From Futility to Understanding

What a Bayesian Lens Reveals in Rare Disease Trials

Louise Perreault | CEO
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Making your innovations reach patients

0 Before We Begin

A few housekeeping notes

Duration & Format

~20 minutes of content followed by an open Q&A session

Your Questions

Drop questions in the chat at any time — I'll address them at the end, or follow up by email if we run short on time

Recording & Slides

This session is being recorded. Slides will be shared afterward with all participants

Feedback Welcome

Your input on length, level of technicality, and overall content helps shape future sessions — all comments appreciated

0 | About the speaker

Louise Perreault

Founder and CEO

Rare disease focus

Specializing in statistical frameworks where traditional methods struggle with small sample sizes and high uncertainty.

Market Access Strategy

Founder of a boutique consulting firm supporting pharma and biotech companies in building strong value strategies.

20+ Years Experience

Generating evidence that helps innovations reach patients by bridging the gap between clinical data and regulatory needs.

Agenda

Context of the Study

Case Study Overview

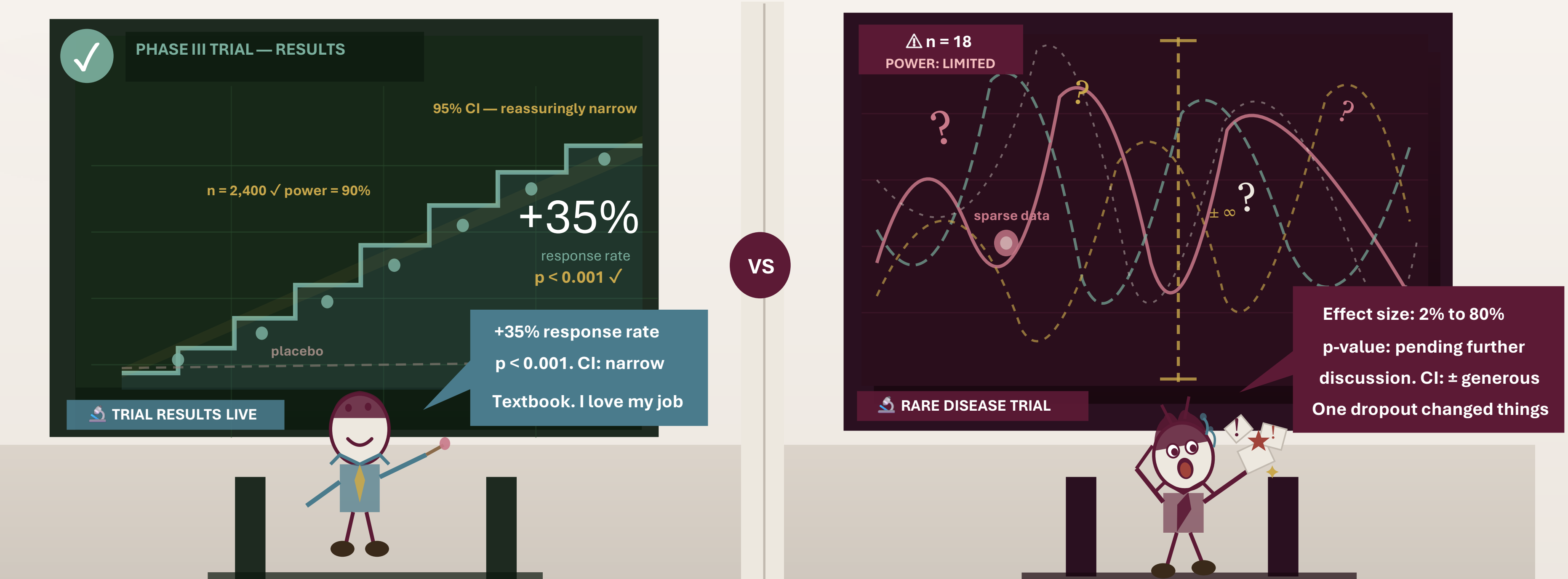
Key Results

Bayesian Perspective

Conclusion

1 Rare Diseases Live at the Edge of Statistics

Standard statistical tools were built for a world that rare diseases don't live in



LARGE POPULATION TRIAL · n = 2,400

stable event rates · predictable variance · tight confidence intervals

Large trial: assumptions hold · results reliable

n=2,400. Assumptions behaving.

RARE DISEASE TRIAL · n = 18

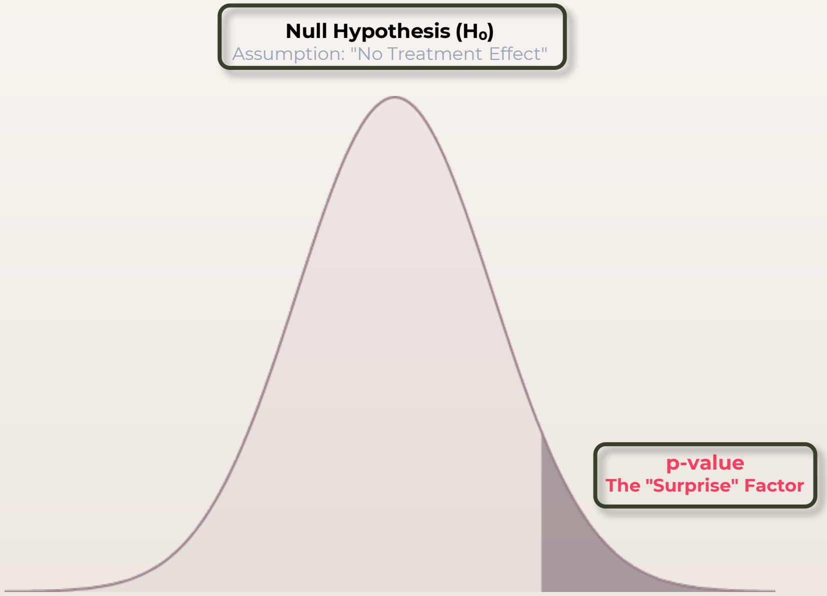
n=18 · heterogeneous patients · limited prior data · one dropout changes everything

Rare disease trial: assumptions break down

n=18. Assumptions under negotiation.

Context : p-value: What It Is (and Isn't)

Why rare diseases struggle with this metric



What It Is

It measures how likely it is to observe results like these if the drug truly had no effect.

P(Data | Null Hypothesis)

What It Is Not

It does not measure how likely it is that the drug truly had an effect.

≠ P(Hypothesis | Data)

Rare diseases = Small sizes ; p-value : unstable and highly sensitive

3 Case Study: LMNA-related Dilated Cardiomyopathy

A rare, aggressive, genetic heart condition

Genetic Cause

LMNA mutation

Heart Failure

Transplant needed

Arrhythmic Risk

Sudden death risk

Trial challenges

Small Population

Phase 3 Interim Results

A strong signal masked by statistical imprecision

57%

Estimated risk reduction

vs placebo at interim

$p = 0.23$

CI: 0.11–1.74

Not statistically significant

Did not meet $p < 0.05$ threshold

STOPPED

Trial halted for futility

At pre-specified interim check

What the Numbers Mean

The data were pointing to a 57% lower risk of getting worse or dying — that is not a small signal. But the result was so imprecise that the test could not rule out chance. Imprecise is not the same as wrong. Uncertain is not the same as absent.

The program was stopped. But what else could we have learned from these data before walking away?

5

The Bayesian Approach

Combining prior knowledge with trial data to update our estimate

Prior

Phase 2 Study

- n = 12 patients
- ~7/12 responded
- Strong directional signal
- Becomes our starting point

Phase 3 Data

Frequentist result

- 57% risk reduction
- Very wide CI : [0.11, 1.74]
- p = 0.23
- High uncertainty alone

Posterior

Combined estimate

- ~46% lower risk
- Narrower uncertainty : CrI [0.24, 1.19]
- Two sources pooled
- More stable inference

Key insight: Pooling two sources of information narrows the range of uncertainty — not to zero, but enough to give a more informative picture than either study alone.

6 From Uncertainty to Probability

What the Bayesian result actually gives you

94%

Probability the drug reduces risk

Based on combining the Phase 2 signal and the Phase 3 data — the posterior probability of any benefit exceeds 94%

84%

Probability of clinically meaningful benefit

An 84% chance the benefit is not just marginal — but the kind of reduction that would genuinely matter in a patient's life

Compare: $p = 0.23$ versus 94% probability of benefit — 84% probability of clinically meaningful benefit.
The underlying evidence is exactly the same. What changes is the language — and the language changes what decisions are possible.

7 What If We Had Assumed Something Different?

Sensitivity analysis across four prior assumptions

We ran the analysis four times, each with a different starting assumption about what we expected before the trial.

Prior Assumption	Starting Point	Posterior Probability of Benefit	Interpretation
Informed (Phase 2)	~60% response rate	≥ 94%	Strongest signal; uses all available data
Optimistic	Assume drug works well	≥ 95%	High; prior boosts the Phase 3 signal
Conservative	Drug may not do much	~85%	Still high; Phase 3 data carry the weight
Uninformative (skeptical)	No prior expectation at all	~76%	Even with zero prior belief, the Phase 3 data alone give a 76% chance of benefit

Key insight: Standard methods also make assumptions — but they are buried in the design phase and rarely revisited. The Bayesian approach puts them on the table and tests them openly. That transparency is a feature, not a limitation.

8 What the Trial Design Tells Us

The futility call may say more about the trial than the drug

Mixed patient population

Some patients enrolled had a version of the LMNA mutation where it was unclear they would benefit from treatment — diluting the treatment signal across the whole group

Unvalidated outcome measures

The endpoints being used had not been validated specifically in this patient population, adding noise to what was being measured

Signal in the right patients

A follow-on study enrolled only patients the clinician believed most likely to benefit. Over nearly 3 years, those patients maintained their ability to exercise — a meaningful finding

A trial stopped for futility might tell us the drug did not work — or it might tell us we asked the wrong patients, measured the wrong things, or used a framework that could not hear the signal. Those are very different lessons.

9 The Question to Carry Forward

A practical shift in how we read trial results

Is the result telling us the drug failed — or is it telling us we did not have enough patients for the test to hear the signal clearly?

The approach sits alongside, not instead of, standard methods

Reach for it when the classic analysis gives a close call and you need to understand what the data are really saying

The shift is in the question

From 'did the p-value pass?' to 'what is the probability this drug actually helps patients?'

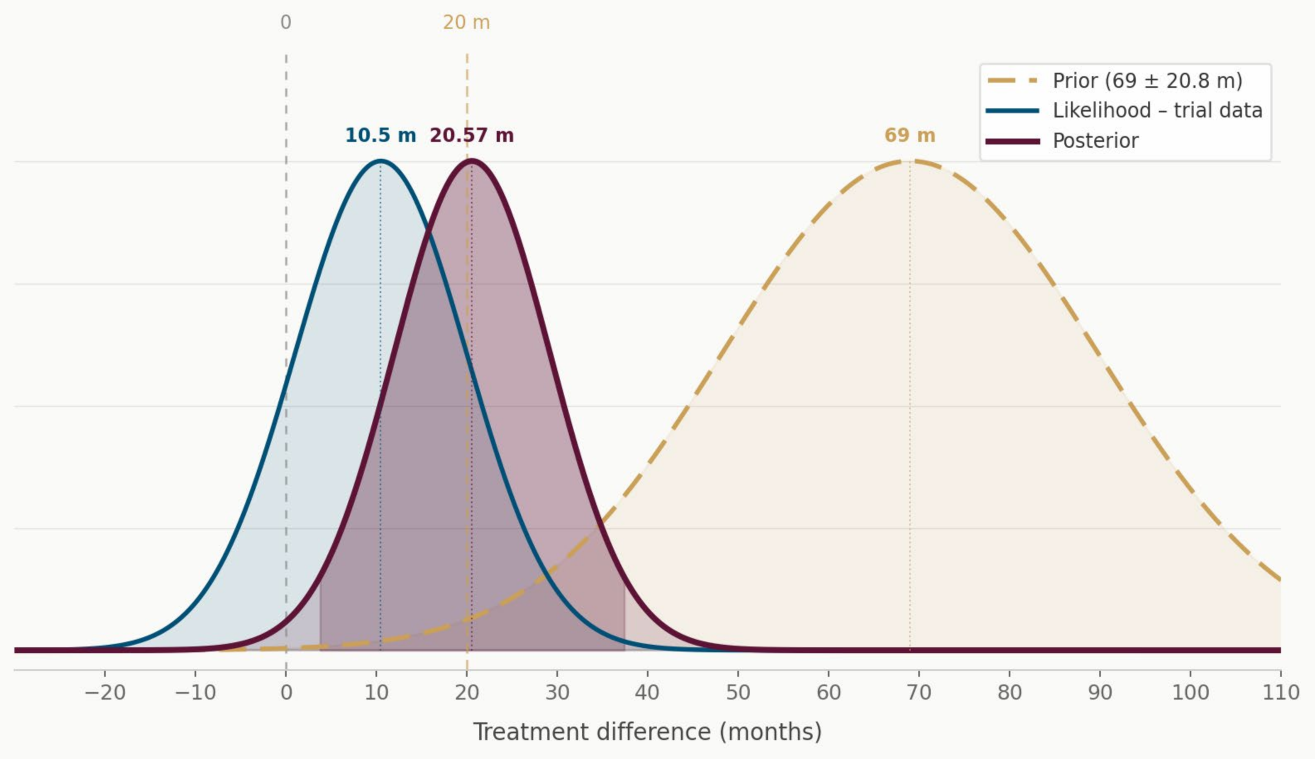
In rare disease, every trial matters

These trials are expensive, take years, and real patients participated. We owe it to them to read the results as carefully as we possibly can

Thank you — I look forward to your questions.

Informative prior

Historical data strongly weighted (69 ± 20.8 m) — posterior pulled toward prior



POSTERIOR RESULTS

20.6 m Posterior mean	**[3.7, 37.5]** 95% CrI
99.1% P(diff > 0)	**52.7%** P(diff ≥ 20 m)

DISTRIBUTION CURVES

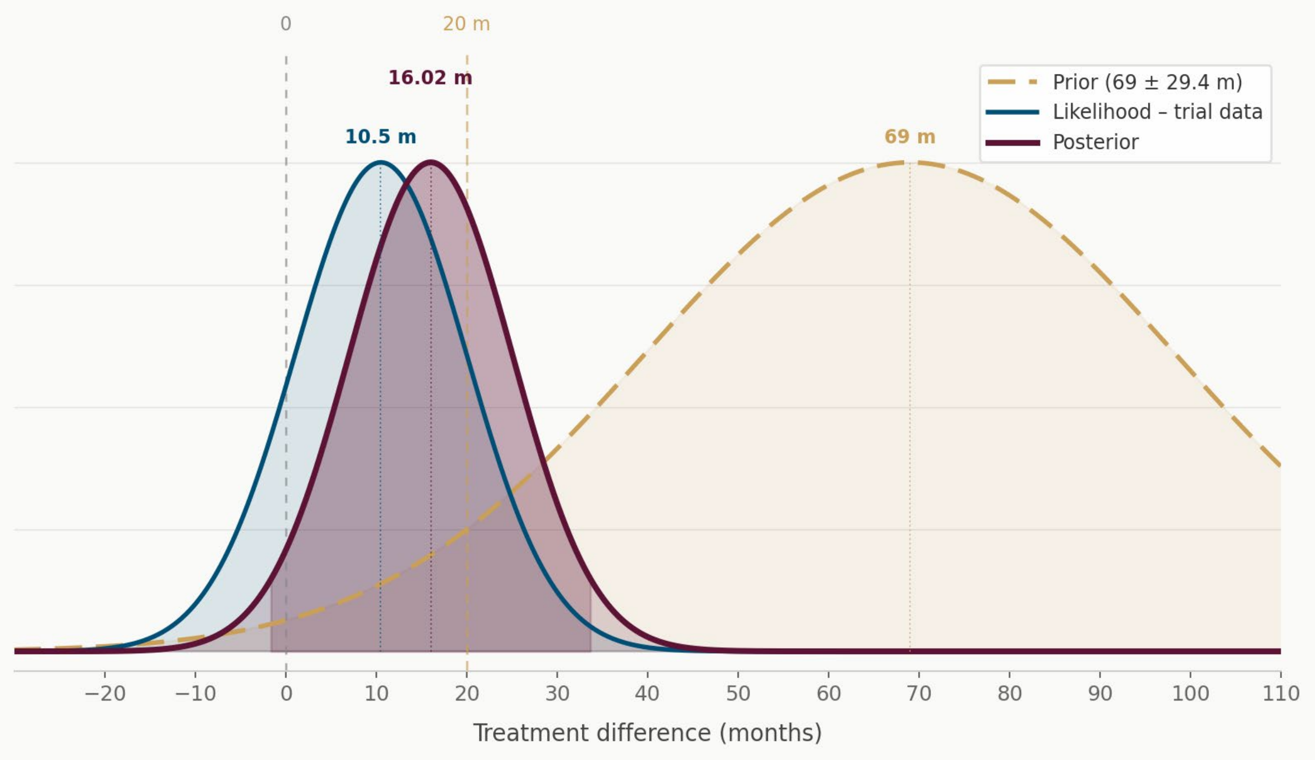
Prior
μ = 69 m, σ = 20.8 m

Likelihood
μ = 10.5 m, σ = 9.5 m

Posterior
μ = 20.6 m, σ = 8.6 m

Down-weighted prior

Prior uncertainty inflated (69 ± 29.4 m) — reduced pull, posterior shifts toward data



POSTERIOR RESULTS

16.0 m
Posterior mean

[−1.7, 33.7]
95% CrI

96.2%
P(diff > 0)

33.0%
P(diff ≥ 20 m)

DISTRIBUTION CURVES

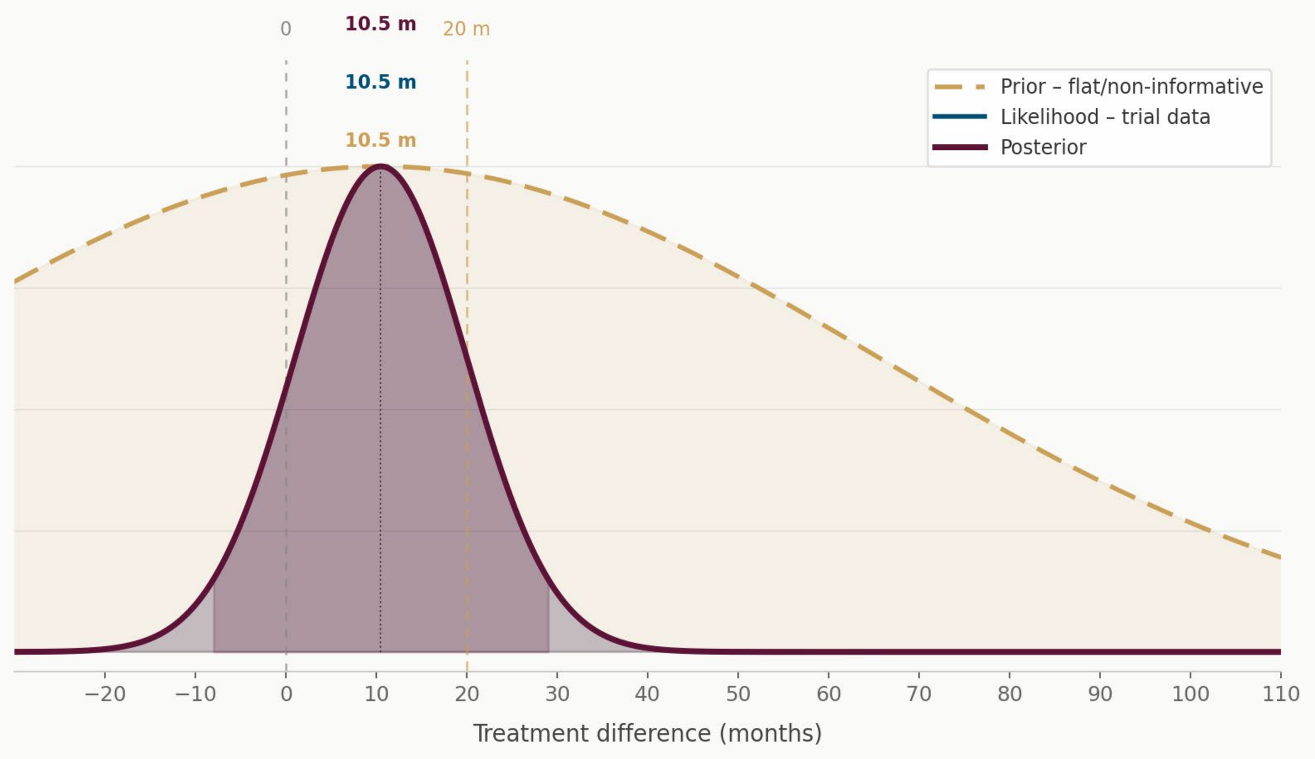
Prior
μ = 69 m, σ = 29.4 m

Likelihood
μ = 10.5 m, σ = 9.5 m

Posterior
μ = 16.0 m, σ = 9.0 m

Non-informative prior

Flat prior — posterior collapses onto the trial likelihood; prior carries no weight



POSTERIOR RESULTS

10.5 m
Posterior mean

[−8.1, 29.1]
95% CrI

86.6%
P(diff > 0)

15.8%
P(diff ≥ 20 m)

DISTRIBUTION CURVES

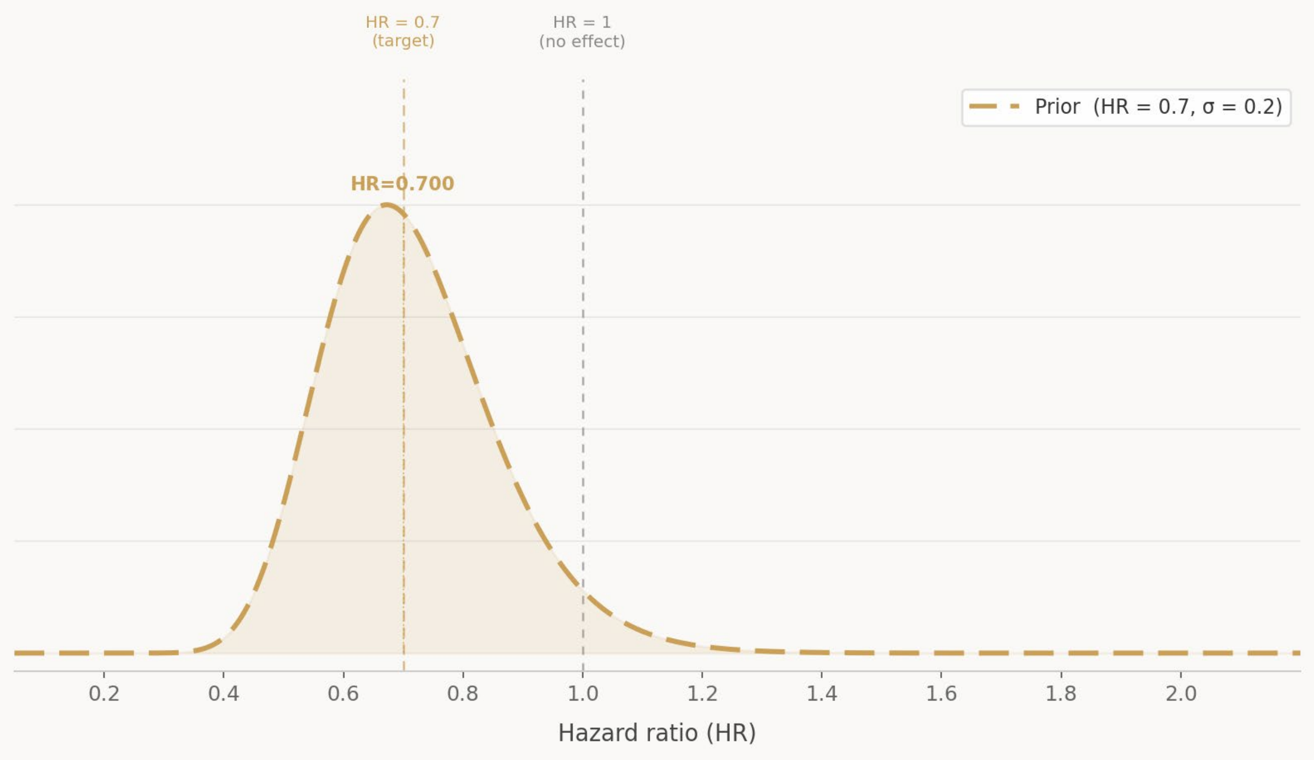
Prior
Flat / non-informative

Likelihood
μ = 10.5 m, σ = 9.5 m

Posterior
μ = 10.5 m, σ = 9.5 m

Informative prior

Prior HR = 0.7 ± 0.2 (tight prior) — posterior strongly anchored to historical data



POSTERIOR RESULTS

0.675 Posterior HR	**[0.463, 0.984]** 95% CrI
98.0% P(HR < 1)	**81.2%** P(≥20% efficacy)

DISTRIBUTION CURVES

Prior
HR = 0.700, σ = 0.2 (log scale)

Likelihood
HR ≈ 0.43 (trial data only)

Posterior
HR = 0.675, 95% CrI [0.46, 0.98]

SCENARIO 01

Informative prior

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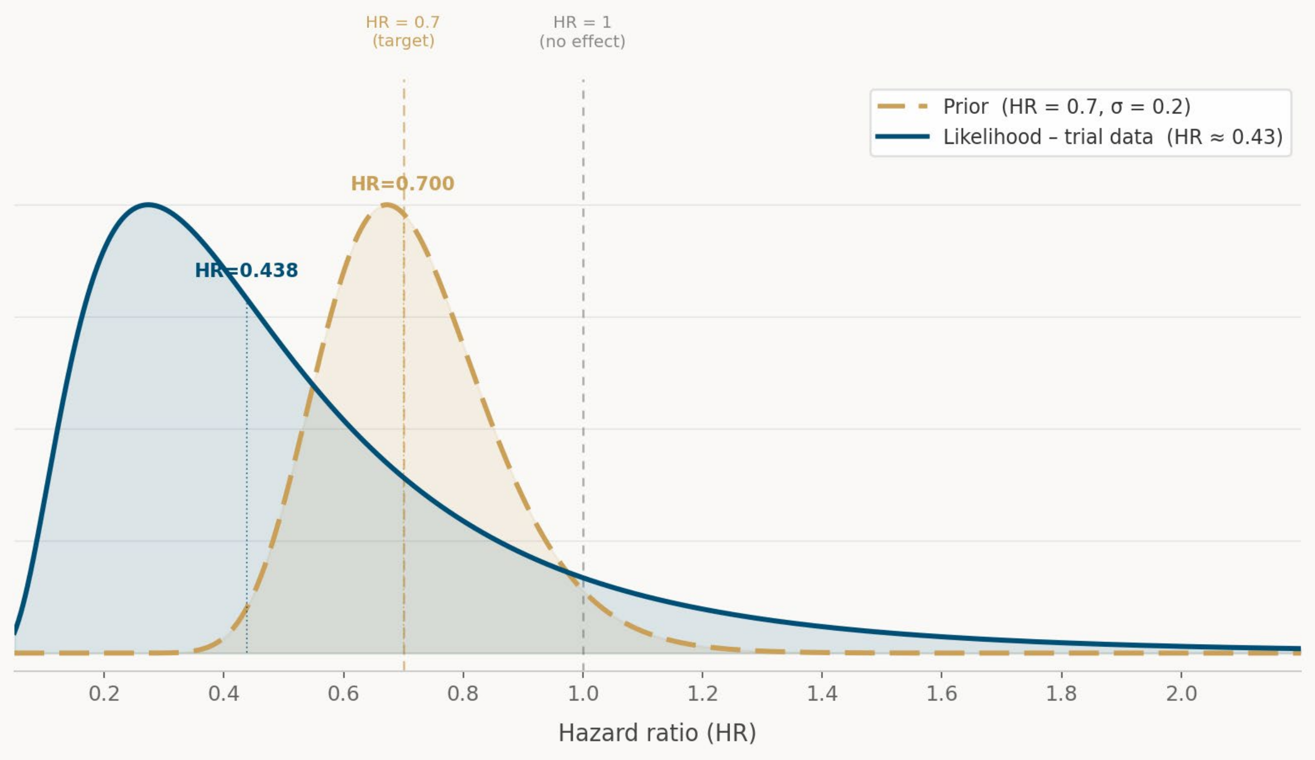

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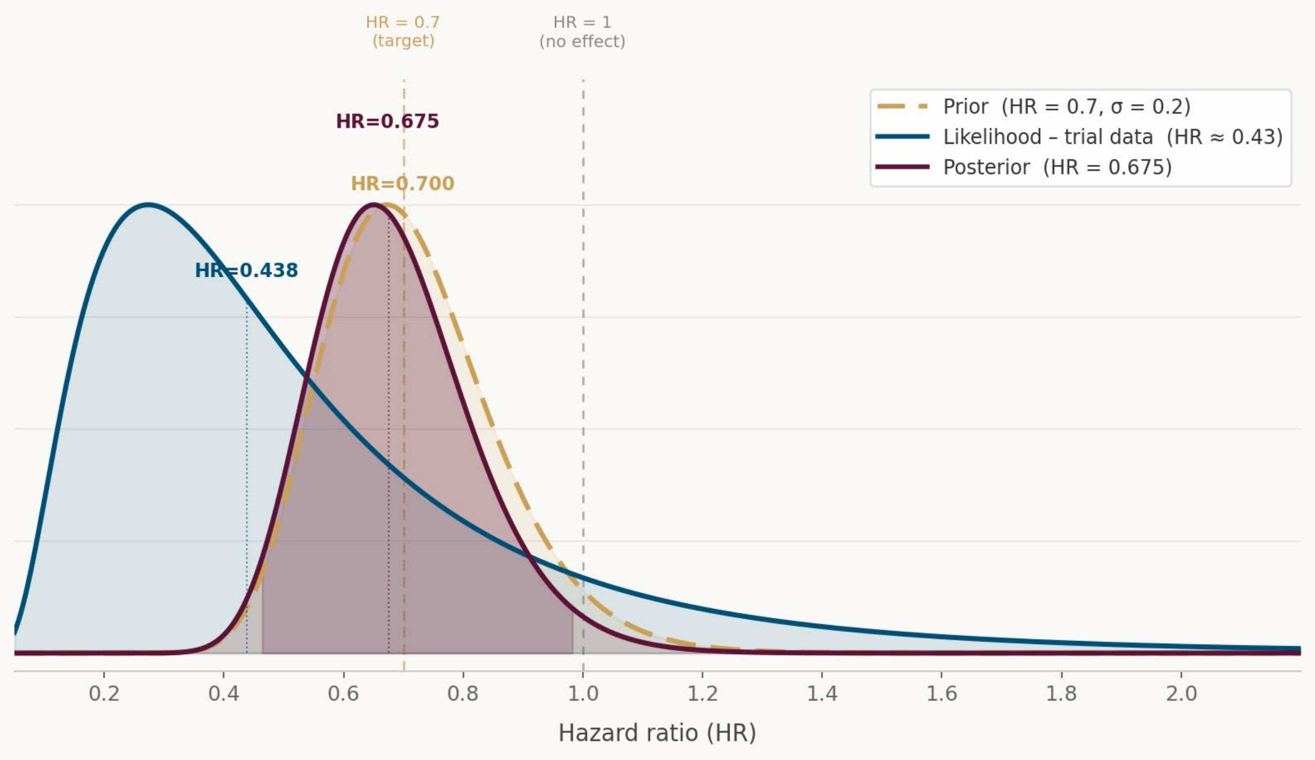

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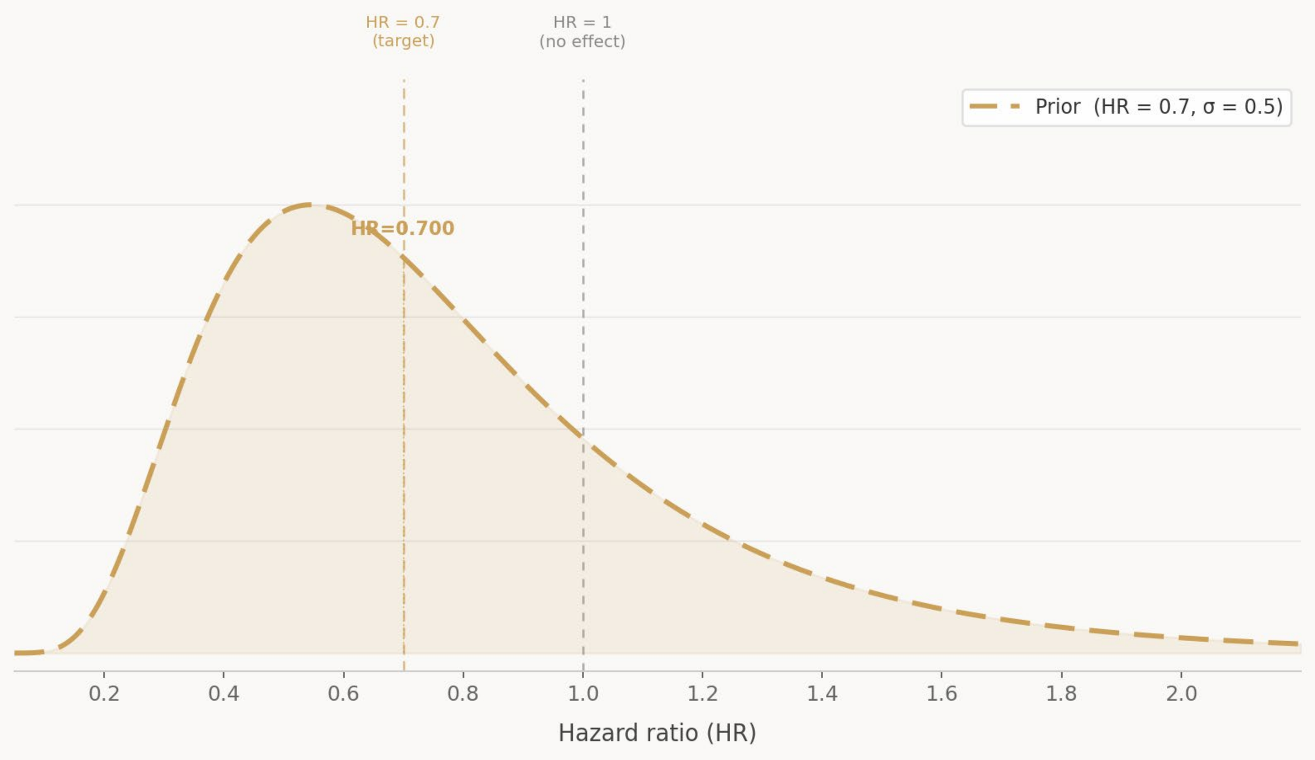
SCENARIO 02

Down-weighted prior

Prior HR = 0.7 ± 0.5 (moderate prior) — posterior shifts toward trial data



POSTERIOR RESULTS

0.595
Posterior HR

[0.267, 1.322]
95% CrI

89.8%
P(HR < 1)

76.5%
P(≥20% efficacy)

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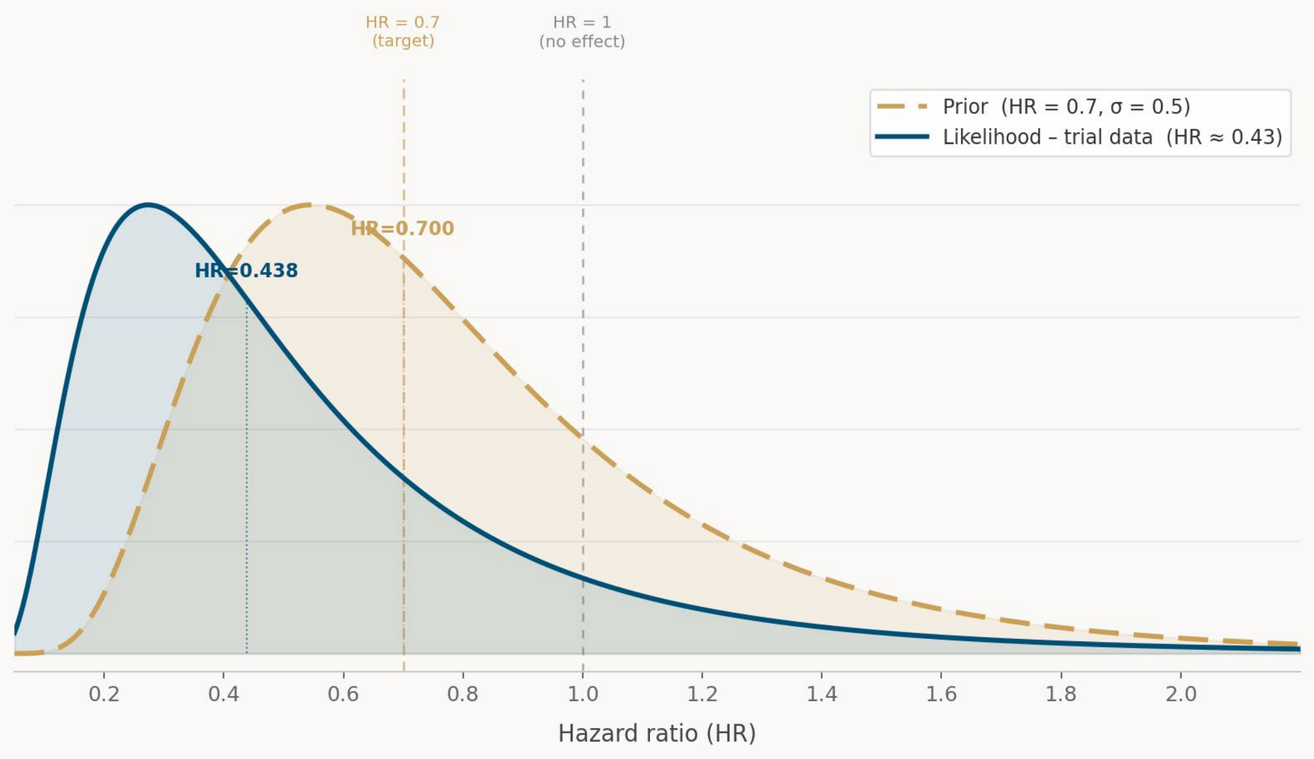

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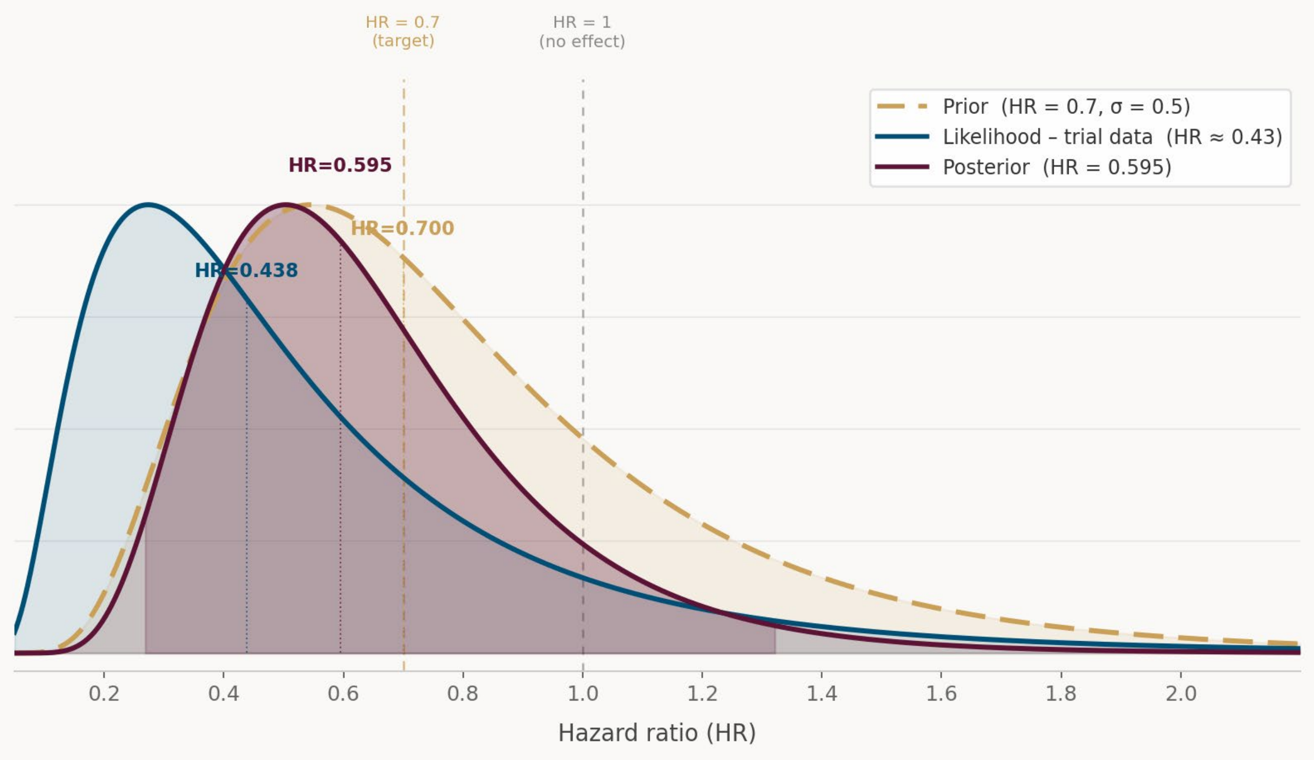

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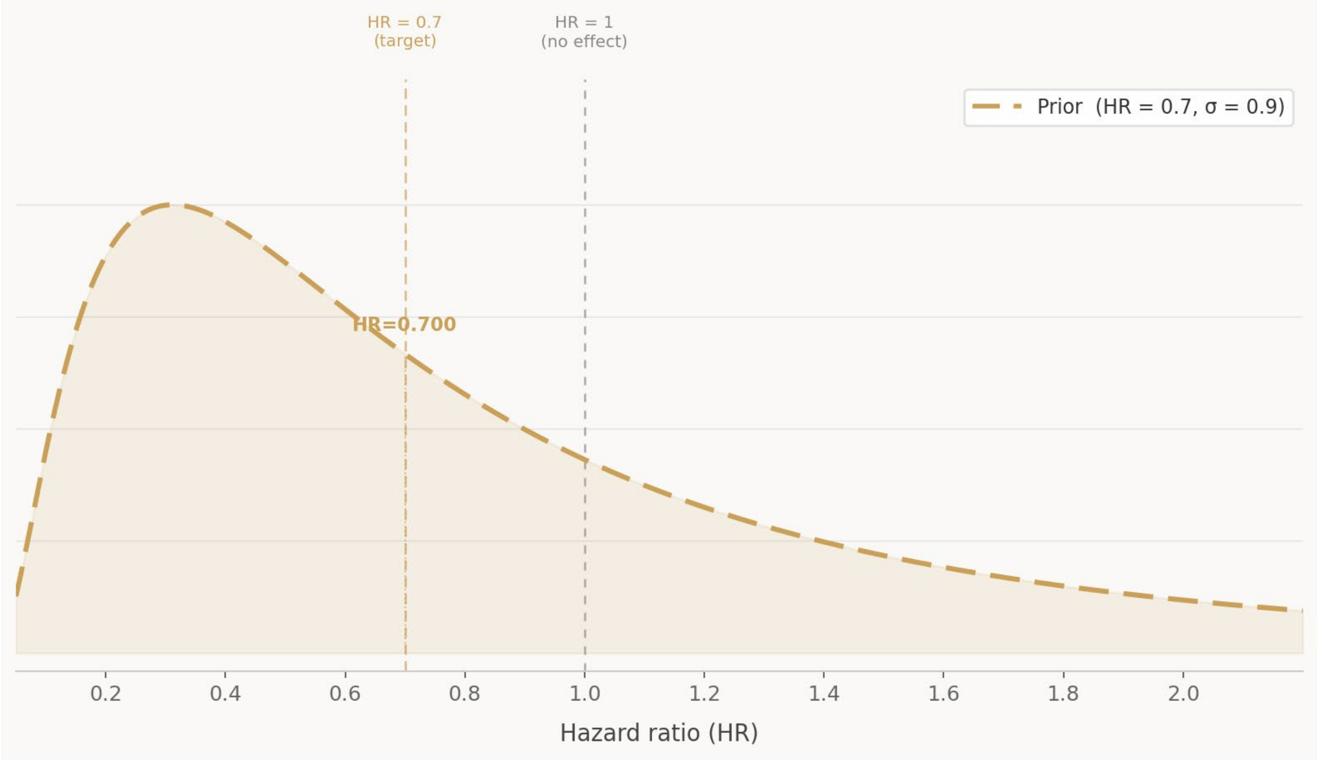
SCENARIO 03

Non-informative prior

Step 1 of 3 — Prior

Prior HR = 0.7 ± 0.9 (vague prior) — posterior driven entirely by trial data



POSTERIOR RESULTS

0.517 Posterior HR	**[0.174, 1.535]** 95% CrI
88.3% P(HR < 1)	**78.3%** P(≥20% efficacy)

DISTRIBUTION CURVES

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Posterior
HR = 0.517, 95% CrI [0.17, 1.54]

Step 2 of 3 — + Likelihood

Non-informative prior

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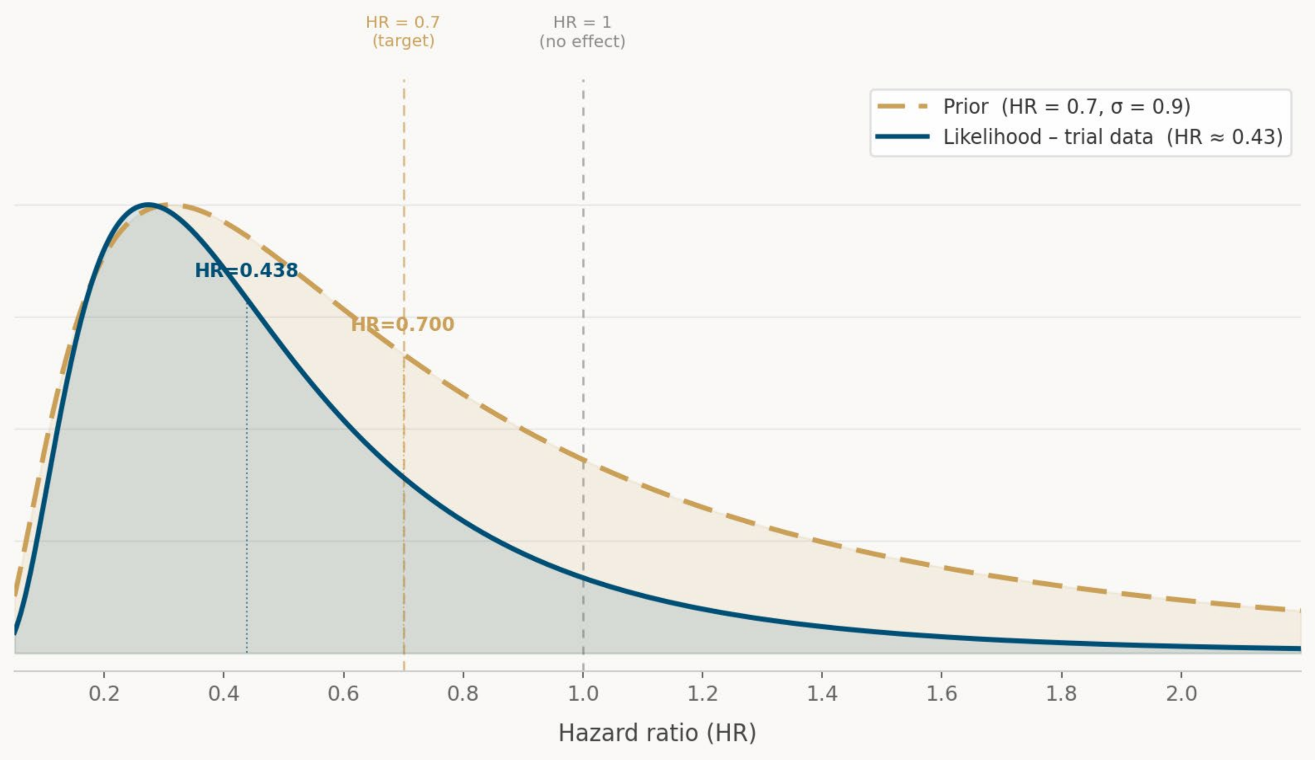

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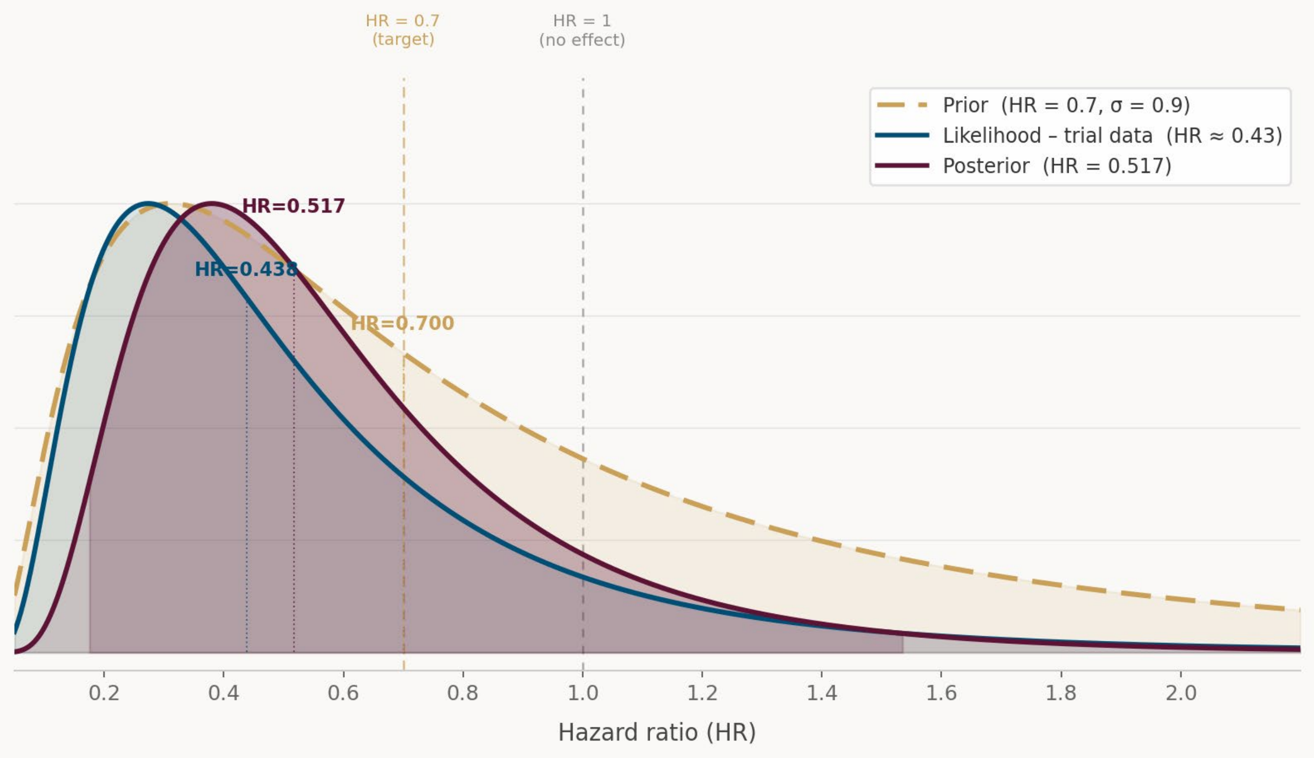

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