

# **Decision-making in clinical development strategies:**

- a union between biology, pharmacology and statistics**

Amy Racine & Mick Looby

B&SR, Novartis

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# Agenda

- Approach to Proof of Concept (PoC)
- Planning the decision making process
  - Framing the problem
  - Generating the information
  - Defining the decision criteria
- Problems with p
- Level of Proof – A statistical threshold for decision making
- Take home messages
- Lessons learnt

# POC Strategy, Decisions & Full development

## Prior Quantitative Information

- Preclinical Information
  - Pharmacology
  - Toxicology
- Other compounds (preclinical/clinical)
- Other indications
- Clinical (PoC) Endpoints
  - Time course
  - Size of effect
  - Variability

## **Full Development**

## Backward Induction from full development strategy

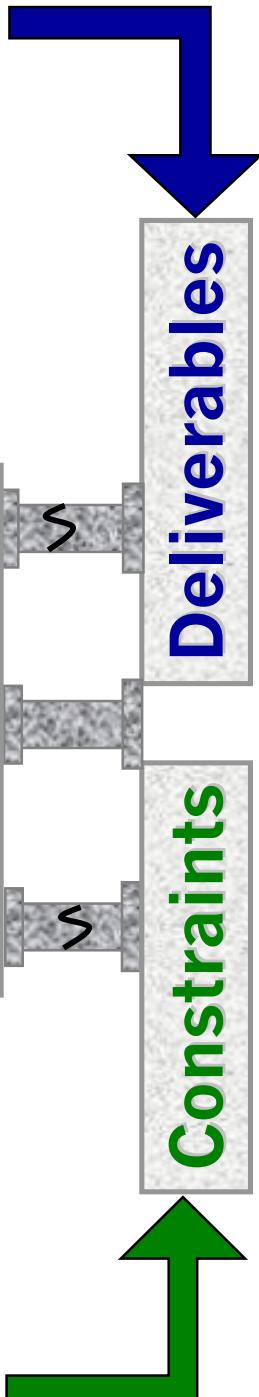
- TPP
  - Quantitative considerations
    - Endpoints
    - Duration
    - Competitor status
    - Cost of next step
    - Benefit of success
  - Objectives

## **PoC Decision**

## **PoC Strategy**

## **Deliverables**

## **Constraints**



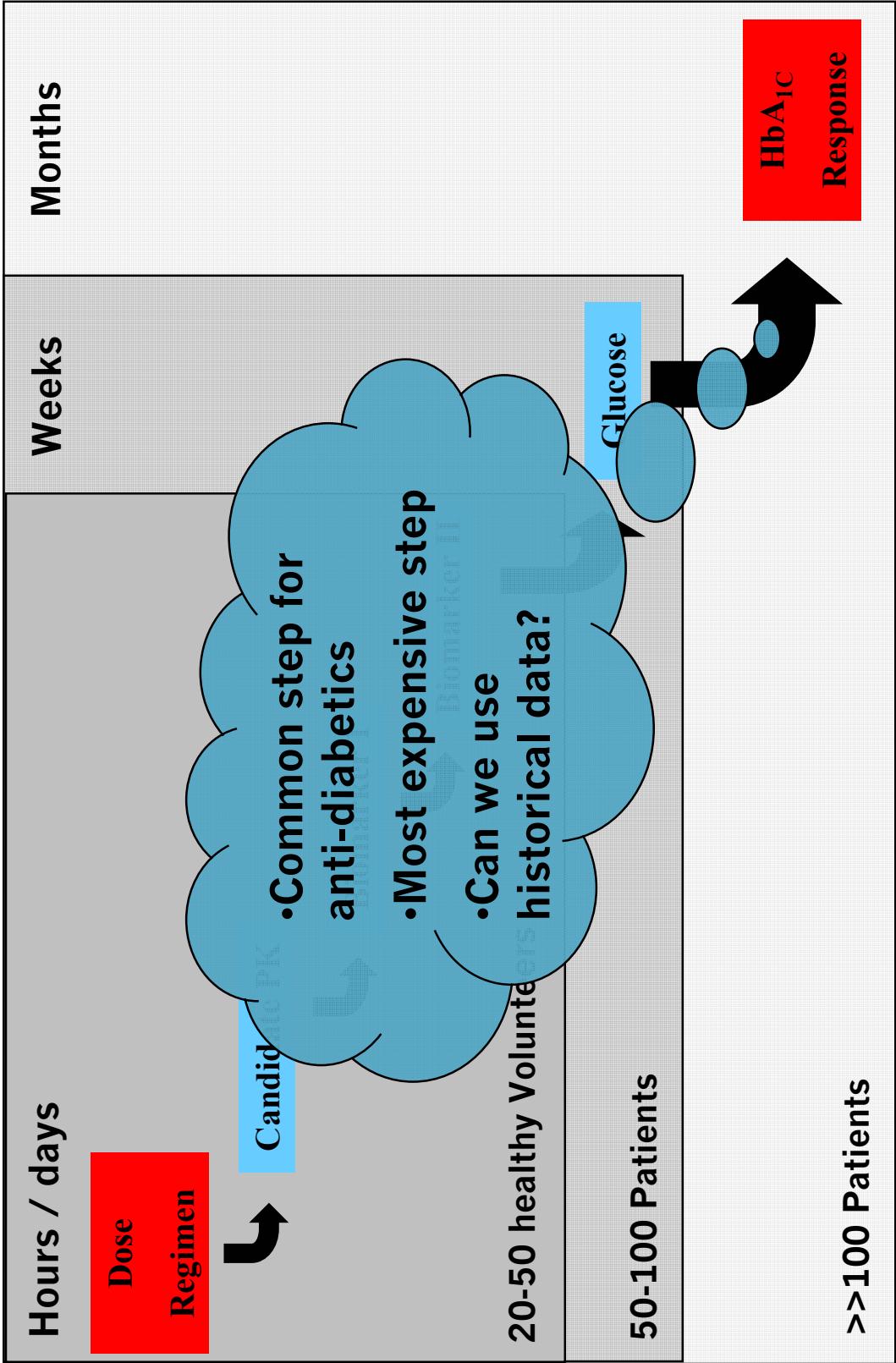
# Planning the decision making process

- **Framing the problem**

- Sketch out the Proof of Concept Strategy
  - the scientific & clinical constraints (clinical pharmacology)- the knowledge
  - the development decisions
  - the information generation steps
  - the data collection steps within and across studies
- **Define the decision criteria in quantitative terms**

- The PoC decision must take into account
  - relevant treatment differences
  - current cost
  - future cost & future potential gain
- **Design studies and M&S plan within the strategy**
- Align study designs with analyses
  - Identify opportunities to exploit underlying drug science
  - Use available historical data
  - Ensure learning in one study flows into design of subsequent study
  - Write Master Modelling Plan

# Framing the problem: the clinical pharmacology



# Framing the problem: the development decisions

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- **Proof of Mechanism (PoM):**

- Does candidate have desired and adequate pharmacological effect?
- Deliverable: if successful, dose regimen for PoC

- **Proof of Concept (PoC):**

- Does candidate have desired anti-diabetic effect in terms of glucose lowering?
- Deliverable: if successful, dose range for PoE

- **Proof of Efficacy (PoE):**

- Does candidate have demonstrable and adequate clinical effect?
- Deliverable: if successful, doses for Phase II/III

# Framing the problem: data & information

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- PoM
  - Phase I study in healthy volunteers
  - Use biomarker response to assess PoM
  - Use a PK/PD nonlinear mixed effects modelling approach to characterise pharmacological dose response
  - Select POC regimens based on the PK/PD model
- ♦ PoC
  - Phase II study in “responsive” diabetic patients (enrichment)
  - Generate information for PoC decision
  - Measure and model biomarkers including glucose to further characterise causal chain
  - Incorporate historical glucose & HbA1c to predict clinical response given the glucose response of candidate

# The Relevant Treatment Difference

- Standard biomarker: 24 h glucose level at 4 weeks
- Clinical endpoint: HbA<sub>1c</sub> at 3 to 6 months
- Classical approach to PoC: short term study using glucose as main endpoint
- Relevant effect: reduction in 24 h glucose level  $\geq 1 \text{ umol/L}$ 
  - This approximately translates into a clinically relevant reduction in HbA<sub>1c</sub>  $\geq 0.5$

• This is a clinical definition and *not* a statistical concept

• Setting this target is not trivial for many indications

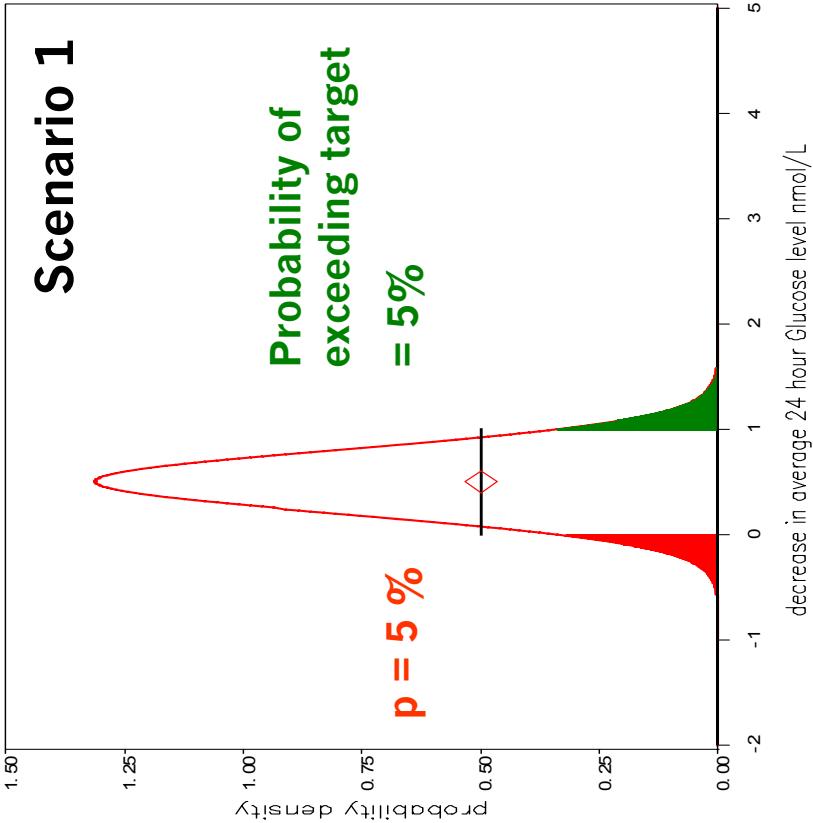
# Defining the decision criteria: general points

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- PoC strategy should:
  - quantify the probability of attaining a relevant treatment benefit
  - use this information to assess risk of continuing development
  - quickly terminate poor compounds
  - generate information to support further development
- The assessment risk/benefit must be tailored:
  - depends on the program, the drug, the indication, ...
  - depends upon the level of risk the company is willing to accept

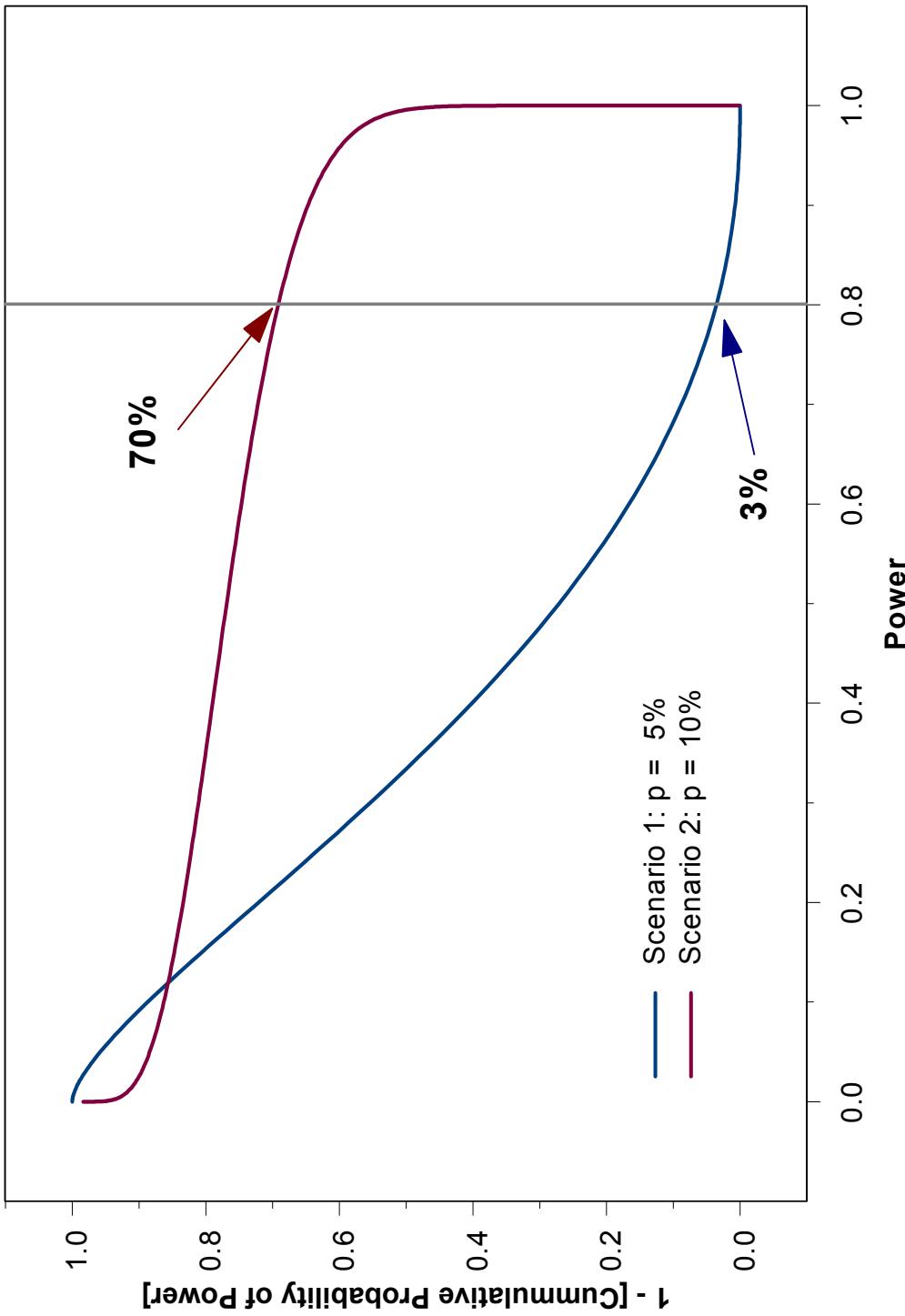
⇒ The conventional p-value approach usually doesn't achieve this!

# Limitations in p-value approach (1)



- Probability of attaining clinically relevant target is a better quantification for decision making

## Limitations in p-value approach (2)

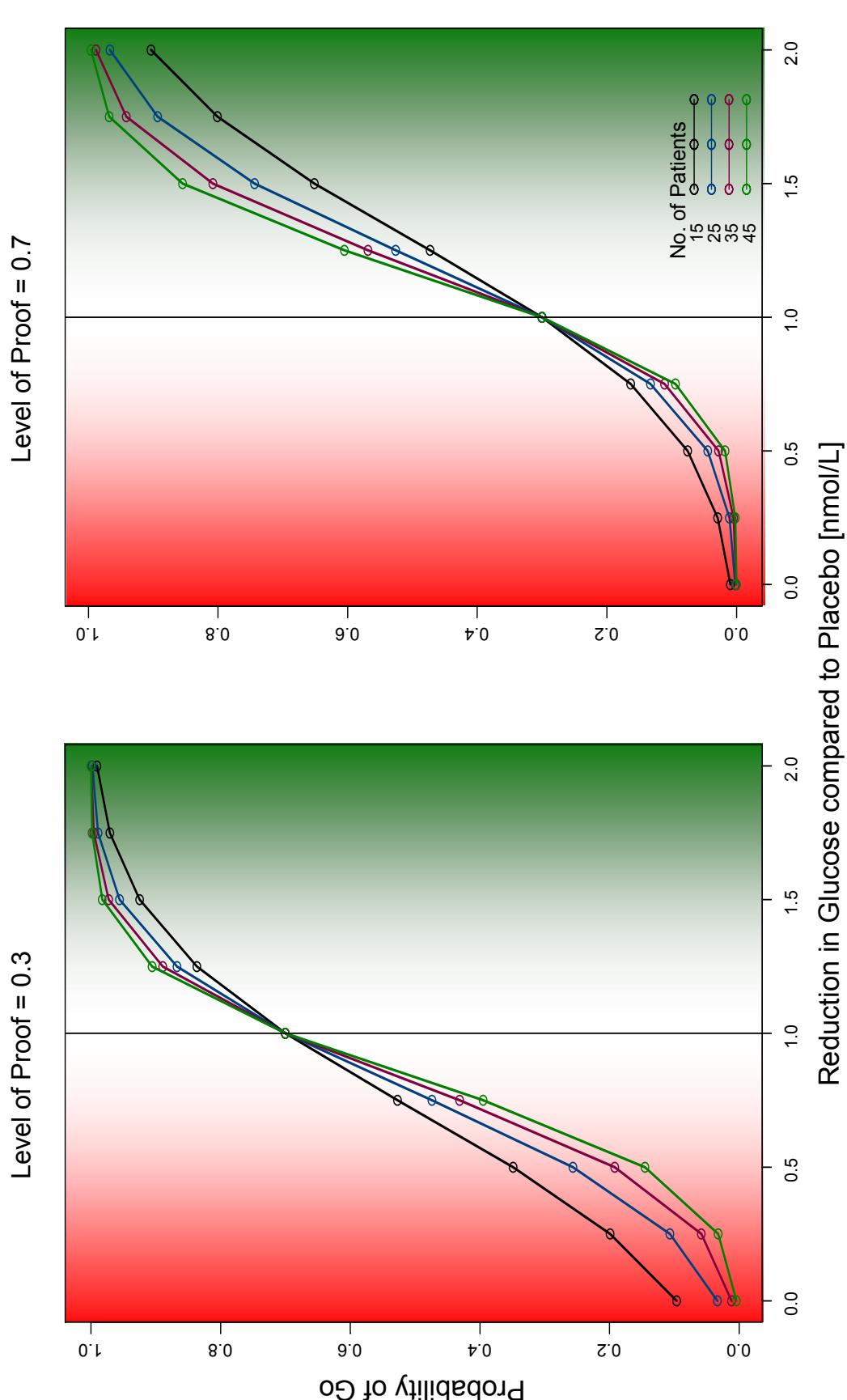


# Level of Proof - A probabilistic threshold for decisions

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- Need a metric which sets the “level of support” for a decision based on a definition of a clinically relevant treatment difference
- Level of Proof is a common sense concept based on Bayesian thinking
- Definition: the **Level of Proof** is the **probability** that the true treatment effect is **clinically relevant** given our **current data** - up to and including the current decision point
- This leads to the decision criteria:
  - **P ( $\delta$  is clinically relevant | current data) > Level of Proof**

# Selecting Level of Proof: - based on a given relevant treatment difference



# Example of decision scenarios

- Discuss scenarios with team
- Simulate scenarios depending on design, decision criteria and level of proof
  - Level of Proof X%, n=Y
    - Probability of go for a “good compound” A%
    - Probability of go for a “poor compound” B%
  - Level of Proof 30%, n=25
    - Probability of go for a “good compound” 94%
    - Probability of go for a “poor compound” 26%
  - Level of Proof 70%, n=25
    - Probability of go for a “good compound” 73%
    - Probability of go for a “poor compound” 4%

# Decisions: Balancing risk & reward

POC design		Consequences (😊 😐 😞 )				
n	Level of Proof	Current \$\$\$	False +ve	False -ve	+ve POC	Next Phase Risk
↑	↔	↑	↓	↓	↑	→
↓	↔	↓	↑	↑	→	↑
↔	↑	↔	↓	↑	↓	→
↔	↓	↔	↑	↓	↑	↑
↑ #modelers	Early W&S involvement	↑	↓	↓	↑	→

The decision criteria must obtain a proper balance between:

False positive rate

→ failure in later phase

False negative rate

→ missed opportunities

Size of the study

→ current investment

Potential reward

→ level of risk worth taking

# Take home messages

- Decision criteria must be aligned with the constraints and deliverables of each development program
- The relevant treatment difference is a clinical and not a statistical concept
- The choice of sample size and **Level of Proof** of the PoC should take into account
  - the current development cost
  - cost of next development step
  - future potential gain
- The appropriate level of proof is derived by simulating desired scenarios and discussing these with the decision makers
- Decision making strategies is a multi-disciplinary task:
  - Decisions making given uncertainty requires good statistics
  - Generating informative data requires good quantitative pharmacology and biology
  - Extracting decision relevant information requires an integrated M&S approach
  - The challenge is building an organisation that can foster and blend these skills

# Lessons learnt so far

- M&S activities can be broadly divided into activities which:
  - Quantify the underlying science and ensure informative data is collected
  - Generate information relevant to designs and decisions
  - Compare and contrast designs and decision rules
- Early involvement of M&S essential
  - Initial involvement might not involve any explicit M&S at all
  - First time round this approach can be resource intensive
  - However, work on subsequent projects is much easier
- All these activities must be coordinated in an explicit plan which is part of the ultimate statistical plan
- An explicit approach probabilistic approach to decisions reveals the latent complexity and uncertainty in early decisions
  - Documentation of all scenario simulations should be appended to final strategy
- The integration of M&S into the PoC strategy is not trivial
  - it requires reorganisation, retraining, and continual reassessment

# Development Decisions are a Balancing Act

