More complex success criteria

More complex success criteria can be considered, for example:

- A significant p-value and an observed effect size above a minimum relevant limit
- A q% confidence interval of which the lower limit exceeds a minimum relevant limit
- A significant p-value for the null hypothesis that the effect is smaller or equal to the minimum relevant limit
- Criteria based on multiple endpoints
- Bayesian success criteria, e.g. $P[\delta > \Delta] > \pi$
- ...

FERRING PHARMACEUTICALS

Exercise 3 – adding a requirement on the minimum relevant effect to assurance

1. To the plot from Exercise 2, add a line for assurance where success is declared if the p-value is significant AND the effect estimate is at least 1.5
   - Hint: modify the formula from Slide 31
2. What is the upper bound for this version of assurance?
3. Also add to the plot a line for assurance where success is declared in case of a significant p-value for evaluating the null hypothesis that the effect equals 1.5
   - Hint: modify the formula from Slide 31
4. What is the upper bound for this version of assurance?
5. Which version of assurance do you prefer for the case study?

Bonus: what sample size would we need for the confirmatory trial if we wish to reject a null hypothesis that the effect equals 1.5 and we assume the effect is 2 under the alternative and we require 90% power and wish to control the false positive rate at 2.5% one-sided?

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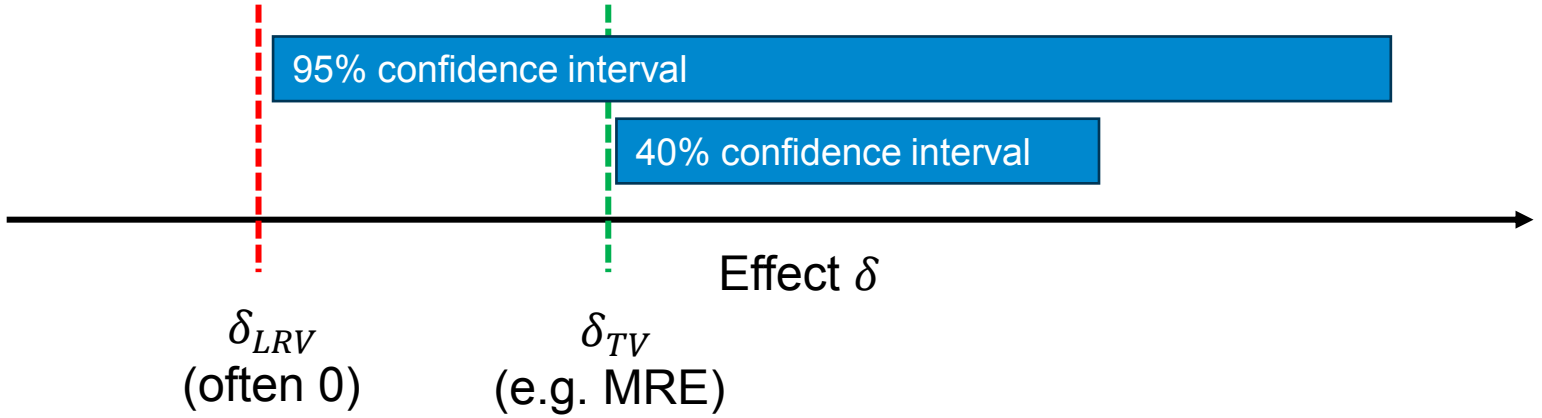
Dual success criteria



- **Criterion 1 (minimum requirement)**: at least 97.5% confidence that the effect exceeds δ_{LRV}
- **Criterion 2 (relevance requirement)**: at least 70% confidence that the effect exceeds δ_{TV}

- **Lower reference value (δ_{LRV}):** usually, but not always, the threshold for 'statistical significance', e.g. 0 difference in mean response, odds ratio of 1, hazard ratio of 1 etc.
- **Target value (δ_{TV}):** usually clinically relevant (or commercially viable) value.

Note that we can choose other values than 97.5% and 70% for the levels of confidence

Declaring success with dual success criteria

Success is declared if:

The minimum requirement is met: $\bar{y}_1 - \bar{y}_0 > \delta_{LRV} + Z_{1-\alpha_0}\tau$

AND

The relevance requirement is met: $\bar{y}_1 - \bar{y}_0 > \delta_{TV} + Z_{1-\alpha_1}\tau$, with for example $\alpha_0 = 0.025$ and $\alpha_1 = 0.3$

		Minimum requirement met?	
		Yes	No
Relevance requirement met?	Yes	Success	Consider
	No	Consider	No Success

Dual decision criteria – operating characteristics

Both criteria are met (*SUCCESS*) if $\bar{y}_1 - \bar{y}_0 > \max\left(\delta_{LRV} + Z_{1-\alpha_0}\tau,\ \delta_{TV} + Z_{1-\alpha_1}\tau\right) = MAX$

Neither are met (*NO SUCCESS*) if $\bar{y}_1 - \bar{y}_0 < min\left(\delta_{LRV} + Z_{1-\alpha_0}\tau,\ \delta_{TV} + Z_{1-\alpha_1}\tau\right) = MIN$

Decision	Probability of the Decision
SUCCESS	$P_{SUCCESS} = \Phi\left(\frac{-MAX + \mu_\delta}{\sqrt{\tau^2 + \sigma_\delta^2}}\right)$
NO SUCCESS	$P_{NO\ SUCCESS} = \Phi\left(\frac{MIN - \mu_\delta}{\sqrt{\tau^2 + \sigma_\delta^2}}\right)$
CONSIDER	$P_{CONSIDER} = 1 - P_{SUCCESS} - P_{NO\ SUCCESS}$

Dual decision criteria – upper bound

As $n \to \infty$, $MAX \to \delta_{TV}$ and $MIN \to \delta_{LRV}$ and therefore the upper bounds become

Decision	Probability of the Decision
SUCCESS	$P_{SUCCESS} = \Phi\left(\frac{-\delta_{TV} + \mu_\delta}{\sigma_\delta}\right)$
NO SUCCESS	$P_{NO\ SUCCESS} = \Phi\left(\frac{\delta_{LRV} - \mu_\delta}{\sigma_\delta}\right)$
CONSIDER	$P_{CONSIDER} = 1 - P_{SUCCESS} - P_{NO\ SUCCESS}$

Same upper bound as assurance with success criteria:

1. Significant p-value for $H_0: \mu_1 - \mu_0 = 0$ AND point estimate > δ_{TV}
2. Significant p-value for $H_0: \mu_1 - \mu_0 = \delta_{TV}$

But more rigorous than 1. as it incorporates uncertainty around point estimate and more flexible than 2. allowing for smaller sample sizes.