Making Drug Development More Quantitative: Applying Bayesian Decision-Making to Stage-Gate the Risk of Development

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ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop

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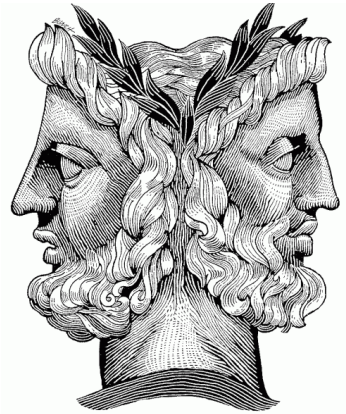
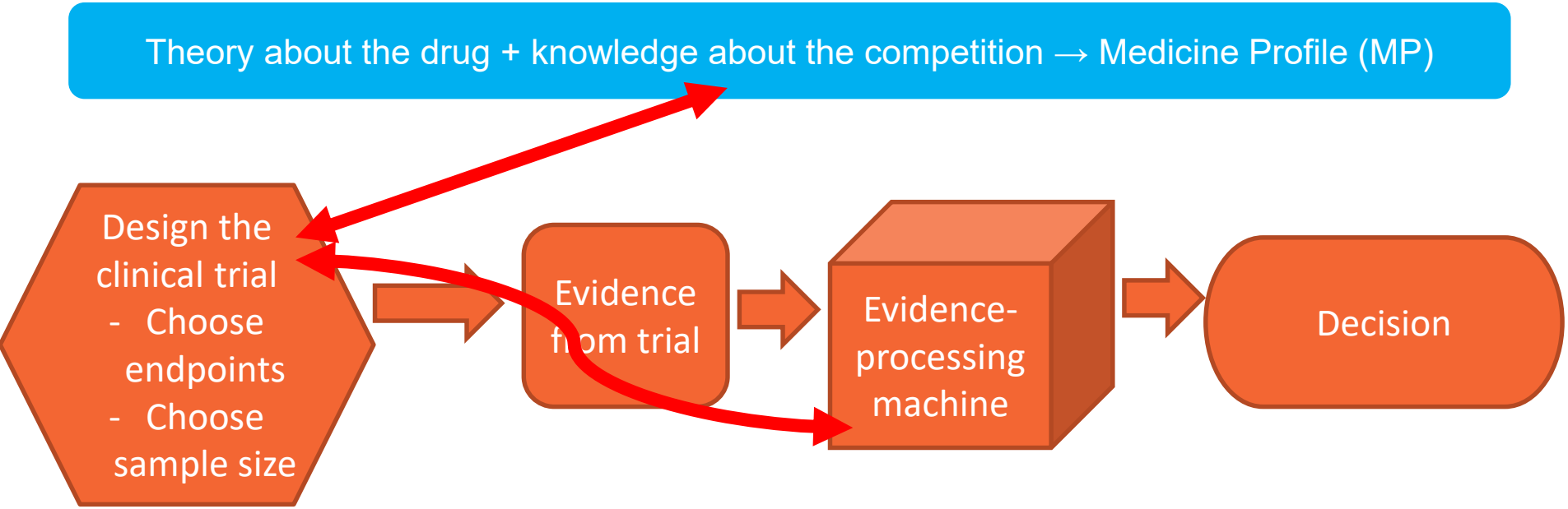


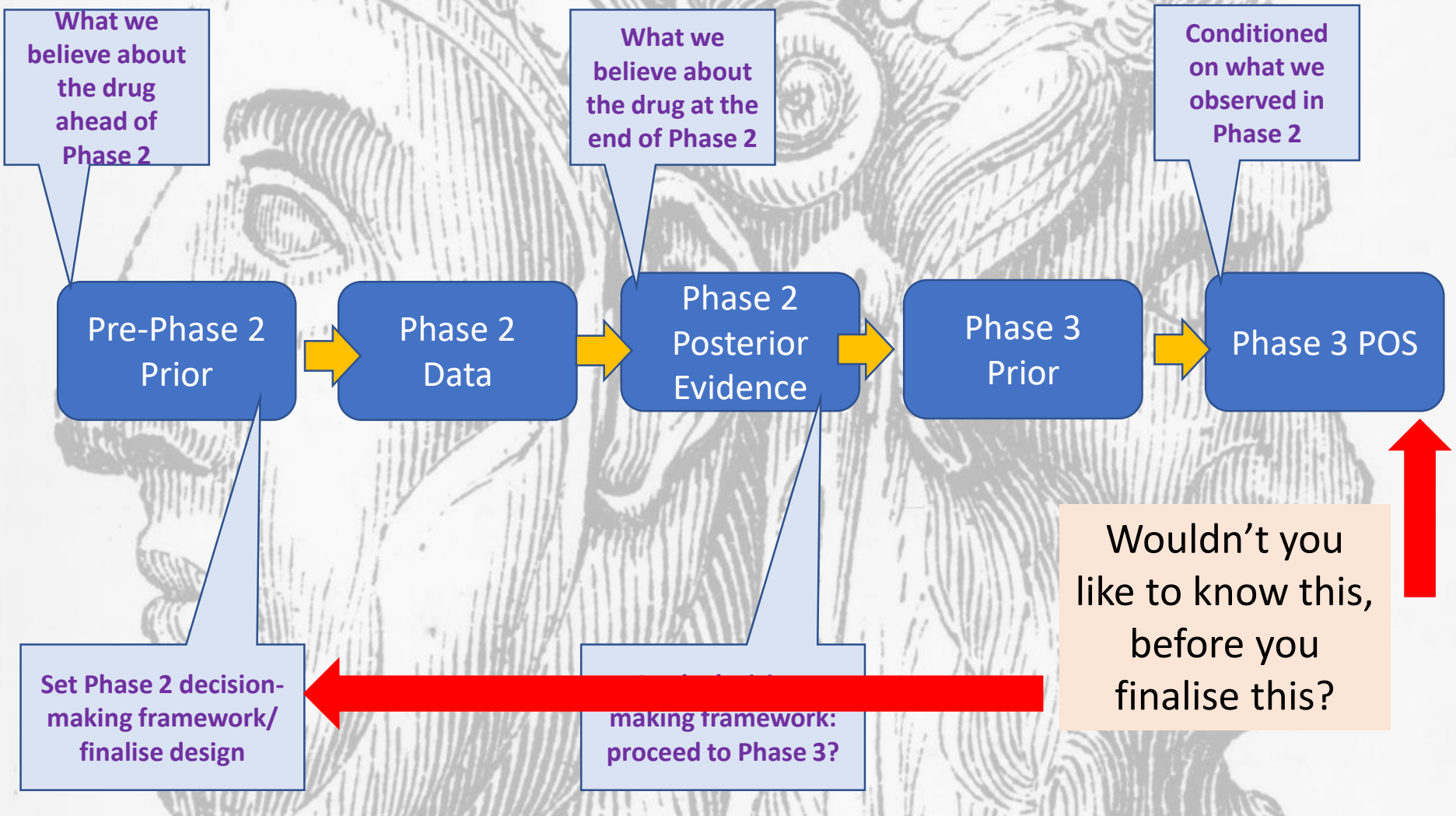


Decision about what? The trial?

The trial was a SUCCESS! Therefore we must continue!

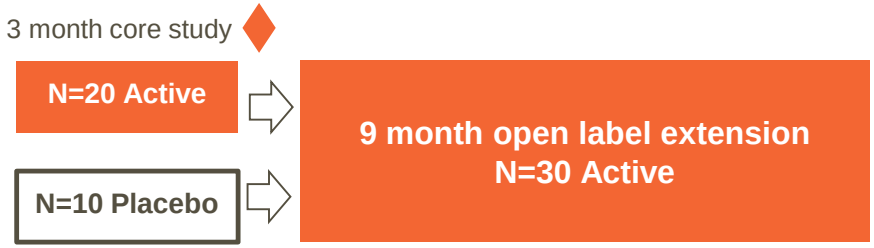
Decision about the Medicine Profile?

Given this trial's evidence, we're now more/less likely to achieve the MP


What we believe about the drug ahead of Phase 2
What we believe about the drug at the end of Phase 2
Conditioned on what we observed in Phase 2
Pre-Phase 2 Prior
Phase 2 Data
Phase 2 Posterior Evidence
Phase 3 Prior
Phase 3 POS
Wouldn't you like to know this, before you finalise this?
Set Phase 2 decision-making framework/ finalise design
making framework: proceed to Phase 3?

ALS Example Used for Illustration

Phase 1b (PoC)

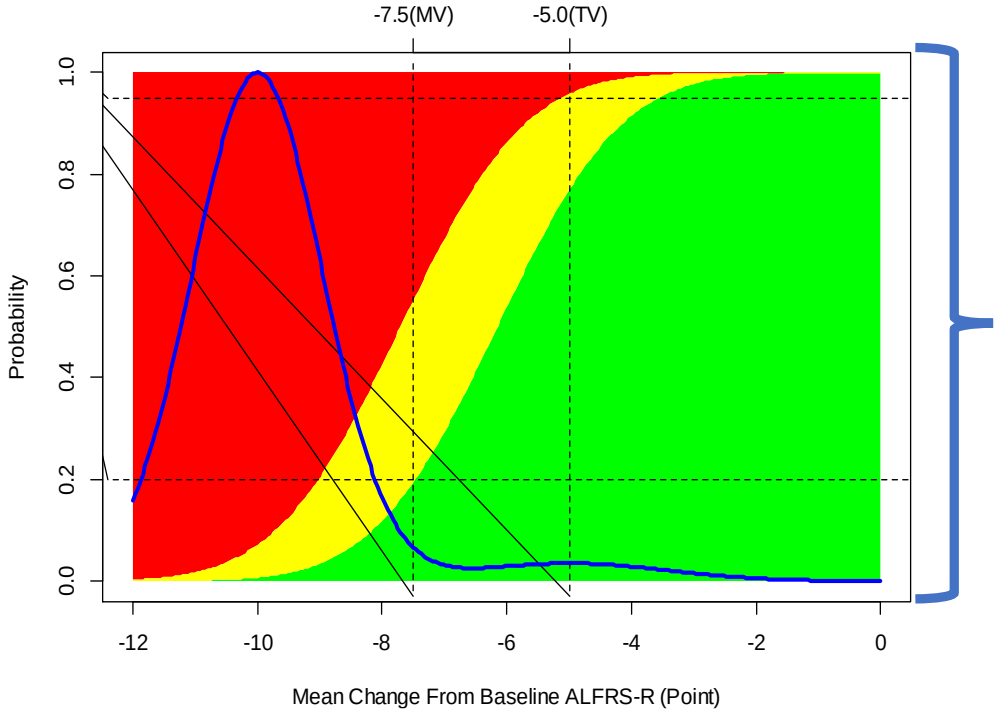


- Outcome: 12 month ALSFRS-R; compared to natural history 10 points/year drop
  - Positive result: observe 6.2 points drop - 80% of at least 2.5 points benefit (Minimum Value)
  - Negative result: observe 7.7 points drop - 5% of at most 5.0 points benefit (Target Value)

Phase 2 (Pivotal)

- Randomized, placebo controlled, 12 month study with 120/arm
- ALSFRS-R as primary endpoint
- Positive result: $p<0.05$ and at least 2 points benefit observed

Operating Characteristics of the decision rule



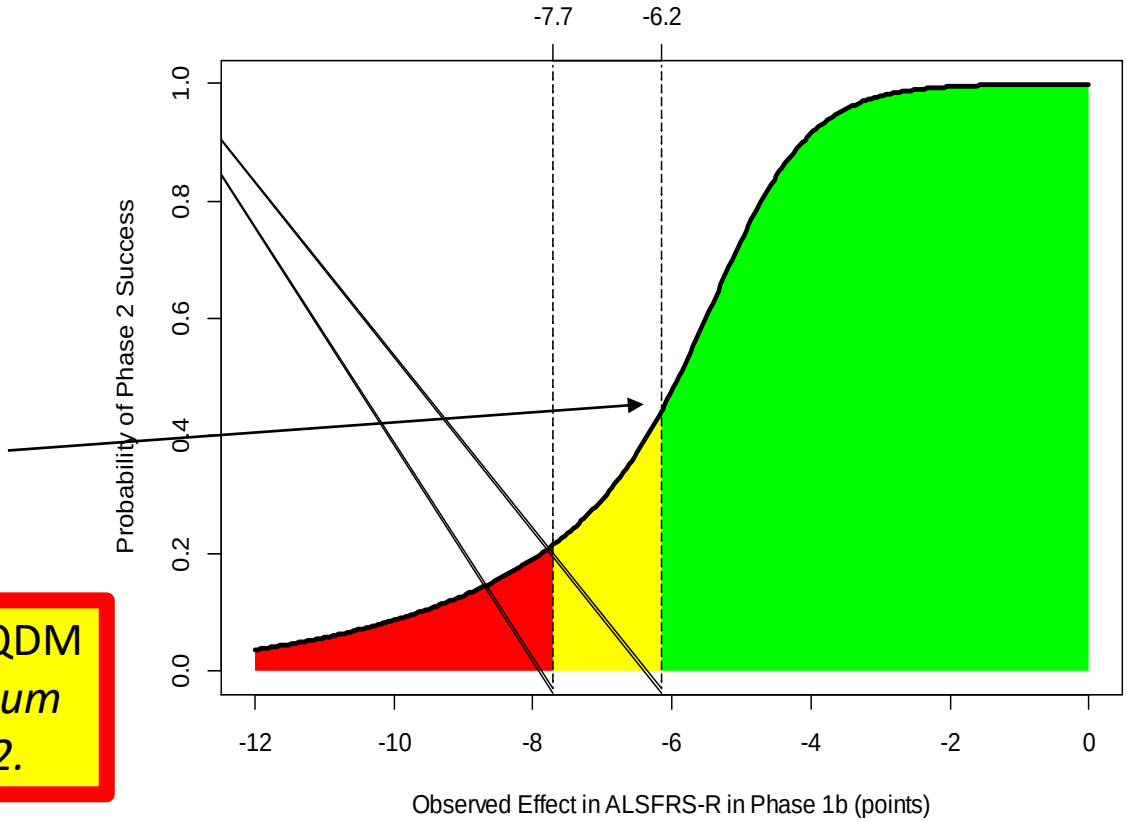
True effect	Probability of making each decision for a given true effect		
	Go (%)	Consider (%)	Stop (%)
TV=5	77%	18%	5%
3	29%	38%	33%
MV=2.5	20%	35%	45%
No effect=0	0.7%	6.3%	93%
Assurance	5.4%	9.6%	85%

Overlaying the prior belief onto the decision rule curves shows how assurance – the average probability to make STOP, GO and CONSIDER decisions – is influenced by current belief about the drug.

Can map any possible observed Phase 1b result to Phase 2 POS (conditional Phase 2 POS)

Minimum Phase 1b result that results in a go, gives 44% probability of phase 2 success

The *tougher we set the Phase 1b* QDM framework, the *higher the minimum Probability of success in Phase 2.*

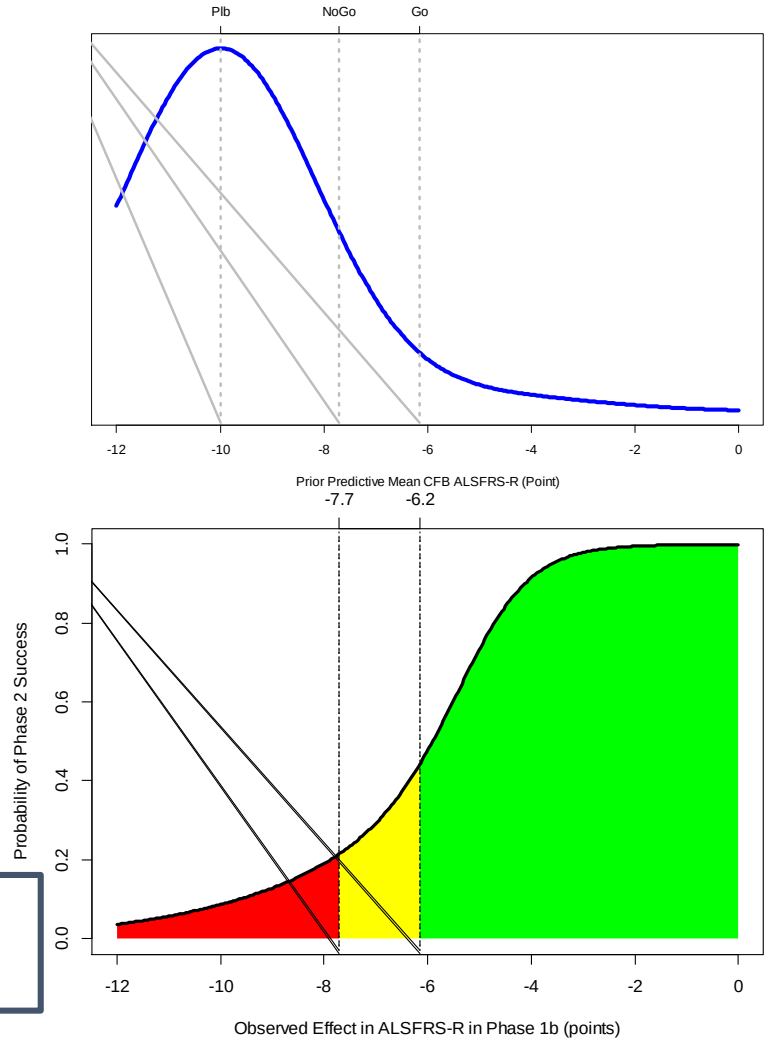


Through current prior we believe **some values of Δ are more likely than others to be observed** in Phase 1b.

Can take this into account to get the **“average” or “expected” conditional Phase 2 assurance** – Phase 2 POS given any positive outcome in Phase 1b, weighted by the prior predictive chance:

Phase 1b PoS: 5.4%
Phase 2 PoS based on phase 1b prior: 14%
Minimum Conditional Phase 2 PoS: 44%
Expected Conditional Phase 2 PoS: 75%

Value of the Phase 1b study? If positive it increases Expected Phase 2 PoS by at least 30%



Updated ALS Phase 1b Decision Rules

Phase 1b (PoC)

3 month core study

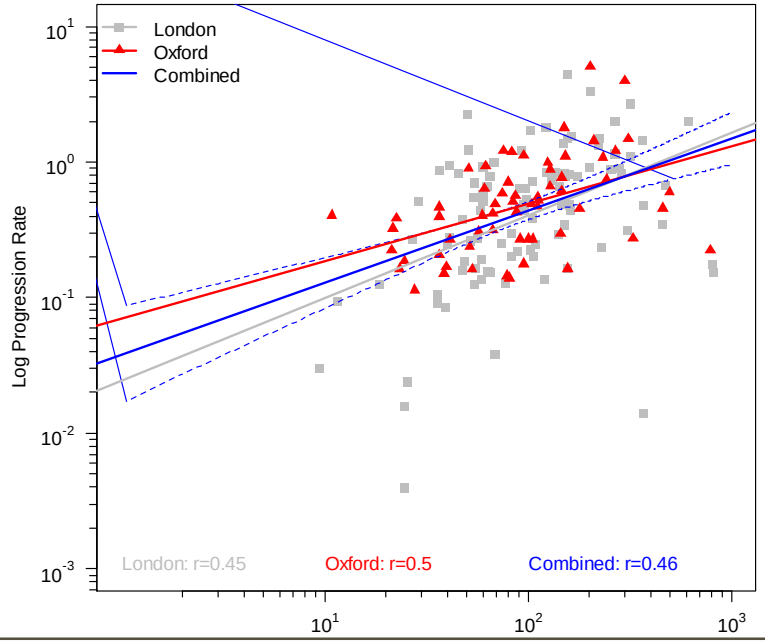
N=20 Active

N=10 Placebo

9 month open label extension
N=30 Active

- **Biomarker: 3 mon neurofilament light (NfL)**
  - **Significant benefit compared to placebo:** observe 20% relative reduction in NfL, which translates to 11% reduction in ALSFRS-R progression rate
- Outcome: 12 month ALSFRS-R; compared to natural history 10 points/year drop
  - Negative result: observe 7.7 points drop - 5% of at most 5.0 points benefit (Target Value)
  - **Positive result: non-negative**

Published NfL vs ALSFRS-R Relationship

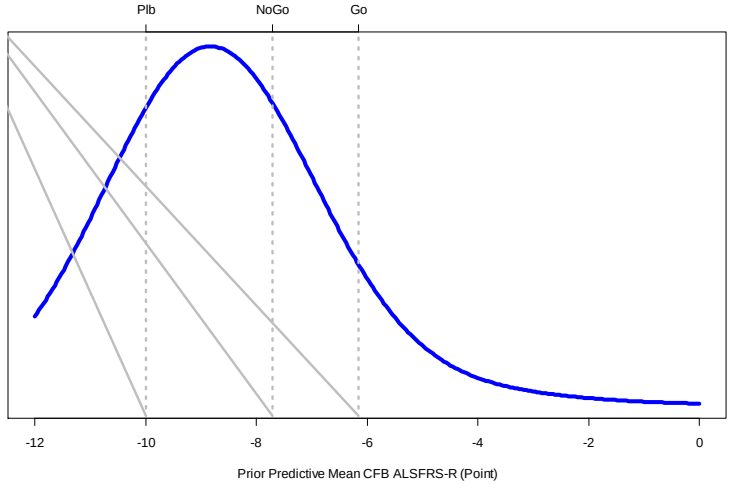


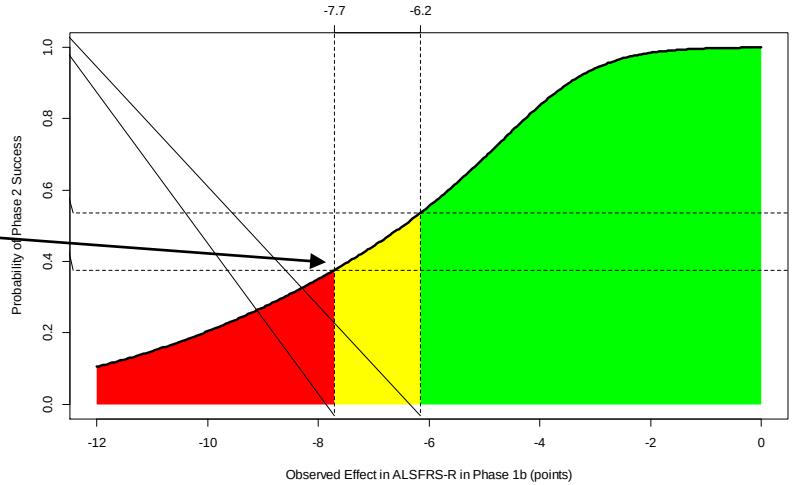
Current:
Phase 1b NfL PoS: 13%
Phase 1b ALSFRS-R PoS: 5.4%
Phase 2 PoS: 14%

Conditional on Minimum NfL success:
Phase 1b ALSFRS-R PoS: 30%
Phase 2 PoS: 32%

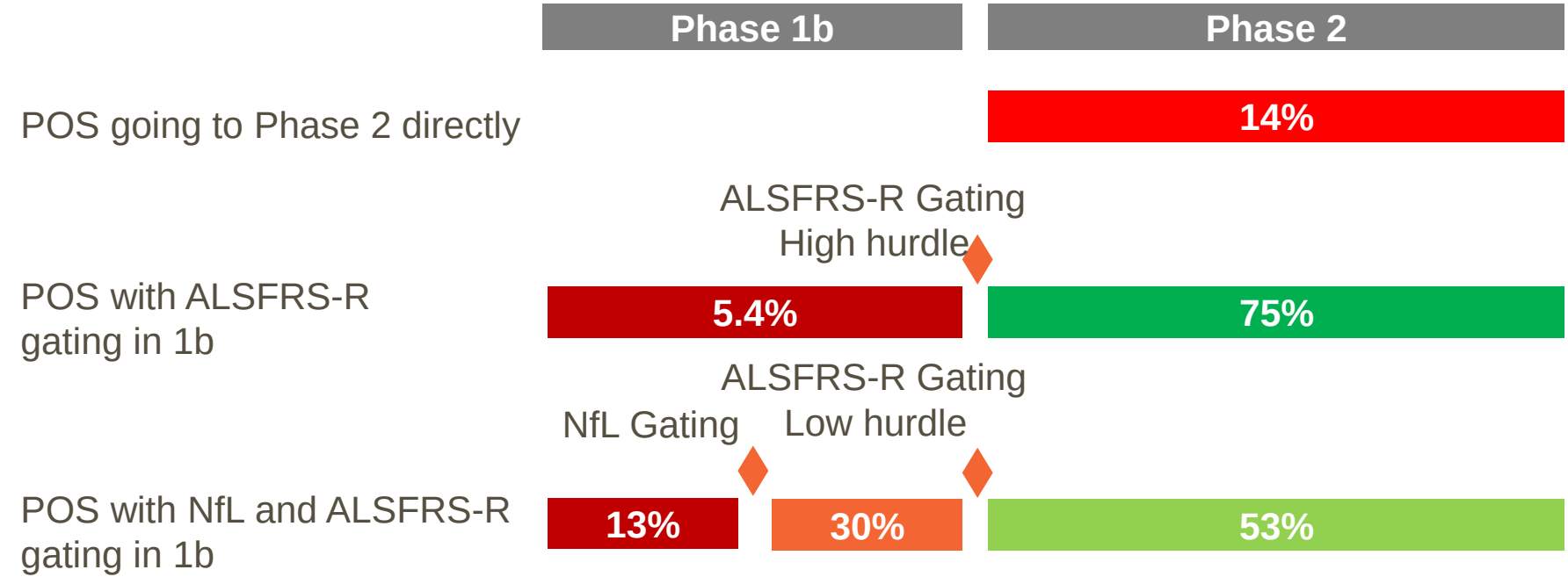
Conditional on Phase 1b success (NfL & ALSFRS-R):
Minimum Phase 2 PoS: 38%
Expected Phase 2 PoS: 53%

Value of the Phase 1b study? If positive it increases Expected Phase 2 PoS by ~40%



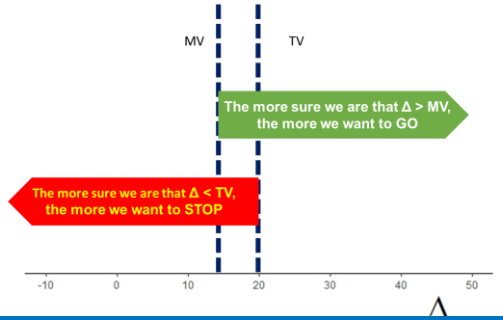


Risks Discharging with Phase 1b

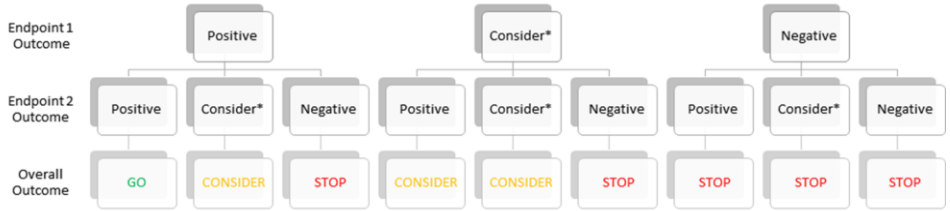


The QDM recipe:

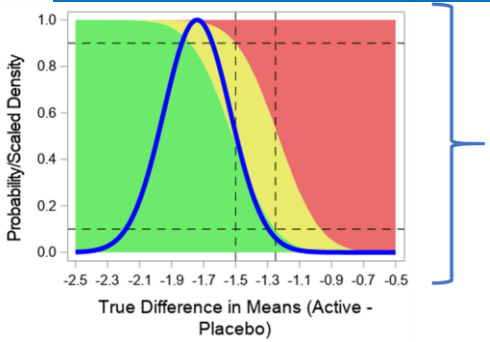
Set relevant thresholds and evidence levels



Map outcomes to decisions

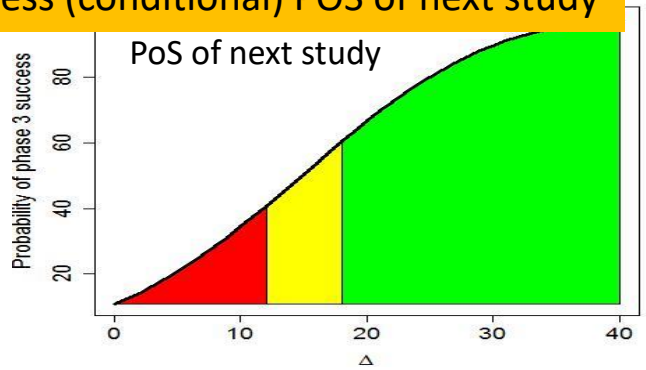


Check risk, and incorporate prior belief



True effect	Probability of making each decision for a given true effect		
	Go (%)	Consider (%)	Stop (%)
TV=-1.5	50%	40%	10%
MV=-1.25	10%	40%	50%
½ MV=-0.625	0%	0%	100%
No effect=0	0%	0%	100%
Assurance	75%	16%	9%

Assess (conditional) POS of next study



Thank you!