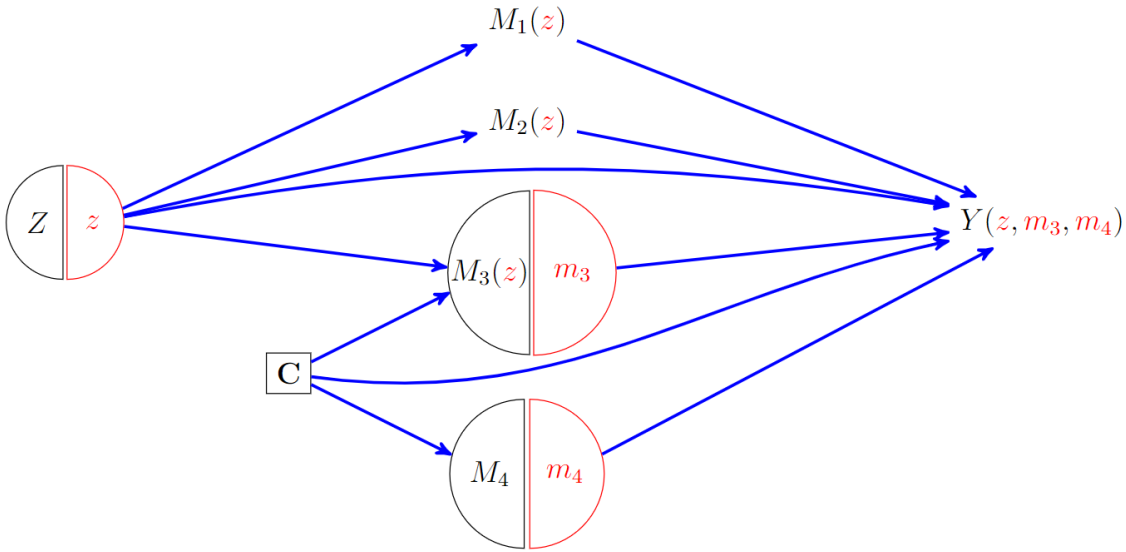


# Single-World Intervention Graphs for Defining, Identifying, and Communicating Estimands in Clinical Trials

Alex Ocampo
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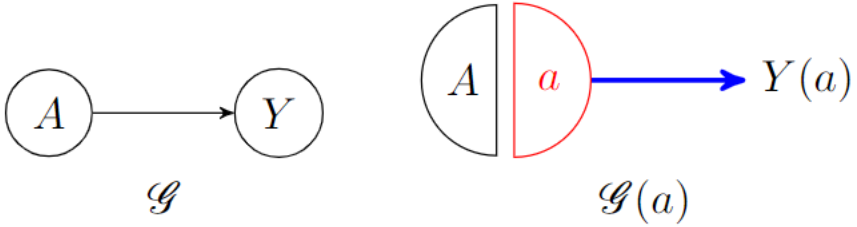
# “Correlation does not imply Causation”

# Agenda




1. Causal Questions
2. Single World Intervention Graphs (SWIGs)
3. ICH-E9 Addendum Intercurrent Event Strategies in SWIGs
4. Application to a Clinical Trial in Chronic Pain
5. Conclusion

**ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS**
**TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS**

**E9(R1)**

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2020, VOL. 12, NO. 1, 39-44
https://doi.org/10.1080/19466315.2019.1629997

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**Estimands in a Chronic Pain Trial: Challenges and Opportunities**

Francesca Callegari, Mouna Akacha, Peter Quarg, Shaloo Pandhi, Florian von Raison, and Emmanuel Zuber

Novartis Pharma AG, Basel, Switzerland



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| | $Y(0)$ | $Y(1)$ | $Z$ | $Y$ |
|---|---|---|---|---|
| **1** | ? | 52 | 1 | 52 |
| **2** | 45 | ? | 0 | 45 |
| **3** | ? | 38 | 1 | 38 |
| **4** | ? | 67 | 1 | 67 |
| **5** | 21 | ? | 0 | 21 |

# Causal Questions

# What is a Causal Question?

- What if....?
- Causal questions use **potential outcomes**
  - $Y(1)$ is the outcome if the *experimental* treatment is taken
  - $Y(0)$ is the outcome if the *reference* treatment is taken
- A causal effect contrasts:

$$Y(0) \text{ vs. } Y(1)$$

- **Estimand framework - ICH E9 addendum**:
  - *Section A.3.1*: "how the outcome of treatment compares to what **would** have happened to the **same subjects** under alternative treatment"
  - *Section A.3.2*: "A scenario is envisaged in which the intercurrent event **would not** occur."
- By formulating a question causally, we can move **beyond correlation!**

| | $Y(0)$ | $Y(1)$ | $Z$ | $Y$ |
|---|---|---|---|---|
| **1** | 60 | 52 | 1 | 52 |
| **2** | 45 | 37 | 0 | 45 |
| **3** | 46 | 38 | 1 | 38 |
| **4** | 75 | 67 | 1 | 67 |
| **5** | 21 | 15 | 0 | 21 |

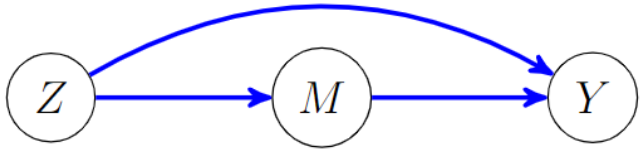
**Table.** Potential outcomes (God's table)

(Consistency)

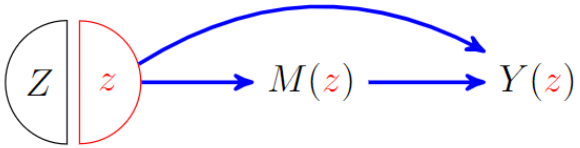
(Missing Data)

# Causal Graphs

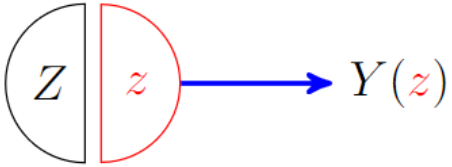
- Using **causal graphs** can aid in answering causal questions
- Explain intercurrent event strategies visually
  - Intercurrent events are at the heart of the ICH E9(R1) addendum on estimands
- Notation
  - $Z =$ Treatment $\in \{0,1\}$
  - $M =$ Intercurrent Event
  - $Y =$ Clinical Outcome
- No potential outcomes $Y(z)$ on the graph?

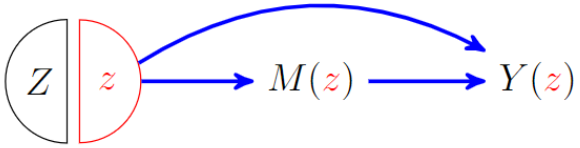



Directed Acyclic Graph (DAG)




Single-World Intervention Graph (SWIG)



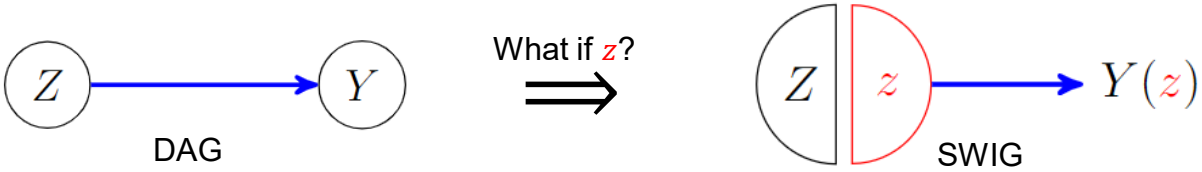




# Single-World Intervention Graphs

Richardson, T. S. & Robins, J. M. Single world intervention graphs (SWIGs): A unification of the counterfactual and graphical approaches to causality. (2013)

# Single-World Intervention Graph (SWIG)

- SWIGs unify the potential outcome and graphical approaches to causality




- For a binary treatment there are two SWIGs (worlds) for $z = 0$ or $z = 1$:


(a) SWIG for Experimental Treatment

(b) SWIG for Reference Treatment

- On the SWIG you can clearly see the exchangeability assumption $Z \perp\!\!\!\perp Y(z)$ holds

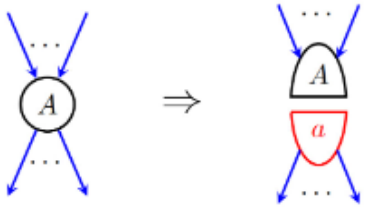
# Making SWIGs from DAGs

Given a graph, perform the following two steps:

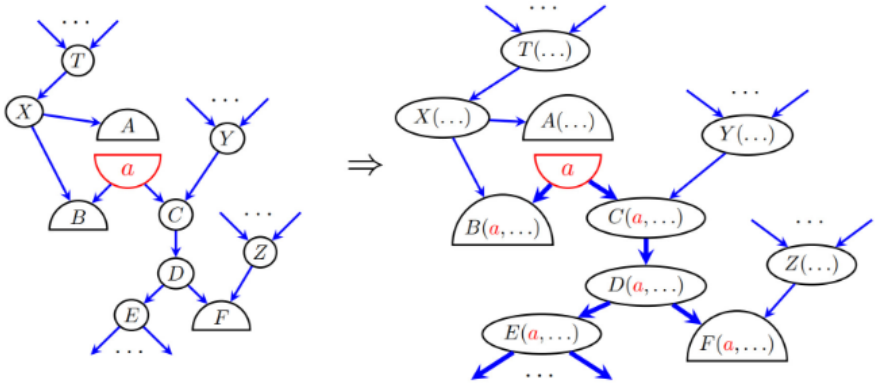
1. **Node splitting**:
   - Split the nodes of variables to be intervened on
   - Represents the “what if?” question(s) you are asking

2. **Relabel**:
   - all children of intervened variables with their potential outcomes

Step 1: Node Split




Step 2: Relabel Affected Nodes



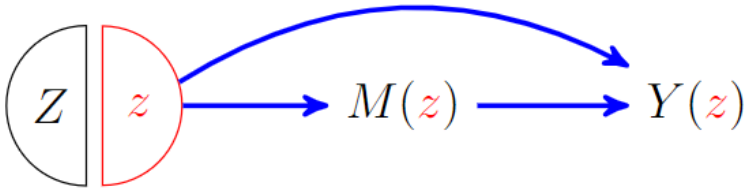

Source: Richardson, Thomas S., and James M. Robins. "Single world intervention graphs (SWIGs): A unification of the counterfactual and graphical approaches to causality." *Center for the Statistics and the Social Sciences, University of Washington Series. Working Paper* 128.30 (2013)

**ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS**
**TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS**

**E9(R1)**

Final version

Adopted on 20 November 2019




# ICH-E9 Addendum Intercurrent Event Strategies in SWIGs

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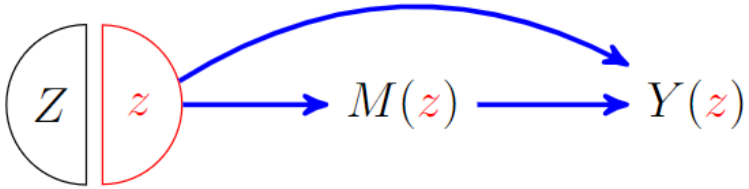
# Treatment Policy

- For the **treatment policy** estimand, the intercurrent event is considered irrelevant

$$\Delta_{TP} = E[Y(1)] - E[Y(0)]$$

- Splitting the node asks the question, "what if $Z = 0$ or $Z = 1$?" considered in the contrast above




- From the graph we see that $Z \perp\!\!\!\perp Y(z)$ because there is no path connecting $Z$ to $Y(z)$
- Therefore, based on this graph we can show that **correlation is causation**:

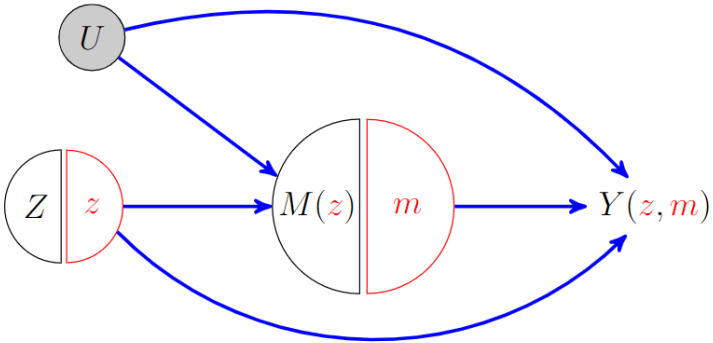
$$\Delta_{TP} = E[Y(1)] - E[Y(0)] = E[Y(1)|Z = 1] - E[Y(0)|Z = 0] = E[Y|Z = 1] - E[Y|Z = 0]$$

# Hypothetical Estimand

- An example of a **hypothetical** estimand is:

$$\Delta_{hypo} = E[Y(z = 1, m = 0)] - E[Y(z = 0, m = 0)]$$

- This hypothetical estimand postulates "what if" the intercurrent event had not occurred ($m = 0$)




- $Y(z, m)$ not independent of $M(z)$ because of backdoor path through unobserved confounder $U$
- Therefore, we cannot estimate the hypothetical estimand from the observed data

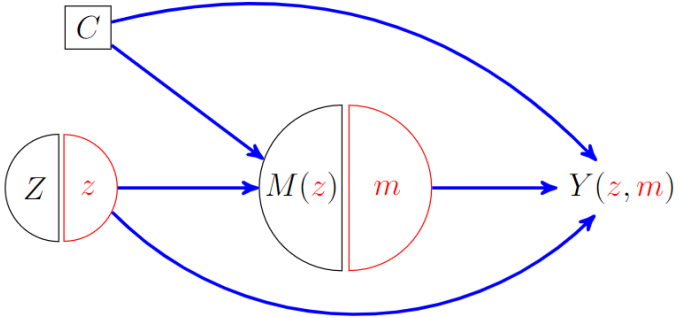
$$\Delta_{hypo} = E[Y(z = 1, m = 0)] - E[Y(z = 0, m = 0)] \neq E[Y|Z = 1, M = 0] - E[Y|Z = 0, M = 0]$$

# Hypothetical Estimand

- An example of a hypothetical estimand is:

$$\Delta_{hypo} = E[Y(z=1, m=0)] - E[Y(z=0, m=0)]$$

- This hypothetical estimand postulates "what if" the intercurrent event had not occurred ($m = 0$)



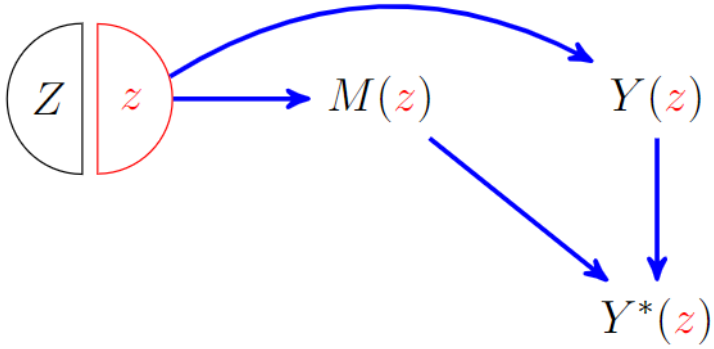

- If $C$ is a rich enough set of confounders to block the backdoor path, we have: $Y(z,m) \perp\!\!\!\perp M(z) | C$
- With this, and $Z \perp\!\!\!\perp Y(z,m)$, we can identify the hypothetical estimand from the observed data:

$$\Delta_{hypo} = \sum_C E[Y|Z=1, M=0, C=c]P(C=c) - \sum_C E[Y|Z=0, M=0, C=c]P(C=c)$$

- Only if adjustment is sufficient, then correlation is causation for the hypothetical estimand

# Composite Estimand

- The intercurrent event is incorporated into the variable definition $Y^*(z)$




- Similar as the treatment policy, randomization yields $Z \perp\!\!\!\perp Y^*(z)$

$$\Delta_c = E[Y^*(1)] - E[Y^*(0)] = E[Y^*|Z=1] - E[Y^*|Z=0]$$

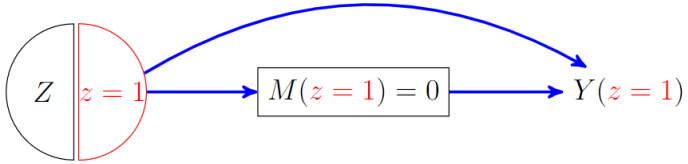
- The graph demonstrates that **correlation is causation** for this composite estimand
  - Causal for what? Difficulty lies in interpretation....

# Principal Stratum Estimand

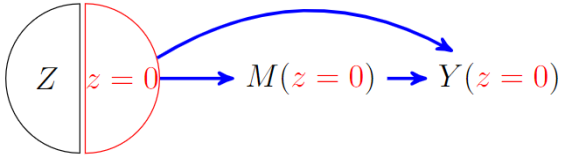
- An example of a Principal Stratum (PS) estimand of interest is:

$$\Delta_{PS} = E[Y(1)|M(1) = 0] - E[Y(0)|M(1) = 0]$$

- Which is the treatment effect among those who would not have the IE if they took the experimental treatment
  - Other PS may be of interest (e.g., $M(1) = 1$)




Experimental Treatment Given $z = 1$




Control Treatment Given $z = 0$

- SWIGs make clear that additional (cross-world) assumptions are needed to identify $\Delta_{PS}$

$$\Delta_{PS} = E[Y|Z = 1, M = 0] - E[Y|Z = 0, M(1) = 0]$$

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2020, VOL. 12, NO. 1, 39-44
https://doi.org/10.1080/19466315.2019.1629997

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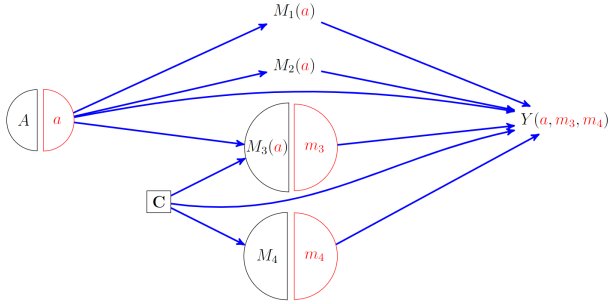
## Estimands in a Chronic Pain Trial: Challenges and Opportunities

Francesca Callegari, Mouna Akacha, Peter Quarg, Shaloo Pandhi, Florian von Raison, and Emmanuel Zuber

Novartis Pharma AG, Basel, Switzerland

**ABSTRACT**

An estimand clearly defines the target treatment effect to be estimated in a clinical trial. A recently published draft International Conference on Harmonization E9 addendum introduces the concept of estimand in clinical trials and provides a structured framework to link trial objectives, design, conduct, statistical analysis, and interpretation in a coherent way. In the meantime, regulators are already keen to discuss the definition of estimands for new clinical trials. In this manuscript, we focus on the primary clinical question of interest and on the corresponding estimand specification for a future Phase 2 study in chronic pain. This entails, in particular, the identification and handling of intercurrent events relevant in the chronic pain field. The primary estimand with its detailed rationale for consideration is presented, together with the primary estimation method. Other supplementary estimands are also defined to assess slightly different treatment effects. Some practical considerations arising from the development of the estimand concept for this trial are summarized, outlining the challenges encountered, how these have been overcome and the opportunities discovered during this process.




# Example from a Clinical Trial for Chronic Pain

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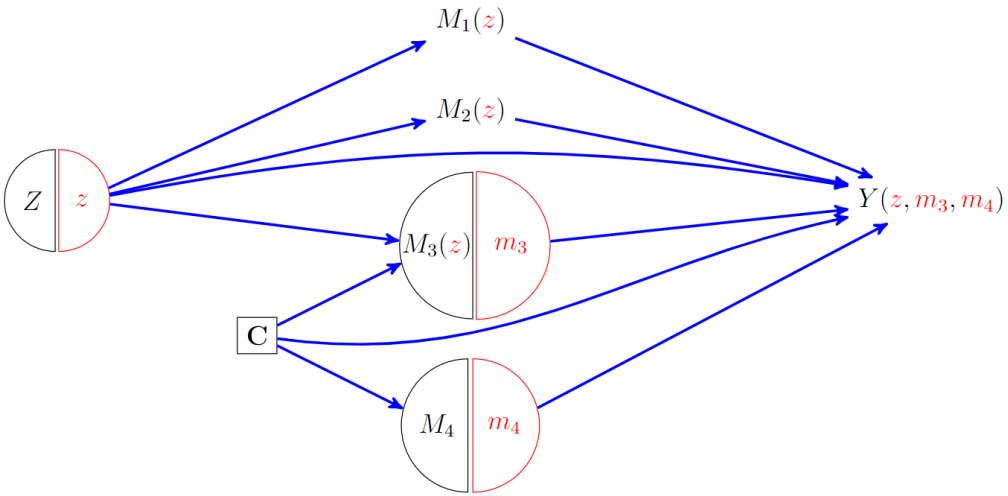
# Primary Estimand

- Paper provides detailed exposition of various estimands in chronic pain RCTs
- We focus on their proposed primary estimand as defined in section 3.1

| Intercurrent Event | Description |
|---|---|
| 1. Intake of short acting pain relief medication | "In case of intake of short-acting pain relief medication, the weekly mean of the 24-hr average pain score at the end of the study **regardless of intake** of such medication is of interest" |
| 2. Treatment discontinuation due to Adverse Event, Loss of Efficacy, or intake of prohibited medications | "For such patients, it is **not plausible to check what would have happened** if the patient had continued to be treated."<br><br>"**Retrieved drop out (RDO)** data collected after study treatment discontinuation will be used for analysis in case of discontinuation of study treatment due to AEs, lack of efficacy, or due to the use of other concomitant medications for pain" |
| 3. Change of dose of allowed concomitant medication for pain | "..., we are interested in the weekly mean of the 24-hr average pain score change from baseline to the end of the double-blind treatment period that would be observed if the patient **had not changed** the doses of the allowed concomitant medication for pain." |
| 4. Treatment discontinuation due to Administrative or Other reasons | "we are interested in the weekly mean of the 24-hr average pain score at the end of the study that would be observed if the patient **had not discontinued** and continued the randomized treatment." |

**Source:** Callegari, Francesca, et al. "Estimands in a chronic pain trial: challenges and opportunities." *Statistics in Biopharmaceutical Research* 12.1 (2020): 39-44.

# SWIG for an RCT in Chronic Pain

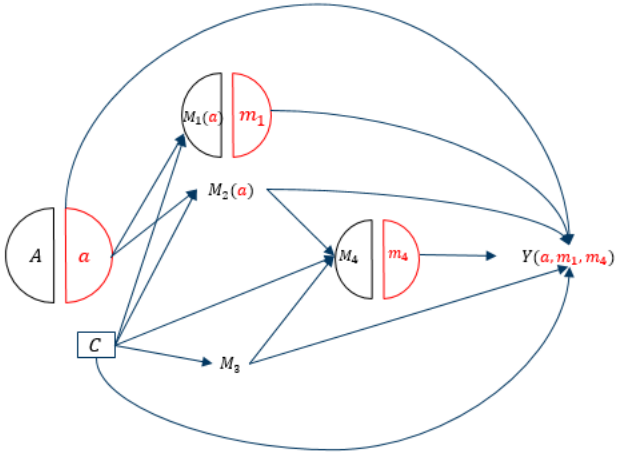


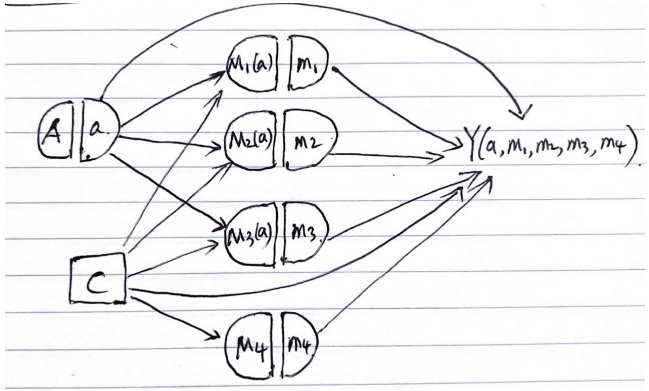

- $M_1$ = Intake of short acting pain relief medication (Treatment Policy)
- $M_2$ = Treatment discontinuation due to Adverse Event, Loss of Efficacy, or intake of prohibited medications (Treatment Policy)
- $M_3$ = Change of dose of allowed concomitant medication for pain (Hypothetical)
- $M_4$= Treatment discontinuation due to Administrative or Other reasons (Hypothetical)

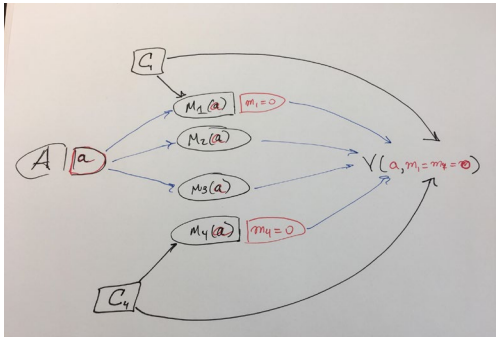
$$\Delta_{RCT} = E[Y(z = 1, m_3 = 0, m_4 = 0)] - E[Y(z = 0, m_3 = 0, m_4 = 0)]$$

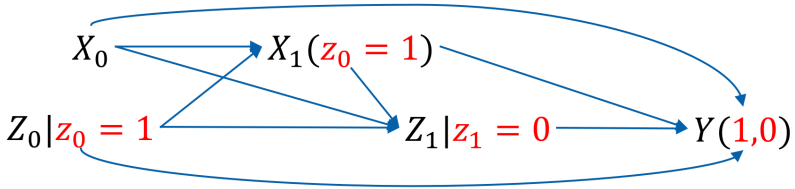
# Conclusions

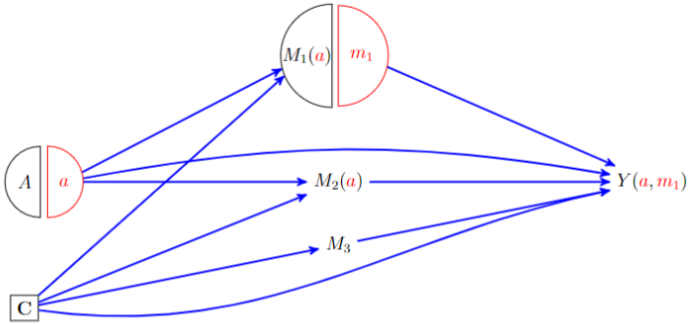
# Examples at Novartis



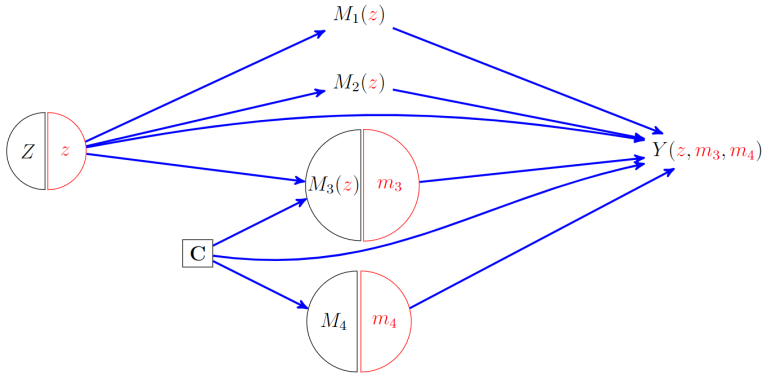



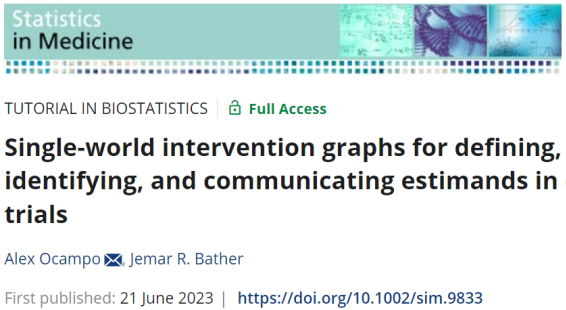



# Conclusions

- **Casual Graphs** (SWIGs) allow us to clearly display our estimands and the intercurrent events of interest
  - Define
  - Identify
  - Communicate
- ~ 65% of people are **visual learners**[1]
- For more, see our recent publication in ***Statistics in Medicine***
- Embrace the **causal revolution**!






[1] Bradford WC. Reaching the visual learner: teaching property through art. *Law Teacher*. 2004; **11**.

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~~"Correlation does not imply Causation"~~

"When is correlation causation?"

"Is this correlation causal?"

# Thank you

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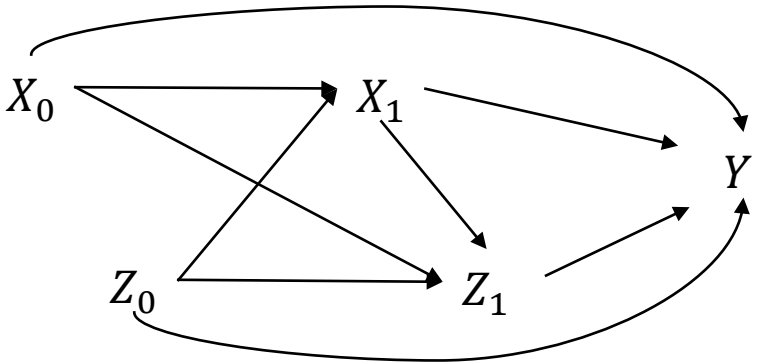
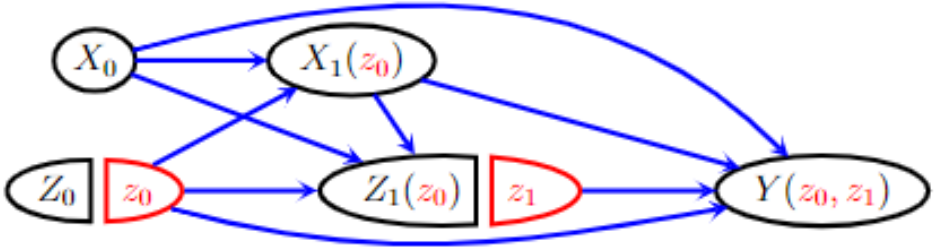
# From DAGs to SWIGs

- Only difference between the DAG and the SWIG is that we split the nodes that represent the “what if?” question our estimand postulates
- The SWIG helps us visualize the potential outcomes used to define our estimand

$$E[Y(z_0 = 1, z_1 = 0) - Y(z_0 = 0, z_1 = 0)]$$



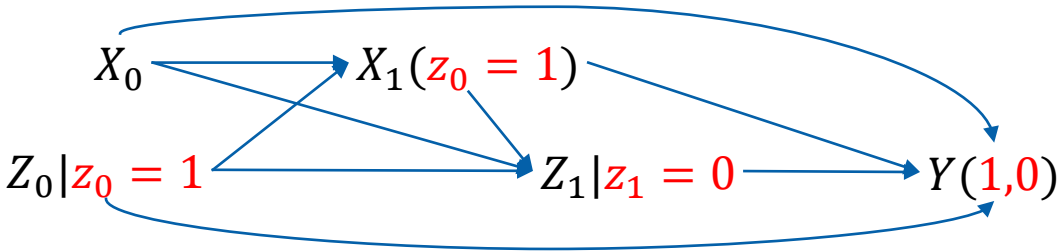
# What two worlds are we comparing?

- The treatment effect (causal estimand) or interest is:

$$E[Y(z_0 = 1, z_1 = 0)] - E[Y(z_0 = 0, z_1 = 0)]$$

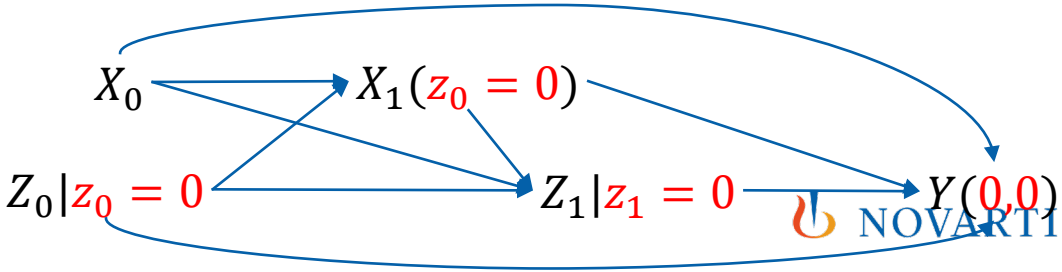
- This estimand compares the following two worlds:
  - 1) A world where everyone took the active treatment and did not take rescue

SWIG for $z_0 = 1, z_1 = 0$




  - 2) A world where everyone took the placebo and did not take rescue

SWIG for $z_0 = 0, z_1 = 0$

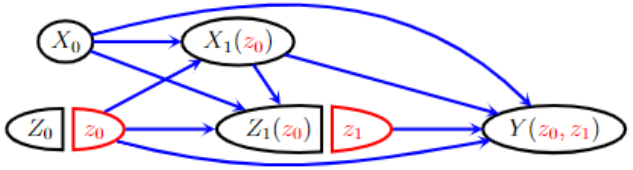


# G-computation for this hypothetical estimand scenario

- The treatment effect (causal estimand) or interest is:

$$E[Y(z_0 = 1, z_1 = 0)] - E[Y(z_0 = 0, z_1 = 0)]$$

- We can recover each term above from the observed data as follows




$$\begin{aligned}
E[Y(z_0,0)] &= E\left[Y(z_0,0)|Z_0 = z_0\right] \\
&= E_{\boldsymbol{X}|Z_0}\left[E\left[Y(z_0,0)|Z_0 = z_0, X_0, X_1\right]\Big|Z_0 = z_0\right] \qquad (\boldsymbol{X} = (X_1, X_0)) \\
&= E_{\boldsymbol{X}|Z_0}\left[E\left[Y(z_0,0)|Z_0 = z_0, X_0, X_1, Z_1 = 0\right]\Big|Z_0 = z_0\right] \\
&= E_{\boldsymbol{X}|Z_0}\left[E\left[Y|Z_0 = z_0, X_0, X_1, Z_1 = 0\right]\Big|Z_0 = z_0\right] \qquad (\text{consistency}) \\
&= \int_{x_0}\int_{x_1}\left[E\left[Y|Z_0 = z_0, X_0, X_1, Z_1 = 0\right]\Big|Z_0 = z_0\right] f(x_0, x_1|z_0)\partial x_1 \partial_{x_2}
\end{aligned}$$

# Causal Reasoning

Judea Pearl, one of the pioneers of causal graphs

"You cannot answer a question that you cannot ask, and you cannot ask a question that you have no words for."
- Judea Pearl, The Book of Why

~~"Correlation does not imply Causation"~~

~~"Correlation is not Causation"~~

"When is correlation causation?"

"Is this correlation causation?"