Science For A Better Life

# How To Gamble If You Must: Early Clinical Statistics in Decision Processes

October 6th, 2017 / Richardus Vonk, Head of Medical Writing and Statistics Oncology

# Disclaimer

The views expressed in this presentation
is the personal view of the author,
and do not necessarily represent the view of his employer

# Agenda

- Introduction
- Three examples
  - Decision Making in PoC Studies
  - MAP approach in early clinical development
  - Bayesian dose-expression in biomarker analyses
- Discussion and Conclusions

# Acknowledgments


- Heinz Delesen for work and slides on Bayesian Concepts for PoC Studies
- Rong Liu and Oliver Boix for further work on visualization for decision making
- Andreas Kaiser and Stefan Klein for work and slides on MAP approach
- Harry Mager and RCSS for discussions and continued appetite for innovation

# Translational Assessment Aspects

- Starting evidence 11%
- Human evidence 13%
- **Biomarkers for efficacy and safety prediction** 37%
- PoM, PoP, **PoC** 13%
- Personalized medicine aspects 8%

Wehling (2009). Assessing the translatability of drug projects: what needs to be scored to predict success? Nat Rev Drug Discov 8:541-546.

- Biomarkers and personalized medicine aspects play an important role (~45%)
  - **Biomarkers** 37%
  - Biomarker strategy (PoM, PoP, **PoC**) 5%
  - Disease subclassification and concentration of “responders” (personalized medicine aspects 3%

# Translation for Clinical Development

## General

- The average rate of successful translation from animal models to clinical cancer trials is less than 8%. [1]
- “Only about a third of highly cited animal research translated at the level of human randomized trials” [2]
- Determination of scalability of results from research to clinical application
- Deal with differences between species
- Harmonization of experimental settings between clinical and research experiments
  - Ensure that the measurements in research are aligned with those in clinical development
- Harmonization of (statistical) methodology used in research and clinical development
- Communication between pre-clinical research and clinical development
  - Ensure knowledge transfer – not only about the compound, but also about experimental setting – in both directions

1: Mak, I, Evaniew, N, Ghert, M (2014). Lost in translation: animal models and clinical trials in cancer treatment. Am J Trans Res 6: 114-118
2: Hackam DG, Redelmeier DA (2006) Translation of research evidence from animals to humans. JAMA 296: 1731–1732.

# Statistics…

Statistical thinking and methods
are an integral part of the decision processes,
and form the indispensable basis
of all drug discovery and development phases

# Statistical Reasoning
## In Early Clinical Development and beyond!

Moving towards quantitative transition decisions

- Quantitative techniques help to consider different scenarios earlier in the project
  - Earlier accumulation of quantitative knowledge, increased use of estimates and specification of (un-)certainty allows better planning for future trials in early and late stage development
  - Clearer risk / benefit evaluation
  - Increased level of confidence
  - Guides translational efforts between preclinical and clinical phase as well as between different clinical phases of drug development
- More focus on estimation of effect sizes and variability in addition to statistical testing
- Increased use of Bayesian methods to quantify “risks and opportunities” for PoC decisions and beyond
- Requires implementation of up-to-date statistical techniques

# Proof of Concept Studies
## And Bayes

Proof of concept (PoC) studies are generally dealing with one-sided hypotheses. Without loss of generality ('symmetry'), hypotheses of the form $H_0$: $\theta \leq \theta_0$ and $H_1$: $\theta > \theta_0$ will be considered in the following.

The general idea is

- to have a 'Go' decision if the posterior probability of $\theta > \theta_0$ is greater or equal than some pre-specified probability $p_U$,
- to have a 'No Go' decision if the posterior probability of $\theta \leq \theta_0$ is greater or equal than some pre-specified probability $p_L$,
- to have an 'indecisive' result if none of the two posterior probabilities is high enough.

$$P(\theta > \theta_0 \mid data) \begin{cases} \geq p_U \rightarrow H_1\ (\text{"}Go\text{"}) \\ \leq 1 - p_L \rightarrow H_0\ (\text{"}No\ Go\text{"}) \\ else \rightarrow \text{'}indecisive\text{'} \end{cases}$$

# Bayes and PoC (2)
## Scenarios

Additional desirable (classical) features of such a decision rule are that

- one has an appropriate power of at least $1-\beta_U$ at a chosen value $\theta_U \in H_1$ for a 'Go' decision,
- and of at least $1-\beta_L$ at $\theta_L \in H_0$ for a 'No Go' decision.

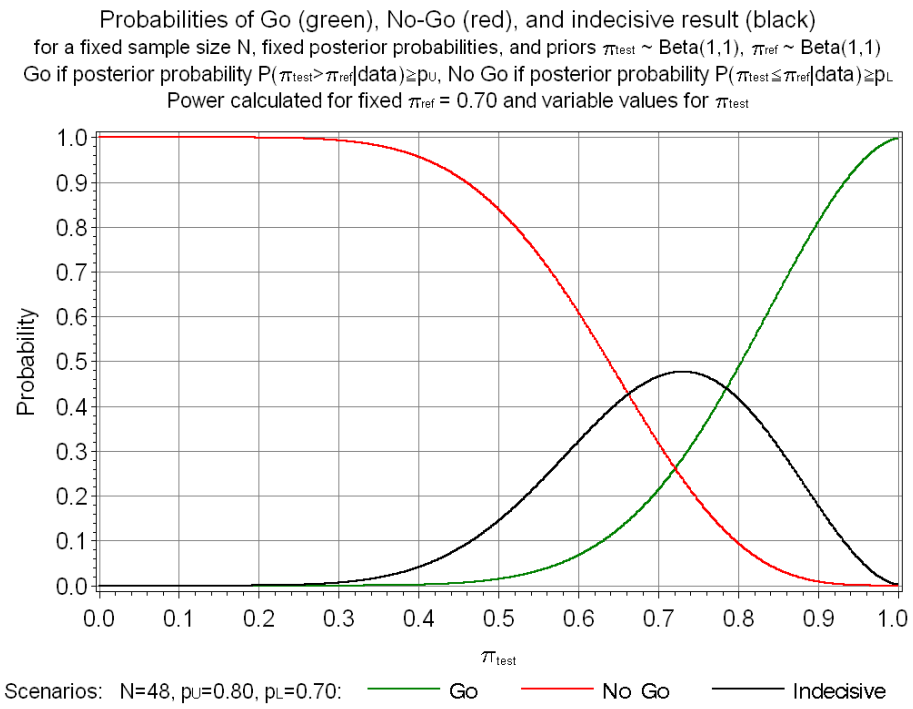
These criteria determine the sample size n based on given values for $p_U$, $\theta_U$,$1-\beta_U$, $p_L$, $\theta_L$,$1-\beta_L$

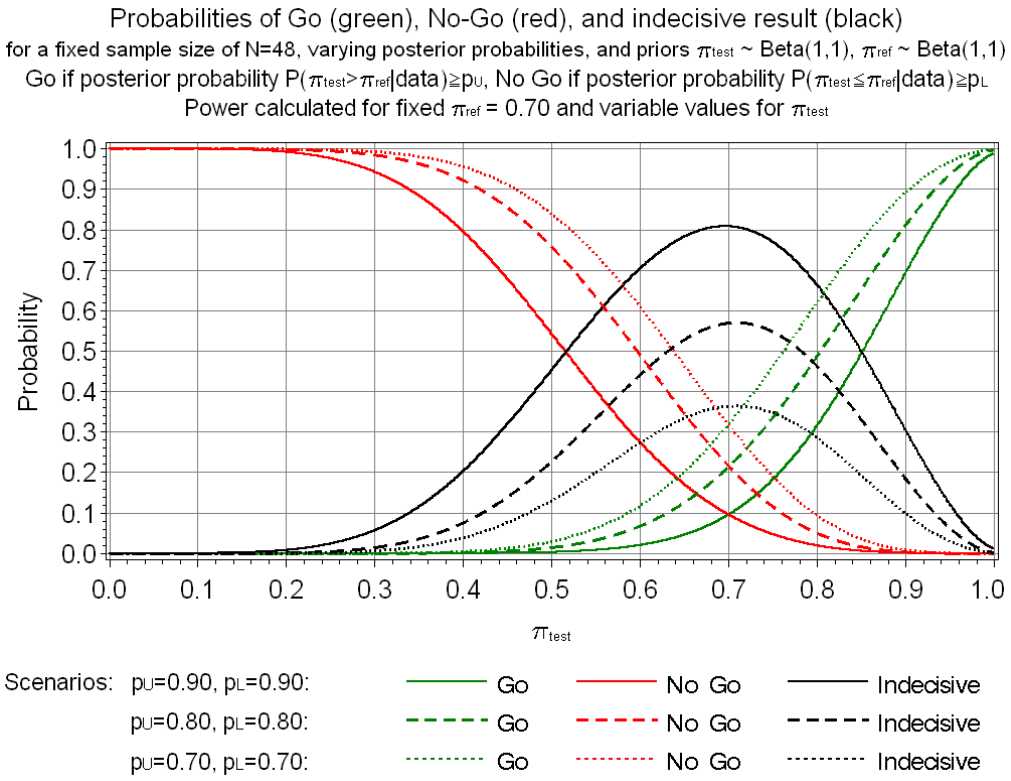
Four common scenarios are currently considered as a standard:

- Normally distributed data
  - One-sample scenario with non-informative priors $p(\mu,\sigma^2) \propto 1/\sigma^2$
  - 2-sample scenario with non-informative prior $p(\mu_1,\mu_2,\sigma^2) \propto 1/\sigma^2$
- Binomial distributed data
  - One-sample scenario with prior Beta(a,b)
  - 2-sample scenario with priors Beta($a_i$,$b_i$), i =1,2

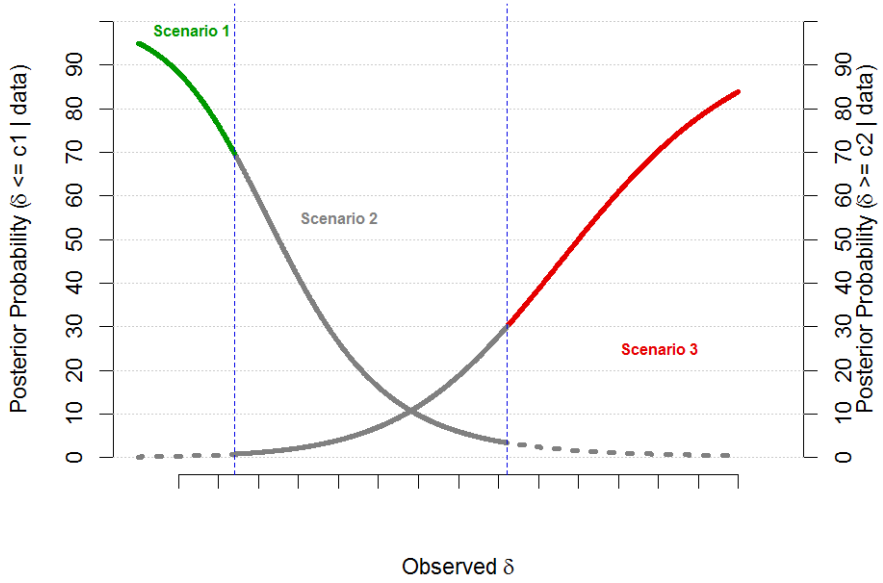
# PoC Design Properties
## Visualization

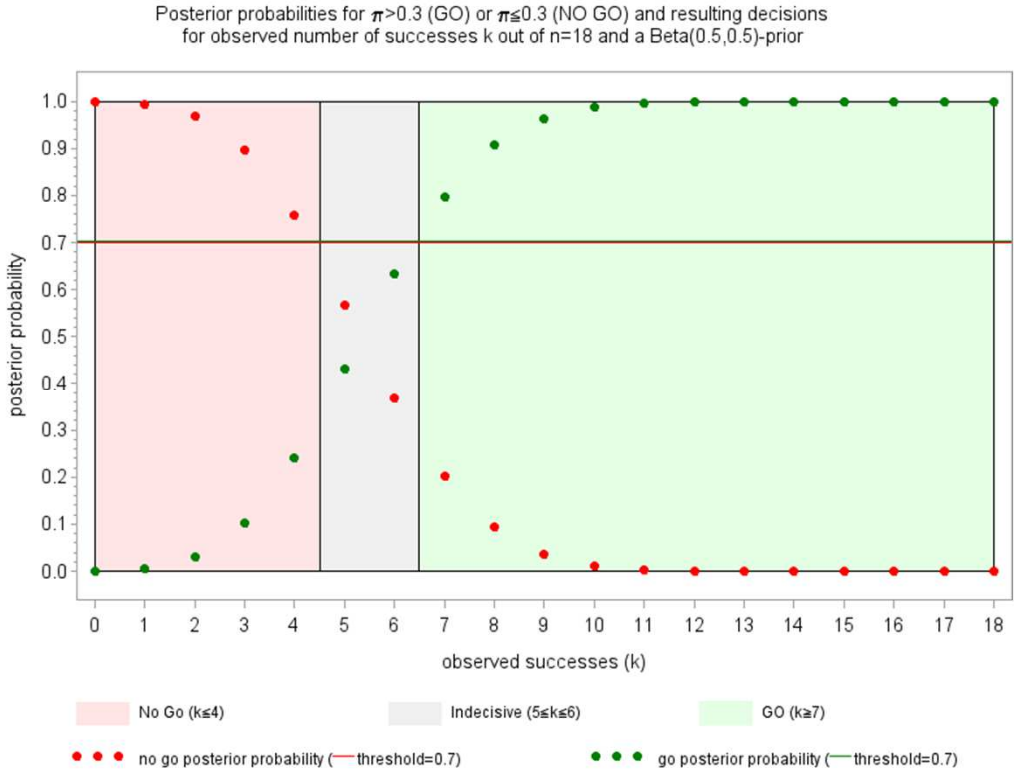
- Standard display of design properties



# Decision Making
## Visualization



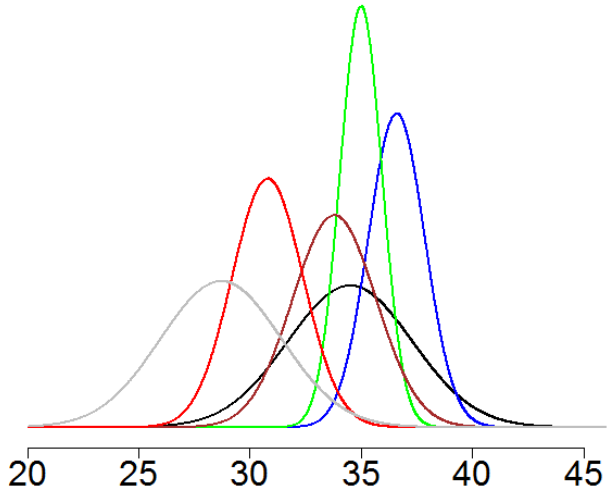
# Meta-Analytic Predictive Approach
## Application

- Introduced formally by Neuenschwander et al. (2010), but similar methods were described already in Spiegelhalter et al. (2004)
- General idea
  - Starting point: mean and SD of historical studies
  - Variability of historical studies to be decomposed into two sources: **between-trial** and **within-trial** variability
  - **Between trial variability**: nuisance parameter, but to be taken into account
  - Perform a random effects meta analysis  to assess sources of variability
  - Determine the predictive distribution for a new study and use it as a prior distribution
- Application
  - Currently applied routinely in several endpoints to assess prior distribution for (placebo or active) control arms using R programs
  - Usage of Bayesian meta analytic approaches as well as ‚normal' random effects meta analysis
  - Main outcome parameter: Effective sample size

# MAP: Dose Finding

- Study Design:
  - Phase IIb dose finding study:
    4 doses vs. active control, each 30 patients
  - primary variable: approx. normally distributed)

- Prior Information
  - 6 studies with sample sizes between 28 and 471 patients (overall: N=974)
  - Effective sample size: 80 subjects
  - Prior distribution for active control: normal distribution with $\mu$=35 and $\sigma$=20, weighted as coming from 45 patients




- Outcome
  - Smaller than maximum ESS used in order to get substantial influence from actual study data.
  - (Mean) Power increase of 10%
  - FDA: “The proposed Bayesian statistical approach … is acceptable”

# Informative Priors
## Advantages and Challenges

- Advantages
  - Saving patients by up to 30% (depending of amount of incorporated information)
  - Increase of power for decision making by up to 10%
  - Higher precision in estimation or treatment effects and model parameters
  - Increased numerical stability when estimating complex models
  - Better assessment of current trial outcome in context of historical trials
  - Better overview and more scientific discussion about realistic scenarios for trial planning
  - Positive experience regarding interaction with health authorities
- Challenges
  - Systematic deviation between study data (measurement methods, assays, endpoint definitions, population, in- and exclusion criteria, disease categories, standard of care, …)
  - Between-trial variability
  - Selection bias
  - Amount of literature available for prior derivation
  - Derivation of prior information for model parameters from published response data

# MAP and Informative Priors

Pooling of historical data

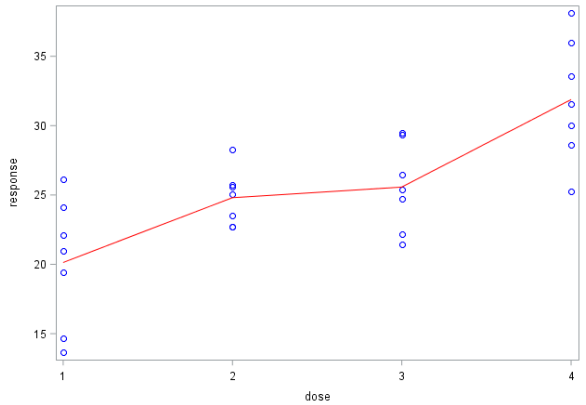
- Down weighting necessary to cope with between-trial variability
  - Enlarging the variability of prior distribution / power priors
  - Challenge: unknown parameter for down weighting
  - Robust priors (Challenge: unknown weight for mixing distribution)

Meta-Analytical Prediction

- Able to cope with between-trial variability
- Leads to a more agreeable prior
- Challenge: Low amount of extracted information, effective sample size often ≤ 10% of overall N
- Challenge: Improvement in information extraction possible?

# Dose – Response / Expression

- Interest to classify potential biomarkers according to dose-expression profiles
  - Any relationship
  - Shape of profile
- Order constraints: higher (lower) expression as dose increases
  - Monotone increases / decreases
  - No parametric assumptions about dose – expression profiles
  - Follow approach developed by Otava (2013-2014)

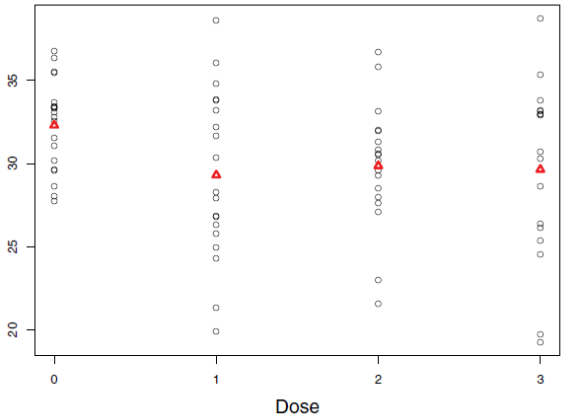



Otava M., Shkedy Z., Lin D., Göhlmann H.W.H., Bijnens L., Talloen W., Kasim A. (2014). Dose–Response Modeling Under Simple Order Restrictions Using Bayesian Variable Selection Methods. *Statistics in Biopharmaceutical Research*, 6:3, 252-262.
Otava M. (2014). Bayesian variable selection in dose-response relationship concept. International Biometric Conference, Florence.
Otava M. (2013). Bayesian Variable Selection Method for Modeling Dose-Response Microarray Data Under Simple Order Restrictions. Bayes2013, Rotterdam.

# Monotone Dose-Response Example

Order-restricted alternative as an example:

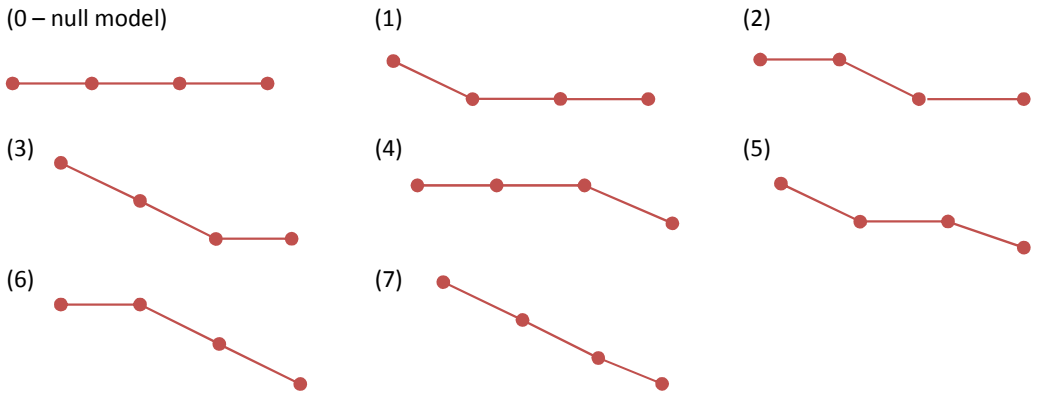
- ANOVA model: $Y_{ij}=\mu_i + \varepsilon_{ij}$, $\varepsilon_{ij}\sim N(0,\sigma^2)$, $i=0,\ldots 3$, $j=1,\ldots, n_i$
- $H_0$: $\mu_0 = \mu_1 = \mu_2 = \mu_3$ versus
  $H_{down}$: $\mu_0 \geq \mu_1 \geq \mu_2 \geq \mu_3$ with at least one strict inequality




- Decompose into $2^K - 1$ sub-alternatives
- K=3: 7 sub-alternatives (downward trend!)

$$H_1^3 = \bigcup_{k=1}^{7} H_{1,k}^3 \quad \text{where}$$

$$H_{1,1}^3 : \mu_0 > \mu_1 = \mu_2 = \mu_3$$
$$H_{1,2}^3 : \mu_0 = \mu_1 > \mu_2 = \mu_3$$
$$H_{1,3}^3 : \mu_0 > \mu_1 > \mu_2 = \mu_3$$
$$H_{1,4}^3 : \mu_0 = \mu_1 = \mu_2 > \mu_3$$
$$H_{1,5}^3 : \mu_0 > \mu_1 = \mu_2 > \mu_3$$
$$H_{1,6}^3 : \mu_0 = \mu_1 > \mu_2 > \mu_3$$
$$H_{1,7}^3 : \mu_0 > \mu_1 > \mu_2 > \mu_3$$



# Example: Biomarker

Assume possible downward trend.

- Re-parametrisation:

$$\mu_i = \begin{cases} \mu_0, & i = 0 \\ \mu_0 - \sum_j^i I_j \beta_j, & i = 1,...,K \text{ with indicator variable } I_j \text{ and } \beta_j \geq 0 \end{cases}$$

- Use priors and hyperpriors as discussed by Otava

| Hypothesis/Sub - alternative | $(I_1, I_2, I_3)$ | $g = \sum_{j=1}^{3} I_1 2^{j-1}$ |
|---|---|---|
| $H_0^3 : \mu_0 = \mu_1 = \mu_2 = \mu_3$ | $(0,0,0)$ | 0 |
| $H_{1,1}^3 : \mu_0 < \mu_1 = \mu_2 = \mu_3$ | $(1,0,0)$ | 1 |
| $H_{1,2}^3 : \mu_0 = \mu_1 < \mu_2 = \mu_3$ | $(0,1,0)$ | 2 |
| $H_{1,3}^3 : \mu_0 < \mu_1 < \mu_2 = \mu_3$ | $(1,1,0)$ | 3 |
| $H_{1,4}^3 : \mu_0 = \mu_1 = \mu_2 < \mu_3$ | $(0,0,1)$ | 4 |
| $H_{1,5}^3 : \mu_0 < \mu_1 = \mu_2 < \mu_3$ | $(1,0,1)$ | 5 |
| $H_{1,6}^3 : \mu_0 = \mu_1 < \mu_2 < \mu_3$ | $(0,1,1)$ | 6 |
| $H_{1,7}^3 : \mu_0 < \mu_1 < \mu_2 < \mu_3$ | $(1,1,1)$ | 7 |


Otava M., Shkedy Z., Lin D., Göhlmann H.W.H., Bijnens L., Talloen W., Kasim A. (2014). Dose–Response Modeling Under Simple Order Restrictions Using Bayesian Variable Selection Methods. *Statistics in Biopharmaceutical Research*, 6:3, 252-262.
Otava M. (2014). Bayesian variable selection in dose-response relationship concept. International Biometric Conference, Florence.
Otava M. (2013). Bayesian Variable Selection Method for Modeling Dose-Response Microarray Data Under Simple Order Restrictions. Bayes2013, Rotterdam.

# Priors and Hyperpriors

As priors, we have

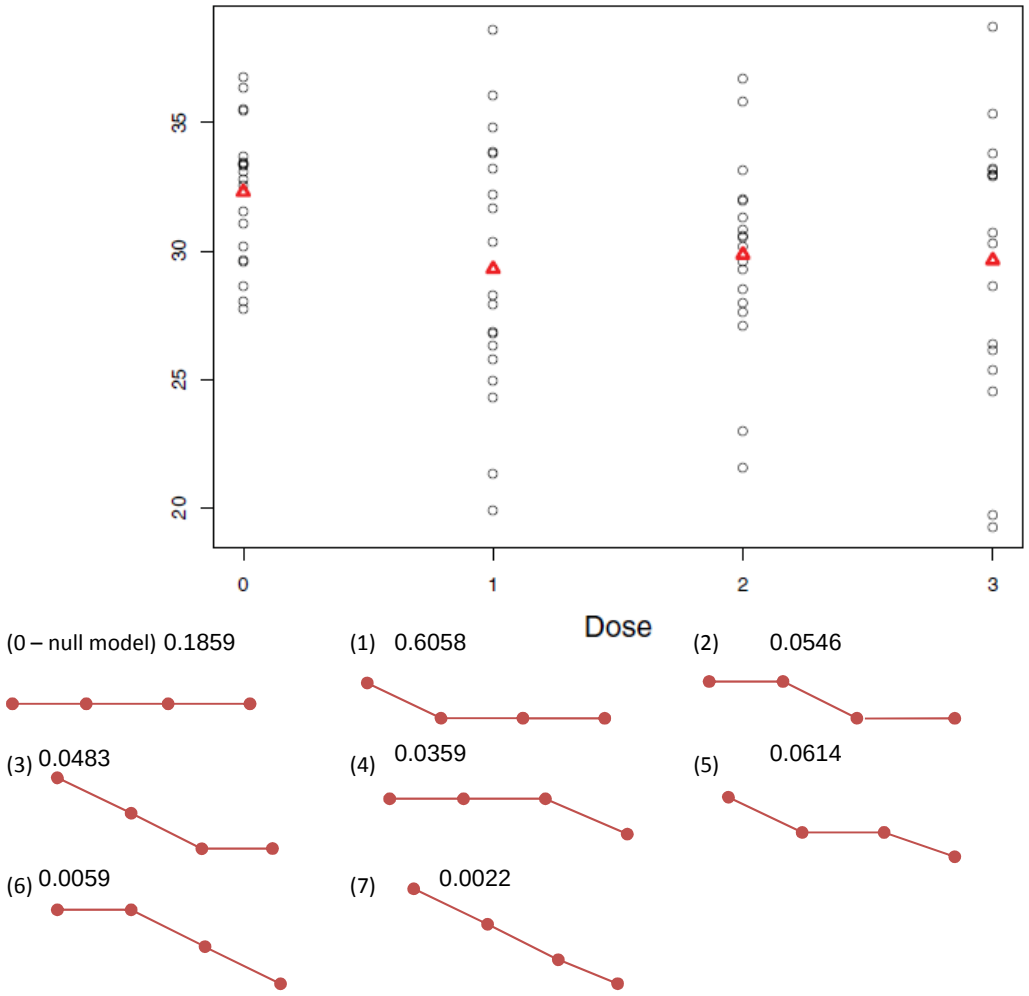
- $\mu_0 \sim N(\eta_0, \sigma_0^2)$
- $\beta_i \sim N(\eta_{\beta_i}, \sigma_{\beta_i}^2) I(0, A)$; *A* denotes the expected difference in the response
- $I_i \sim Bernoulli(\pi_i)$

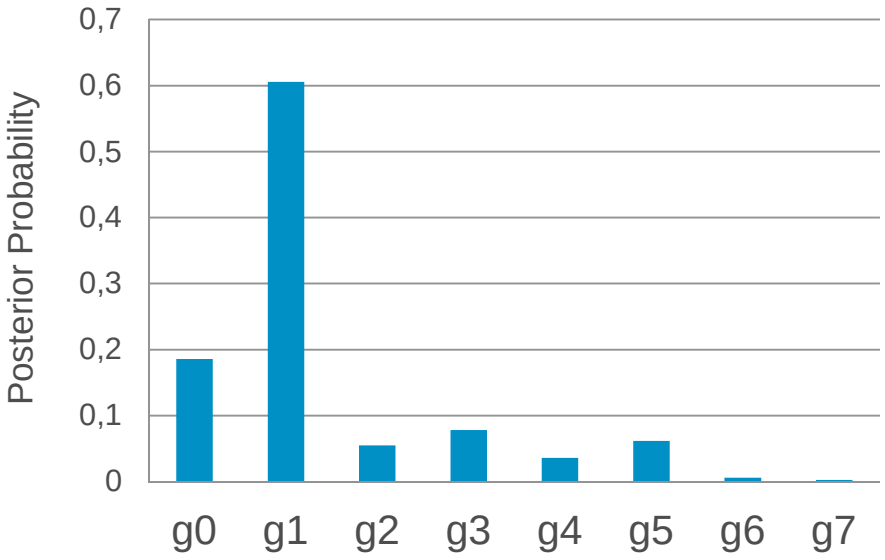
And hyperpriors

- $\pi_i \sim Uniform(0,1)$
- $\eta_0, \eta_{\beta_i} \sim N(0, 10^6)$
- $\sigma_0^2, \sigma_{\beta_i}^2 \sim i\Gamma(10^{-3}, 10^{-3})$

If we now define $g = \sum_{i=1}^{K} I_i 2^{i-1}$, the posterior distribution of ***g*** **describes the distribution of the monotone dose-response shapes.**

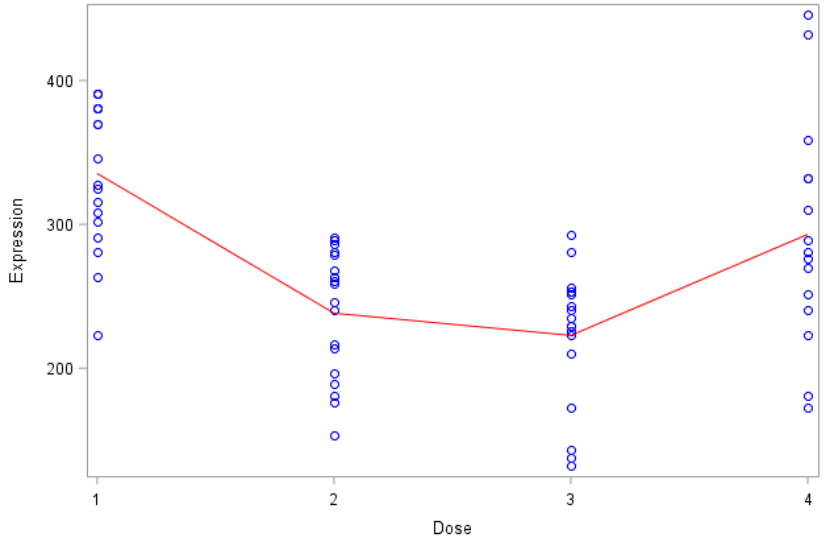
# Results


20
25
30
35
0
1
2
3
Dose
(0 – null model) 0.1859
(1) 0.6058
(2) 0.0546
(3) 0.0483
(4) 0.0359
(5) 0.0614
(6) 0.0059
(7) 0.0022


Posterior Probability
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
g0
g1
g2
g3
g4
g5
g6
g7

# Discussion of Methods

- Computationally expensive in SAS
- Effect of truncation:
  - $\beta_i \sim N\left(\eta_{\beta_i}, \sigma^2_{\beta_i}\right) I(0, A)$; $A$ denotes the expected difference in the response
  - Empirical Bayes?
- Can (easily) be extended to be used with correlated data:
  - Only compound symmetry in SAS PROC MCMC
- Down-turn / Up-turn protection is needed



# Implementation

- PoC Studies are developed and analyzed using Bayesian methods
  - Unless clear scientific or regulatory reasons speak against this
- SAS Macros for 4 most frequent planning scenarios in PoC studies, covering:
  - Sample size determination
  - Design properties
  - Decision making
- Training of early clinical development function
  - Standard terminology
  - Standard summary of prior elicitation
  - Standard display of trial characteristics
- Increasingly used in other areas
  - Biomarkers / Genomics
  - Research / Preclinical Development

# Summary and Discussion

- Increased used of advanced statistical methods in early clinical development
  - Increasing use of Bayesian methodology in early clinical development
  - Discussions started around 10 years ago
  - Focus: early clinical development
  - Bayesian level of proof as one decision metric in PoC
- Rather high acceptance of Bayesian methods in Early Clinical Development
  - Supported by head of Clinical Sciences
  - Build on this also for early biomarker development / biomarker detection
- Standard “displays” / methods to facilitate understanding
- High level of interaction needed
  (specification of questions, determination of priors, … )
- Highly interdisciplinary
  - Quantitative functions (“mathematical functions”)
  - Clinical and preclinical functions

**The business of the statistician is to catalyze the scientific learning process.**

- George Box

Science For A Better Life

# Thank you!