Dose-response, small data, big decisions.

Mike K Smith (Pfizer R&D UK Ltd)

  @MikeKSmith

RSS / PSI Award for statistical excellence in the pharmaceutical industry 2019

"…for pioneering practical Bayesian methods with drug development in the context of optimising decision making within trials and modelling dose response with pharmacokinetic / pharmacodynamic modelling."


SMALL - BATCH ARTISANAL DATA
• EST. JUST NOW •

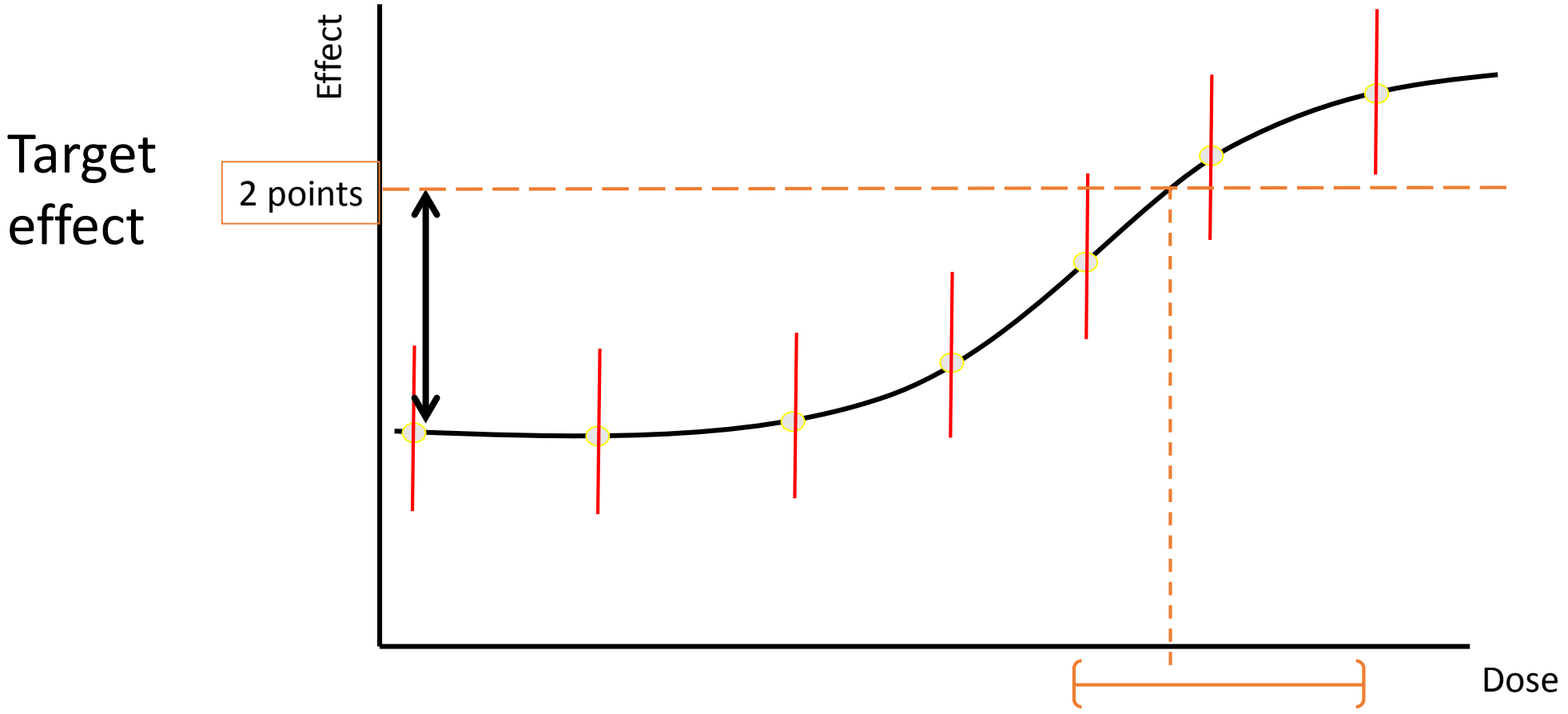
Pt 1. Dose-response, decision making and design

The problem statement

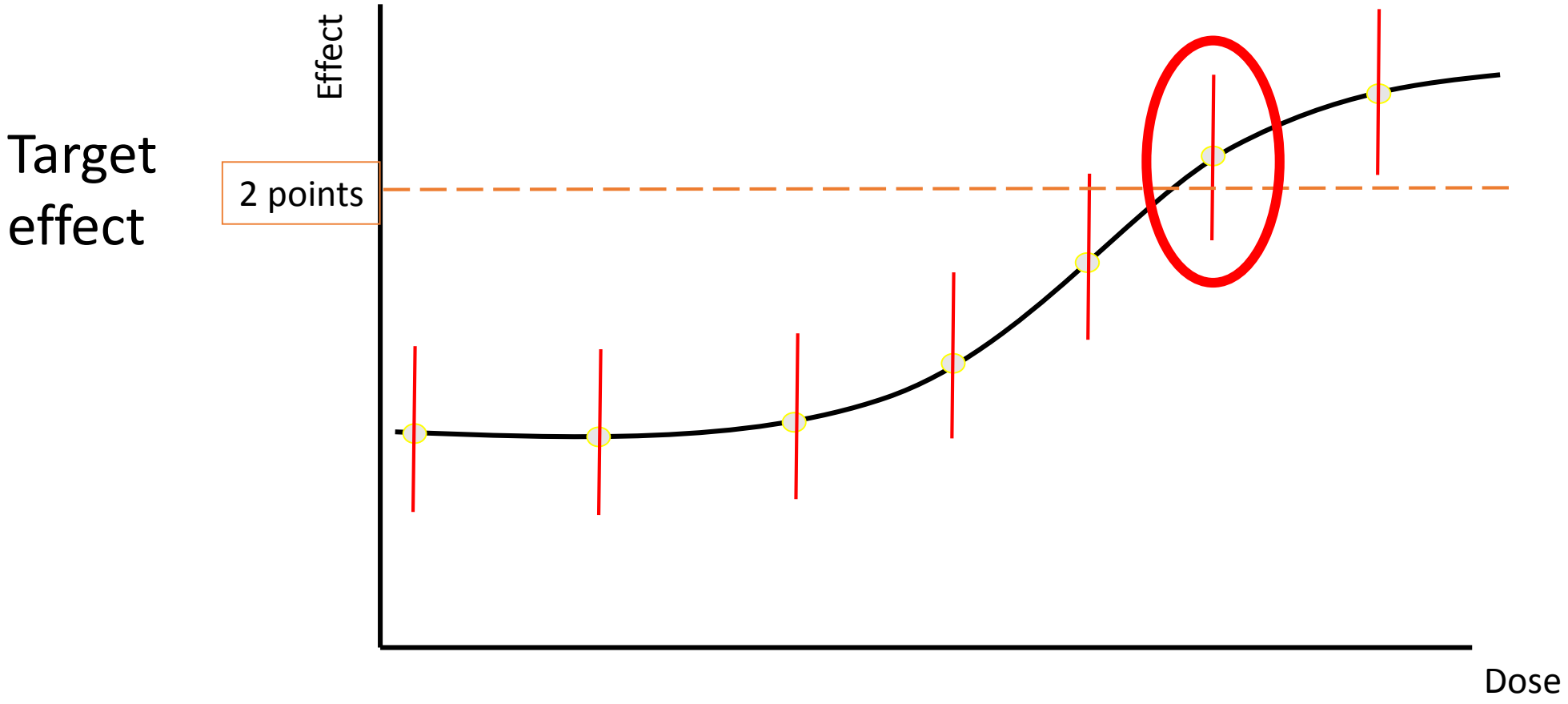
The Clinical Question

- “What do you need to know? How well do you need to know it?” – *Lewis Sheiner*

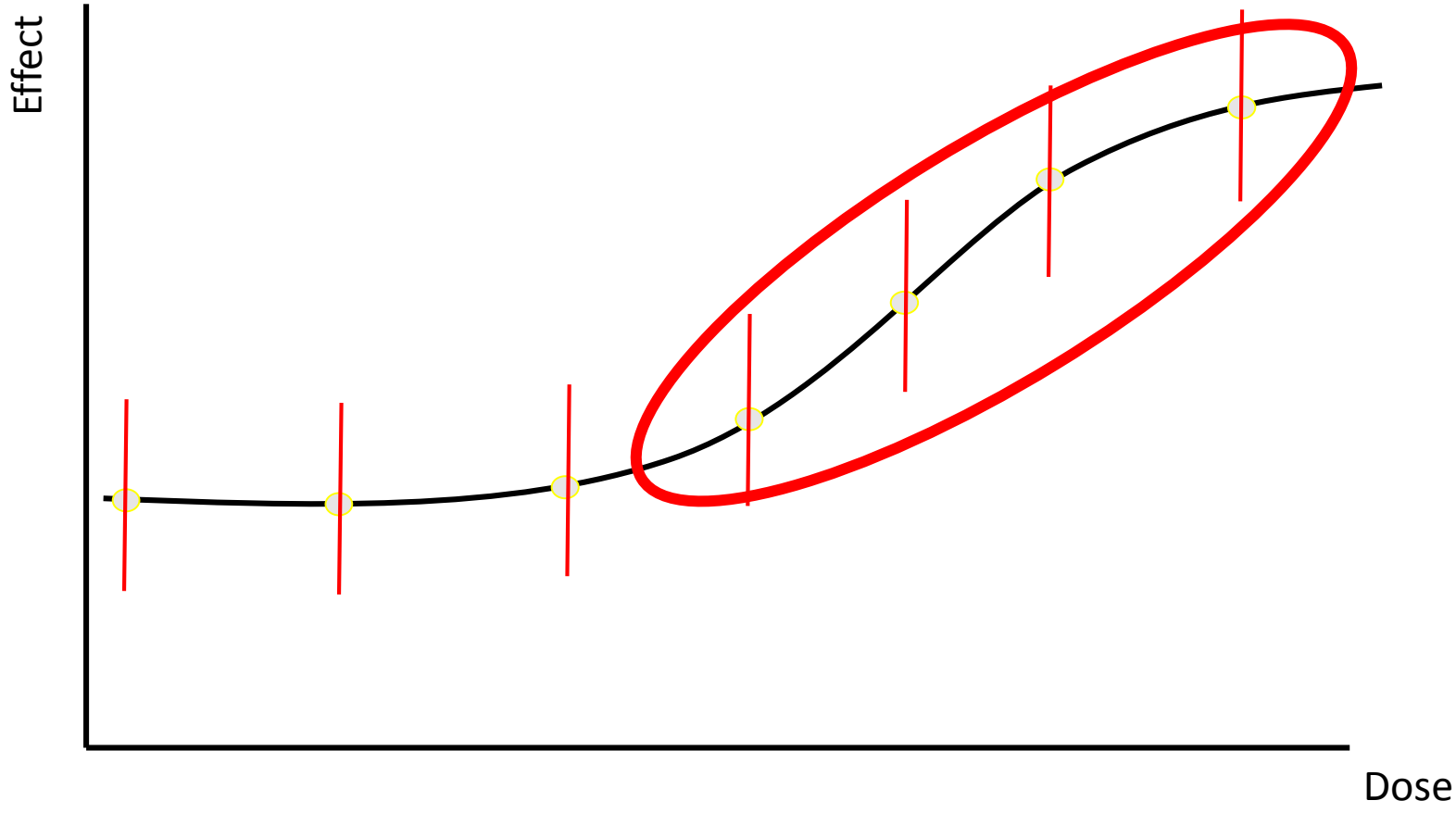
Dose to give 2 points improvement



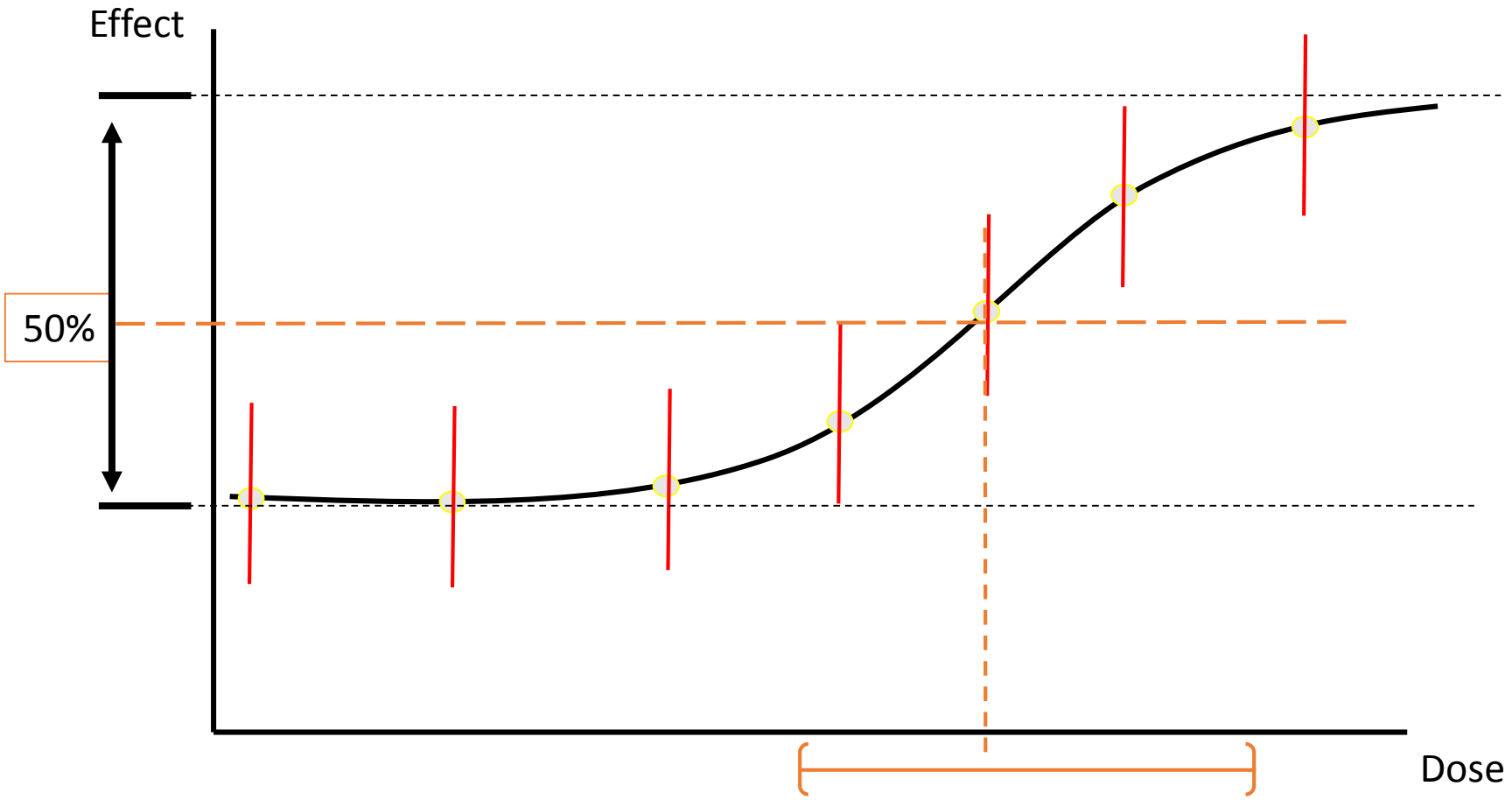
Pick one dose for future trials



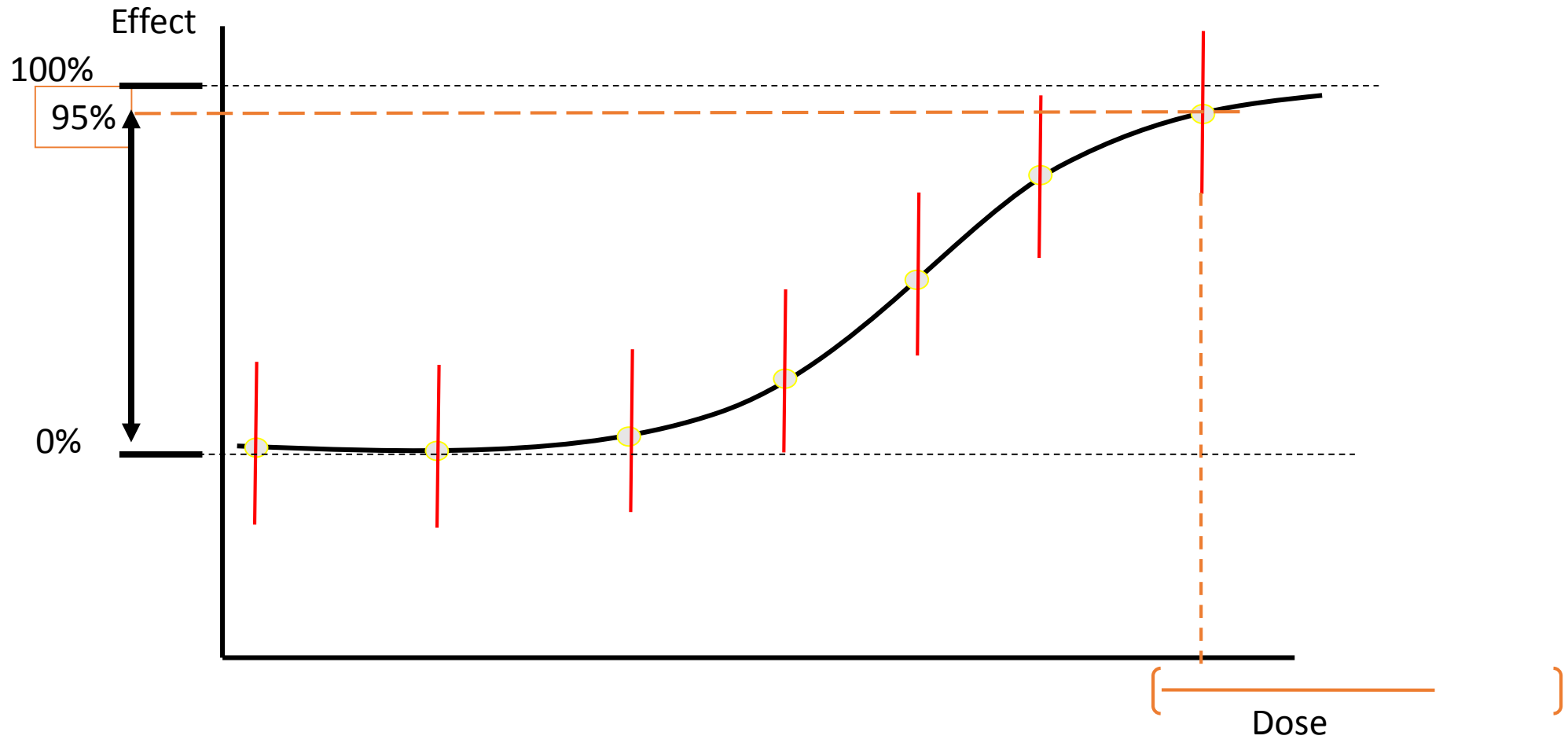
Refining the dose-range



ED50



ED95



The Clinical Question

- "What do you need to know? How well do you need to know it?" – *Lewis Sheiner*

- Pick ***ONE***.
  - Then design and optimise for that ONE objective.

Decision making

- We need to turn the clinical question into a metric which we can use to select / drop doses:
  - (Posterior) variance on ED50.
  - P(Effect at Dose X > 0) > 1-beta.
  - Interval on ED95 less than 2-fold span.
  - Drop if P(Effect at Dose X > Y) < alpha.
    - Y is Marketable difference / clinically meaningful difference.

Pt 2. Bayesian adaptive designs

Key players

Mike Krams

Don Berry

Andy Grieve

Peter Mueller

Tom Parke

…and many more

Normal Dynamic Linear Model

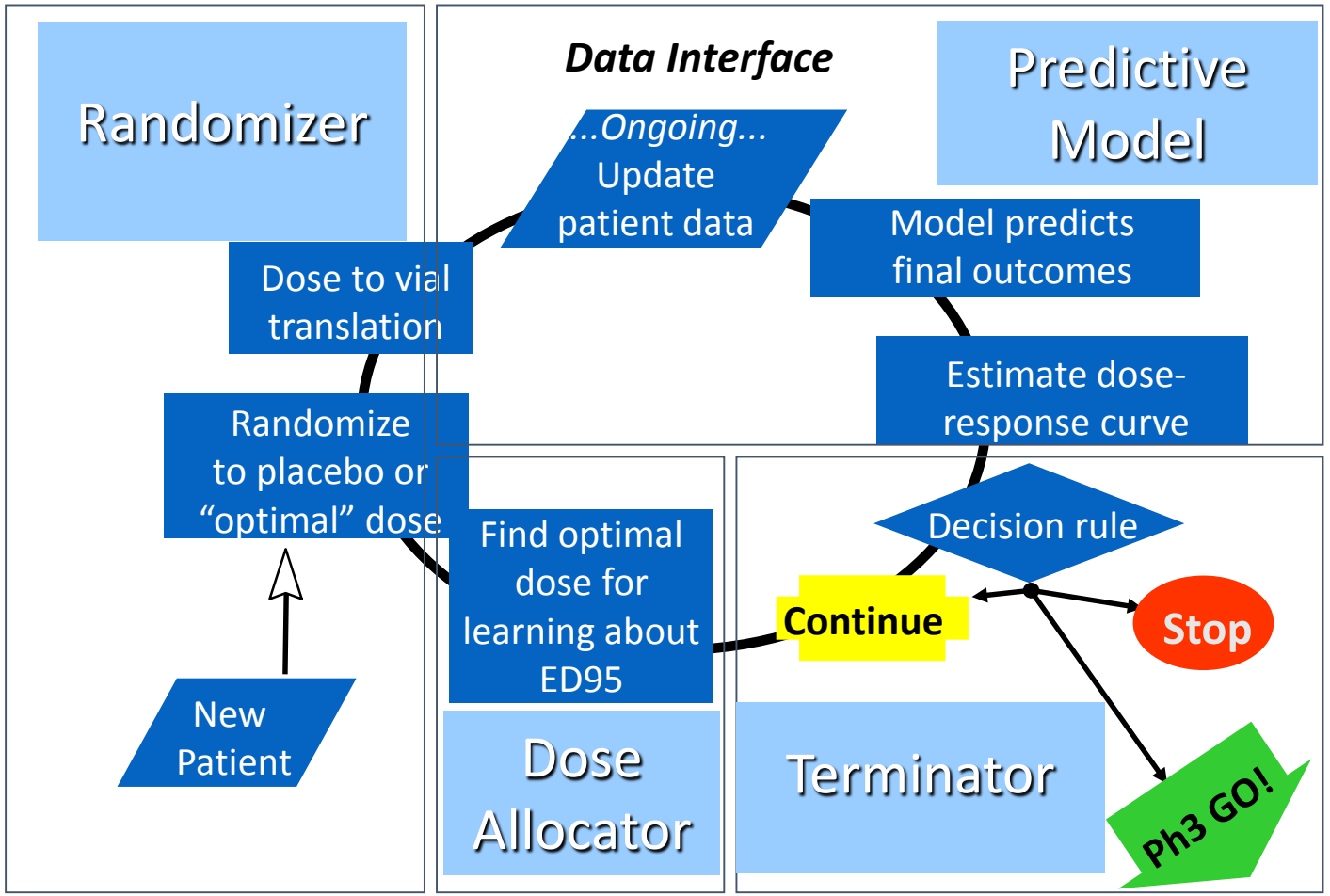
- Flexible model that describes effect at each dose using simple updating function.
  - FAST updating, Normality assumptions, means + variances
  - $\mu_{dose = X} = \mu_{dose = X-1} + \delta_{dose = X-1} + \omega$
  - $\delta_{dose = X} = \delta_{dose = X-1} + \varepsilon$

  $\omega \sim N(0, V\sigma^2)$

  $\varepsilon \sim N(0, W\sigma^2)$

  W is a smoothing parameter, as a function of estimated variability

Bayesian adaptive design

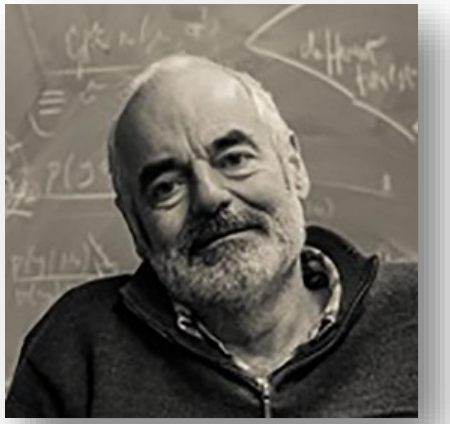


Surrogate/ Early Response

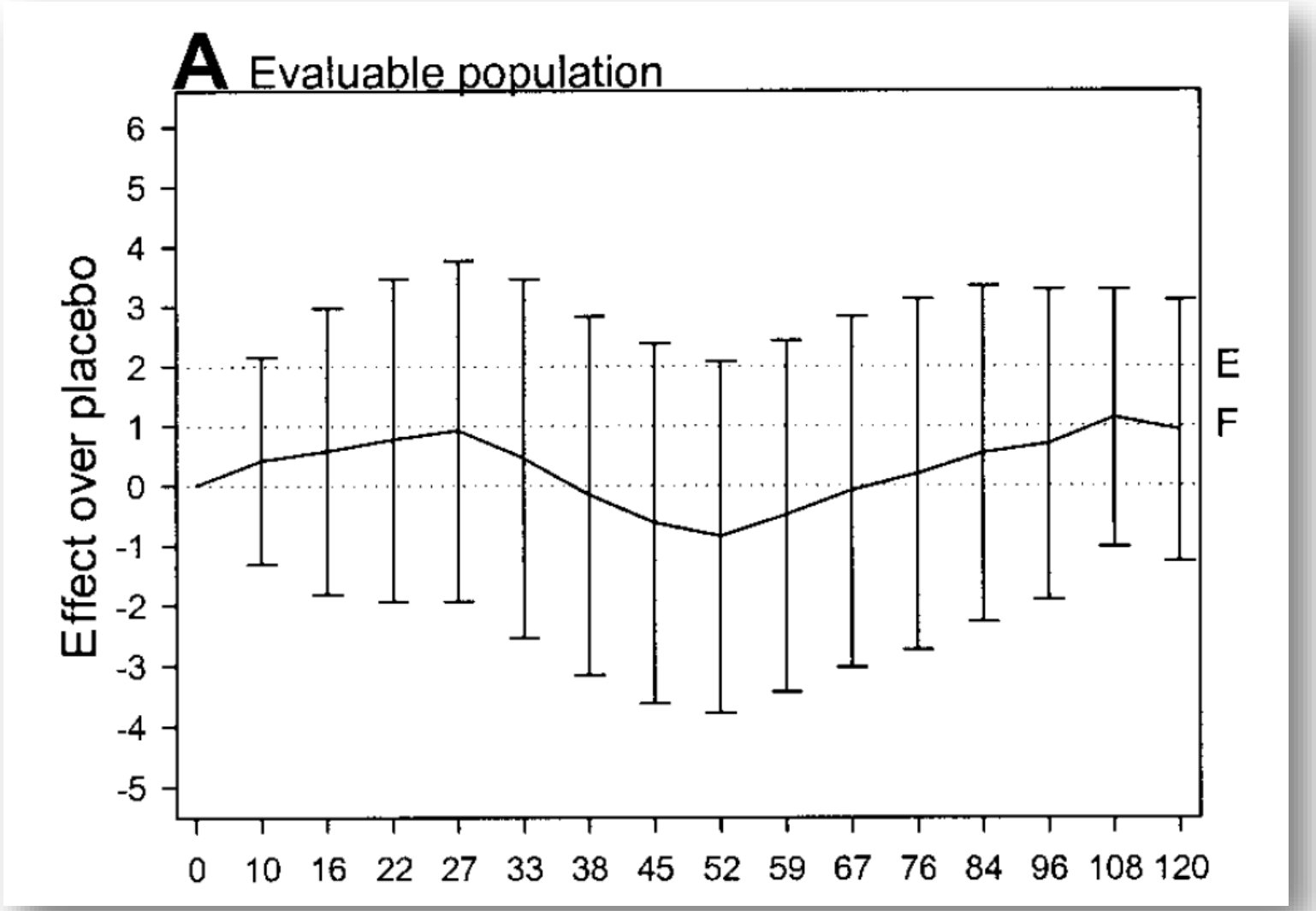
Bayesian Analysis

ASTIN study in stroke

Margaret Jones



David Spiegelhalter



Pfizer Phase 2 pain study

Keith Tan

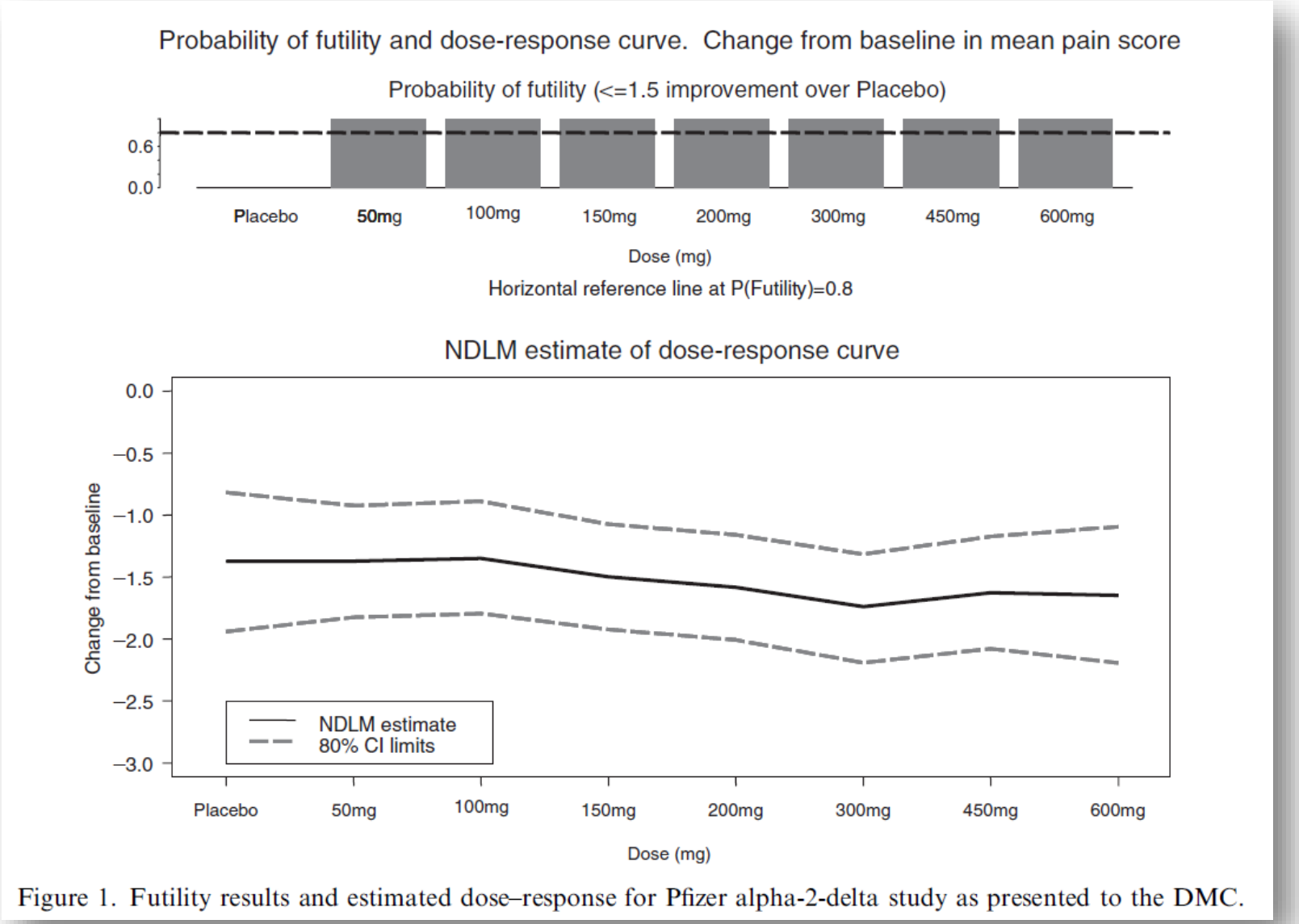


Figure 1. Futility results and estimated dose–response for Pfizer alpha-2-delta study as presented to the DMC.

2006

NDLM – Good, bad and ugly

- Good
  - Quick! Able to make predictive inferences about effect at each dose.
  - Flexible! Non-monotonic
  - Worked well in ASTIN where there was LOTS of information.
  - Seems to kill drug projects very effectively.

- Bad
  - Needs informative prior on smoothing parameter and/or LOTS of data.
  - Extrapolation outside of individual dose effects is limited.

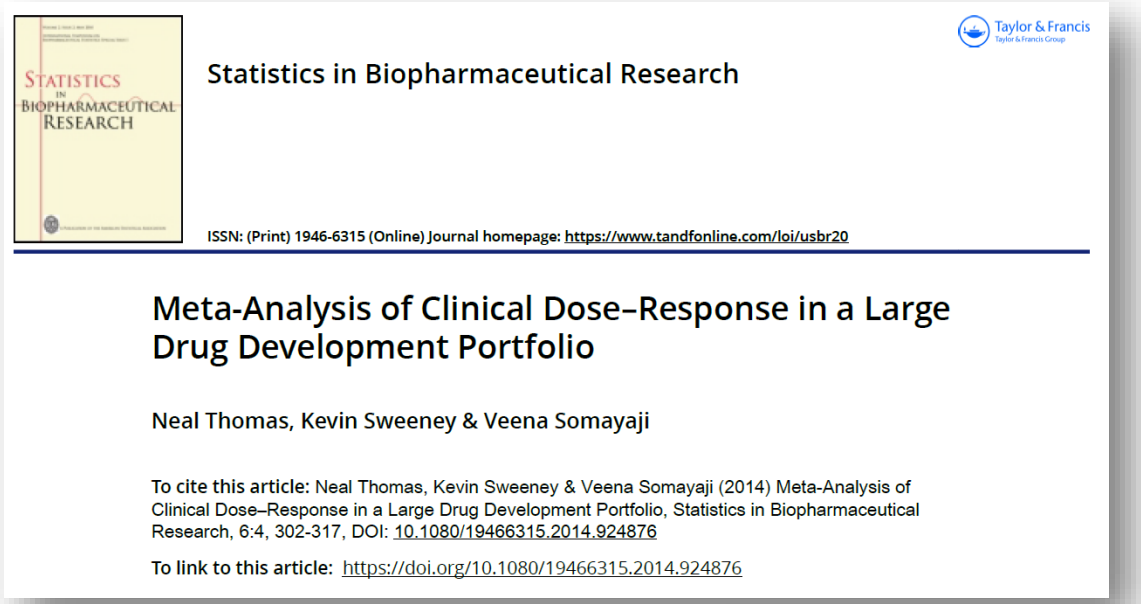
- Ugly
  - Lots of (active) doses can lead to increased placebo effect.

Pt 3: Bayesian design with parametric models

Parametric models

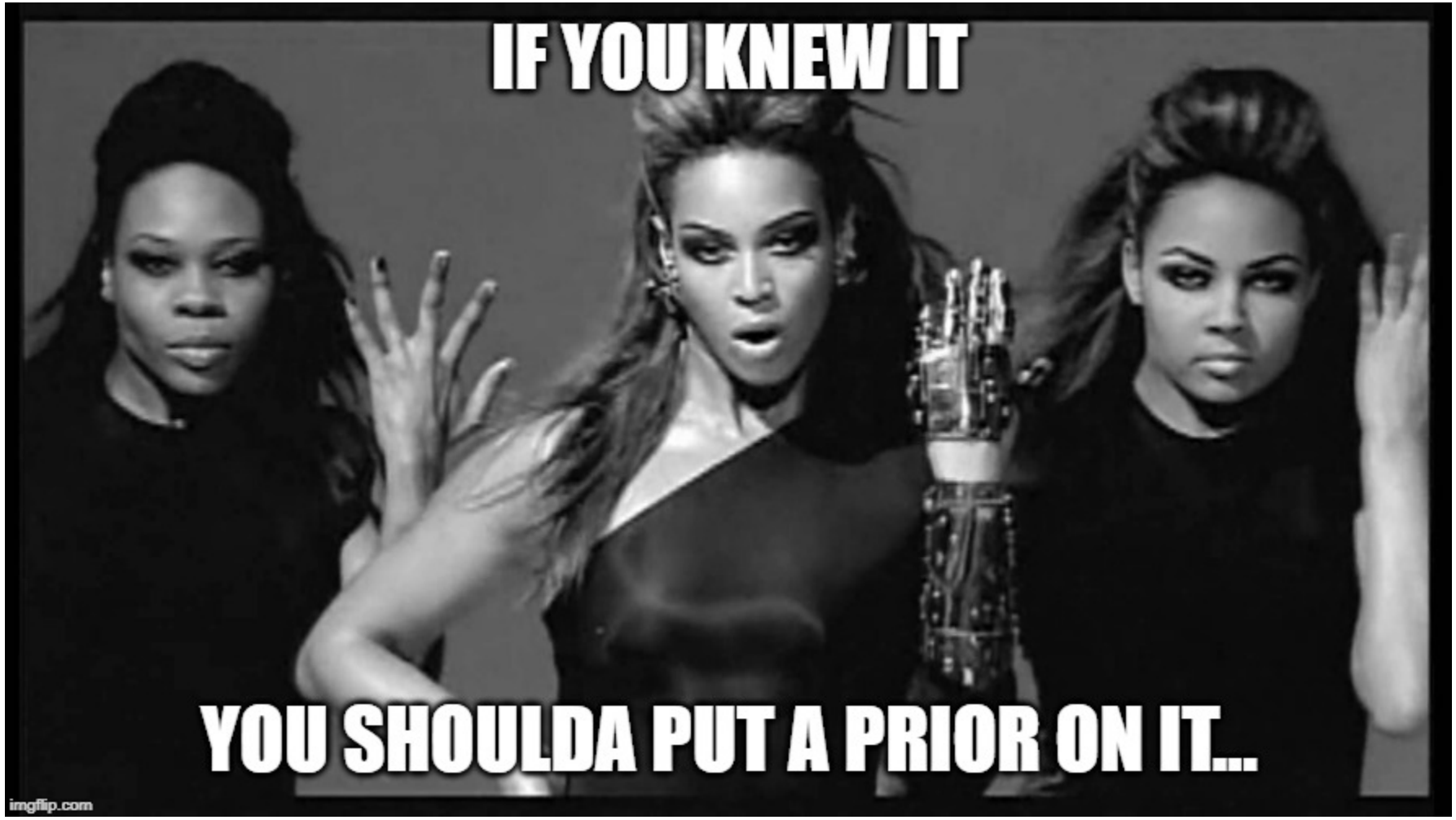
- Neal Thomas and collaborators have found that ***most*** dose-response and dose-finding studies can be described by an Emax model.

$$E(Y|D) = E0 + \frac{Emax * Dose^{\lambda}}{(ED50^{\lambda} + Dose^{\lambda})}$$



Neal Thomas

Informative priors



Informative priors

- We typically know ***something*** about the Placebo response in an indication – prior on E0.

- We can put a sceptical prior on Emax i.e. we need sufficient evidence of effect to go forward, otherwise we stop.
  - Most drugs fail.
  - If we can ***fail quickly*** and ***with confidence*** then that's ***good***.

- Hill parameter (λ) can typically have an informative prior – Neal Thomas' work shows λ in the range (0, 6) and he advocates Beta distribution.

- If comparing against a reference treatment then we should reflect that knowledge in an informative prior.

Problems: ED50 and Emax

- ED50 and Emax are usually highly correlated
  - We can reparameterise using S_0 = Emax / ED50 (as per Schoemaker 1998*)

- Even weakly informative priors are sufficient to constrain parameter space to improve convergence.

- And ***don't forget optimal design ideas.***
  - Importance of low doses to better estimate ED50.

- Estimating Potency for the Emax-Model Without Attaining Maximal Effects. Schoemaker, R.C., van Gerven, J.M.A. & Cohen, A.F. J Pharmacokinet Pharmacodyn (1998) 26: 581. https://doi.org/10.1023/A:1023277201179

Application to design

Table 8 Results of simulations—sensitivity to prior choice

Design (placebo: new drug dose A: new drug dose B: existing drug)	Total sample size, N	Relative potency	Proportion with positive outcome with informative prior	Proportion with positive outcome with uninformative prior
25:25:25:25	100	4	0.73	0.55
10:40:40:10	100	4	0.87	0.33
15:60:60:15	150	4	0.89	0.63
25:50:50:25	150	4	0.87	0.71
10:10:10:10	40	4	0.5	(
80:80:80:80	320	4	0.91	(
40:40:40:40	160	4	0.84	(

From: A Bayesian design and analysis for dose-response using informative prior information.
Smith, MK and Marshall, S. J Biopharm Stat. 2006;16(5):695-709. DOI: 10.1080/10543400600860535

Scott Marshall

Application to design

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80:80:80:80	320	4	0.91	0.9
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Pt 4: Quantitative decision making

Key players

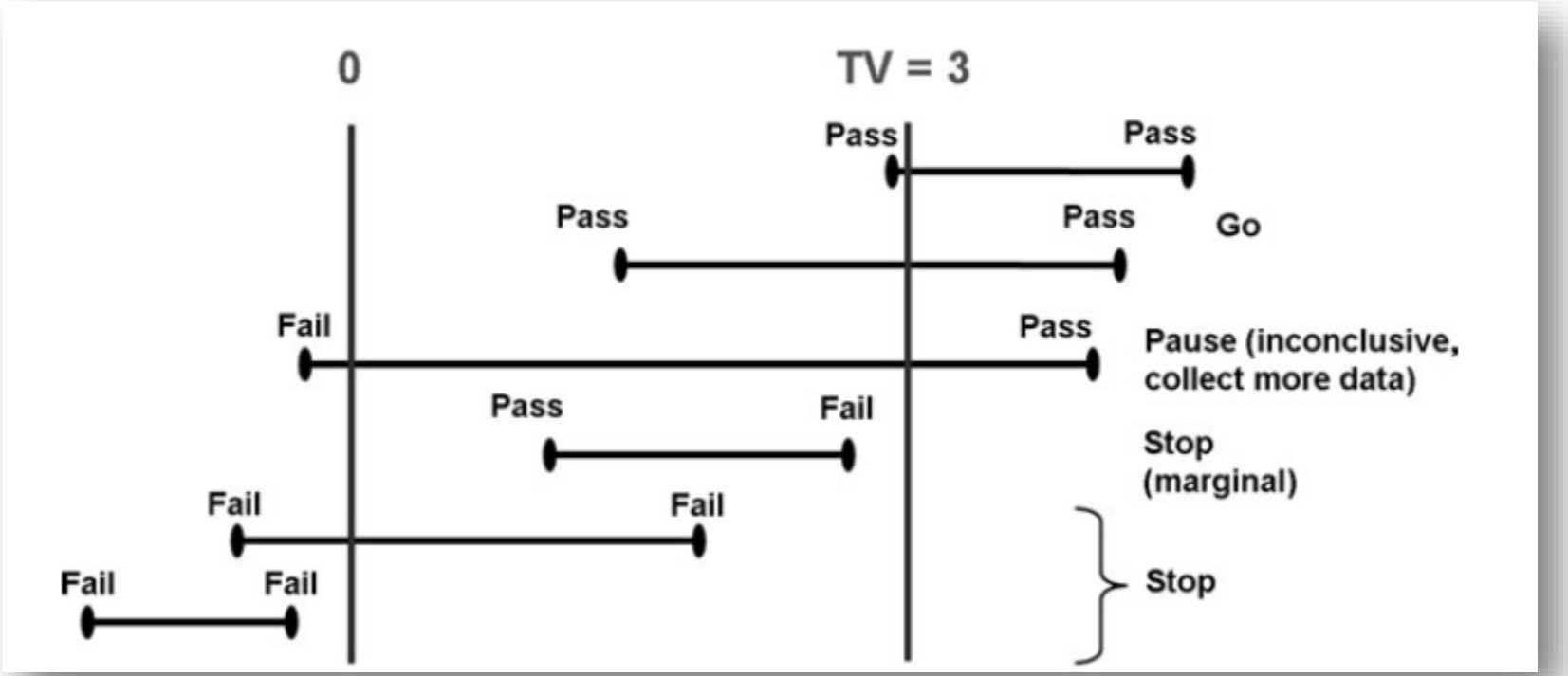
Ken Kowalski

Jonathan French

Matt Hutmacher

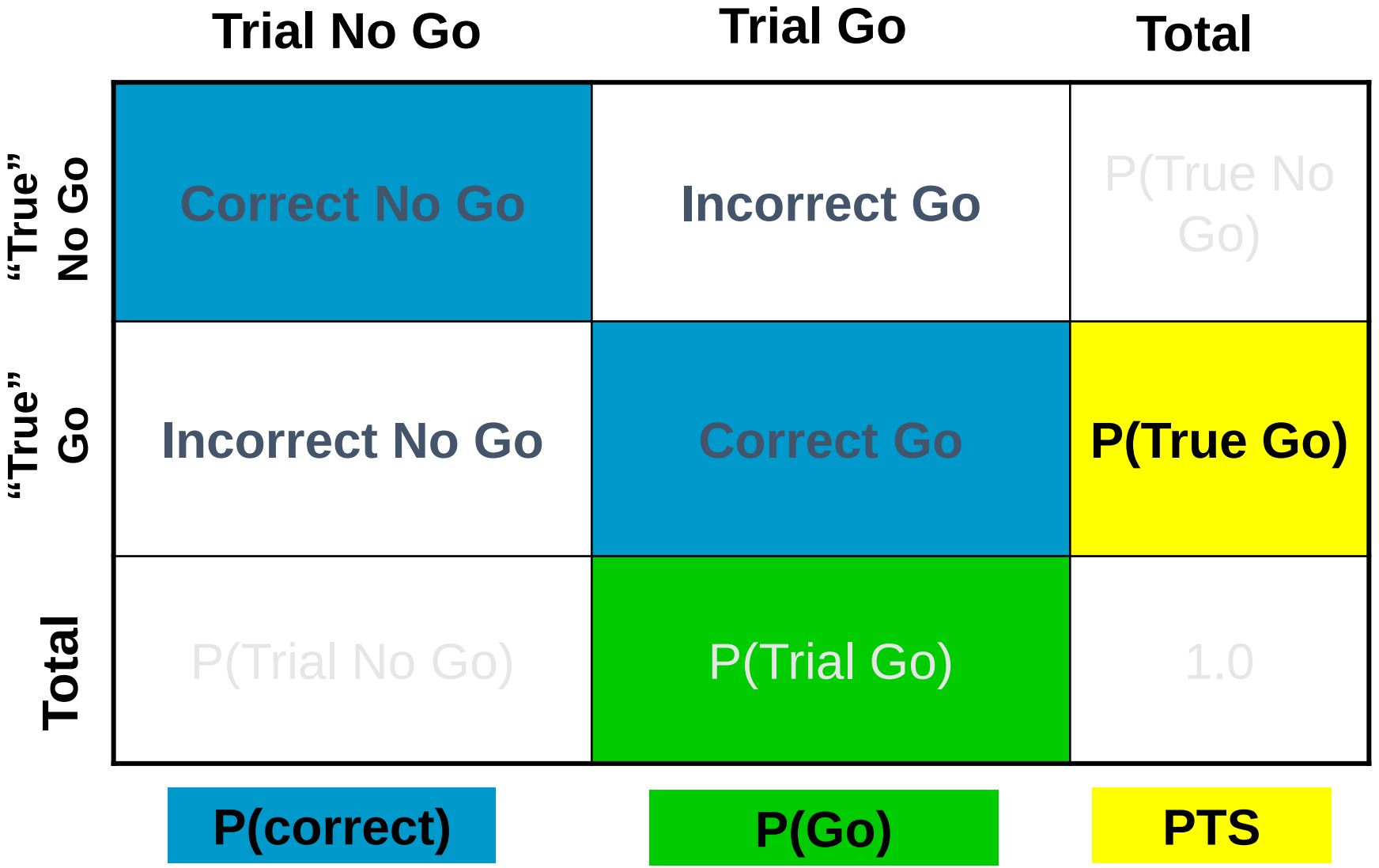
Quantitative decision making – making the right decision

Decisions using lower bound > 0 and upper bound <= 3



From: Decision-Making in Drug Development: Application of a Model Based Framework for Assessing Trial Performance. Smith M.K., French J.L., Kowalski K.G., Hutmacher M.M., Ewy W. (2011) In: Kimko H., Peck C. (eds) Clinical Trial Simulations. AAPS Advances in the Pharmaceutical Sciences Series, vol 1. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-7415-0_4

Decision criteria operating characteristics



Application of quantitative decision criteria in Crohn's Disease

Base criteria: 15% improvement over placebo in Response70 at week 4.

- ***adalimumab-like***

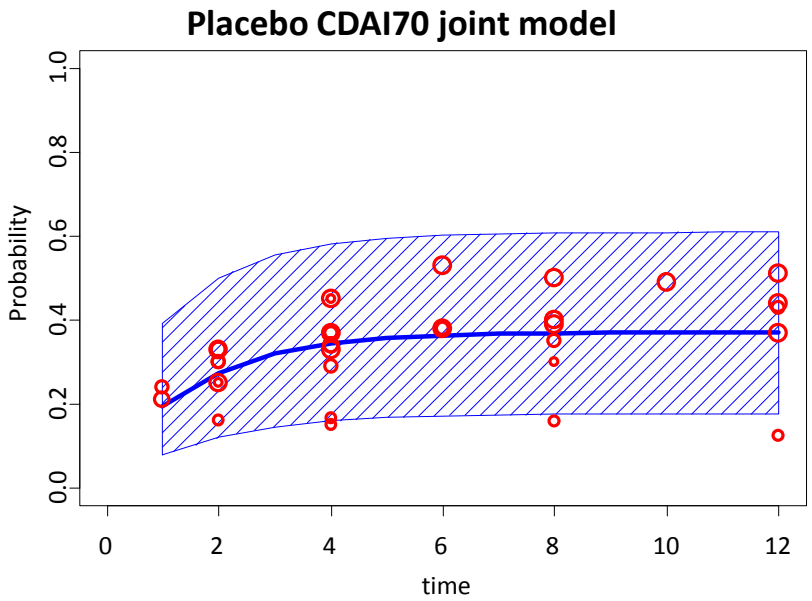
Pessimistic: 10% improvement over placebo in Response70 at week 4.

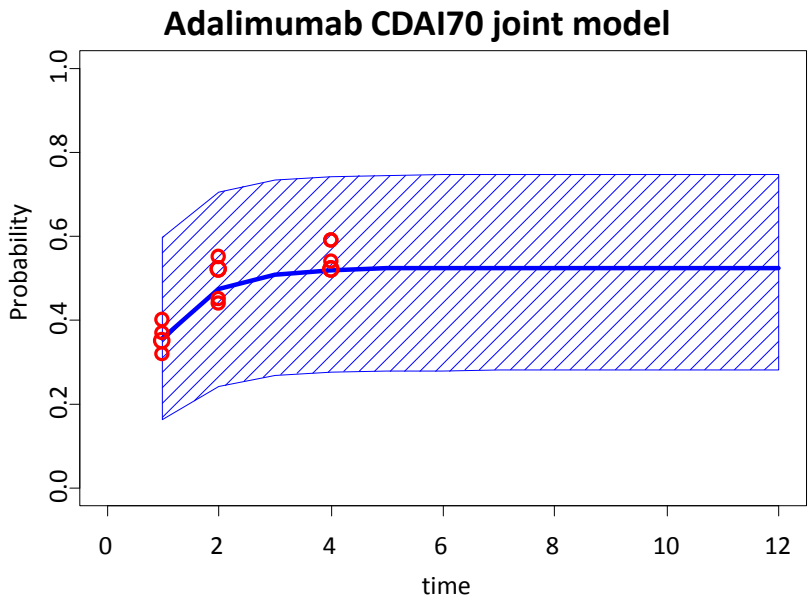
- ***certolizumab-like***

Optimistic: 20% improvement over placebo in Response70 at week 4

- ***infliximab-like***

Meta-analysis of prior data



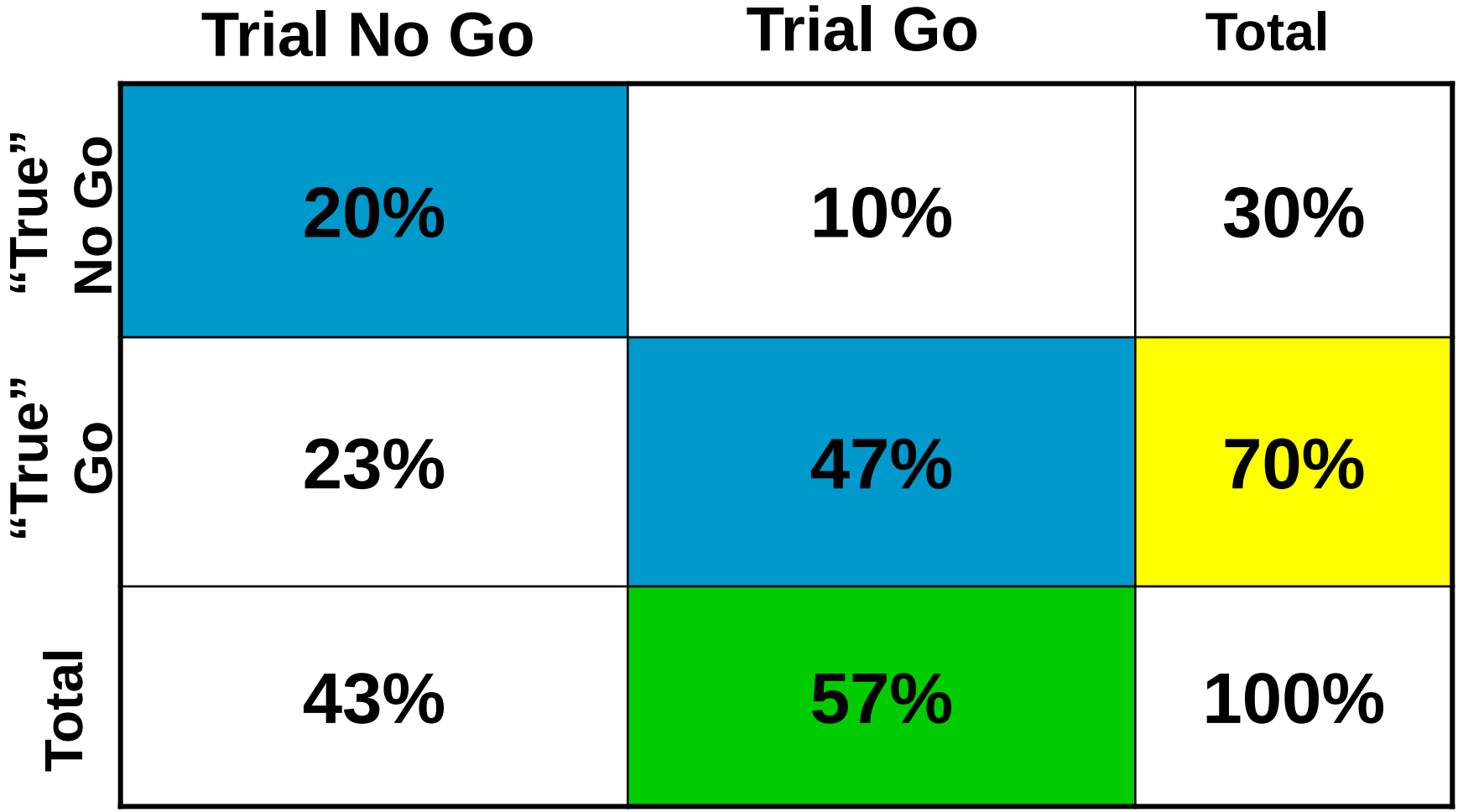


Question: “If we had adalimumab efficacy then would we make the right decision with our Proof of Concept study design (n/group=155)?”

Simulation

- **Truth**: Each simulation replicate has a set of model parameters + individual “study” effect.
  - “Go” if difference in probabilities is >0.15
- **Trial:** Use these response probabilities in a Binomial dist. with size n=155 to get observed number of responses in each arm.
  - “Go” if difference in ***observed*** response rate is >0.15

Simulation results using QDC



P(correct) = 20%+ 47% = 67%

PTS = 70%

Simulation results using QDC

- Probability of achieving base case (a 15% difference over placebo) is 70%.
  - Regardless of design or sample size.

- Pessimistic: P(Delta>10%) = 84%
- Optimistic: P(Delta>20%) = 28%

- Sponsor choice about whether this is sufficient to ***START*** a trial.

Simulation results using QDC

- Probability of correct decision is 67%
  - Sponsor choice about the accuracy of the quantitative decision metric.
  - 67% probably isn’t high enough.

- P(Trial NO GO | True GO) is 23%.
  - Not good at this stage of development (POC)
  - Kills good drugs.

- Probability of correct decisions is a function of design + analysis methodology + decision criteria.

In Summary

I have been ***VERY*** lucky in having interesting and very clever people to work and collaborate with...

I have been ***VERY*** lucky in having managers who have allowed me to “play”, but who held me to account to deliver the things I played with…

Being “lucky” means being in the right place, at the right time, with the right interests, the right skill-set, the right mind-set and having the right people around you to help you achieve something amazing.

- ***But… YOU*** can manufacture some luck if you’re ready to engage when the opportunities come...

Have good ideas. But implement them, and turn that into something that somebody else could use.

Number one rule: Be kind…

…all else is details.

http://teachtogether.tech/