Investigating the impact of Data Monitoring Committee recommendations on the probability of trial success

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Hybrid Bayesian/frequentist design of a superiority phase III trial

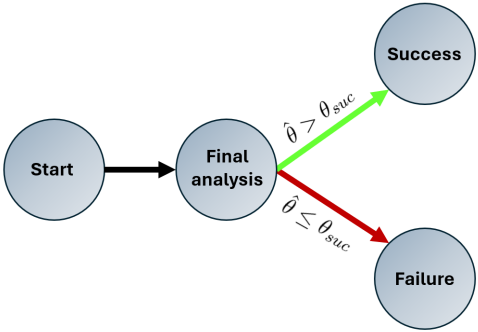
θ is the treatment effect (e.g., mean treatment difference between T and R)

Success is defined as rejecting H_0 (e.g., $H_0 : \theta \leq 0$)

$q_0(\theta)$ is the prior distribution of the treatment effect

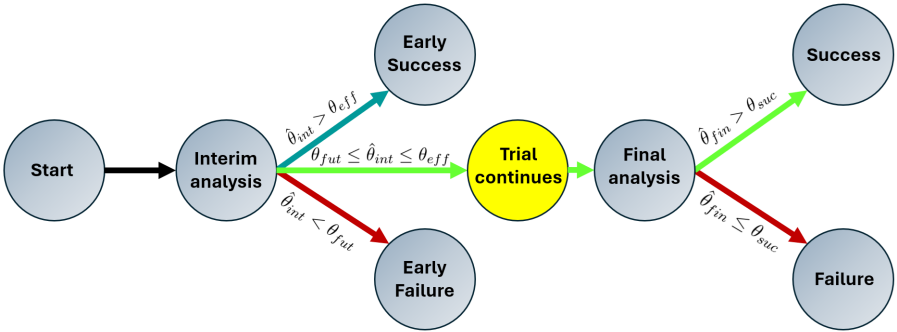
$\Rightarrow$ used to compute the *Probability of Success* (*PoS*)

PoS in a one-stage clinical trial



$$PoS = P(\textit{trial success}) = \int P(\hat{\theta} > \theta_{suc}|\theta)\, q_0(\theta) d\theta$$

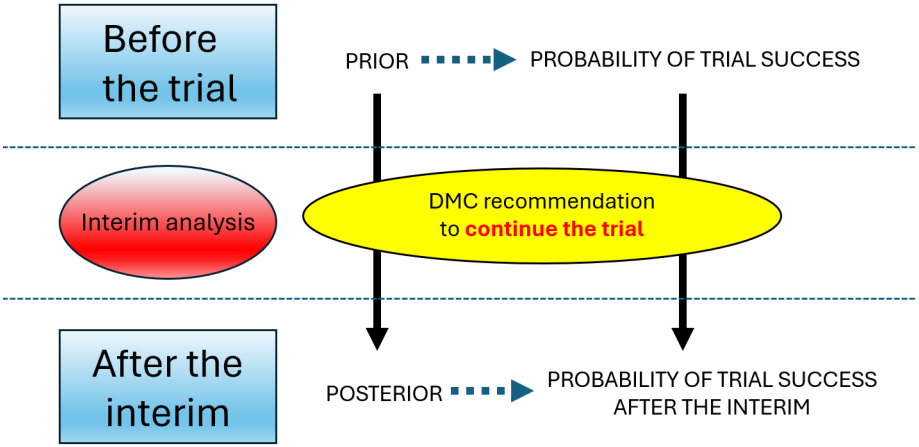
PoS in a two-stage clinical trial



$$PoS = P(\textit{early stop for efficacy}) + P(\textit{no early stop and success at final analysis})$$

$$= \int P(\hat{\theta}_{int} > \theta_{eff}|\theta)\, q_0(\theta) d\theta + \int P(\theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff},\, \hat{\theta}_{fin} > \theta_{suc}|\theta)\, q_0(\theta) d\theta$$

Incorporating DMC recommendation to continue the trial



PoS post interim

PoS is updated using the information $\theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff}$:

$$PoS_{post} = \int P(\hat{\theta}_{fin} > \theta_{suc} | \theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff}, \theta)\, q_1(\theta) d\theta$$

where $q_1(\theta)$ is the posterior:

$$q_1(\theta) = \frac{P(\theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff} | \theta)\, q_0(\theta)}{\int P(\theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff} | \theta')\, q_0(\theta') d\theta'}$$

Relationship between PoS and PoS_{post}

$$PoS_{post} = \int P(\hat{\theta}_{fin} > \theta_{suc} | \theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff}, \theta)\, q_1(\theta) d\theta$$

$$= \int \frac{P(\theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff},\, \hat{\theta}_{fin} > \theta_{suc} | \theta)}{P(\theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff} | \theta)} \frac{P(\theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff} | \theta)\, q_0(\theta)}{\int P(\theta_{fut} \leq \hat{\theta}_{int} \leq \theta_{eff} | \theta')\, q_0(\theta') d\theta'} d\theta$$

$$= \frac{P(\textit{no early stop and success at final analysis})}{P(\textit{no early stop})}$$

$$= \frac{PoS - P(\textit{early stop for efficacy})}{P(\textit{no early stop})}$$

Fictive case study

Parallel group trial (2 arms: T and R)
Continuous response (treatment effect assessed as mean difference T vs. R)
Power $= 0.9$
Alpha $= 0.025$ (one-sided)
Standardized treatment effect of interest $\Delta = 0.3$

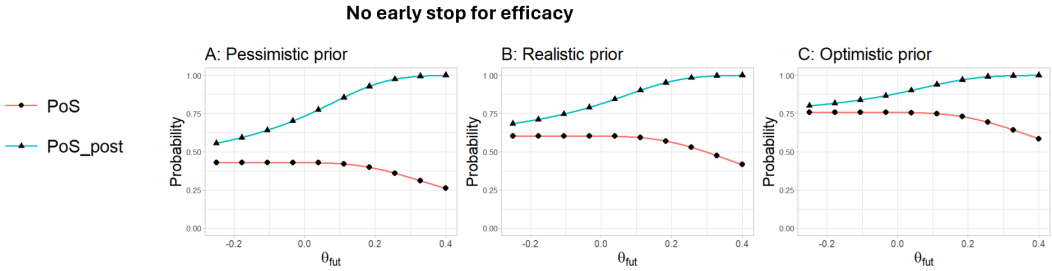
PoS is evaluated over 3 different priors of the form $\theta \sim \mathcal{N}\left(\theta_0, \frac{2}{n_0}\right)$

$n_0 = 10$

Pessimistic	Realistic	Optimistic
$\theta_0 = \Delta - 0.2$	$\theta_0 = \Delta$	$\theta_0 = \Delta + 0.2$

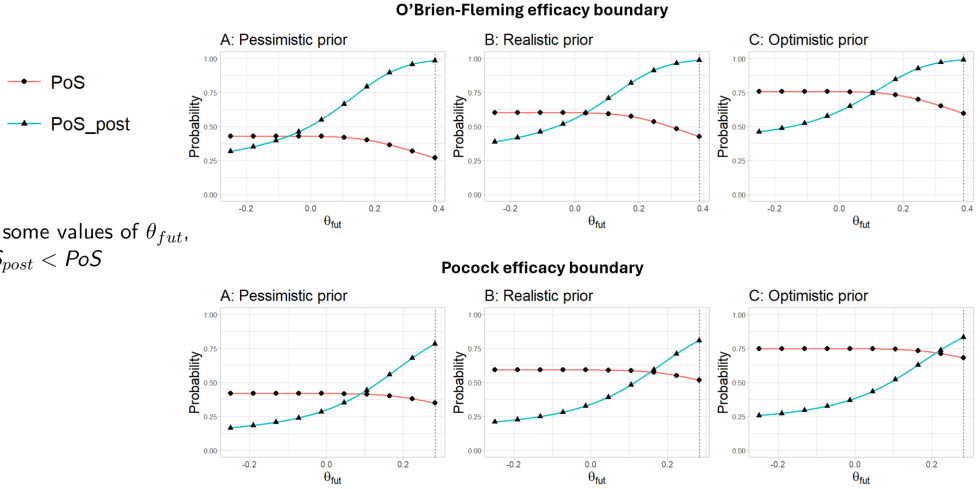
Case with no early stop for efficacy ($\theta_{eff} = +\infty$)

Tradeoff in the choice of the futility boundary: $\theta_{fut} \nearrow \implies \begin{matrix} PoS \searrow \\ PoS_{post} \nearrow \end{matrix}$



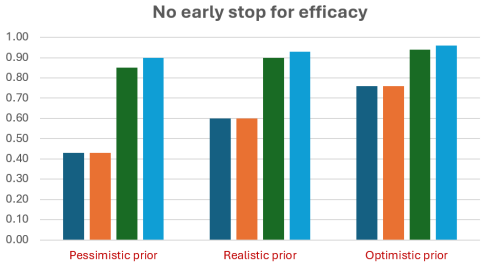
$$PoS_{post} = \frac{PoS}{P(\text{no early stop})} \implies PoS_{post} > PoS \quad (\text{not true for } \theta_{eff} < +\infty)$$

Case with an efficacy boundary



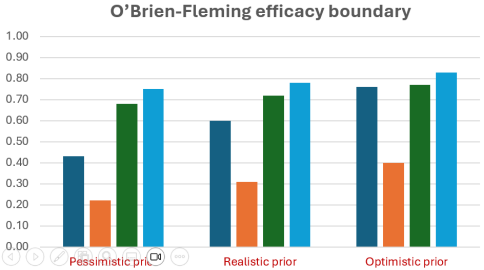
For some values of θ_{fut}, $PoS_{post} < PoS$

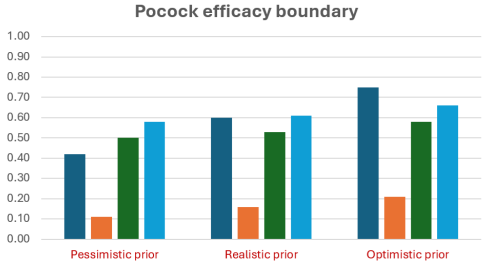
PoS and PoS_{post} trade-off



PoS reduced by a small amount with θ_{fut}
$\Rightarrow$ PoS_{post} increased by a large amount

PoS without futility
PoS_post without futility
PoS_post when PoS is reduced by 0.01
PoS_post when PoS is reduced by 0.02





Take-home messages

With an efficacy stopping rule, continuing after the interim may reduce the probability of success.

Tradeoff in the choice of the futility boundary: $\theta_{fut} \nearrow \implies \begin{matrix} PoS \searrow \\ PoS_{post} \nearrow \end{matrix}$

An appropriate choice of θ_{fut} may lead to a significantly larger PoS_{post}, with minimal losses in PoS.

Some reference

[1] K.J. Carrol. "Decision making from phase II to phase III and the probability of success: reassured by "assurance"?" In: *Journal of Biopharmaceutical Statistics* 23 (2013), pp. 1188–1200.

[2] C. Chuang-Stein. "Sample size and the probability of a successful trial". In: *Pharmaceutical Statistics* 5 (2006), pp. 305–309. DOI: https://doi.org/10.1002/pst.232.

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[4] A. O'Hagan, J.W. Stevens, and M.J. Campbell. "Assurance in clinical trial design". In: *Pharmaceutical Statistics* 4 (2005), pp. 187–201. DOI: https://doi.org/10.1002/pst.175.

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[6] J.R. Temple and J.R. Robertson. "Conditional assurance: the answer to the questions that should be asked within drug development". In: *Pharmaceutical Statistics* (2021), pp. 1–10. DOI: https://doi.org/10.1002/pst.2128.