Futility analyses - a strategic tool in drug development and not futile fat all!

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Effective Statistician Academy, 15th February 2024

Dr. Alexander Schacht • 1st

Fear is a reaction. Courage is a decision. Medical affairs/RWE/HTA expert ...

5d •

500 registrations already and still many more register for **The Effective Statistician** conference happening next week.
It is still time for you to register!

One of the reasons for the many registrations is the line-up of speakers.

One of them is **Kaspar Rufibach**.

Kaspar is not only an outstanding statistician who has a significant influence as a methods statistician at Roche and beyond his company. He is also an excellent speaker.

His presentations are always interesting, relevant, and entertaining.

Having worked closely with many statistical teams, his experience and advice has great relevance for any statistician in clinical research.

I am thrilled that he will speak at my conference again this year.

And his contributions always stimulate a very good discussion.

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I am a statistician after all!

Reduce number of observations if drug does not work.

Risk to stop working molecule typically small.

Not only about "your" trial, but about patients, risk mitigation, other projects!

No threat to integrity or regulatory acceptance.

What are futility interim analyses?

Option to stop trial early.

Protect patients.

Even if continued to final analysis trial unlikely to be significant.

How much do we gain with futility interim analyses in clinical trials?

Design:

- 2-sided significance level: $\alpha = 0.05$.
- Power: $\alpha = 80\%$.
- Hazard ratio to detect: **0.75**.

Timing:

- $n = 1200$.
- Medians in months: 72 and 96.
- Accrual: ramp-up first six months, then 42/month.

Single-stage design (no interim):

- **380** events needed in any case.
- Time to cutoff (months): 60 under H_0.

Add futility interim analysis:

After 30% (= 114) of events.

Stop trial if hazard ratio > 1.

We do not compensate for power loss.
All computations under H_0.

P(stop at interim) = 0.5.

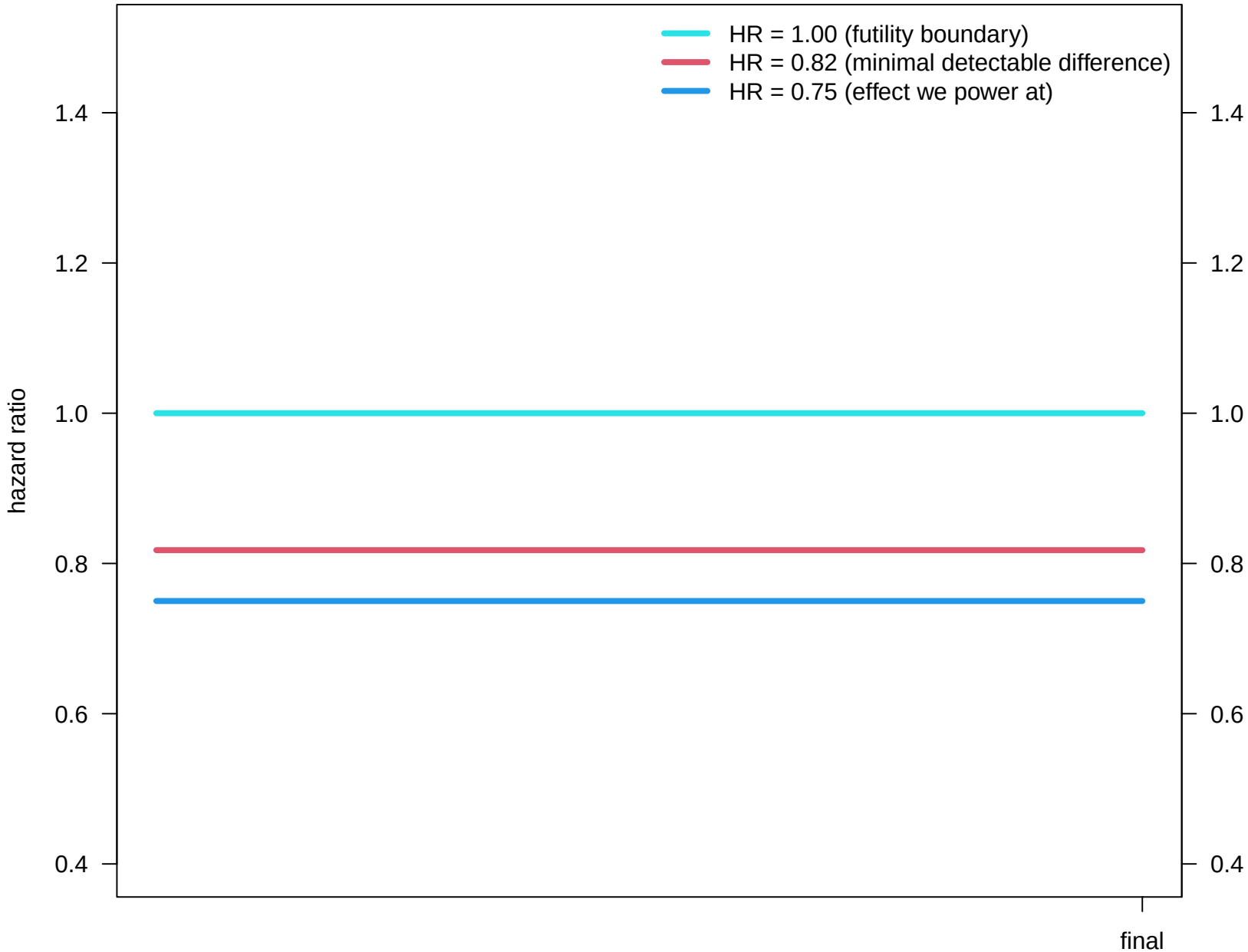
$$0.5 \cdot 114 + 0.5 \cdot 380 = 247.$$

On average 380 - 247 = 133 or 35% less events.

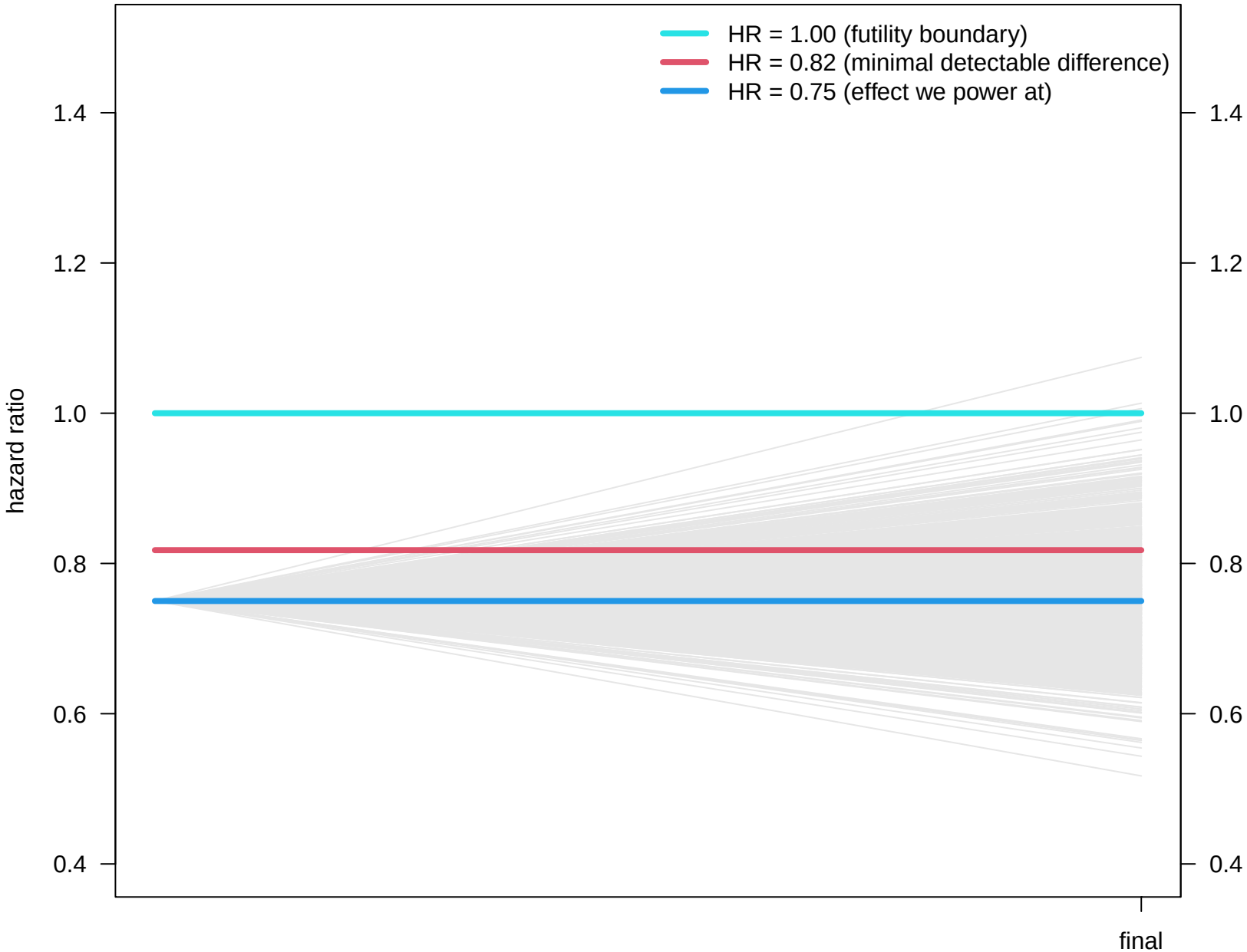
Expected time to cutoff: 44 vs. 60 months.

Power loss

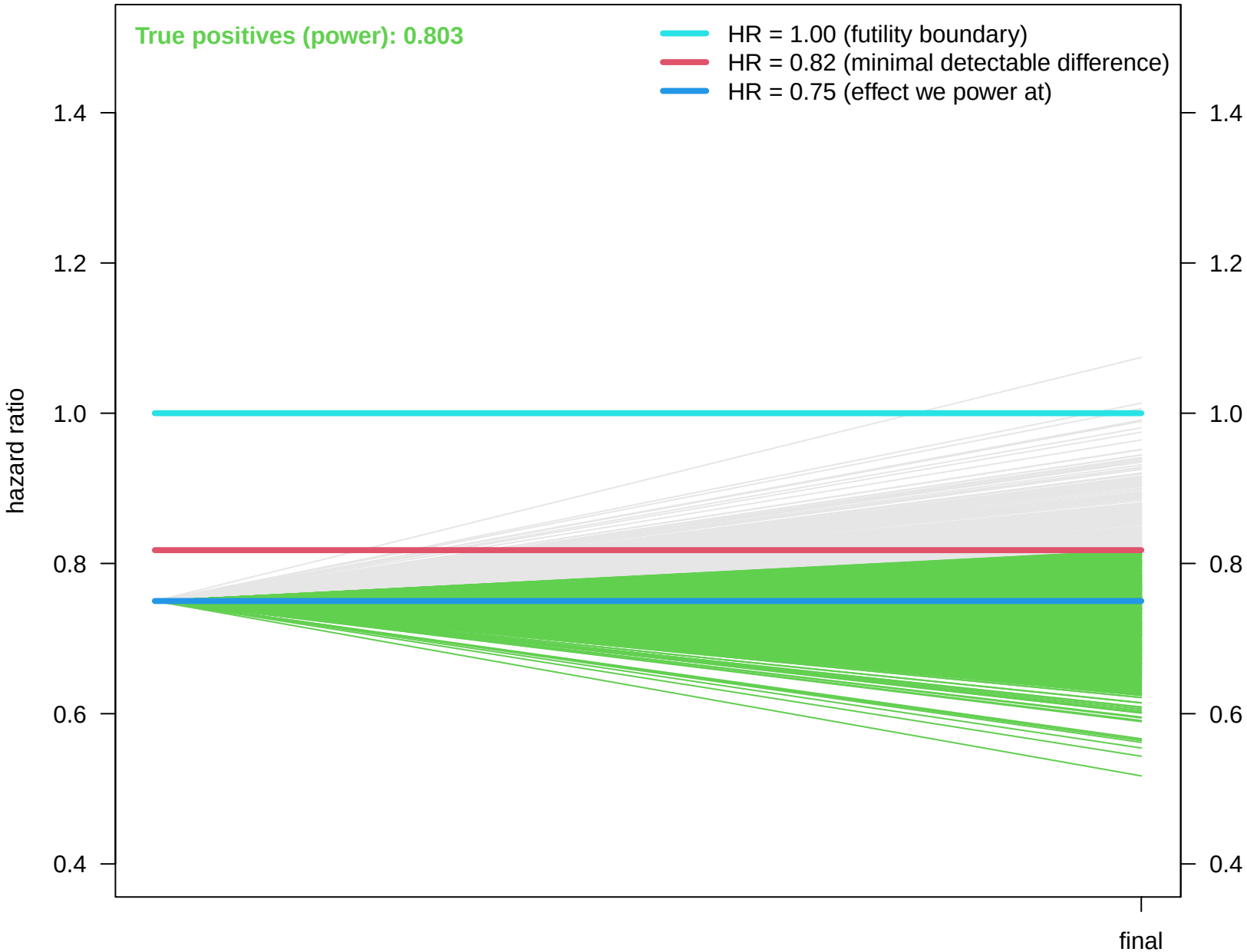
1000 simulated trials assuming HR = 0.75, no interim



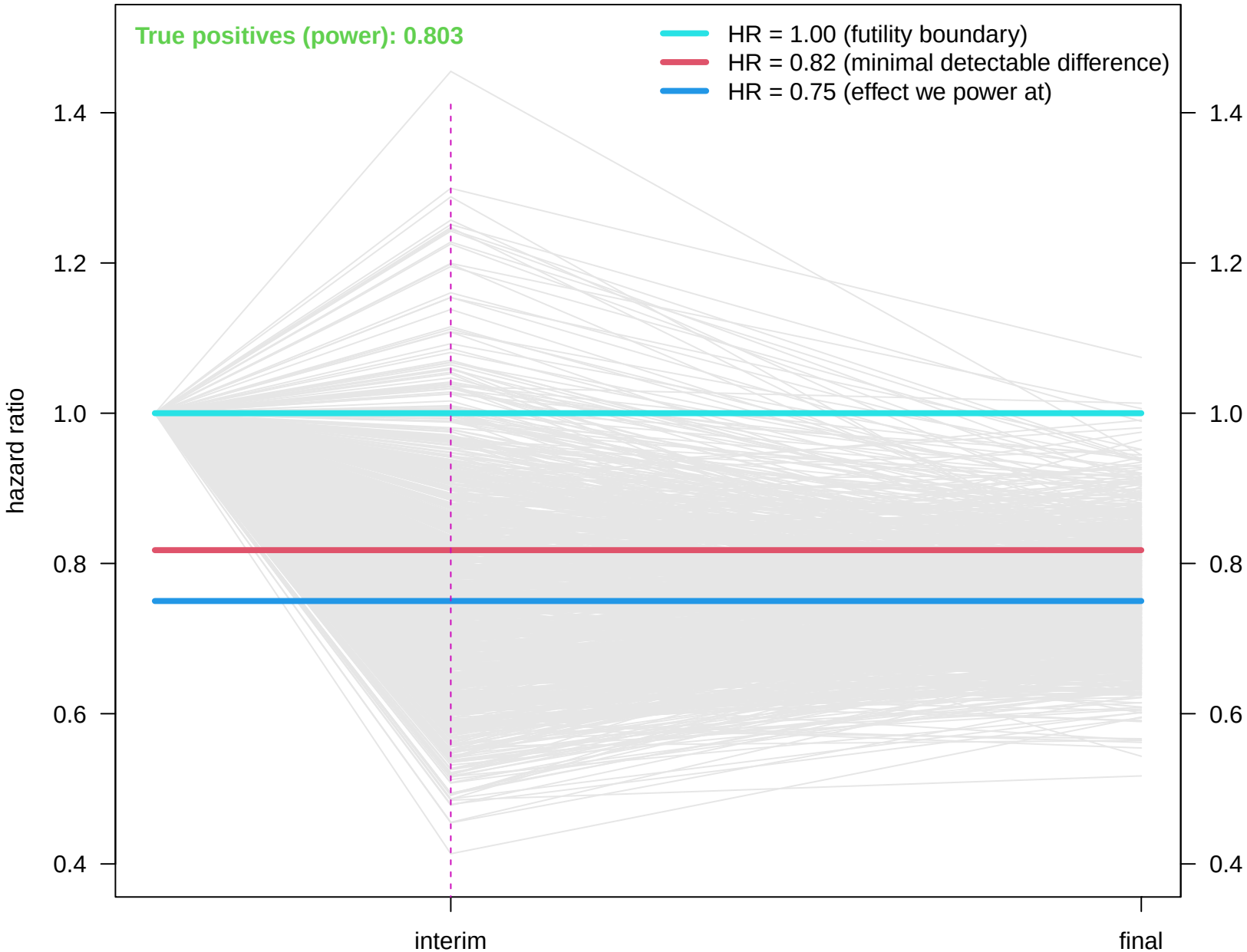
1000 simulated trials assuming HR = 0.75, no interim



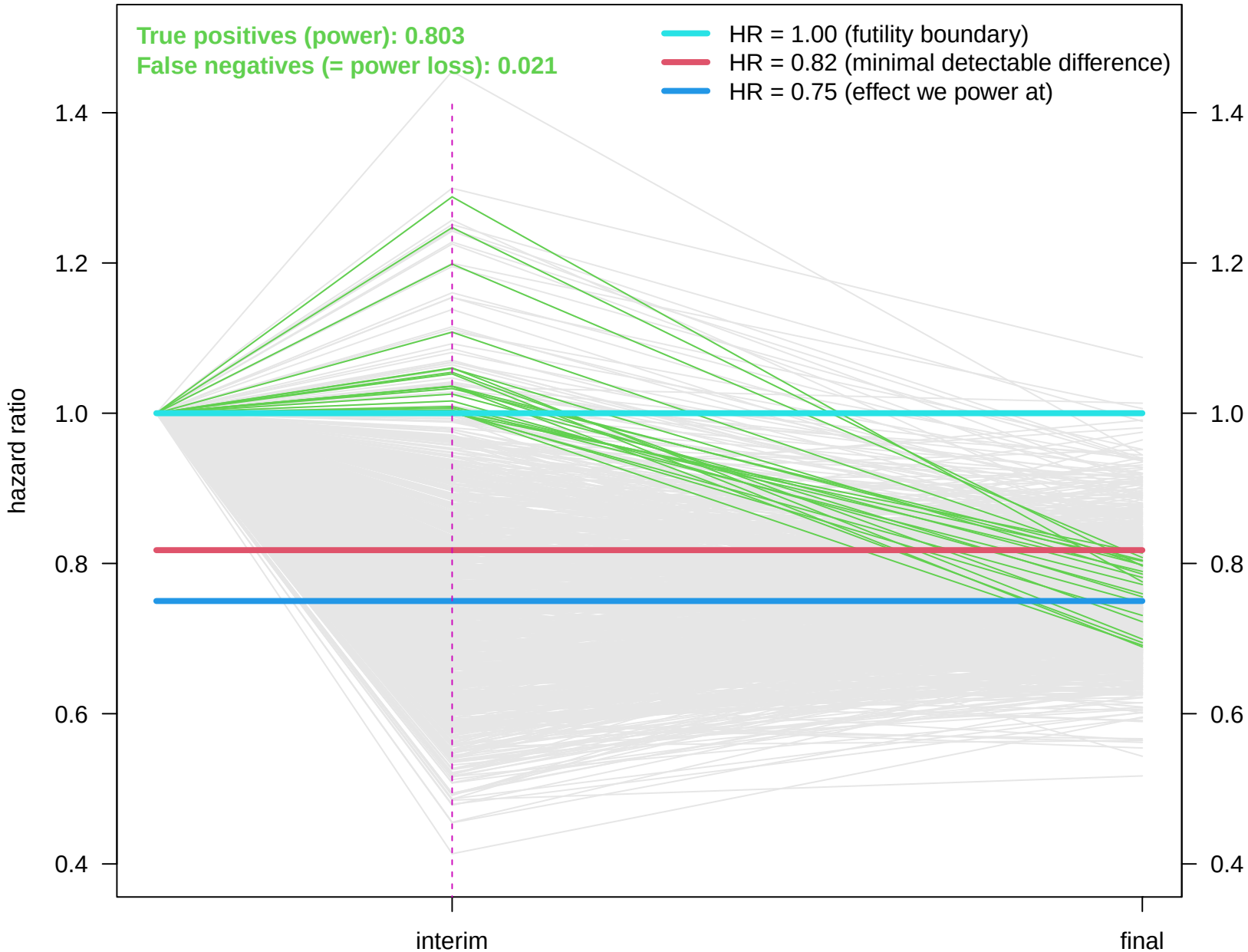
1000 simulated trials assuming HR = 0.75, no interim



1000 simulated trials assuming HR = 0.75, with interim



1000 simulated trials assuming HR = 0.75, with interim



Fixed design: 380.

Futility added, maintain power:
406 events, + 6.8%.

Futility interim: reduce expected number of patients / events under H_0.

Efficacy interim: reduced expected number of patients / events under H_1.

So, among statisticians we agree:

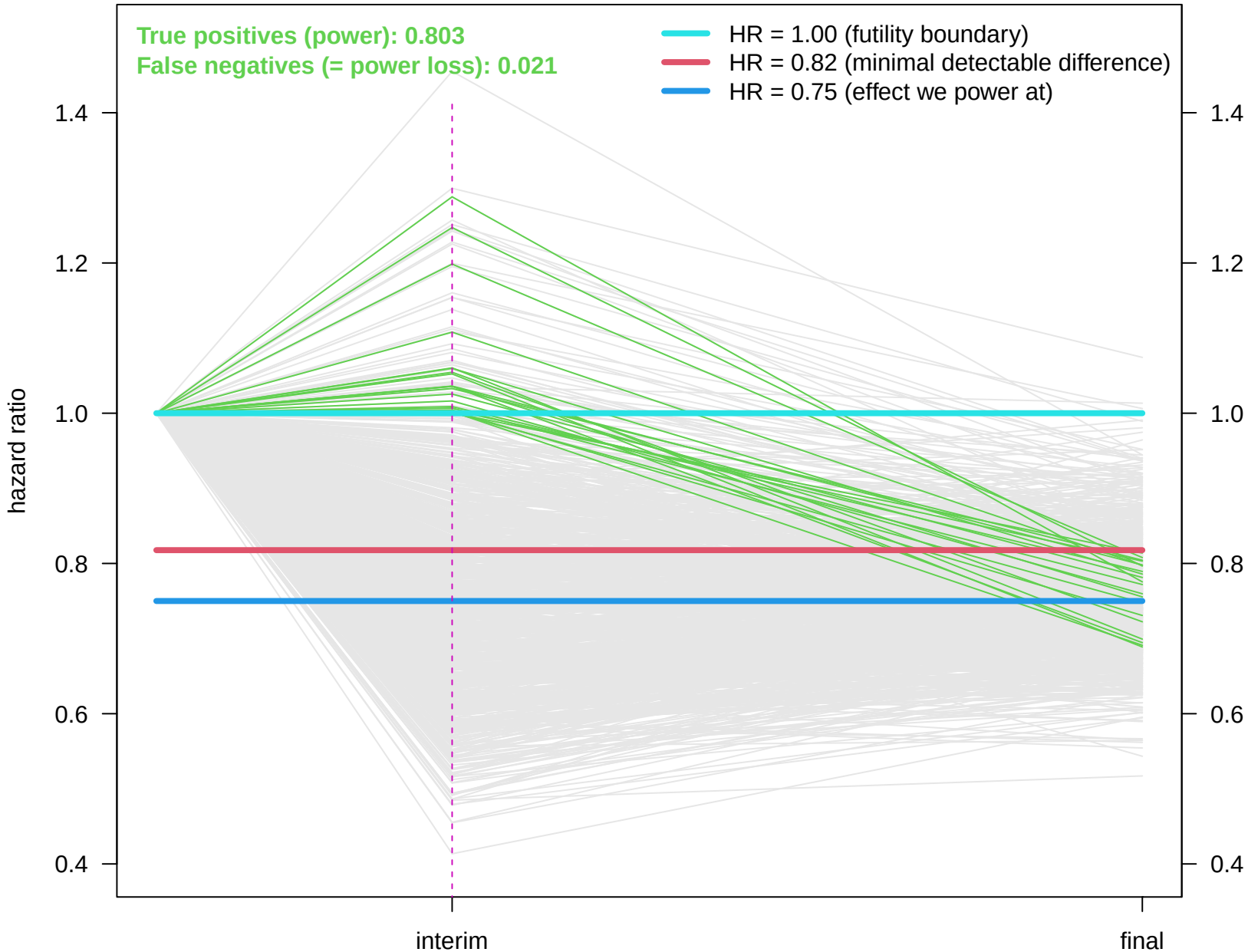
Futility analyses are a useful tool.

Meet the team:

Cartoon courtesy of Gaëlle Klingelschmitt.

"We risk to stop a trial which could be positive at the final analysis."

1000 simulated trials assuming HR = 0.75, with interim



If you power a trial at 80% you already have "false-negative" risk of 20%.

Futility adds 2.4% on top of that.

But reduces average sample size by 35% if drug is useless.

And you can compensate for power loss in trial design, if you wish.

Roche: retrospective analysis.

Virtually never you would have stopped a molecule that works.

114 events with HR > 1.

266 events with HR such that final analysis HR ≤ 0.818.

Two heterogeneous parts. Regulatory risk!

Sponsor bought in to design multimillion trial based on HR = 0.75.

But is not confident to pass futility analysis with boundary HR > 1 after 114 events?

"Trial costs are not linear in trial duration.
We do not save much money if we stop at a futility."

Often true.

But a futility is not only about your trial!

Protect patients.

Portfolio view.

Inform other projects. Efficiency of drug development.

"My molecule may just barely make it at the final. A futility is too risk."

That is exactly when you need one most!

"A futility puts the integrity of the trial at risk."

iDMC. Same process as for efficacy interim.

"Regulators do not like futilities."

Just plain wrong.
Futility considered sponsor's risk.

What regulators do not like: badly designed trials. With or without futility.

"We have a delayed effect."

Fair point.

Need to very carefully design a potential futility.

"Our primary endpoint is not mature at a typical futility timepoint."

Fair point.

Can use "totality of evidence", surrogate endpoints, etc.

Much more (regulatory) freedom to design futility compared to efficacy.

You will not make an efficacy claim!

Futilities derisk Phase 3 trials.

Potential for acceleration.

Reduce number of observations if drug does not work.

Risk to stop working molecule typically small.

Not only about "your" trial, but about patients, risk mitigation, other projects!

No threat to integrity or regulatory acceptance.

Marcel Wolbers

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and many more!

Thank you for your attention.

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www.kasparrufibach.ch

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