Estimand Sample Sizes

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Estimand Sample Sizes

Acknowledgment and Disclaimer

- The following people were also part of the ongoing work and discussions highlighted in this talk:
  - Dan Bratton (GSK).
  - Sunita Rehal (GSK).
  - Fi Guillard (Veramed UK).

The talk reflects my own opinions and are not necessarily the views of GSK or the people acknowledged above

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Introduction

- The estimands framework has made the target of inference more specific (clearer).
- Information on intercurrent events (IEs) required and how they are reflected in the effect (IE strategy).
- The release of ICH E9(R1) is positive step increasing awareness and discussions around:
  - The effect of interest – Which effects are well aligned to answer the main clinical question?
  - The conduct of trials – Awareness that data may need collecting post-IE.
  - The statistical analysis – Are the standard estimation methods good enough anymore?

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Introduction

- However, the addendum also spells out trial design should be informed by the chosen estimand:

> *"The specification of appropriate estimands (see A.3.) will usually be the main determinant for aspects of trial design, conduct (see A.4.) and analysis (see A.5.)…"*

- So far, across industry the impact of IEs on study design and sample size seems a bit vague.
- Only found a single paper* looking at sample size and IE impact.
- Anecdotally have seen implicit assumptions:
  - Sample sizes based on effects and variability for **patients receiving the treatment**.
  - Sample sizes based on effects and variability which is "***some aggregate of everything***" pre- and post-IEs.

* Fang, Y., & Jin, M. (2021). Sample Size Calculation When Planning Clinical Trials with Intercurrent Events. Therapeutic Innovation and Regulatory Science, 55(4), 779–785.

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Introduction

- It would be **better** to do **more thorough** assessments of **sample size** and power.
- One option is using **patient level simulation.**
  - Generally, **time consuming** to develop code and run large simulations.
  - Creates a **lot of work** for study statisticians.

Can we approximate power for estimands without patient level simulations?

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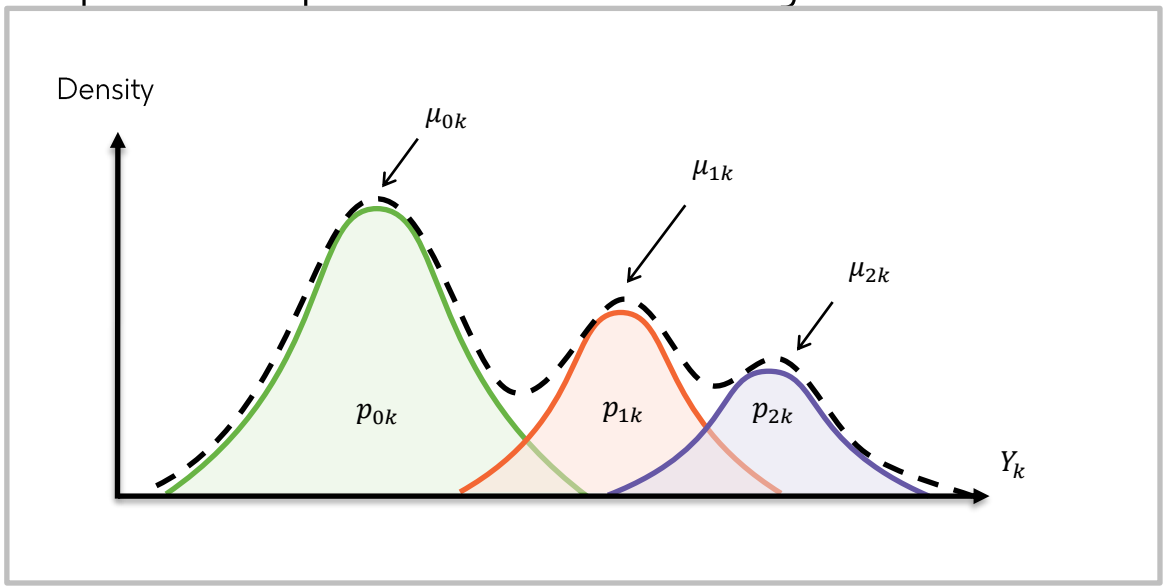
The outcomes are a mixture

- Patients in group k at the primary timepoint are either still "**as randomized**" or in some other "**post-IE**" states S.
- The **outcome distribution** is then a **mixture** of patients in different "**states**".
- Can **use mixture theory** to help with the power calculation – e.g. for continuous outcomes:



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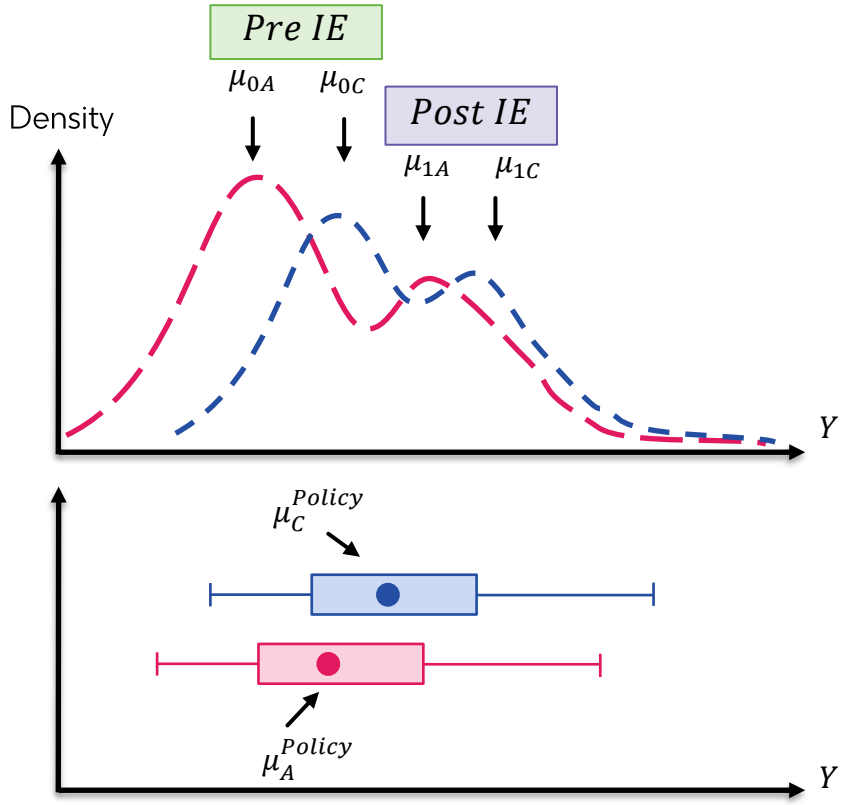
Simple continuous example with a single IE

Single IE “Discontinuation from assigned treatment” using the treatment policy strategy.



- From finite mixture theory:

$$E\left[Y_k^{Policy}\right] = (1-p_k)\cdot\mu_{0k} + p_k\cdot\mu_{1k}$$
$$\mathrm{V}\left[Y_k^{Policy}\right] = (1-p_k)\cdot\sigma_{0k}^2 + p_k\cdot\sigma_{1k}^2 + (1-p_k)\cdot p_k\cdot(\mu_{0k}-\mu_{1k})^2$$

- Assuming independence between groups:

$$\Delta^{Policy} = E\left[Y_A^{Policy}\right] - E\left[Y_C^{Policy}\right]$$
$$\sigma^{Policy} = \sqrt{\mathrm{V}\left[Y_A^{Policy}\right] + \mathrm{V}\left[Y_C^{Policy}\right]}$$

$$N = \left(Z_{\alpha/2} + Z_\beta\right)^2 \cdot \left(\frac{\sigma^{Policy}}{\Delta^{Policy}}\right)^2$$

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Simple continuous example with a single IE

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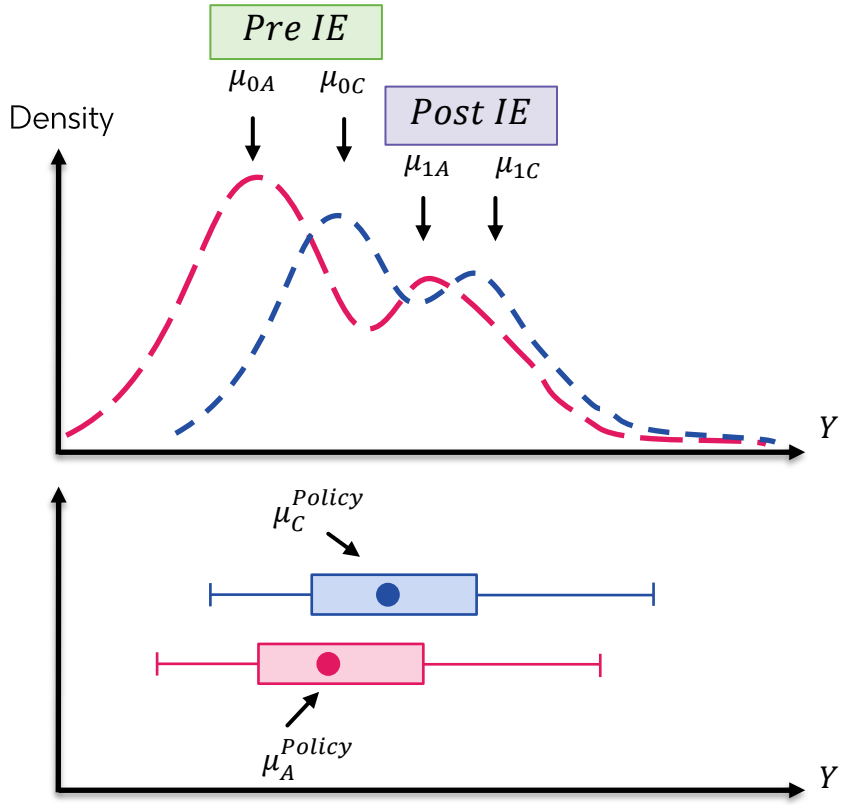

- From finite mixture theory:

$$E[Y_k^{Policy}] = (1 - p_k) \cdot \mu_{0k} + p_k \cdot \mu_{1k}$$
$$V[Y_k^{Policy}] = (1 - p_k) \cdot \sigma_{0k}^2 + p_k \cdot \sigma_{1k}^2 + (1 - p_k) \cdot p_k \cdot (\mu_{0k} - \mu_{1k})^2$$

- Assuming independence between groups:

$$\Delta^{Policy} = E[Y_A^{Policy}] - E[Y_C^{Policy}]$$
$$\sigma^{Policy} = \sqrt{V[Y_A^{Policy}] + V[Y_C^{Policy}]}$$

$$N = (Z_{\alpha/2} + Z_\beta)^2 \cdot \left(\frac{\sigma^{Policy}}{\Delta^{Policy}}\right)^2$$

- Requires information on a lot of quantities.
- Unlikely to have reliable information from the literature.

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Create simple but reasonable assumptions

- If we are **happy** to make **reference-based assumptions** in our **analyses (e.g. Reference based MI)**.
- We can **do the same** in the **sample size calculation** to get a reasonable "rule of thumb".
- The **most common IE strategies** are generally:
  - **Treatment Policy** – Could assume mean shift to control (e.g. **Jump to Reference**) as likely conservative.
  - **Composite** – Could assume shift to agreed failure value (e.g. **zero change**, or **percentiles** or **SD from mean**).
  - **Hypothetical** – Could assume post IE outcome removed (**set to missing**) collapses to standard SS calc.

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Key benefits to formula approximations for power calculations

- Allows **fast assessment of power** compared to patient level simulation.
- Allows **clear assessment** of the **impact of IEs** and **missing data**:
  - Chosen **IE strategy**.
  - Expected **IE rates**.
  - Expected **Missingness rates**.
- Allows **easier simulation of assurance (PoS)**.

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Simple continuous example with treatment policy IE

Primary Estimand

Population	Patients with mild cognitive impairment due to Alzheimer's disease.
Endpoint / Variable	Change from baseline clinical dementia rating sum of boxes (CDR-SoB) at week 96 including any subsequent effects of treatment discontinuation.
Treatments	Assignment to Active or Control.
Summary Measure	Difference in mean.
Intercurrent Events	Treatment discontinuation (treatment policy).

Description:

Difference in mean change from baseline clinical dementia rating sum of boxes (CDR-SoB) at week 96 for patients with mild cognitive impairment due to Alzheimer's disease assigned to Active or Control including any subsequent effects of treatment discontinuation.

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Simple continuous example with treatment policy IE

- Assumptions for power calculation:
  - When **control is taken for 96 weeks** the average change from baseline CDR-SoB is -2.0 (negative = worse).
  - When **active is taken for 96 weeks** the average change from baseline CDR-SoB is -1.4 (30% effect).
  - The **SD is** 2.8 for **both control and active when "on-treatment"**.
  - The rates of **treatment discontinuation** are 15% in each arm.
  - Any **treatment discontinuation** creates instant loss of effect (likely conservative).
  - The **off-treatment SD is** 3.0 for **both control and active** (different treatment options).
  - Aiming for 90% **power** with 5% **significance** (two-sided).

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Simple continuous example with treatment policy IE

```
data power_formula1;

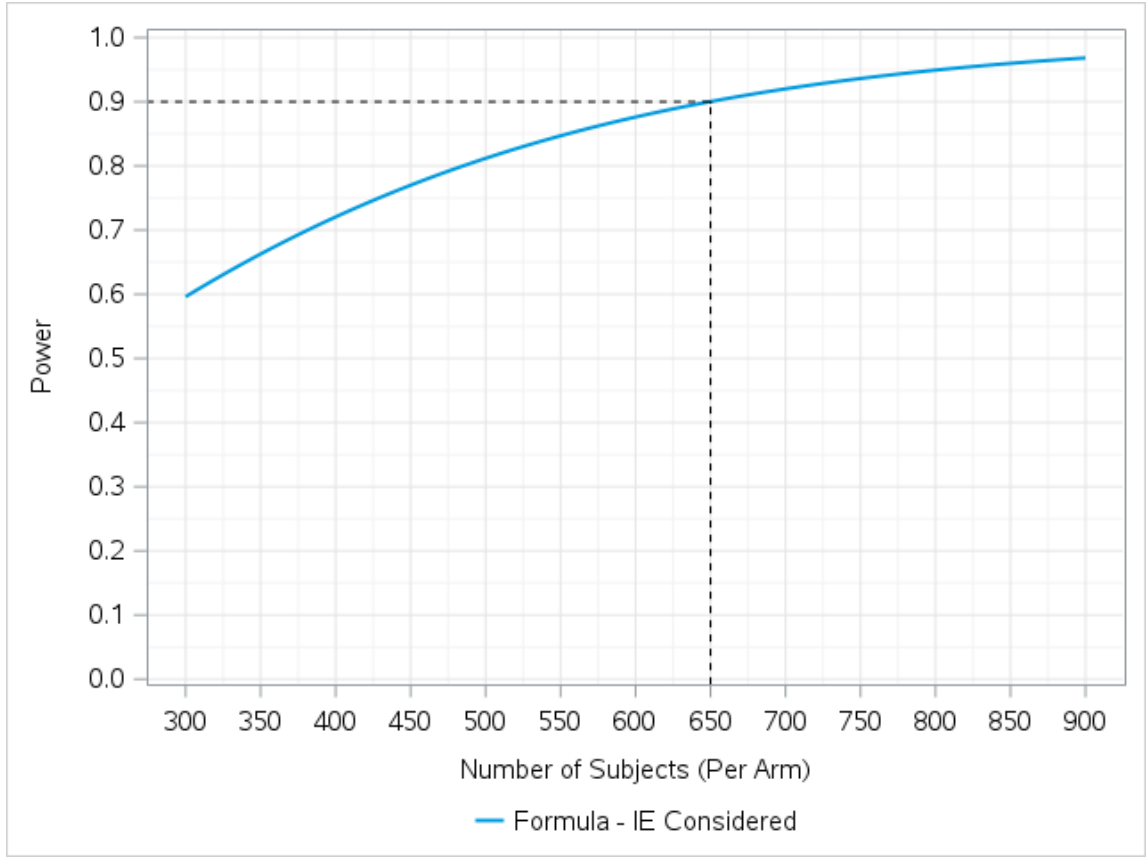
 mu0_c = 2.00; mu1_c = 2.00;   *** ON AND OFF CONTROL MEANS ***;
 mu0_a = 1.40; mu1_a = 2.00;   *** ON AND OFF ACTIVE MEANS  ***;
 sd0_c = 2.85; sd1_c = 2.85;   *** ON AND OFF CONTROL SD ***;
 sd0_a = 2.85; sd1_a = 2.85;   *** ON AND OFF ACTIVE SD  ***;
 p_c   = 0.15;                 *** PROPORTION OF IES IN CONTROL ARM ***;
 p_a   = 0.15;                 *** PROPORTION OF IES IN ACTIVE ARM ***;
 alpha = 0.05;                 *** SIGNIFICANCE LEVEL ***;

 m_policy_c = (1-p_c)*mu0_c + p_c*mu1_c;
 m_policy_a = (1-p_a)*mu0_a + p_a*mu1_a;

 v_policy_c = (1-p_c)*(sd0_c**2) + p_c*(sd1_c**2) + ((1-p_c)*p_c*(mu0_c - mu1_c)**2);
 v_policy_a = (1-p_a)*(sd0_a**2) + p_a*(sd1_a**2) + ((1-p_a)*p_a*(mu0_a - mu1_a)**2);

 do nsub = 300 to 900 by 1;
  delta = abs(m_policy_a - m_policy_c);
  se    = sqrt((v_policy_c/nsub) + (v_policy_a/nsub));
  power = probnorm((delta/se)-probit(1-alpha/2));
  output;
 end;

run;
```



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Simple continuous example with treatment policy IE

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 sd0_c = 2.85; sd1_c = 2.85;   *** ON AND OFF CONTROL SD ***;
 sd0_a = 2.85; sd1_a = 2.85;   *** ON AND OFF ACTIVE SD  ***;
 p_c   = 0.15;                 *** PROPORTION OF IES IN CONTROL ARM ***;
 p_a   = 0.15;                 *** PROPORTION OF IES IN ACTIVE ARM ***;
 alpha = 0.05;                 *** SIGNIFICANCE LEVEL ***;

 m_policy_c = (1-p_c)*mu0_c + p_c*mu1_c;
 m_policy_a = (1-p_a)*mu0_a + p_a*mu1_a;

 v_policy_c = (1-p_c)*(sd0_c**2) + p_c*(sd1_c**2) + ((1-p_c)*p_c*(mu0_c - mu1_c)**2);
 v_policy_a = (1-p_a)*(sd0_a**2) + p_a*(sd1_a**2) + ((1-p_a)*p_a*(mu0_a - mu1_a)**2);

 do nsub = 300 to 900 by 1;
  delta = abs(m_policy_a - m_policy_c);
  se    = sqrt((v_policy_c/nsub) + (v_policy_a/nsub));
  power = probnorm((delta/se)-probit(1-alpha/2));
  output;
 end;

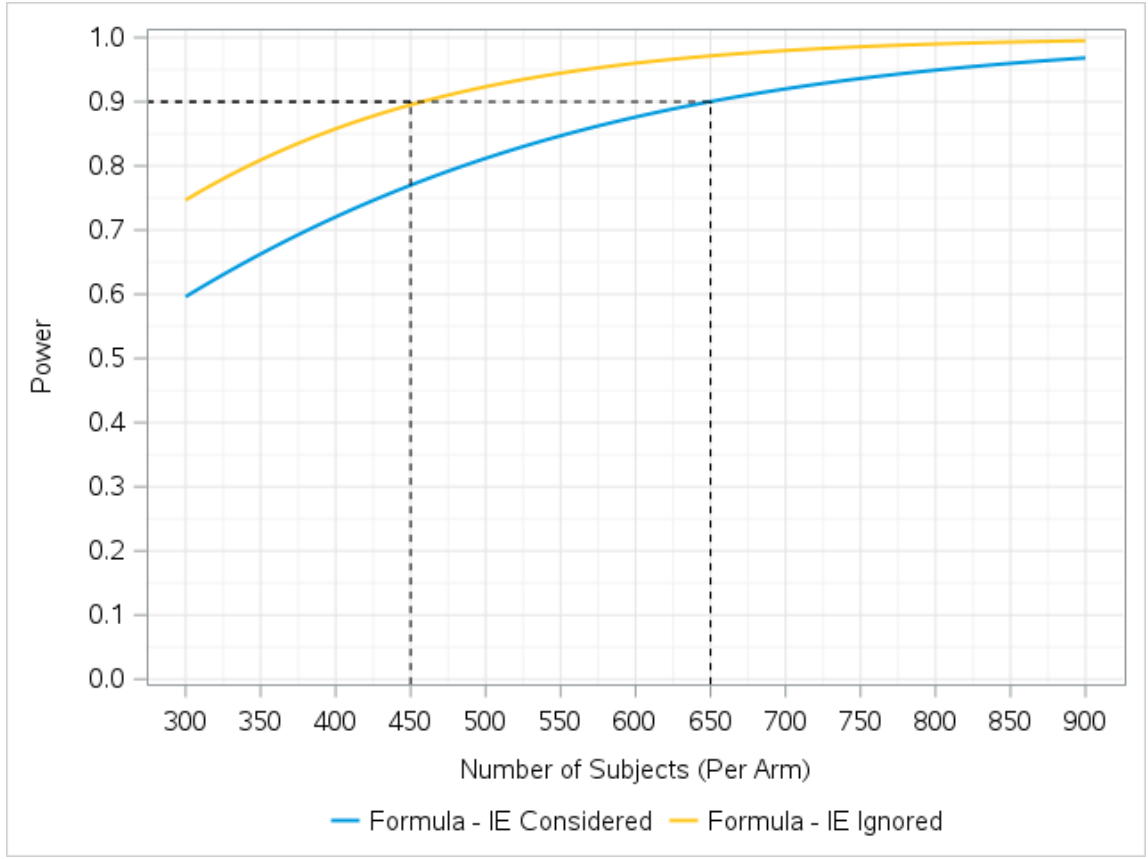
run;
```

```
data power_formula2;

 mu_c = 2.0;     *** ON CONTROL MEANS ***;
 mu_a = 1.4;     *** ON ACTIVE MEANS  ***;
 sd_c = 2.8;     *** ON CONTROL SD ***;
 sd_a = 2.8;     *** ON ACTIVE SD  ***;
 alpha = 0.05;   *** SIGNIFICANCE LEVEL ***;

 do nsub = 300 to 900 by 1;
  delta = abs(mu_a - mu_c);
  se = sqrt(((sd_c**2)/nsub) + ((sd_a**2)/nsub));
  power = probnorm((delta/se)-probit(1-alpha/2));
  output;
 end;

run;
```



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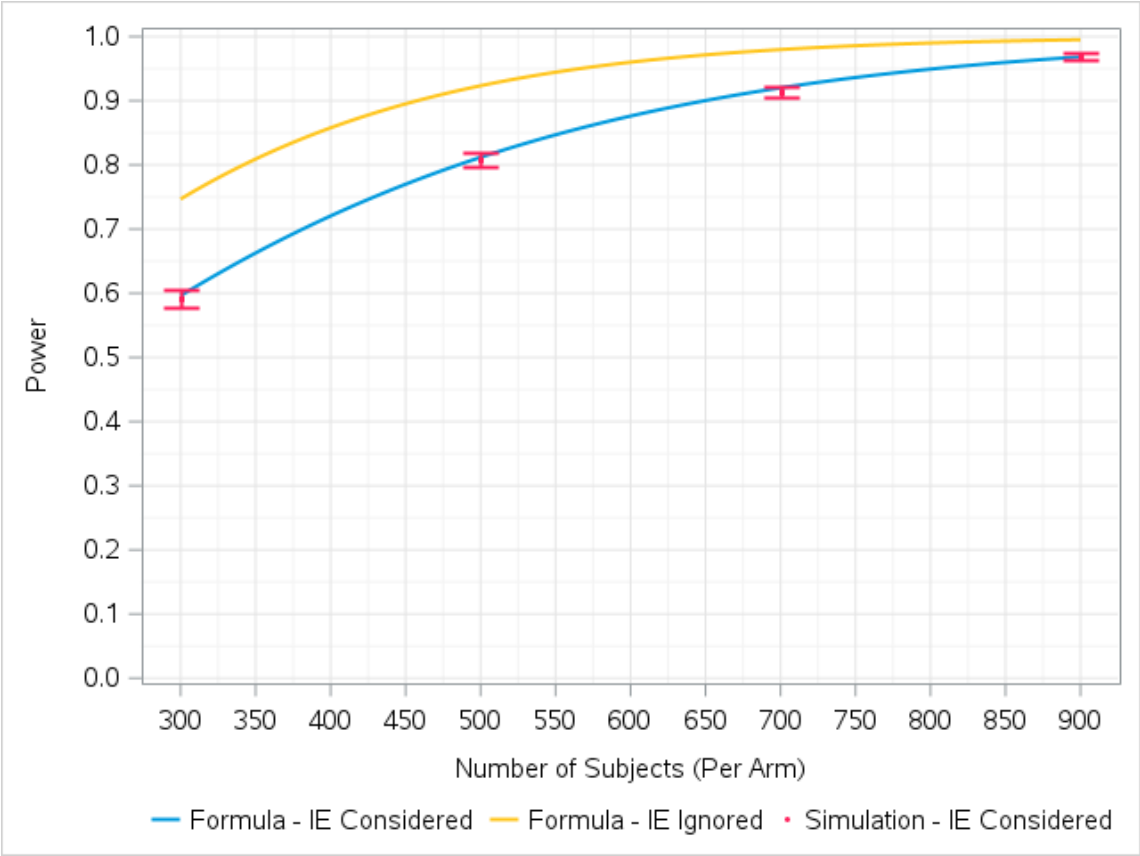
Simple continuous example with treatment policy IE

- Comparing to simulated power:
  - Approximate agreement (most 95% CIs overlap).
  - Formula ~ 1 second.
  - Simulation (5000 sims on 1 core) ~ 3 minutes.
  - Only 4 estimates → 90% power **between** 500-700.



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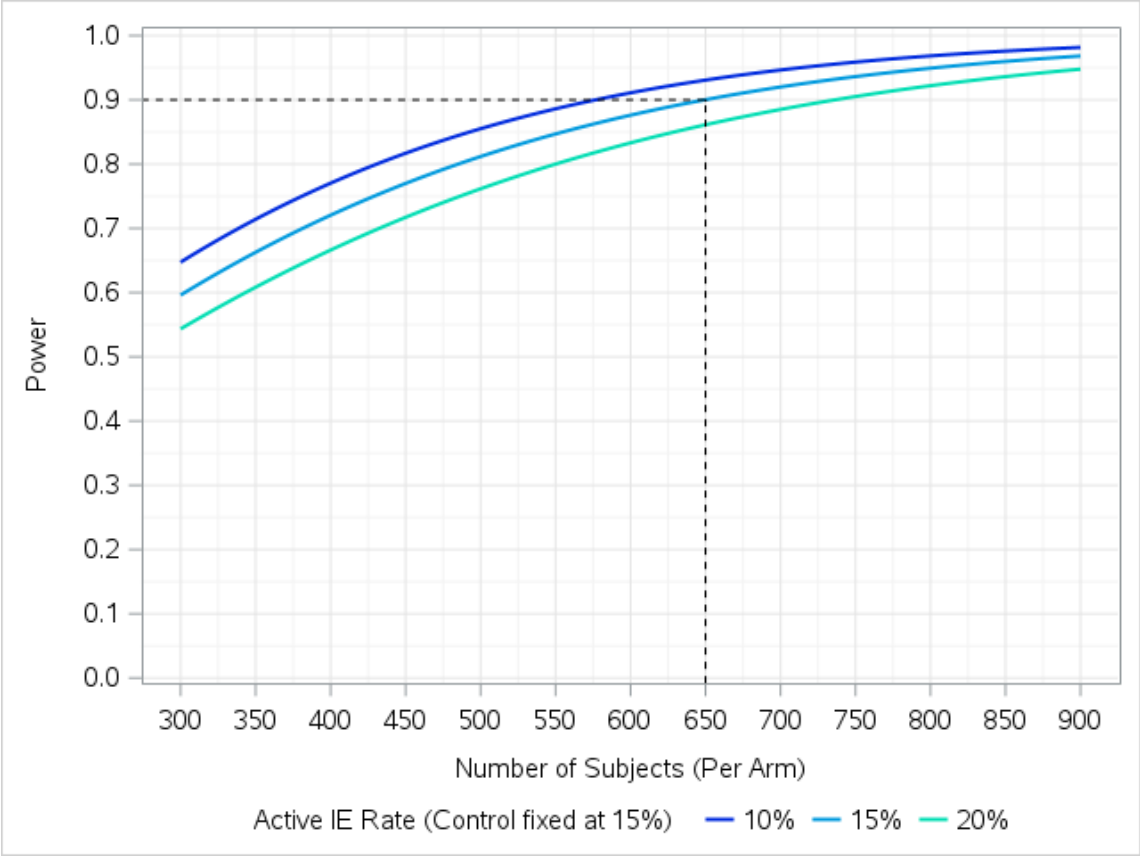
Simple continuous example with treatment policy IE

- Sample Size Sensitivity:
  - What if the IE rates are different?
  - E.g. assume active IE rates 10% or 20%.
  - Different IE rates can **improve** or **reduce** power.
  - Expected IE rates quite important.



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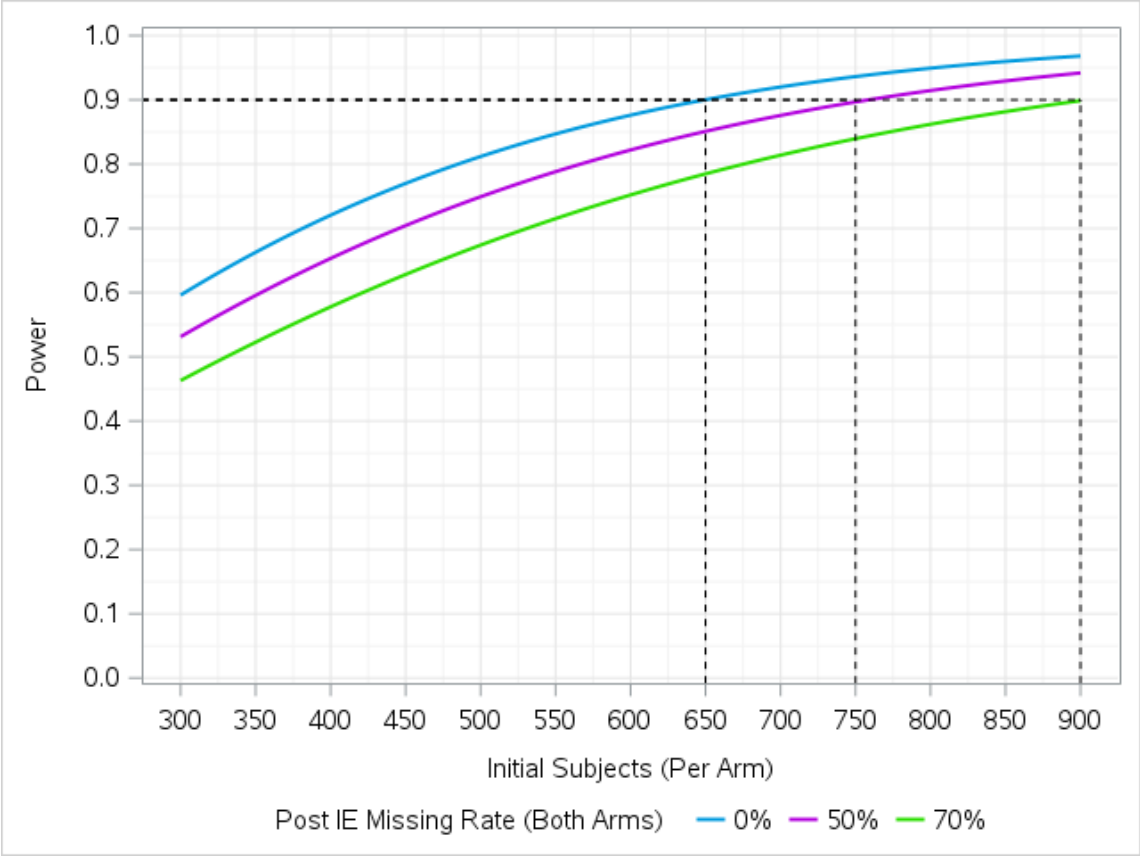
Simple continuous example with treatment policy IE

- Sample Size Sensitivity – Missing Data:
  - Methods get more complex – but still possible*.
  - Power can depend on missing data assumptions.
  - Eg. assume missing data like post-IE data (RDMI).
  - Assume 50% or 70% missing data (post-IE).
  - Marginally ~ 7.5% and 10% overall missing data.



** Bell, J., Drury, T., Mütze, T., Pipper, C.B., Guizzaro, L., Mitroiu, M., Rantell, K.R., Wolbers, M. and Wright, D. (2025), Estimation Methods for Estimands Using the Treatment Policy Strategy; a Simulation Study Based on the PIONEER 1 Trial. Pharmaceutical Statistics, 24: e2472.* https://doi.org/10.1002/pst.2472

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Simple continuous example with treatment policy IE

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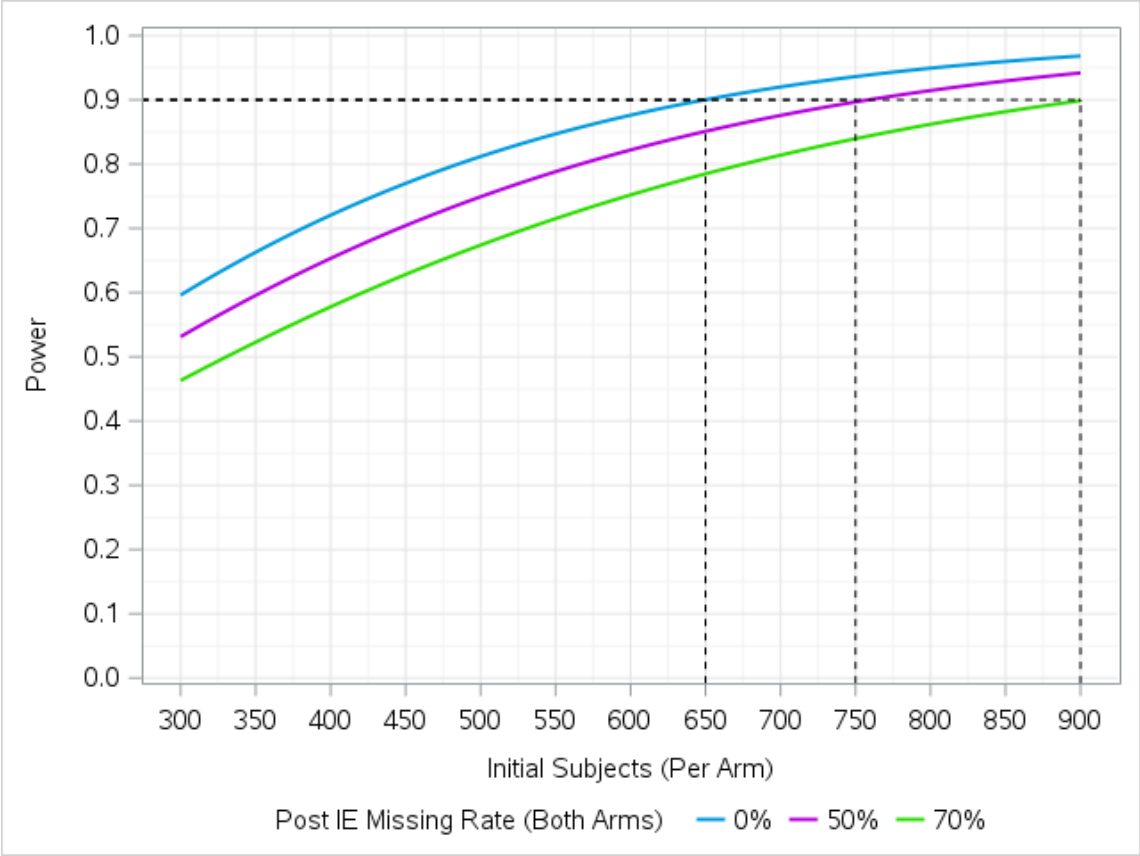
  - Methods get more complex – but still possible*.
  - Power can depend on missing data assumptions.
  - Eg. assume missing data like post-IE data (RDMI).
  - Assume 50% or 70% missing data (post-IE).
  - Marginally ~ 7.5% and 10% overall missing data.

The missing data rate can be **very** important.



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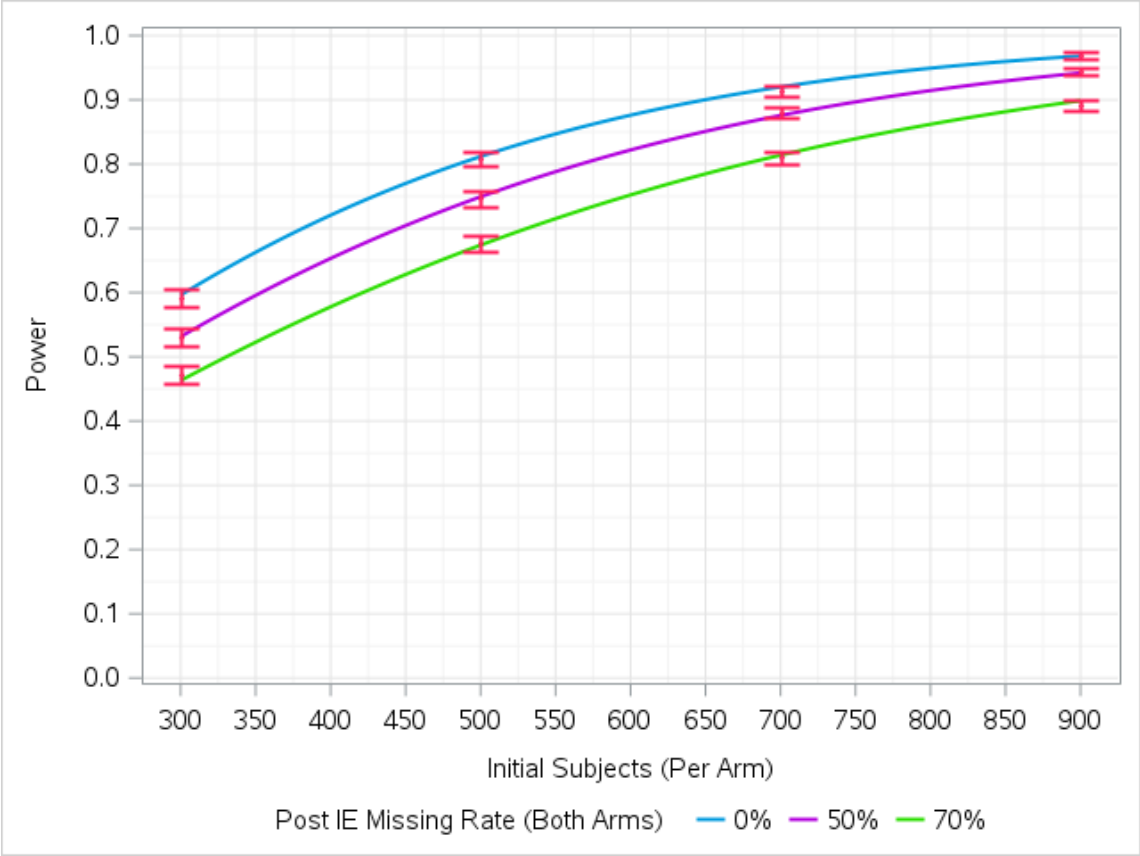
Estimand Sample Sizes

Simple continuous example with treatment policy IE

- Comparing to simulated power:
  - Approximate agreement (most 95% CIs overlap).
  - Formula ~ 1 second.
  - 5000 simulations on 1 core ~ 30 minutes.
  - Simulation requires multiple imputation.
  - Again, only 12 power estimates simulated.



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Simulation validation work in progress – continuous outcomes

- **Stage 1**: Compare power for a **single IE vs. simulation** over large part of the **estimand "design space"**.
  - Effect sizes.
  - IE strategies, rates, and mechanisms.
  - Missing data.
- **Stage 2**: Develop and test methodology for **two IEs** (using same scenarios as stage 1).
- **Stage 3**: Develop **software tools** on Github to simplify work at the design stage.

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Other ongoing simulation work

- Time to events – Hazard Ratios (PSI poster P045 – Dan Bratton).
- Binary outcomes – Risk Differences & Odds Ratios.
- Recurrent events – Rate Ratios for Negative Binomial.
- Comparing assurance calculations vs. subject-level simulations.

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Summary

- The **design** of a clinical trial should be **aligned to the primary estimand**(s).
- The **rates of IEs and missing data** can have a **large impact** on the required sample size.
- Using **mixture theory** to account for IEs is **quicker and easier** than simulating patient level data.
- All results and code from our sample size comparison work will be opened sourced on GitHub*.

* *https://github.com/GSK-Biostatistics*

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Summary

Thank you for listening!

Questions?