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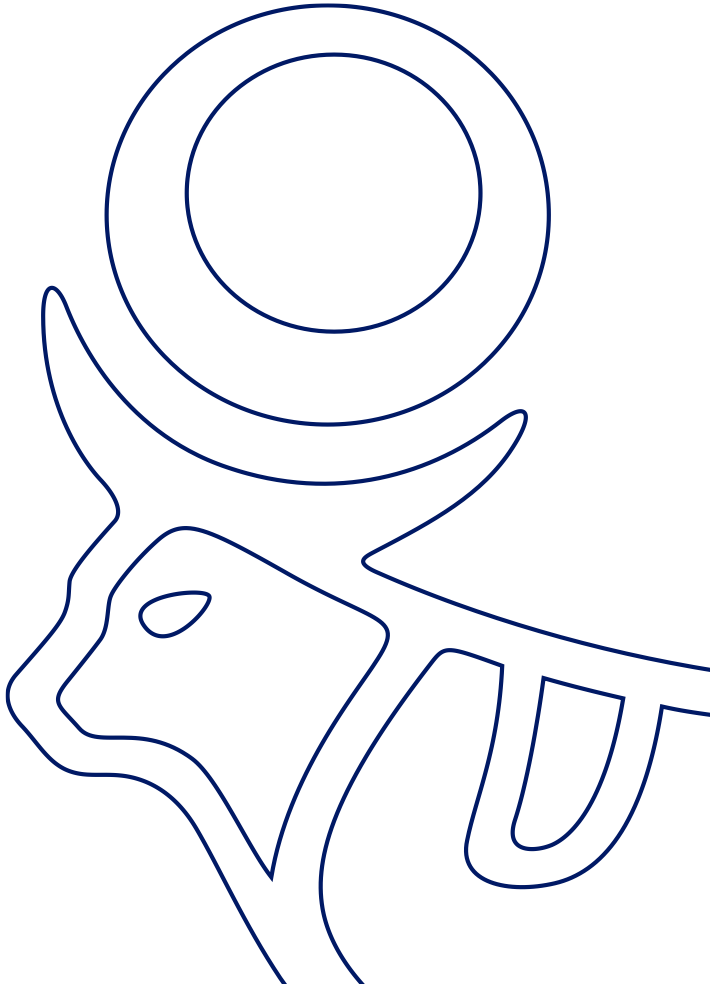
Crafting a recipe for success : Aligning Target Product Profiles and study design to ensure statistical significance translates to clinical relevance and role of DGF

Statistical significance ≠ Clinical significance (not always)



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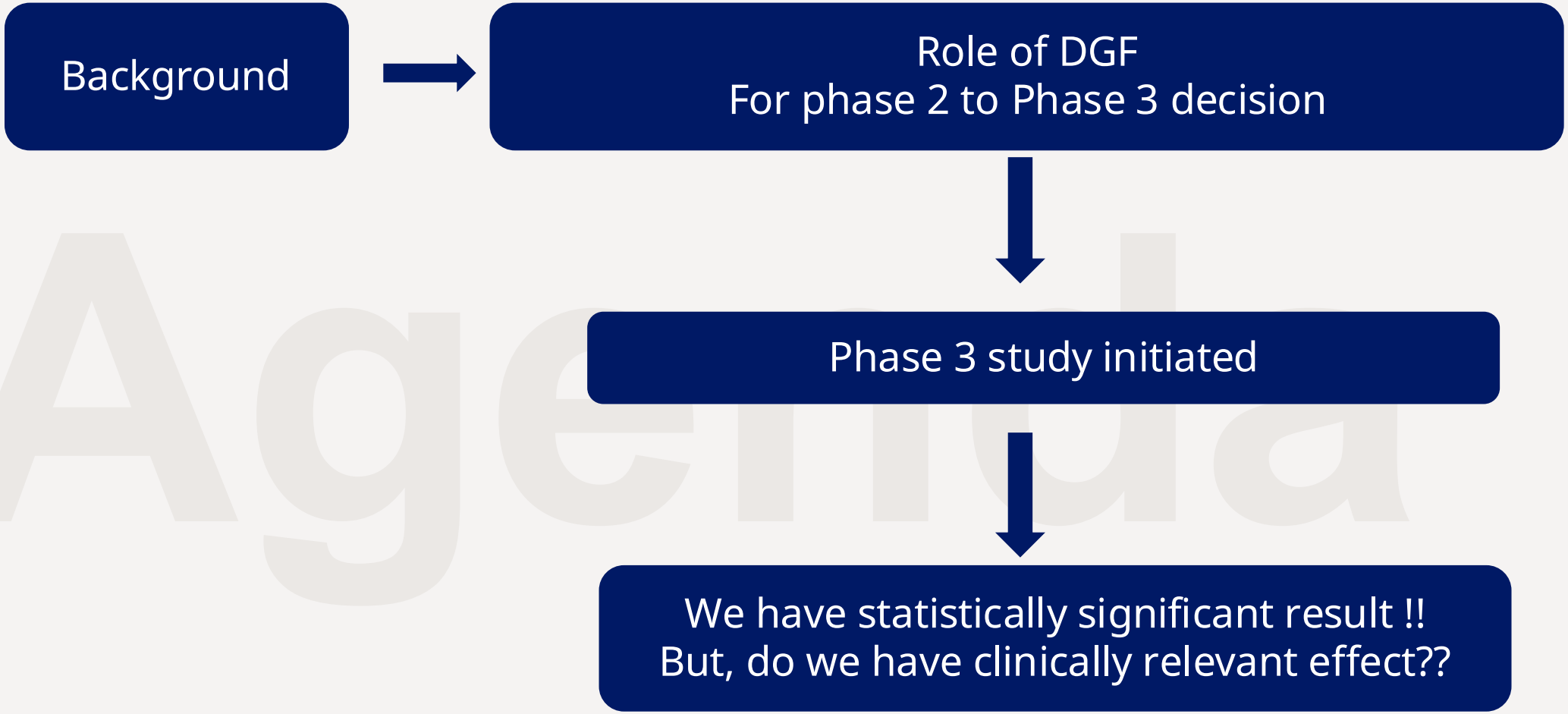
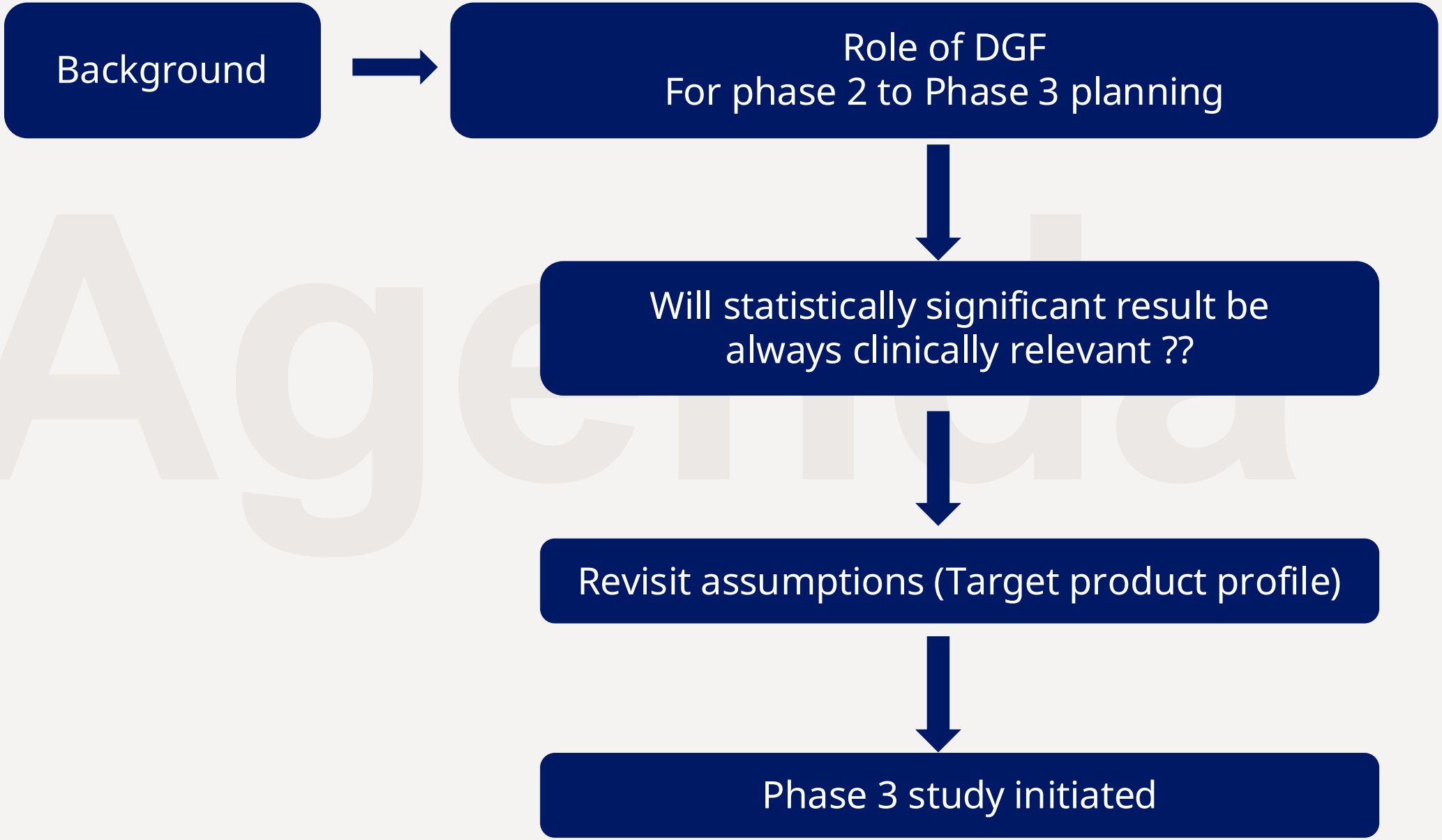

Background
Role of DGF
For phase 2 to Phase 3 decision
Phase 3 study initiated
We have statistically significant result !!
But, do we have clinically relevant effect??


Background
Role of DGF
For phase 2 to Phase 3 planning
Will statistically significant result be always clinically relevant ??
Revisit assumptions (Target product profile)
Phase 3 study initiated

Background

- Company X has a drug for cardiomyopathy that completed a Phase 1 study.
- Four dose levels (10–100 mg/kg) were well tolerated with no safety signals. Global longitudinal strain (GLS), a cardiac function marker, indicated a potential benefit.
- The company plans to proceed to a Phase 2 study using “Biomarker XX", a well-established biomarker for diagnosis and prognosis in heart failure. Phase 3 planning will be based on the Phase 2 results.
- During Phase 2 (before Database lock), the team requires a tool to guide the Phase 3 decision.
- What could be a suitable tool ?

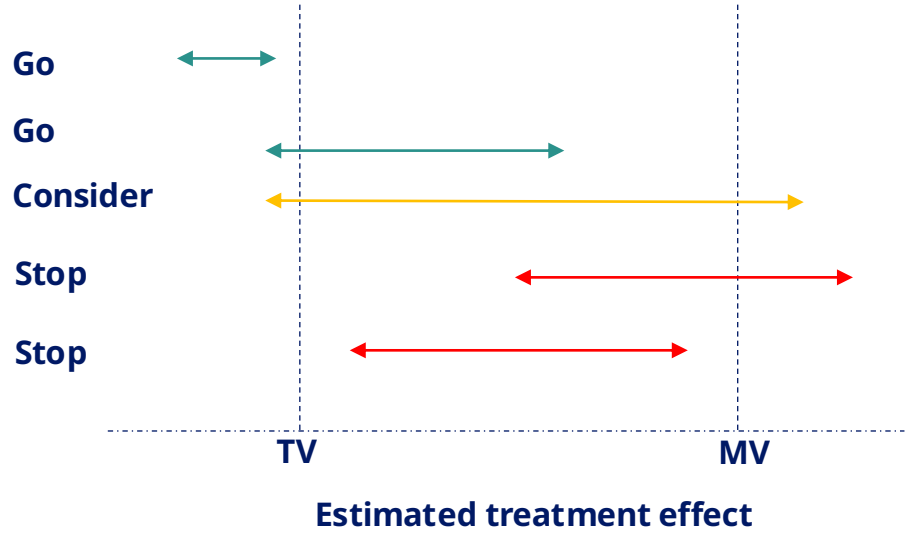
Decision Guiding Framework (DGF)

Construction of DGF and interpretation

Input parameter	Description
Target value (TV)	Highest treatment effect according to guided decision where the business case is attractive in-line with TPP (Also inline with results of competitor)
Minimum value (MV)	At least the lowest treatment effect with clinical/commercial value
False stop risk	Risk of stop if true treatment effect is at TV (e.g. 10%)
False go risk	Risk of go if true treatment effect is at MV (e.g. 15%)

* Frewer et al 2016 DOI:10.1002/pst.1746
** Lower values are better; higher values are worse.

Decision rule (For ratios**)



Interpretation :

- **Stop**, if there is ≥ 90 % probability that the true treatment effect is above TV

Else,

- **Go**, if there is ≥ 85 % probability that the true treatment effect is at least lesser than MV

Else, **Consider**

Will come back to this in few moment ..

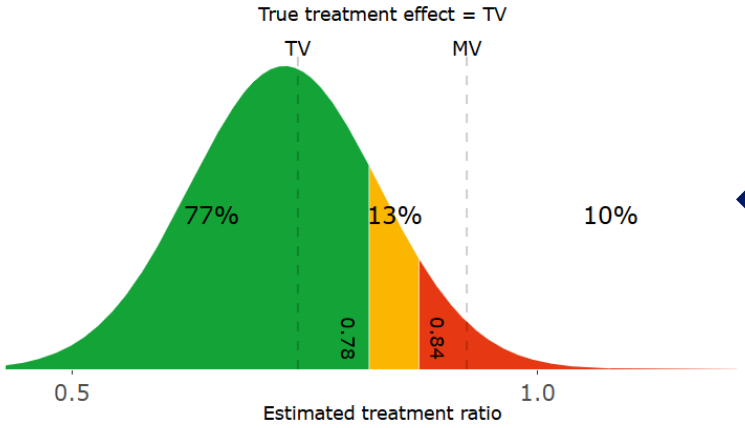
Construction of DGF and interpretation

Biomarker XX *- DGF guiding Phase 3 decision based on phase 2 results*

	Justification/Assumptions
Parameter: **Ratio of "Biomarker XX" from baseline to 64 weeks for 100mg/kg vs placebo**	Well established biomarker for diagnosis and prognosis of heart failure. Competitors demonstrating an effect on survival have also demonstrated an effect on change in "Biomarker XX" versus placebo A consistent correlation between change in "Biomarker XX" and hard outcomes has not yet been established in internal or external resources.
Target Value: **0.7**	30% is considered progression threshold in particular Disease area. *(Based on literature, competitive intelligence and Commercial perspective)*
Minimum Value: **0.9**	SME input: Anticipate laboratory preceding clinical/functional changes hence should demonstrate 'early' improvement.
Risk setting: **False Stop: 10 %** **False Go: 15 %**	
Variation: **<Specify observed variation>**	CV = 80% (Based on variation at week 64 observed data (For around 25% data))
Sample size: **<Specify actual number of subjects>**	N = 50 per arm

Construction of DGF and interpretation

Biomarker XX *- DGF guiding Phase 3 decision based on phase 2 results*




```
> ## Calculation for DGF Zones for Phuse APAC
> (sigma_square <- log(0.8**2+1)) # Transforming CV
[1] 0.4946962
>
> # False stop (10%) : Cutoff calculation [ Under TV ]
> exp(qnorm(0.9)*sqrt(sigma_square*(2/50))+log(0.7)) # Assuming mean ratio=0.7 (equal to TV), Each arm=50 participants, under which value 90% of values lie ?
[1] 0.8382826
> round(exp(qnorm(0.9)*sqrt(sigma_square*(2/50))+log(0.7)),2)
[1] 0.84
>
> # False go (15%) : Cutoff calculation [ Under MV ]
> exp(-qnorm(0.85)*sqrt(sigma_square*(2/50))+log(0.9)) # Assuming mean ratio=0.9 (equal to MV), Each arm=50 participants, under which value 85% of values lie ?
[1] 0.7779019
> round(exp(-qnorm(0.85)*sqrt(sigma_square*(2/50))+log(0.9)),2)
[1] 0.78
```

Probability of recommended decisions

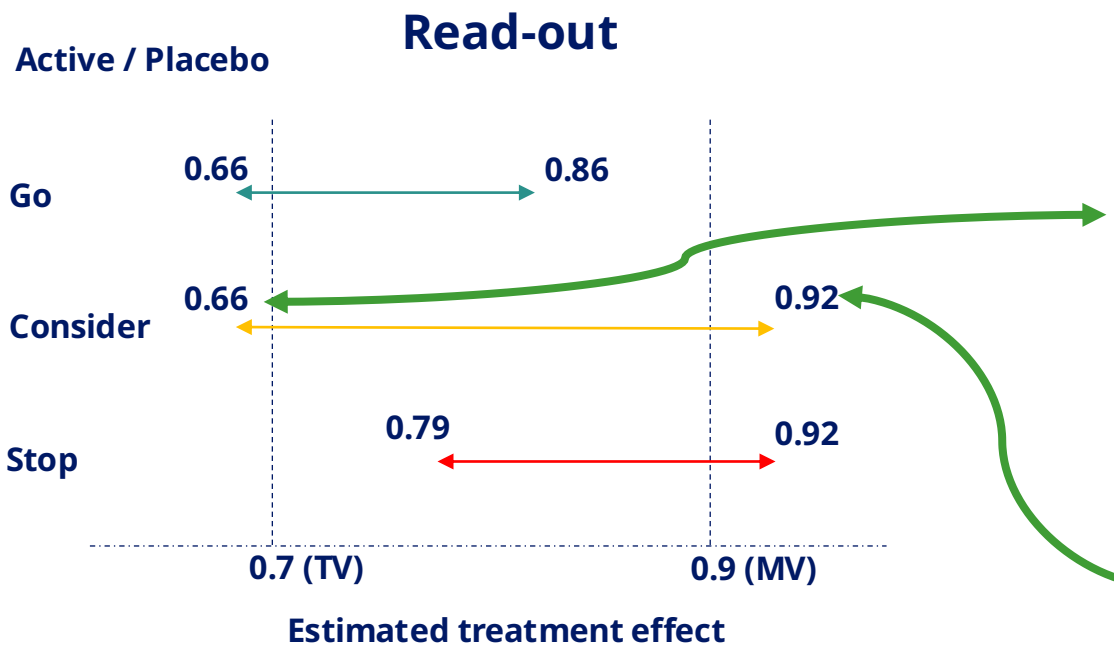
True treatment effect	Scenario	Go (%)	Consider (%)	Stop (%)
0.7	Target value	77.3	12.7	10.0
0.9	Minimum value	15.0	15.7	69.3

```
> # Under TV
> round(plnorm(0.7779019,log(0.7),sqrt(sigma_square*2/50)) * 100,1) # Prob of Go Zone
[1] 77.3
> round((plnorm(  0.8382826,log(0.7),sqrt(sigma_square*2/50))-plnorm(0.7779019,log(0.7),sqrt(sigma_square*2/50)))*100,1)  # Prob of Consider Zone
[1] 12.7
> round((1-plnorm( 0.8382826,log(0.7),sqrt(sigma_square*2/50)))*100,1) # Prob of Stop Zone
[1] 10
> # Under MV
> round(plnorm(0.7779019,log(0.9),sqrt(sigma_square*2/50)) * 100,1) # Prob of Go Zone
[1] 15
> round((plnorm(  0.8382826,log(0.9),sqrt(sigma_square*2/50))-plnorm(0.7779019,log(0.9),sqrt(sigma_square*2/50)))*100,1)  # Prob of Consider Zone
[1] 15.7
> round((1-plnorm( 0.8382826,log(0.9),sqrt(sigma_square*2/50)))*100,1) # Prob of Stop Zone
[1] 69.3
```

- Stop, if treatment effect is **< 16 (% decrease),** corresponding to treatment ratio of **0.84**
- Go, if treatment effect is **≥ 22 (% decrease),** corresponding to treatment ratio of **0.78**

Construction of DGF and interpretation

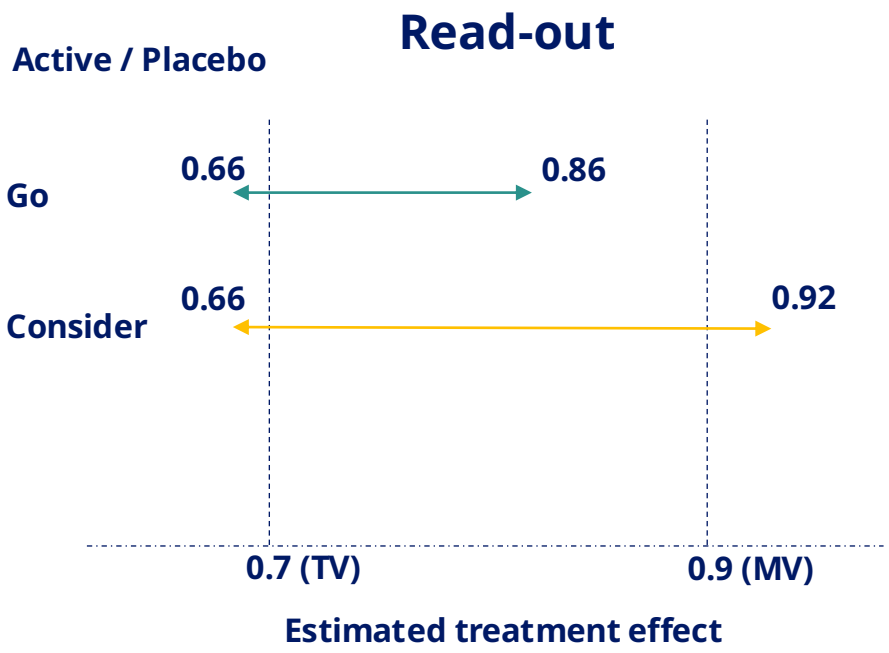
***NT-proBNP** - DGF guiding Phase 3 decision based on phase 2 results*




```r
# summarise based on final model ------------------------------------------
# Use mice for treatment ratio and difference

dif_sum <- map(final,
               ~lm(LOGCHG ~ TRTP + V200 + STRATAR, data = .x)) %>%
  pool(rule = "rubin1987", dfcom = ndof)

# get one-sided lower 10% limit for 90% CI ~ lower confidence limit for 2 sided 80% CI

dif_ll <- dif_sum %>%
  tidy(conf.int = TRUE, conf.level = 0.8) %>%
  filter(grepl("Treatment", term)) %>%
  mutate(contrast = paste(str_remove(term, "TRTP"), "/", "Placebo"),
         ratio = exp(estimate),
         SE = std.error*exp(estimate),
         "{lcl_nm}" := exp(conf.low),
         "{ucl_nm}" := exp(conf.high)) %>%
  select(contrast, all_of(c(lcl_nm)))

# get one-sided upper 15% limit for 85% CI ~ upper confidence limit for 2 sided 70% CI

dif_ul <- dif_sum %>%
  tidy(conf.int = TRUE, conf.level = 0.7) %>%
  filter(grepl("Treatment", term)) %>%
  mutate(contrast = paste(str_remove(term, "TRTP"), "/", "Placebo"),
         ratio = exp(estimate),
         SE = std.error*exp(estimate),
         "{lcl_nm}" := exp(conf.low),
         "{ucl_nm}" := exp(conf.high)) %>%
  select(contrast, ratio, SE, df, all_of(c(ucl_nm)), p.value) %>%
  left_join(dif_ll, by = 'contrast')
```

Construction of DGF and interpretation

Biomarker XX *- DGF guiding Phase 3 decision based on phase 2 results*



Consider zone :

- Stakeholders to discuss with : Portfolio manager, M&S, Safety, Commercial, Competitive intelligence.
- Develop decision criteria based on other parameters/ secondary endpoints.

  For example, hsCRP, 6MWT, MRI/Echo parameters (ECV/GLS

  etc) and take a decision based on historical data.

(This should be planned earlier before database lock as a backup plan)

- This approach can also inform portfolio-level decisions. For example, when resources are limited, a company may opt not to assume the additional risk of advancing a compound in the Consider zone and instead allocate resources to candidates with a clear positive decision.

Target product profile

- A set of specifications that define the key product attributes required at launch to ensure commercial viability and market appeal.
- Sets the direction for clinical programme.
- Guiding document for regulatory activities, CMC and product supply planning as well as patient access initiatives.

TPP comprises of :

- Indications and usage
- Dosing and administration
- Dosage forms and strengths
- Clinical efficacy/pharmacology
- Safety and tolerability
- Storage
- Use in specific populations
- Health economics and PROs

Figure source : AI generated

Reference :
U.S. Food and Drug Administration (2007). Guidance for Industry and Review Staff Target Product Profile - A Strategic Development Process Tool. Draft guidance

Phase-3 study read-out

Primary endpoint :

Time to first occurrence of a 3-component MACE endpoint comprising CV death, Non-fatal MI, Non-fatal stroke

The study is designed using an unstratified Cox model and a **power of 90%** to confirm superiority using a study-wise type I error rate of **2.5%** (one-sided) for the primary endpoint. Using a **randomisation ratio of 1:1** and **assuming a true HR of 0.7** a total of 331 primary endpoint events are required.

```
> Z_alpha <- qnorm(1-0.05/2)  # ~1.96
> Z_beta <- qnorm(0.90)    # ~1.28
> HR = 0.7
> p1 = 1/2  # 1:1 randomization
> p2=1-p1
> event_required <- (((Z_alpha + Z_beta)/log(HR) )**2)*(1/(p1*p2))
> event_required # 331 events
[1] 330.3779
```

$$\text{Number of events} = \text{E} = \frac{(\text{Z}_{1-\beta} + \text{Z}_{1-\frac{\alpha}{2}})^2}{\text{p}_\text{A} * \text{p}_\text{B} * \log(\text{HR})^2}$$

$$\text{p}_\text{A} = \text{p}_\text{B} = 1/2$$

Study read-out

Study reads out positive with p-value*<0.05

Obs(HR) = 0.806

Is this HR clinically relevant?

* : 2-sided p-value

Questions around study read-out

- Note that, to actually observe the HR=0.7, we would need very large effect (p-value = 0.0012)
- If clinicians/commercial teams expect a hazard ratio (HR) of 0.7 when the study reaches statistical significance and treat 0.7 as the boundary of clinical relevance given the competitive landscape — there is a risk of disappointment.
- Specifically, if the final estimate falls between 0.70 and 0.806, the result may be statistically significant but clinically marginal; in the extreme, the trial could be "**statistically significant but clinically as well as commercially irrelevant**."

1. Is the observed hazard ratio consistent with the minimal clinically important difference (MCID)?
2. Do we "really" care at which effect we have 90% power?

Ultimately, we want studies that are powered in such a way that are both statistically significant for all effects which are also clinically relevant.

$$P(\text{Surpassing the MDD*}) \neq P(\text{Surpassing the Target})$$

*MDD as the minimal value we need to have to get a statistically significant difference.

Minimal detectable difference

How to calculate?

$$H_0 : \text{HR} \geq 1 \text{ ag. } H_1 : \text{HR} < 1$$

Let, $\theta = \log(\text{HR})$

$\hat{\theta}$ = log(HR) follows approximately $N(\theta, \frac{4}{d})$

$SE(\hat{\theta}) = \sqrt{\frac{4}{d}}$

$$\frac{\hat{\theta} - \theta}{SE(\hat{\theta})} \sim N(0,1)$$

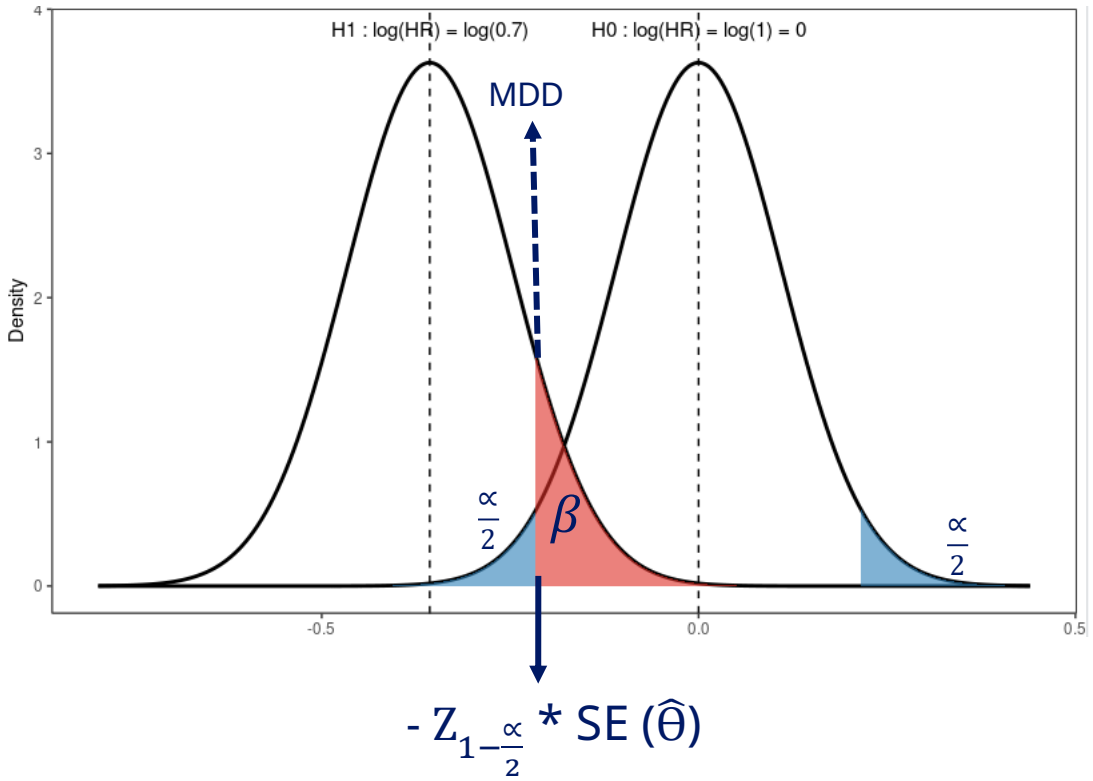
So, Minimal detectable difference = $- Z_{1-\frac{\propto}{2}} * SE(\hat{\theta})$

```
> round(exp(-qnorm(1 - 0.05 / 2) * sqrt(4 / 331)),3)
[1] 0.806
```

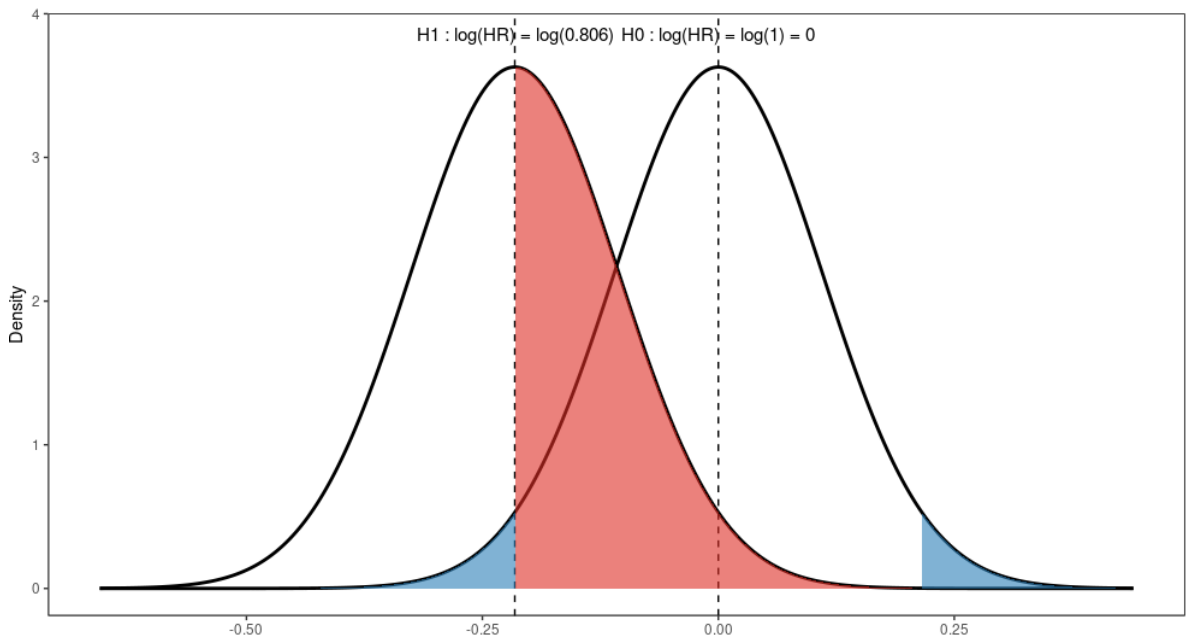
```
> # Sample size
> library(rpact)
> samplesize <- getSampleSizeSurvival(sided = 2, alpha = 0.05, beta = 1-0.9, hazardRatio = 0.7)
> samplesize$eventsPerStage
         [,1]
[1,] 330.3779
>
> # MDD from rpact
> mdd <- as.vector(samplesize$criticalValuesEffectScaleLower)
> mdd
[1] 0.8060081
```

How can we match our study design with Target product profile ?

How much power do we have to detect an effect equal to MDD ?



If we shift the distribution of the alternative at MDD then we would see that the red area under the curve would be 50% - the effect at which we have 50% power.



How can we match our study design with Target product profile ?

Upside scenario/Aspirational TPP

HR=0.7

Base TPP

HR=0.8

Figure source : AI generated

How can we match our study design with Target product profile ?

The minimal hazard ratio we need to achieve is 0.8, so we set our MDD=0.8
So, we start our sample size calculation with 50% power

```
> samplesize_new <- getSampleSizeSurvival(sided = 2, alpha = 0.05, beta = 1-0.5, hazardRatio = 0.8)
> samplesize_new$maxNumberOfEvents
[1] 308.594
```

Now we would find the hazard ratio at which with **309 events we can achieve 90% power.**

$$\text{Number of events} = \text{E} = \frac{(Z_{1-\beta} + Z_{1-\frac{\alpha}{2}})^2}{p_A * p_B * \log(HR)^2}$$

$$p_A = p_B = 1/2$$

$$HR = \exp\left(\frac{-2\,(Z_{1-\beta} + Z_{1-\frac{\alpha}{2}})}{\sqrt{E}}\right)$$

```
> exp(-2 * (qnorm(1-0.05/2) + qnorm(1-0.1)) / sqrt (309))
[1] 0.691559
```

Approximately we are in-line with the aspirational TPP with 309 events to achieve 90% power.

Conclusion

Define clinical relevance before statistical success: Pre-specify the magnitude of benefit that would be considered meaningful for patients and the business (TPP-derived Target and Minimum Values). This anchors all downstream decisions and prevents over-reliance on p-values alone.

- Use a Decision Guiding Framework (DGF): A probabilistic DGF that incorporates Target Value, Minimum Value, acceptable false-stop/false-go risks, observed variability, and sample size provides transparent, quantitative guidance at interim or pre-lock readouts to decide Go / Stop / Consider.
- Power studies for clinically meaningful effects: Design trials so they have adequate power to detect effects that meet the TPP (not merely the smallest statistically detectable difference). Align event counts, hazard-ratio assumptions, and MDD calculations with the TPP to avoid statistically significant but clinically irrelevant outcomes.
- Plan for the “consider” zone: Predefine secondary endpoints and decision criteria (biomarkers, functional measures, imaging, safety, commercial context) to inform decisions when primary results fall between Target and Minimum values.
- Interpret results in context: Combine effect size, confidence intervals, safety, cost, and real-world applicability. Even statistically significant results require interpretation against the TPP, clinical meaningfulness, and competitive landscape to be actionable.
- Better portfolio decisions and patient outcomes: Applying these principles reduces the chance of advancing marginal candidates, improves resource allocation across programs, and increases the likelihood that positive trials translate into meaningful clinical benefit.

References

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Thank you