Decision Making in Early Clinical Drug Development

Colloquium in Honor of Hans Ulrich Burger on the Occasion of His Retirement

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Transition and Decision Points in Clinical Drug Development

Prior to drug approval, decisions to . . .

. . . **not proceed** can solely be made by the Sponsor

. . . **proceed** typically will also require approval by IRBs, HAs, etc.

Phases may be skipped, combined etc., but decisons still need to be made.

Well Desigend Studies Enable Informed Decisions

- Endpoints collected with sufficient quality, frequency?
- Population, #Participants, Enrichment
- Control Arm?

- What's the decision to be made?
- What investment is involved (e.g., when deciding on early Phase 3 Go).
- Define Go/No-Go criteria before protocols are endorsed.

- How will the decision be made? When? Based on what data?
- What are the risks to e.g. stop a promising molecule or progress one which may not work?
- Risks acceptable or should study be changed?

Sponsor Decision to File at End of Phase 3

Phase 3 protocols (and statistical analysis plans) are typically discussed (and agreed upon) with Health Authorities:

- **Positive Efficacy Results:** Phase 3 must show that drug is effective at its intended purpose. Includes statistical significance, internal consistency etc.
  - $p < 0.05$ in one or two studies, $p < 0.01$ if only one study, . . . ?
  - Estimated effect clinically meaningful?
- **Favorable Safety and Tolerability:** May be ok, after all the DMC has not stopped the trial?
- **Positive Benefit-Risk Profile:** Benefits should outweigh possible risks.
- **Overall robust data package**.

Health Authority input supports setting expectations and making sure the study is fit for purpose. Acknowledging the expectations should simplify (filing) decisions.

Phase 3 Go Decision at End of Phase 2

Key objectices of Phase 2: Establish Proof of Concept (efficacy, acceptable safety) and enable dose / regimen selection for pivotal trials.

Here: Simplify matters by

- focusing on a single primary endpoint and considerations for setting Go/No-Go criteria; and
- assuming Phase 2 and Phase 3 endpoint are similar or relationship sufficiently characterized

Questions:

- What observed result warrants progressing to Phase 3?
- What are the false positive and false negative risks?

Competitive landscape, business case, resource situation, sponsor portfolio, etc., may change over the course of a Phase 2 study → Ideally revisit decision criteria prior to analysis.

Phase 2 Planning Considerations

Define the objectives? What's of primary importance for Phase 3 Go?

Endpoint Selection:
- Clinical endpoint? Surrogate endpoint?
- Effect size?

Study Design:
- Parallel? Placebo controlled? External control? Adaptive? Interim Analysis?

Statistical Considerations:
- Effect size? Power? Analysis? Sample size? Interim analyses? Multiplicity etc. Subgroups? Go/no-Go criteria?

Clinical Considerations:
- Safety information? I/E criteria to describe target population?

Target Product Profile – Focus on Efficacy

Describes the requirements for a product to be «successfull», typically covers

- **Indication:** Treatment of XX disease as add-on to background therapy.
- **Population:** Patients with XX disease (score 1 or 2) and on stable background therapy with ….
- **Efficacy:** Clinically meaningful improvement in mean change from baseline of the ABC endpoint at Week 52 (ES ≥ 0.3)
- **Safety:** Suitable for chronic use, manageable long term safety, etc.

Likelihood to Achieve Success in Phase 3
«Probability of Success»

- Derive «prior» distribution $p(\Delta)$ incorporating current knowledge about the drug effect.
  May be determined by Phase 2 results, but can take other information into account.

$$PoS = \int P(\text{Succes in Phase 3 Study} \mid \Delta) \cdot p(\Delta)\, d\Delta$$

Ibrahim et al. (2015)

- «Success» may refer to statistical significance paired with a requirement for the observed drug effect to exceed thresholds as per product profile

Phase 2 Result (Effect Size (ES))	0.2	0.3	0.33	0.35	0.4	0.5
Probability of Success (ES ≥ 0.3) at end of Phase 3	31%	50%	56%	60%	69%	84%

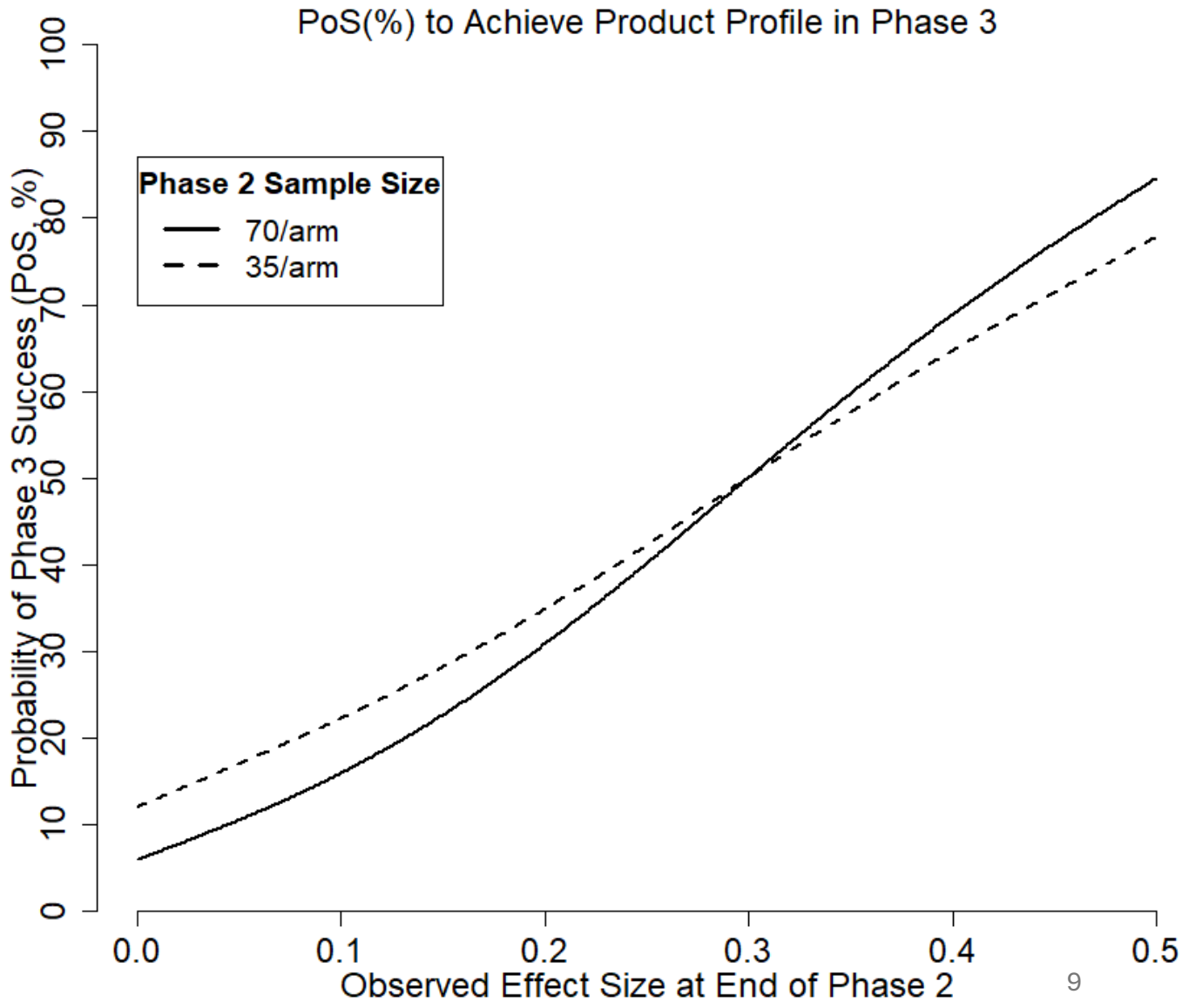
Table assumes Ph3/Ph 2 sample size of 175/70 per arm.

Inclusion of historical data (Ibrahim et al. 2015)); Use simulation for more complex Phase 3 trials (Wang et al. (2013)); Multiple Phase 3 studies (Zhang et al. (2013)); Contrast with power (Zierhut et al. (2016)); Updating PoS after interim analyses (Rufibach et al. (2016); Broglio et al. (2014)); etc.

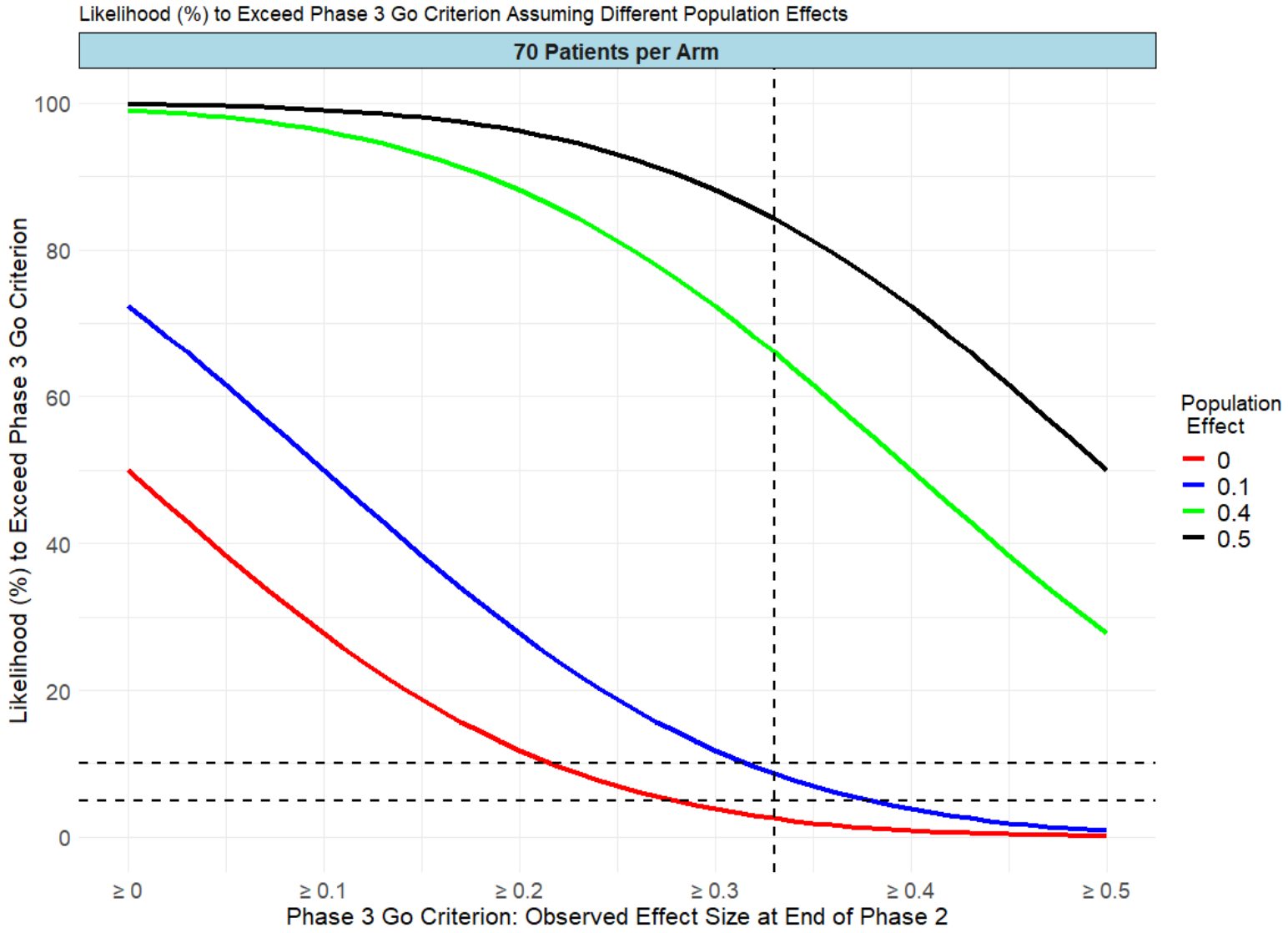
PoS is Not Very Sensitive to Sample Size

- Phase 3 planned with 175 pts/arm; Phase 2 with 70 pts/arm (possibly multiple arms)
- Population, treatment duration, etc. similar between Phase 2 and Phase 3.
- Phase 3 PoS derived as likelihood for $p < 0.05$ & Phase 3 result $\geq$ product profile (ES=0.3)

- **Not the best tool for sample sizing Phase 2 studies.**
- **Role at Interim Analyses?**



Risk of False GO and NO-GO Decisions



- Ineffective drugs (ES=0) have virtually no chance to exceed the threshold of 0.33
- Drugs with a clinically irrelevant effect (ES=0.1) have a less than 10% chance to exceed the threshold of 0.33
- Good drugs (ES=0.5) have a high chance to be successfull.

Decision Making at Interim Analysis – Futility or Early GO?

Phase 2 studies using clinical endpoints can take several years (e.g., Pagano et al. (2022), Swanson et al. (2022), Mintun et al. (2021)).

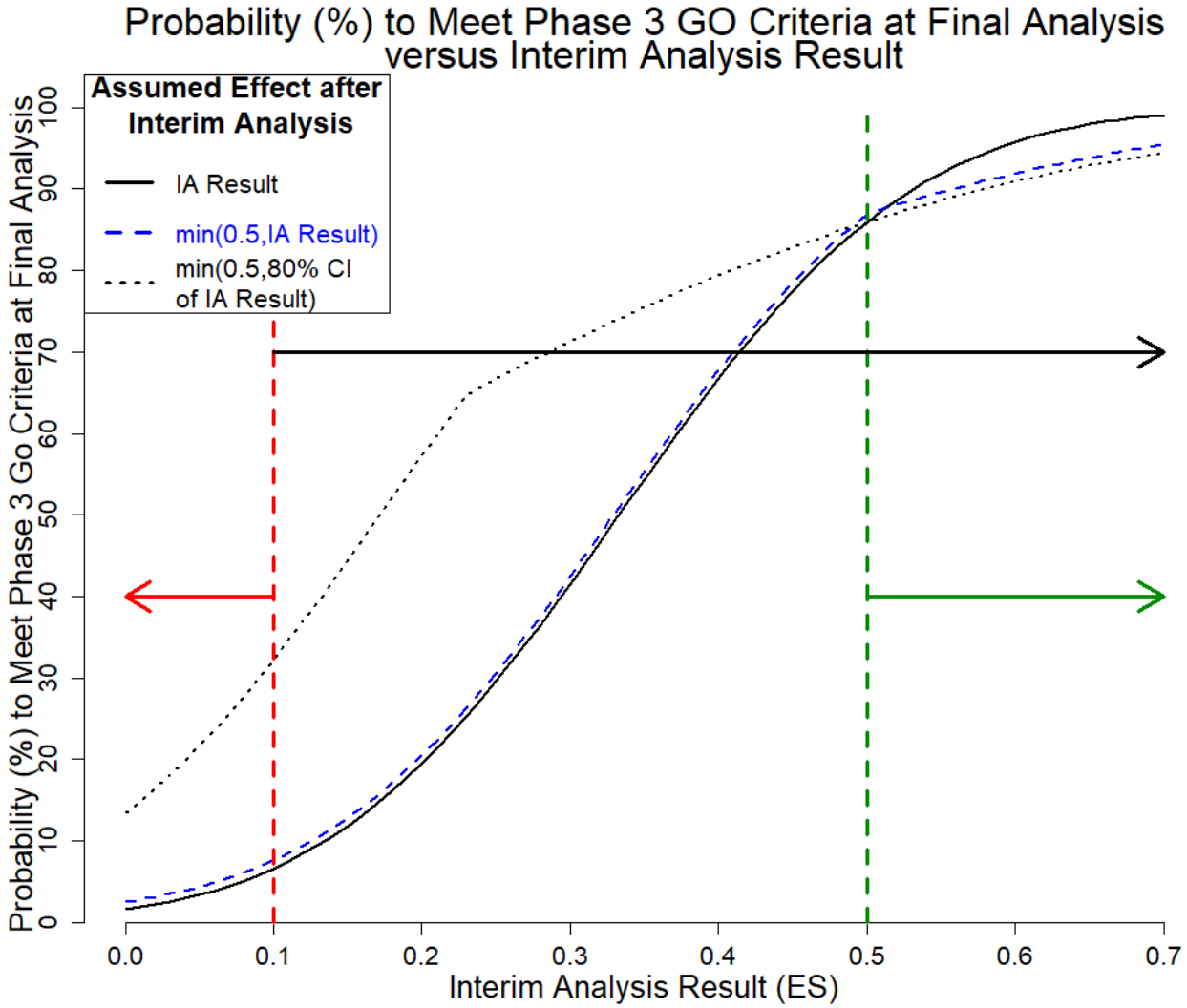
Interim analyses may enable stopping studies (dropping dose arms) early in case they do not work and/or accelerate Phase 3 activities.

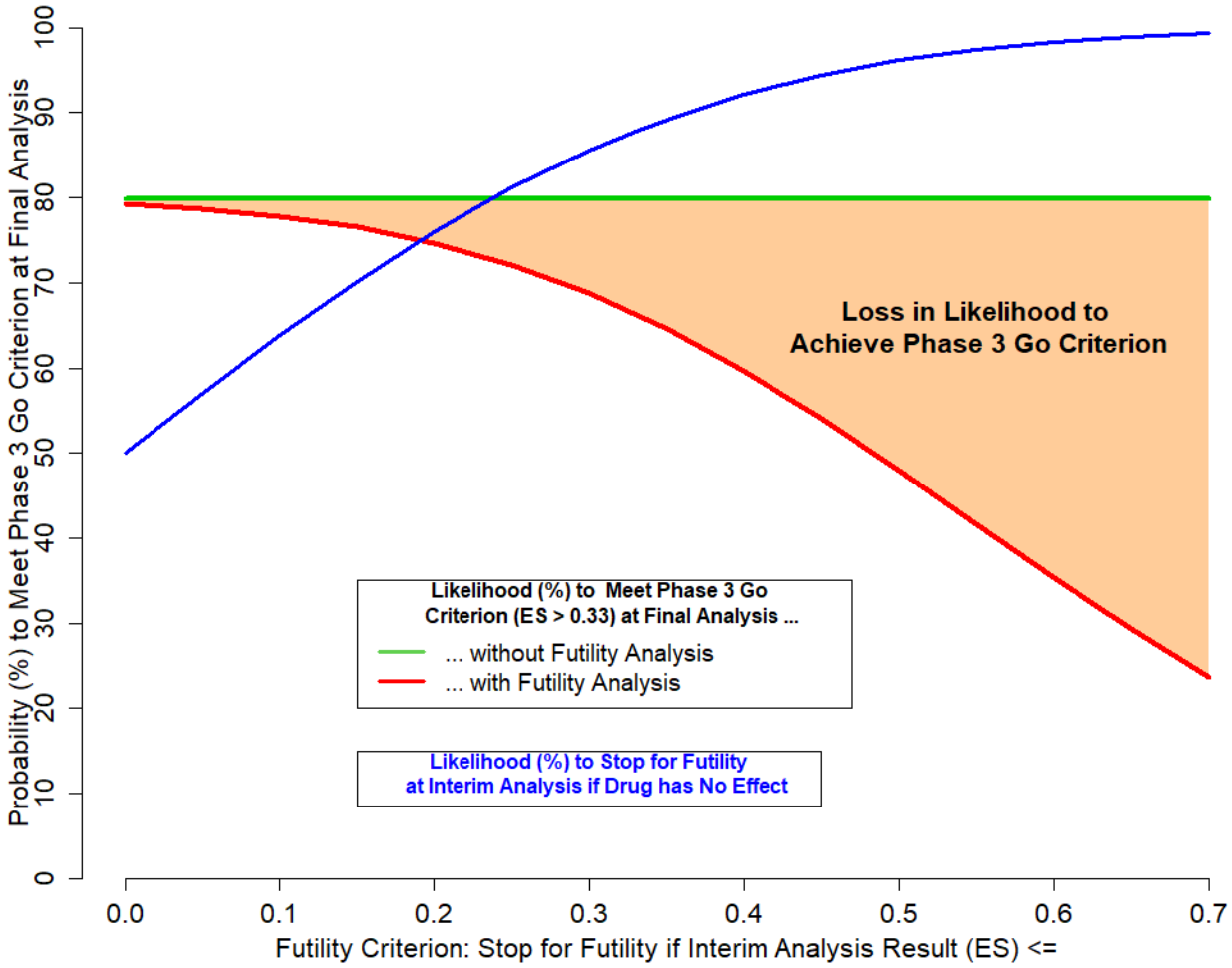
Can not plan interim analyses without agreed «Phase 3 Go» criteria at study end.

Questions:

- **Based on the interim analysis results, what is the (conditional) likelihood to reach the agreed «Phase 3 Go» criteria at study end?**
  Conditional power, Bayesian predictive power (Saville (2023), Ellenberg (2022))
  Plays a role for both, «futility» as well as «acceleration» decisions.
- **How does futility impact the likelihood of success at the end of Phase 2?**
  Evaluate «Power loss»

Conditional and Loss in Likelihood to Achieve Phase 3 GO at EoP2





Ellenberg et al. (2022)

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