



Precision Medicine In Action: Designing A Trial With A Biomarker Threshold Optimization

Guillaume Desachy¹

Anel Mahmutovic²

Beatriz Seoane Nuñez²

Sofia Tapani²

¹Biometrics, Late-stage Development, Respiratory and Immunology (R&I),
BioPharmaceuticals R&D, AstraZeneca

²Early Biometrics & Statistical Innovation, Data Science & Artificial Intelligence,
R&D, AstraZeneca

Biomarker Europe Congress 2023 - November 15th, 2023



A summit attempt with 1 key question



Compound efficacious?



This sounds easy-*ish*, let's go for a Phase IIa!





You Should *Play To Win*



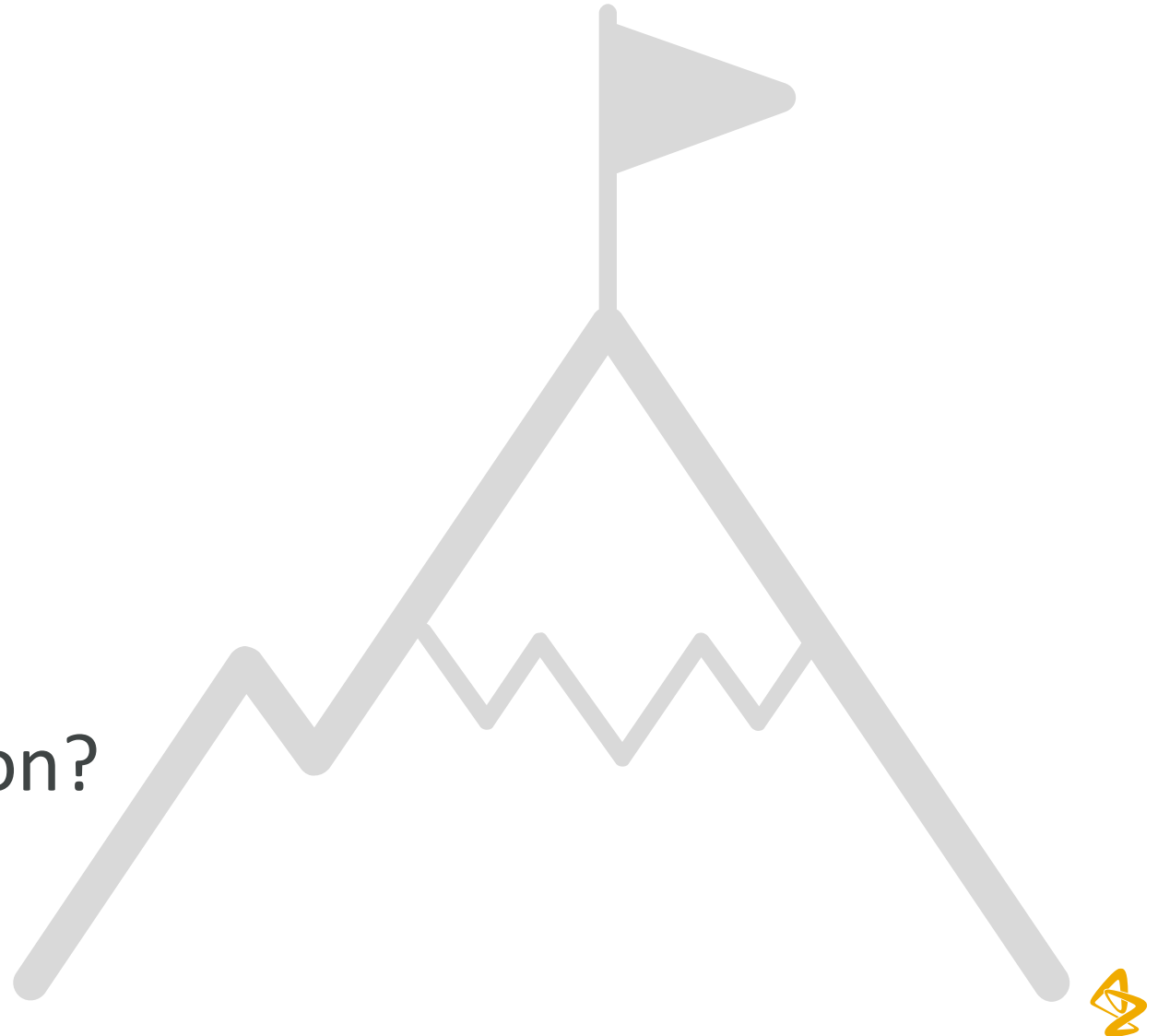
A summit attempt with 2 key questions



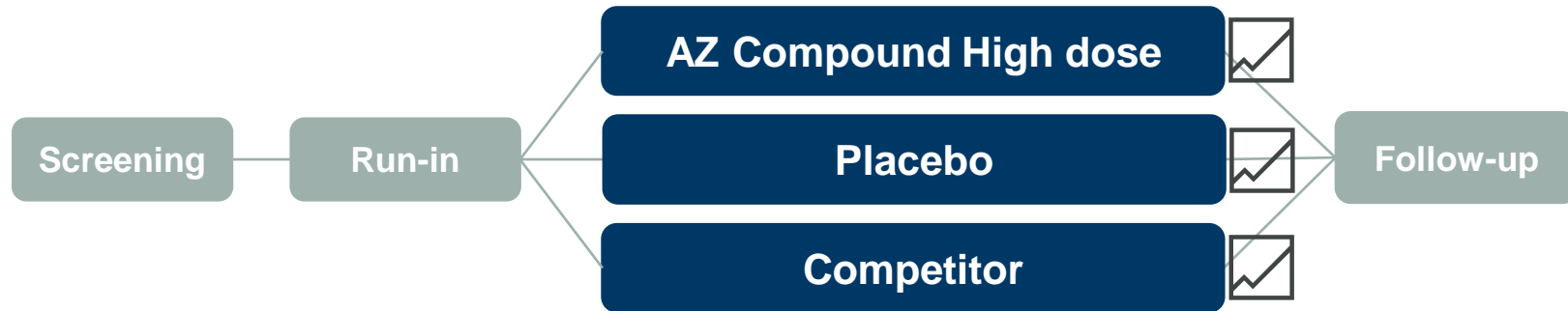
Superior to the competition?



Compound efficacious?



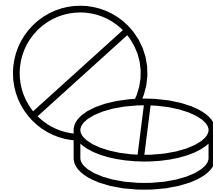
Ok, let's go for a PhIIb with a dual primary endpoint then!



A summit attempt with 3 key questions



Superior to the competition?



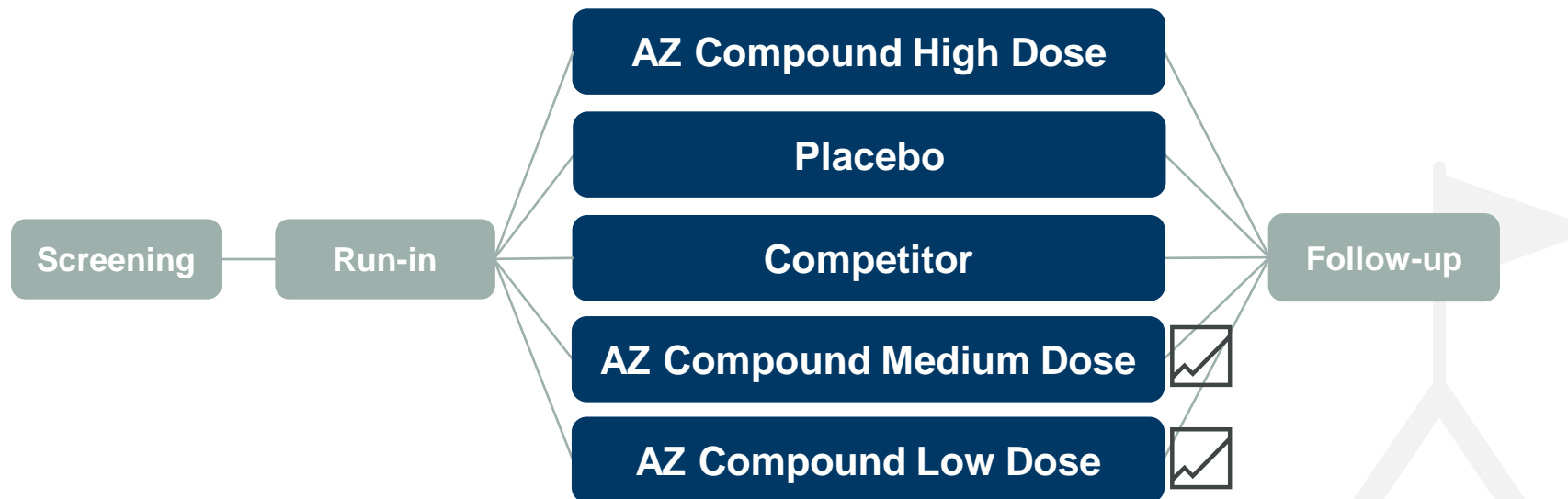
Right dose?



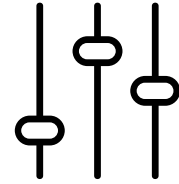
Compound efficacious?



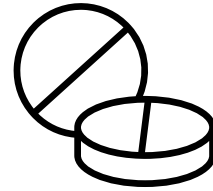
Ok, let's go for a larger PhIIb then!



A summit attempt with 4 key questions



Biomarker threshold?



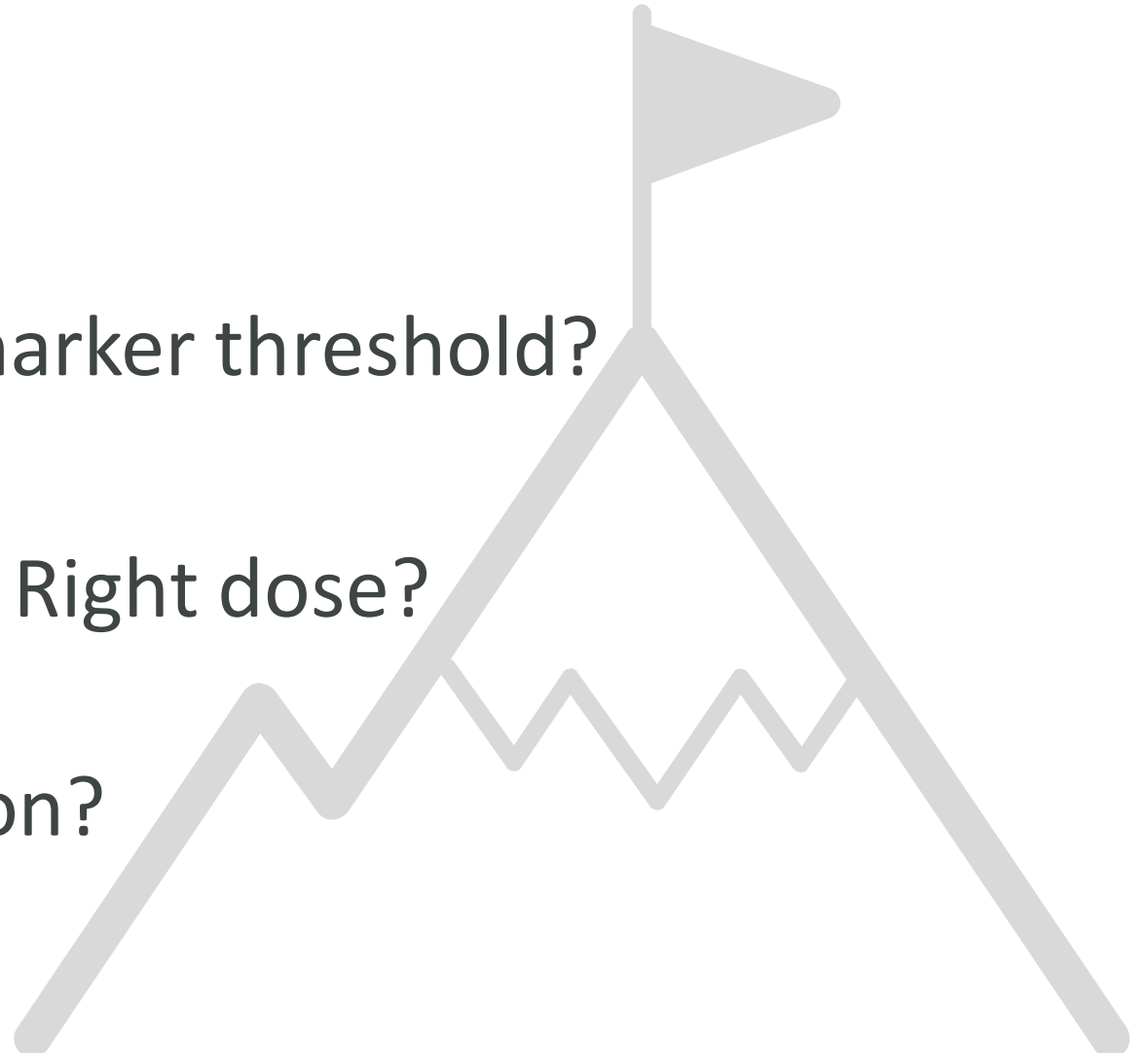
Right dose?



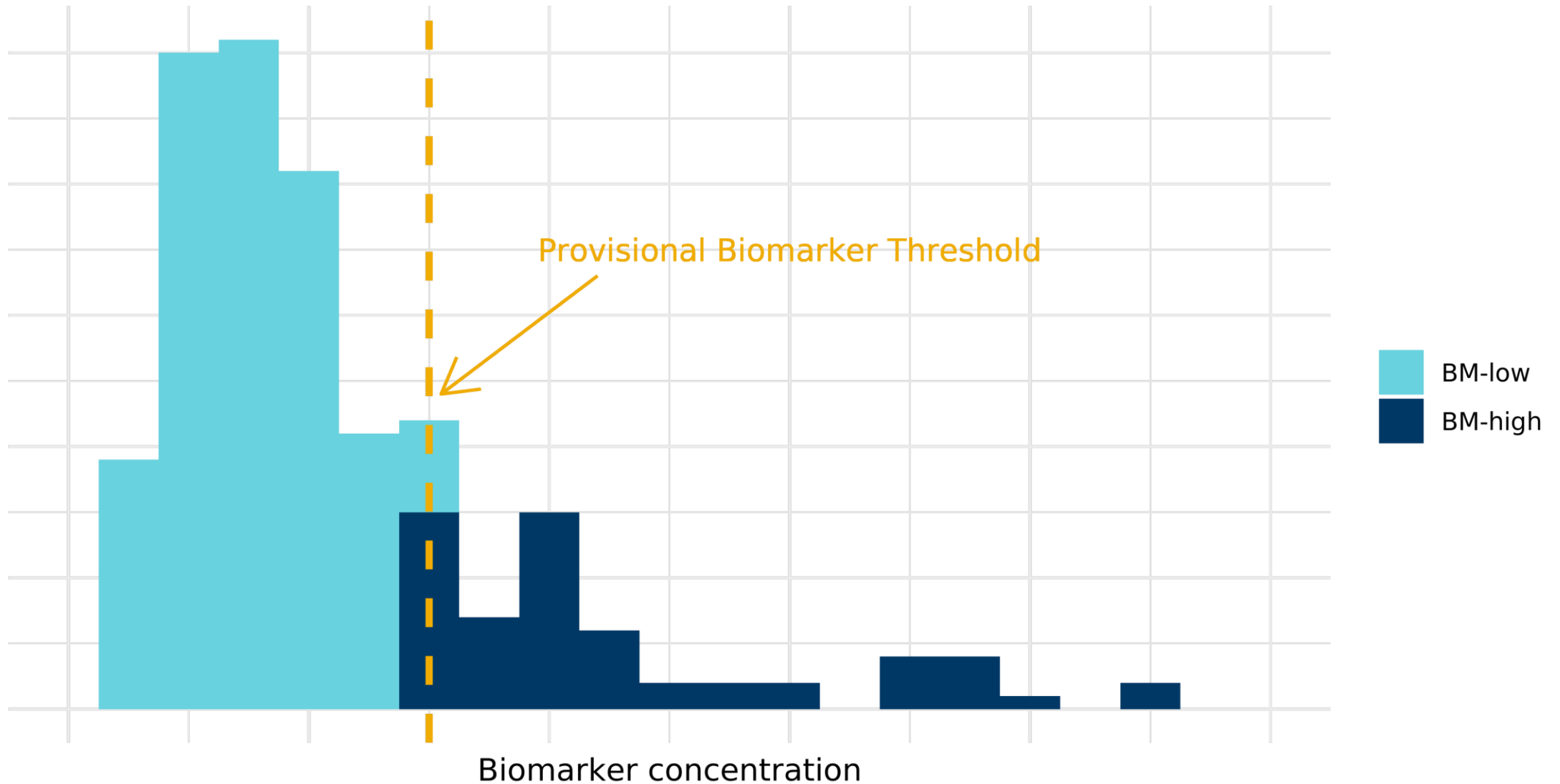
Superior to the competition?



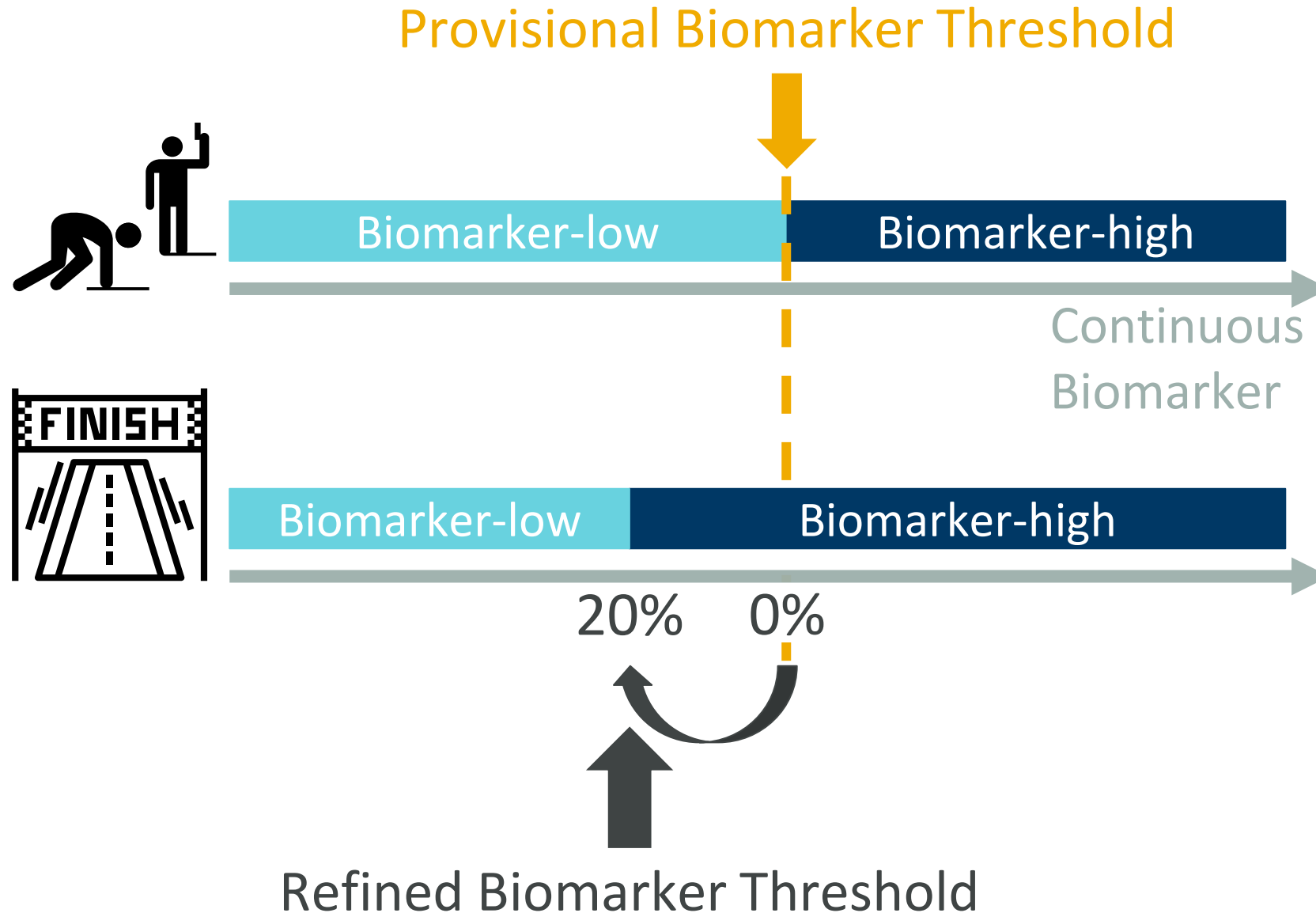
Compound efficacious?



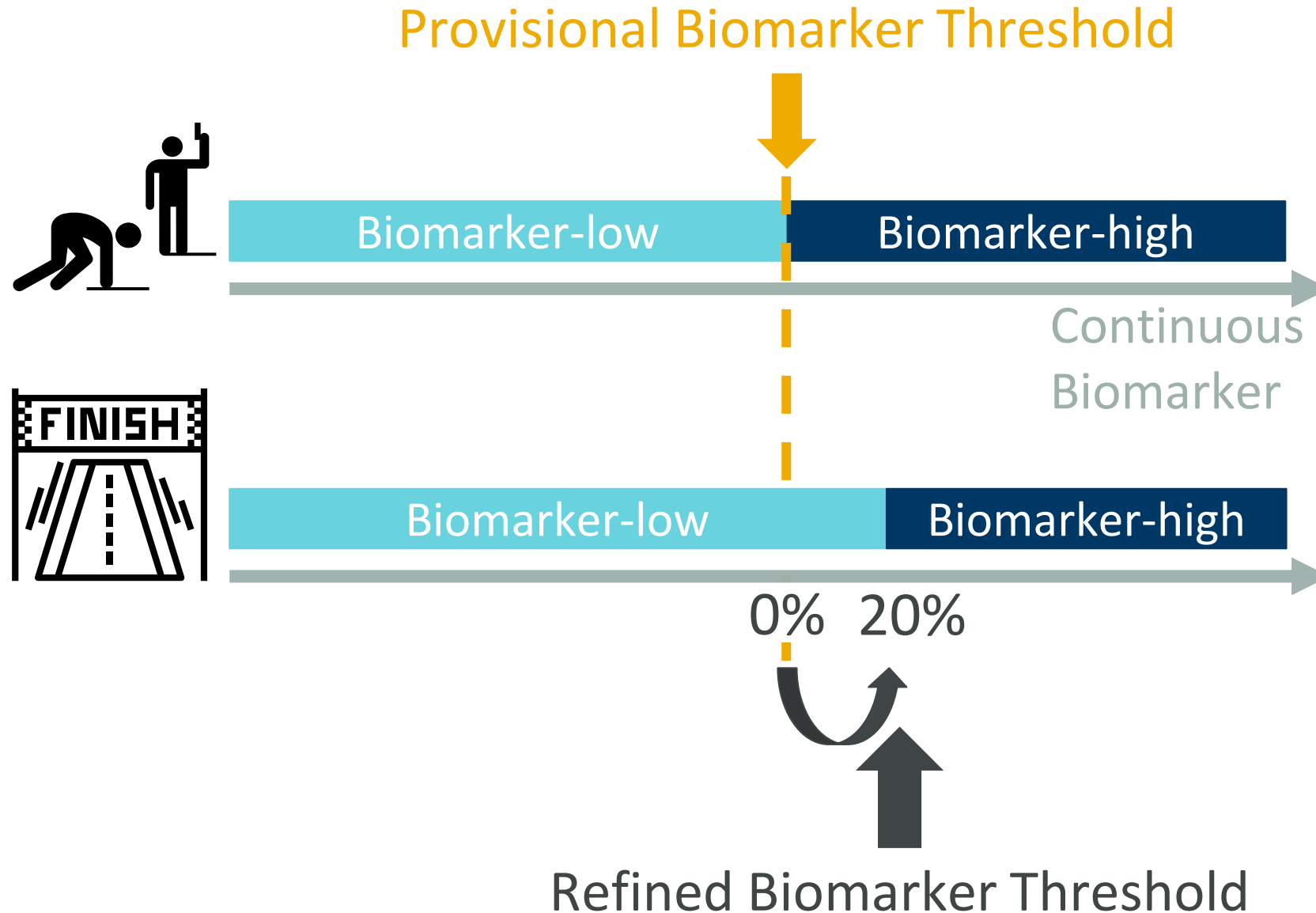
Provisional biomarker threshold defined with real-world data



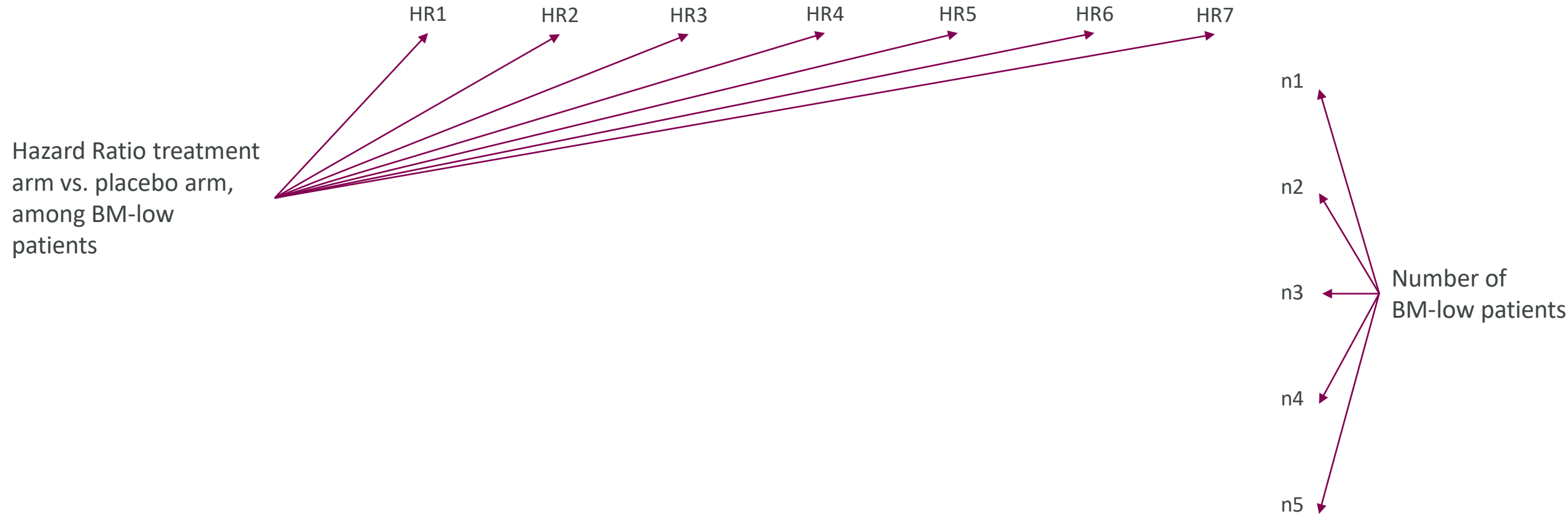
Biomarker threshold refinement, moving it lower



Biomarker threshold refinement, moving it higher



Let's add some biomarker-low patients, but how many?



Hazard Ratio, in short

$$\begin{aligned} &\text{Hazard Ratio (treatment vs. placebo)} \\ &\approx \\ &\frac{\text{chance of an event occurring in treatment arm}}{\text{chance of event occurring in placebo arm}} \end{aligned}$$

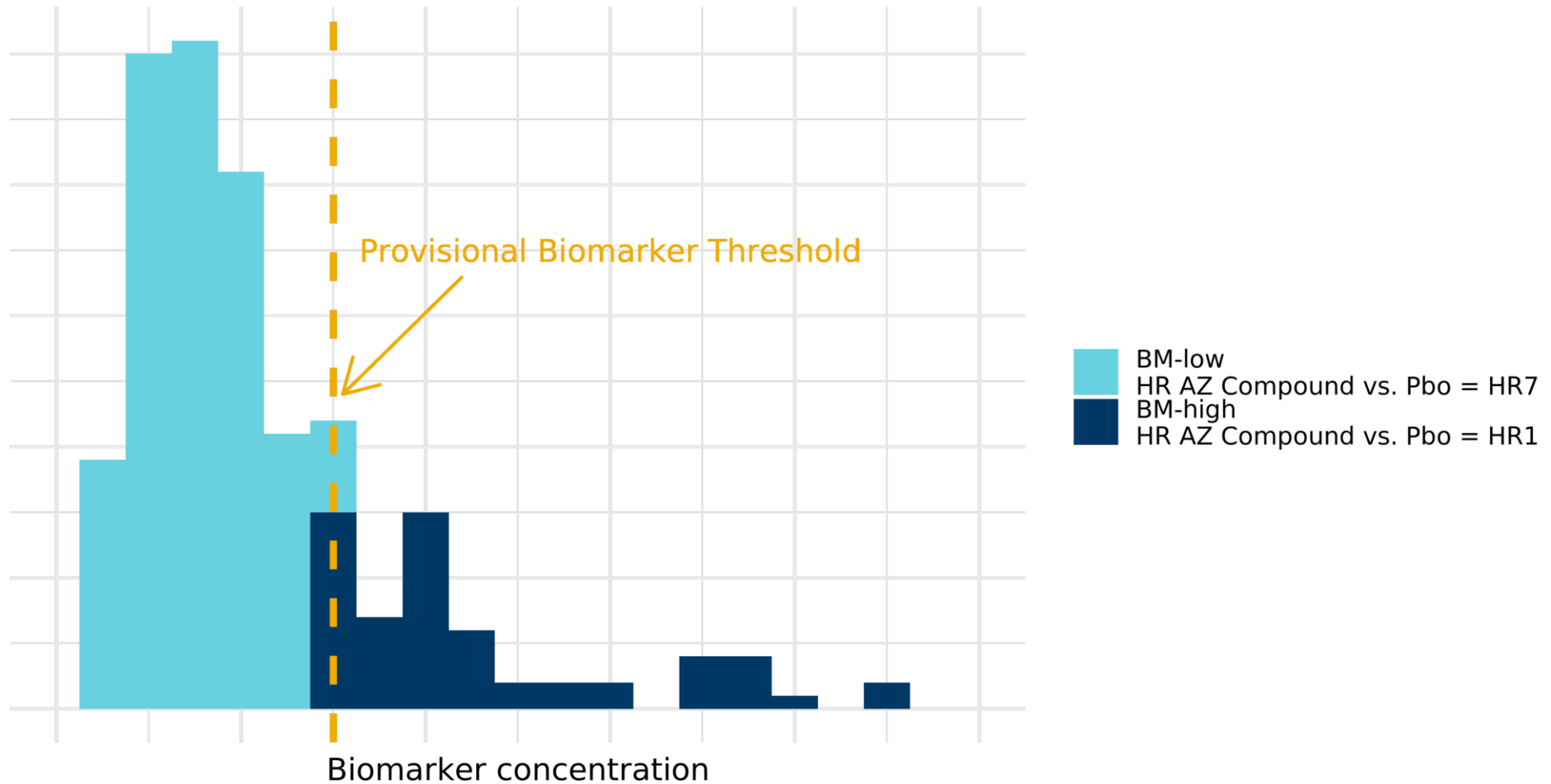
$$\text{HR} \in [0 ; +\infty[$$

HR < 1: treatment is beneficial

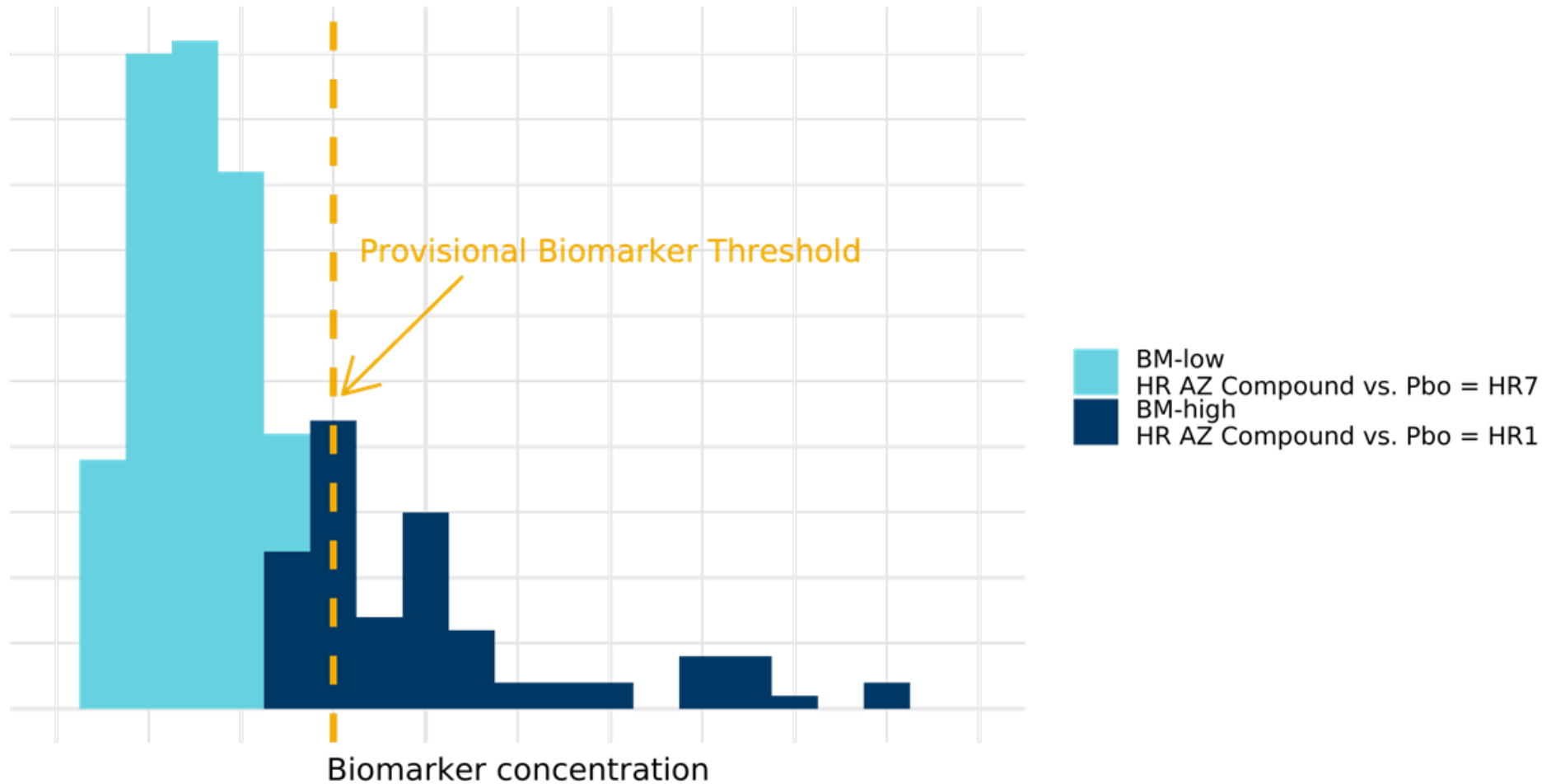
HR > 1: treatment is deleterious



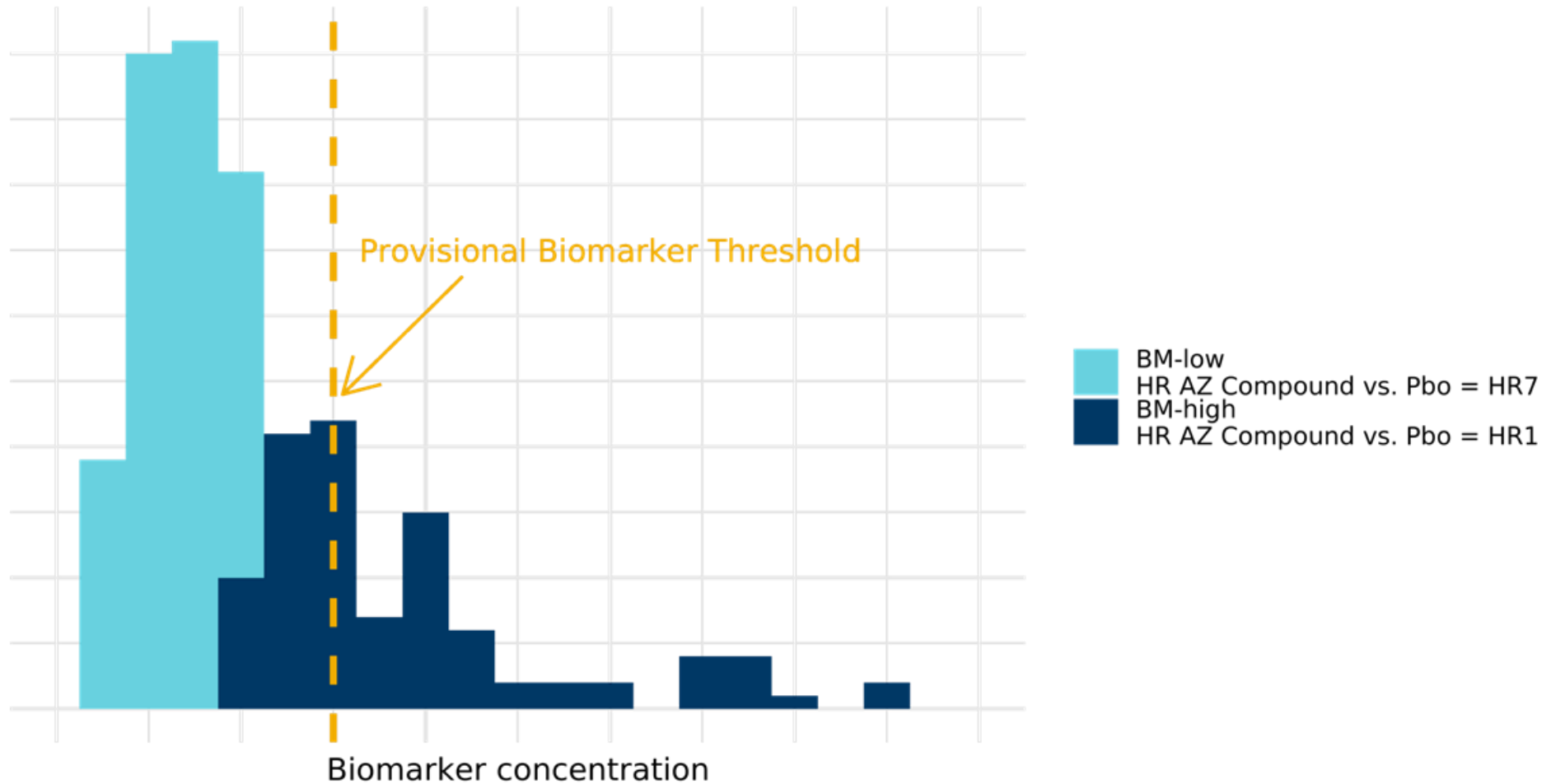
Simulating what the reality could look like



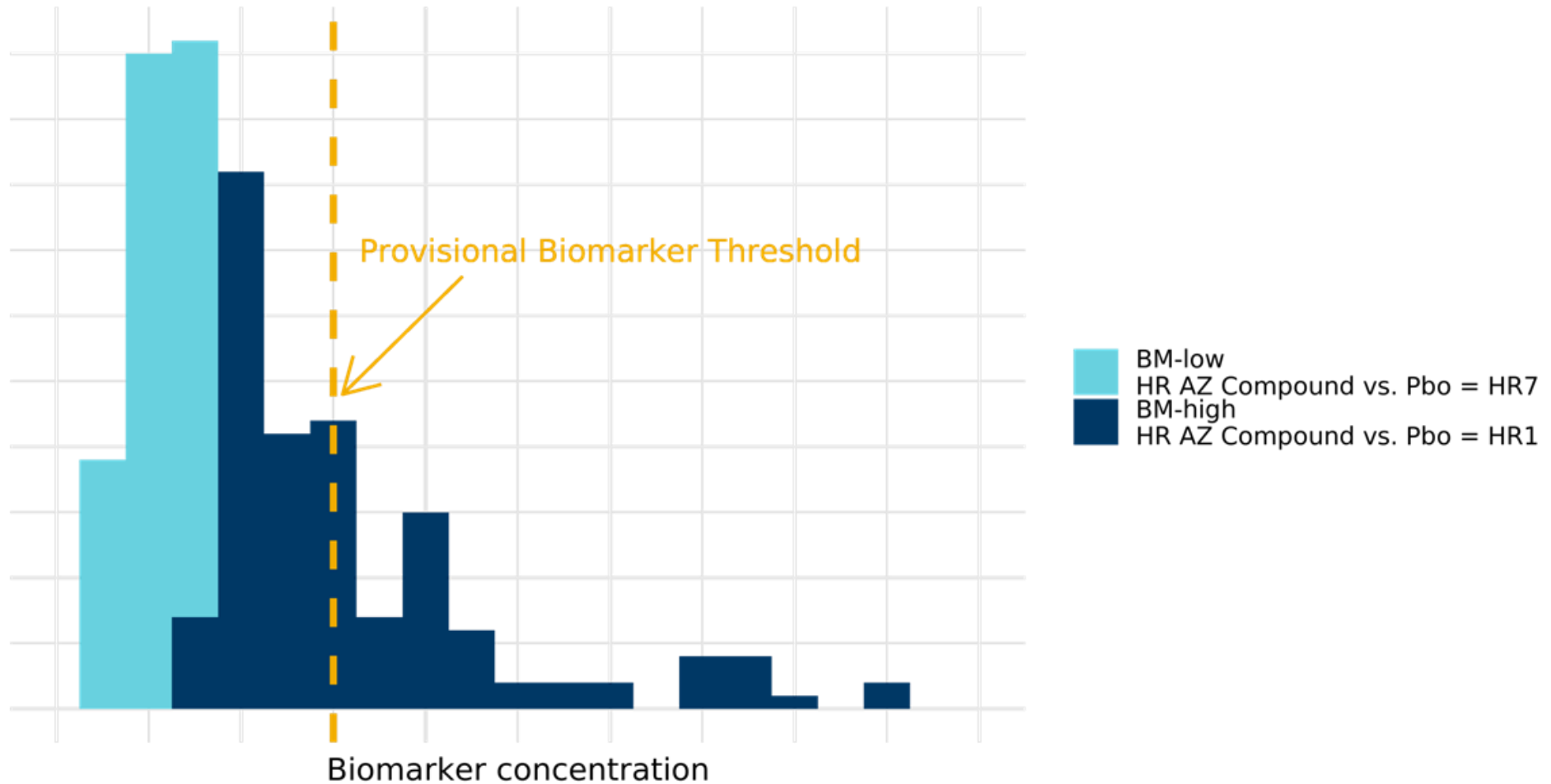
Simulating what the reality could look like



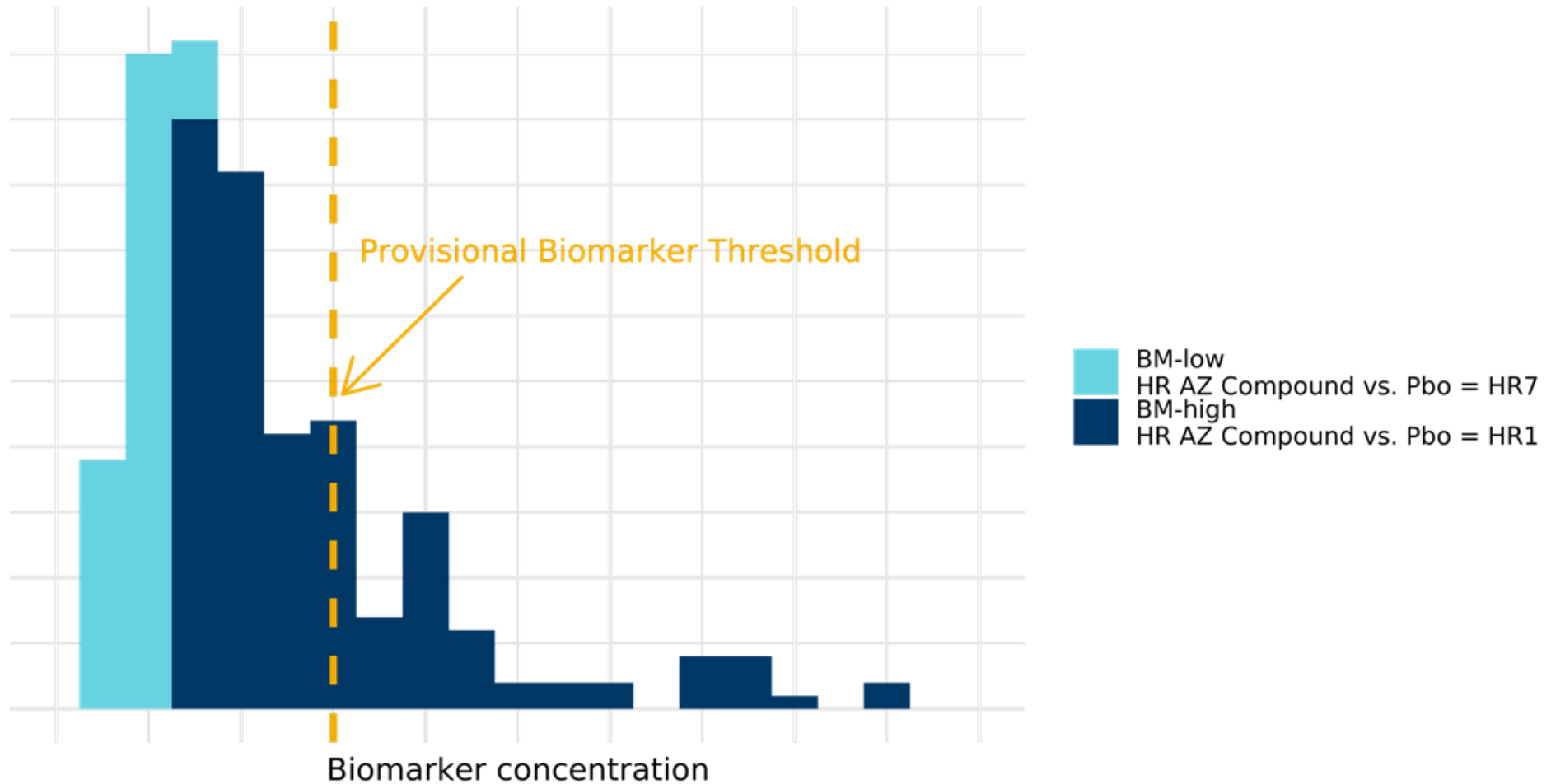
Simulating what the reality could look like



Simulating what the reality could look like



Simulating what the reality could look like



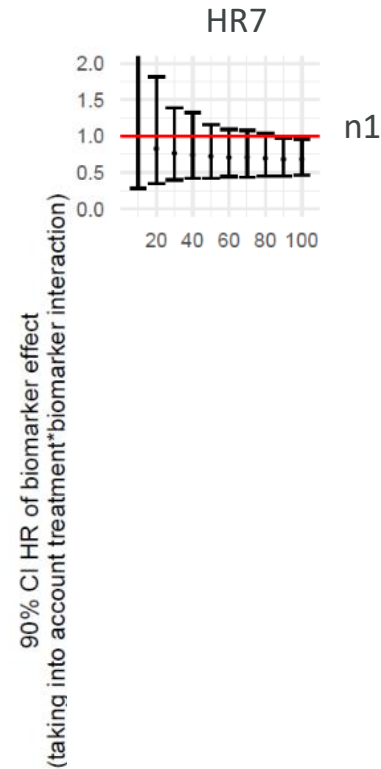
Let's add some biomarker-low patients, but how many?

Hazard Ratio BM-high vs. BM-low, taking into account the treatment*biomarker interaction



Let's add some biomarker-low patients, but how many?

Hazard Ratio BM-high vs. BM-low, taking into account the treatment*biomarker interaction

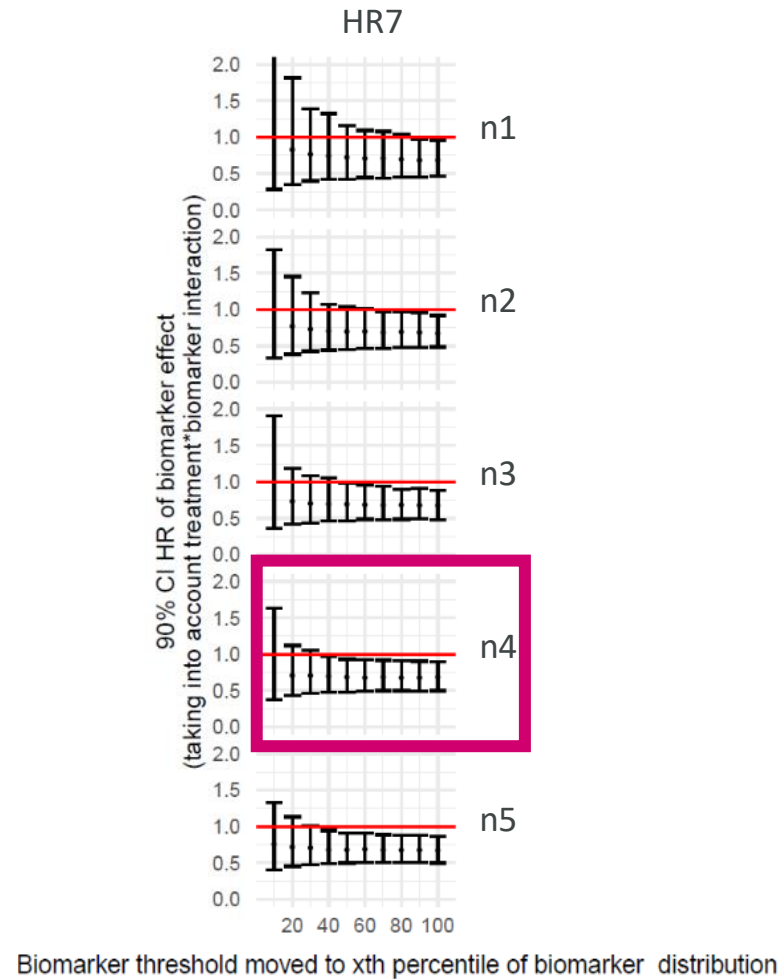


Biomarker threshold moved to xth percentile of biomarker distribution

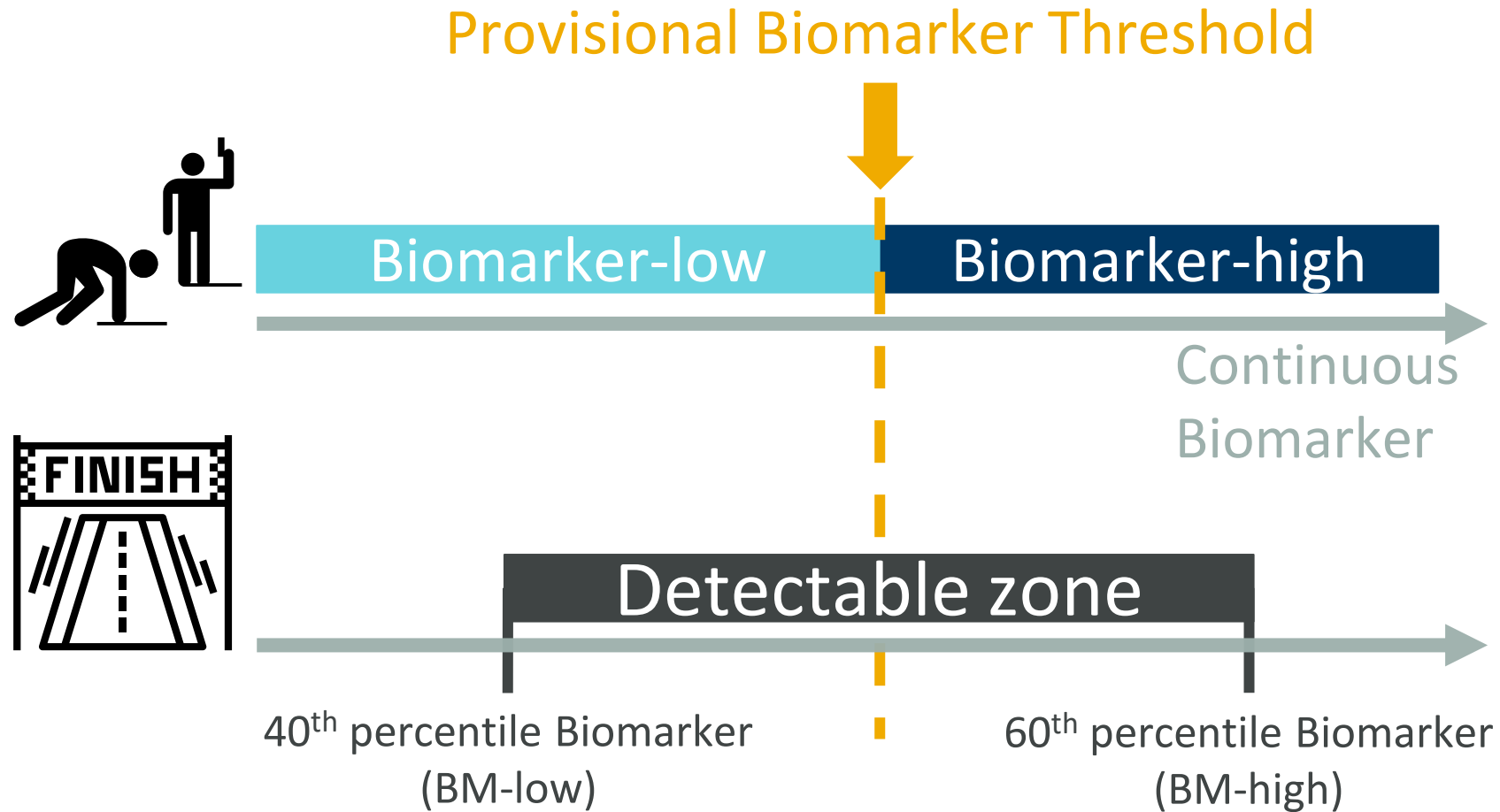


Let's add some biomarker-low patients, but how many?

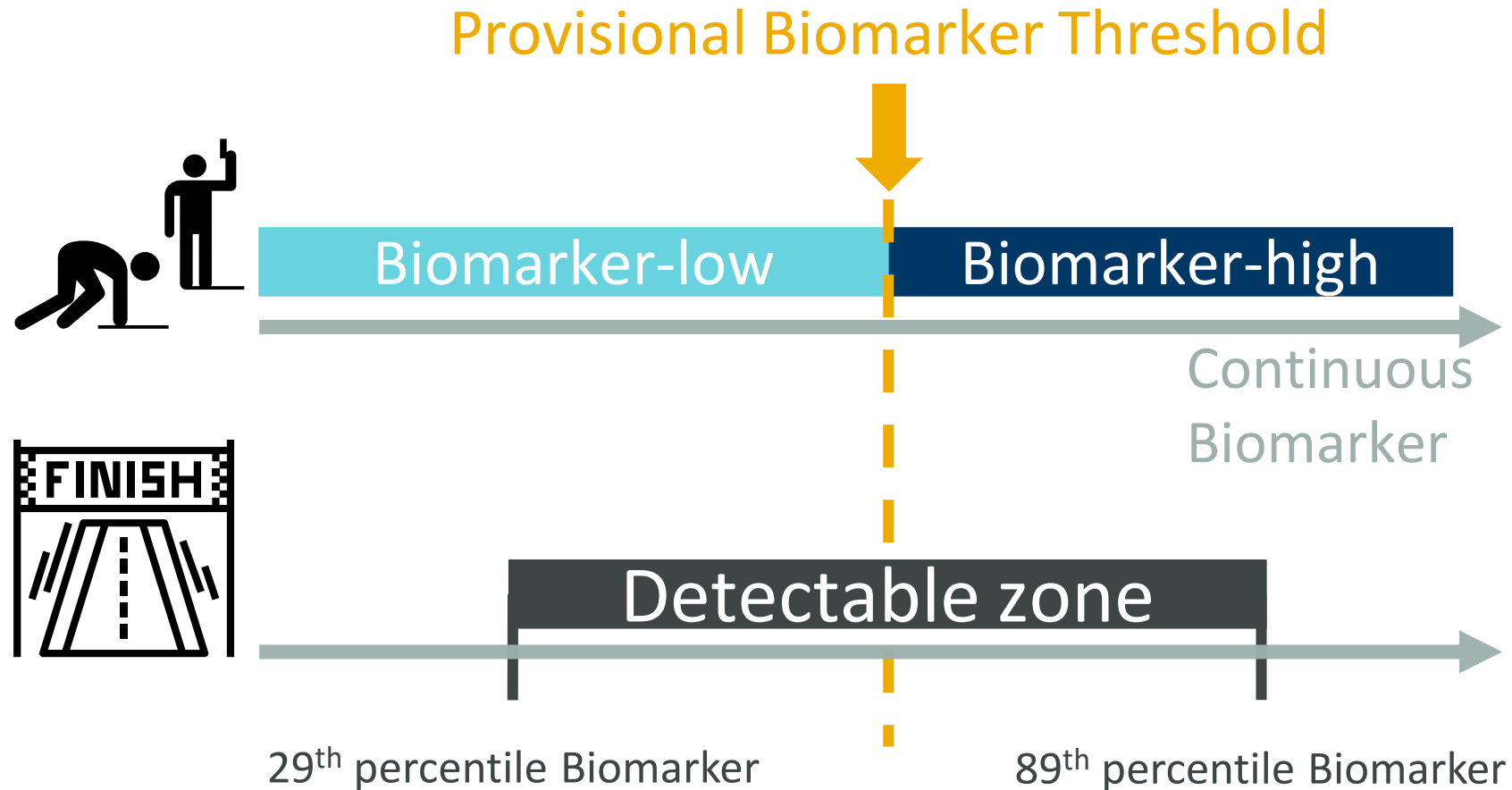
Hazard Ratio BM-high vs. BM-low, taking into account the treatment*biomarker interaction



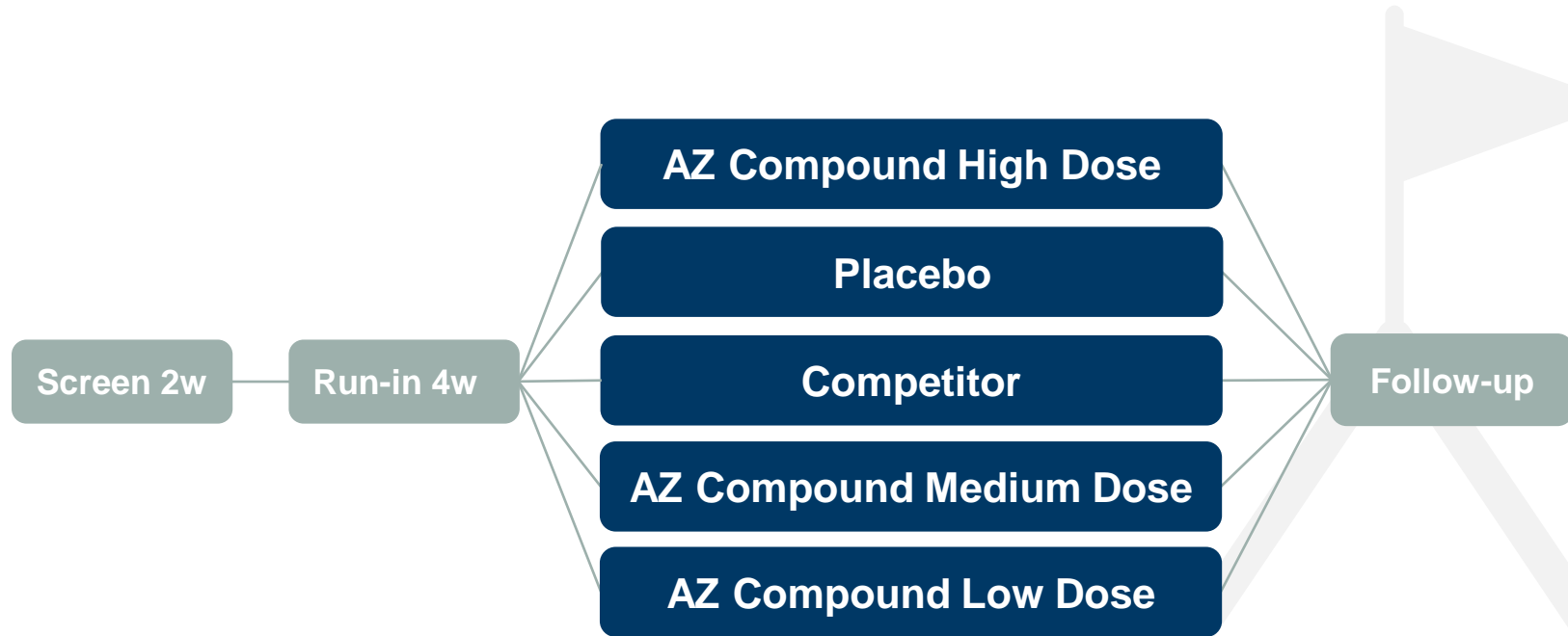
Adding as many BM-low patients as there are BM-high patients to fine-tune the biomarker threshold



Adding as many BM-low patients as there are BM-high patients to fine-tune the biomarker threshold



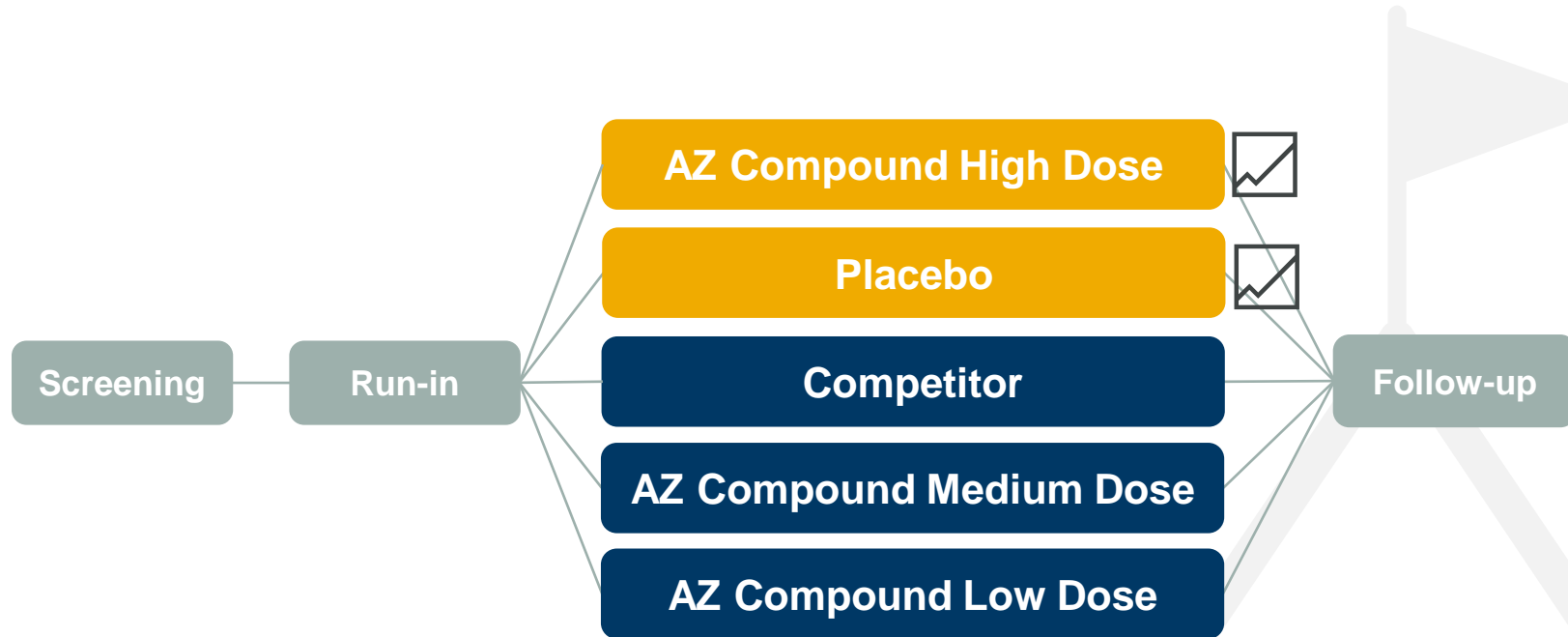
The PhIIb, without the biomarker-low patients



BM-high patients only



With biomarker-low patients, that's a quite large PhIIb!

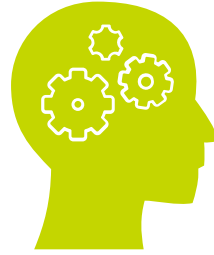


BM-high patients only

BM-high & BM-low patients



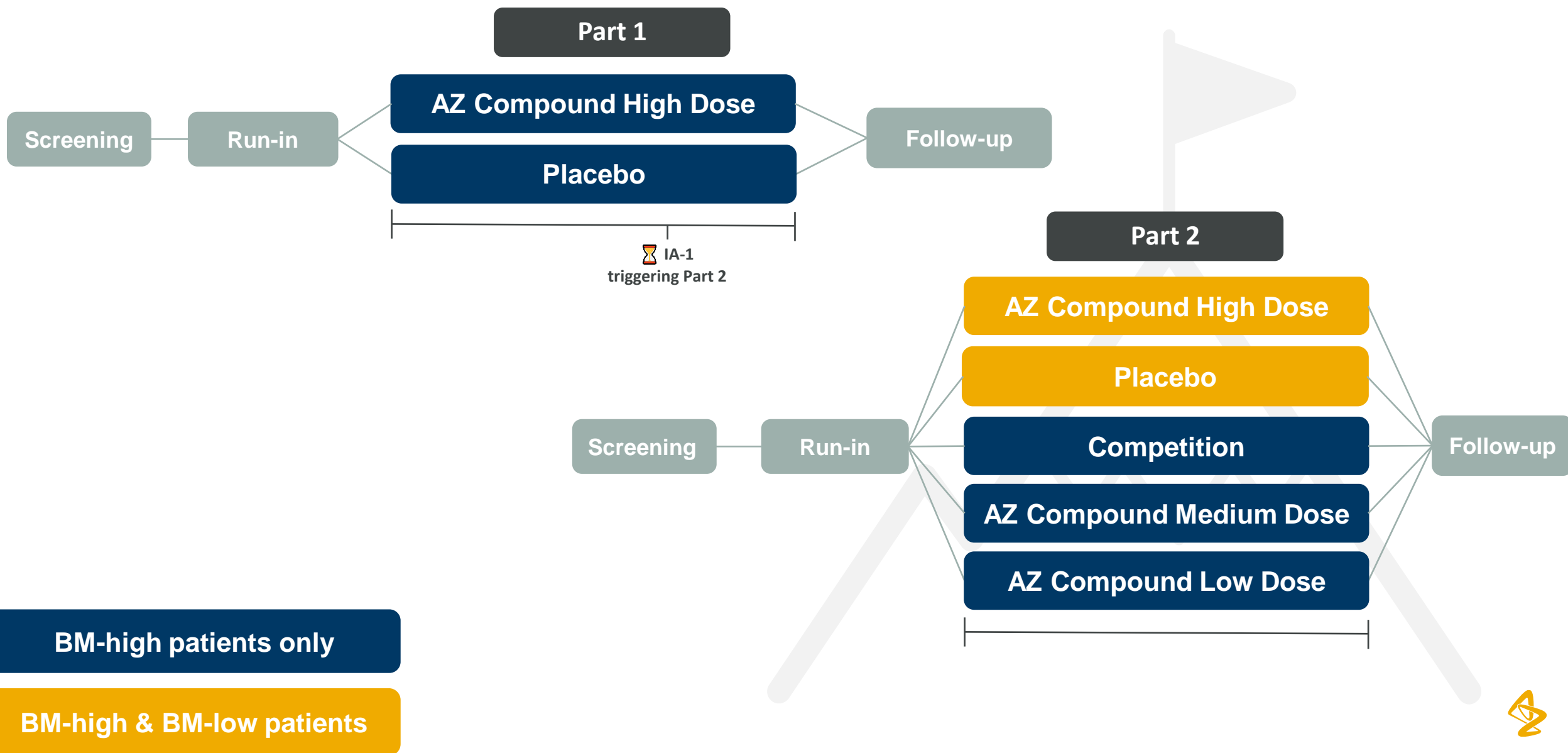
That's a very big upfront investment for a PhII!



You Should Be Entrepreneurial



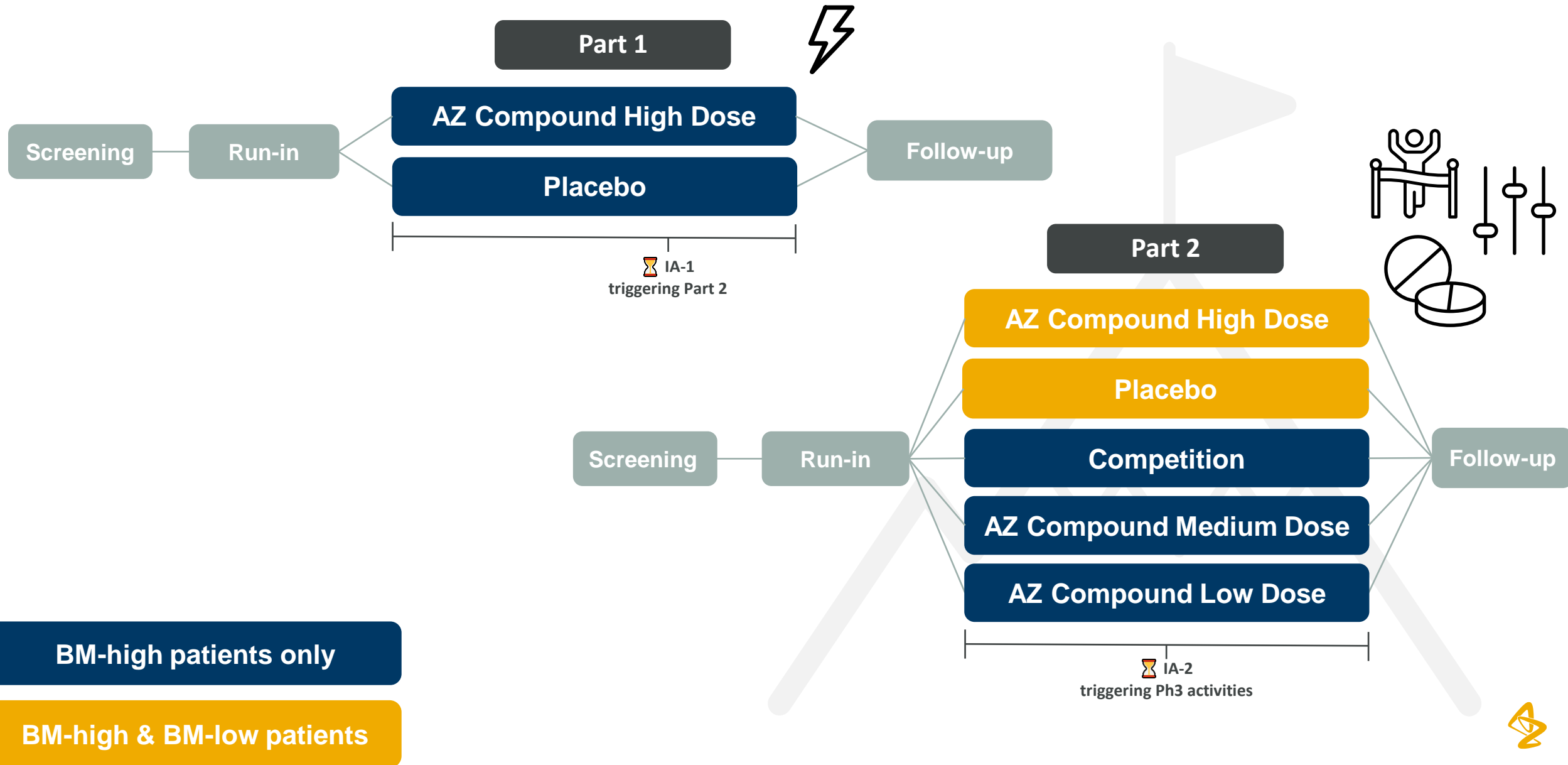
Ok, let's go for a seamless PhII with one interim then!



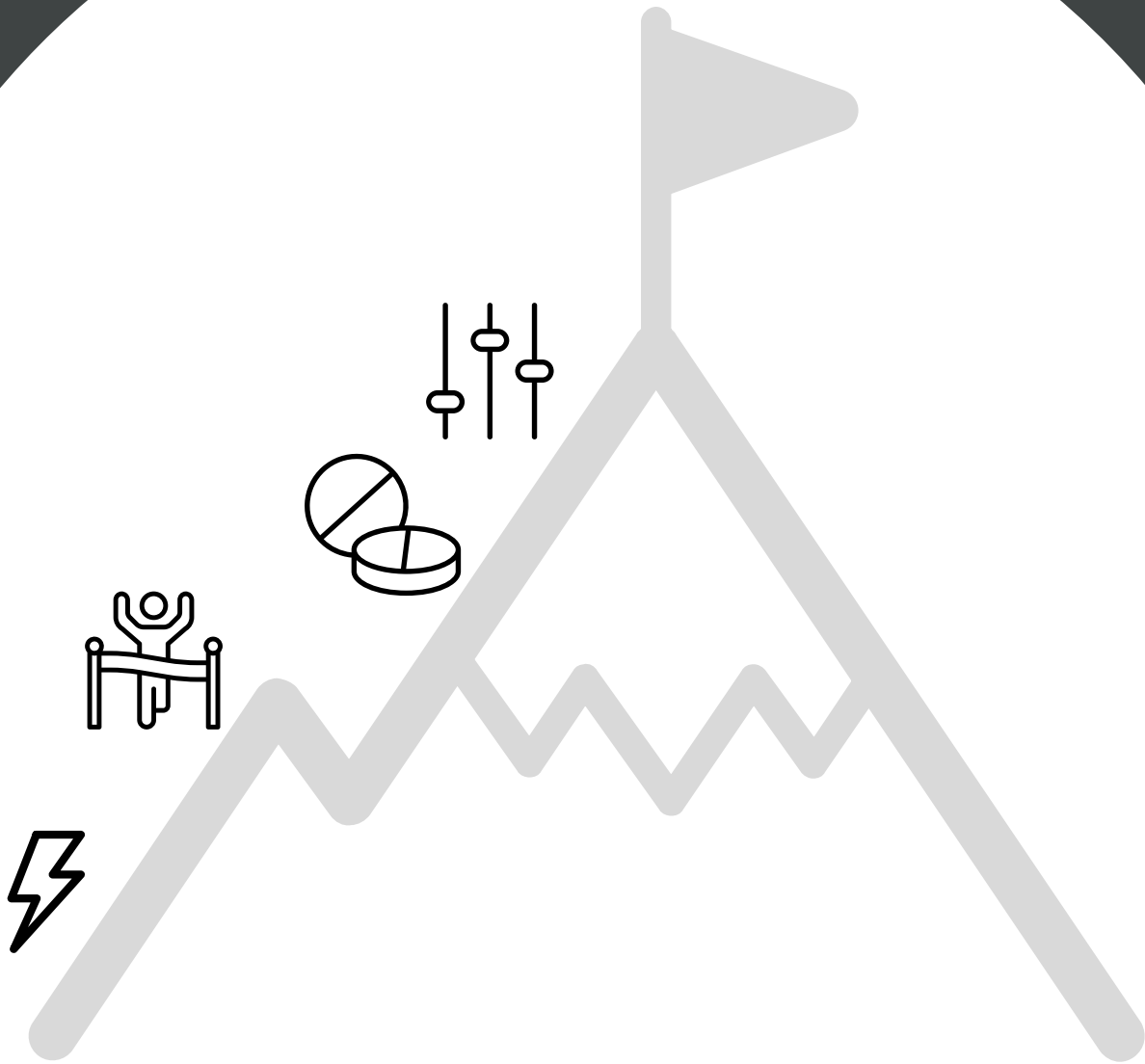
Can you not be a bit more entrepreneurial? 🤔



Let's go for a seamless PhII with 2 interim analyses!







Thank you.

Confidentiality Notice

This file is private and may contain confidential and proprietary information. If you have received this file in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this file is not permitted and may be unlawful. AstraZeneca PLC, 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA, UK, T: +44(0)203 749 5000, www.astrazeneca.com

