2025-09-10

Skyddsnivå:

Sätt ett kryss (X) framför rätt skyddsnivå!

X (K0) Ingen/låg
(K1) Grundläggande
(K2) Utökad
(K3) Hög

# ICH E20, Regulatory perspective

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# Issue 1: Correct study but insufficient evidence

ICH E20 is more liberal to adaptive design than previous (EMA) guidance

Dream scenario:

- Reduce cost
- Reduce risk of failure
- Reduce burden to study patients

Nightmare scenario:

- True positive benefit/risk and
- studies according to guidelines but
- product unapprovable

??

# Issue 1: Correct study but insufficient evidence

Statistical assessment in Market Authorisation Procedures:

- Can we be certain enough that the effect is real?
- How large is the effect? (for benefit/risk assessment)

This is not checkbox based but about understanding the uncertainties in the data

# Example 1: Failure by design

- One pivotal study: Statistical evidence considerably stronger than $p<0.05$ is usually required
- Proposed study design: Several interim analyses to stop for efficacy (alpha protected at 0.05)

Study is designed to protect against cost of ”too strong” evidence

Very unlikely to produce statistical evidence considerably stronger than $p<0.05$

# Example 2: Added uncertainties

PLAN

Hard to see how this could go wrong…

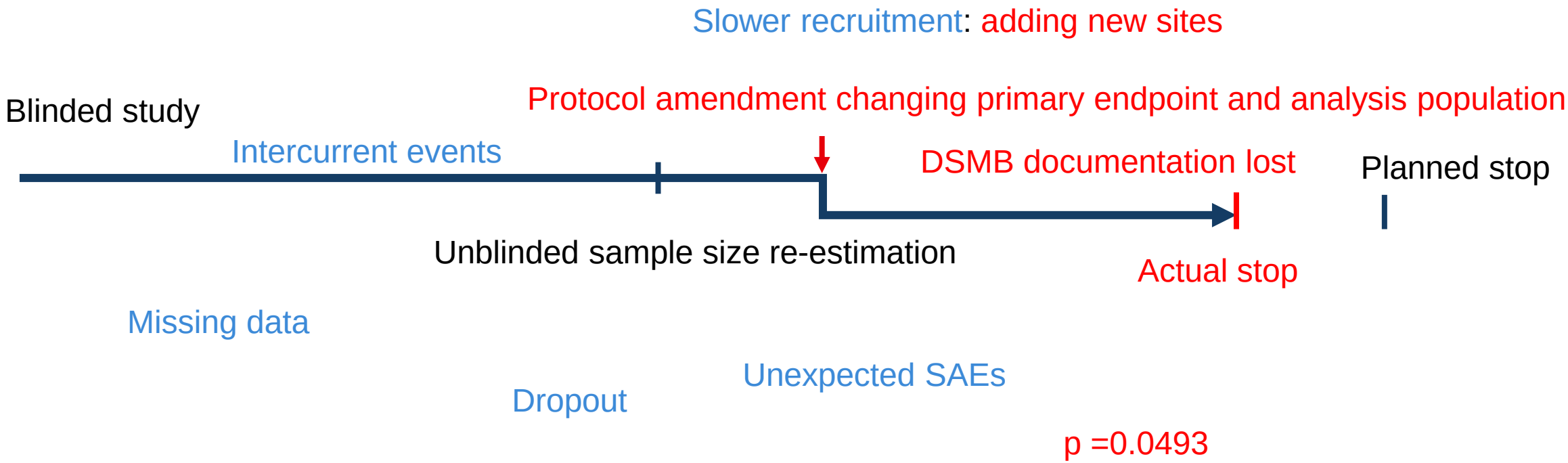
Blinded study

Unblinded sample size re-estimation

# Example 2: Added uncertainties

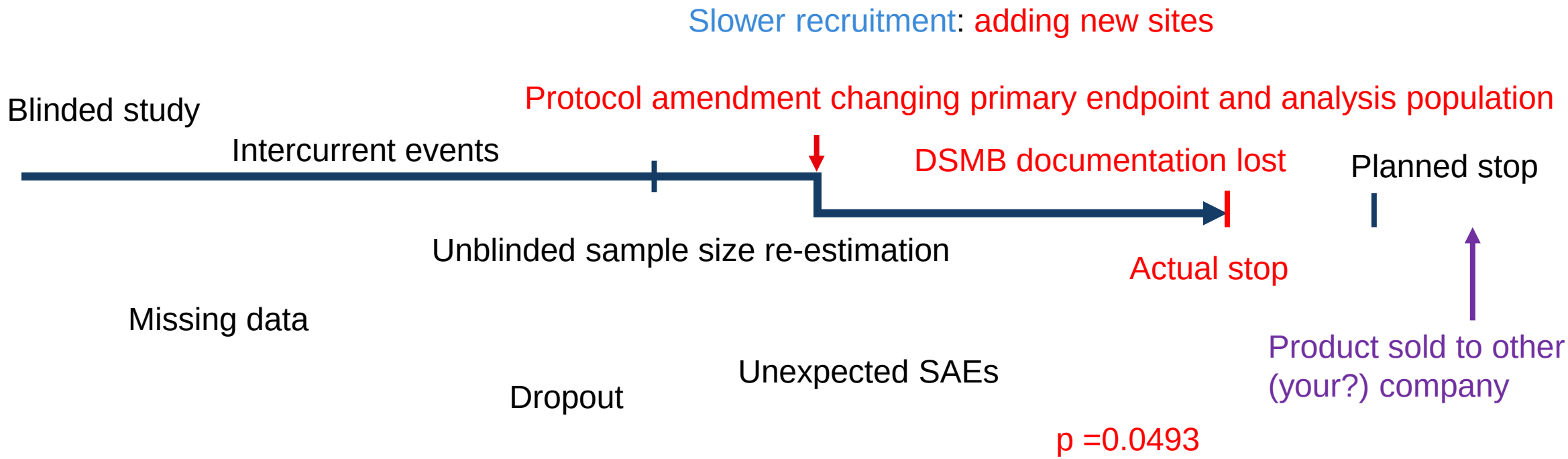
But my company would not do this!

REALITY



# Example 2: Added uncertainties

REALITY



# Issue 1: Added uncertainties

- Take home messages:
  - It is not always optimal to optimise
  - Leave margins for the unexpected, something unexpected always happens

# Issue 2: Simulations

- ICH E20 proposes simulation studies to investigate operating characteristics and bias in estimation

” If simulations are critical to understand operating characteristics of an adaptive design, the simulation study should be carefully planned, conducted, and reported”

…

“The scenarios included in the simulation study should cover the plausible range of assumptions to ensure a robust assessment of the performance of the proposed adaptive design.”

# Issue 2: Simulations

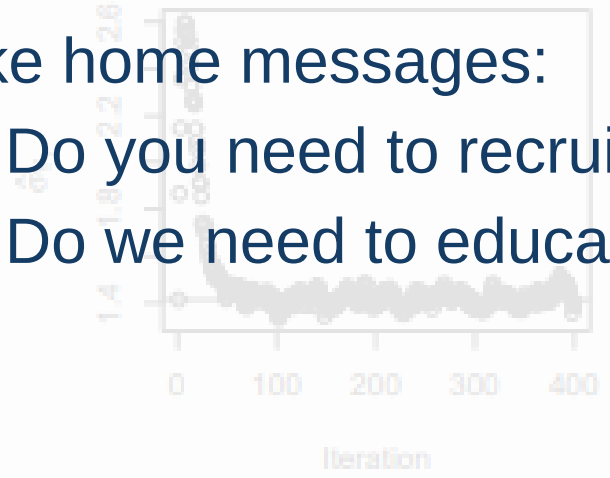
- Excellent idea! … But:

- Takes skill (Inference+clinical trials+simulations) and time!
  - Are skilled people available?
  - Do we train students in these skills?
  - Is it efficient use of resources?
  - What do we do when the simulations are not submitted?”

- ”Om miniräknare finnes” (Swedish for ”If a pocket calculator is available…”)

# Issue 2: Simulations

- Take home messages:
  - Do you need to recruit?
  - Do we need to educate?



# Thank you for listening!