NIT outcome measures for MASH should reflect clinical significance

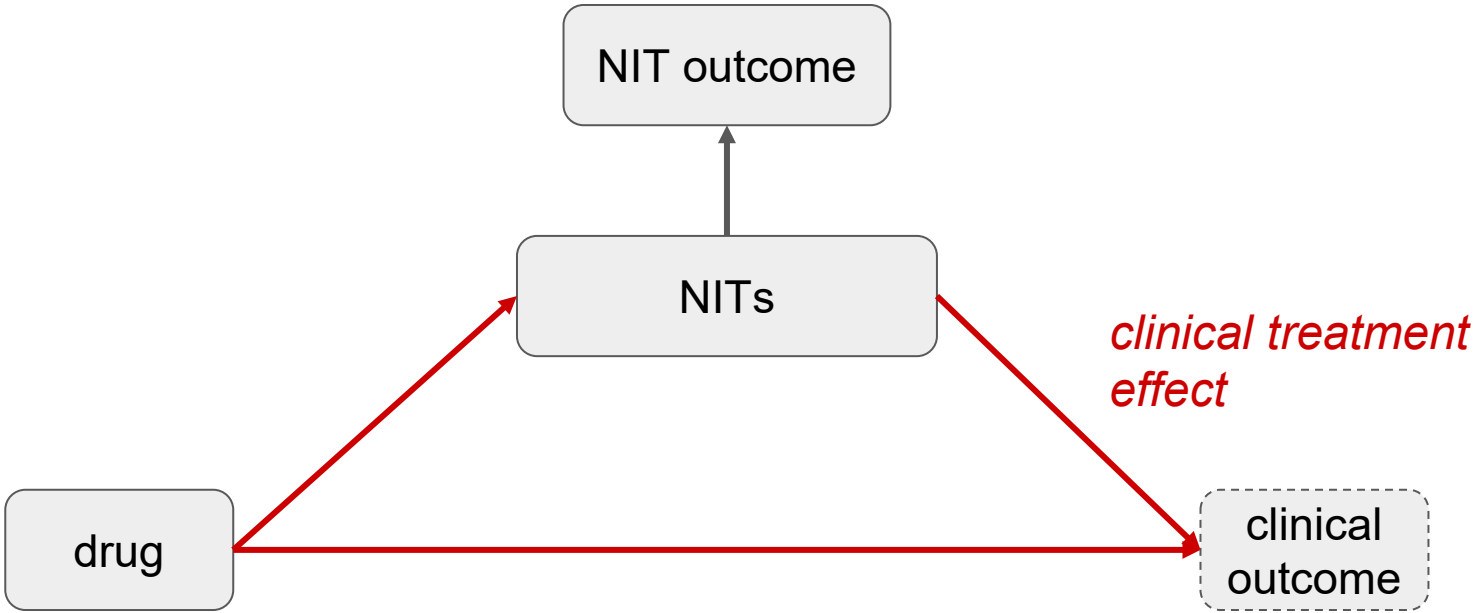
Alejandro Schuler
Asst Prof, UC Berkeley Biostatistics

Brief introduction

- **Asst Professor, UC Berkeley Biostat 2022+**
  - PhD, Stanford Biomedical Informatics (N. Shah) 2018
  - Data Scientist, Kaiser Division of Research 2018-2020
  - Statistician, Unlearn.AI 2020-2021
  - Postdoc, UC Berkeley CTML (M. van der Laan) 2021-2022

- **Methods:** semiparametric methods for causal inference, heterogeneous treatment effects, gradient boosting, model selection
- **Applications**: clinical trial design, data fusion, predictive models in the clinic, observational studies from EHR data

Setting


NIT outcome
NITs
clinical treatment effect
drug
clinical outcome

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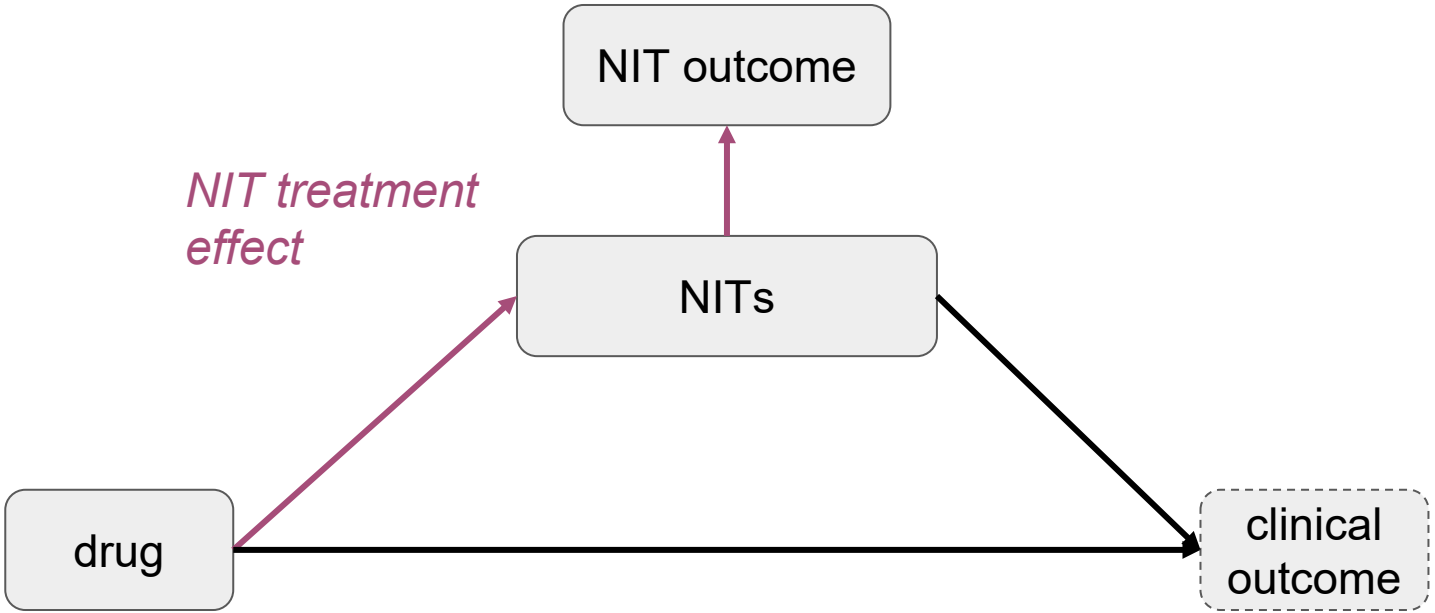
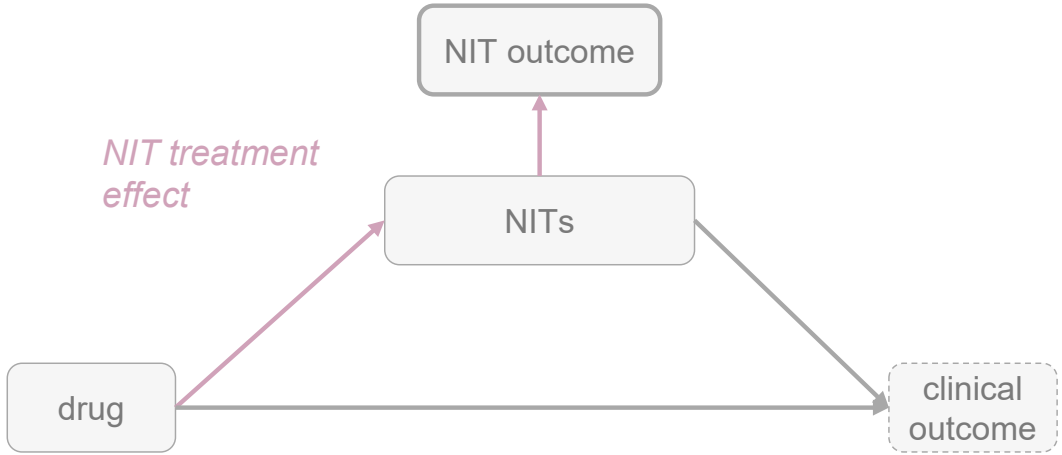

NIT outcome
NIT treatment effect
NITs
drug
clinical outcome

How do we **construct the NIT outcome** so that the trial NIT treatment effect is similar to the population clinical effect?



This is a **well-studied problem**, addressed with modern causal hygiene

- **VanderWeele**, Tyler J. "Surrogate measures and consistent surrogates." Biometrics 69.3 (2013): 561-565.
- Gilbert, Peter B., and Michael G. **Hudgens**. "Evaluating candidate principal surrogate endpoints." Biometrics 64.4 (2008): 1146-1154.
- Price, Brenda L., Peter B. Gilbert, and Mark J. **van der Laan**. "Estimation of the optimal surrogate based on a randomized trial." Biometrics 74.4 (2018): 1271-1281.
- **Athey**, Susan, et al. The surrogate index: Combining short-term proxies to estimate long-term treatment effects more rapidly and precisely. No. w26463. National Bureau of Economic Research, 2019.

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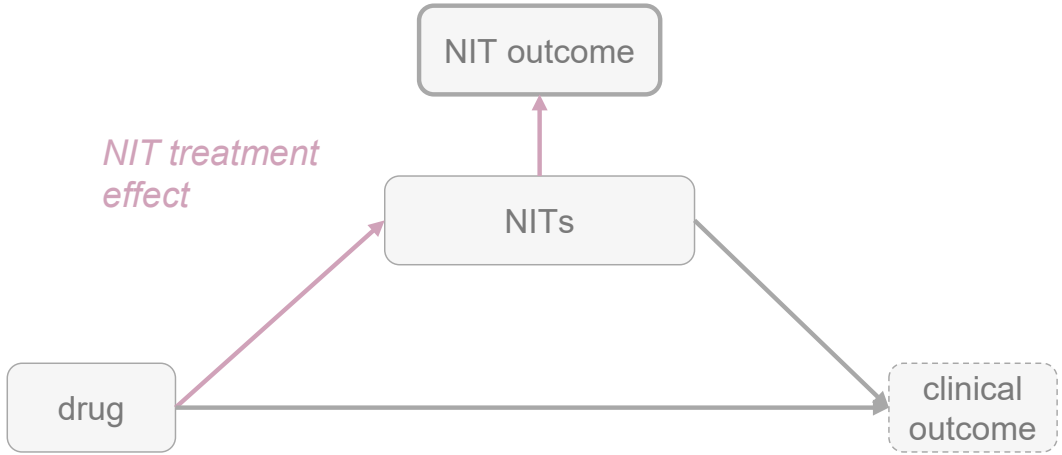
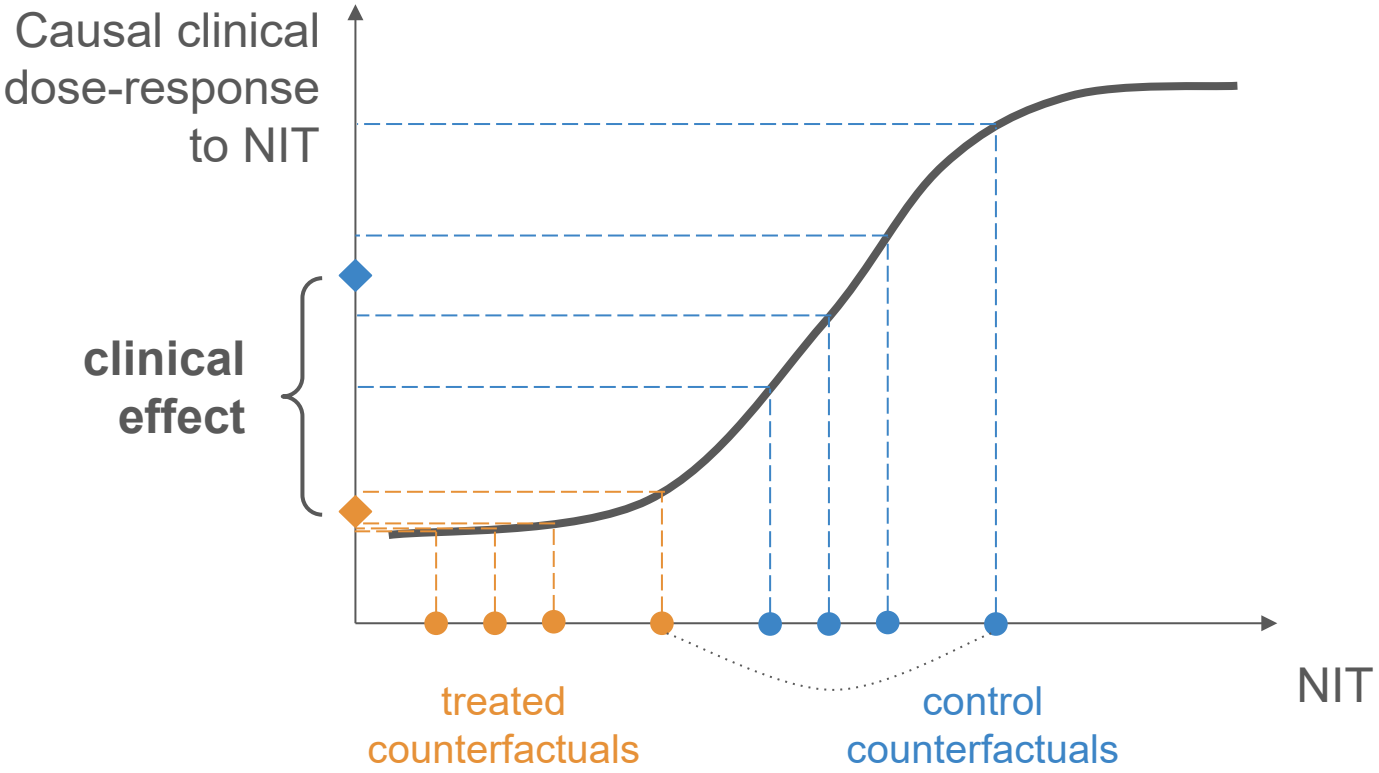


Let's simplify.
if we can't do it when it's easy, we can't do it when it's hard

Assume...

1. **Infinite data** (i.e., entire population)
    - if we can't get it right with a huge trial, no point doing a small one either
    - power is not a concern!
2. **No clinical direct effect**
    - all of the clinical effect of the drug is mediated through the NIT
    - again best-case, essentially assumes NIT is a good proxy
3. **Single, continuous NIT**
    - not a real assumption, just makes it easy to draw pictures

... so clinical effect only depends on NIT levels



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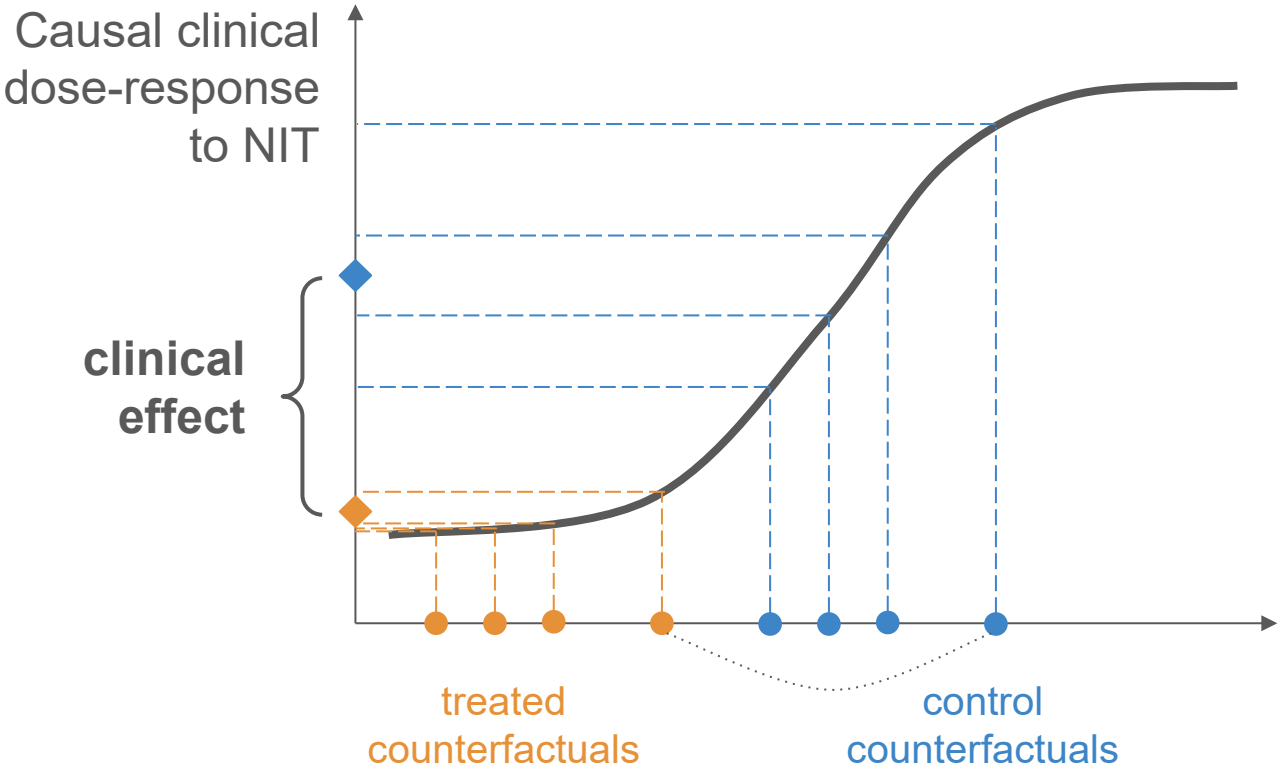
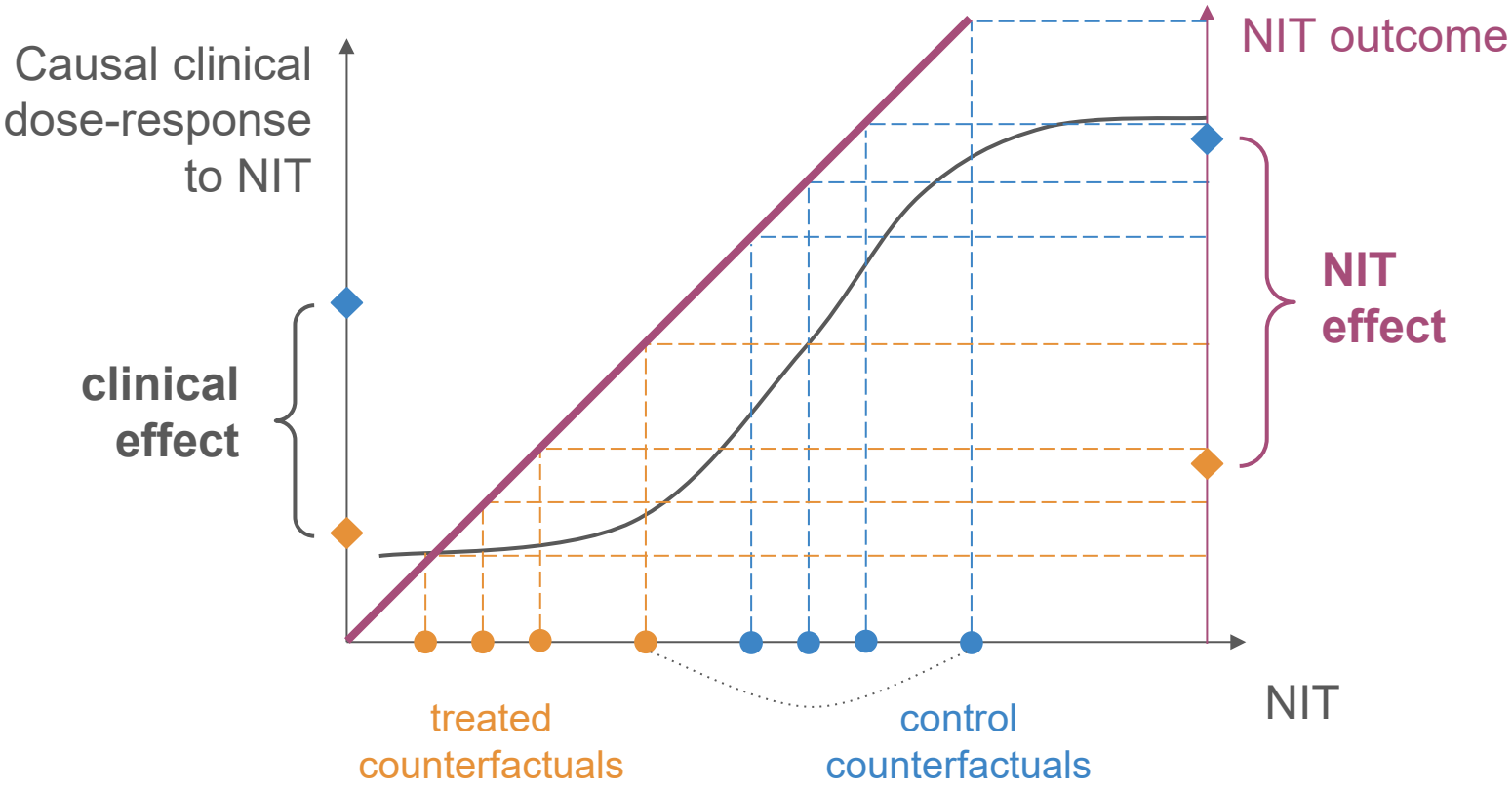
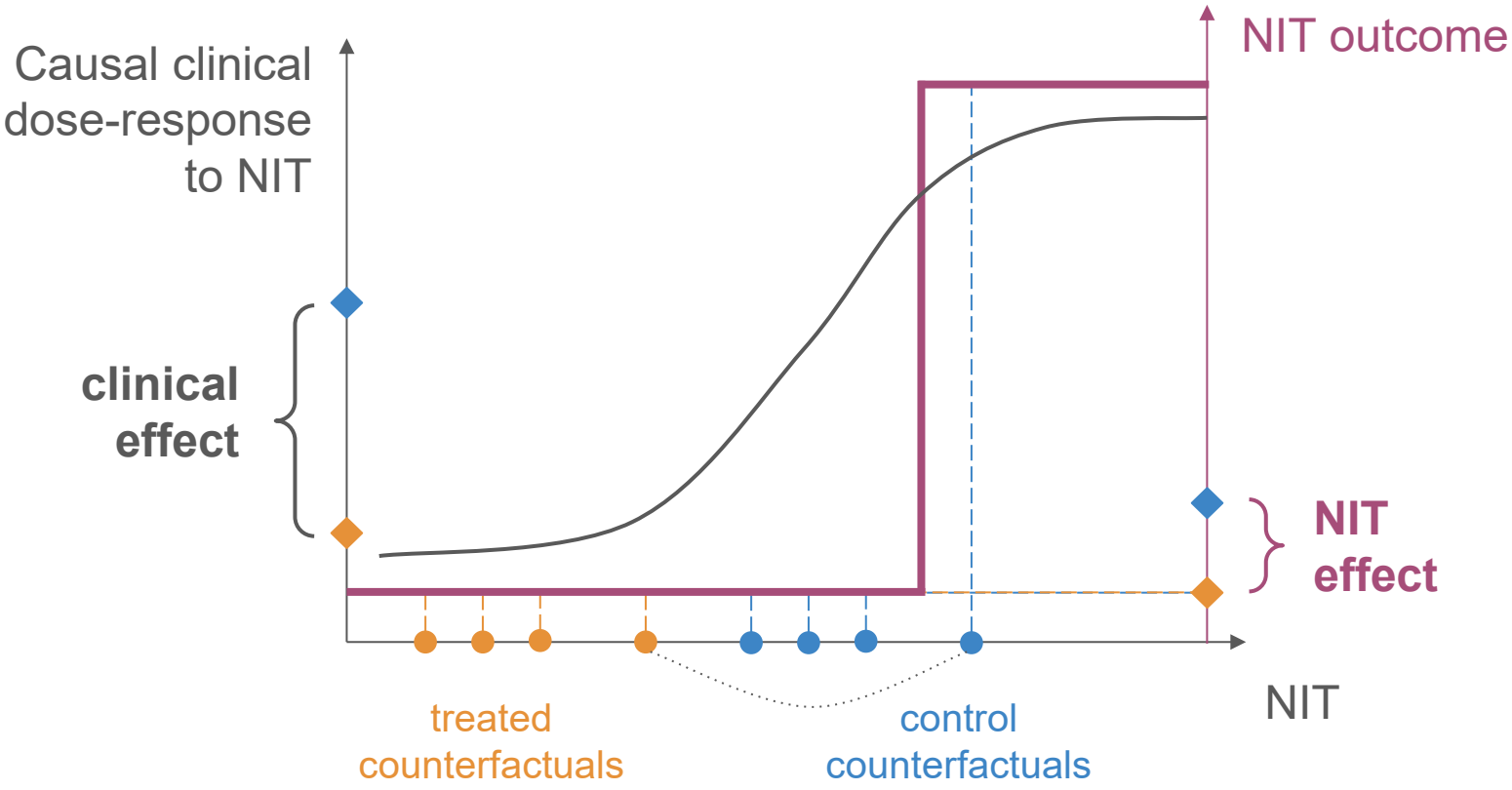


In this scenario, the NIT increases the risk in a particular region - normal variation is fine, and above some point it's all bad

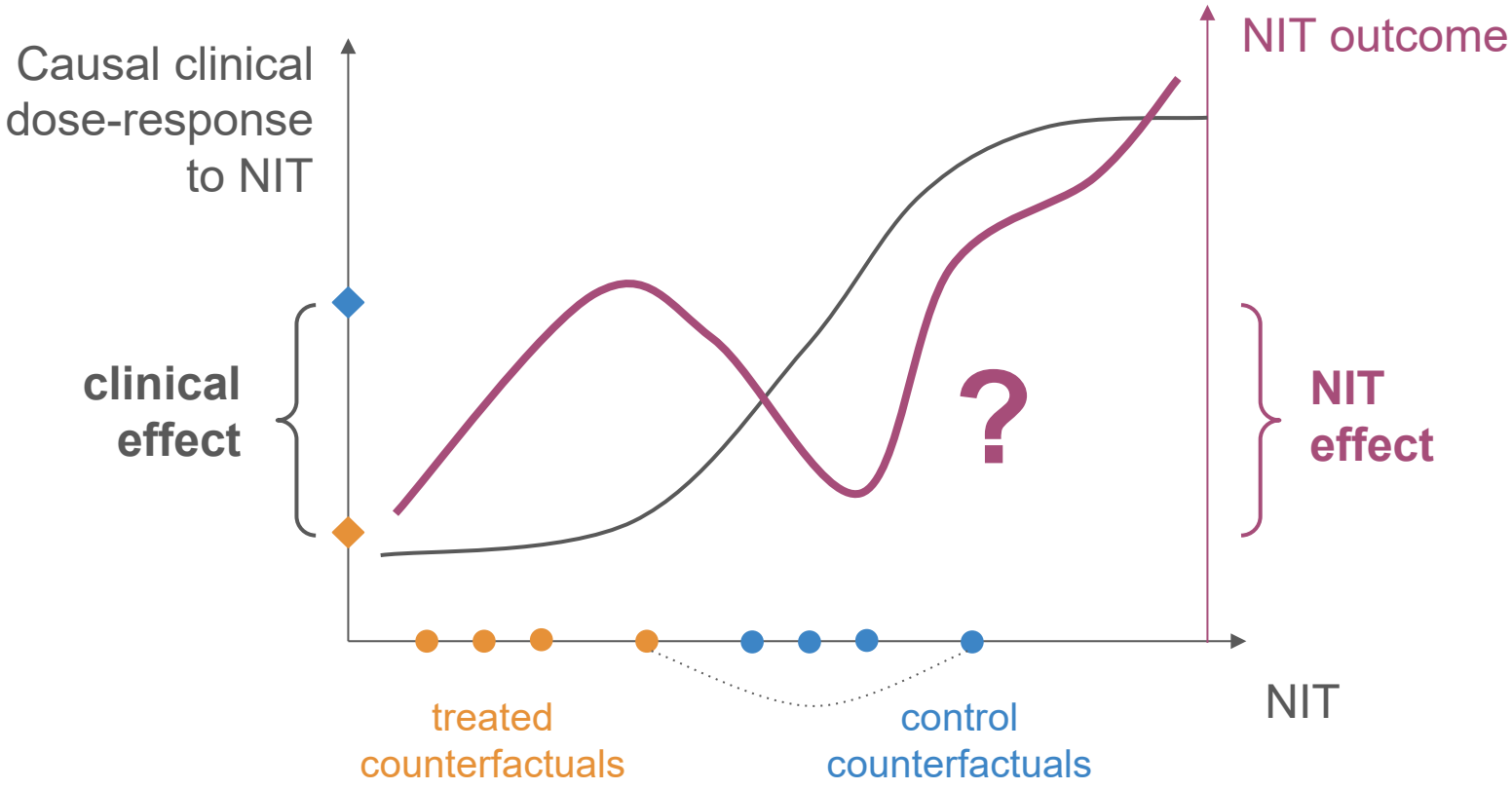
How does the effect compare to the effect on the **continuous** NIT?



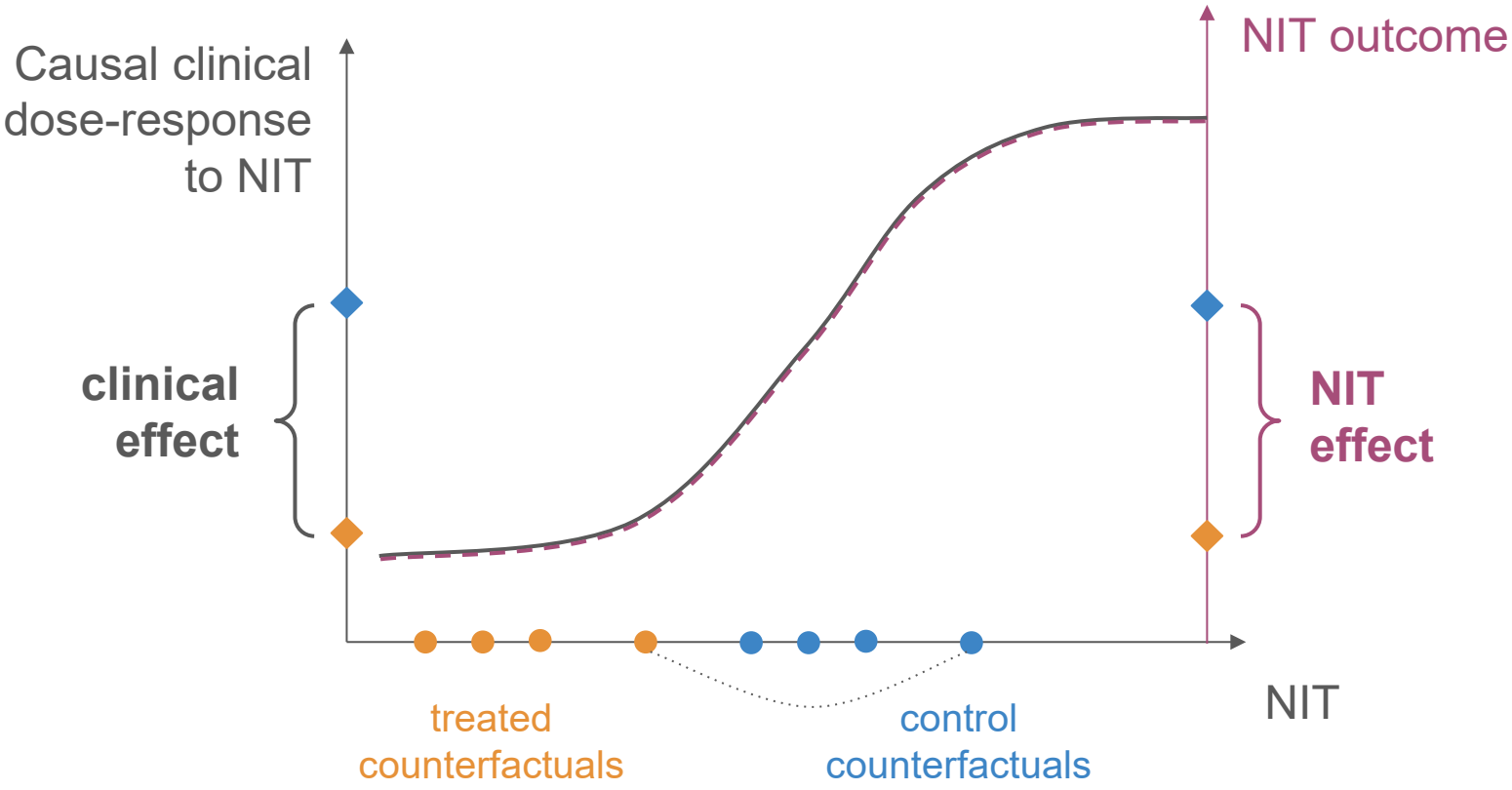
How does the effect compare to the effect on the **binarized** NIT?



What shape do we make the NIT outcome curve so the effects **match**?



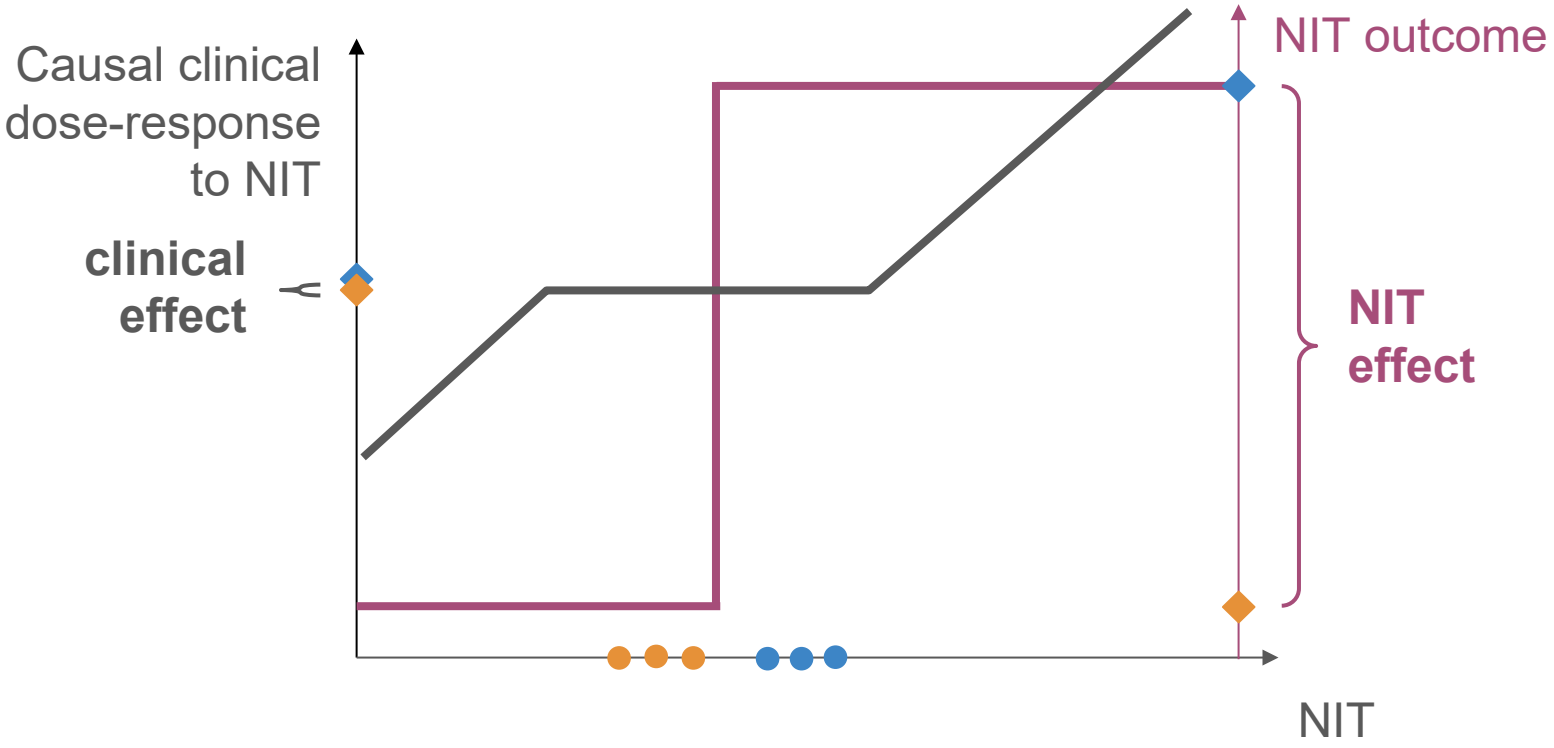
Match the dose-response curve and the effects will match too



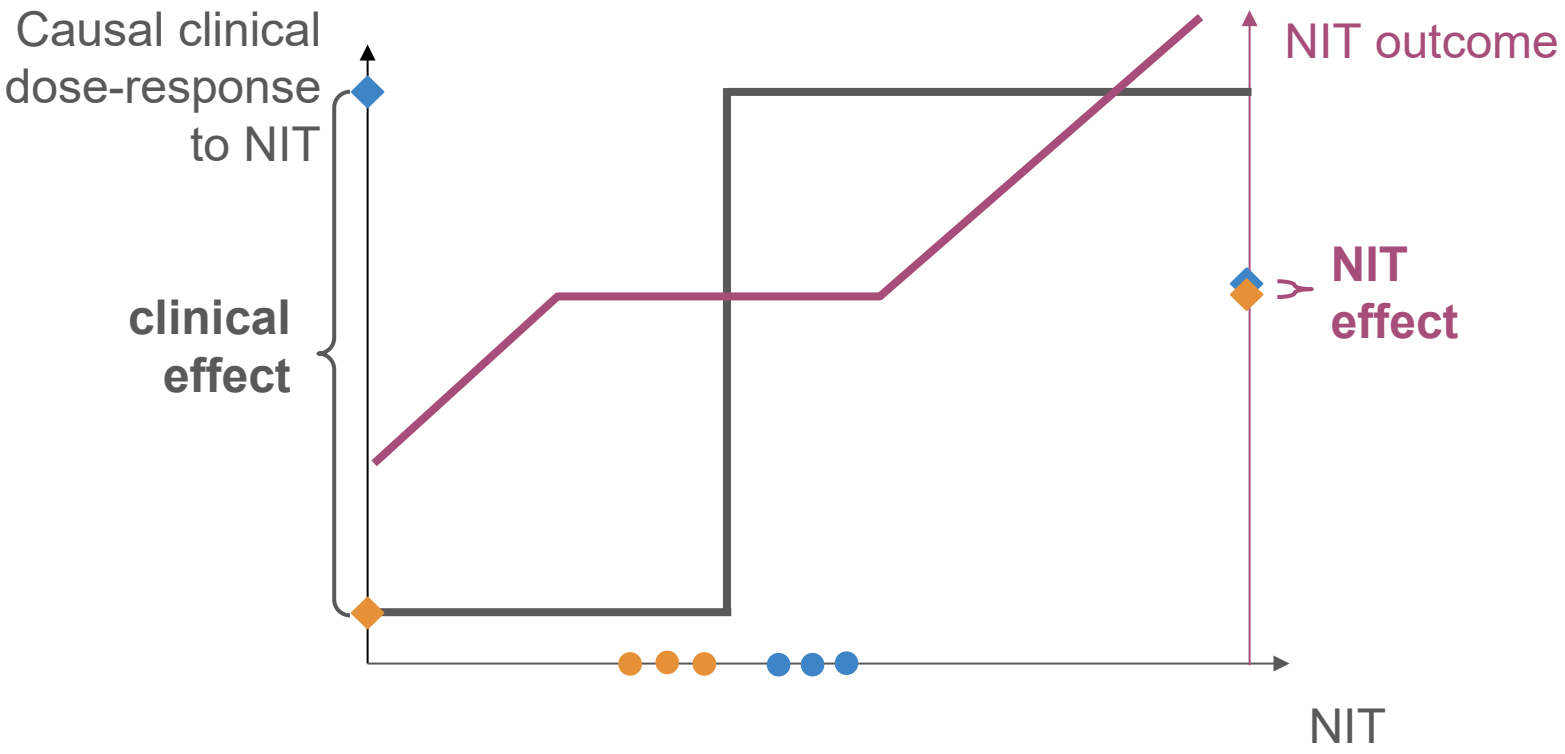
Must define power and error with respect to **clinical effect**

NIT Effect	~~NIT~~ Clinical Effect: present	~~NIT~~ Clinical Effect: not present
detected	True positive (power)	False positive (type I error)
not detected	False negative (failed trial)	True negative

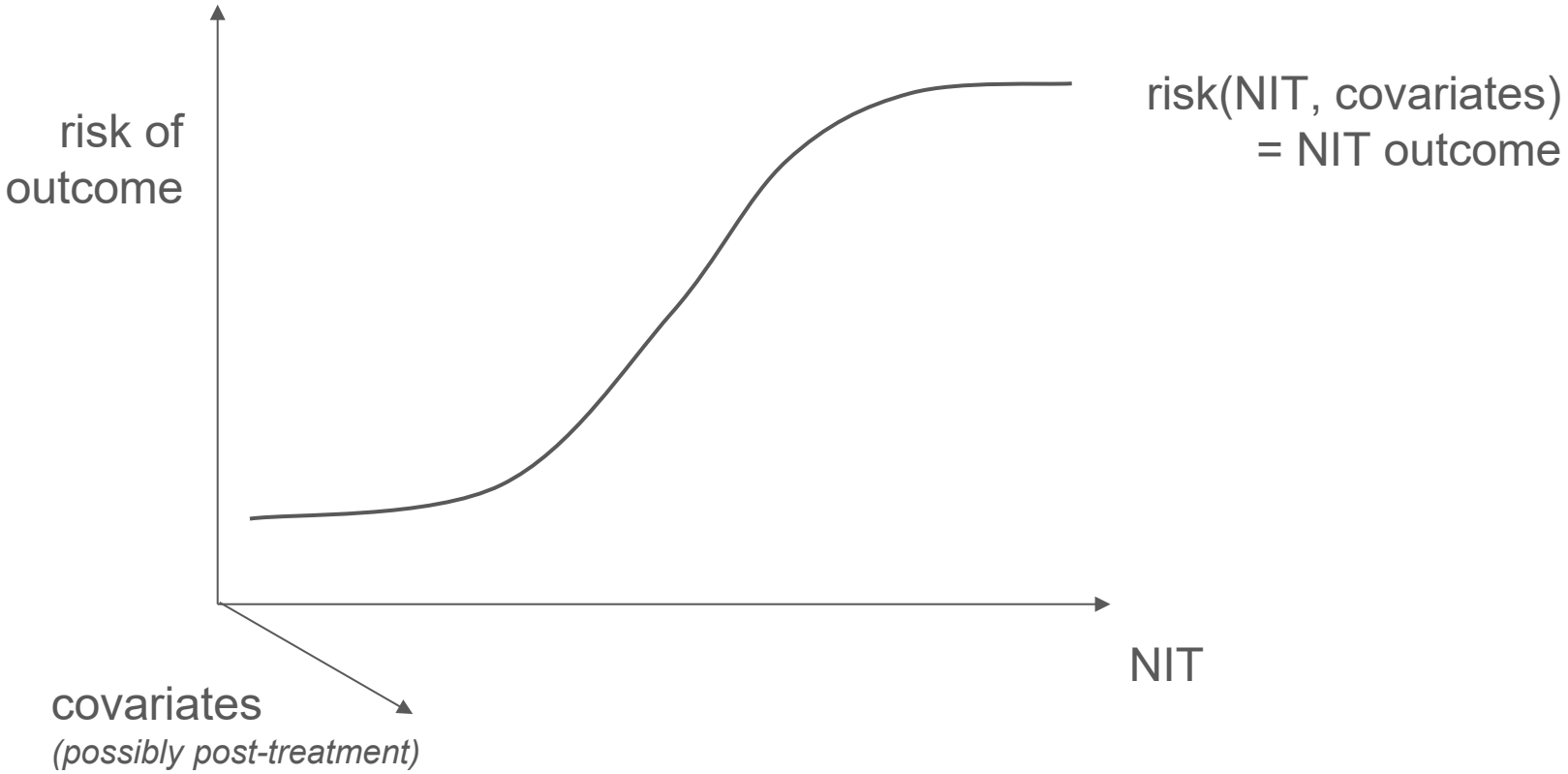
If shapes don't match, **type I error** rate can be 100%



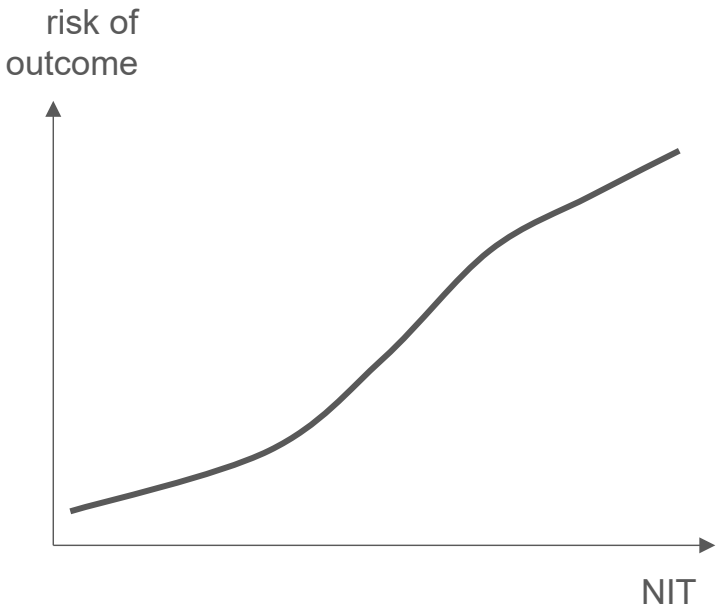
If shapes don't match, **power** can be 0%



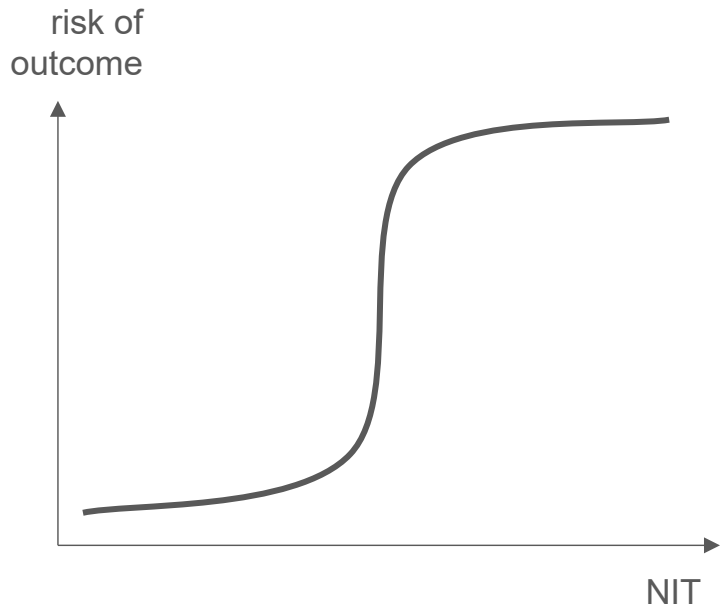
If the NIT-clinical outcome relationship is unconfounded, the dose-response curve is equal to the **observable risk curve** and this is the **ideal** NIT-based outcome



In practice, **theorize** what the shape of this curve roughly looks like and decide based on that



→ Use the continuous NIT as the outcome



→ Binarize NIT at the obvious threshold

Worry a little about assumptions...

- Could there be a **direct clinical effect** in the opposite direction?
  - Think of alternative mediators that could be affected: different biological processes
  - Nothing to do about it except get different NITs

- Is the NIT - clinical outcome relationship **sufficiently unconfounded** to allow for risk to stand in for causal dose response?
  - Again, think of factors (not necessarily affected by treatment) that could create the NIT-outcome association even if NIT does not causally affect the outcome

Takeaways:

- A good NIT outcome depends on how the **NIT relates to the clinical outcome**
  - E.g., binarize if obvious jump in risk, leave continuous if constant rate of increase, clip high/low values if little risk change outside of some region
  - Power for continuous vs. binary outcomes has nothing to do with it
    - no point if you can’t get it right with infinite data!
    - comparing apples and oranges!
- When selecting NITs in the first place, think about **minimizing indirect effects and confounding**