Quantitative Decision Making: How Frameworks Could Help You!

(Session by the PSI QDM E-SIG)

I) Clinical Stage Gates: Reflections on improving decision making in drug development

by Gustaf Rydevik

II) Financially Calibrated Risk-Scale: A Proposed Futility Design Framework to Enhance Portfolio-Level Profitability and Performance

by Nima Shariati

Clinical Stage Gates: Reflections on improving decision making in drug development

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Inspired by **patients.**
Driven by **science.**

All examples in this deck are hypothetical and does not reflect any real drug development program

Three challenges for clinical drug development

Developing a drug is **complex** with many moving parts, evidence gaps, and risks

Any clinical development plan intended to resolve the gaps and risks, come with **trade-offs** that need to be **transparent** for good decision making

There is a need for **clarity and alignment** around defined **quantitative targets** when designing and evaluating clinical trials

How can we resolve these challenges?

Approaching drug development in a structured way creates clarity in decision making

Review the particular **evidence gaps and risks** that characterize a program.

Create and compare scenarios for resolving these gaps and risks.

Integrate the development of **quantified progression criteria** with **the qualitative risks,** gaps, and scenarios.

Ensure that the **progression criteria** and scenarios are **aligned with a target product profile** to promote end-to-end thinking

What steps move a drug towards patients?

Create **development scenarios** that balance speed vs cost vs quality

When would a scenario progress or pivot?

Set **decision criteria** with quantitative and qualitative elements for critical gaps and risks

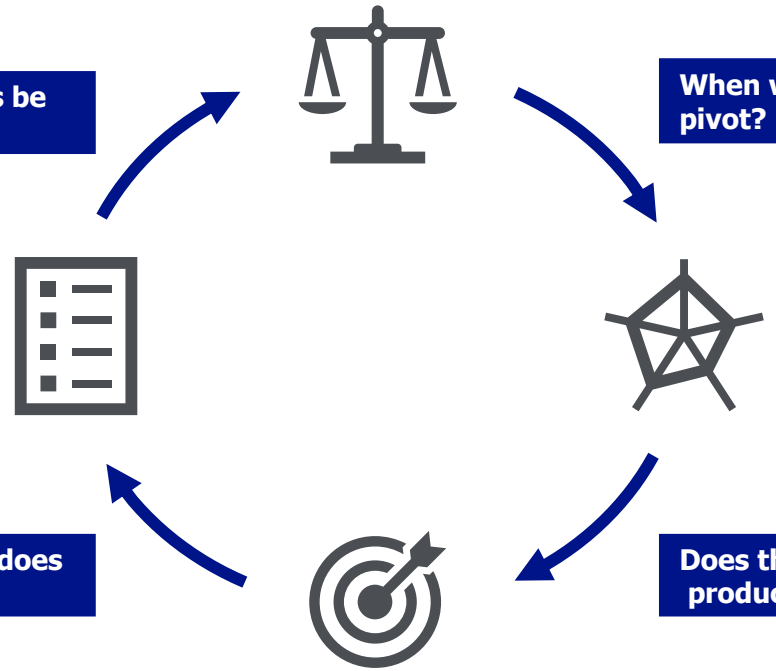
Does the decision criteria match the product profile?

Ensure that all pieces are aligned with the **target product profile**

Are there elements missing, or does anything needs to be revisited?

Identify the gaps and risks of a project

How & when will evidence gaps be resolved and risk discharged?



How can we best capture the complexity of development?

Consistency of evaluation helps transparency and allows different programs to be compared.

In a stage-gate process (1), this is done by developing a **comprehensive** list of **pre-specified** criteria or **questions** across multiple key domains for a project to be evaluated against.

In a clinical setting, it can be helpful to distinguish **evidence gaps** (aspects of the candidate or program that we need to understand) and **risks** (a hurdle or constraint to resolving an evidence gap) such as recruitment challenges.

Open-ended questions encourage discussion and engagement.

Using an **ordinal grading** of high/medium/low level of gap or risk can limit the temptation of scoring projects which hides complexity.

	Question	Answer with a grading of challenge	
Evidence Gap	How will dosing affect the longevity of response?	Based on existing science, this relationship is highly uncertain, and possibly variable	H
Challenge/Risk	Are safety risks easily monitorable and reversible in the clinic?	No serious safety risks anticipated for the compound, and any side-effect would be reversible based on the MOA	L
Evidence Gap	What is the risk of immunogenicity, and what is the potential impact to the study/future development?	….	M
Evidence Gap	Is the relationship between the early endpoint and the regulatory efficacy endpoint strong/well defined?	…	L

(1)The stage-gate idea-to-launch process, by Robert G Cooper, Journal of product innovation management, 2008

How can we provide structure to risks and challenges?

PK/PD	Patient	Commercial	Safety	…
• Dosing vs longevity uncertainty • Unclear if required exposure is achievable	• Well defined target patient population • No need for biomarkers	• Competitive landscape. • unclear differentiation strategy	• Good monitorability of safety risks • Well understood safety profile for the MOA	• …

- There are many options for how to structure review questions.
- AstraZeneca introduced their 5Rs in 2011(1), using the domains of Right Target, Right Patient, Right Tissue, Right Safety, and Right Commercial potential.
- Pfizer's 3 pillars of survival(2) used Exposure, Binding, and Evidence of downstream effect, as domains to be confirmed before a Ph2 investment.
- Domains can and should be adapted based on organisational structure and scope of the evaluation.

- **Organising questions by key domains** help in providing an overview and to ensure all critical aspects of development are covered
- The overview can be used **in communication** with stakeholders and **to increase transparency and awareness** in the organisation
- This awareness can help **drive scenario building**, and **define** the structure of **decision frameworks**

(1)Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework | Nature Reviews Drug Discovery (2014)
(2)Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival – PubMed (2012)

How can we design and select plans for getting our drug to patients?

Consider options for derisking, define alternative scenarios, and compare trade-offs

PK/PD	Patient	Commercial	Safety	…
• Dosing vs longevity uncertainty • Unclear if required exposure is achievable	• Well defined target patient population • No need for biomarkers	• Competitive landscape. • Unclear differentiation strategy	• Good monitorability of safety risks • Well understood safety profile for the MOA	• …

Options for derisking

Longer single-dose study In patients	No optionality needed	Include multiple efficacy endpoints in POC	Include an SMC in the study?	• …
Healthy volunteer PD study followed by multi-dose study		Include single efficacy endpoint to reduce burden and dropouts	Lead-in safety study?	

Longer single-dose study In patients	Speed ++	Cost +	Risk/ Quality ++
Healthy volunteer PD study followed by multi-dose study	Speed +	Cost +++	Risk/ Quality +++
?	Speed ?	Cost ?	Risk/ Quality ?

Speed vs Cost vs Quality seem to create comparisons that are meaningful to a range of audiences

Asking for **three scenarios** gives clarity on trade-offs, and open up the discussion of posibilities

What makes up a meaningful target for a trial?

Using an endpoint, a reference value, and a degree of confidence can help define what **good (acceptable)** looks like

Target

- **Endpoint** → Key decision-making endpoint
- **Reference value** → A value of the endpoint relevant for a viable program
- **Degree of confidence** → Minimum required amount of confidence in beating the Gate-relevant value

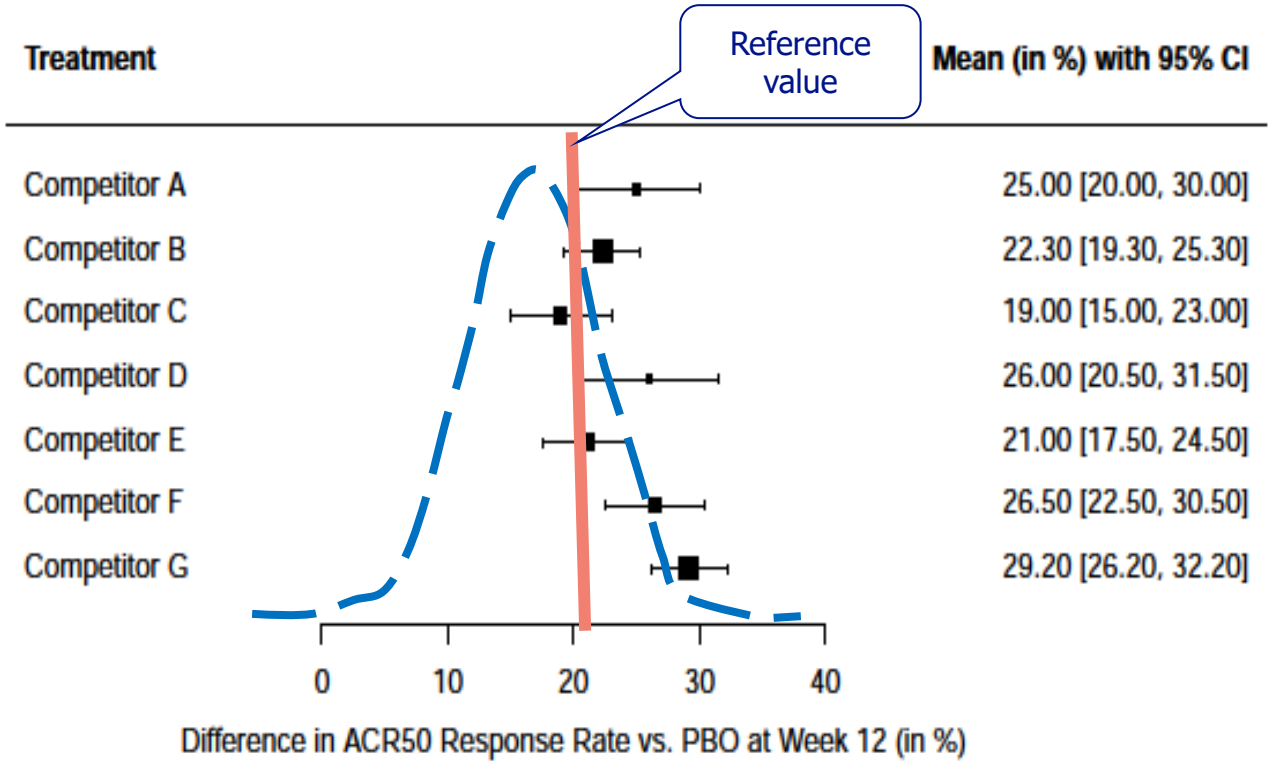
Target Example: 'For ACR50 at week 12, we target to be at least 45% confident that the test drug is ≥40 points better than PBO'

- Endpoint
- Degree of Confidence
- Reference value

How can we set targets for progressing or pivoting scenarios?

Setting reference values that define a viable product for development

- **Review the landscape of outcomes**
  - Discuss within the team what values of the endpoint at the end of development* would correspond to a viable product
  - Among the viable values, identify a **minimum** acceptable value for the compound
    – this is an **upper reference value**
  - Among the viable values, identify a value the compound has to beat
    – this is a **lower reference value**
  - Ensure that the reference values chosen are reasonable and **consistent with the Target profile ambition**



* Where the endpoint will not be measured directly at the end of development, what values at this stage would provide evidence that a viable product is likely

How can we ensure nuanced decision making?

PoC data aligned to target	PoC data partially aligned to target	Lack of Efficacy OR significant Safety signal
Achieved target 1 **AND** Achieved target 2 **AND** Clean safety profile **AND** Expected PK/PD profile	Missed target 1 **OR** Missed target 2 **OR** Some safety issue **OR** PK/PD problematic	Missed target 1 **AND** Missed target 2 **OR** Serious safety issue
Go to next stage	**Consider alternative scenarios**	**Evaluation prior to stop**

As has been suggested by others(1),using **dual criteria with Go, Consider, and Stop** is helpful to remove a binary success/fail.

It is also possible to include pre-specified **qualitative criteria** to ensure a more holistic process

Consider any **key gaps** and what endpoints and targets speak to those

(1) Decision-making in early clinical drug development - Frewer - 2016 - Pharmaceutical Statistics - Wiley Online Library

What do we do when the results are not clear?

Anticipating yellow scenarios helps with decision making, planning post-readout analyses, and reduces white space

Efficacy endpoint 1	Efficacy endpoint 2	PK/PD	Safety	Landscape
• Observed Mean < green target OR • Low confidence	• No evidence of effect	Unexpected PK/PD pattern (e.g. weight dependency, lack of linearity)	• New safety signals	• New Competitor results raise competitive bar
or	or	or	or	

Possible path forward

Clear signal of effect	Clear signal of effect	Clear PK/PD	Clear Safety	Competitor effect on Endpoint 1, not 2
Clear signal	Little evidence of effect	Clear PK/PD	Surmountable safety	No competitor
Some signal	Clear signal of effect	Mitigable PK/PD issue	Clear Safety	No Competitor

Maybe

Some signal	Little evidence of effect	Significant difference from Pbo	Clear Safety	No Competitor

Not very strong paths forward

No signal of efficacy	Clear signal	Mitigable PK/PD issue	Clear Safety	No competitor

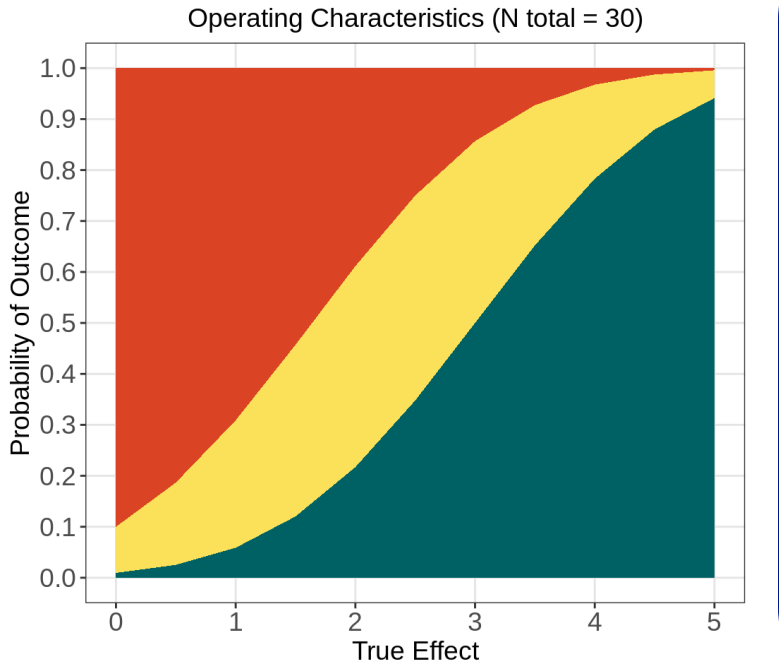
Is the compound still competitive without endpoint 2?

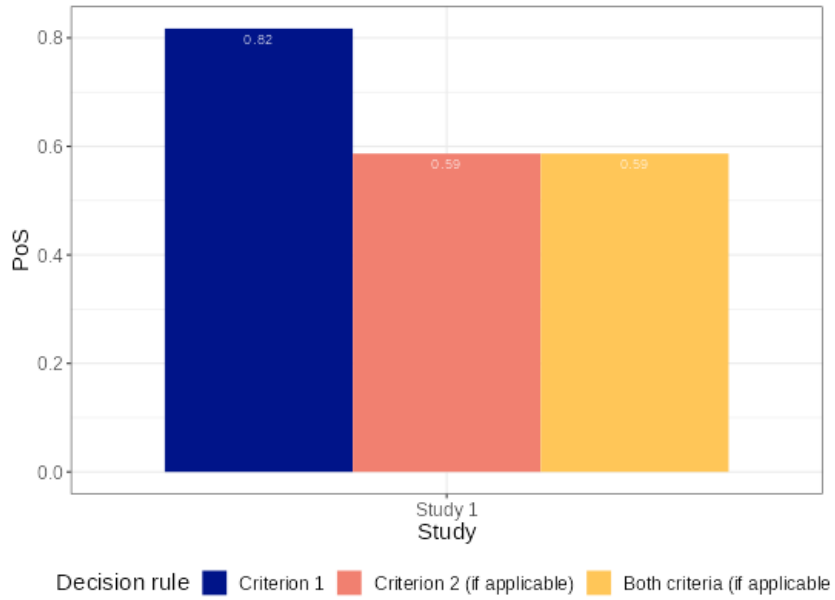
Does the asset need to derisk further before expensive next steps?

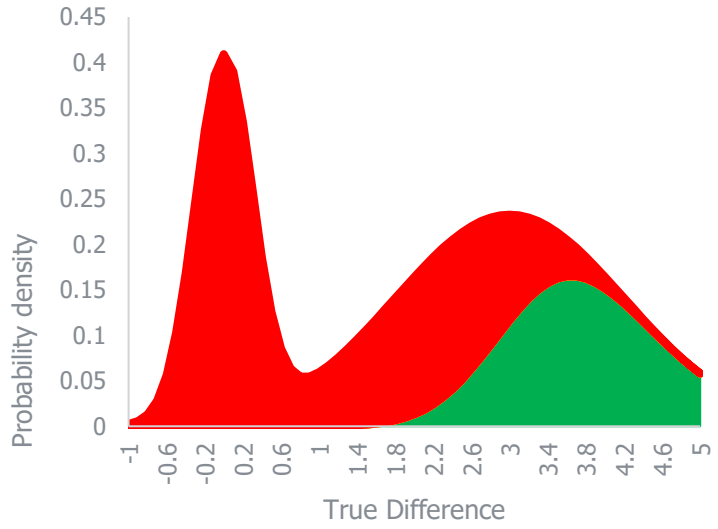
Lack of effect on primary endpoint, but effect on secondary may allow for indication pivot?

How can we pressure test our targets and plans?

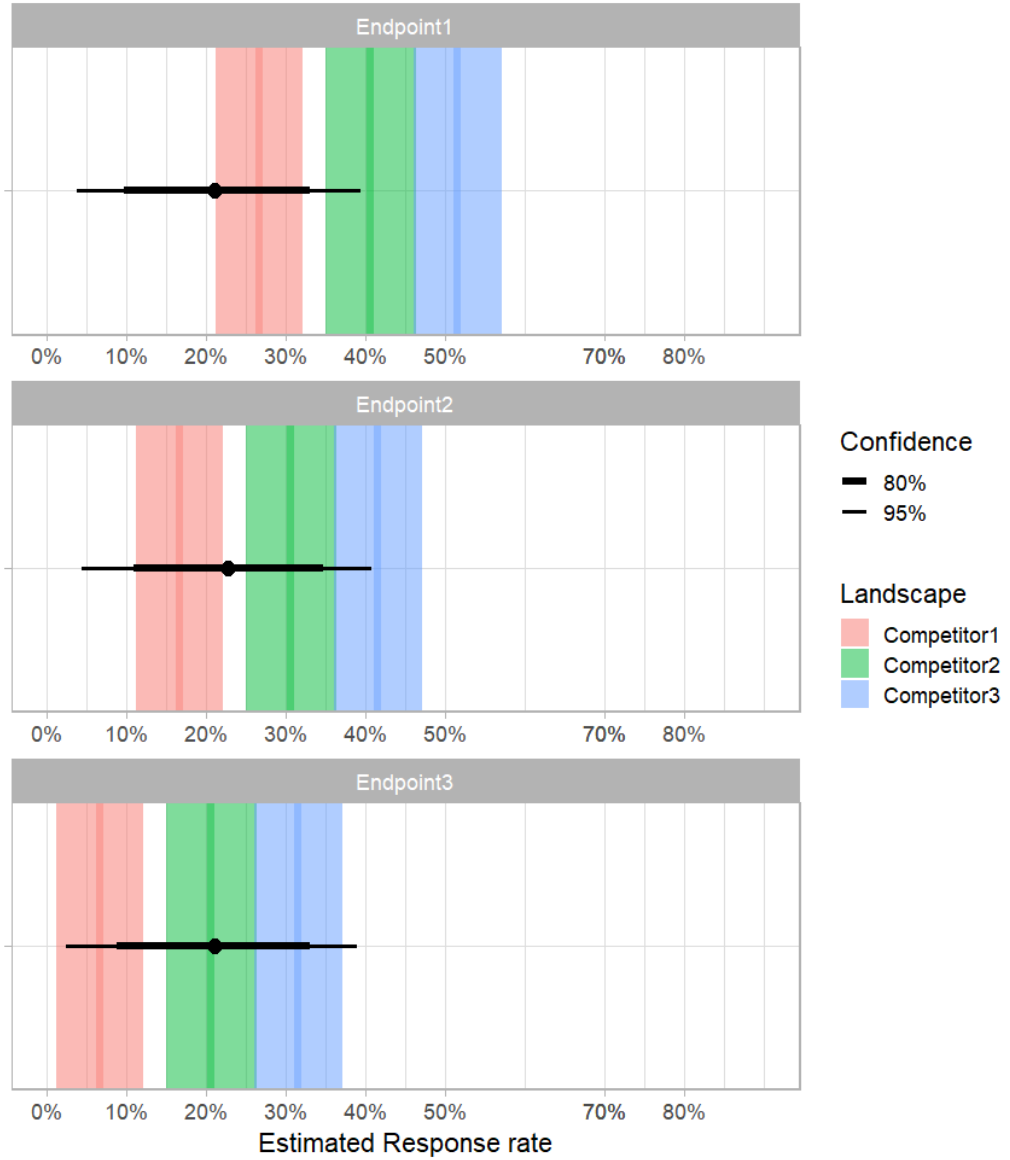
Any decision making needs to have input using the full statistical toolbox of operating characteristics, PoS, pre-posteriors, to check whether targets or designs are fit-for-purpose







How can we communicate the impact and meaning of targets?



An **entire team** need to come together to **set targets**

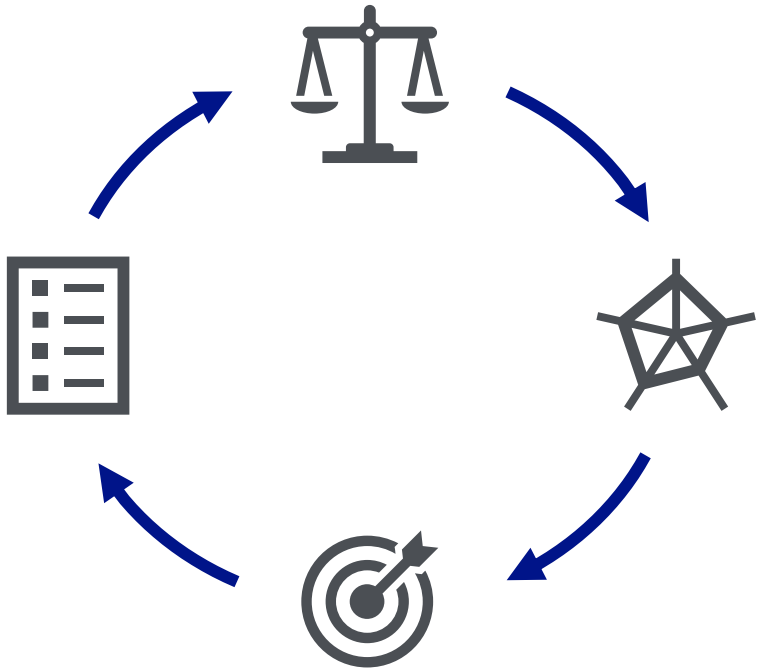
They will have to be **understood** by a **range of audiences**

Visualizations are key, and **contextualizing outcomes** can help

Iterate!

Structuring the development process allows for more transparent discussions with stakeholders, and therefore rapid iteration

Create **development scenarios** that balance speed vs cost vs quality



Set **decision criteria** with quantitative and qualitative elements for critical gaps and risks

Ensure that all pieces are aligned with the **target product profile**

Review the gaps and risks of a project

Benefits of structuring the development process

Reviewing gaps and challenges anchor clinical plan discussions

A qualitative context makes it easier to define and set quantitative targets

Comparing scenarios help transparency and agility

Aiming at getting a target drug to patients encourage end-to-end thinking

Thanks for listening!
Any questions?

Evolving practices for decision frameworks

Align

- **Close collaboration with Commercial lead on target** — Collaborate with the commercial lead to ensure clarity on the target profile and validate meaningful reference values together
- **Align on stage-appropriate expectations** — Align the team on achievable levels of de-risking for the current study phase
- **Use the systematic review to identify key measures** — The systematic review is a powerful tool to identify key domains measures that may impact decision-making.
- **Emphasise holistic decision making** — Emphasising that this is a multi-domain decision process create safety for defining good/bad outcomes for specific measures

Define

- **Anchor threshold using potential study outcomes** — Facilitate discussions using potential study outcomes makes it easier to agree on outcomes that indicate a green, yellow or red signal
- **Use easily interpretable confidence levels** — As far as possible, stick to 50/80/95% confidence levels and instead tweak reference values as needed to define a target
- **Pressure-test criteria with classic tools** — Analysing decision criteria in terms of e.g. OCs help with reality-checks and communication
- **Consider joint criteria across multiple domains** — Defining multi-dimensional outcomes can help clarify borders between green/yellow/red

Communicate

- **Communicate with commercial confidence** — Contextualise thresholds with the level of confidence in the competitive landscape and probability of success in future trials to clarify business impacts.
- **Using decision framework as guidance, not rule** — **Any framework aids in framing and aligning on the strength of evidence strength but should not replace informed judgment**