graded?

Homework: SHEA White Papers

Class Discussion: Designs for studying antimicrobial stewardship

- Randomized controlled trials
- Quasi-experimental
- Observational

Group Work: Case Studies



GRADES

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Evidence-Based, Study Design Pyramid

As you move up the pyramid:

- **Stronger methodology**
- **Less Bias**
- **Controls for comparison**
- **Fewer studies**

Establish causality

Observe Associations

Generate Hypothesis

Duke University Medical Center Library and Archives. http://guides.mclibrary.duke.edu/ebm/studydesign Accessed 11-1-2016.

Goals for Stewardship Researchers

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1] Sara E. Cosgrove,[2] Lilian M. Abbo,[3] Conan MacDougall,[4] A[illegible]rey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenki[illegible][12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. [illegible]hl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

Provide a guideline that diverse stakeholders find useful

More detailed, implementation-oriented focus compared with prior guidelines

Use the GRADE system to rank the guideline's recommendations and the level of evidence

My work here…

Slide: Dr. Tamar Barlam, Boston Univ

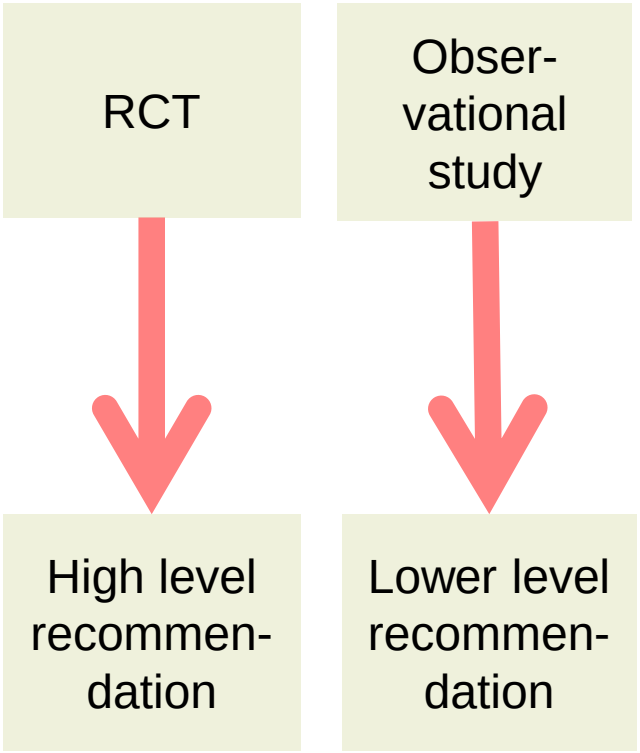
GRADE and PICO

Develop PICO questions to frame topics

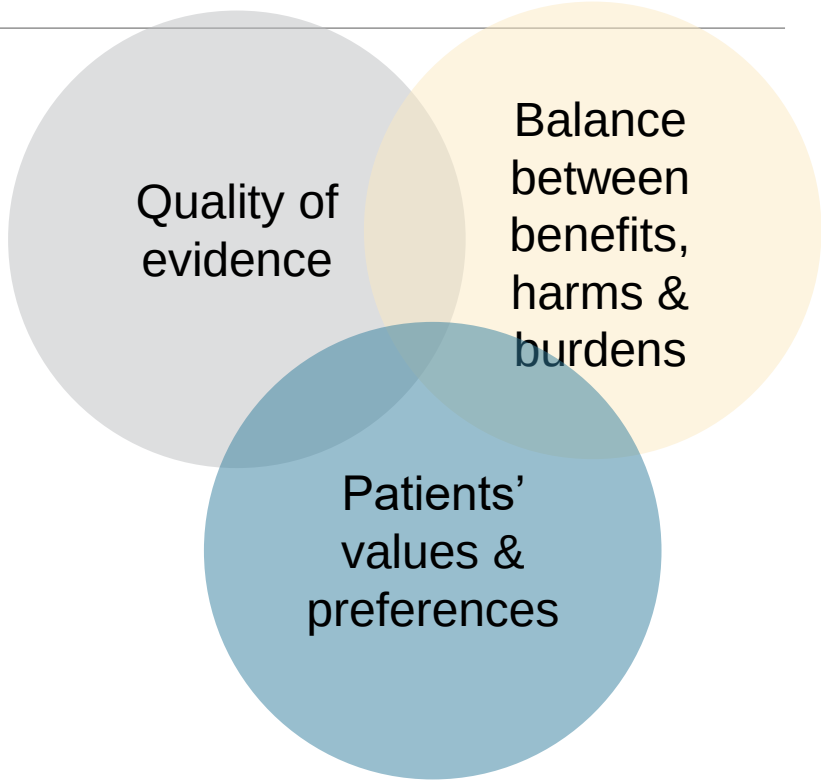
- Population of interest
- Intervention or indicator
- Comparator or control group
- Outcome

Slide: Dr. Tamar Barlam, Boston Univ

From evidence to recommendations



Old system



Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Slide: Dr. Yngve Falck-Ytter and Dr. Tamar Barlam

GRADE

Quality of Evidence

GRADE: all evidence may be examined

If there is a question, then there is evidence

Lack of RCTs does not mean weak evidence

Higher quality indirect data may be preferable than low quality direct data

Slide: Dr. Yngve Falck-Ytter and Dr. Tamar Barlam

Your Charge…

Research that can help inform stewardship interventions

Qualitative and quantitative implementation scientific inquiry

Hopefully, the next revision of this guideline will have many more strong recommendations as the quality of the evidence improves

Slide: Dr. Tamar Barlam, Boston Univ

Homework: Read *ICHE*

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

SHEA WHITE PAPER

Research Methods in Healthcare Epidemiology and Antimicrobial Stewardship

Daniel J. Morgan, MD, MS;[1,2] Nasia Safdar, MD, PhD;[3,4,5] Aaron M. Milstone, MD, MHS;[6] Deverick J. Anderson, MD, MPH[7]

Topics, published in *ICHE* 2016

- Randomized Controlled Trials
- Quasi-experimental Designs
- Use of Administrative and Surveillance Databases
- Survey and Qualitative Research
- Observational Studies
- Mathematical Modeling

CLASS DISCUSSION: DESIGNS FOR ANTIMICROBIAL STEWARDSHIP RESEARCH

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HE/Stewardship Study Design Pyramid

Experimental Studies:
Randomized Controlled Trials
Quasi-experimental Studies

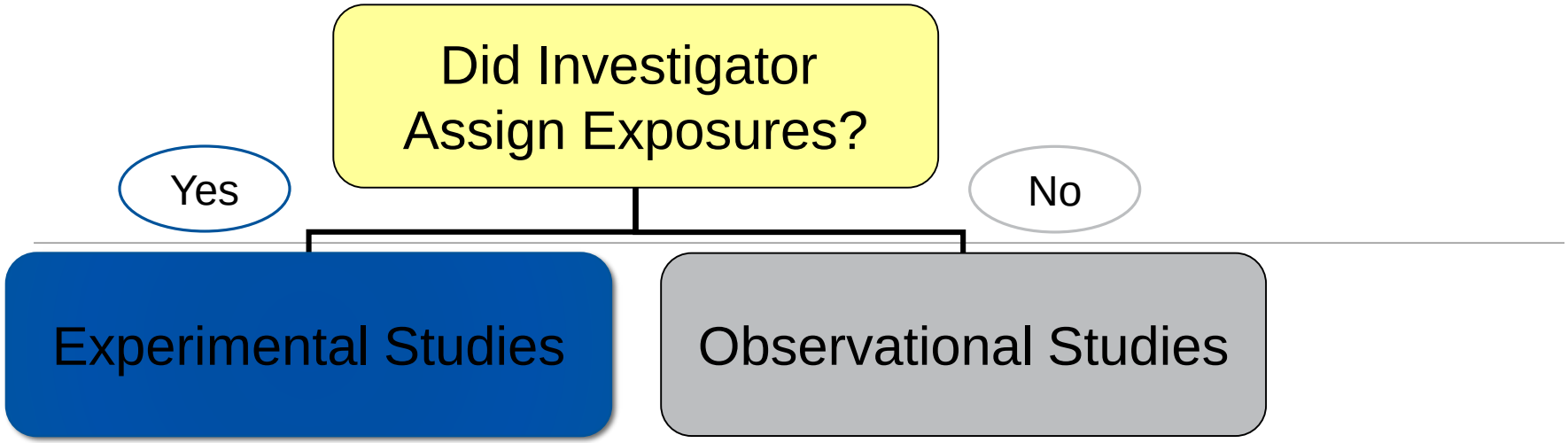
Observational Studies:
Cohort Studies
Case Control Studies
Cross-Sectional Studies
Ecologic studies
Case Series

Establish causality

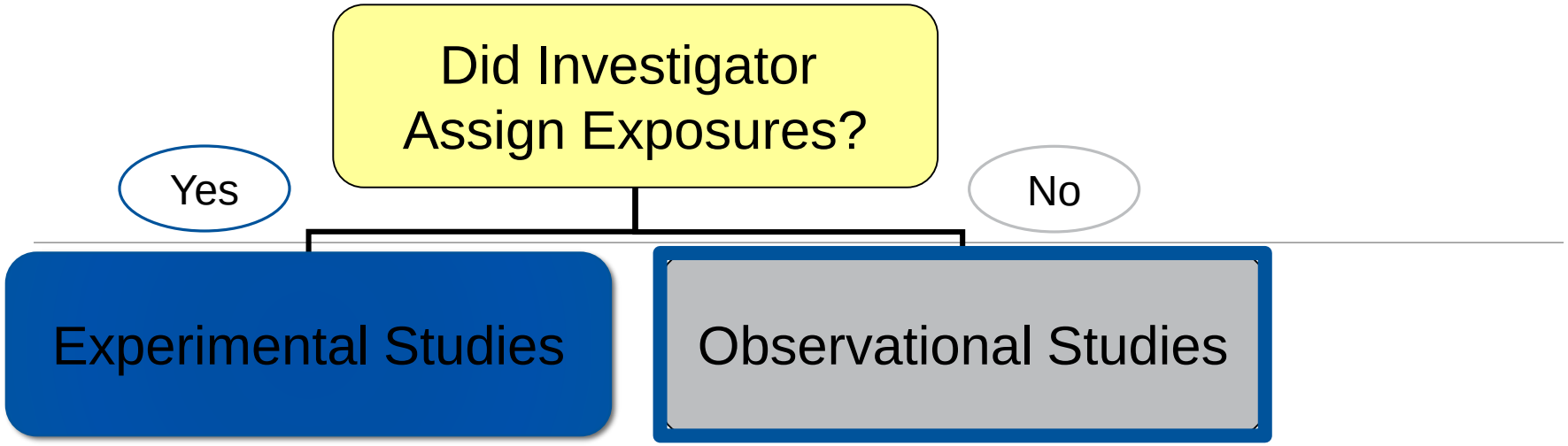
Observe Associations

Generate Hypothesis

Duke University Medical Center Library and Archives. http://guides.mclibrary.duke.edu/ebm/studydesign Accessed 11-1-2016.



Slide: Dr. Daniel Morgan, Univ Maryland



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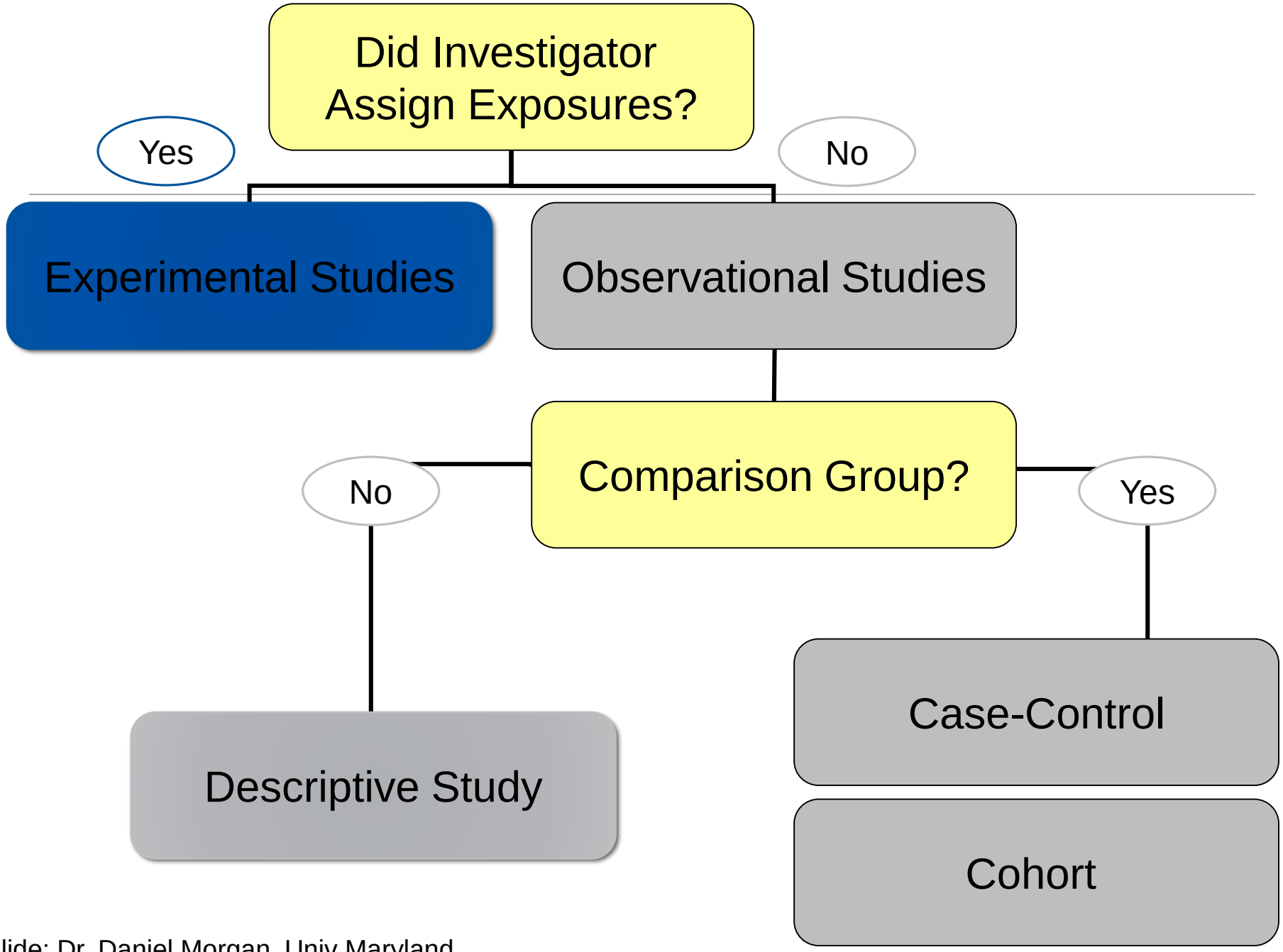
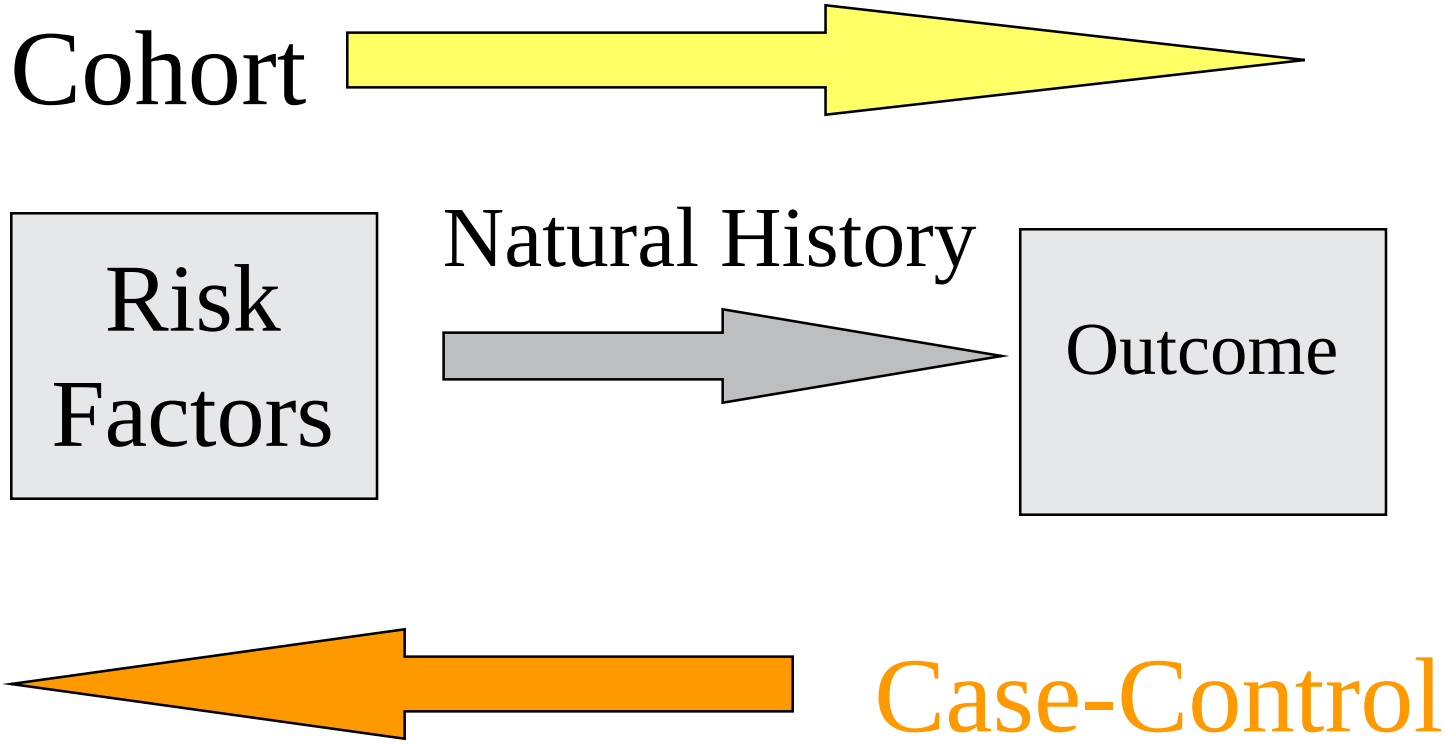


Slide: Dr. Daniel Morgan, Univ Maryland

Observational Studies



Slide: Dr. Daniel Morgan, Univ Maryland

Observational studies – Good things

Take advantage of existing datasets

Cohorts: analyze rare outcomes

Cost-effective, low resource compared to RCT

Can't hurt anyone

Association – first step in demonstrating cause/effect

STROBE Statement

Strengthening the reporting of observational studies in epidemiology

http://strobe-statement.org/

Cohort Study

- Cohort is well-defined
- Exposure status is determined
  - Do they have certain risk factors?
- Followed over time
- Identify development of disease/outcome
- Compare incidence of disease in two groups
  - Exposed vs. unexposed

Cohort:

A defined population, i.e. a group of individuals sharing a common characteristic, who will be observed over time for epidemiologic study

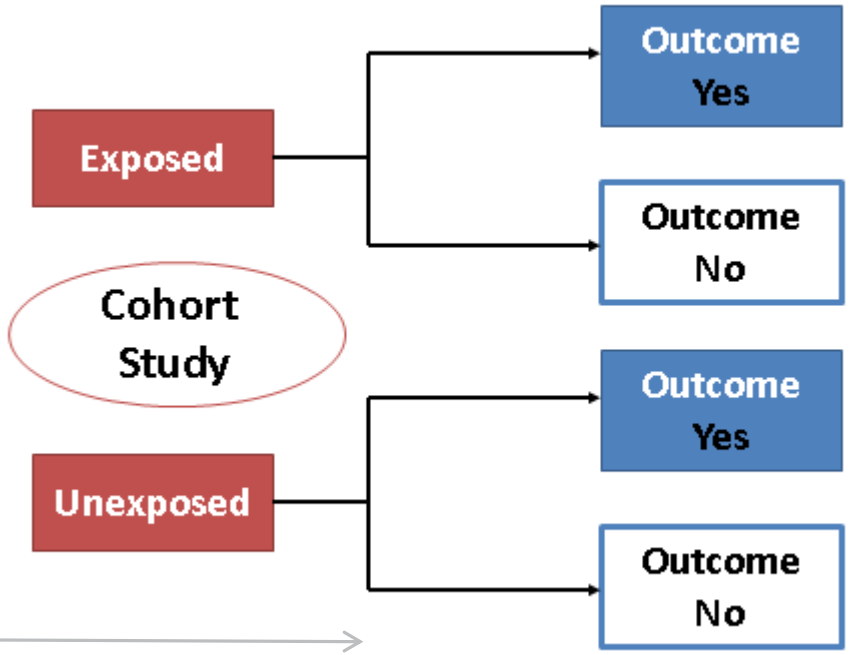
- *Healthy persons, aged 30-62 in Framingham, MA*
- *Nurses, aged 30-75*
- *ICU patients at your hospital*

Slide adapted from: Dr. Daniel Morgan, Univ Maryland

A Cohort Study can be "Retrospective" or "Prospective"

Retrospective
"Historical"

Prospective
"Forward Looking"



Time (years)

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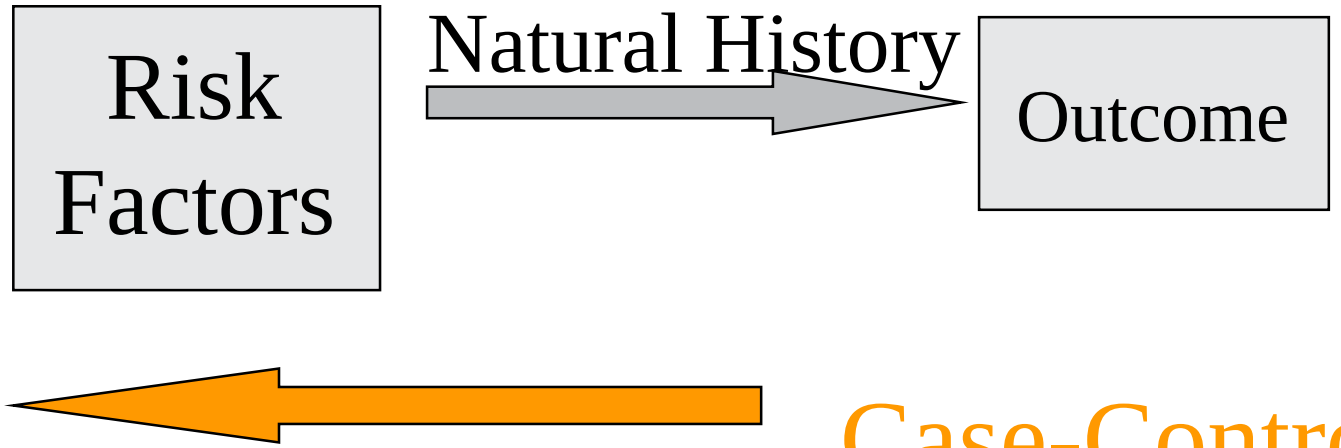
Case-control studies

Subjects are selected on the basis of whether they **do** (cases) or **do not** (controls) have a particular disease or outcome of interest.

Cases and controls are then compared for their exposure or risk factor history



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Observational studies -- Pitfalls

Both	Case Control	Cohort

• Multiple potential biases:
  • Selection
  • Assessment
  • Time-dependent
  • Loss to follow up
  • Recall
• Poorly defined source population
• Statistically significant association, but not true causal relationship (type 1 error)
• Failure to significantly demonstrate a true causal association (type 2 error)
	• Inefficient for the evaluation of rare exposures (OR vs. RR)	• Expensive/slow
		• Does not correct for confounding by indication (need randomization)

Limitation: "measured and unmeasured confounders"
(A more comprehensive table is available in SHEA White Paper)

Selection Bias

Inherent in observational studies and is the major disadvantage

Definition: Systematic error due to difference in characteristics between those selected for a study and those not selected.

Examples: Healthy volunteer; hospital controls

Slide: Dr. Daniel Morgan, Univ Maryland

Confounding by indication

Patients receive different treatment because they are different

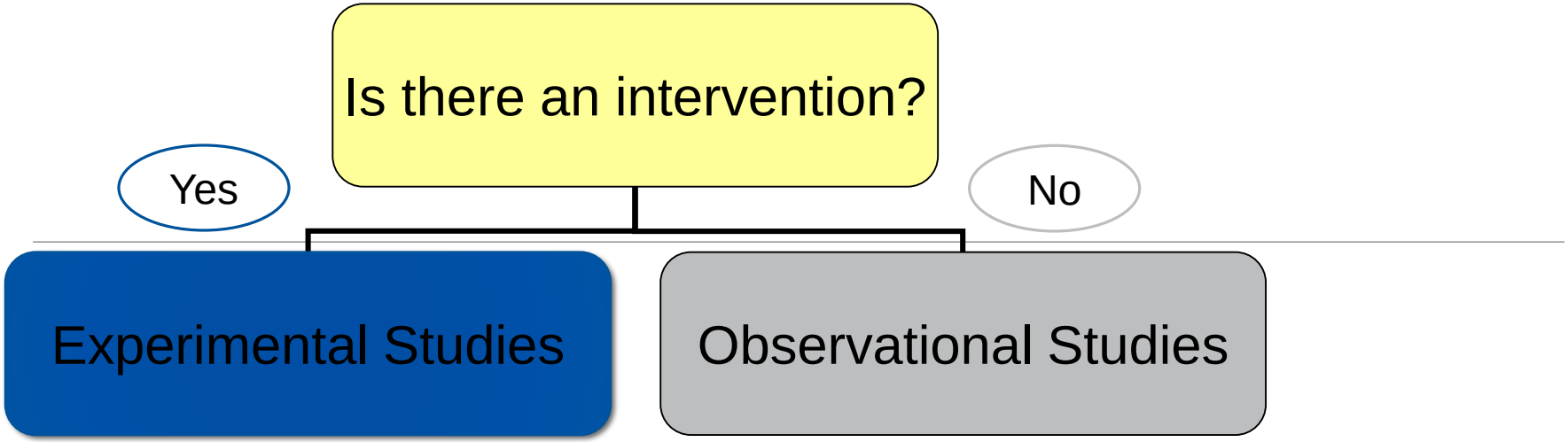
- Drug A vs. B: Drug A may have fewer side effects and be used in sicker population
- Patients with BSI who die early do not get an ID consult

Without randomization can adjust:

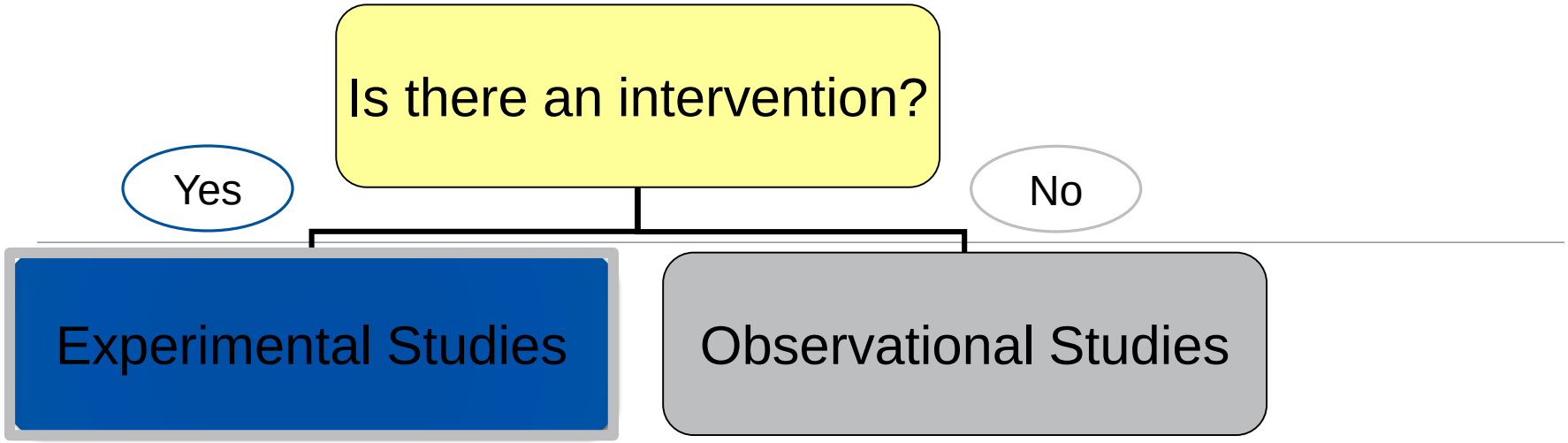
- Adjust or limit sample
- Propensity scores or similar stats tools.

Adjustment is always imperfect

Slide Adapted from: Dr. Daniel Morgan, Univ Maryland



Slide: Dr. Aaron Milestone, Hopkins



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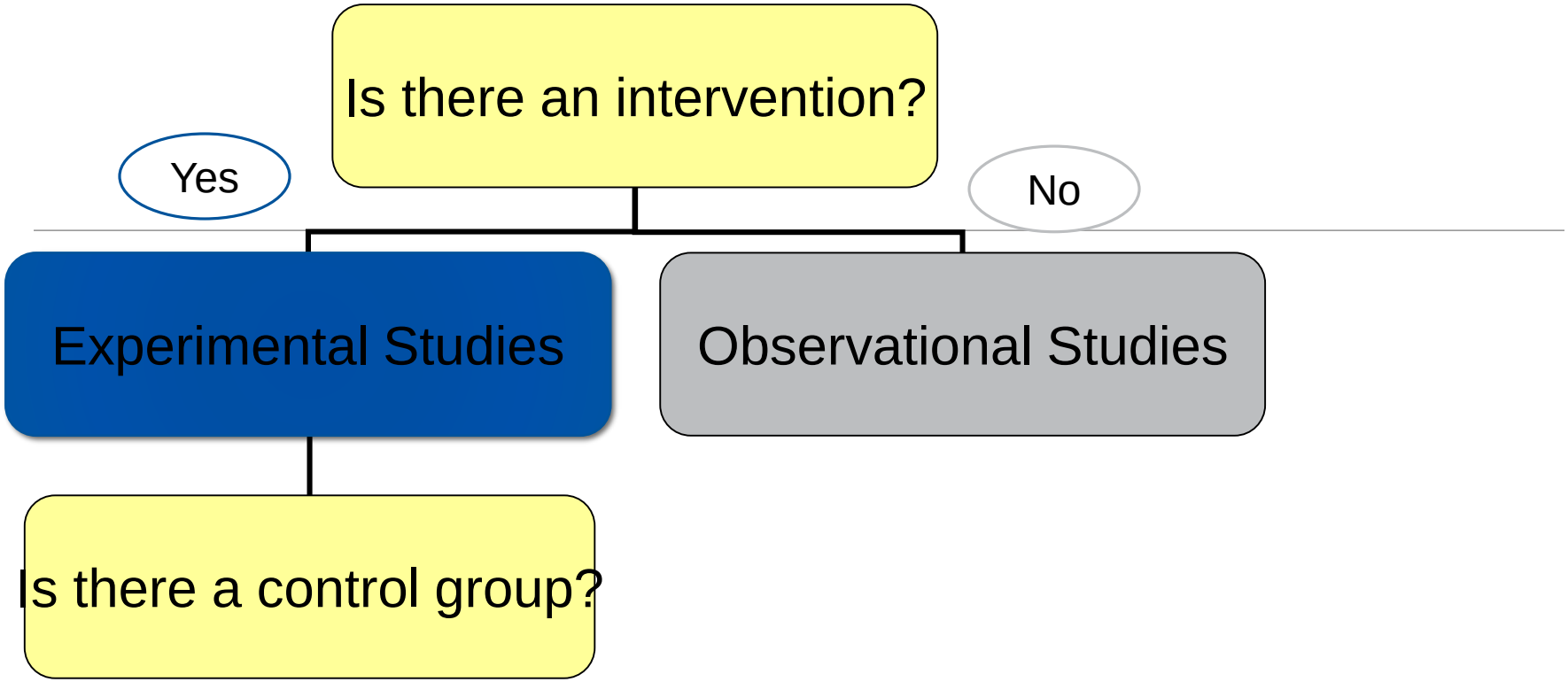

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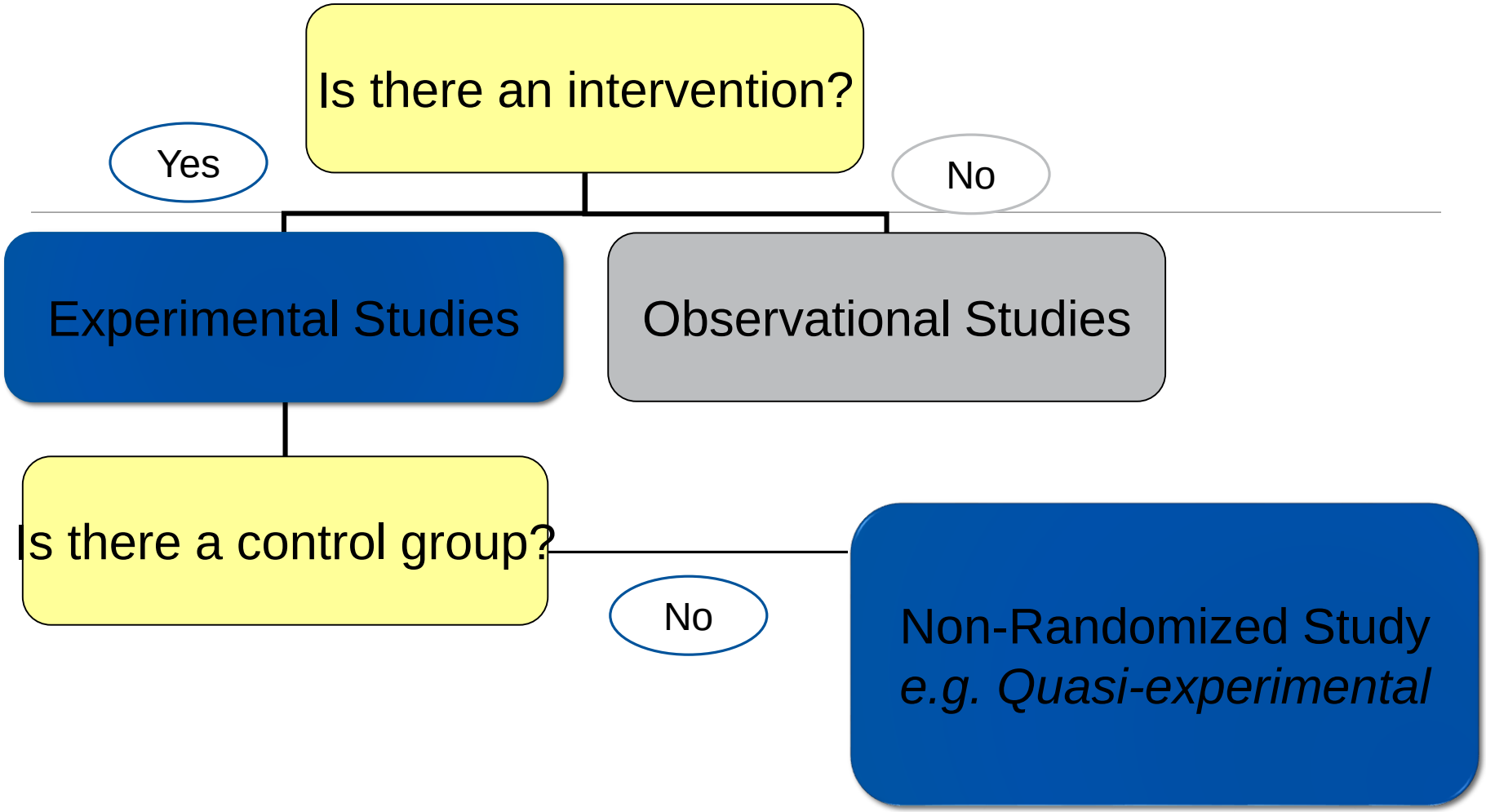

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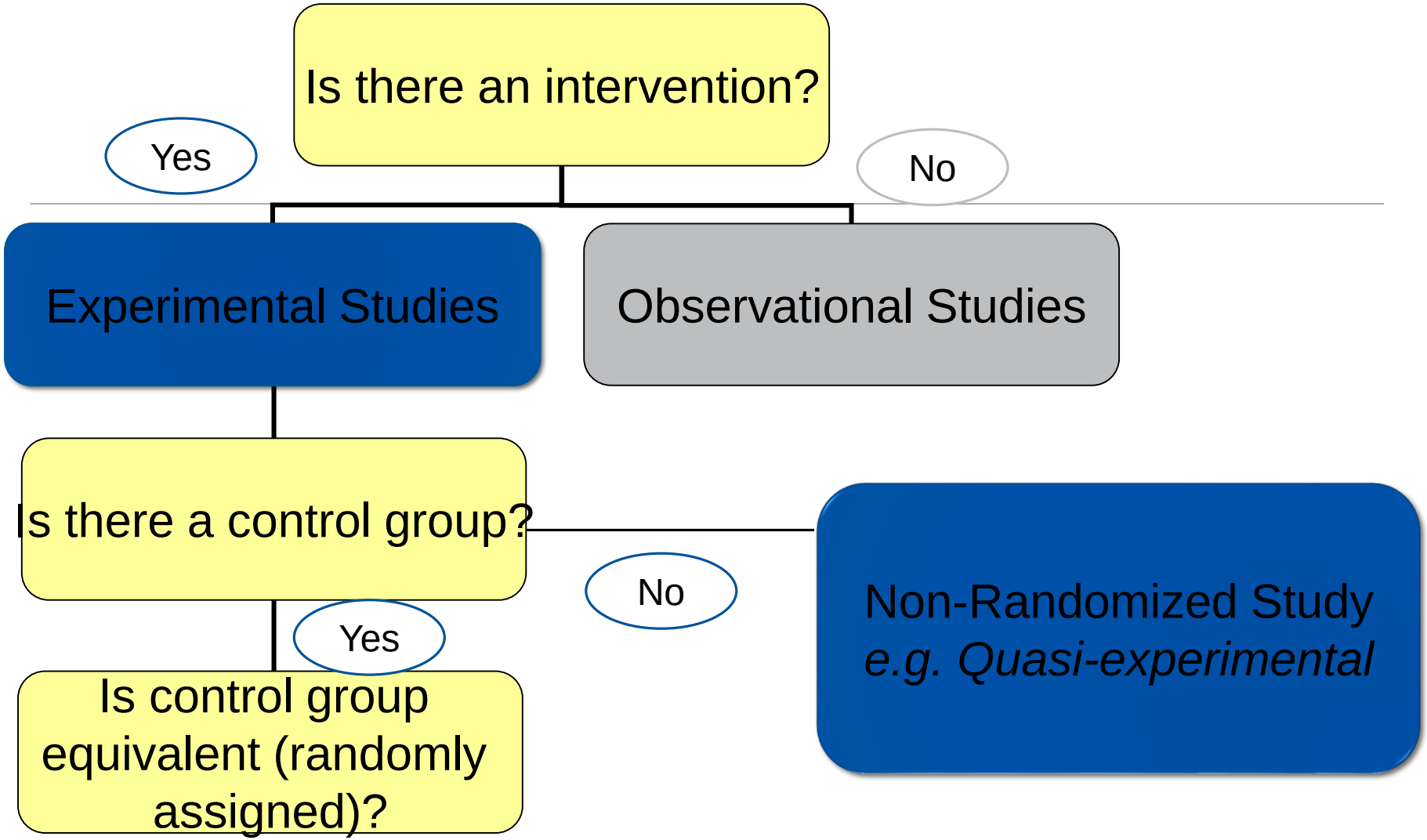

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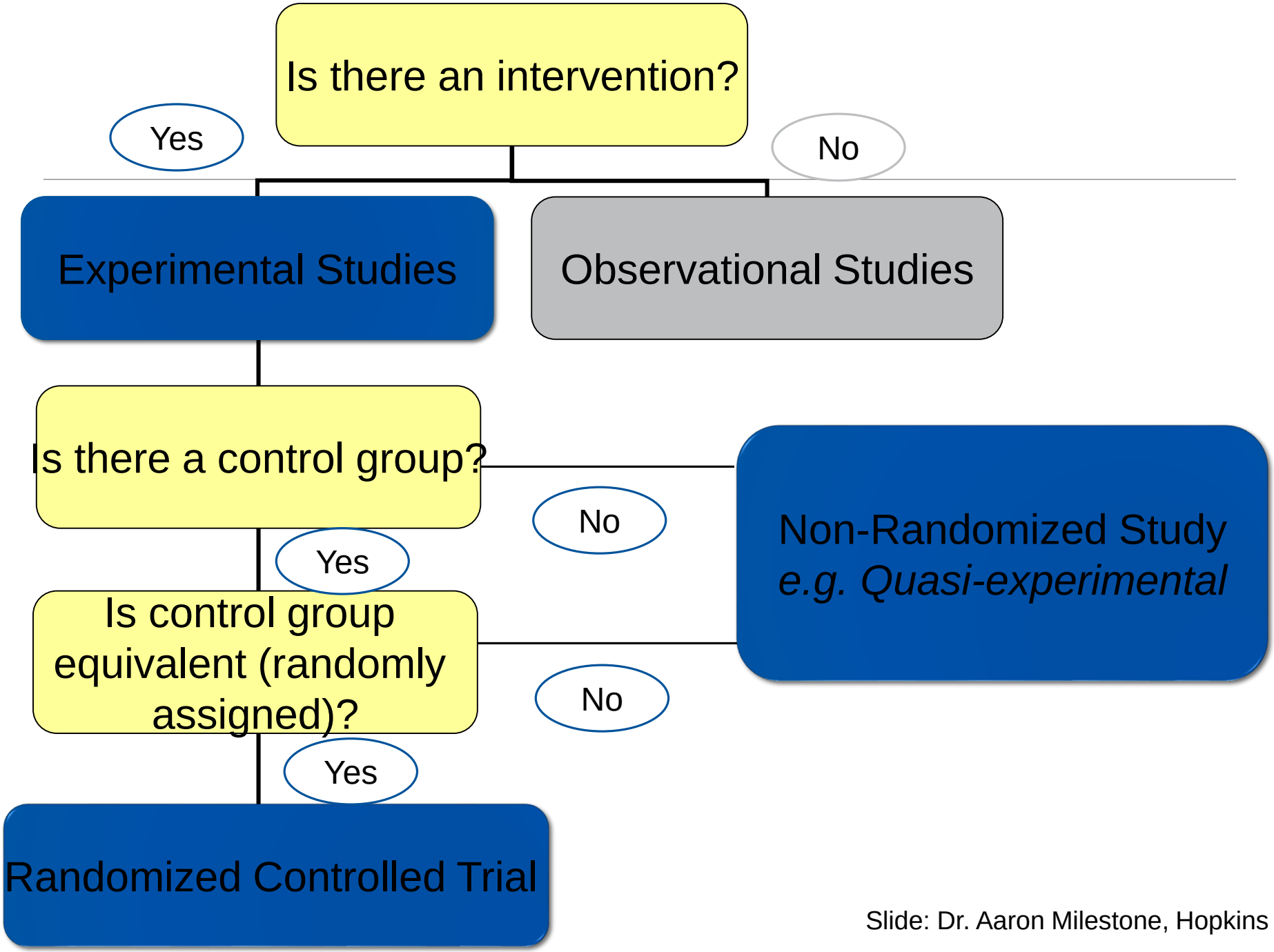

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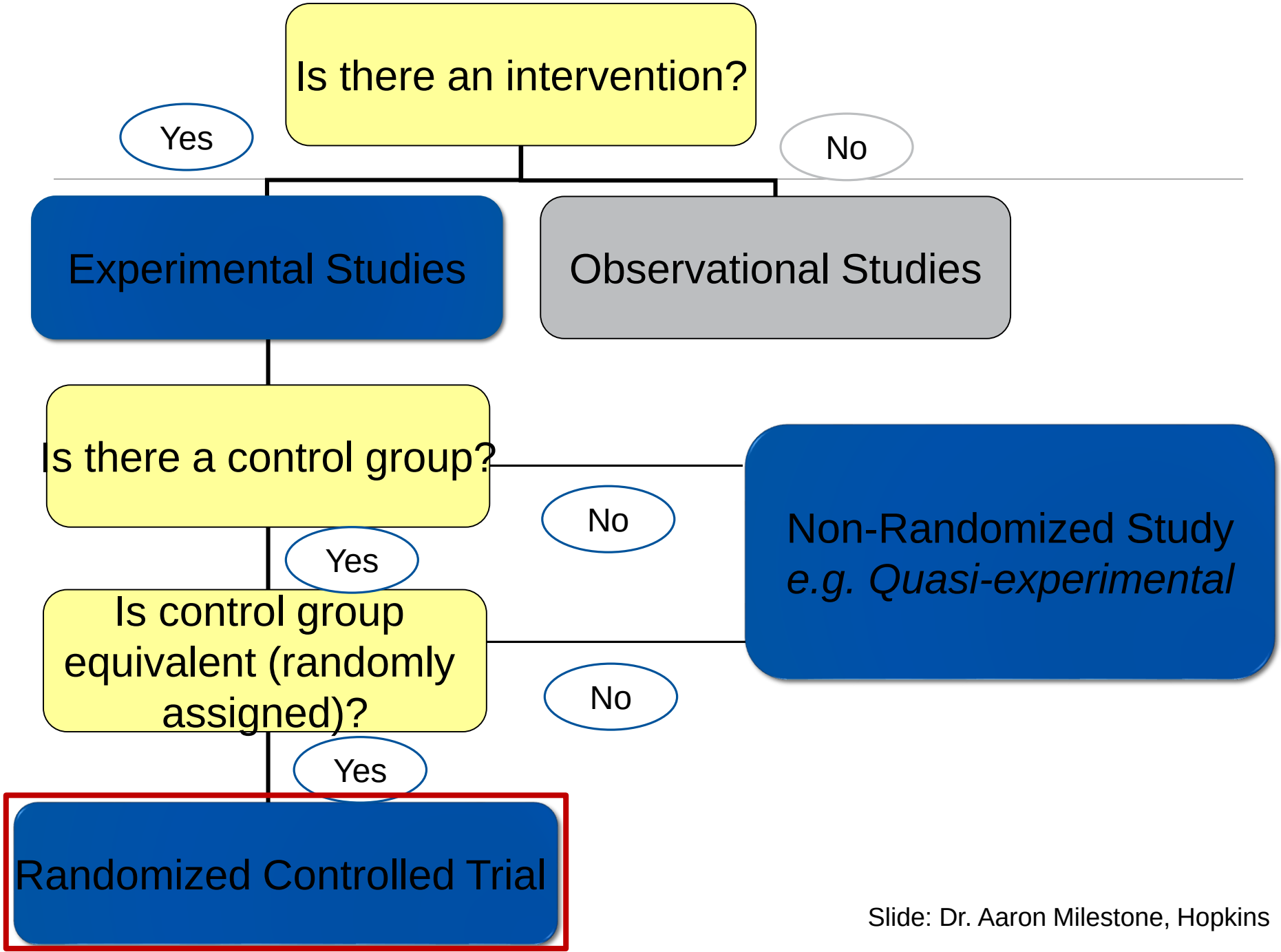


Slide: Dr. Aaron Milestone, Hopkins

Randomized Controlled Trials

MANY designs possible

Goal: Establish causality

Participants (either individuals or groups) are randomly assigned to the experimental arm(s)

Typically requires: research funds, statistician, ++time/effort, regulatory oversight

Key questions (equipoise):

- Is RCT really necessary for practice change?
- Is it ethical?

Randomized Controlled Trials – Pitfalls

How was randomization accomplished and was it effective?

- Contamination of study arms
- Selection bias

Outcome definition/ascertainment

- Loss to follow up

Adequately powered?

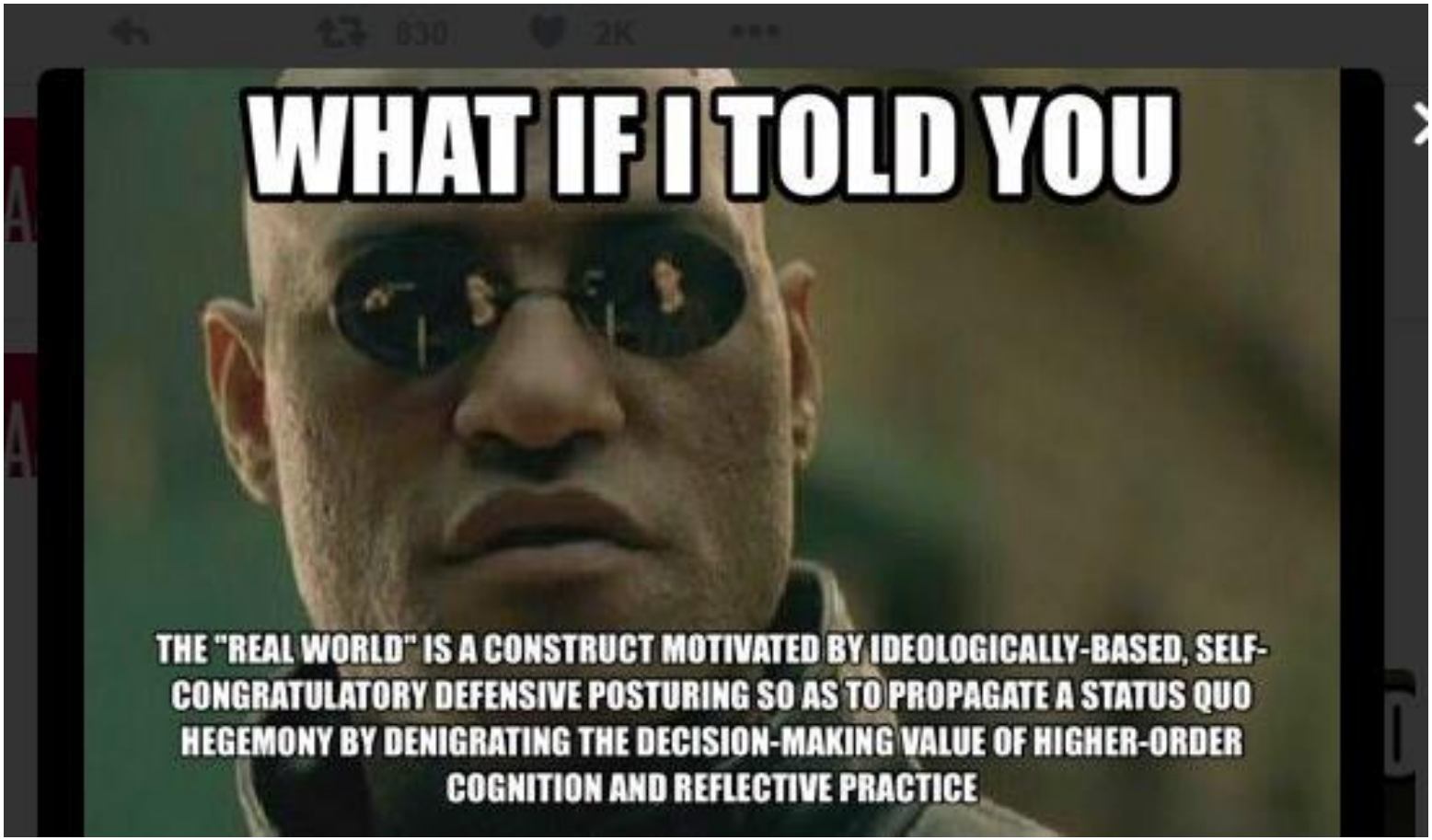
How well was study protocol followed?

- Insufficient documentation/data collection
- Insufficient implementation data

Could study protocol be implemented in other practice settings?

- Generalizability
- Applicability
- External validity

Slide: Dr. Deverick Anderson, Duke



@academicssay

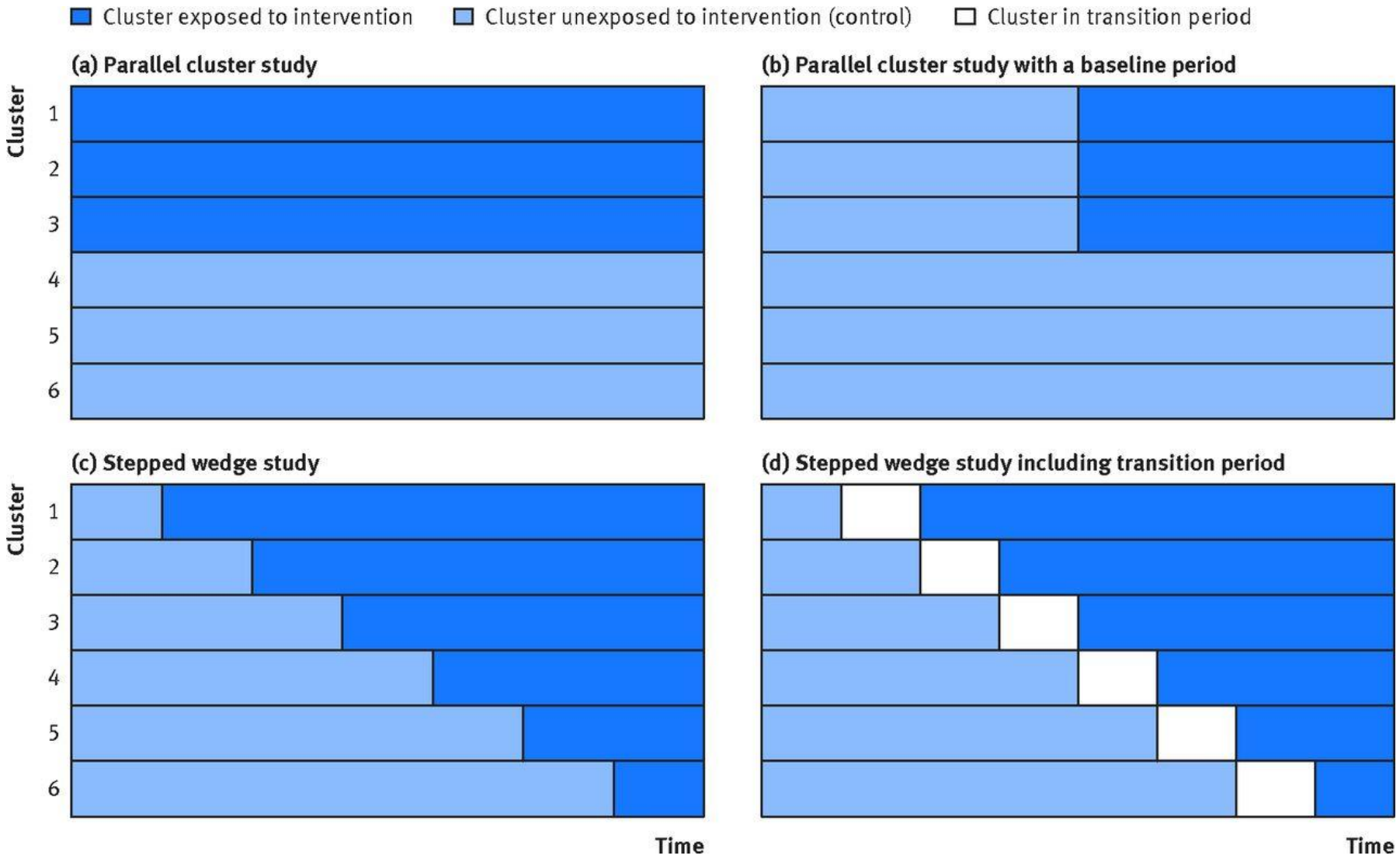
RCT Designs in AS Research

Problem: Cannot blind; cannot deliver intervention without policy/system/practice change; hard to “undo” (crossover); don’t want to enroll/consent patients

Solution(s):

Cluster trials: randomize to groups (units, practices, hospitals) instead of enrolling individuals (patients or providers)

Stepped Wedge: random and sequential crossover of clusters from control to intervention until all clusters are exposed



BMJ 2015;350:h391

Example: Cluster Randomized Trial

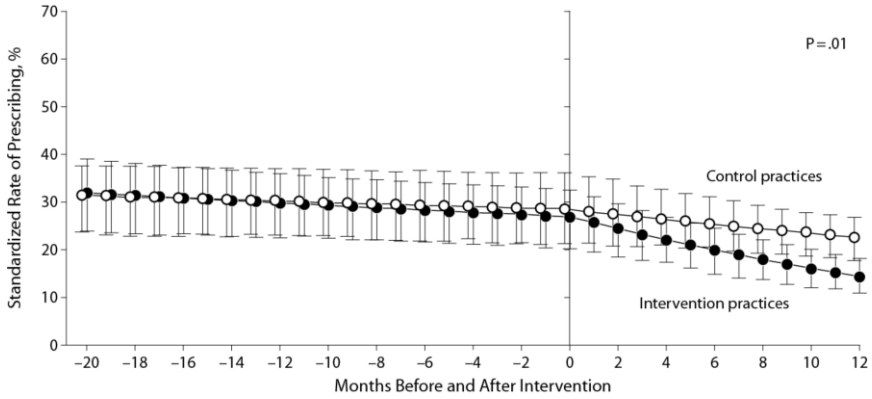
Outpatient stewardship intervention

- Personalized quarterly audit and feedback of prescribing for acute RTI

18 practices and 162 physicians

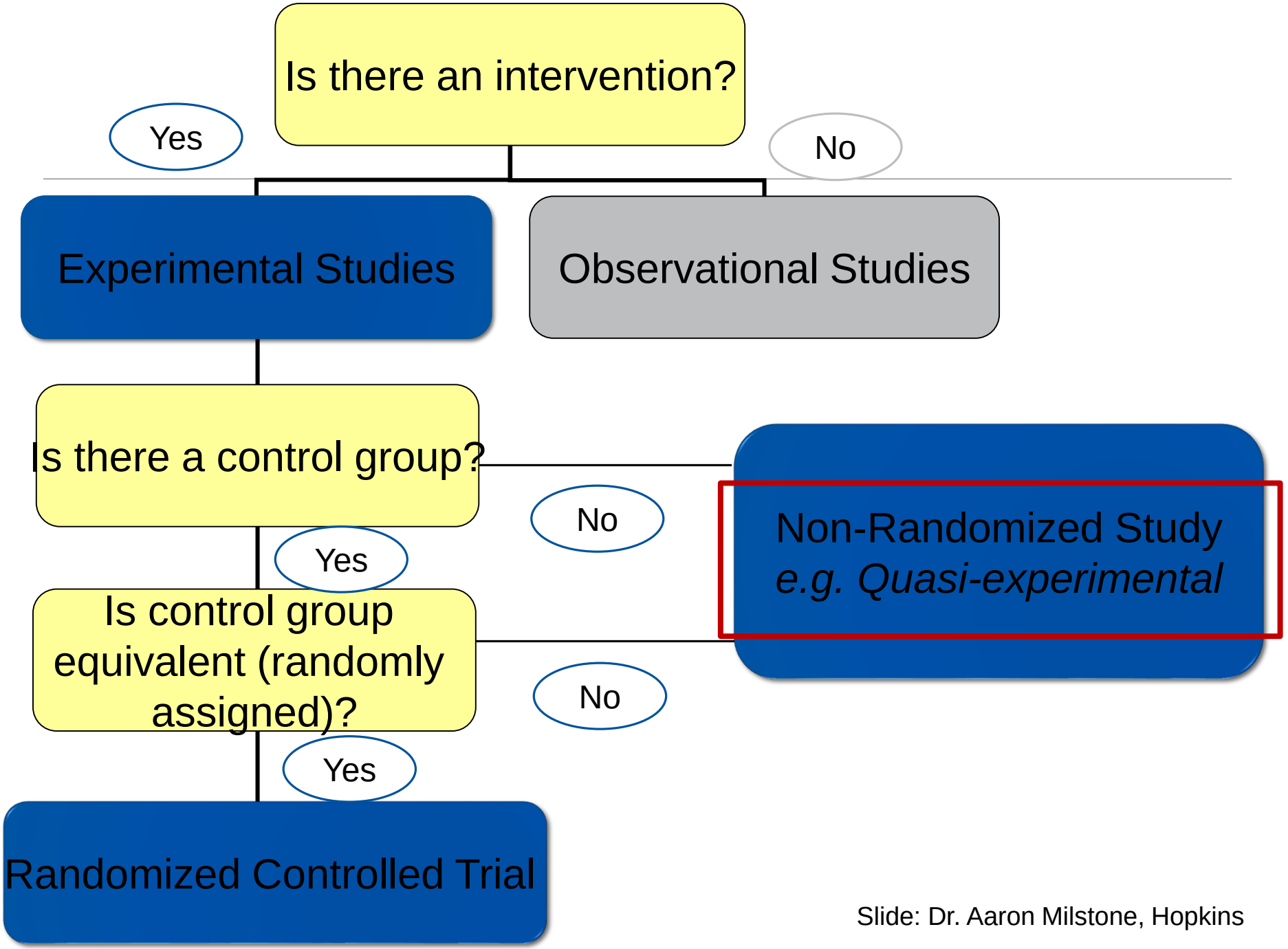
Intervention led to decrease in antimicrobial utilization

- Relied heavily on common electronic health record



Slide: Dr. Deverick Anderson, Duke

Gerber et al JAMA 2013



Slide: Dr. Aaron Milstone, Hopkins

Quasi-experimental Studies

Evaluate association between an intervention and an outcome

Intervention is not randomly assigned

Intervention implemented at group level

Referred to as pre-post or before-after studies

Three major types:

- interrupted time series designs (repeated measures)
- designs with control groups
- designs without control groups

Slide: Dr. Aaron Milstone, Hopkins

When and Why to Use QE Design

Unit- or group-level intervention

Outcomes of interest are reported in aggregate ideally with multiple, repeated measures

- Change in: AU, Cost, CDI

Less expensive, fewer resources than RCT

OK when randomization is not ethical

Can include patients/populations that would not be good for RCTs

Good external validity, pragmatic, i.e. “real world”

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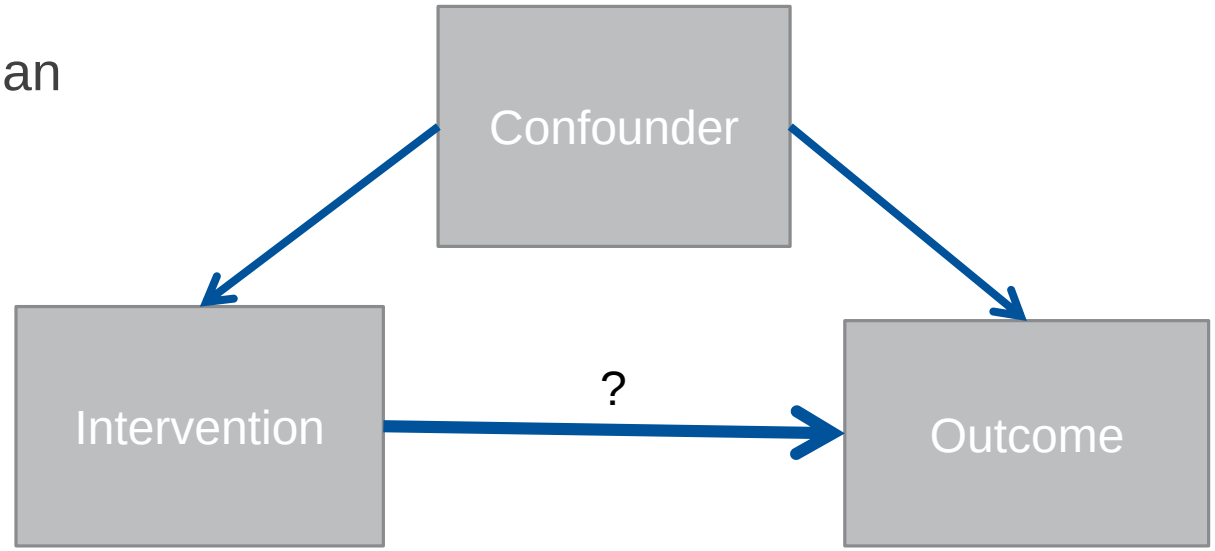
QE - Pitfalls

Not randomized, limiting causal association between intervention and outcome

Many potential biases

- Selection bias
- Maturation bias
- Regression to the mean
- Historical bias
- Instrumentation bias
- Hawthorne effect
- Reporting bias

Confounding



Slide adapted from: Dr. Aaron Milstone, Hopkins

Avoiding Common Pitfalls of QE Studies

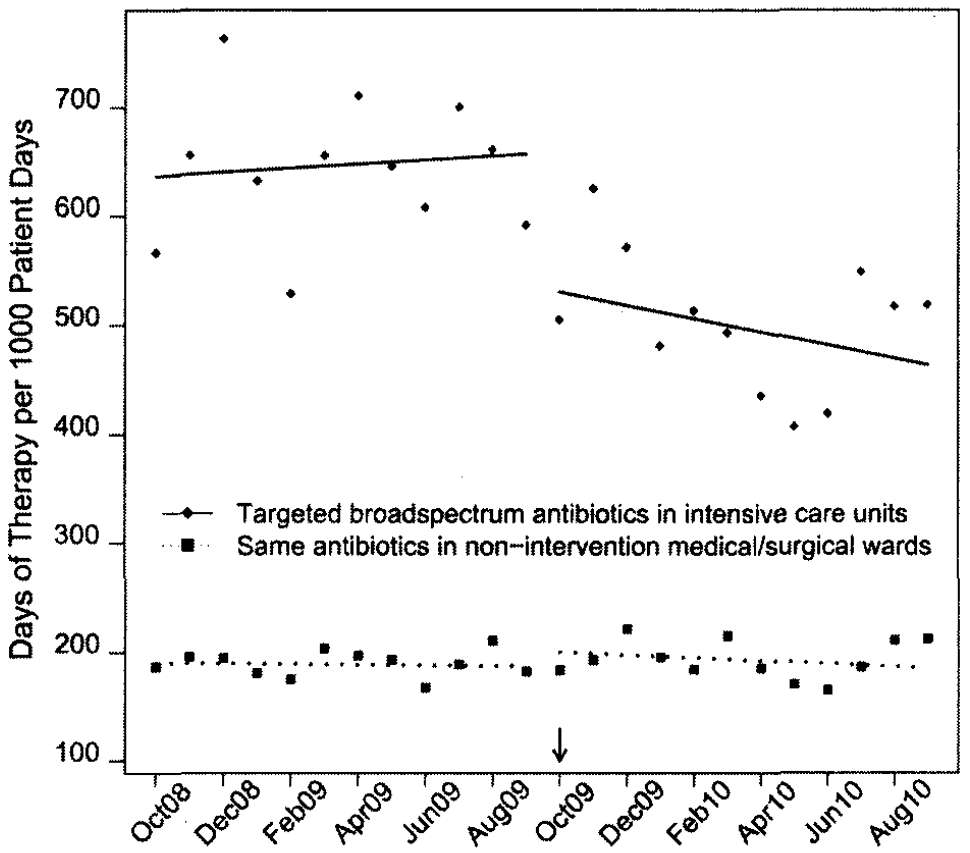
Consider study design

- Addition of concurrent control groups
  - Seasonal, historical bias
  - Mask those who collect outcome data
- Other advanced design elements
  - removed-treatment design, a repeated treatment design or a switching replications design
- Time series measurements
  - Seasonality, maturation bias

Slide: Dr. Aaron Milstone, Hopkins

QE -- Example

- Broad spectrum PAF @day 3, in 3 ICUs
- Prospective, controlled, single center, ITS
- Controls: non-ICU wards, PPI use
- Outcome: Broad AU



Elligsen. ICHE 2012.

Summary

Study designs of any type can have impact on AS, as long as they are done well.

AS, as a field, requires study designs that address implementation as well as effect.

Read and utilize SHEA White Papers on Research Methods.

Know design limitations. Make plans to address them up front.

Acknowledgements

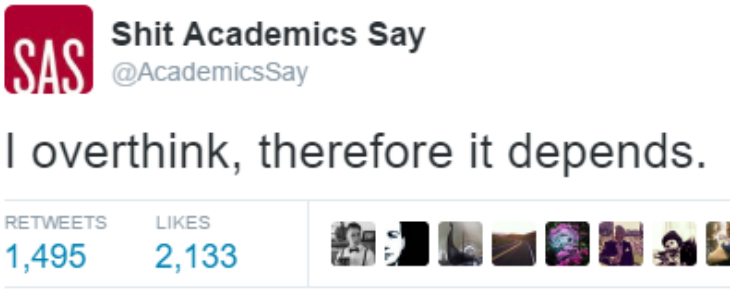
Deverick Anderson

Tamar Barlam

Libby Dodds Ashley

Aaron Milstone

Daniel Morgan



GROUP WORK!

CASE STUDIES EXERCISE

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