OHDSI Tutorial: Design and implementation of a comparative cohort study in observational healthcare data

13 October 2017

Bethesda, MD

Faculty:

Martijn Schuemie (Janssen Research and Development)

Marc Suchard (UCLA)

Patrick Ryan (Janssen Research and Development)

James Weaver (Janssen Research and Development)

Today's Agenda

Time	Activity	Faculty
8:00am-8:30am	Welcome, get settled, get laptops ready	
9:00am-10:00am	Presentation: Overview of the new-user cohort method design, large scale propensity scores and outcome models	Jamie Weaver
10:00am-11:00am	Exercise: Dissect a published cohort study	Marc Suchard
11:00am-11:15am	Break	
11:15am-12:30pm	Presentation: Walkthrough of implementing a cohort study using ATLAS	Jamie Weaver
12:30pm-1:30pm	Lunch	
1:30pm-2:45pm	The CohortMethod R package & review of R code generated by ATLAS	Martijn Schuemie
2:45pm-3:00pm	Break	
3:00pm-4:30pm	Exercise: Collaborate on the design of a study	Patrick Ryan
4:30pm-5:00pm	Team progress reports and wrap up	Marc Suchard

Overview of the new-user cohort method design, large scale propensity scores and outcome models

OHDSI's mission

To improve health, by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.

To generate reliable evidence for the benefit of patients, providers, researchers, health care systems, industry, and government agencies

What evidence does OHDSI seek to generate from observational data?

- Clinical characterization
  - **Natural history:** Who are the patients who have diabetes? Among those patients, who takes metformin?
  - **Quality improvement:** what proportion of patients with diabetes experience disease-related complications?
- Population-level estimation
  - **Safety surveillance:** Does metformin cause lactic acidosis?
  - **Comparative effectiveness:** Does metformin cause lactic acidosis more than glyburide?
- Patient-level prediction
  - **Precision medicine:** Given everything you know about me and my medical history, if I start taking metformin, what is the chance that I am going to have lactic acidosis in the next year?
  - **Disease interception:** Given everything you know about me, what is the chance I will develop diabetes?

What is OHDSI's strategy to deliver reliable evidence?

- **Methodological research**
  - Develop new approaches to observational data analysis
  - Evaluate the performance of new and existing methods
  - Establish empirically-based scientific best practices
- **Open-source analytics development**
  - Design tools for data transformation and standardization
  - Implement statistical methods for large-scale analytics
  - Build interactive visualization for evidence exploration
- **Clinical evidence generation**
  - Identify clinically-relevant questions that require real-world evidence
  - Execute research studies by applying scientific best practices through open-source tools across the OHDSI international data network
  - Promote open-science strategies for transparent study design and evidence dissemination

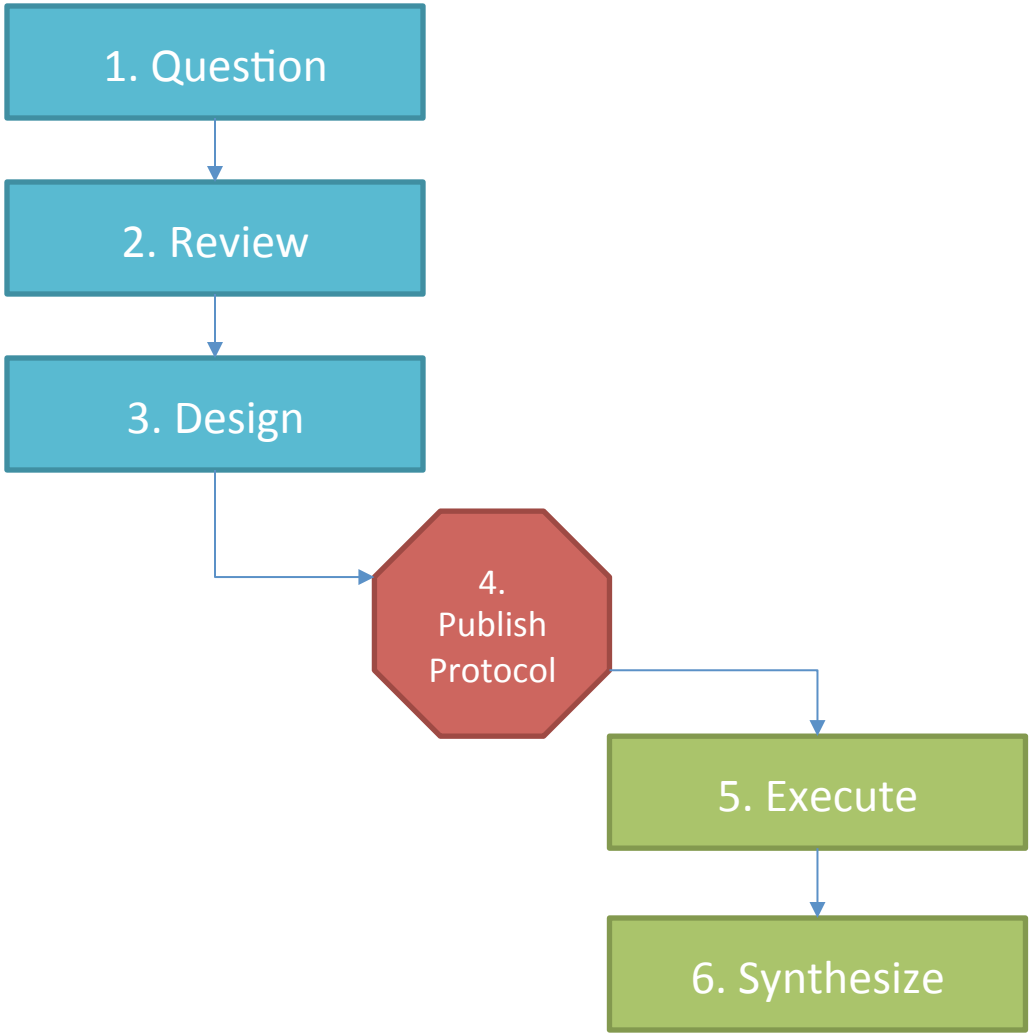
OHDSI activities on display at the symposium

	Methodological research	Open source analytics development	Clinical evidence generation
Clinical characterization			
Population-level effect estimation			
Patient-level prediction			

OHDSI activities on display at the symposium

	Methodological research	Open source analytics development	Clinical evidence generation
Clinical characterization			
Population-level effect estimation			
Patient-level prediction			

A standardized process for evidence generation and dissemination



How OHDSI is trying to help:

OHDSI community

Open-source knowledgebase (CEM)

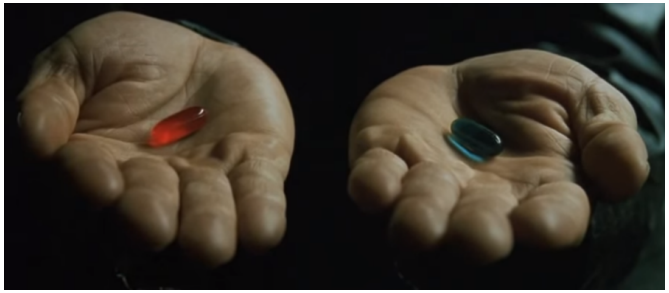
Open-source front-end web applications (ATLAS)

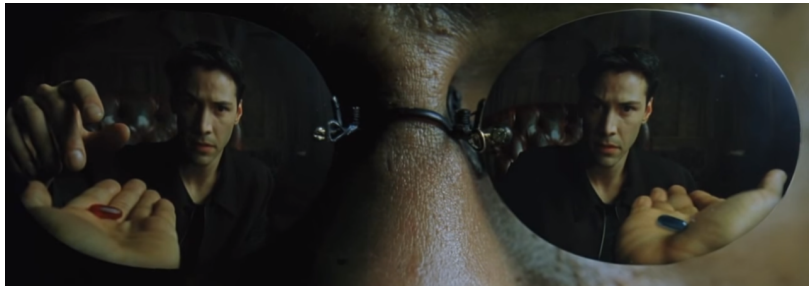
Open-source back-end statistical packages (R Methods Library)

OHDSI network studies

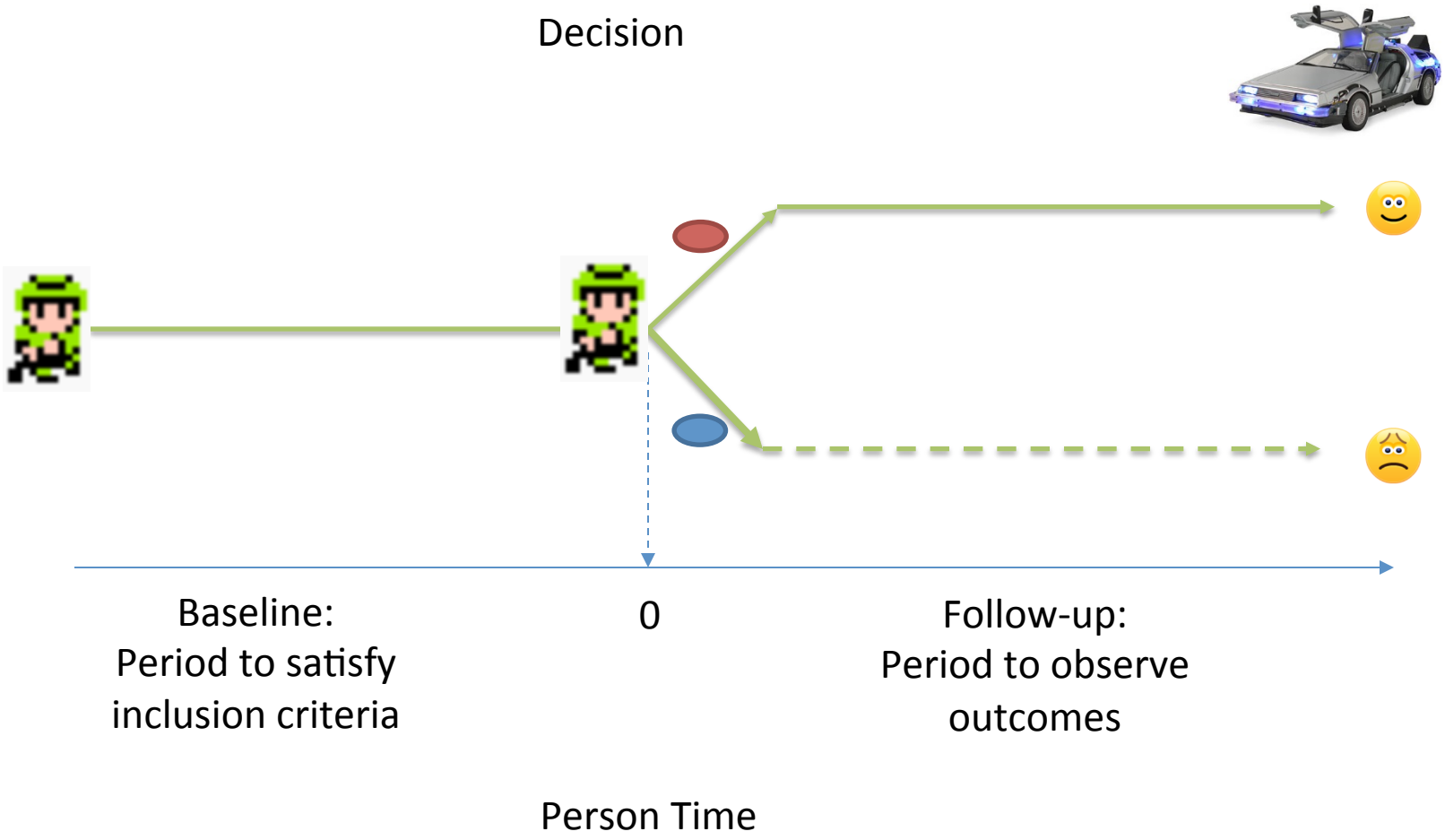
A pop culture mash-up to explain counterfactual reasoning…

A pop culture mash-up to explain counterfactual reasoning…

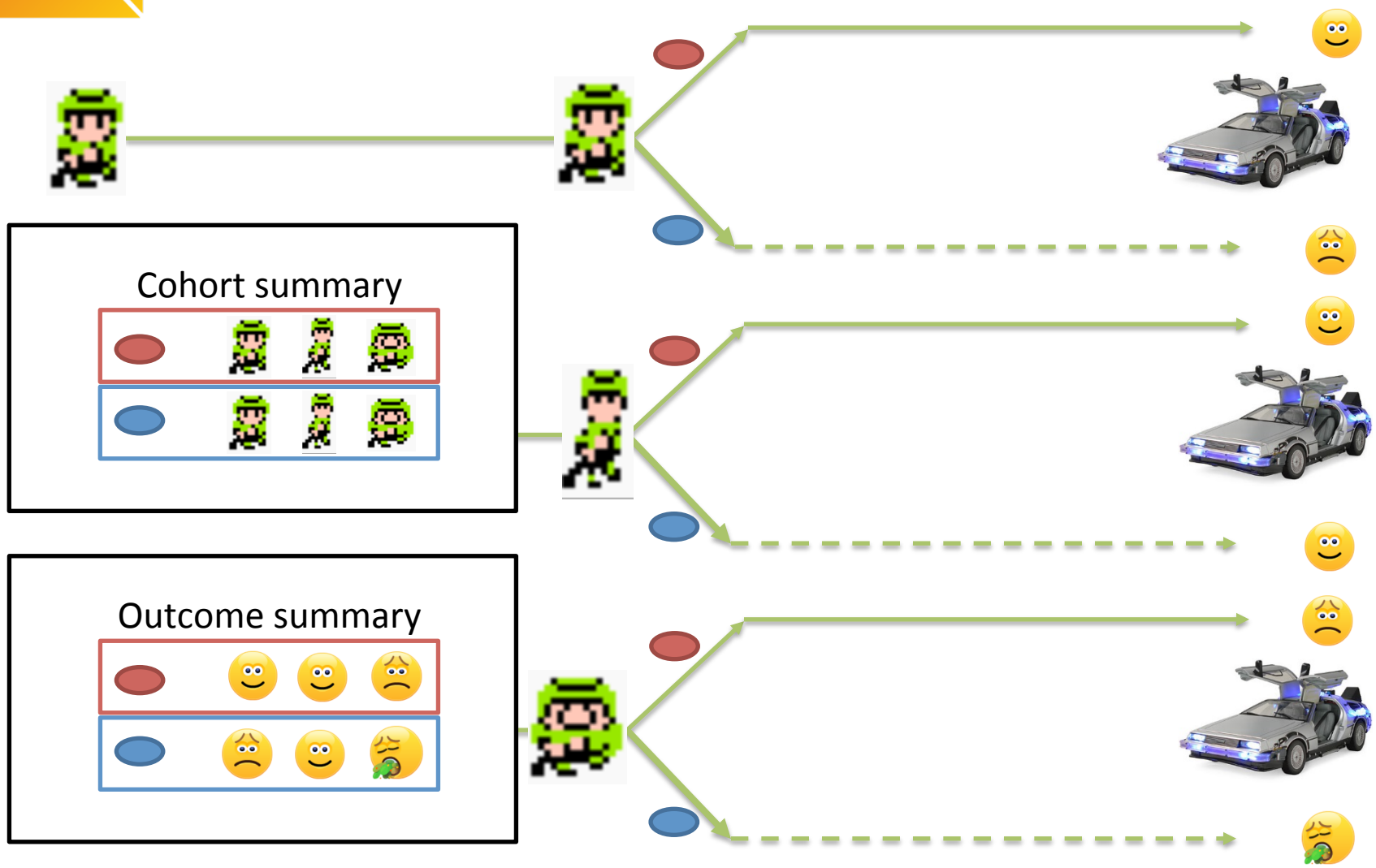




Counterfactual reasoning for one person



Counterfactual reasoning for a population



Counterfactual reasoning for a population

Cohort summary

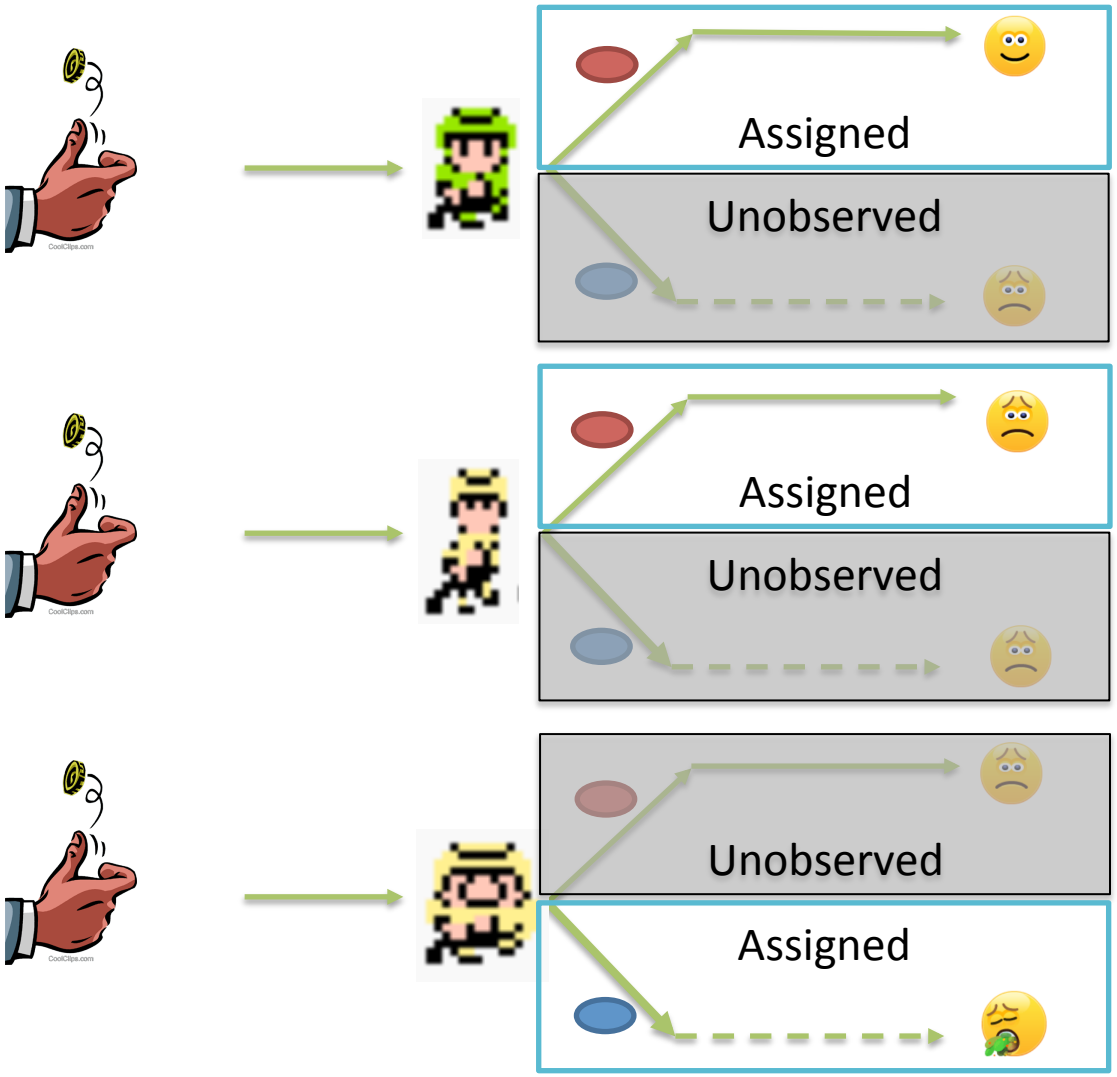
	Outcome under 🔴	Outcome under 🔵
	🙂	😞
	🙂	🙂
	😞	🤢

Alas, we don't have a Delorean…

- What is our *next* best approximation?

- Instead of studying the same population under both decision options, let's define a larger population and randomly assign one treatment to each person, then compare outcomes between the two cohorts…

Randomized treatment assignment to approximate counterfactual outcomes



Cohort summary

	Outcome under 	Outcome under 
 		??
 		??
 	??	

- Randomization allows for assumption that persons assigned to target cohort are exchangeable at baseline with persons assigned to comparator cohort

Alas, we can't randomize…

- What is our *next, next* best approximation?

- Define a larger population, observe the treatment choices that were made, then compare outcomes:
  - Between persons who made different choices (comparative cohort design)

  OR

  - Within persons during time periods with different exposure status (self-controlled designs)

How does Epidemiology define a comparative cohort study?

…it depends on what Epidemiology textbook you read…

"In a retrospective cohort study…the investigator identified the cohort of individu
their su
recent

"Cohort studies are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome. Cohort studies generally compare exposed patients to unexposed patients, although they can also be used to compare one exposure to another."
--Strom, Pharmacoepidemiology, 2005

"In
has experienced the outcome of interest, but all of whom could experience it…
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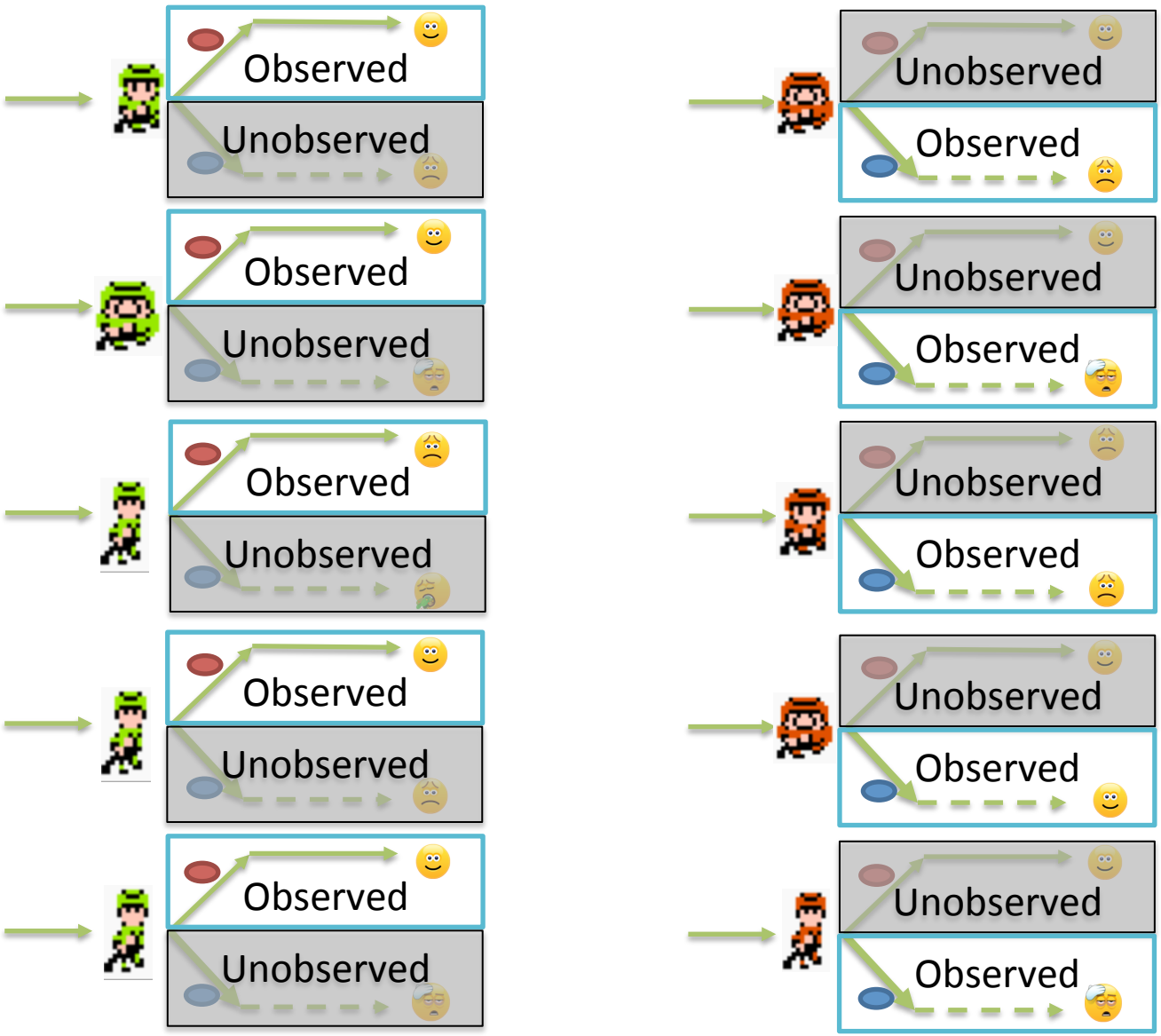
"In the paradigmatic cohort study, the investigator defines two or more groups of people that are free of disease and that differ according to the extent of their exposure to a potential cause of disease. These groups are referred to as the study cohorts. When two groups are studies, one is usually though of as the exposed or index cohort – those individuals who have experienced the putative causal event or condition – and the other is then thought of as the unexposed or reference cohort."
--Rothman, Modern Epidemiology, 2008

An observational comparative cohort design to approximate counterfactual outcomes



An observational comparative cohort design to approximate counterfactual outcomes

	Outcome under	Outcome under
	😐	??
	😐	??
	😟	??
	😐	??
	😐	??
	??	😟
	??	😪
	??	😟
	??	😐
	??	😪

An observational comparative cohort design to approximate counterfactual outcomes

	Outcome under	Outcome under
	🙂	??
	🙂	??
	😟	??
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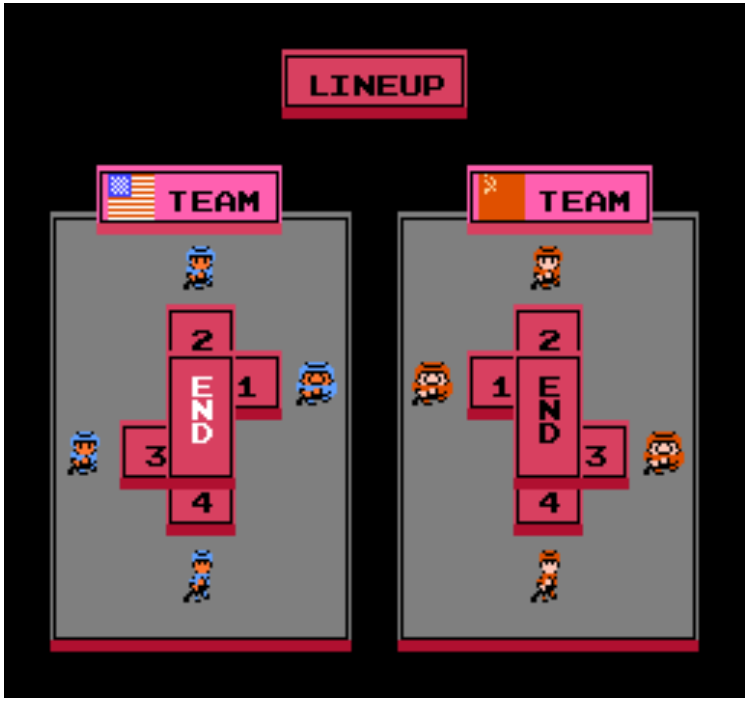


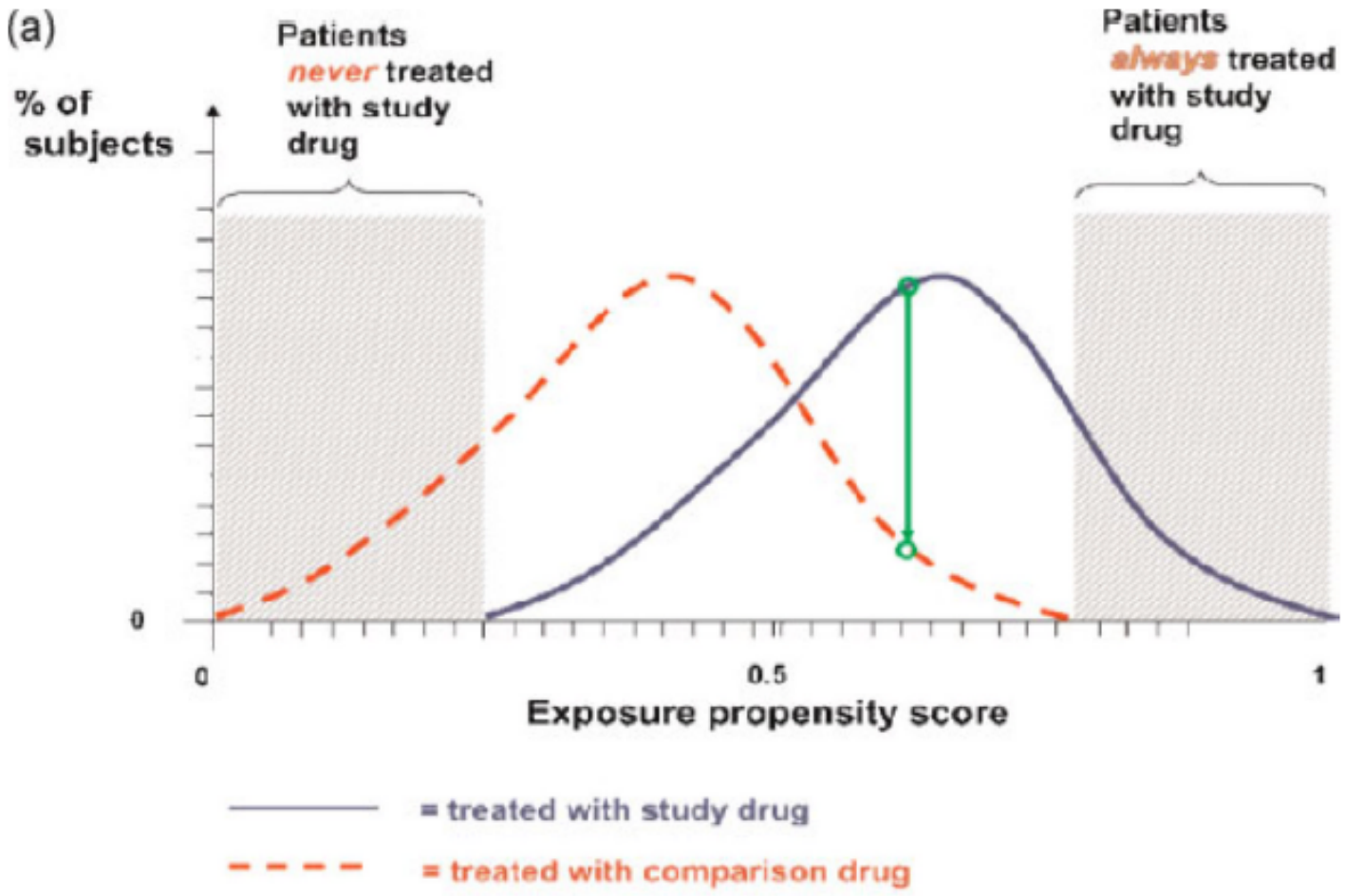
- Exchangeability assumption may be violated if there is reason for treatment choice...and there often is

Propensity score introduction

- $E(x) = Pr(Z=1|x)$
  - Z is treatment assignment
  - x is a set of all covariates at the time of treatment assignment
- Propensity score = probability of belonging to the target cohort vs. the comparator cohort, given the baseline covariates
- Propensity score can be used as a 'balancing score': if the two cohorts have similar propensity score distribution, then the distribution of covariates should be the similar (need to perform diagnostic to check)

Rubin Biometrika 1983

Intuition around propensity score balance



Schneeweiss. PDS 2011

"Five reasons to use propensity score in pharmacoepidemiology"

- Theoretical advantages
  - Confounding by indication is the primary threat to validity, PS focuses directly on indications for use and non-use of drug under study
- Value of propensity scores for matching or trimming the population
  - Eliminate 'uncomparable' controls without assumptions of linear relationship between PS and outcome
- Improved estimation with few outcomes
  - PS allows matching on one scalar value rather than needing degrees of freedom for all covariates
- Propensity score by treatment interactions
  - PS enables exploration of patient-level heterogeneity in response
- Propensity score calibration to correct for measurement error

Glynn et al, BCPT 2006

Methods for confounding adjustment using a propensity score

Regression adjustment	The PS is used as a covariable in an outcome regression model to adjust the as[illegible] assum[illegible] same[illegible] relationship between propensity score and outcome is correctly specified.
Matching	The PS is used to match exposed subjects to unexposed subjects with similar values of the PS. This method assumes that within the matched sample, exposed and unexposed subjects have a similar distribution of baseline characteristics.
Stratification	The PS is used to stratify subjects into (often quintiles or deciles) strata. Treatment effects are estimated separately within each stratum and then combined into an overall estimate of treatment effect. This method assumes that within each stratum, exposed and unexposed subjects have a similar distribution of baseline characteristics.
Inverse Probability Weighting	The PS is used to create weights based on the inverse probability which is defined as: E*/PS + (1-E)/(1-PS). This assumes that baseline characteristics are similar in the exposed and unexposed group.

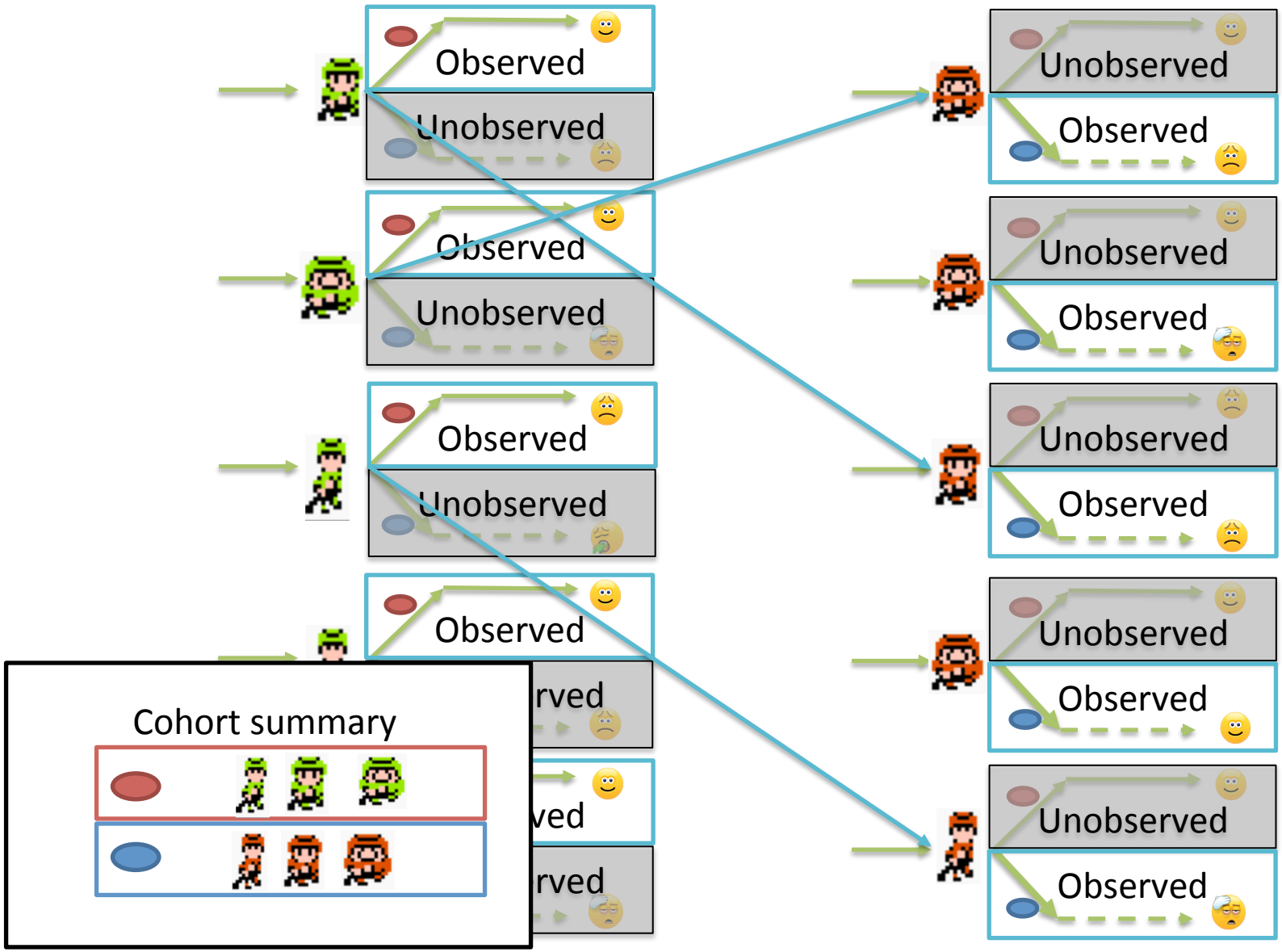
* E: exposure

Not generally recommended

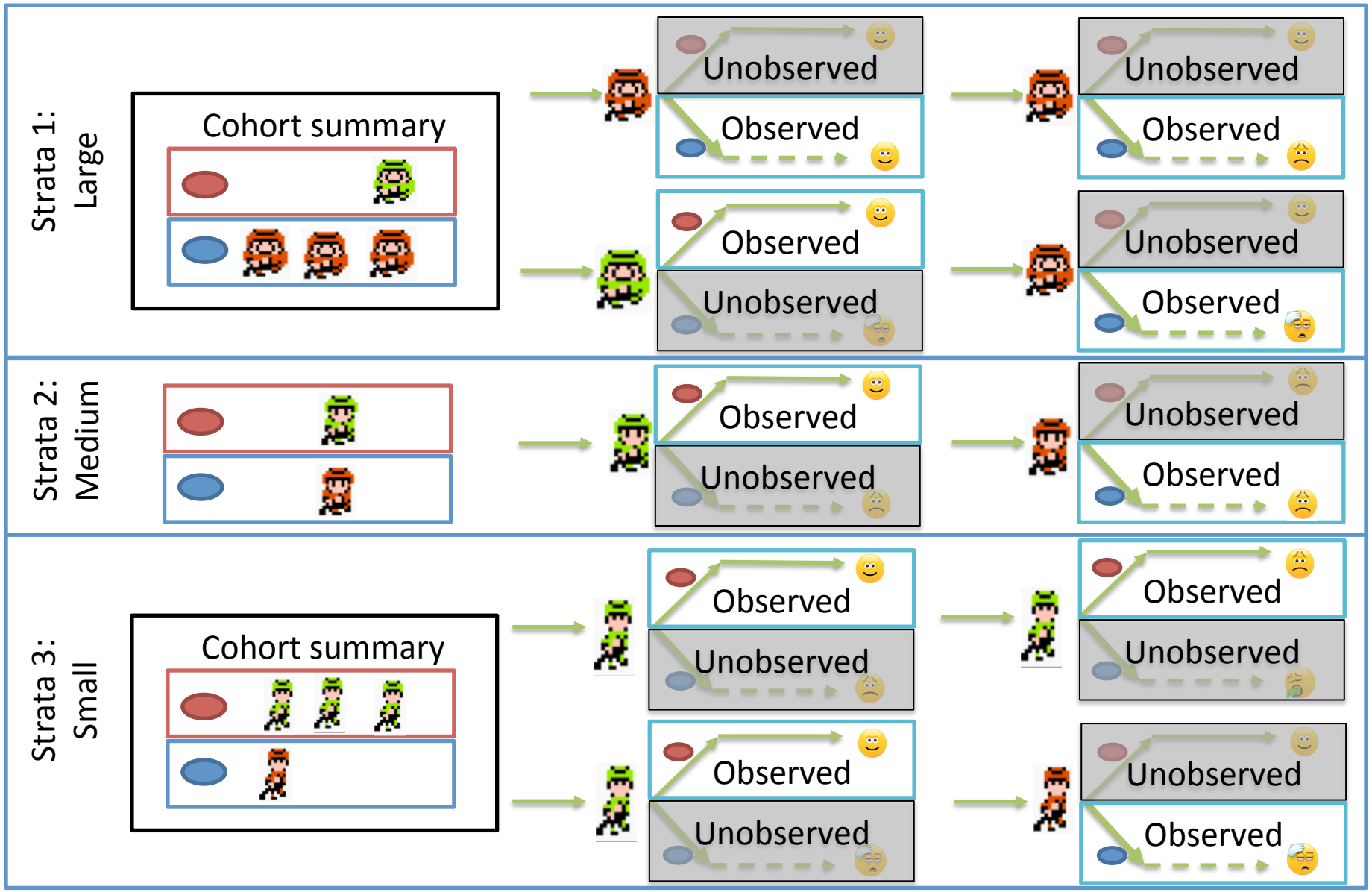
Fully implemented in OHDSI CohortMethod R package

Garbe et al, Eur J Clin Pharmacol 2013, http://www.ncbi.nlm.nih.gov/pubmed/22763756

Matching as a strategy to adjust for baseline covariate imbalance



Stratification as a strategy to adjust for baseline covariate imbalance



Drug Saf (2013) 36 (Suppl 1):S59–S72
DOI 10.1007/s40264-013-0099-6

ORIGINAL RESEARCH ARTICLE

Empirical Performance of a New User Cohort Method: Lessons for Developing a Risk Identification and Analysis System

Patrick B. Ryan · Martijn J. Schuemie · Susan Gruber · Ivan Zorych · David Madigan

Conclusion: The new user cohort method can contribute useful information toward a risk identification system, but should not be considered definitive evidence given the degree of error observed within effect estimates.
Careful consideration of the comparator selection and appropriate calibration of the effect estimates is required in order to properly interpret findings.

OHDSI's definition of 'cohort'

Cohort = a set of persons who satisfy one or more inclusion criteria for a duration of time

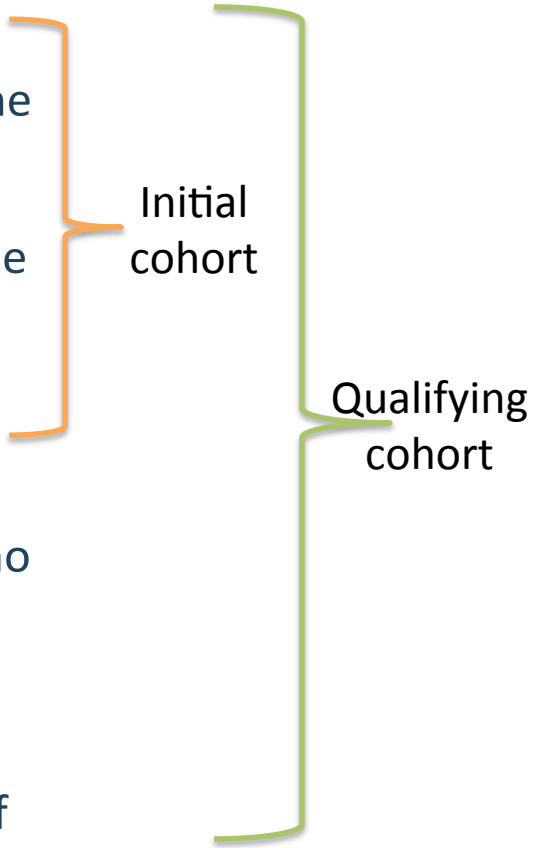
Objective consequences based on this cohort definition:

- One person may belong to multiple cohorts
- One person may belong to the same cohort at multiple different time periods
- One person may not belong to the same cohort multiple times during the same period of time
- One cohort may have zero or more members
- A codeset is NOT a cohort…

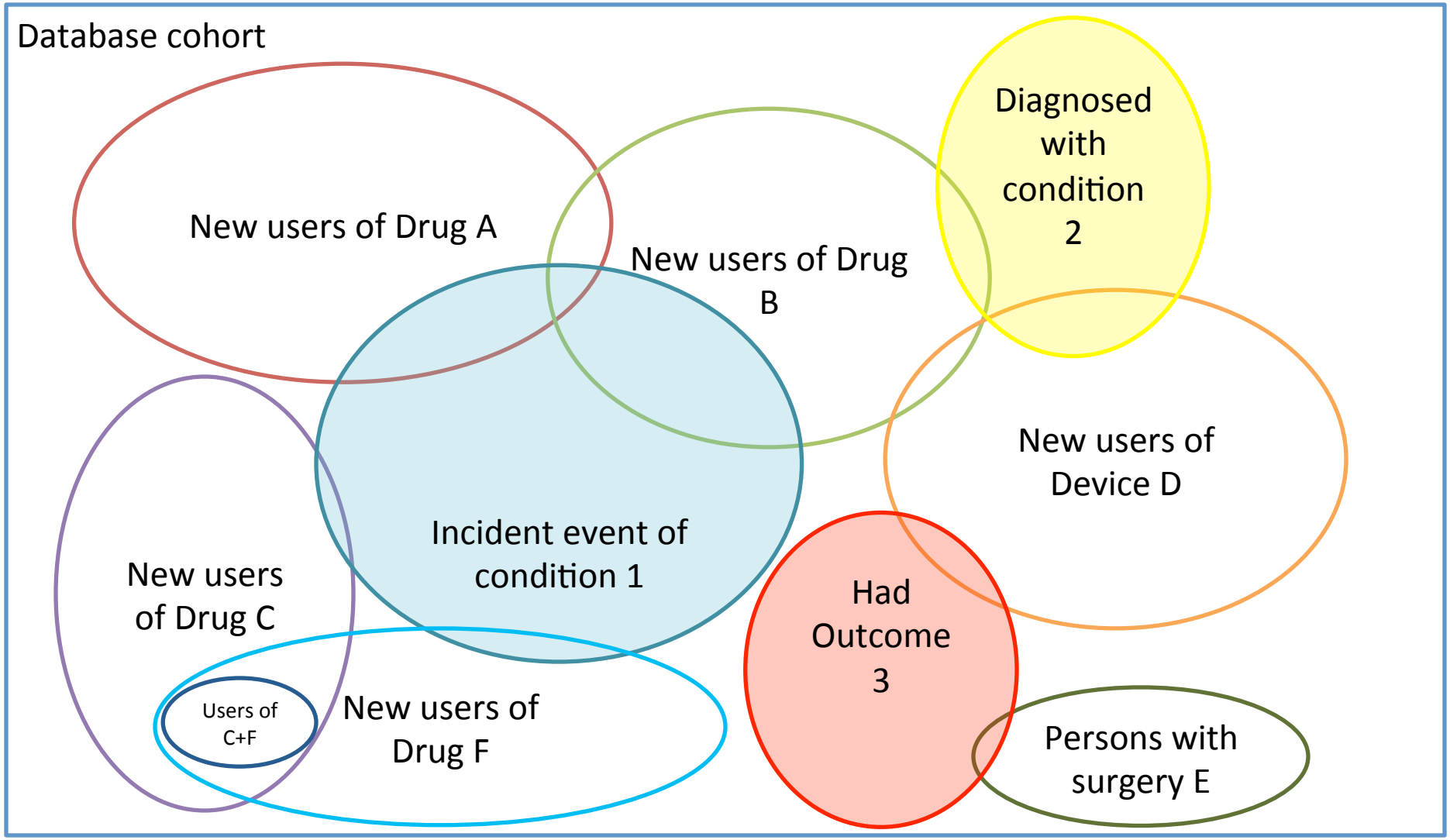
  …logic for how to use the codeset in a criteria is required

Process flow for formally defining a cohort in ATLAS

- Cohort entry criteria
  - Initial events
    - Events are recorded time-stamped observations for the persons, such as drug exposures, conditions, procedures, measurements and visits.
    - All events have a start date and end date, though some events may have a start date and end date with the same value (such as procedures or measurements).
  - Initial event inclusion criteria
  - Additional qualifying inclusion criteria
    - The qualifying cohort will be defined as all persons who have an initial event, satisfy the initial event inclusion criteria, and fulfill all additional qualifying inclusion criteria.
    - Each qualifying inclusion criteria will be evaluated to determine the impact of the criteria on the attrition of persons from the initial cohort.
- Cohort exit criteria



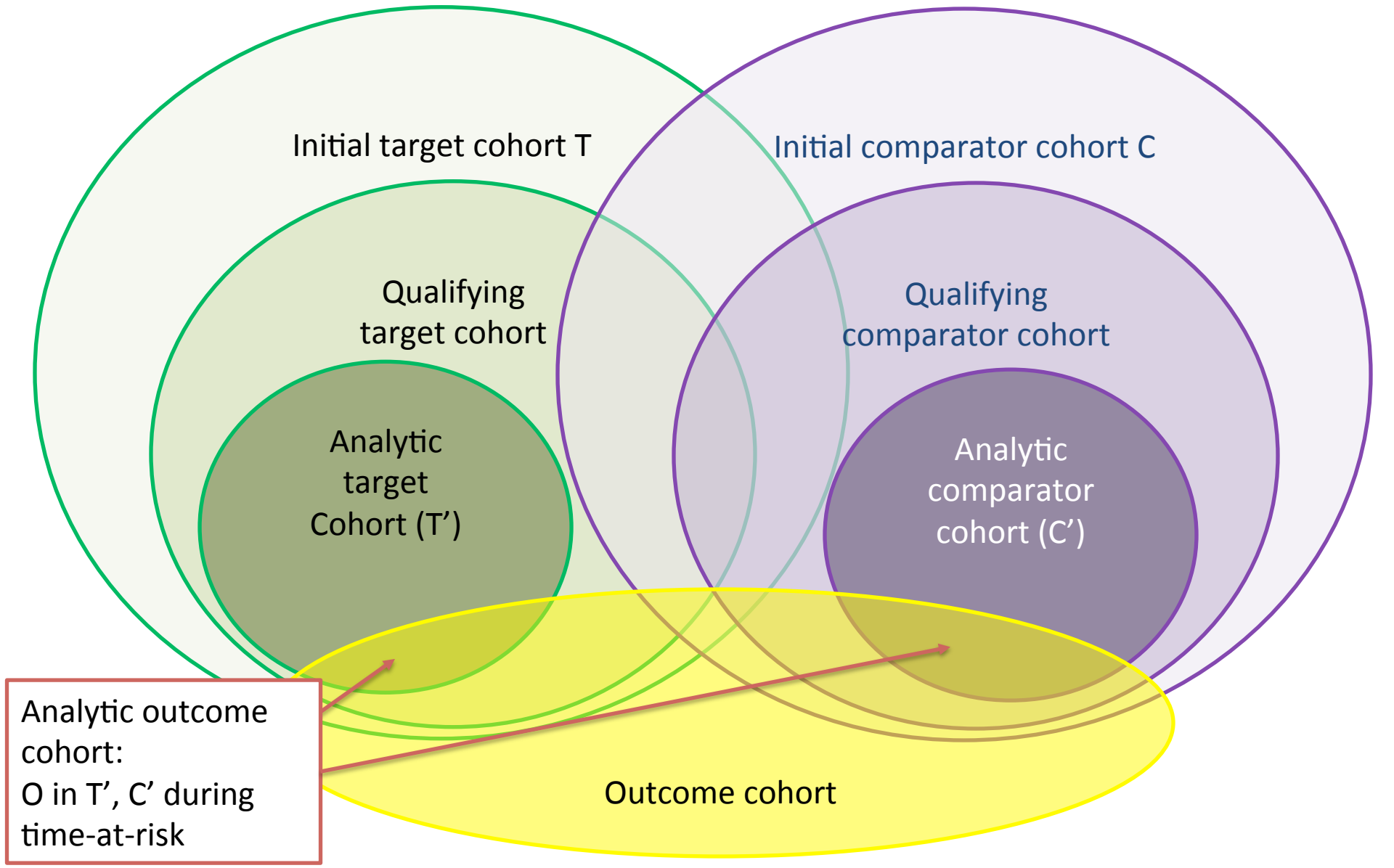
A database is full of cohorts, some of which may represent valid comparisons



What are the key inputs to a comparative cohort design?

Input parameter	Design choice
Target cohort (T)	
Comparator cohort (C)	
Outcome cohort (O)	
Time-at-risk	
Model specification	

Cohort restriction in comparative cohort analyses



The choice of the outcome model defines your research question

	Logistic regression	Poisson regression	Cox proportional hazards
How the outcome cohort is used	Binary classifier of presence/ absence of outcome during the fixed time-at-risk period	Count the number of occurrences of outcomes during time-at-risk,	Compute time-to-event from time-at-risk start until earliest of first occurrence of outcome or time-at-risk end, and track the censoring event (outcome or no outcome)
'Risk' metric	Odds ratio	Rate ratio	Hazards ratio
Key model assumptions	Constant response in fixed window	Outcomes follow Poisson distribution	Proportionality – constant relative hazard

Design an observational study like you would a randomized trial

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Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

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Initially submitted December 9, 2014; accepted for publication September 8, 2015.

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with respect to how
research using big
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vides a structured process
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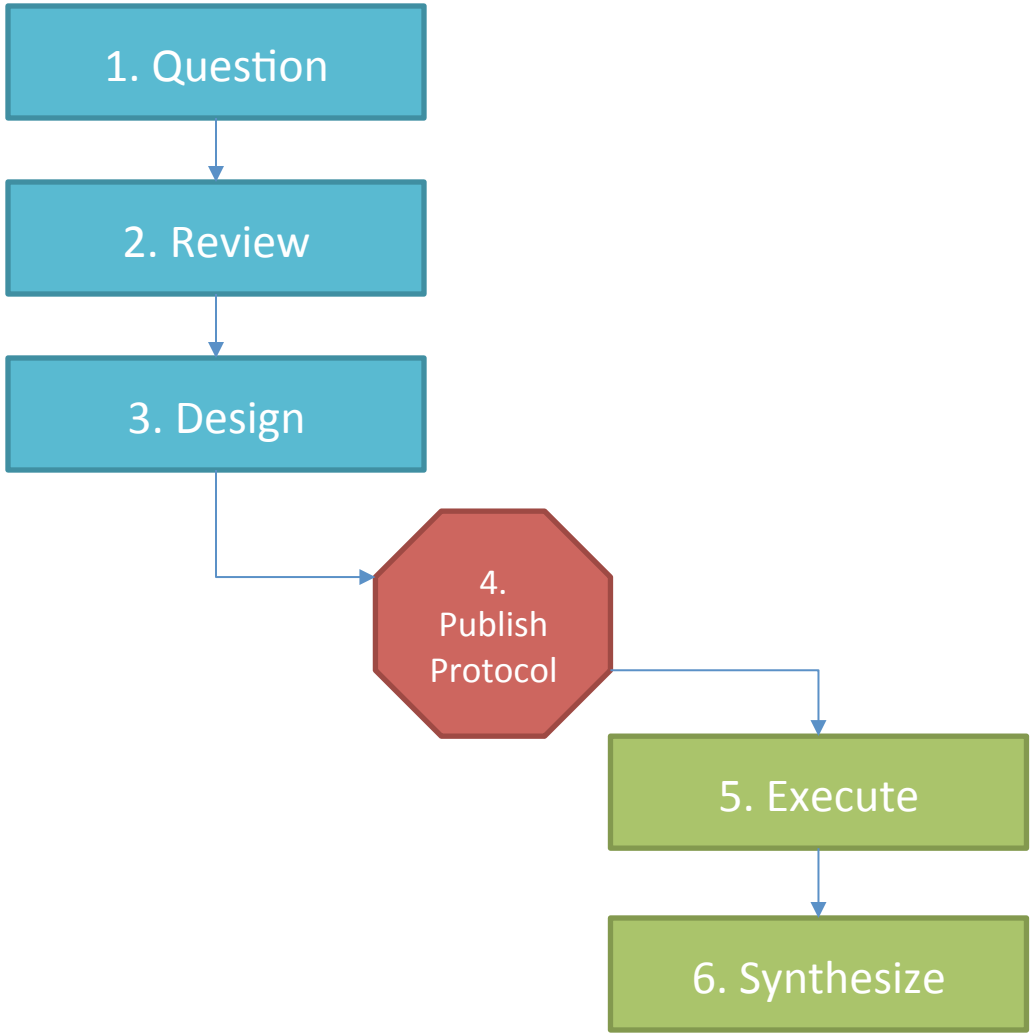
Protocol components to emulate:

- Eligibility criteria
- Treatment strategies
- Assignment procedures
- Follow-up period
- Outcome
- Causal contrasts of interest
- Analysis plan

A standardized process for evidence generation and dissemination



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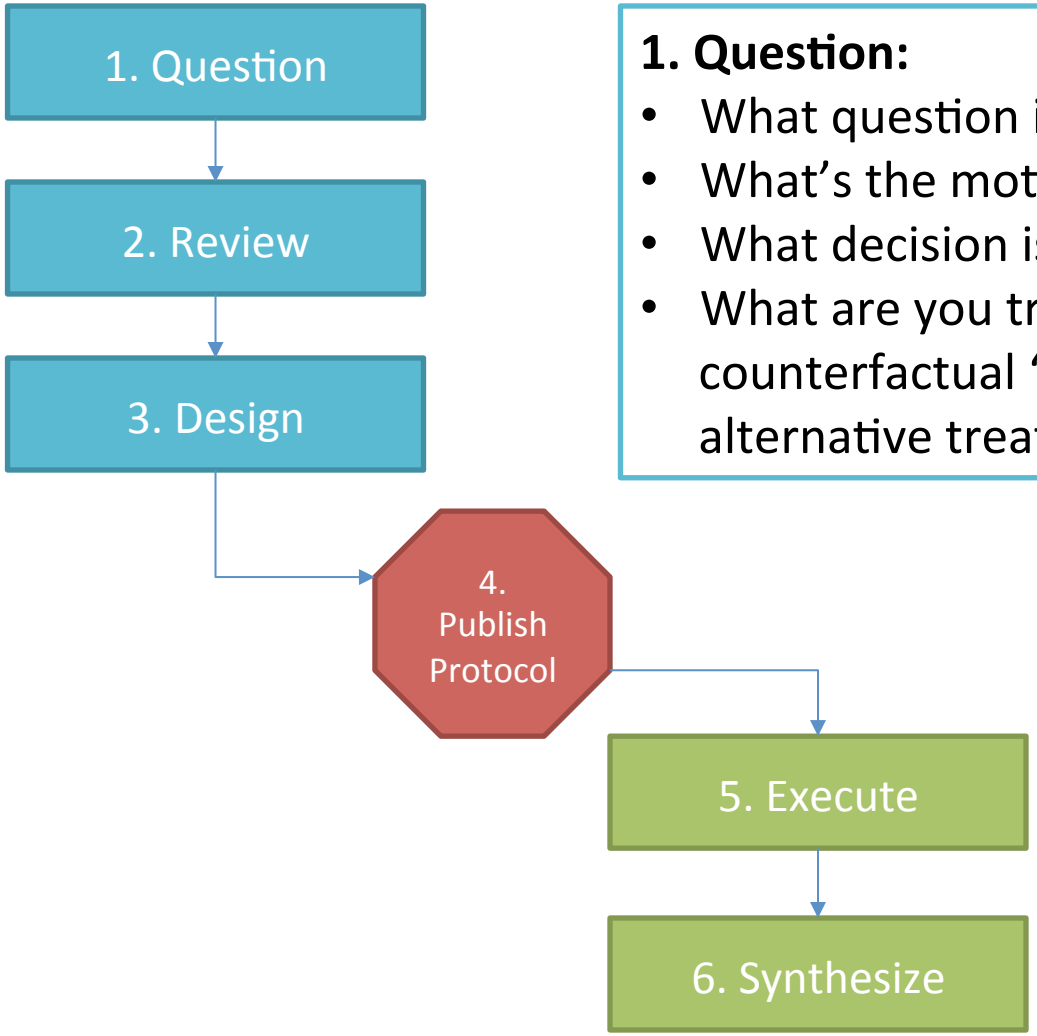
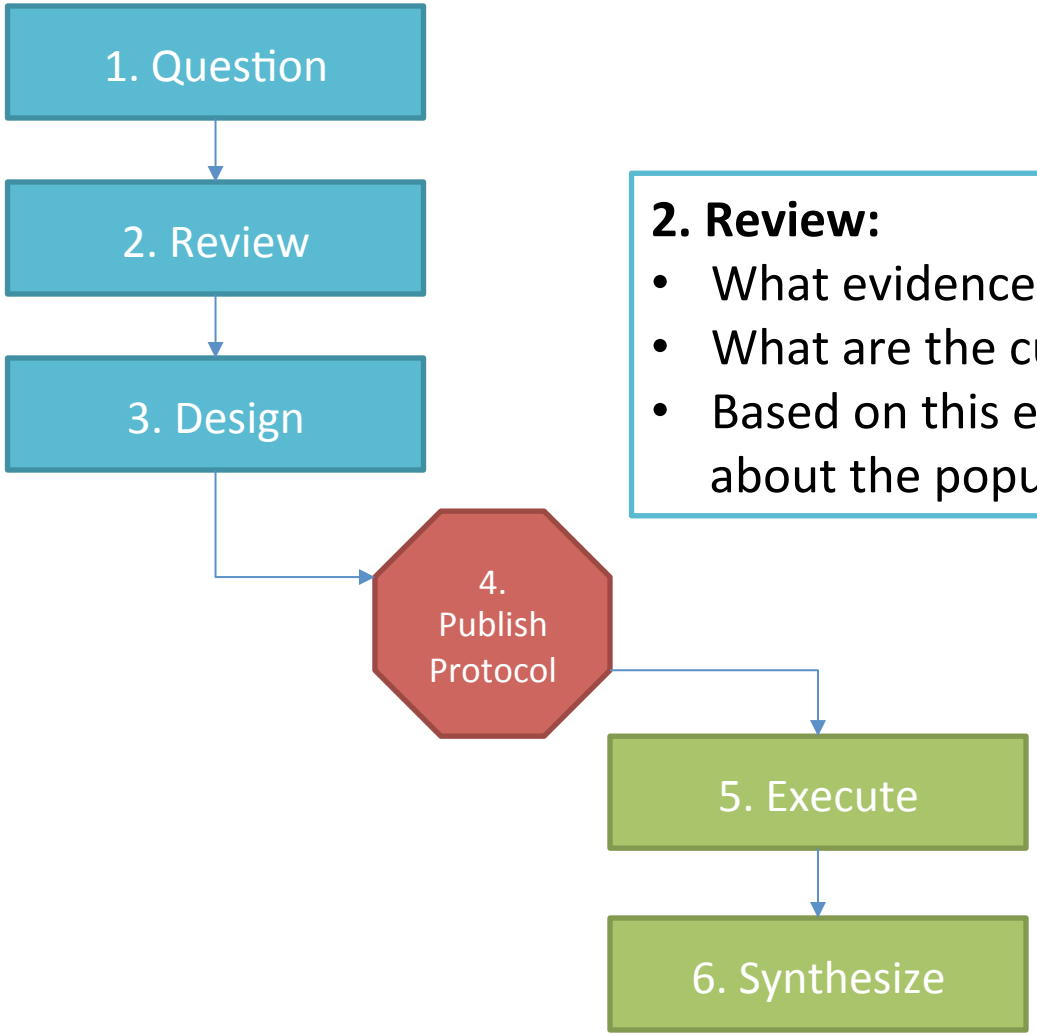


1. Question:

- What question is being asked?
- What's the motivation for asking the question?
- What decision is this evidence trying to inform?
- What are you trying to estimate: effect relative to counterfactual 'unexposed' or effect relative to alternative treatment?

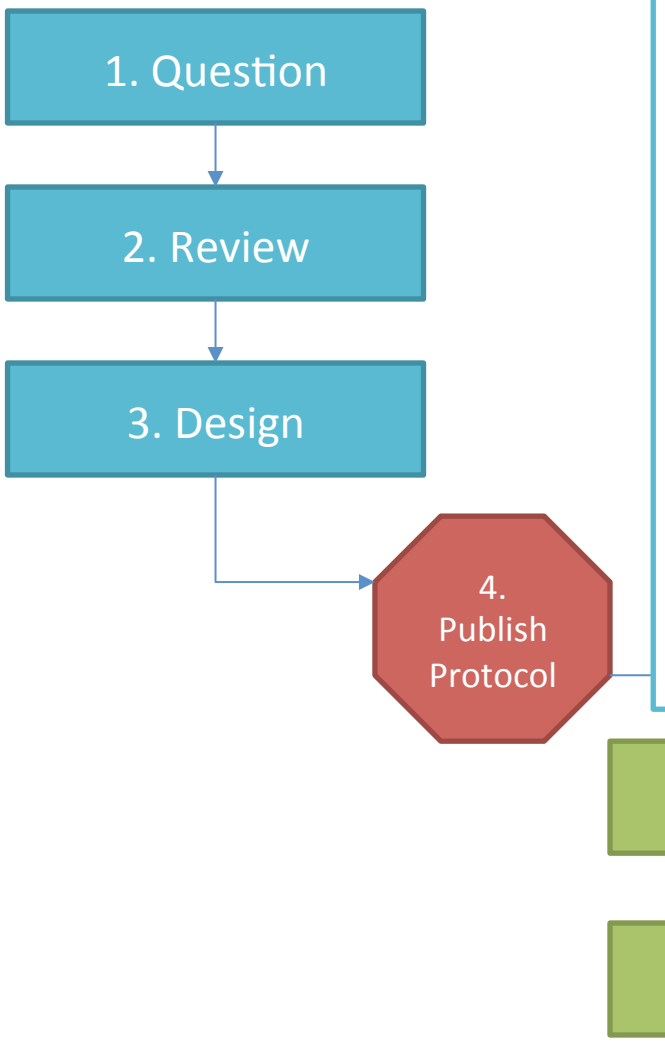
A standardized process for evidence generation and dissemination



2. Review:

- What evidence already exists about this question?
- What are the current evidence gaps?
- Based on this evidence, what is your current belief about the population-level effect?

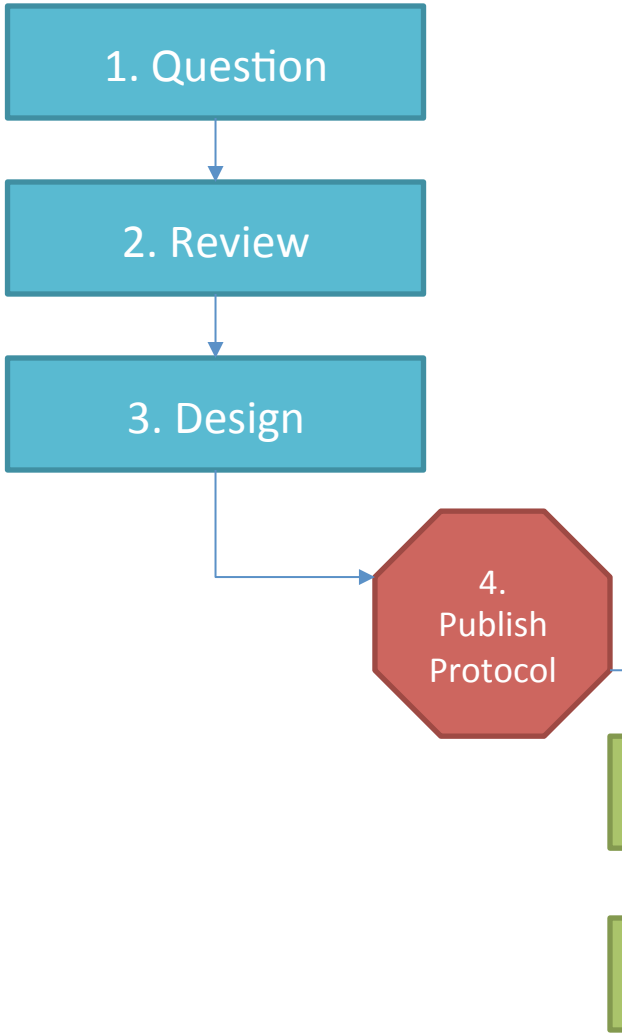
A standardized process for evidence generation and dissemination



3. Design:

- Study team must make decisions about pre-defined inputs to standardized analytics:
  - Target cohort
  - Comparator cohort
  - Outcome
  - Time-at-risk
  - Model specification
- Decisions require clinical domain knowledge, experience with the source observational data, and expertise in statistical modeling

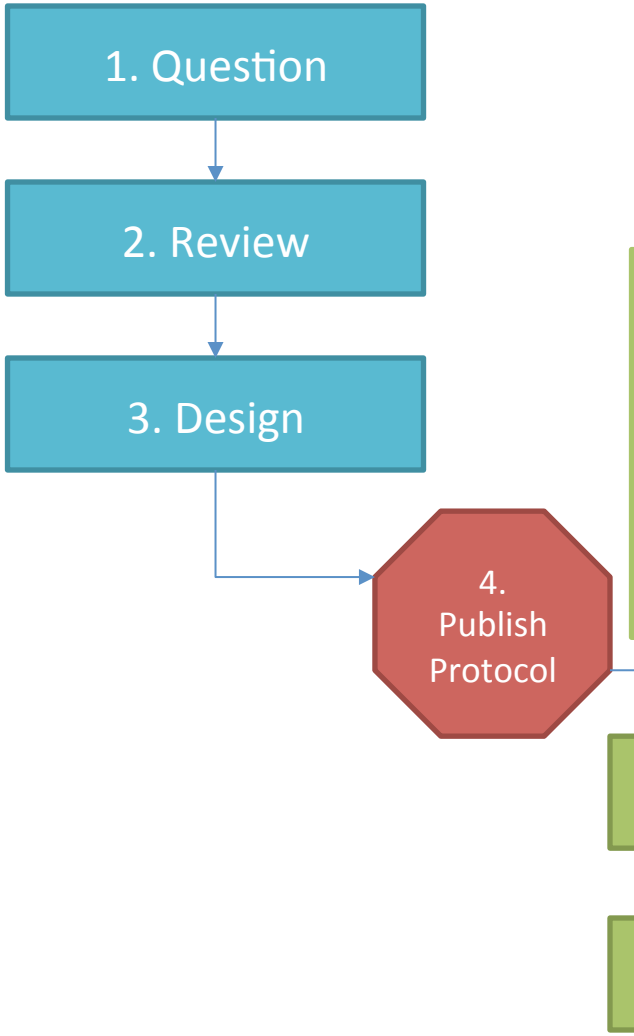
A standardized process for evidence generation and dissemination



4. Publish Protocol:

- Protocol must provide a full specification of all design decisions to enable complete reproducibility
- Publishing protocol with all pre-defined decisions prior to execution ensures transparency

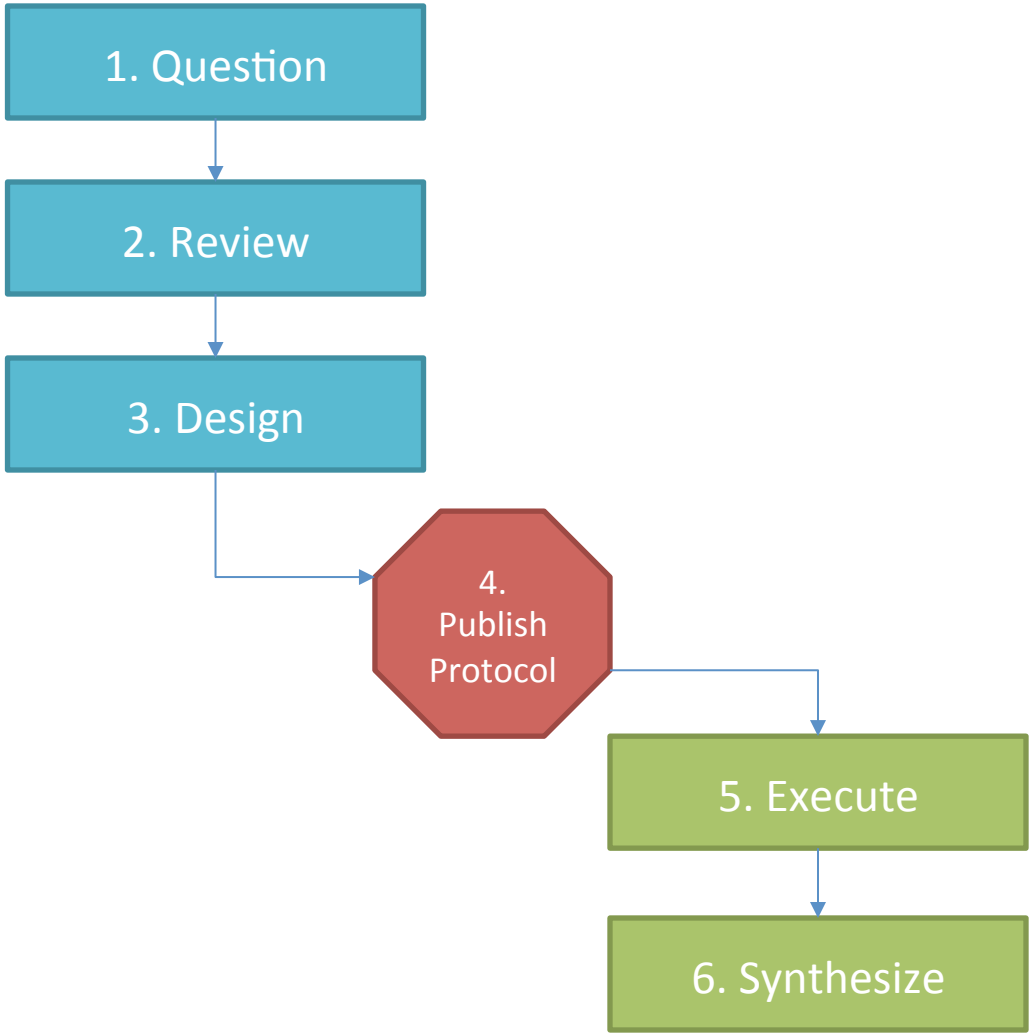
A standardized process for evidence generation and dissemination



5. Execute:

- Generate standardized output based on community best practices
  - source code for transparency and reproducibility
  - model diagnostics to evaluate accuracy
  - aggregate summary statistics (no patient-level data)

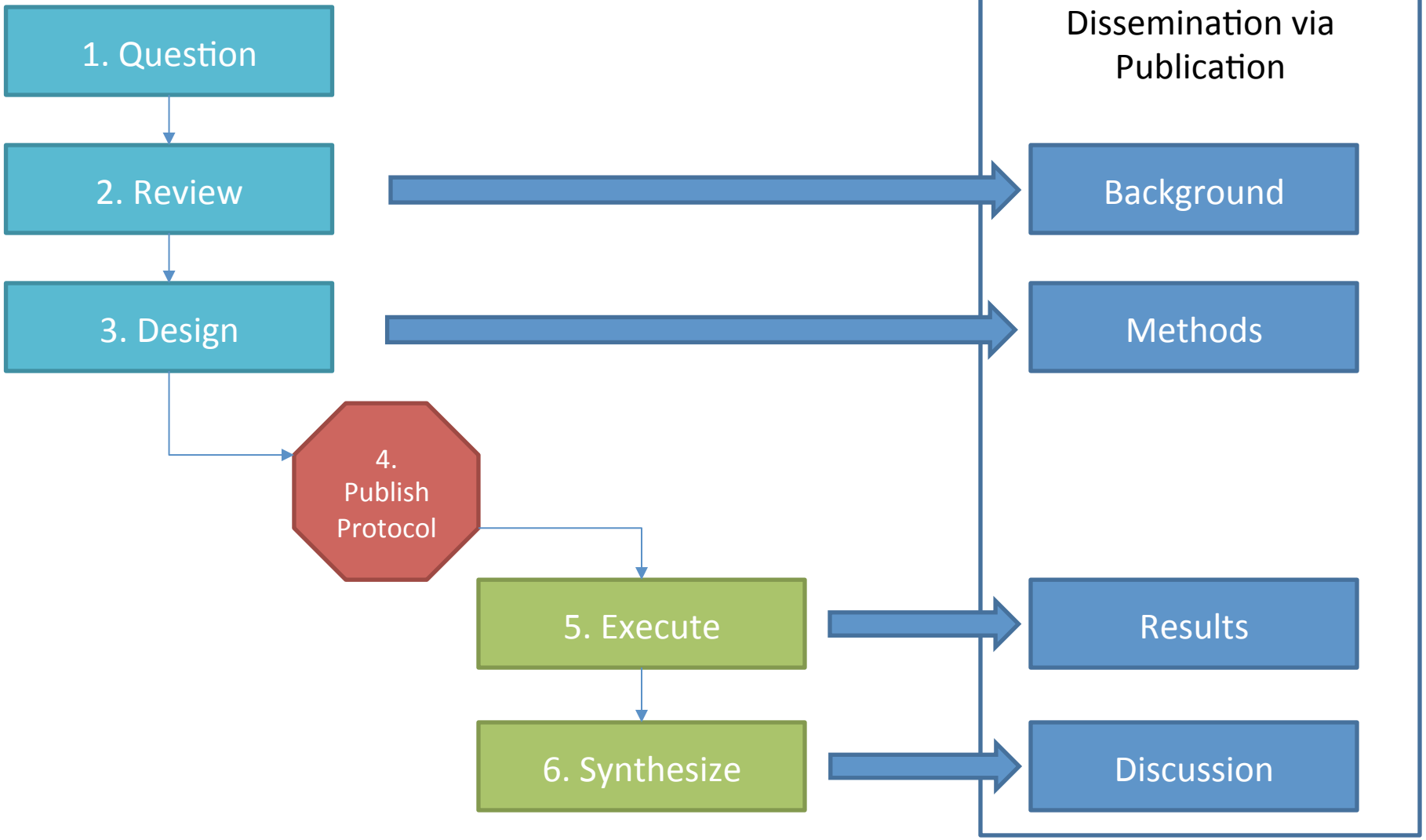
A standardized process for evidence generation and dissemination



6. Synthesize:

- How does the new evidence you've generated compare with prior knowledge?
- What is your new belief about the effect, given your prior knowledge plus this new evidence?

A standardized process for evidence generation and dissemination



When designing or reviewing a study, ask yourself:

Input parameter	Design choice
Target cohort (T)	
Comparator cohort (C)	
Outcome cohort (O)	
Time-at-risk	
Model specification	