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

Luca Rondano

Politecnico di Torino
Dipartimento di Scienze Matematiche
"Giuseppe Luigi Lagrange"
and
Chiesi Farmaceutici

Hybrid Bayesian/frequentist design of a superiority phase III trial

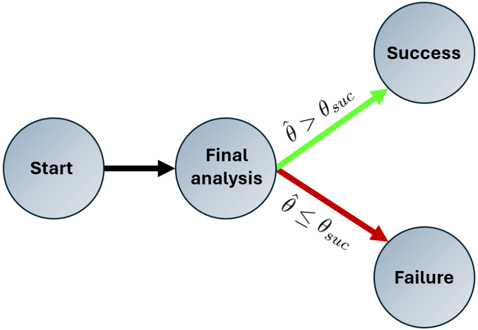
θ is the treatment effect (e.g., mean treatment difference between T and R)

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

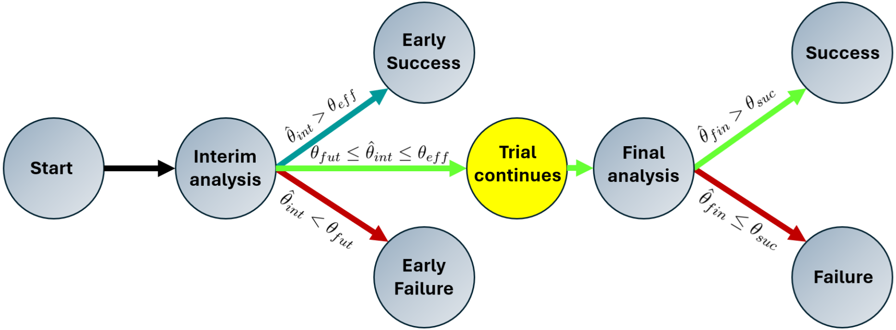
$\Rightarrow$ used to compute the *Probability of Success* (*PoS*)

PoS in a one-stage clinical trial



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

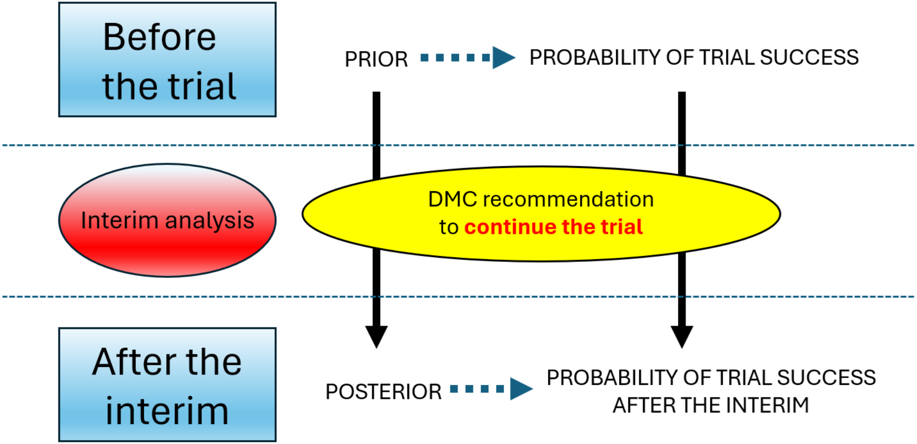
PoS in a two-stage clinical trial



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

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

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 $\Delta = 0.3$

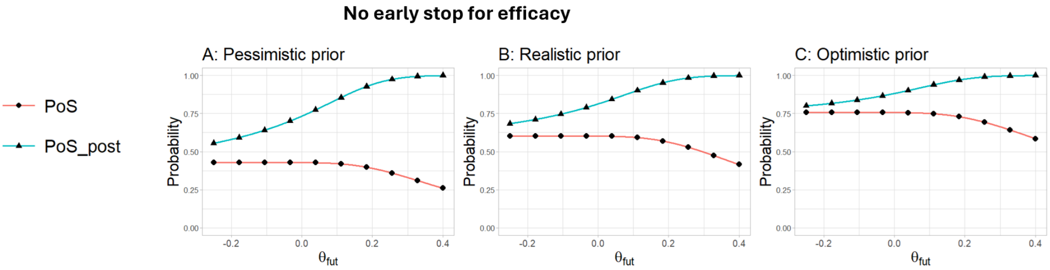
PoS is evaluated over 3 different priors of the form $\theta \sim \mathcal{N}\left(\theta_0, \frac{2}{n_0}\right)$

$n_0 = 10$

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

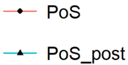
Case with no early stop for efficacy ($\theta_{eff} = +\infty$)

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

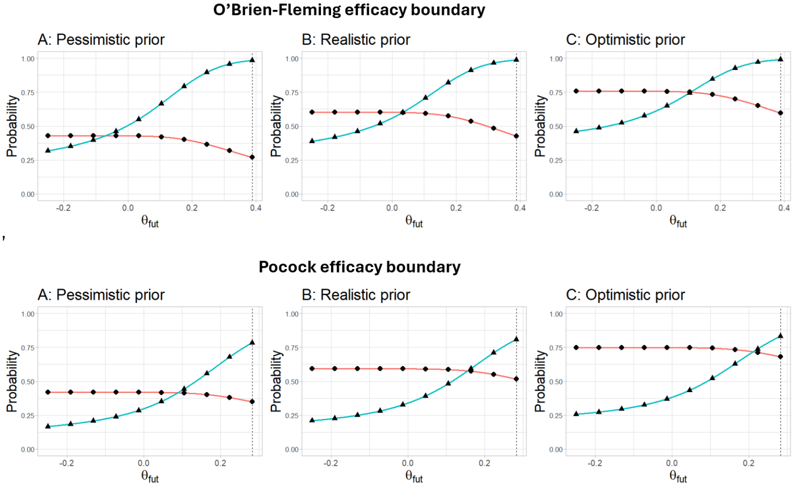


$$PoS_{post} = \frac{PoS}{P(\textit{no early stop})} \implies PoS_{post} > PoS \quad (\textit{not true for } \theta_{eff} < +\infty)$$

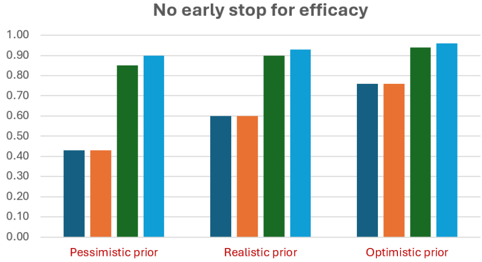
Case with an efficacy boundary



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

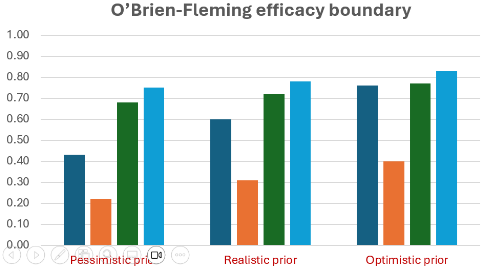


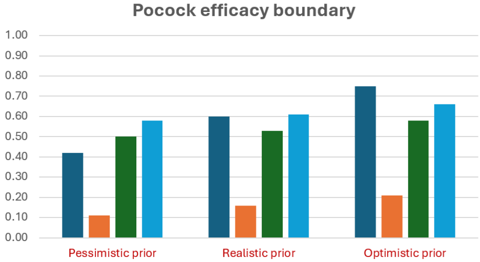
PoS and PoS_{post} trade-off



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: $\theta_{fut} \nearrow \Longrightarrow \begin{array}{r} PoS \searrow \\ PoS_{post} \nearrow \end{array}$

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.

[3] A.P. Grieve. *Hybrid Frequentist/Bayesian Power and Bayesian Power in Planning Clinical Trials*. CRC press, 2022.

[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.

[5] K. Rufibach, P. Jordan, and M. Abt. “Sequentially updating the likelihood of success of a Phase 3 pivotal time-to-event trial based on interim analyses or external information”. In: *Journal of Biopharmaceutical Statistics* 26 (2016), pp. 191–201.

[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.