Causal questions

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SIKS May 31st 2023

UMC Utrecht

This lecture

1. Articulating causal questions

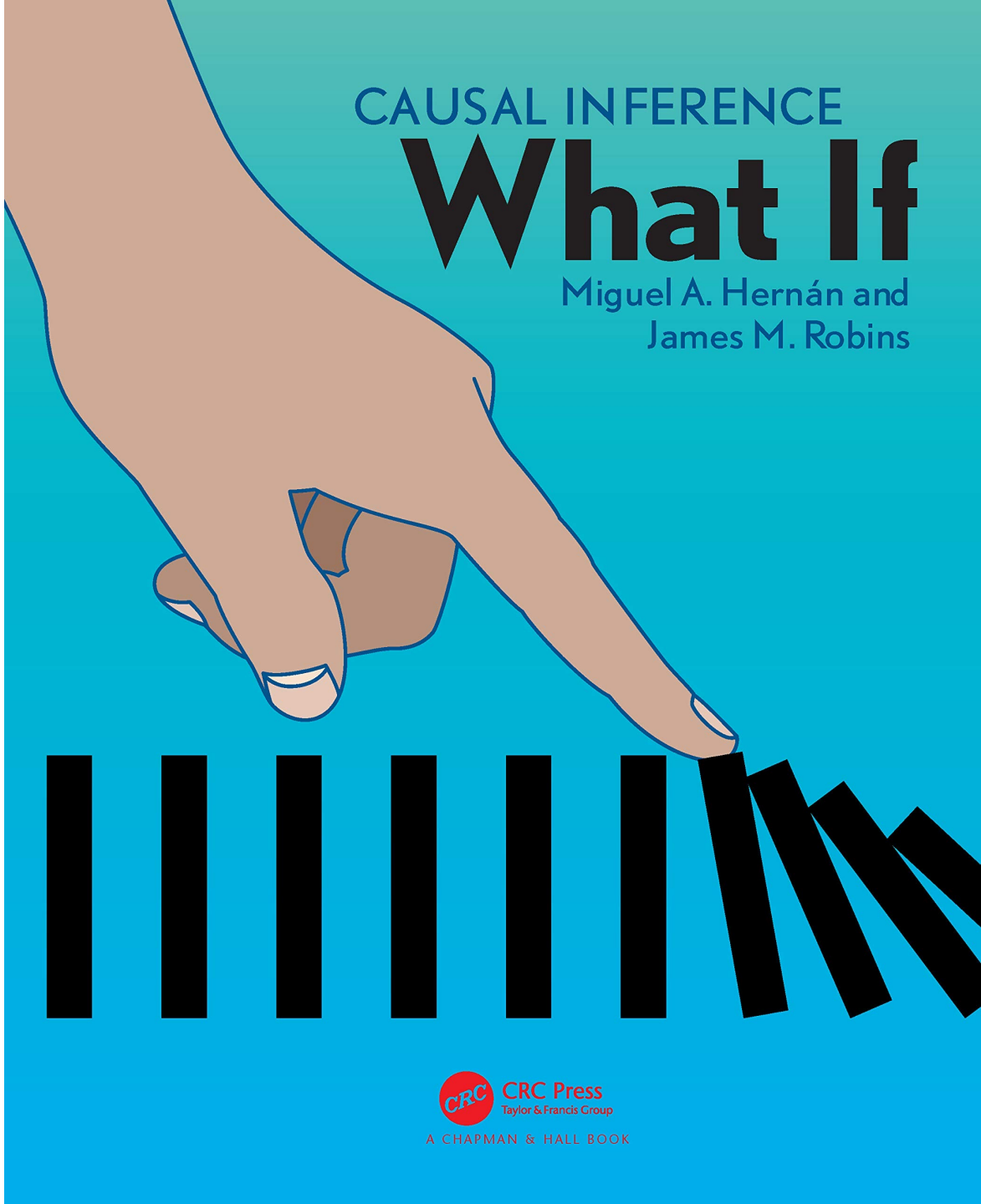
2. Exercise: the importance of articulating a causal question

   Two analyses both suitable to estimate a causal effect,
   yet answering a different causal question

3. Examples of causal questions in a longitudinal setting

Causal questions

What would happen to outcome Y had exposure A been different from what was observed?



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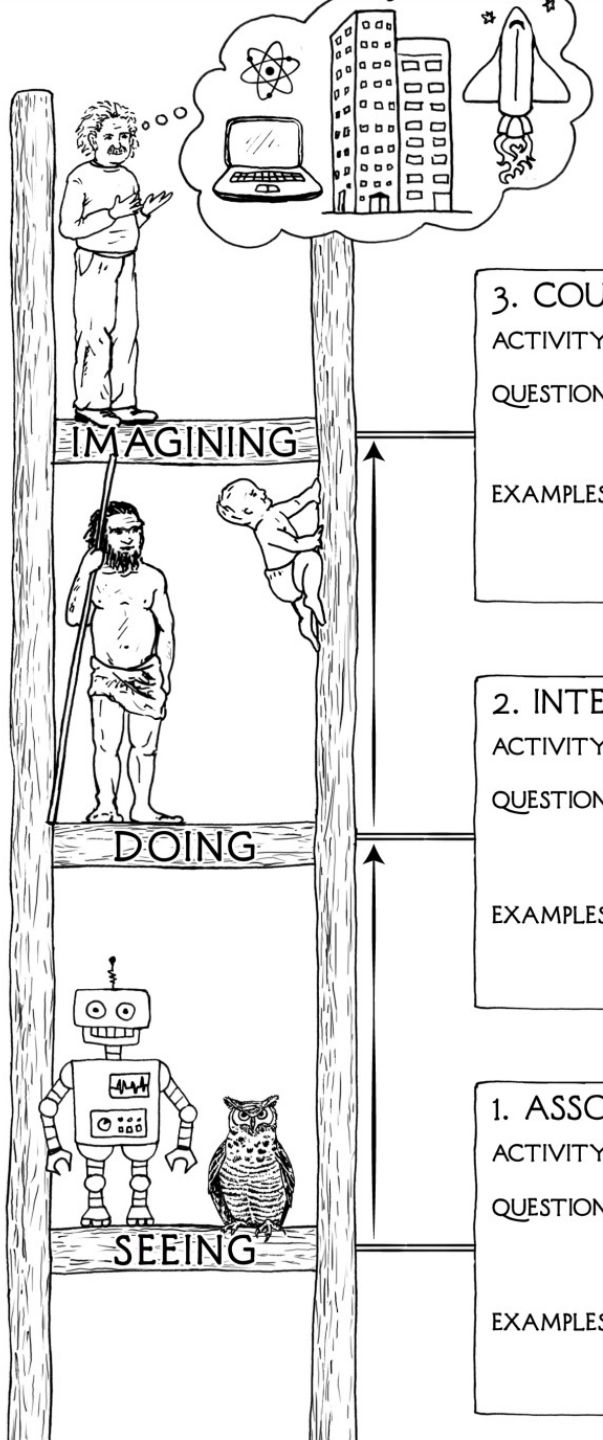


3. COUNTERFACTUALS

ACTIVITY: Imagining, Retrospection, Understanding

QUESTIONS: *What if I had done …? Why?*
(Was it X that caused Y? What if X had not occurred? What if I had acted differently?)

EXAMPLES: Was it the aspirin that stopped my headache? Would Kennedy be alive if Oswald had not killed him? What if I had not smoked for the last 2 years?

2. INTERVENTION

ACTIVITY: Doing, Intervening

QUESTIONS: *What if I do …? How?*
(What would Y be if I do X?
How can I make Y happen?)

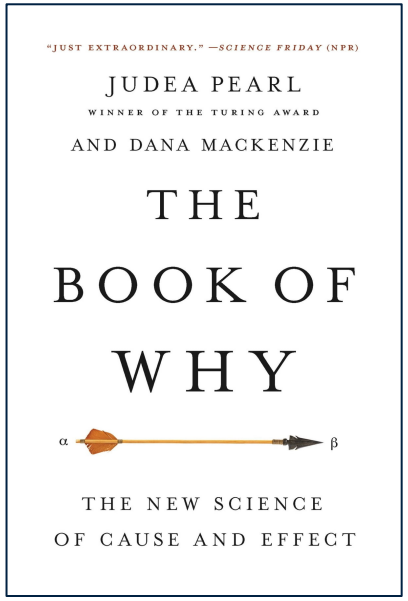
EXAMPLES: If I take aspirin, will my headache be cured? What if we ban cigarettes?

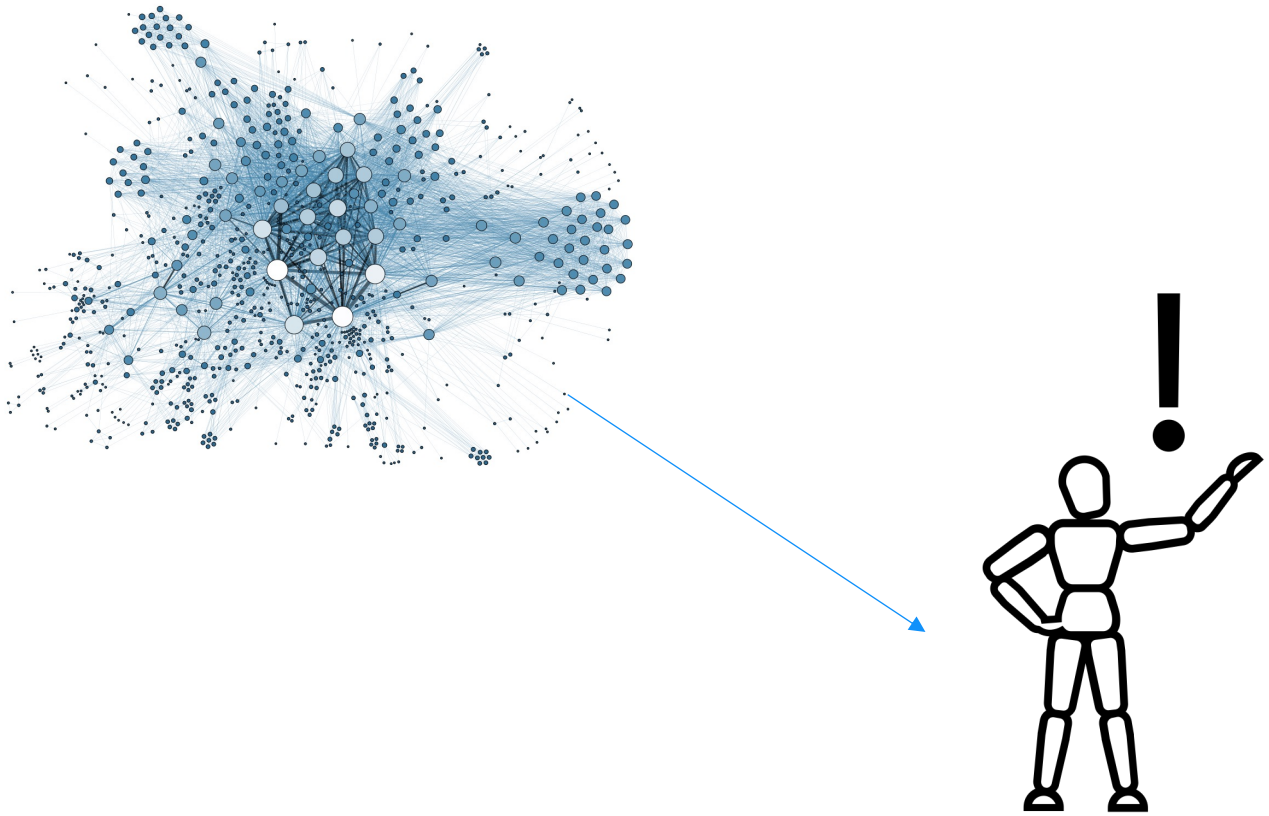
1. ASSOCIATION

ACTIVITY: Seeing, Observing

QUESTIONS: *What if I see ...?*
(How are the variables related?
How would seeing X change my belief in Y?)

EXAMPLES: What does a symptom tell me about a disease? What does a survey tell us about the election results?





Articulating causal questions

- Algorithms with causal aim are intended to inform future decisions
- It is therefore of utmost importance that their outputs are interpreted correctly
- Formulating the causal question addressed in an analysis is quite the challenge → let's practice!

What is the causal question that is answered by a quantitative analysis?

Example on influenza vaccination

- People can receive an invitation for vaccination against influenza through general practitioner in the Netherlands (Oct – Nov)
- Want to know whether the influenza vaccine is effective in reducing mortality risk in people who receive this invitation
- Observational data are available on people invited for vaccination (general practitioner records: vaccination status, mortality, and relevant covariates)

Articulating causal questions

Typical formulation of a causal analysis question would be:

What is the effect of influenza vaccination compared to no vaccination on 3-month mortality risk in adults invited for vaccination?

Do it yourself!

Do it yourself! Exercise 1

Write down the causal questions underlying the two analyses in the practical (around 20 minutes).

- No need to understand all steps of the analysis
- Look at similarities and differences between the two and write down some thoughts how this might affect interpretation of findings

https://github.com/KLuijken/SIKS_2023

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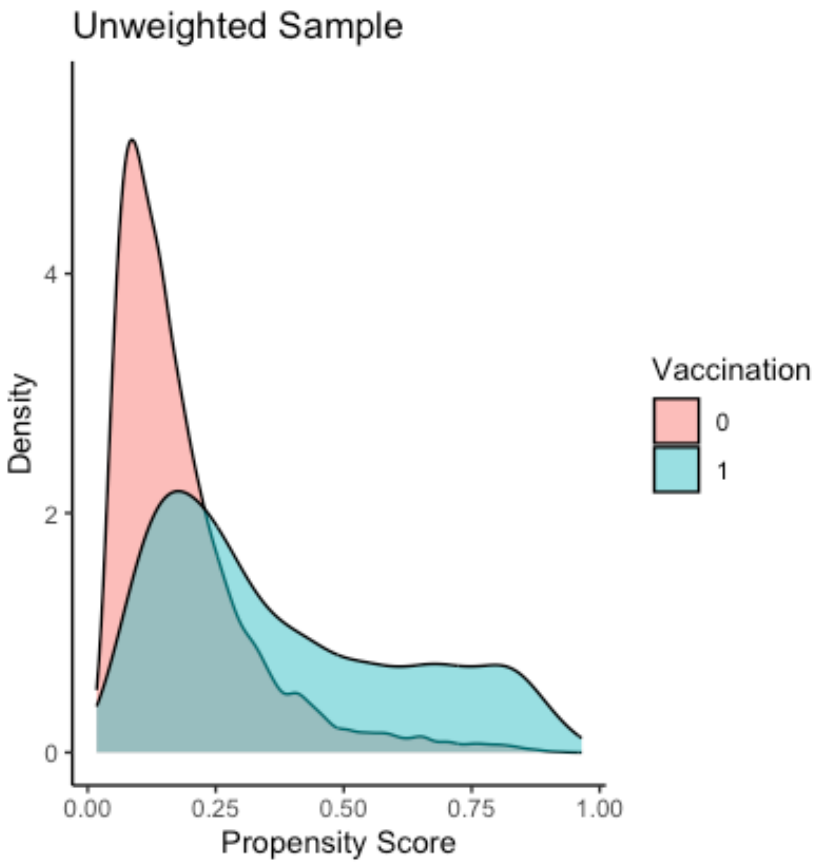
Exercise 1 – Discussion

What is the difference between analysis 1 and 2?

Which causal questions are underlying?

Exercise 1 – Discussion

- Analysis 1: average treatment effect
- Analysis 2: average treatment effect on the treated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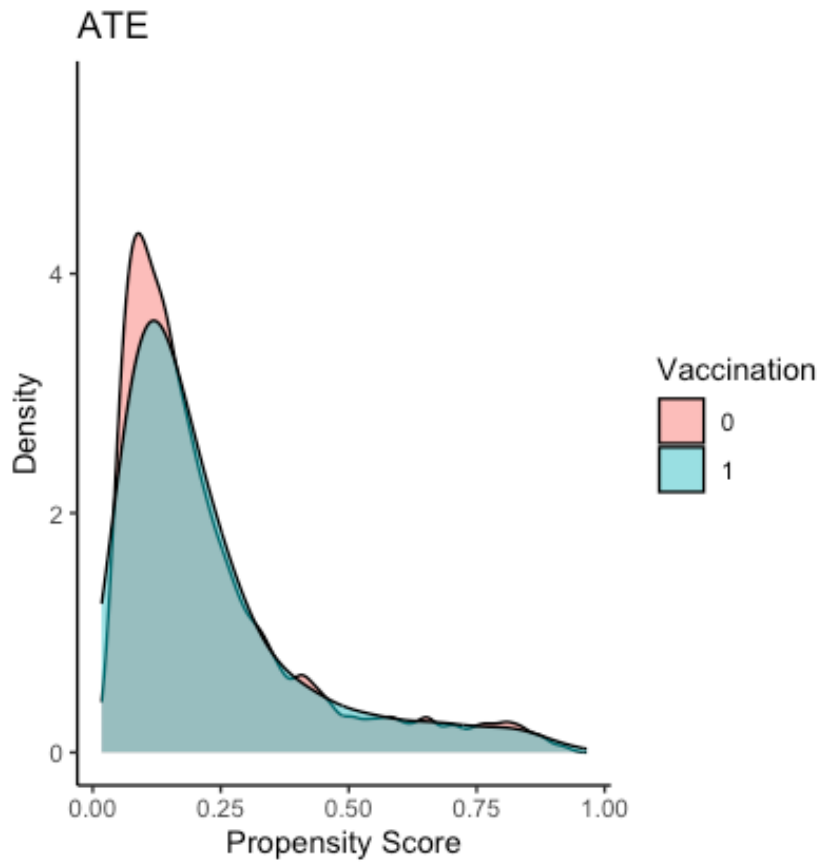
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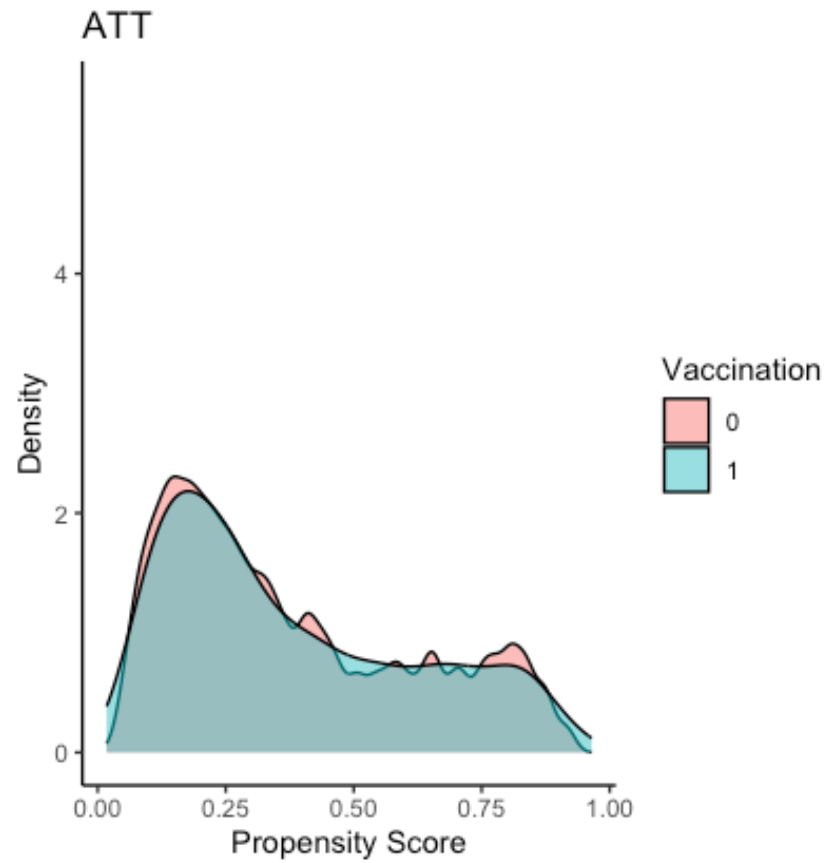
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Exercise 1 – Discussion

Typical formulation of a causal analysis question would be:

What is the effect of influenza vaccination on 3-month mortality risk in adults ≥60 years of age compared to not being vaccinated?

However, this would allow for either analysis, while the interpretation differs!

Exercise 1 – Discussion

		Causal question	Estimate
Average treatment effect (ATE)	$\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$	What would be the difference in average 3-month mortality risk if all adults who were invited to receive the influenza vaccination had taken it, compared to if they had not taken it?	-0.34 (95% CI, -0.36 to -0.33)
Average treatment effect on the treated (ATT)	$\Pr[Y^{a=1} = 1 \mid A = 1] - \Pr[Y^{a=0} = 1 \mid A = 1]$	What would be the difference in average 3-month mortality risk if all adults who took the influenza vaccination had instead not taken it?	-0.50 (95% CI, -0.52 to -0.48)

Exercise 1 – Discussion

		Causal question	Medical decision to be informed by causal question
Average treatment effect (ATE)	$\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$	What would be the difference in average 3-month mortality risk if all adults who were invited to receive the influenza vaccination had taken it, compared to if they had not taken it?	Implementing a population-based influenza vaccination policy, where this study provides information on potential maximal mortality reduction in the population due to the vaccine
Average treatment effect on the treated (ATT)	$\Pr[Y^{a=1} = 1 \mid A = 1] - \Pr[Y^{a=0} = 1 \mid A = 1]$	What would be the difference in average 3-month mortality risk if all adults who took the influenza vaccination had instead not taken it?	Discontinuing an already implemented influenza vaccination policy because of insufficient effectiveness

Exercise 1 – Lesson learned

In this exercise, we did some reverse engineering!
We determined the causal question based on the performed analysis.

The backwards process of the statistical analysis implicitly defining an otherwise unspecified causal research question is not acceptable

(paraphrased from Ratitch, 2020 TIRS)

Exercise 1 – Lesson learned

Formulating a clear causal question:

- Prevents misinterpretation of results
- Informs the choice of data collection and quantitative analysis

Elements of a causal question

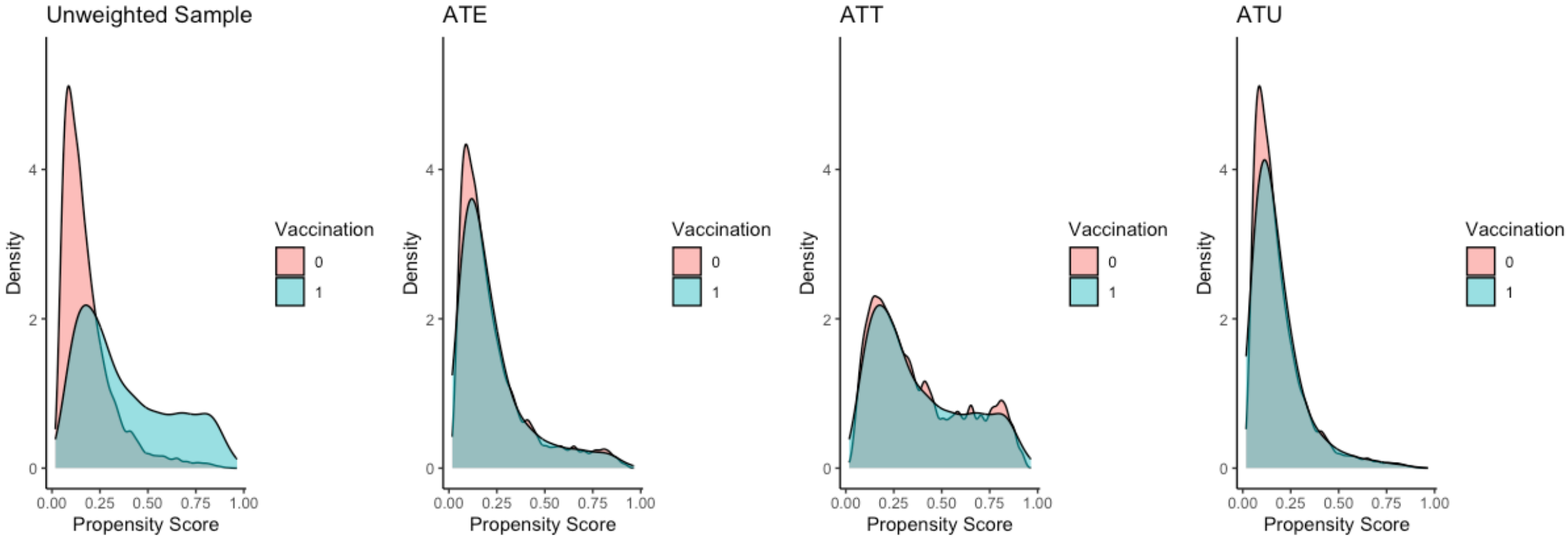
Population	Who and at what time
Contrasted treatments	What, when, and how
Endpoint	What, when, and how
Population-level summary measure	

Elements of a causal question

Population	All individuals registered at a general practice invited for vaccination through a National Influenza Prevention Program in the period October and November
Contrasted treatments	Taking an intramuscular influenza vaccination versus not taking an influenza vaccination
Endpoint	3-Months risk of all-cause mortality
Population-level summary measure	Marginal risk difference

Another causal question

	Causal question	Medical decision to be informed by causal question
Average treatment effect (ATE)	What would be the difference in average 3-month mortality risk if all adults who were invited to receive the influenza vaccination had taken it, compared to if they had not taken it?	Implementing a population-based influenza vaccination policy, where this study provides information on potential maximal mortality reduction in the population due to the vaccine
Average treatment effect on the treated (ATT)	What would be the difference in average 3-month mortality risk if all adults who took the influenza vaccination had instead not taken it?	Discontinuing an already implemented influenza vaccination policy because of insufficient effectiveness
Average treatment effect on the untreated (ATU)	What would be the difference in average 3-month mortality risk if all who did not take the influenza vaccination had instead taken it?	Stimulating uptake of an implemented vaccination policy among individuals who do not take up the invitation for vaccination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Exercise 1 – Summary

Formulating a clear causal question:

- Prevents misinterpretation of results
- Informs the choice of data collection and quantitative analysis

Break


Who wants to estimate causal effects from observational data?
Who wants to define the target estimand and effect estimator?
@statsystem
Who wants to use propensity score matching?

Know how to interpret a causal analysis

- Each quantitative analysis has a specific result
- Understanding what the purpose of the analysis implies in words
- Alignment between results and subsequent acts

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ORIGINAL ARTICLE

WILEY

Tell me what you want, what you really really want: Estimands in observational pharmacoepidemiologic comparative effectiveness and safety studies

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Abstract

Purpose: Ideally, the objectives of a pharmacoepidemiologic comparative effectiveness or safety study should dictate its design and data analysis. This paper discusses how defining an estimand is instrumental to this process.

Methods: We applied the ICH-E9 (*Statistical Principles for Clinical Trials*) R1 addendum on estimands – which originally focused on randomized trials – to three examples of observational pharmacoepidemiologic comparative effectiveness and safety studies. Five key elements specify the estimand: the population, contrasted treatments, endpoint, intercurrent events, and population-level summary measure.

Results: Different estimands were defined for case studies representing three types of pharmacological treatments: (1) single-dose treatments using a case study ab the effect of influenza vaccination versus no vaccination on mortality risk in an a population of ≥60 years of age; (2) sustained-treatments using a case study ab the effect of dipeptidyl peptidase 4 inhibitor versus glucagon-like peptide-1 ago on hypoglycemia risk in treatment of uncontrolled diabetes; and (3) as needed tr ments using a case study on the effect of nitroglycerin spray as-needed versus

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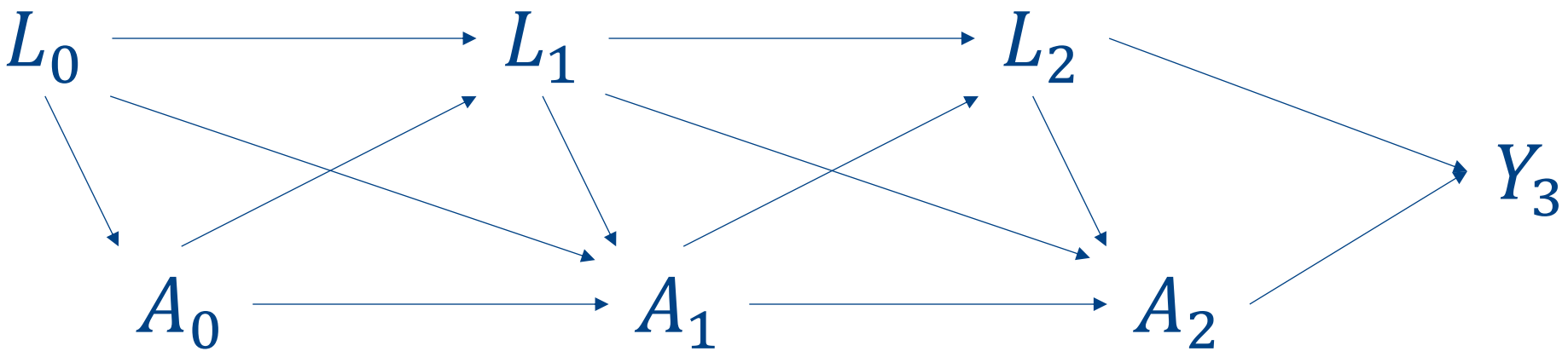
Longitudinal questions

- Exercise focused on point exposure to treatment and differences in target population
- What about sustained exposure to treatment?

Longitudinal setting



Elements of a causal question

Population	Who and at what time
Contrasted treatments	What, when, and how
Endpoint	What, when, and how
Population-level summary measure	

Exercise

Come up with two causal questions that differ in contrasted treatments (around 10 minutes).

Setting:

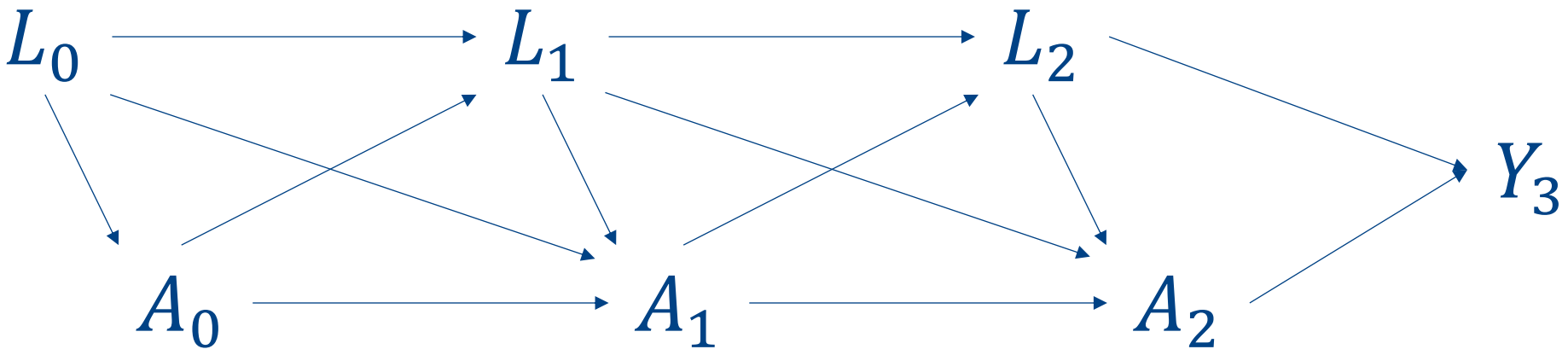
- Individuals with uncontrolled diabetes
- Diabetes medication A versus B (DPP-4 versus GLP1)
- Outcome of interest is blood sugar (HbA1c level, continuous)

Examples

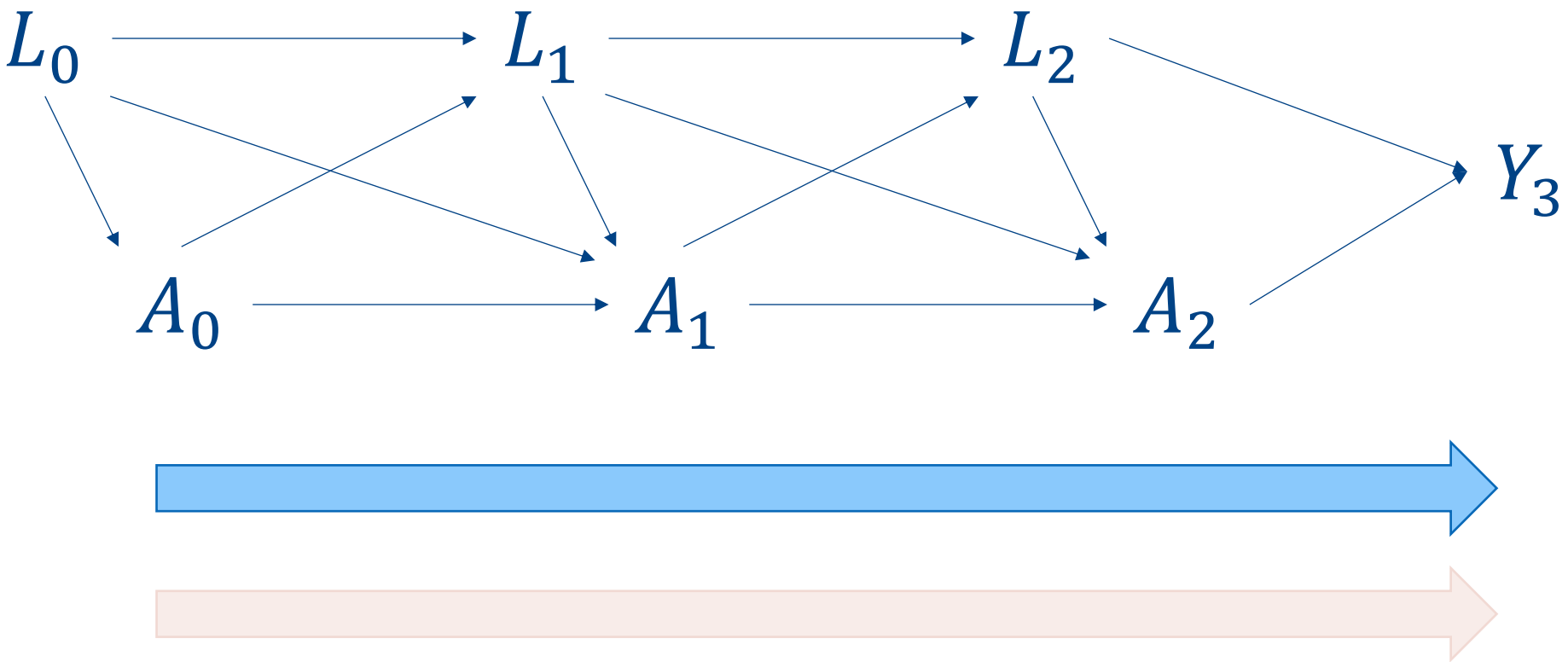
1. What would be the difference in average 1-year HbA_1c level if all adults with uncontrolled diabetes had initiated a DPP-4 inhibitor, compared to if they had initiated a GLP1 agonist?

2. What would be the difference in average 1-year HbA_1c level if all adults with uncontrolled diabetes had initiated and compliantly used a DPP-4 inhibitor, compared to if they had initiated and compliantly used a GLP1 agonist?

Example 1



Example 2



Examples

1. What would be the difference in average 1-year HbA_1c level if all adults with uncontrolled diabetes had initiated a DPP-4 inhibitor, compared to if they had initiated a GLP1 agonist?

2. What would be the difference in average 1-year HbA_1c level if all adults with uncontrolled diabetes had initiated and compliantly used a DPP-4 inhibitor, compared to if they had initiated and compliantly used a GLP1 agonist?

Examples

1. What would be the difference in average 1-year HbA_1c level with uncontrolled diabetes had initiated a DPP-4 inhibitor, if they had initiated a GLP1 agonist?
   Advising on treatment initiation in the population of adults with uncontrolled diabetes mellitus type 2 in a population with similar treatment compliance and add-on treatments to the study sample

2. What would be the difference in average 1-year HbA_1c level if all adults with uncontrolled diabetes had initiated and compliantly used a DPP-4 inhibitor, compared to if they had initiated and compliantly used a GLP1 agonist?
   Making a medical decision about sustained treatment with DPP-4 inhibitor and GLP1 agonist under perfect adherence for the population of adults with uncontrolled diabetes mellitus type 2

Causal questions in longitudinal setting

We focused on causal questions which compare pre-defined exposure contrasts

- These are also referred to as “static exposures”

Alternatively, one could be interested in the effect of exposure based on a treatment rule

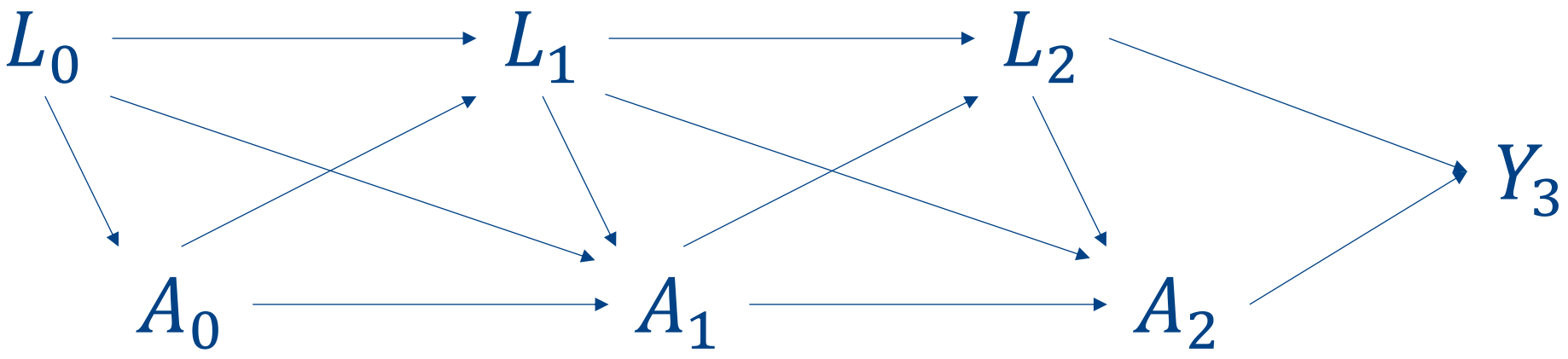
- These are also referred to as “dynamic exposures”

Basic principle dynamic exposure

Example:
Up the dose of GLP1 from 7mg to 14mg daily if HbA1c ≥ 54 mmol/mol

This is based on patient history on HbA1c

Basic principle dynamic exposure



Basic principle dynamic exposure

- ”Modern” analysis techniques: finding optimal treatment rule
- What causal question would fit here?

Estimands

1 Prepare Chocolate Cake Batter

Preheat oven to 350 degrees, and prepare Yo's Ultimate Chocolate Cake batter. Prepare your pans with parchment. Pour 2 ½ lbs into each 7" round pan, 1 ½ lbs into your 6" round pan, and divide the remaining batter evenly between your 5" round pans.

2 Bake Cakes

Bake your 7" round cakes for 50 minutes, your 6" round cake for 40 minutes, and your 5" round cakes for 30 minutes, or until a toothpick comes out clean. Set aside to cool completely in their pans on a wire rack.

3 Prepare Fillings & Simple Syrup

Prepare your dark chocolate ganache, Italian meringue buttercream, and simple syrup. Set aside until you're ready to decorate.

4 Level Cakes

Remove your cooled cakes from their pans and level them with a ruler and serrated knife.

5 Simple Syrup

Give all of your cakes a simple syrup shower with Sir Squeeze, and allow to fully soak in before moving on to the next step.

Estimand

Estimator

Estimate

Credits to Peter Tennant & Oisín Ryan

Estimands

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Estimand

Estimator

Estimate

Credits to Peter Tennant & Oisín Ryan

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2020
EMA/CHMP/ICH/436221/2017
Committee for Medicinal Products for Human Use

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

Step 5

Overview

Each setting requires formulation of a specific causal question

Formulating a clear causal question:

- Prevents misinterpretation of results
- Informs the choice of data collection and quantitative analysis

Questions or further discussion?

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Further reading

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