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

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A summit attempt with 1 key question

Compound efficacious?

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

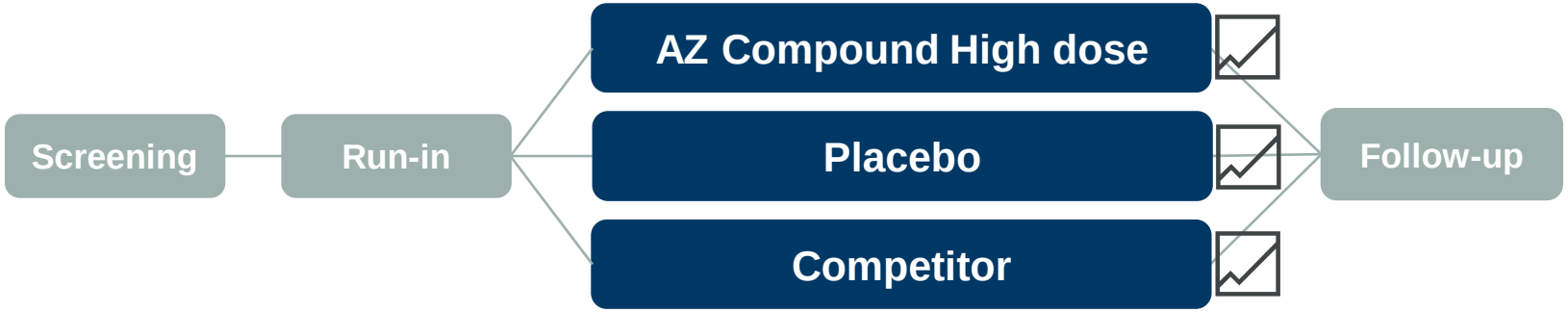
You Should *Play To Win*

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!



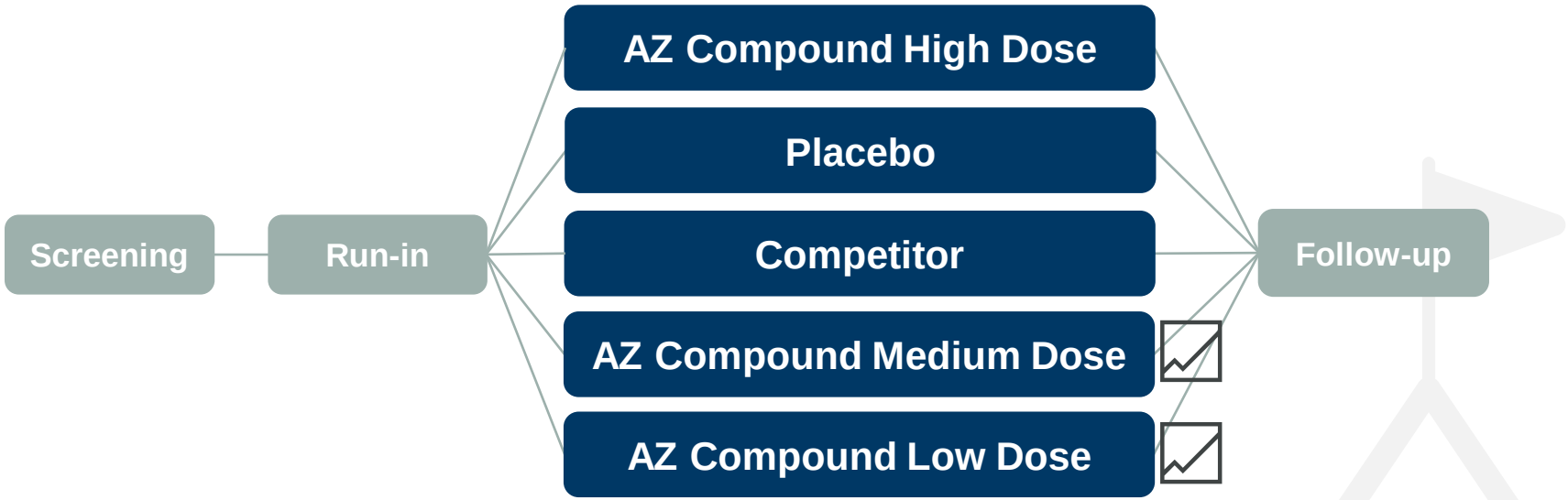
A summit attempt with 3 key questions

Right dose?

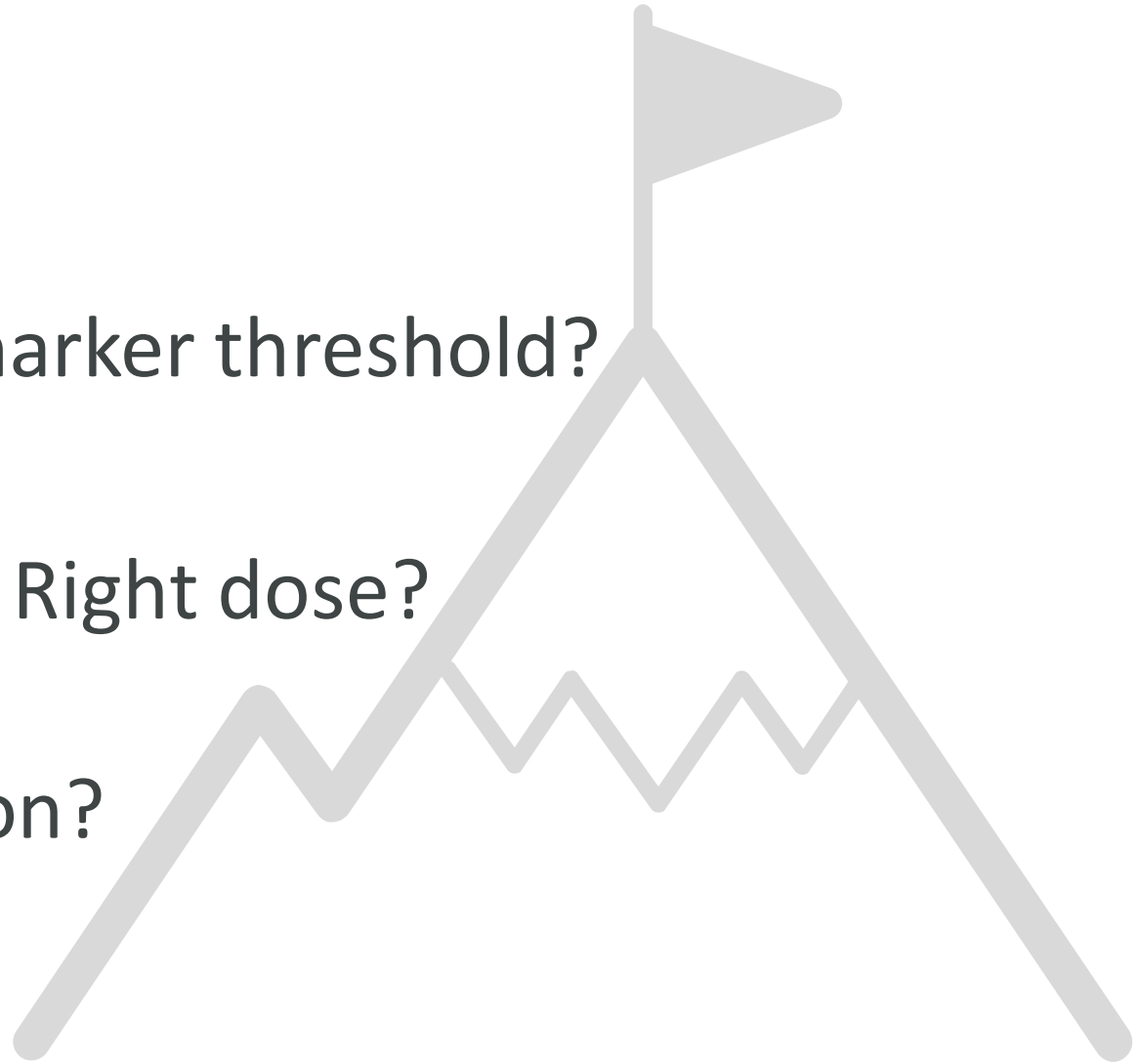
Superior to the competition?

Compound efficacious?

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



A summit attempt with 4 key questions



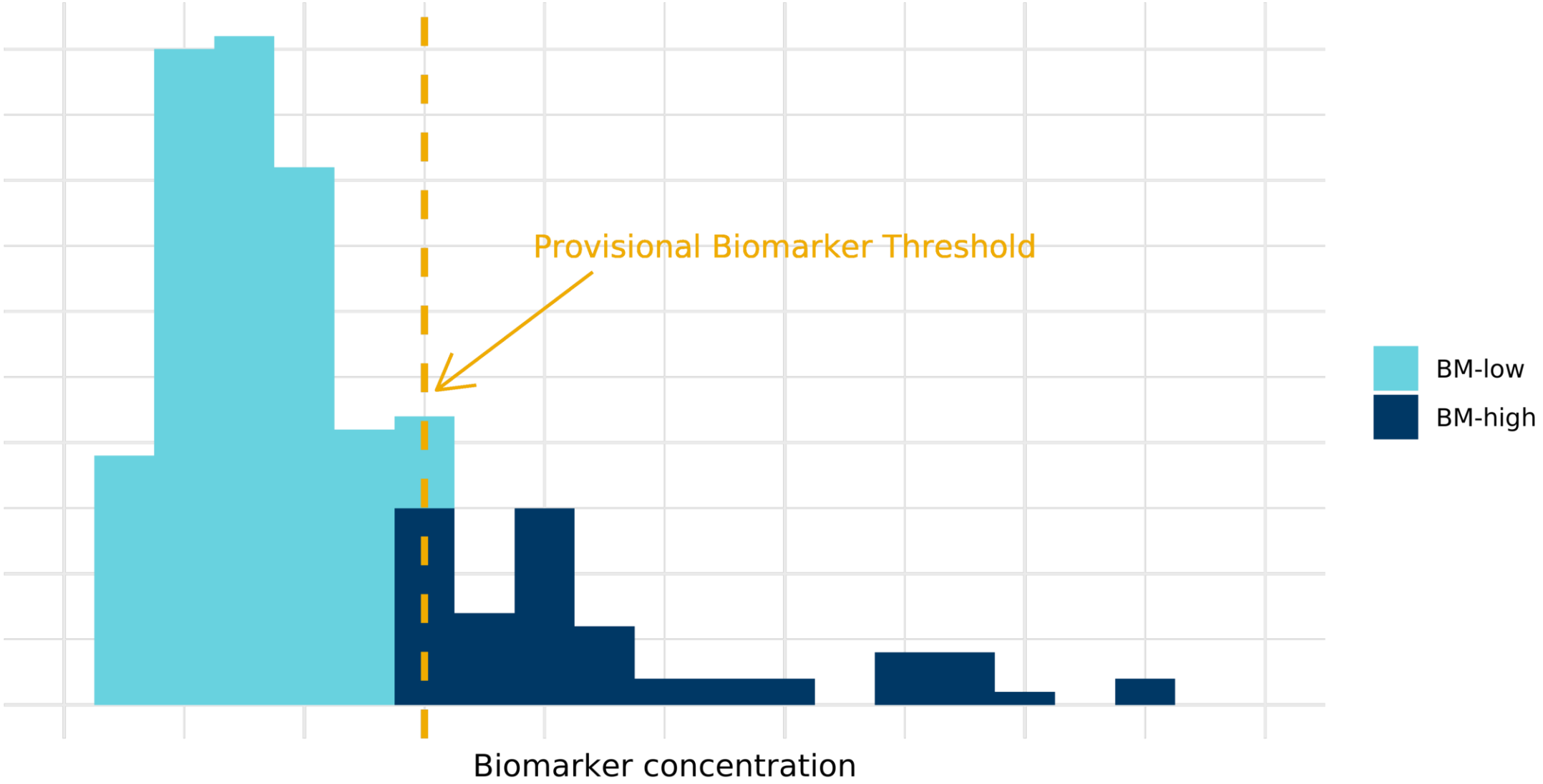
Biomarker threshold?

Right dose?

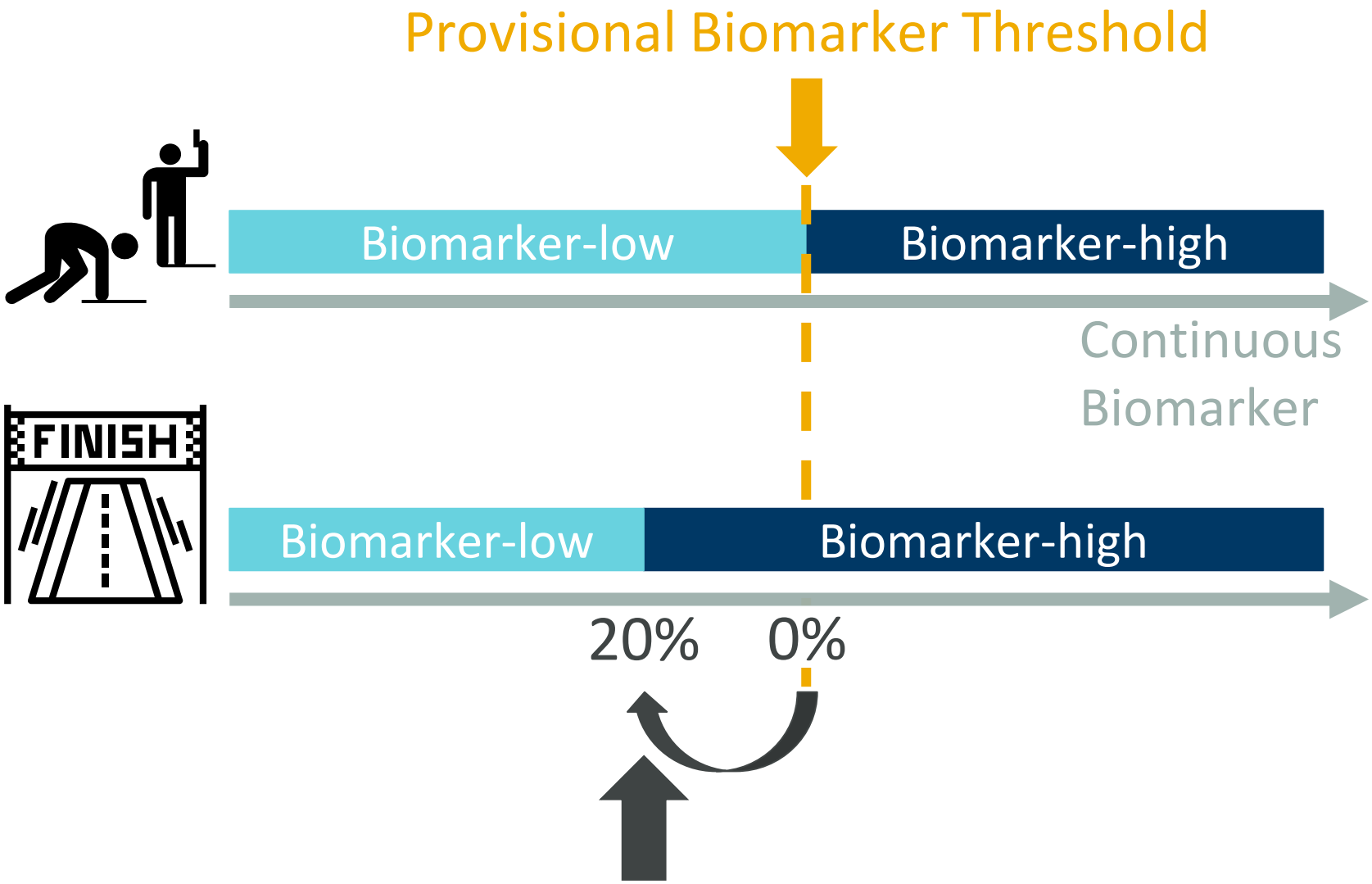
Superior to the competition?

Compound efficacious?

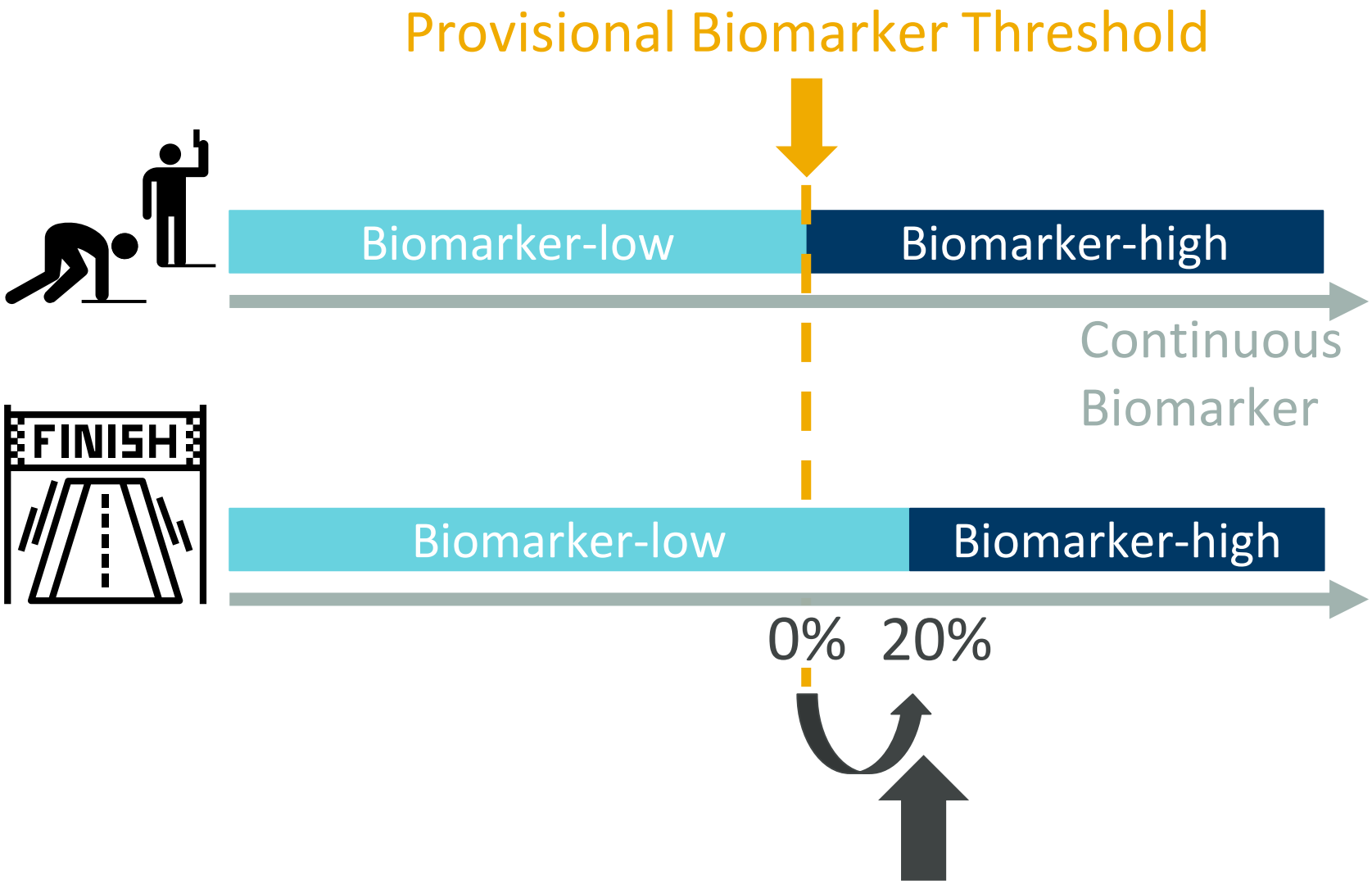
Provisional biomarker threshold defined with real-world data



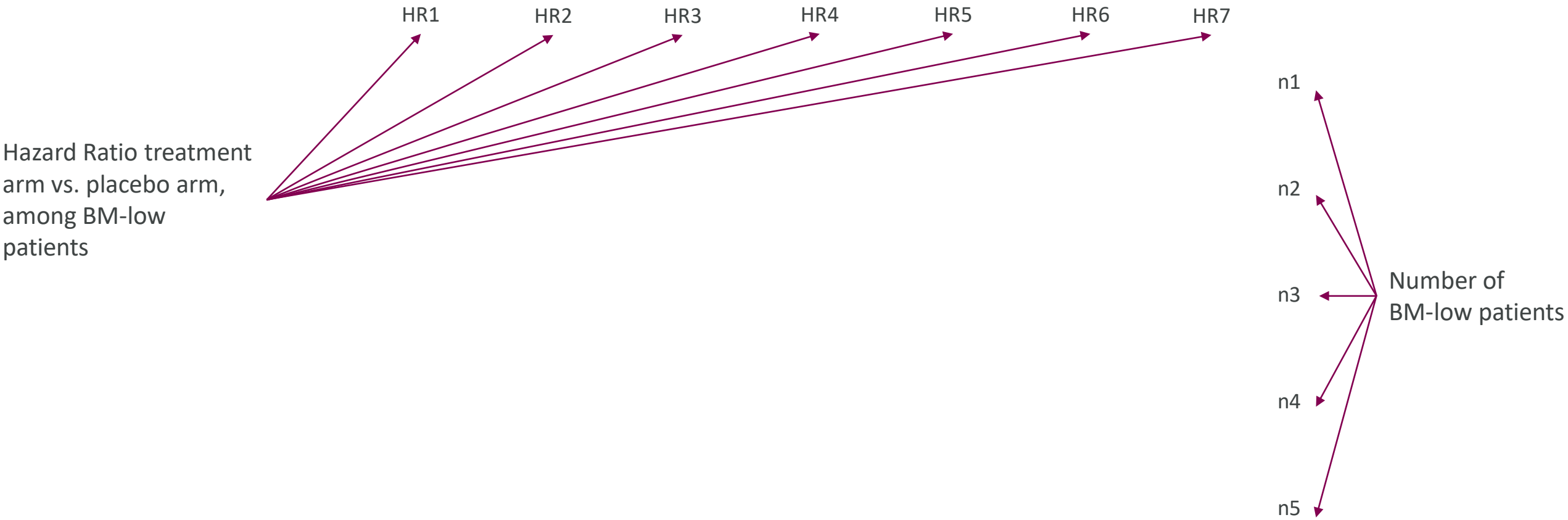
Biomarker threshold refinement, moving it lower



Biomarker threshold refinement, moving it higher



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



Hazard Ratio, in short

Hazard Ratio (treatment vs. placebo)

$$\approx$$

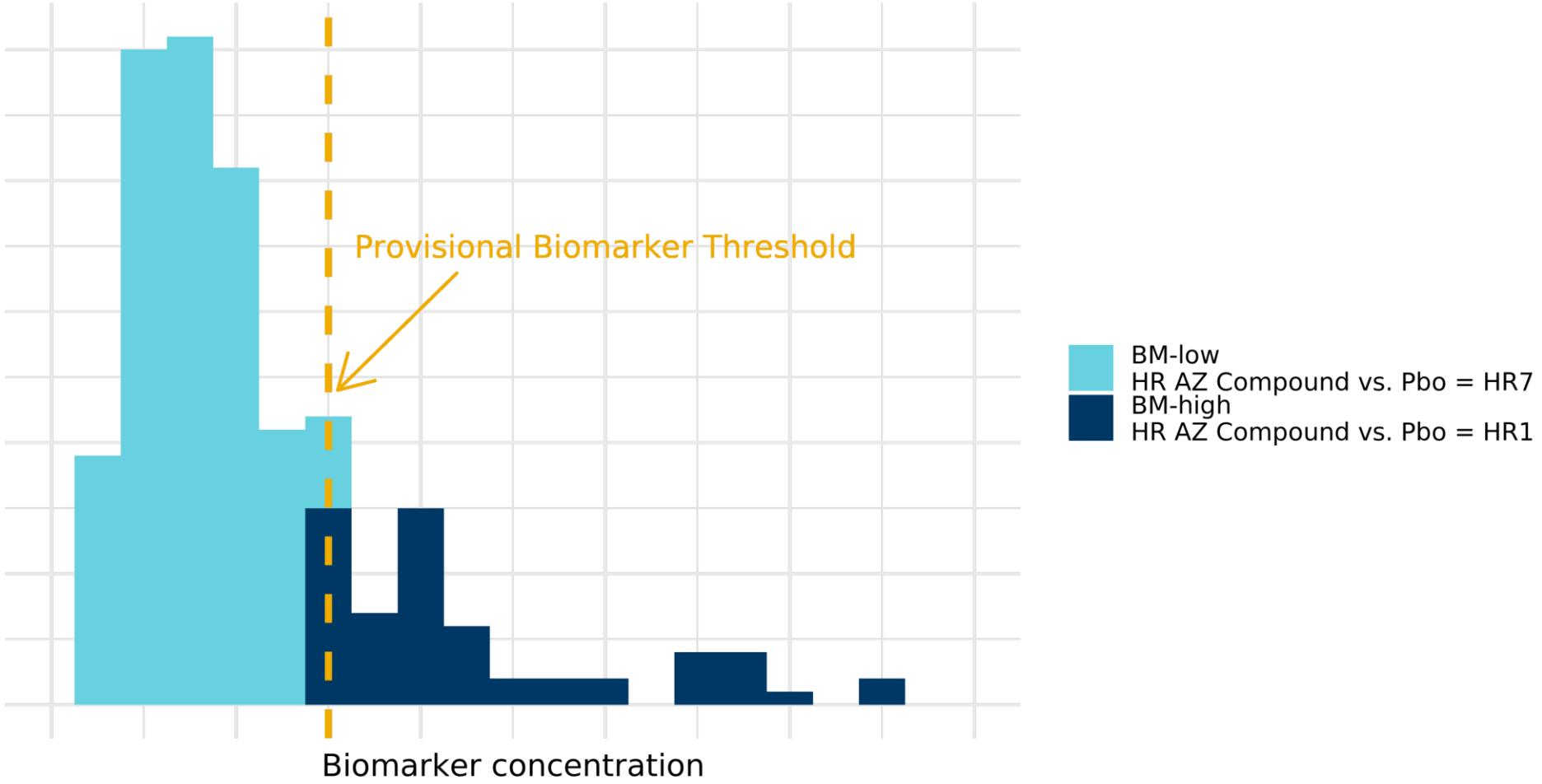
$$\frac{chance\ of\ an\ event\ occuring\ in\ treatment\ arm}{chance\ of\ event\ occuring\ in\ placebo\ arm}$$

$$HR \in [0\ ;\ +\infty[$$

HR < 1: treatment is beneficial

HR > 1: treatment is deleterious

Simulating what the reality could look like



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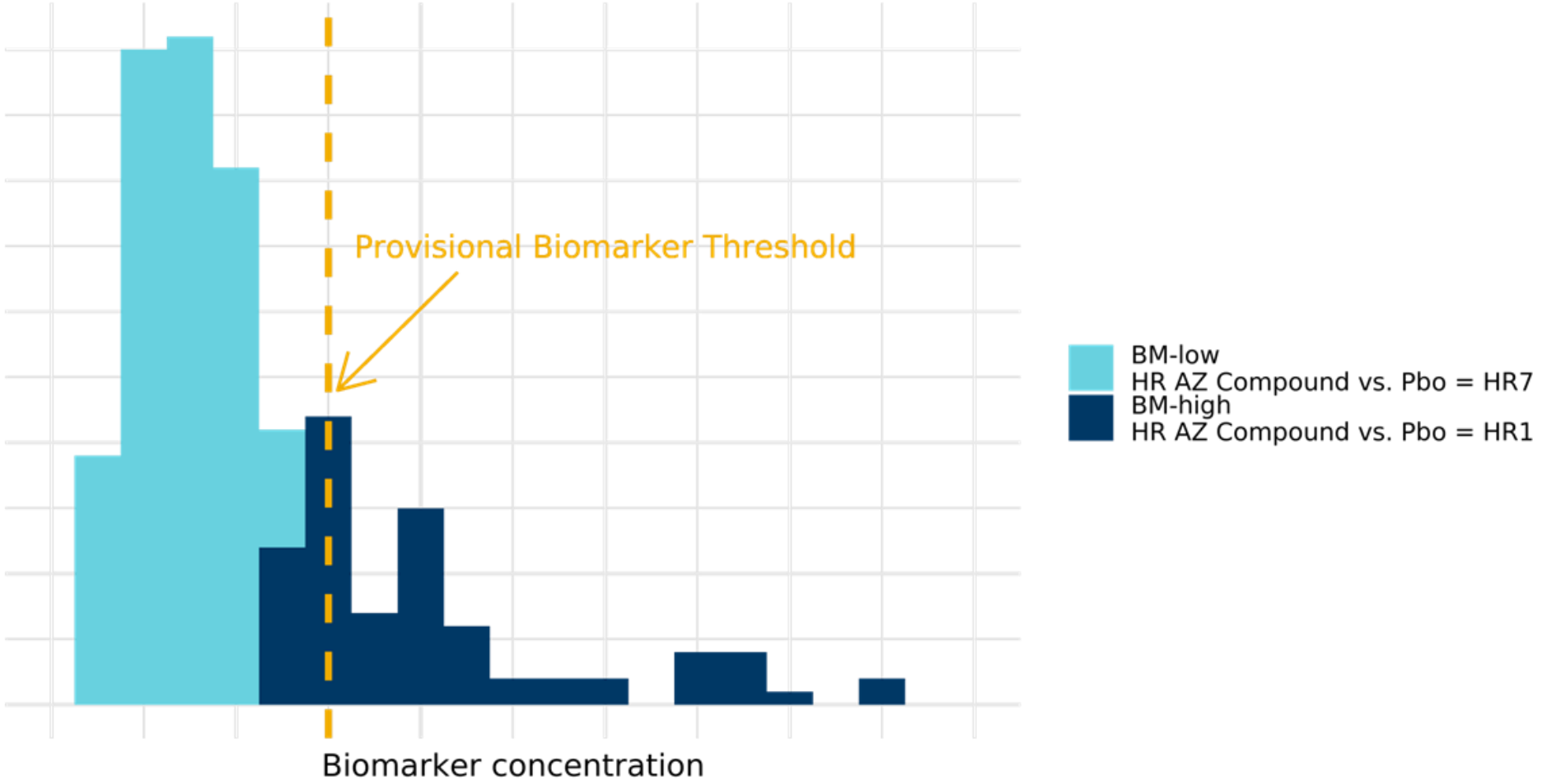

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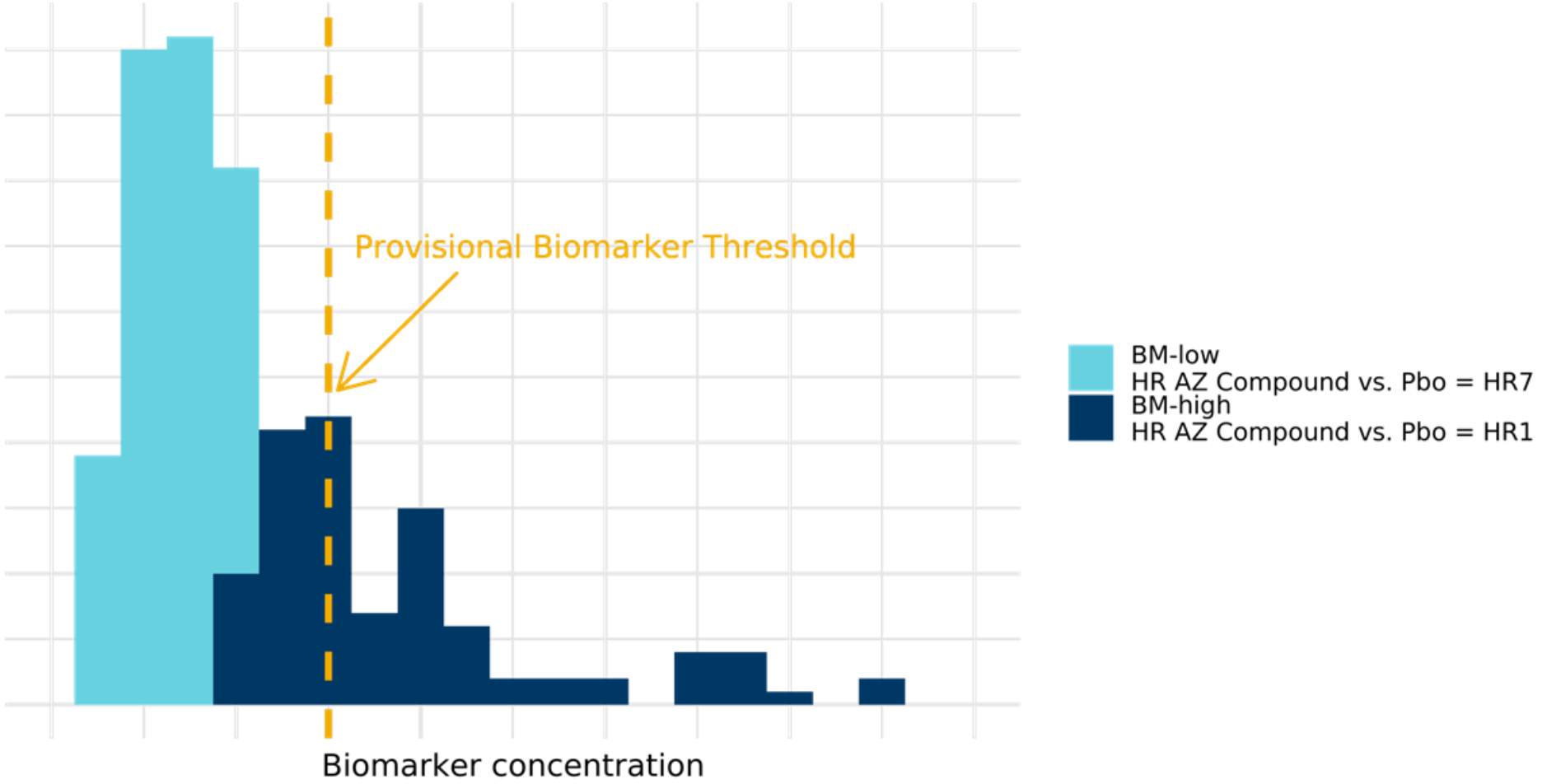

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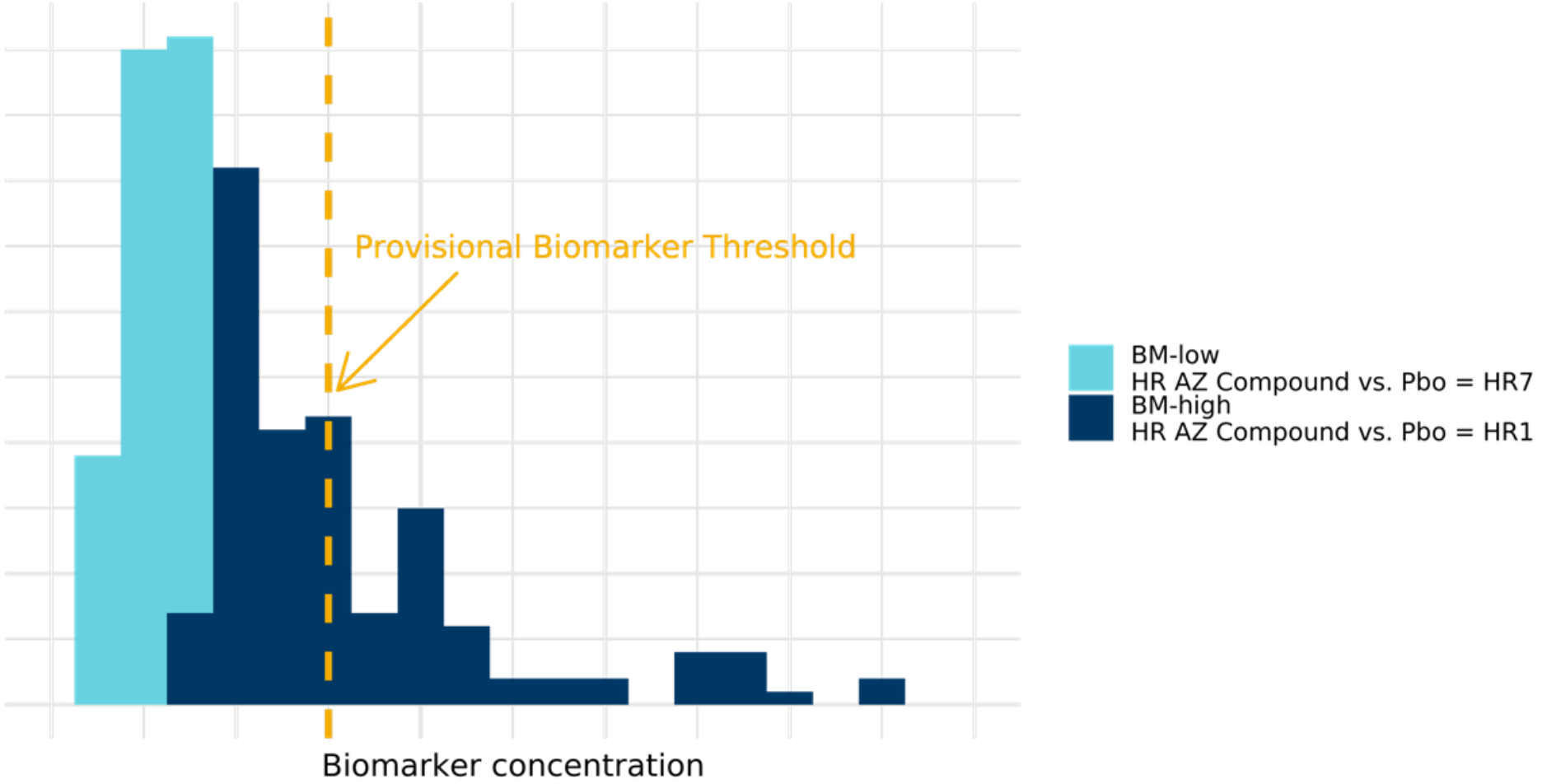

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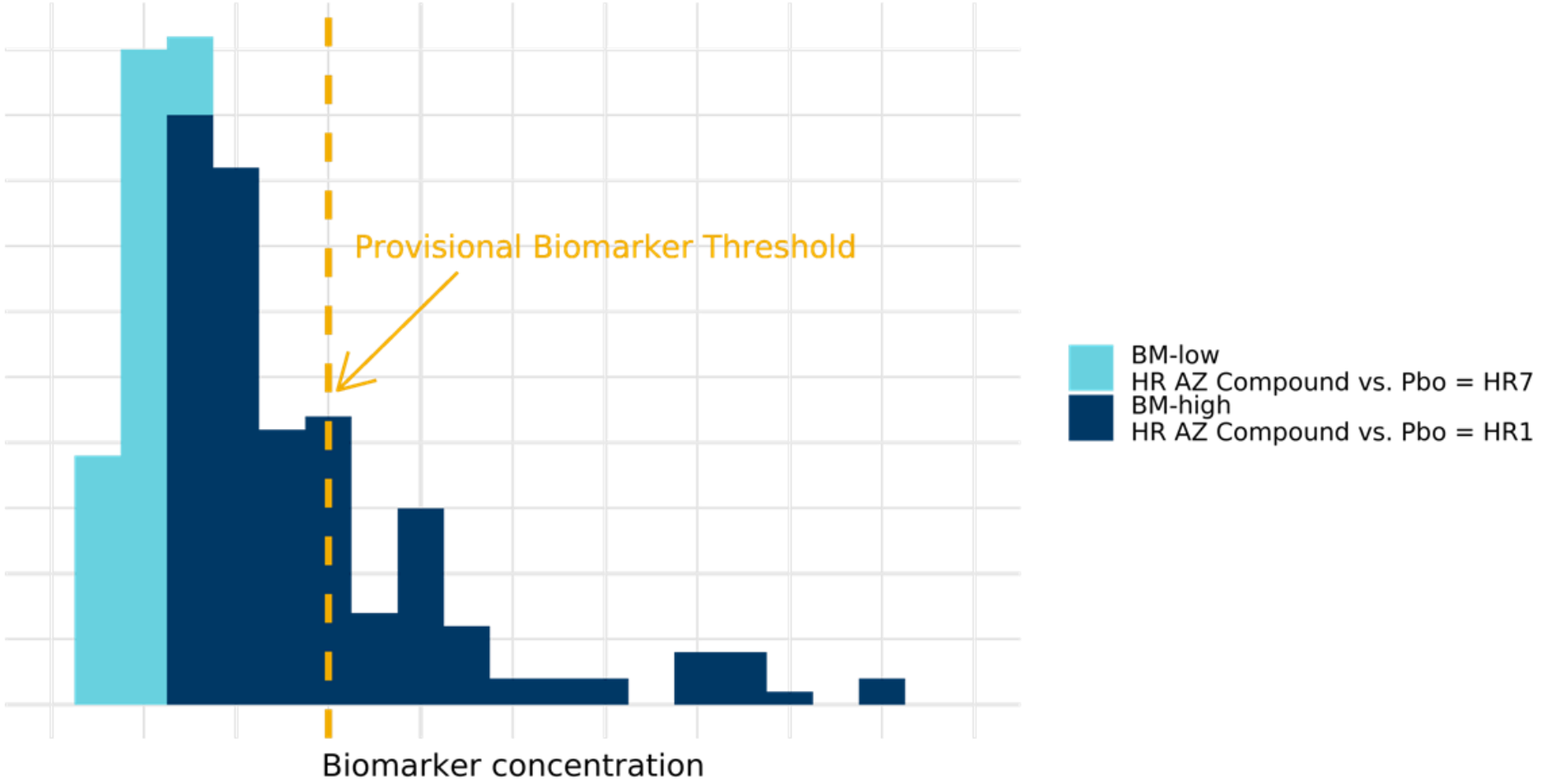

Let’s add some biomarker-low patients, but how many?

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

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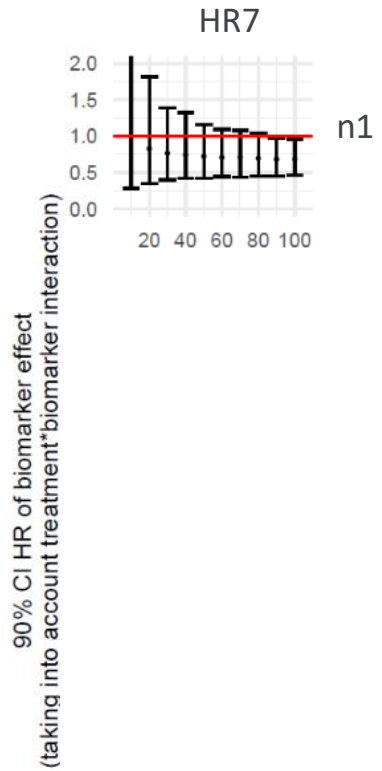

1,000 simulations ; n1 < n2 < n3 < n4 < n5

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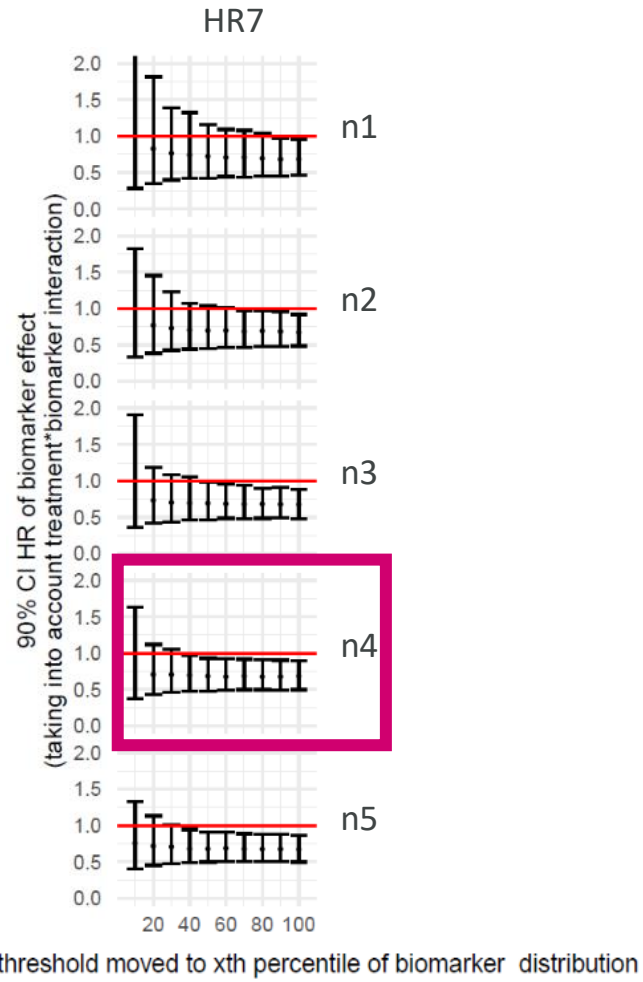
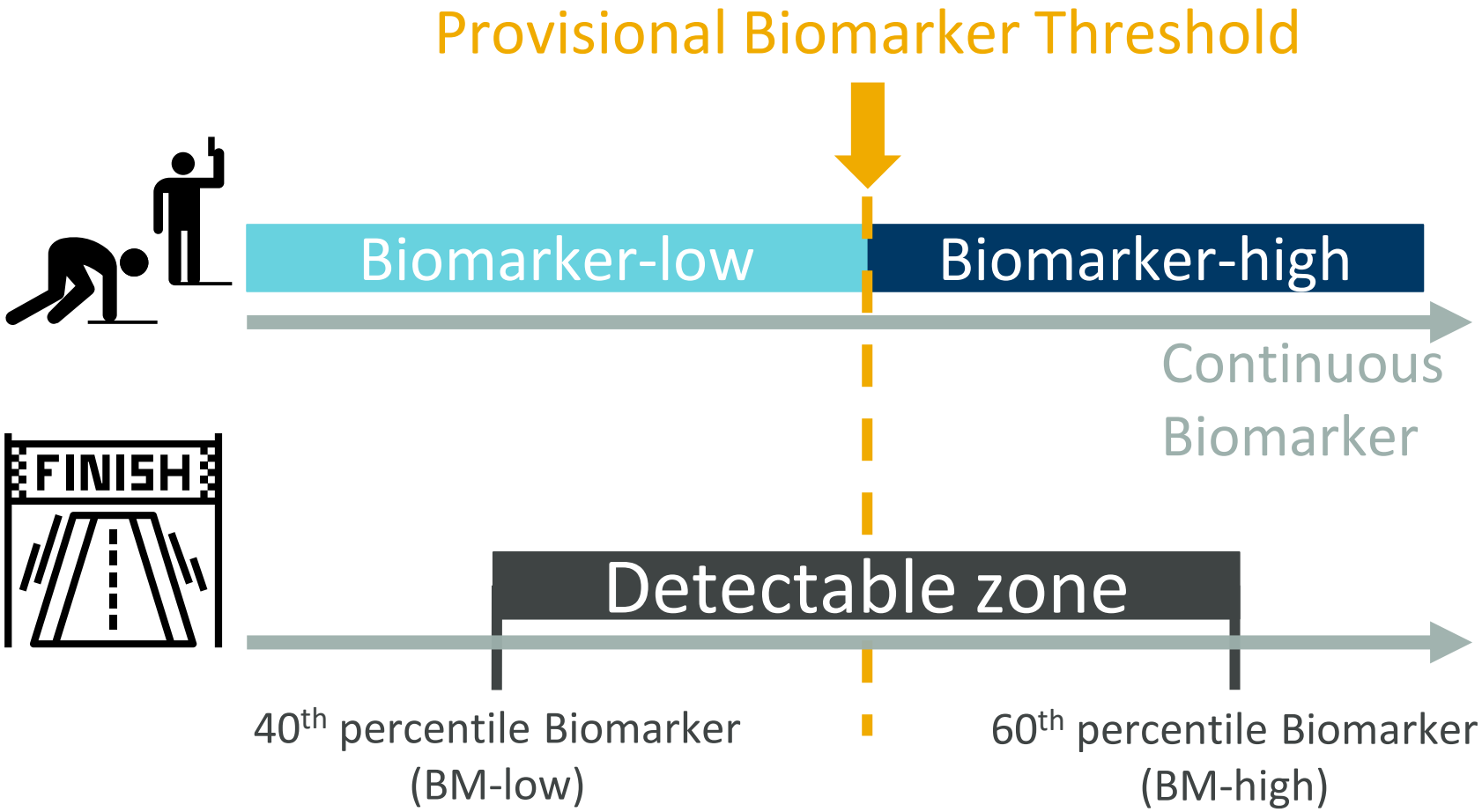
Hazard Ratio BM-high vs. BM-low, taking into account the treatment*biomarker interaction



1,000 simulations ; n1 < n2 < n3 < n4 < n5

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



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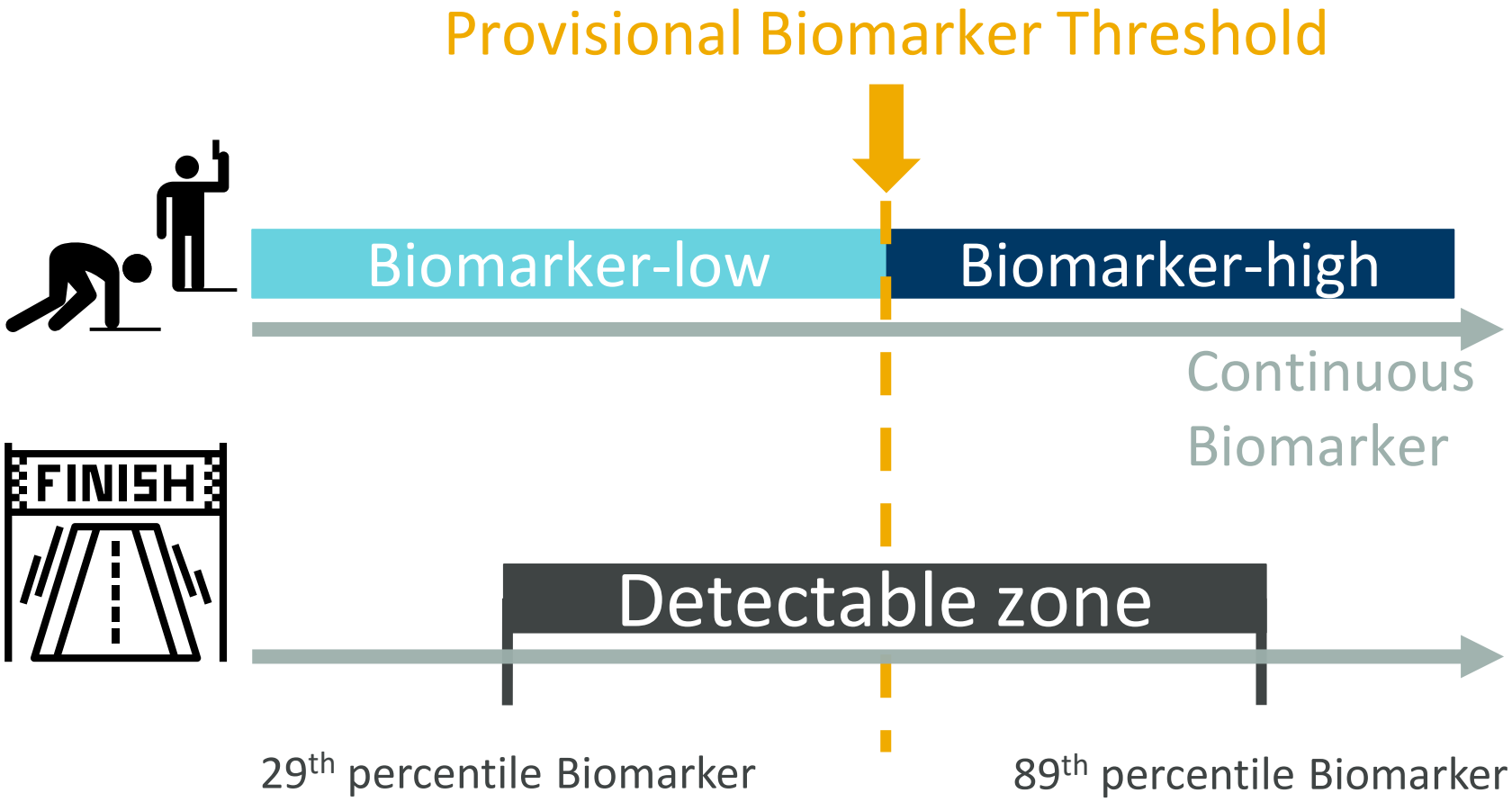
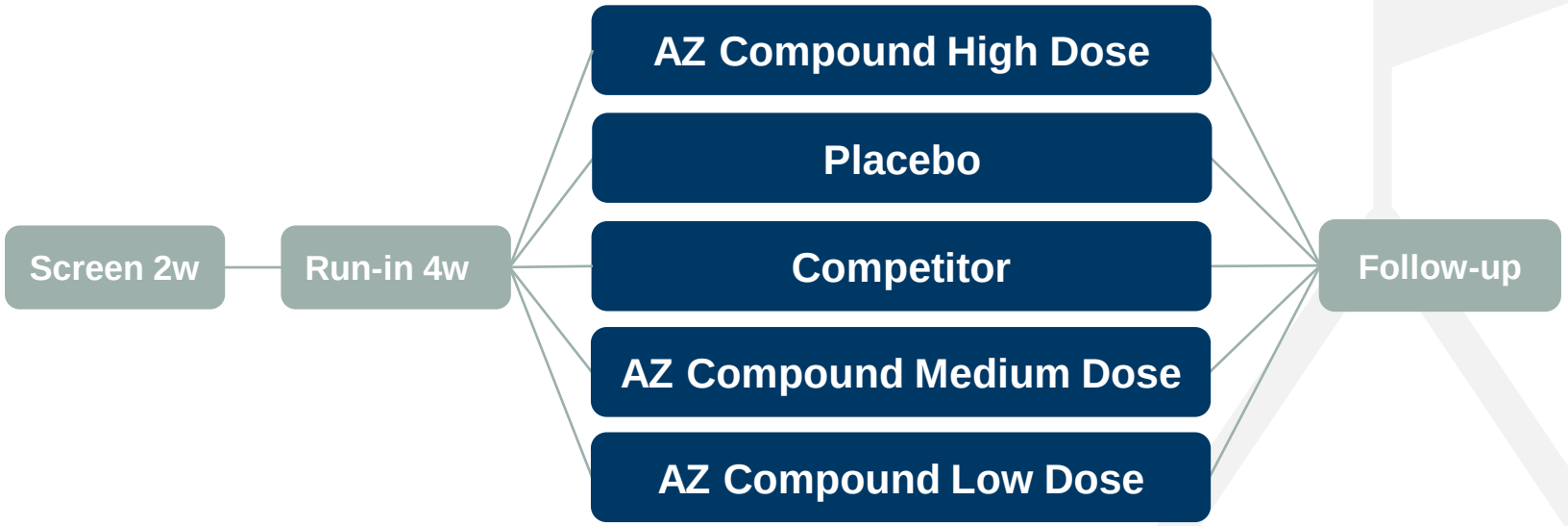
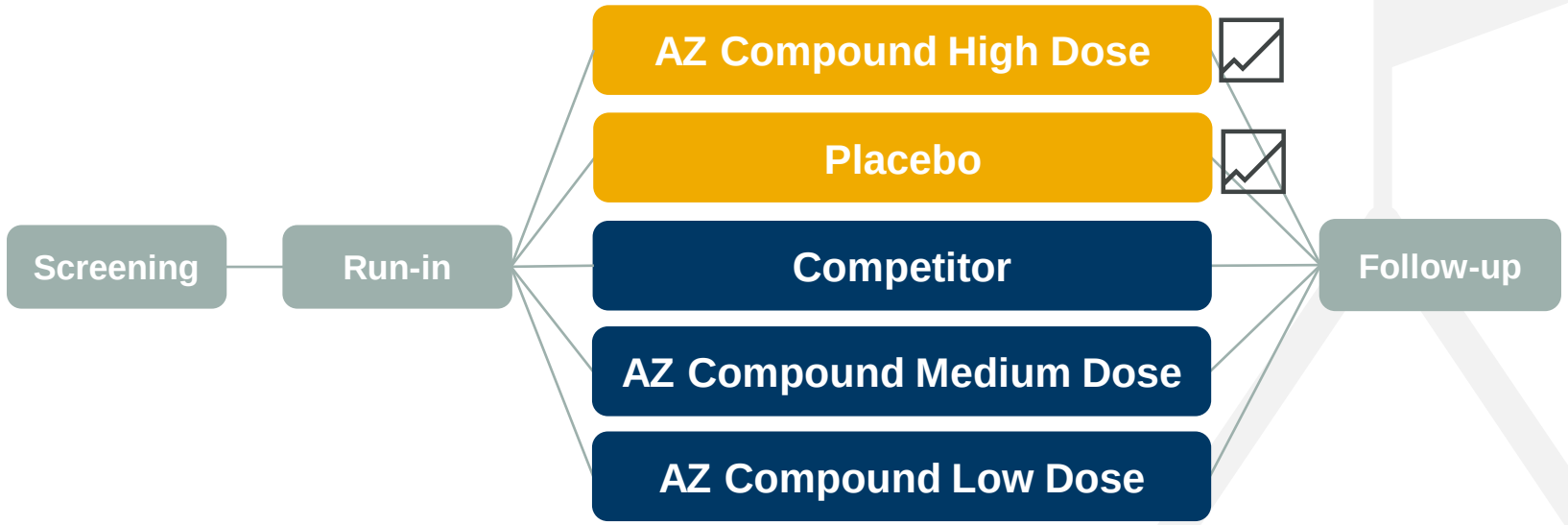


The PhIIb, without the biomarker-low patients



BM-high patients only

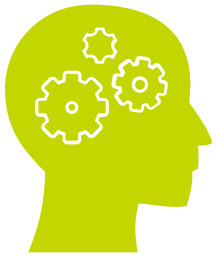
With biomarker-low patients, that's a quite large PhIIb!



BM-high patients only

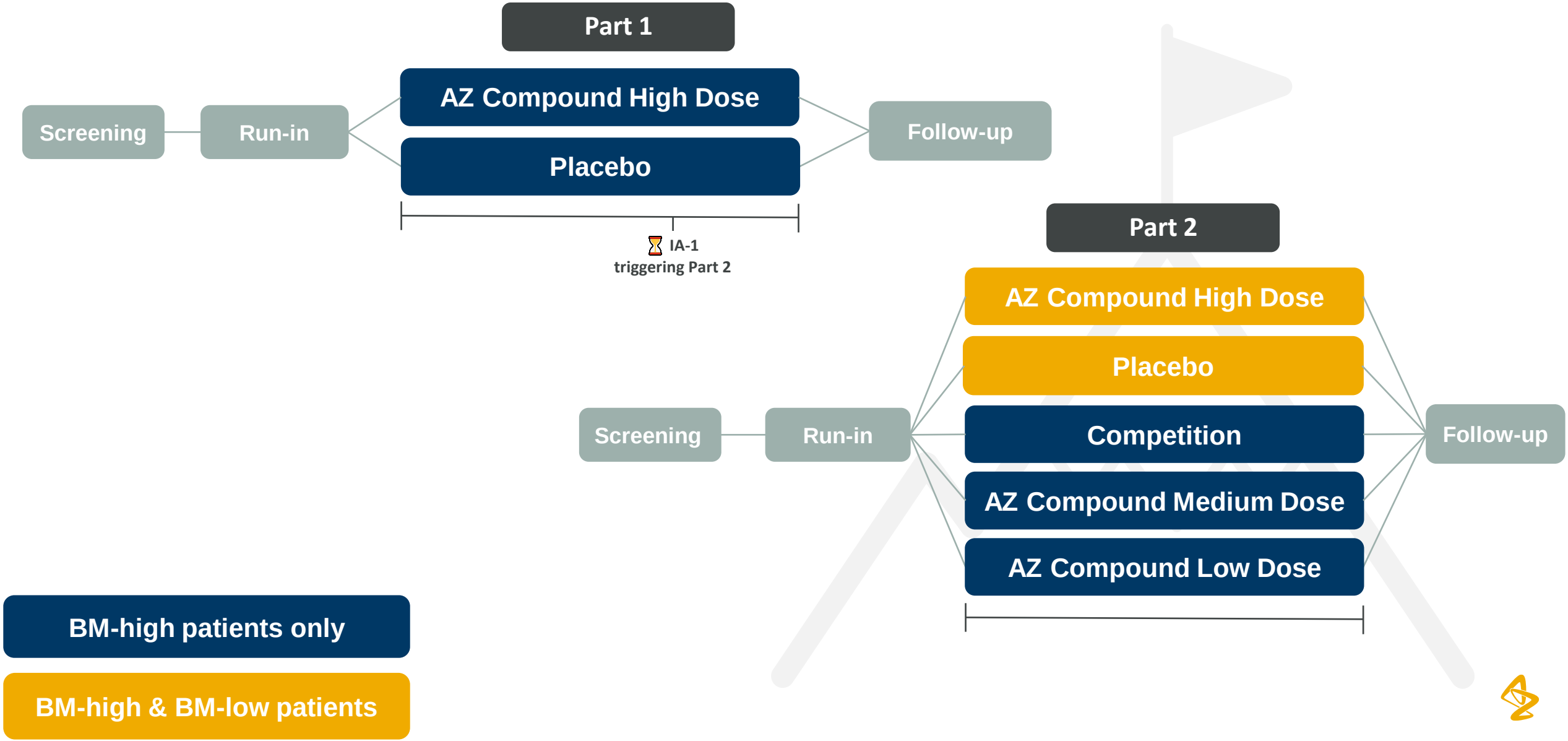
BM-high & BM-low patients

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



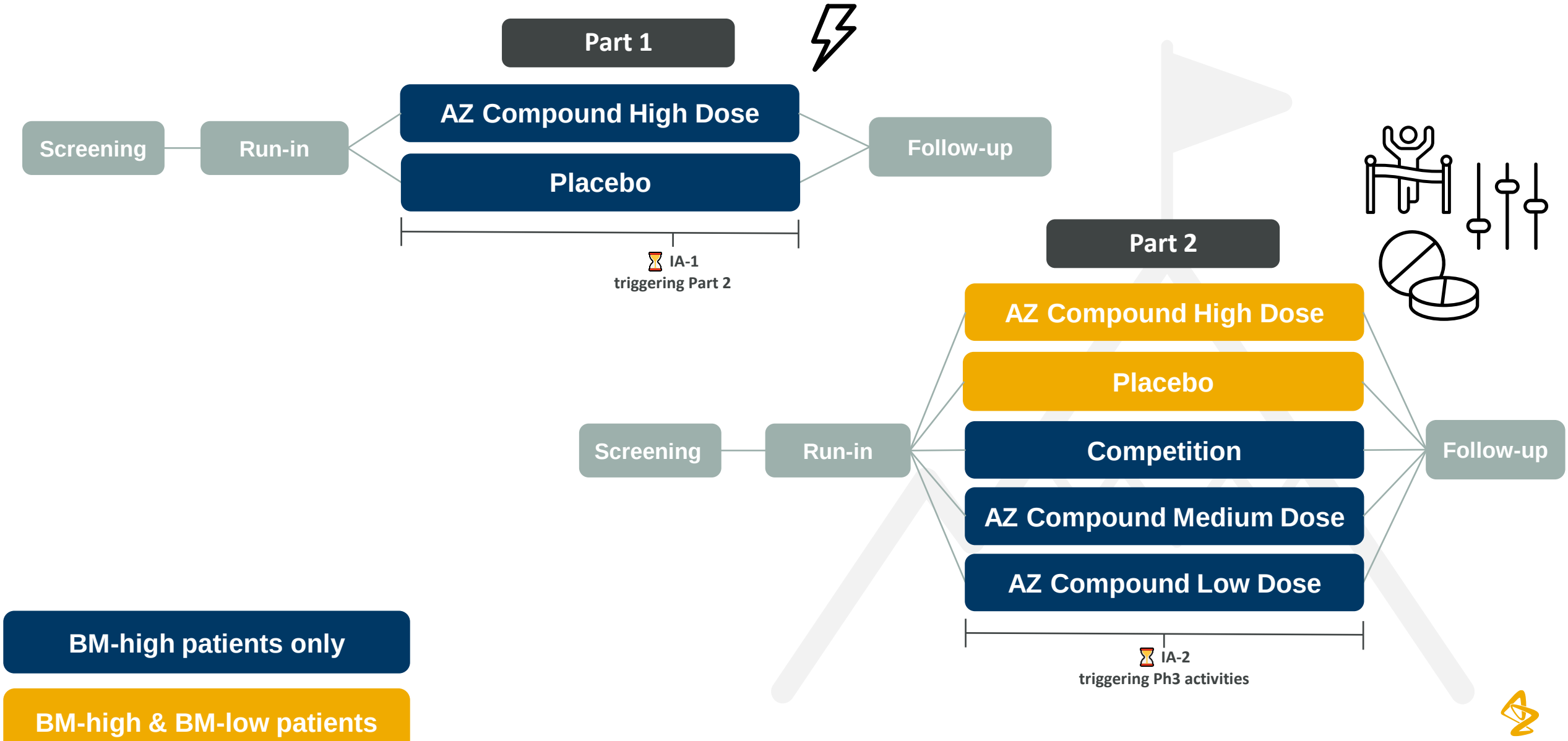
You Should Be Entrepreneurial

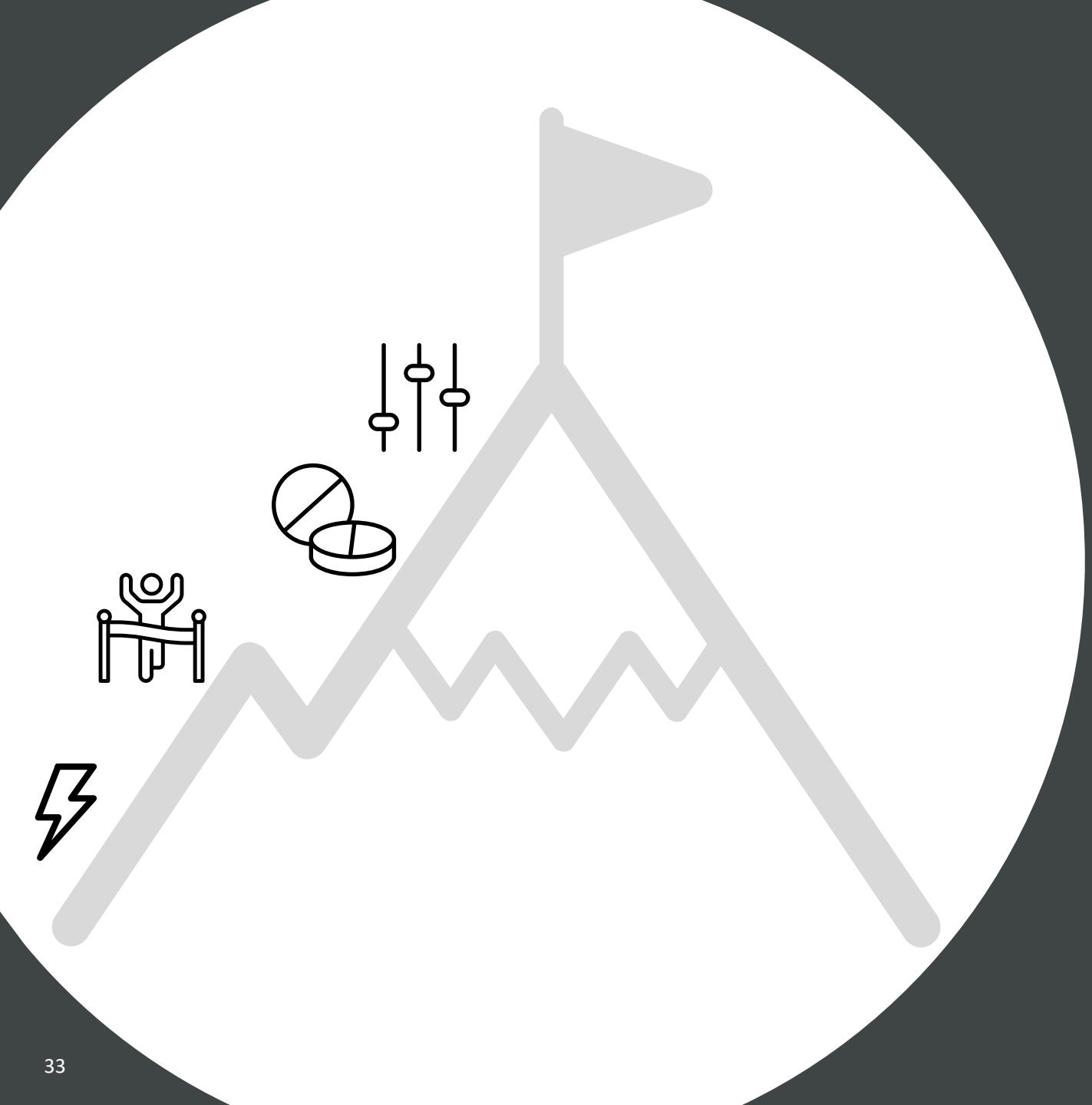
Ok, let's go for a seamless PhII with one interim then!



Can you not be a bit more entrepreneurial? 

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





Thank you.