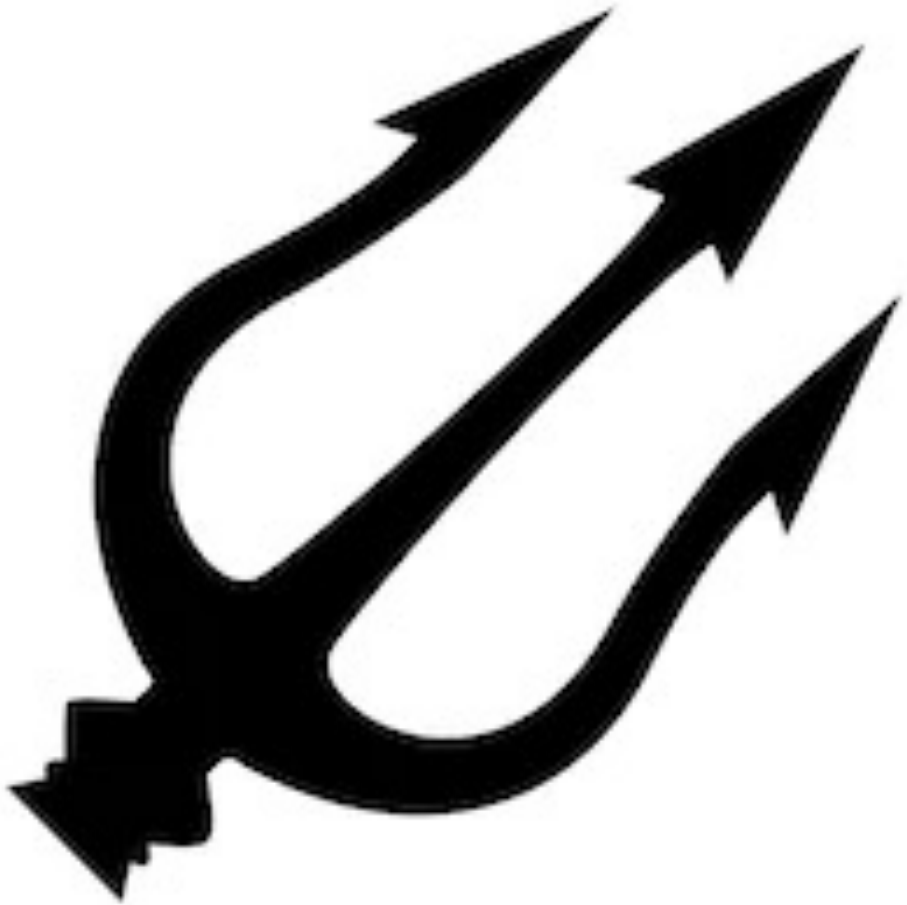


Implementation of decision guiding frameworks for early clinical trials in Novo Nordisk

JEMD

29-Apr-2022

Outline

- Decision frameworks: What and why
- Rationale for introducing decision frameworks in Novo Nordisk
- Decision frameworks as used in Novo Nordisk
- More complicated scenarios and other applications
- Summary

Decision frameworks: What and why

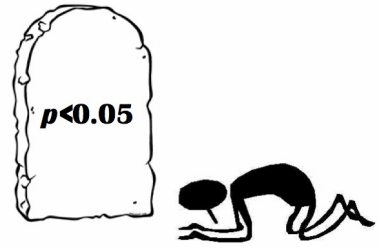
What is a decision framework?

- A pre-defined algorithm for business decisions to be taken based on data
- Input to algorithm are relevant thresholds, e.g. treatment effects and false stop/go risks
- Output is recommended decision, e.g. 

- Different methods proposed in literature
- Can be used both at trial level and portfolio level

Why using a decision framework subsequent to readout from clinical trials?

- Decision-making and study design guided by size and uncertainty of estimated treatment effects
  - In contrast to guidance by control of type I and type II errors



- Input parameters (pre-specified) can be naturally linked to the business case
- Potential faster and better informed decision making

Rationale for introducing decision frameworks in Novo Nordisk

Novo Nordisk therapeutic strategy

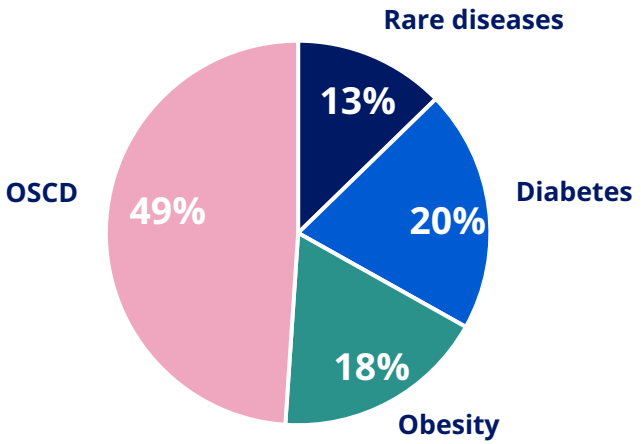
In the past

- Few, well known therapeutic areas
  - Diabetes
  - Obesity
  - Growth disorders
  - Haemophilia
- Relative precise estimate of clinical efficacy already in phase 2
- Most compounds developed in-house
- High success rate

Present

- Expanding portfolio to other serious chronic and/or rare diseases, e.g.
  - CVD/CKD
  - NASH
  - Alzheimer's
  - Parkinson's
  - Sickle cell
  - dry AMD
- Expanding part of in-licensed compounds
- **Aim for early and robust attrition**

Proportion of projects expected to enter phase 1 and 2 next 5 years

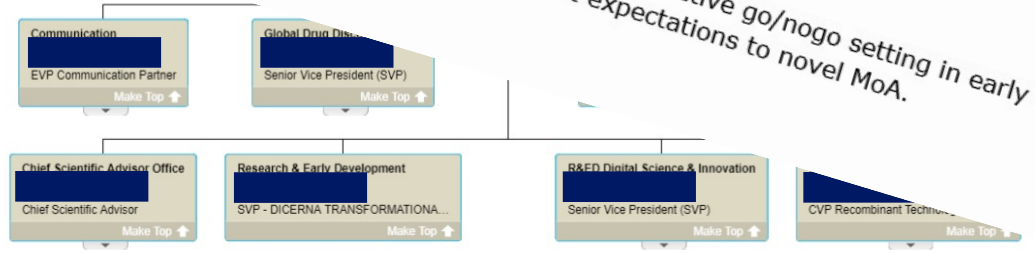


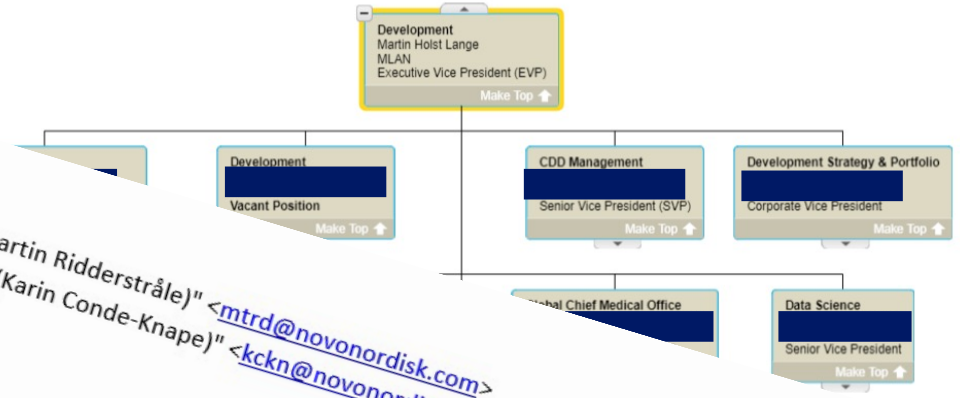
Aspiration to use decision frameworks in Novo Nordisk

From: "SCNM (Marcus Schindler)" <scnm@novonordisk.com>
Date: 22 February 2019 at 17.26.05 CET
To: "ABJE (Anne Bording Jensen)" <abje@novonordisk.com>, "TDW (Tamara Darsow)" <tdw@novonordisk.com>, "MTRD (Martin Ridderstråle)" <mtrd@novonordisk.com>
Cc: "MLAN (Martin Holst Lange)" <mlan@novonordisk.com>, "KWAH (Karin Wahlander)" <kwah@novonordisk.com>, "KCKN (Karin Conde-Knape)" <kckn@novonordisk.com>, "MDTC (Mads Tang-Christensen)" <mdtc@novonordisk.com>
Subject: FW: Decision-making in early clinical drug development - Frewer et al

Please see attached. A good & proven system for an unbiased proactive go/nogo setting in early clinical development which we should consider implementing. It will facilitate decision making and is particular useful to start thinking early about expectations to novel MoA.

Best wishes, M





MAIN PAPER

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1746 Published online 17 March 2016 in Wiley Online Library

Decision-making in early clinical drug development

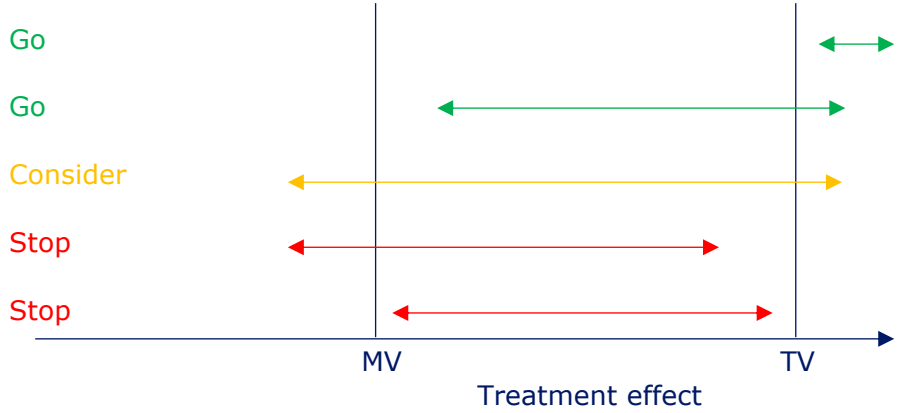
Paul Frewer,[a]* Pat Mitchell,[a] Claire Watkins,[b] and James Matcham[a]

Decision frameworks as used in Novo Nordisk

Decision *guiding* framework* used in Novo Nordisk

Input parameter	Description
Target Value (TV)	Lowest treatment effect where clinical/commercial case is attractive (for assets where there is confidence that the treatment effect is below the TV, further development should be stopped)
Minimum Value (MV)	The lowest treatment effect value 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. **20%**)

Decision rule



← Lower limit in a one sided 80%## CI
→ Upper limit in a one sided 90%# CI

Interpretation

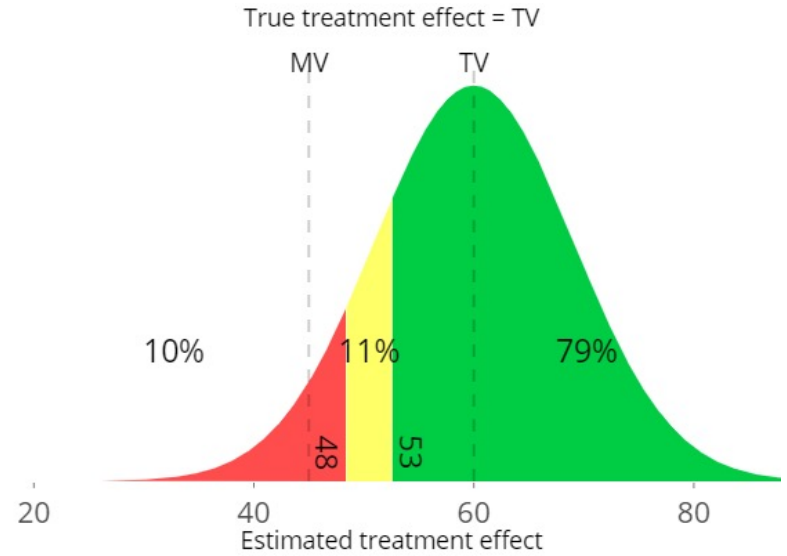
STOP, if there is ≥90%# probability that the treatment effect is less than the TV
otherwise
GO, if there is ≥80%## probability that the treatment effect is at least the MV
otherwise
CONSIDER

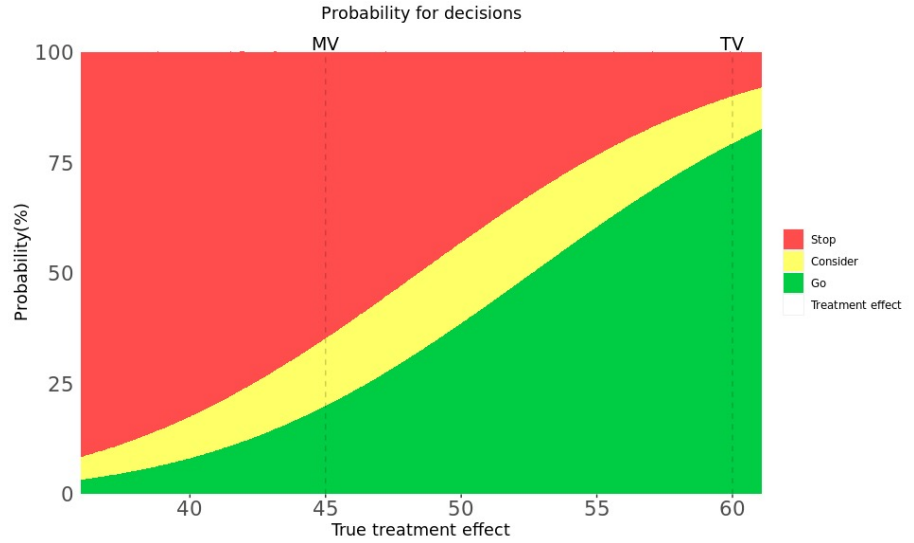
* *Frewer et al 2016 DOI:10.1002/pst.1746 # Assuming false stop risk of 10% ## Assuming maximum false go risk of 20%*

Using decision framework at the design stage

- R-shiny app developed
  - One/two sample normal, log-normal and binomial models supported
- In addition assume a certain true variation (e.g. SD or CV) of endpoint
- Then, for a certain true treatment effect one can calculate
  - Probability of recommended decision (“operating characteristics”)
  - Expected* thresholds for the point estimate
    - Stop if <=48, Go if >=53, otherwise consider

True treatment effect	Scenario	Go (%)	Consider (%)	Stop (%)
45	Minimum value	20.0	15.3	64.7
60	Target value	79.3	10.7	10.0

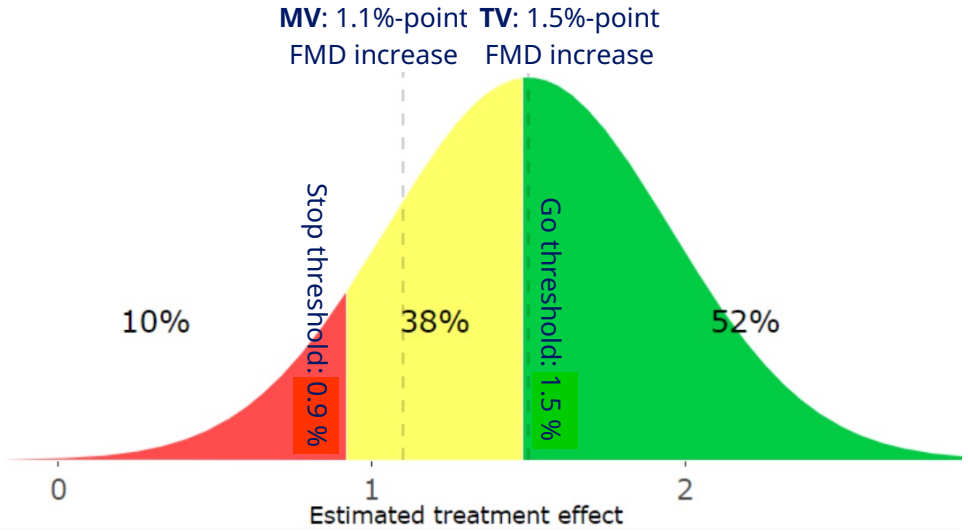




** Assuming estimate of variation = true value*

Criteria to be pre-specified and approved by governance board

PD Endpoint	Justification/Assumptions
Biomarker: Flow-mediated dilation (FMD) change from baseline	Proof-of-mechanism biomarker Brachial FMD has significant predictive value for future cardiovascular events and is inversely associated with cardiovascular events[1-3]
Target Value: 1.5% point FMD increase from baseline vs comparator	Based on the assumtion that 1% point increase in FMD is associated with a reduction in CV event risk by 12%[1]. Target value of 1.5% point increase is considered clinical relevant and aligned with TPP (i.e HR= 0.83)
Minimal Value: 1.1 % point FMD increase from baseline vs comparator	Based on the assumtion that 1% point increase in FMD is associated with a reduction in CV event risk by 12%[1]. Minimum value of 1.1 % point increase in FMD is regarded as the lowest meaningful difference from the literature required to meet the TPP (i.e MACE HR=0.87)
Variation Assumed SD: 2% point	Assumed variation based on variation reported in literature[1-3] (will be updated if the actually observed SD is different)
Population: T2DM (86 randomised, 78 completers)	Each arm will consist of 43 subjects with T2DM, that will receive either active treatment or comparator.



False Go Risk 20%, False Stop Risk 10%
39 in active arm, 39 in comparator arm

[1]Matsuzawa et al. Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2015 10.1161/JAHA.115.002270
[2]Celermajer et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992
[3]Gokce et al. Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. J Am Coll Cardiol 2003

In case of a consider outcome

- Typically the results on key secondary efficacy endpoints will be guiding the decision
- Sometimes also a DGF for a key secondary endpoint is pre-specified to be conducted subsequently

Efficacy is only one part of overall project recommendation

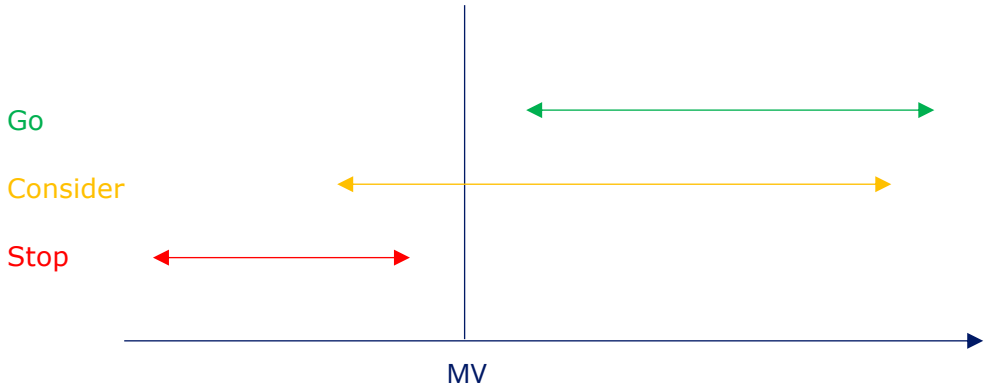
Efficacy	**Is decision guiding framework (DGF) criteria met?**
	• [redacted]
	• [redacted]
		NO
		• [redacted]
		  ○ [redacted]
		• [redacted]
		  ○ [redacted]
			

Safety	**Safe and well tolerated?** • [redacted] • [redacted]	**Yes** • [redacted] ○ [redacted] • [redacted]	
Dosing	**Is dosing conditions met?**	**NO** • [redacted] • [redacted]	
Regulatory	**Is the regulatory path known?**	**YES** • [redacted] • [redacted]	
Business assessment	**Is there a business case?**	**NO** • [redacted] • [redacted]	

Simplified framework (1) – special case with MV=TV

- In some situations where the biomarker is less validated or where a business case has not been made, it may be difficult to set both a TV and a MV, but instead the project can agree on a MV only
- The MV could then be the lowest value that may be associated with a clinically relevant effect
- Operating characteristics could then be calculated for different values of interest

Decision rule



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Interpretation

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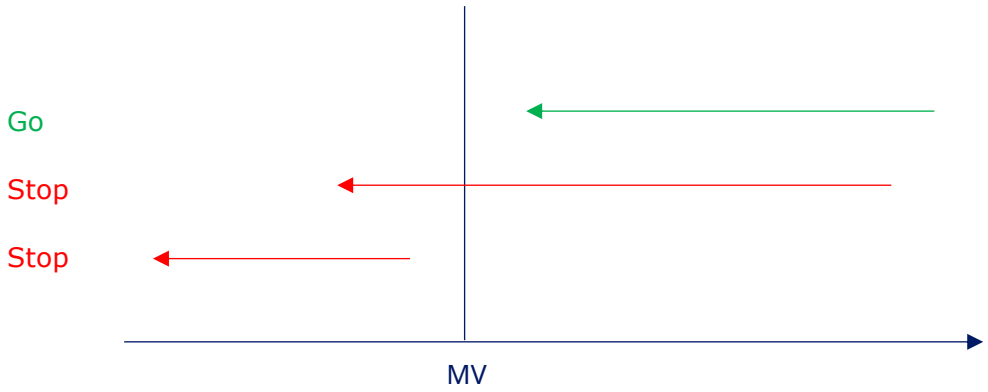
otherwise
GO, if there is ≥80%## probability that the treatment effect is at least the MV
otherwise
CONSIDER

 # Assuming false stop risk of 10% ## Assuming maximum false go risk of 20%

Simplified framework (2) – super-superiority or non-inferiority

- Like the situation in simplified framework (1) where an MV only is set, but where the ”consider” outcomes are mapped to ”stop”
- Could be relevant in case strong evidence of a clinical relevant effect is needed to progress to next phase
- Again, operating characteristics could be calculated for different values of interest
  - For a true value above MV the false stop risk is then 1-”power” for a significance test at the false go level

Decision rule



← Lower limit in a one sided 80%# CI

Interpretation

GO, if there is ≥80%## probability that the treatment effect is at least the MV
otherwise
STOP

 # Assuming maximum false go risk of 20%

More complicated scenarios and other applications

More complicated scenarios

Phase 2b dose finding trials – alternatives to using high dose vs. placebo

- Dose response modelling?

Received: 23 December 2016 | Revised: 11 September 2017 | Accepted: 10 October 2017
DOI: 10.1002/pst.1841

MAIN PAPER

WILEY

Integrating dose estimation into a decision-making framework for model-based drug development

James Dunyak[1] | Patrick Mitchell[1] | Bengt Hamrén[2] | Gabriel Helmlinger[1] | James Matcham[3] | Donald Stanski[1] | Nidal Al-Huniti[1]

Several biomarkers and dependency between MVs and TVs

- **Example -** Compound to reduce TG and potentially LDL
  - As a competitive TG drug (not necessarily LDL lowering)
    - TG: TV -60% MV -45%
    - LDL: TV 0% MV +10%
  - TG lowering drug with additional LDL lowering
    - TG: TV -50% MV -35%
    - LDL: TV -30% MV -20%

Several biomarkers with no clear preference

- ”Go” if e.g. 2 out of 4 looks promising

Decision frameworks for phase 2b dose finding trials – alternatives to high dose vs. placebo

- Use a dose response model and use the confidence limits for estimated treatment effect at a given dose (dose vs. placebo) in the usual decision framework
- As ”output” either
  - use recommended decision at a pre-specified dose, or
  - provide recommended outcomes at all dose levels
    - final decision (including choice of dose) guided by additional outcomes (safety, cmc, etc.)
- Evaluate operating characteristics (e.g. at TV) at one or more given dosen levels (assume model parameters accordingly)

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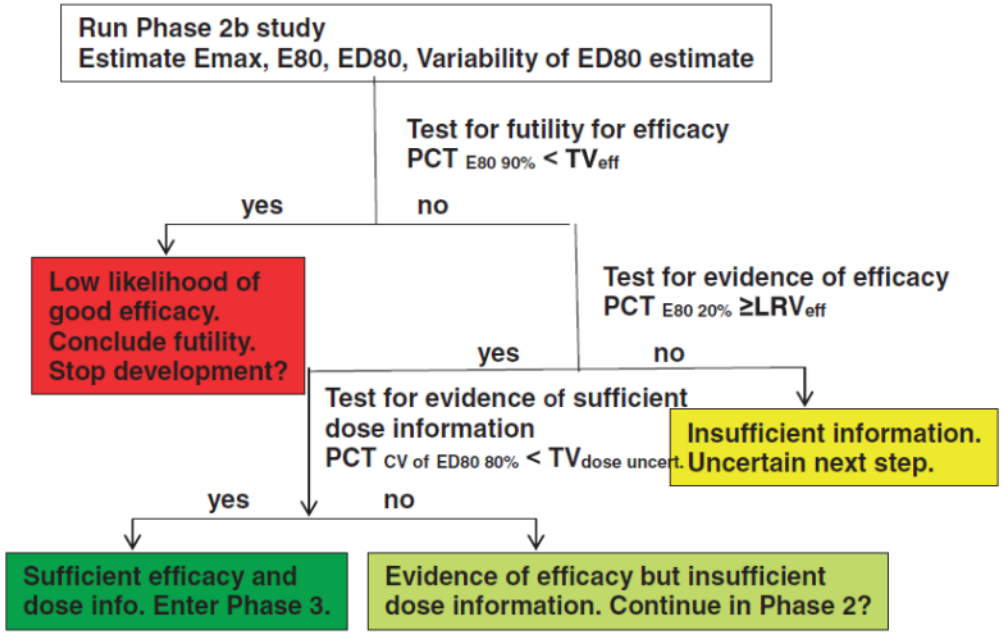
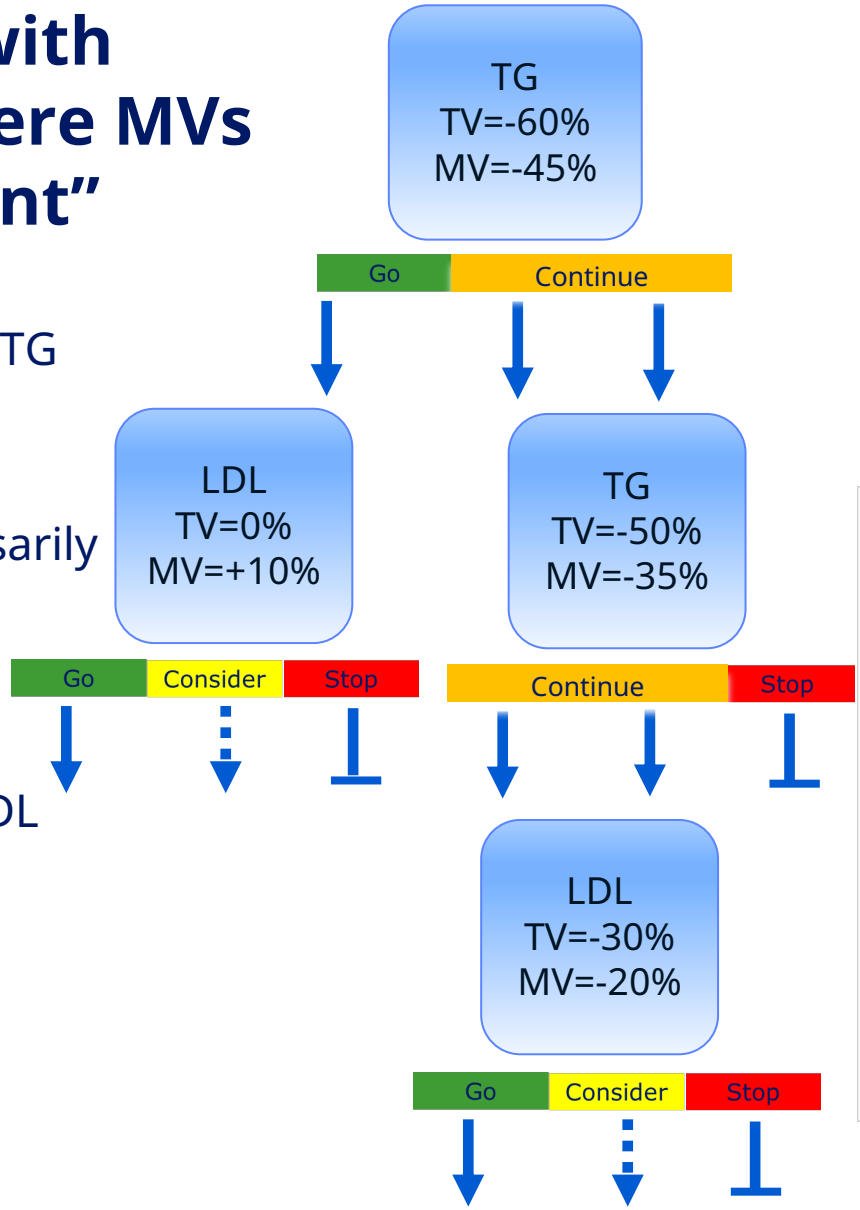


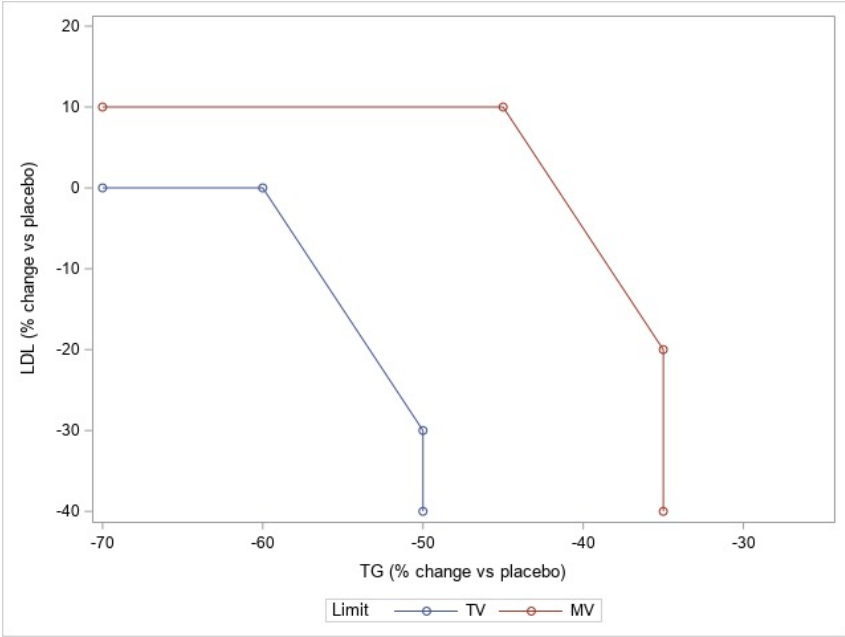
Decision framework with several endpoints where MVs and TVs are “dependent”

Example - Compound to reduce TG and potentially LDL

- As a competitive TG drug
  - TG lowering and not necessarily LDL
  - TG: TV -60% MV -45%
  - LDL: TV 0% MV +10%
- TG lowering with additional LDL lowering
  - TG: TV -50% MV -35%
  - LDL: TV -30% MV -20%



- Two dimensional problem?
  - Use e.g. ”one- sided” two dimensional confidence regions to make decision rule?



Decision ”matrix”

- In some indications (e.g. in CVD), there is not consensus on what biomarkers or functional endpoints should guide decision based on phase 2 data
- Medical specialists tend to favour a ”matrix approach”
  - E.g. a favoural outcome on e.g. 2 of 3 endpoints should imply a ”GO”
- Thus set up a DGF for each endpoint and define decision rule:
  - STOP if 2 or more of 3 are in STOP
  - Otherwise GO if 2 or more of 3 are in GO
  - Otherwise Consider
- How to calculate operating characteristics, overall false go and stop rates?
- 3-dimensional problem?
- Alternatively use a score function based on the relevant biomarkers?

Other applications

- Survival models
- Negative binomial models
- Interim evaluations
  - Nine potential outcomes (one interim evaluation)
- Bayesian analysis (include prior information in decision)

- Use in phase 3
  - Decision to submit
  - Decision to initiate phase 3b trial
- Use for portfolio level decisions

Summary

So far, the key stakeholders in clinical development have been positive towards the implementation of decision frameworks in early clinical trials

An R-shiny app to support calculations in the design phase has been developed

Among some stakeholders lack of understanding (statistical) details remain

Webinar sessions are planned

How to use decision frameworks in more complex scenarios is under investigation