

Early stopping in
Randomized Controlled Trials:
is it right or is it wrong?

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Overview

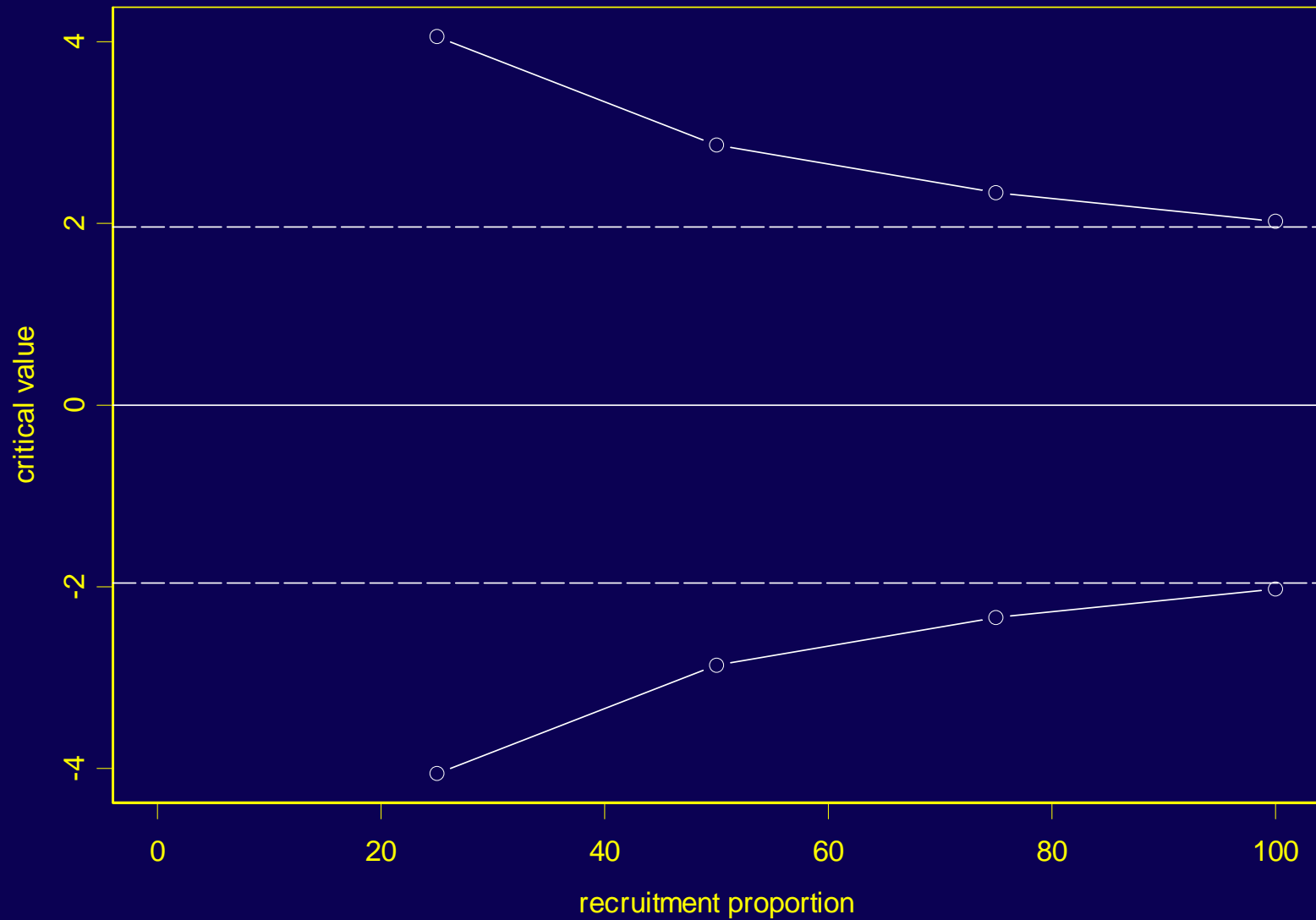
- interim analyses are common in clinical trials
- trials may be stopped early for benefit or harm
- stopping trials early biases estimated effect sizes

I will argue against stopping trials early for benefit

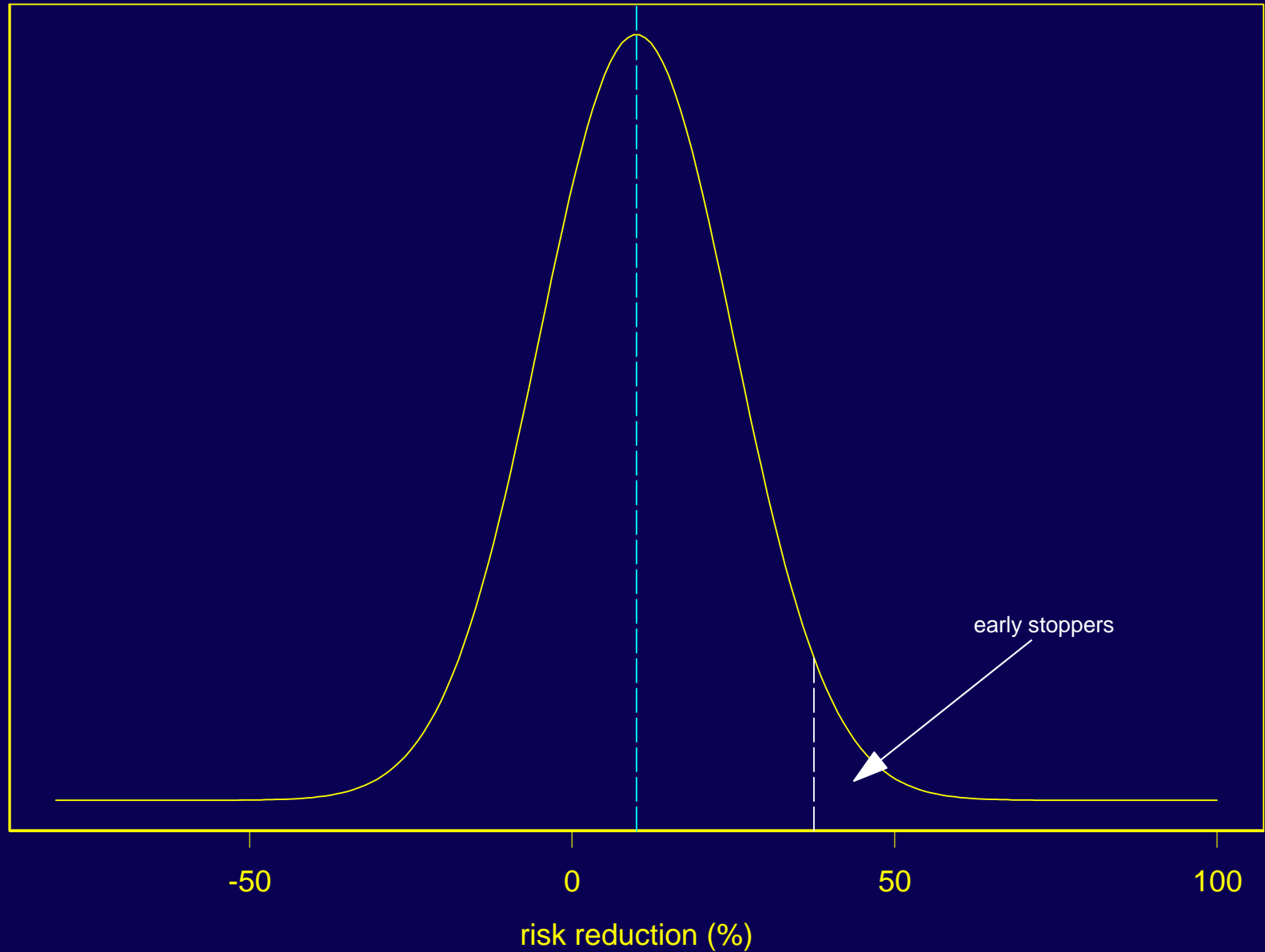
Conceptual Framework

- RCT: experimental treatment vs. control
- Outcome: mortality
 - (any dichotomous outcome)
- Benefit = relative risk reduction
 - *example: relative risk of 0.8* ↔ *20% relative risk reduction*
- DSMC periodically assesses trial progress
 - DSMC: data, safety & monitoring committee
 - may recommend that the trial stop early

O'Brien-Fleming stopping boundaries: 3 interim analyses



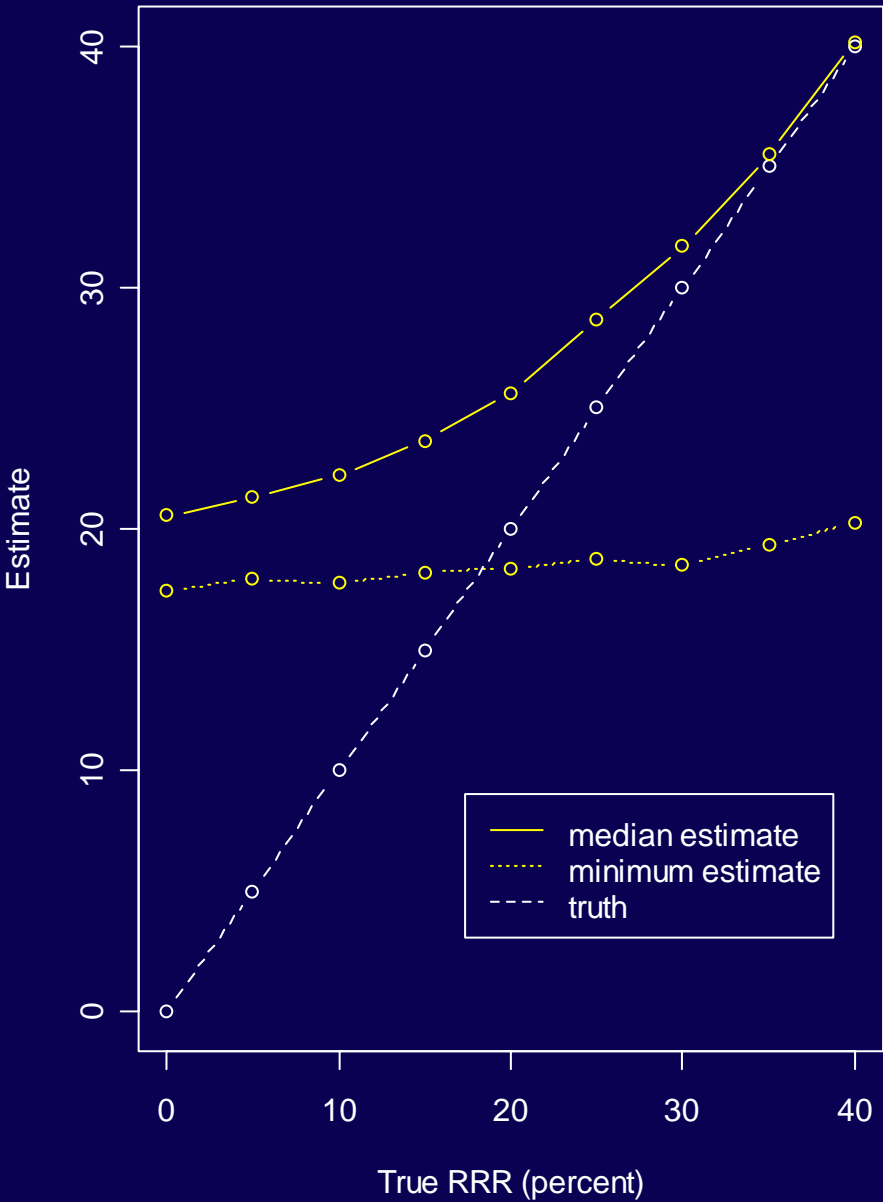
Early stoppers represent truncated distribution



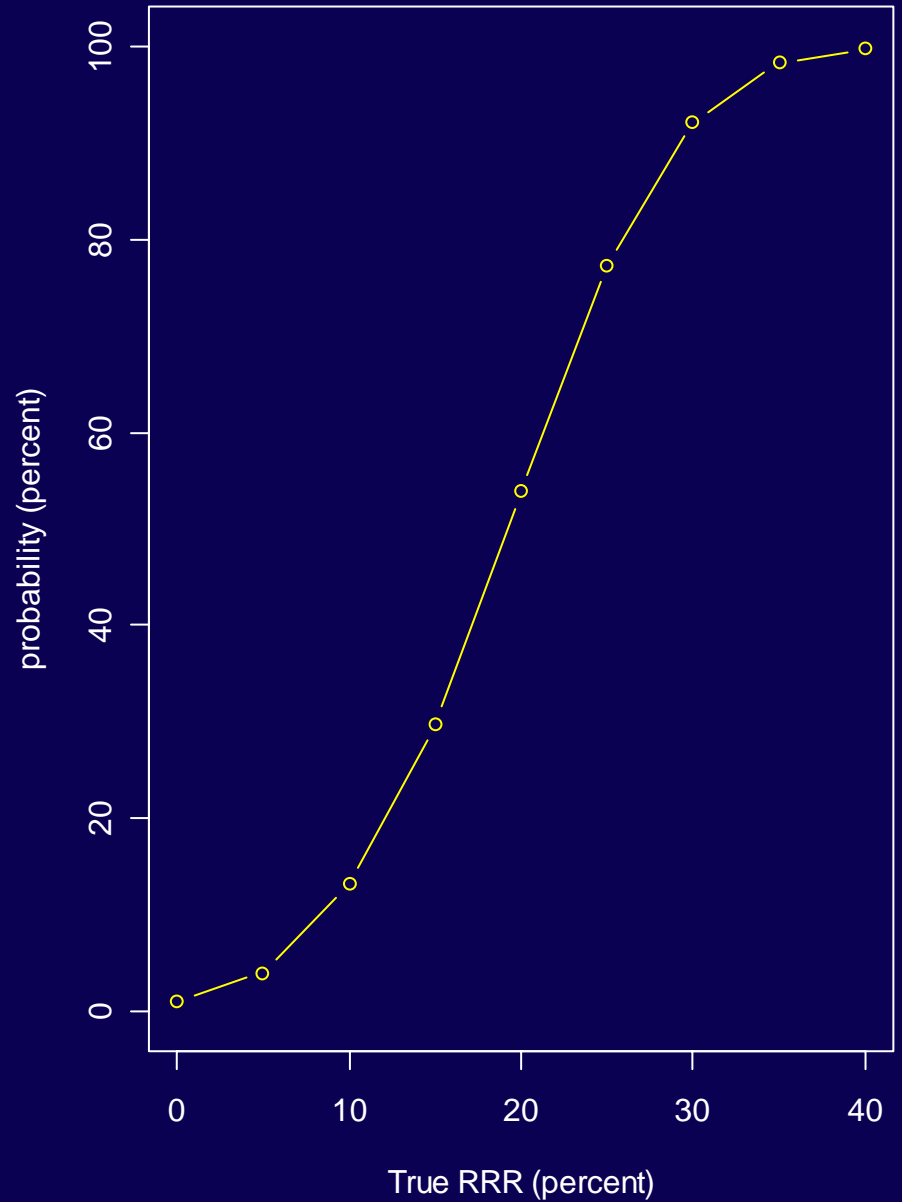
Simulation Study

- **random control group mortality:** varies uniformly between 2% and 20%
- **power:** powered for 20% risk reduction
- **fixed effect size:** 0%, 5%, ... 40% risk reduction
- **early stopping rule:** O'Brien-Fleming with 3 interim analyses

Median estimate



% Early Stops



What about the ethical imperative?

- we can't ethically give patients a treatment (the control) that we know to be inferior...
 - trials that stop early for benefit DO provide evidence of improved efficacy
- superiority isn't the same as efficacy
 - cost-benefit profile
 - adverse effects
- once we understand the severity of the bias, the ethical imperative disappears
 - trials that stop early for benefit don't provide evidence of superiority

Reverse ethical imperative?

- we argue that it is actually *unethical* to stop early for benefit
- positive results from early stopped trials are unconvincing
 - exaggerated
 - may have missed adverse effects
- when we stop early for benefit, we waste the contribution of the trial subjects
 - need confirmatory trial
- enrolling subjects in a trial that won't affect clinical practice is **ethically unacceptable**