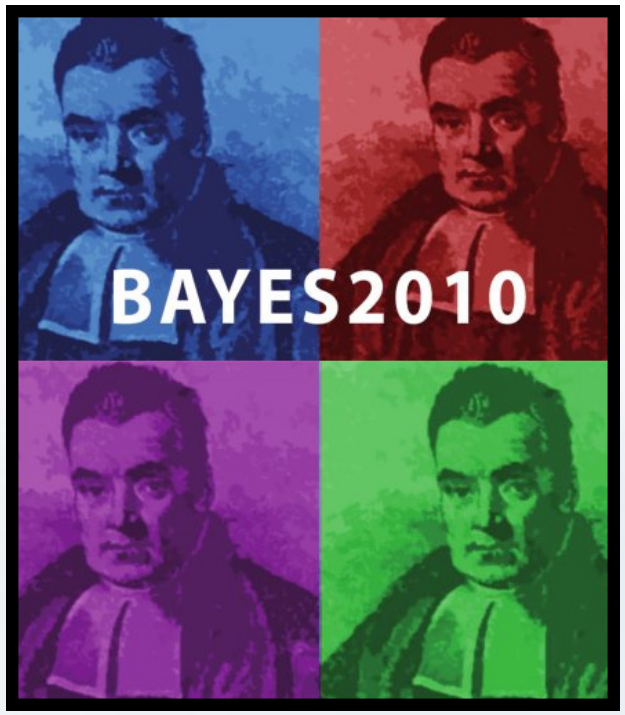


Bruno Boulanger, Arlenda & Ulg

Astrid Jullion, UCB

BAYES2010, Belgium

a prediction-based clinical utility index for dose determination in drug development
design space thinking applied to clinical development

Becoming Bayesian

the objective

an example of clinical trial

modeling of efficacy

modeling of safety

making prediction

Introducing the Design Space concept (again)

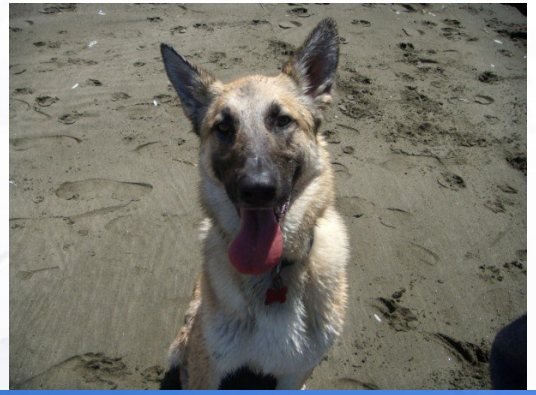
a prediction-based Clinical Utility Index (p-CUI)

results

conclusions

AGENDA

Becoming Bayesian is easy ;-)



The objective

In Early Clinical development

- The purpose is to identify the range of dose, if any, that will guarantee:
  - Efficacy in future late phase trials
  - Safety in the future
- To minimize to risks of investing in low success but costly late phase trials

Facts

- Efficacy usually based on biomarkers available
- The number of subjects or patients is usually limited
- Pre-clinical, historical data or competition prior information is usually available

A typical study

- A study conducted on patients (eg Phase IIa)
- A dose escalating trial, usually multiple dose
- An adaptive trial based on safety, exposure or efficacy is often envisaged 40-80
- patients is common
- Model-Based Drug Development: Population Pharmacokinetics-pharmacodynamics (POP-PKPD) modeling is always performed.
  - Dose → Exposure → Efficacy
  - Dose → Safety

The PK-PD model

PK-PD Model

A system of Differential Equations:

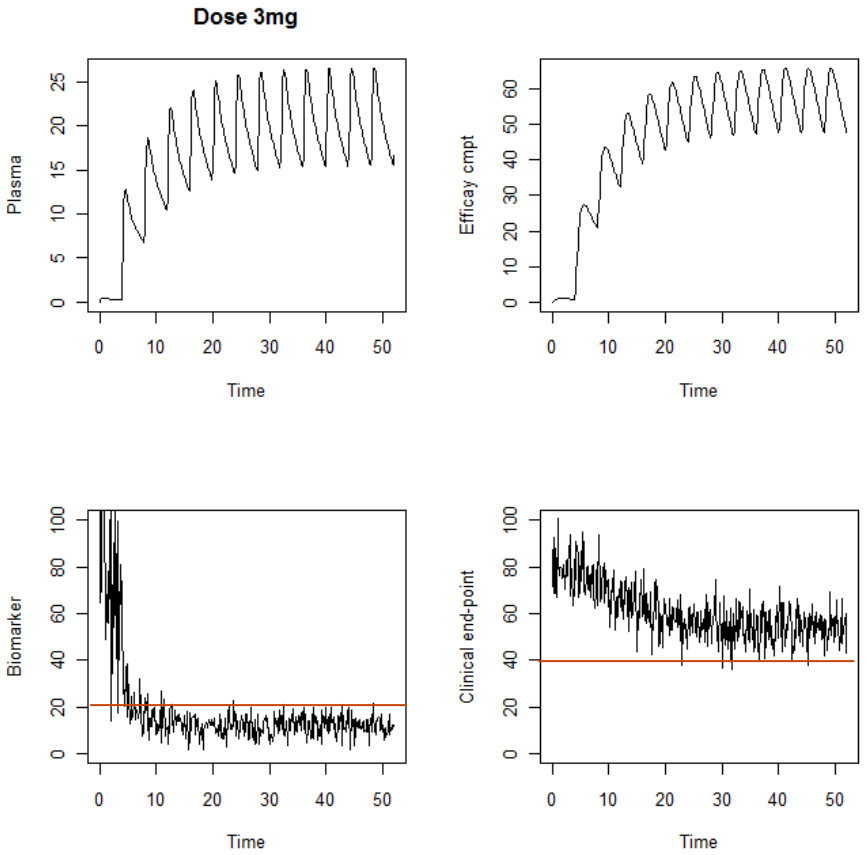
dA/dt =-KA*A+Ri

dB/dt = KA*A-CL/V1*B-Q/V1*B+Q/V2*C

dC/dt = Q/V1*B-Q/V2*C

dD/dt = KE0*((B/V1)-D)

dE/dt = kout*Base*(1-EMAX*C1/(EC50+C1))-kout*E



Hierarchical PKPD Model

- PKPD Structural Model
  - $dA/dt = f_A(\theta_\kappa, t)$
  - $dB/dt = f_B(\theta_\kappa, t)$
  - $dC/dt = f_C(\theta_\kappa, t)$
  - $dD/dt = f_D(\theta_\kappa, t)$
  - $Plasma(t) = B(1+\varepsilon_\iota)$
  - $Biomarker(t) = g(D, \theta_\delta, t)$
- Statistical part: Hierarchical model
  - $\Theta \sim N(\psi, \omega)$
  - $\Psi \sim N(\mu, \Sigma)$
  - $\varepsilon i \sim N(0, \sigma^2)$
- WinBugs allows “easy” modeling of hierarchical ODE models.

ODE in WinBugs/BlackBox

ODE can be written with WBDiff in BlackBox

- Script in “fixed” format
- Compiled in BlackBox
- Called directly from WinBugs
  - ➔ For modeling
  - ➔ For simulations

```
File  Tools  Edit  Attributes  Info  Model  Inference  Options  Doodle  Map  Text  Window  Help
(*1*)  MODULE WBDiffBAYES2010;

       IMPORT
          WBDiffODEMath,
(*2*)     Math;

       TYPE
          Equations = POINTER TO RECORD (WBDiffODEMath.Equations) END;
          Factory = POINTER TO RECORD (WBDiffODEMath.Factory) END;

       CONST
(*3*)     nEq = 3;

(*4*)     DT1= 0; dose = 1; Q = 2;
(*5*)     Vmax = 3; Km = 4;V1=5;V2=6;Cl=7;ke0=8;

(*8*)     Cc = 0; B = 1;Ce=2;

       VAR
          fact-: WBDiffODEMath.Factory;

(*9*)  PROCEDURE (e: Equations) Derivatives (IN theta, C: ARRAY OF REAL; n: INTEGER; t: REAL;
(*10*)                                       OUT dCdt: ARRAY OF REAL);
(*11*) VAR
(*12*)    a: INTEGER;
(*13*)    iinput,ainput: REAL;

(*14*)
(*15*) BEGIN
(*16*)    IF t<=theta[DT1] THEN;
          a:=1;
          ELSE;
          a:=0;
          END;
(*22*)    iinput:=theta[dose];
(*24*)    ainput:=a*iinput;
(*25*)    dCdt[B] := ainput-(theta[Cl]/theta[V1]*C[B])-(theta[Q]/theta[V1]*C[B])+(theta[Q]/theta[V2]*C[Cc])-
(theta[Vmax]*C[B]/theta[V1]*(1/(theta[Km]+(C[B]/theta[V1]))));
(*27*)    dCdt[Cc] := (theta[Q]/theta[V1]*C[B])-(theta[Q]/theta[V2]*C[Cc]);
(*28*)    dCdt[Ce]:=theta[ke0]*((C[B]/theta[V1]) -C[Ce])
(*35*) END Derivatives;

       PROCEDURE (equations: Equations) SecondDerivatives (IN theta, x: ARRAY OF REAL;
                                                           numEq: INTEGER; t: REAL;
                                                           OUT d2xdt2: ARRAY OF REAL);
       BEGIN
          HALT(126)
       END SecondDerivatives;
```

```
solution[j,1:n.grid, 1:dim] <- BAYES2010(init[j,1:dim], grid[1:n.grid], theta[j,1:9], origin, tol)
```

Modeling and Prediction in Bugs

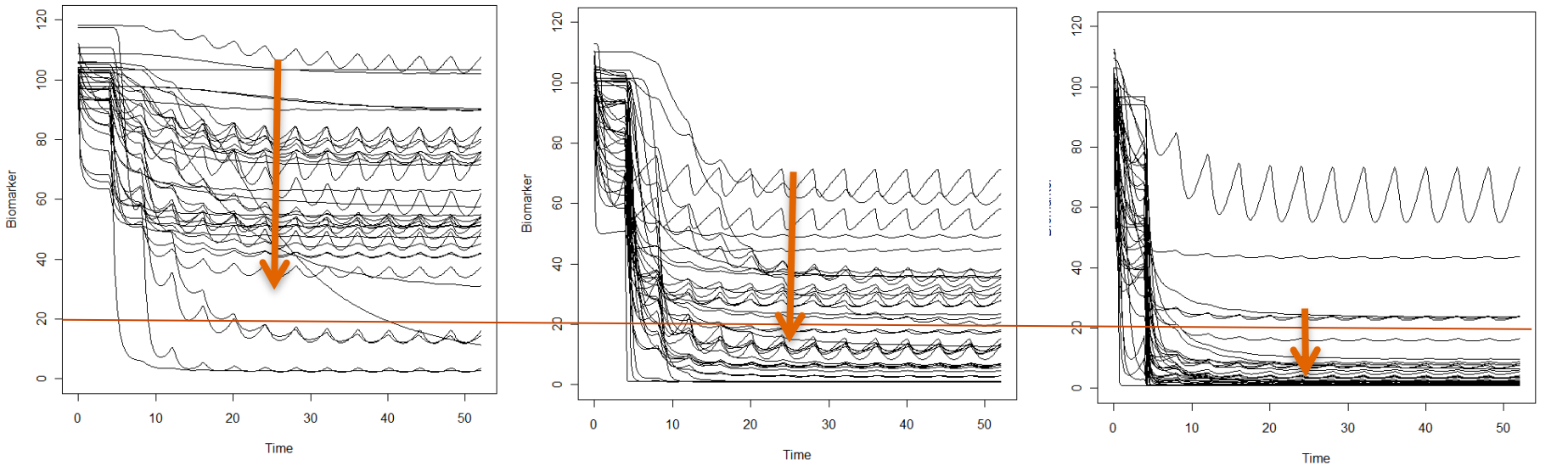
```
## Modeling    ##############################
model {
for (j in 1:N){
solution[j,1:n.grid, 1:dim] <- BAYES2010(init[j,1:dim], grid[1:n.grid], theta[j,1:9], origin, tol)
    ...
    theta[j,7] <- dose[j];
    theta[j,8] <- Cl[j];
    ...
for (i in 1:n.grid) {
       data[j,i]      ~ dnorm(m[j,1],tauu[j,1])
       BMKR[j,i]       ~dlnorm(logCRPmean[j,1],tauCRP[j])
     ...                   }
   Cl[j]      ~dlnorm(logmuCl,tauCl)
     ...
      }

## Prediction  ##############################

for (kk in 1:nnn){
....
thetapop[kk,7] <-(muV2);    ← Contains the chain of posteriors
...
PRED[kk,1:n.grid, 1:dim] <- BAYES2010(init[1,1:dim], grid[1:n.grid], thetapop[kk,1:9], origin,
    tol)
meanconc[kk]<-sol[kk,8,Ce]
                 }
…
```

Predictive probability to achieve Efficacy

The predictive probability to achieve efficacy (biomarker <20 at 24 weeks) increase with dose.

The uncertainty of PK and PD parameters is taken into account.

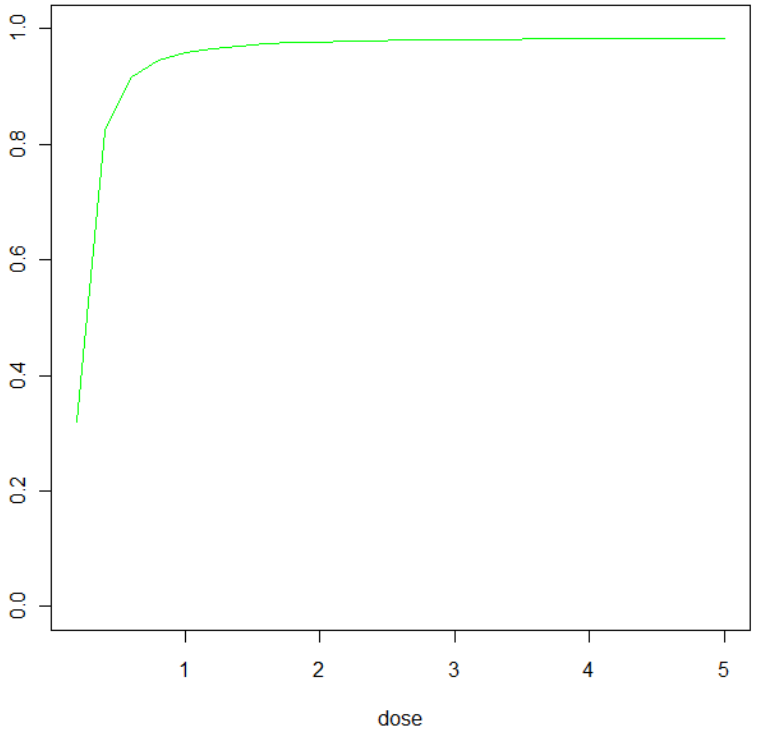
Increasing dose



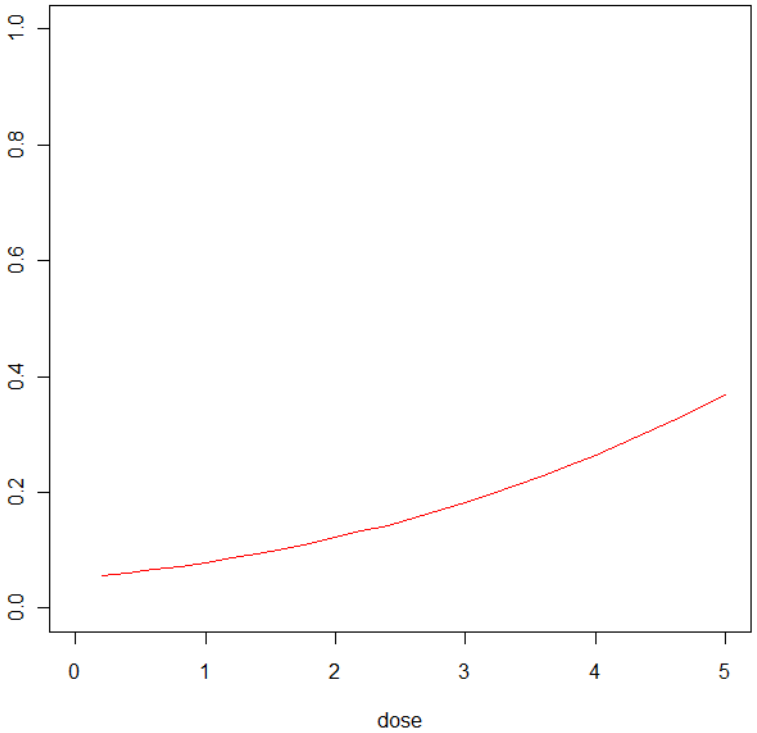
After the study, the model says….

The modeling of the data (PKPD+safety) would suggest that on average the probability of efficacy and safety is:

Pr(bmk<20)=P(efficay)



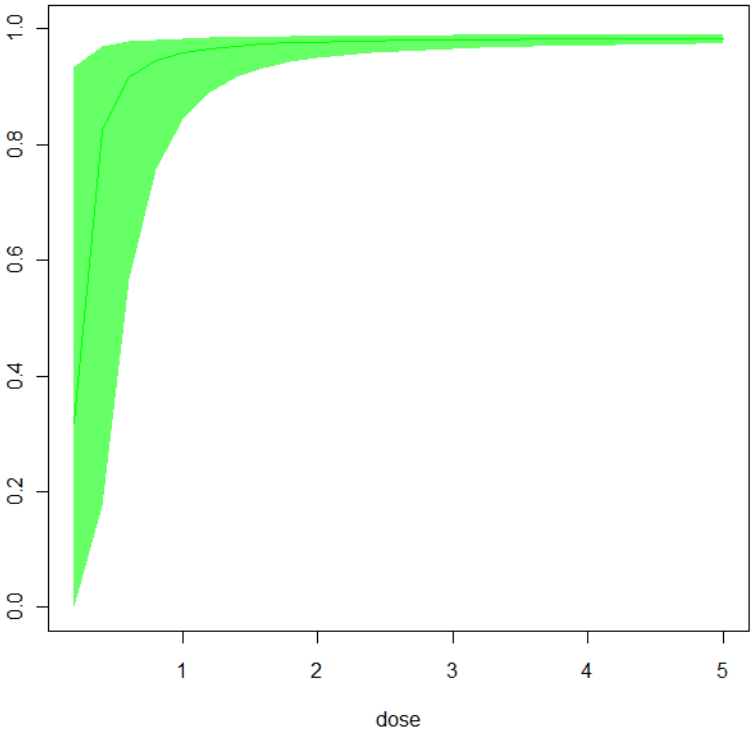
Pr(AE)=1-P(safety)



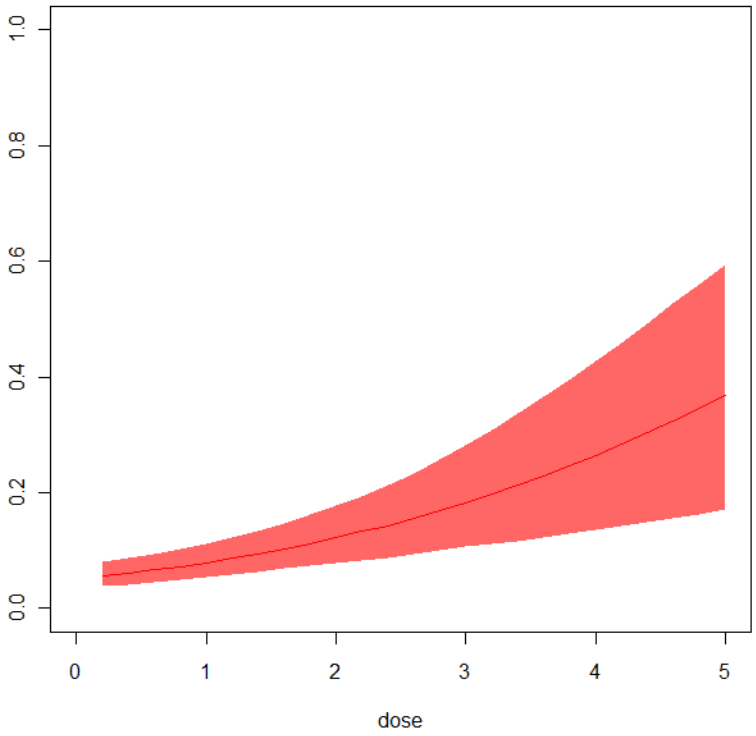
After the study, the model says….

The Bayesian prediction, that takes into account the uncertainty of the parameter estimates and provides a distribution on the probability

Pr(bmk<20)=P(efficay)



Pr(AE)=1-P(safety)



MARCH 2005

FOR GLOBAL BUSINESS AND MARKETING LEADERS

Pharmaceutical Executive

Trans-parent Trade-Offs

A clinical utility index (CUI) openly evaluates a product's attributes—and chance of success

IN DESIGNING CLINICAL TRIALS, THE PHARMA INDUSTRY has been primarily concerned with a drug's efficacy, and therefore, modeling and simulation technologies used for those designs have also focused on effi-

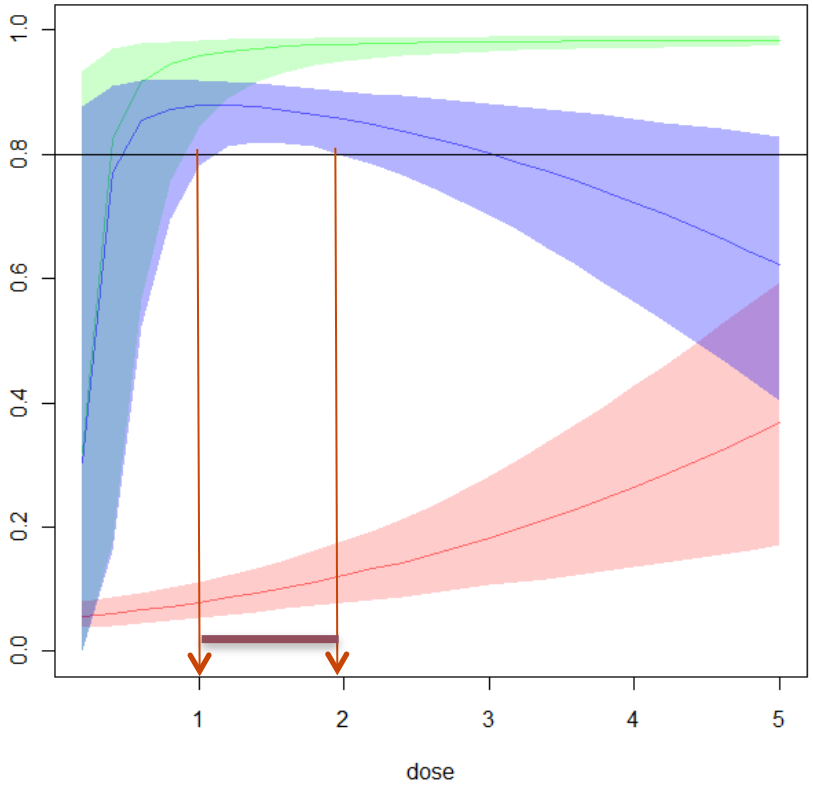
Prediction-Based Clinical Utility Index

The clinical utility index (CUI) quantifies factors like a product's efficacy, safety, cost and makes trade-offs transparent to decision makers.

A CUI provides a single metric for multiple dimensions of benefit and risk

Proposal: Use the predictive probability of Efficacy and Safety:

➔ p(efficacy) * p(safety)

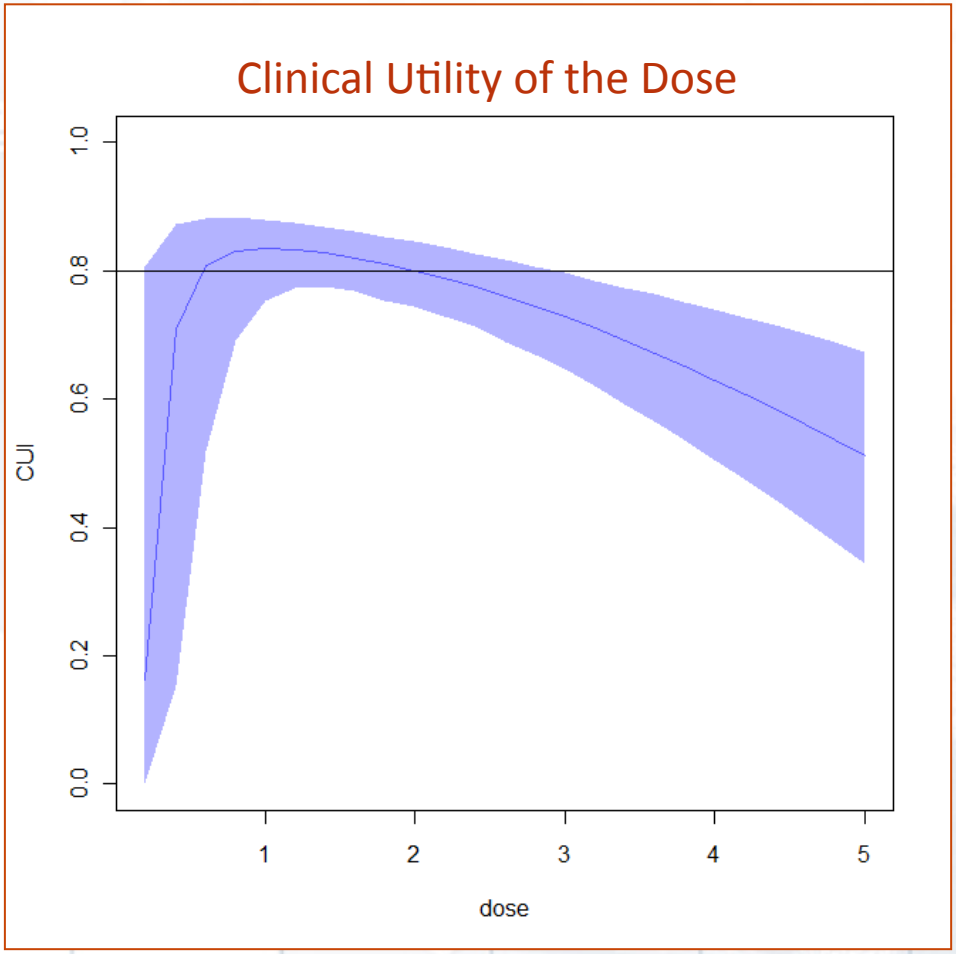


Clinical Utility of the Dose

Once based on joint probability it has a direct interpretation:

➔ The predictive probability the objective will be met

➔ The uncertainty remaining to make a clear cut decision is available

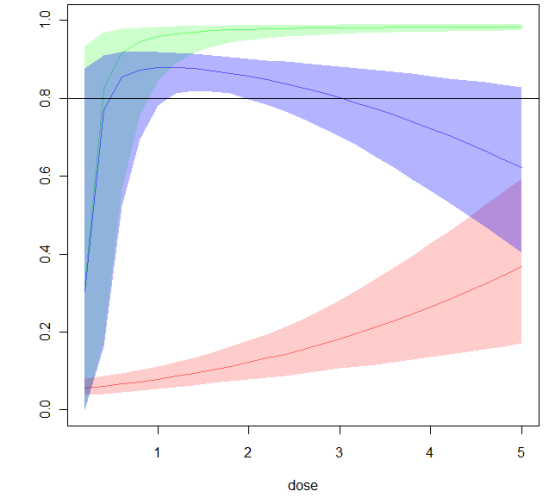


Making Trade-offs

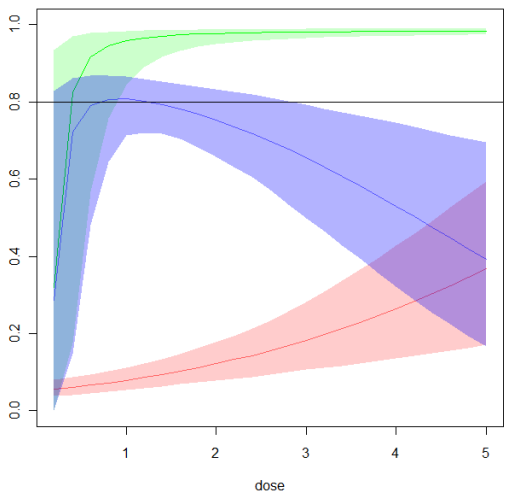
One can say that weight Safety >> weight Efficacy

➔Eg $p(\text{efficacy})^{we} * p(\text{safety})^{ws}$ with ws=2*we

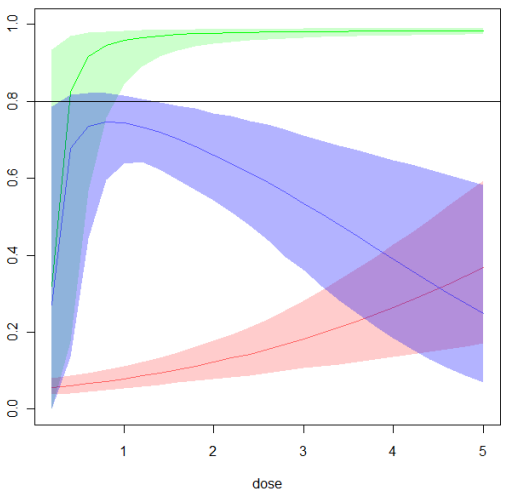
Similarly to Derringer's function, the different factors can be weighted according to the objective.



ws=1*we



ws=2*we

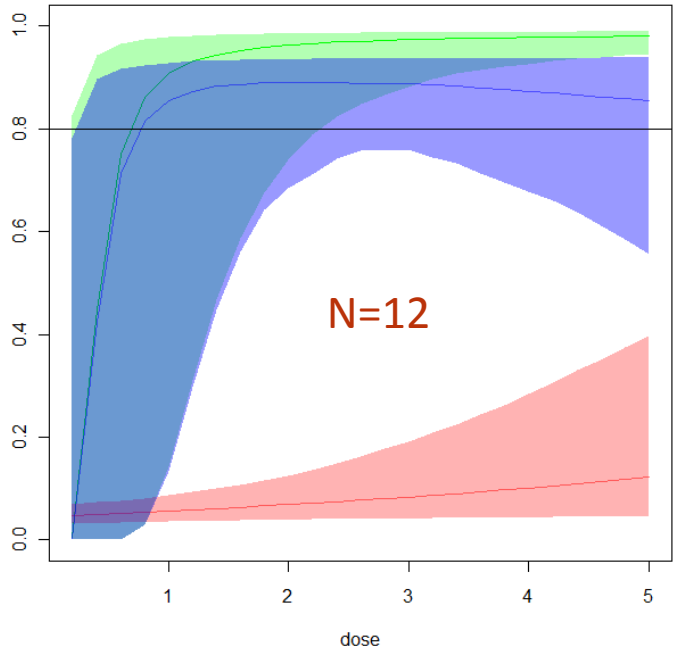


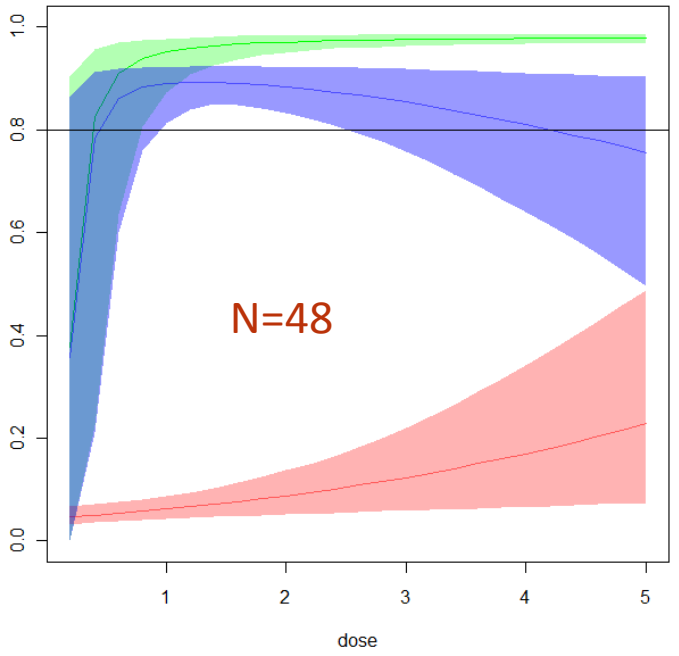
ws=3*we

Making a decision

When increasing the sample size, the credibility increases about the Clinical Utility

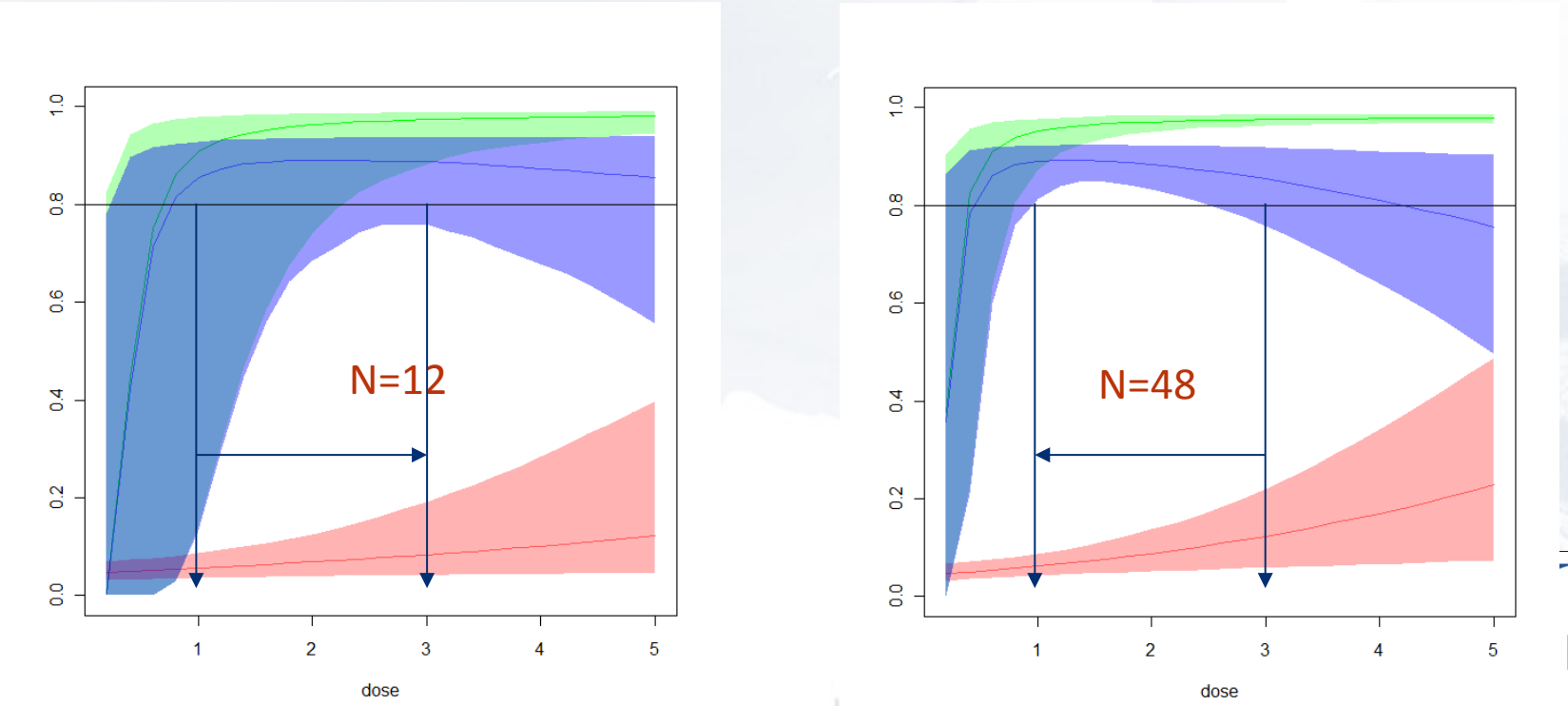
➔ Power early phase studies according to ability to predict and make decision under various scenarios





Dose choice and uncertainty

Increasing the dose is not an alternative to uncertainty.



Priors

Priors should be defined based on information available

- ➔ Pre-clinical data about EC50 (PD)
- ➔ Competitor data about PK and Emax
- ➔ Literature about variability of in population
- ➔ Laboratory documents about assay precision

PK-PD Model

dA/dt =-**KA***A+Ri
dB/dt = **KA***A-**CL**/**V1***B-Q/**V1***B+Q/**V2***C
dC/dt = Q/**V1***B-Q/**V2***C
dD/dt = KE0*((B/**V1**)-D)
dE/dt = kout*Base*(1-**Emax***C1/(**EC50**+C1))-kout*E

$\Theta \sim N(\psi, \omega)$

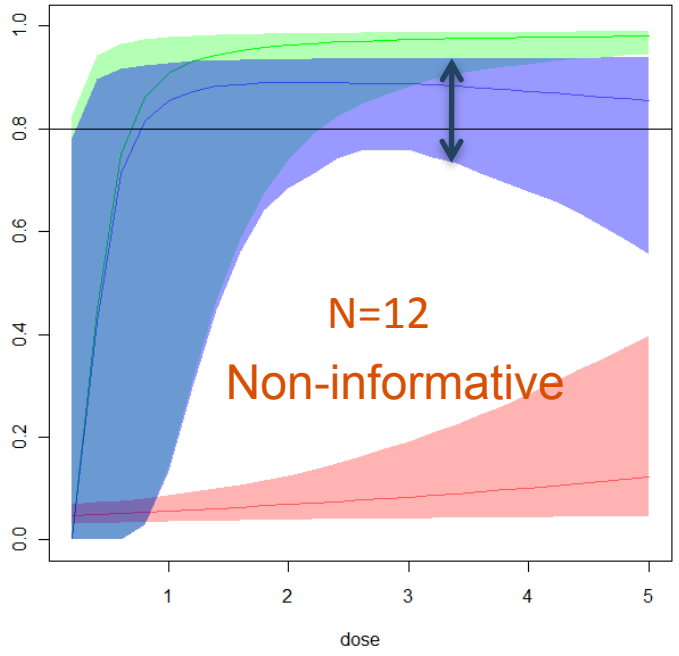
$\Psi \sim N(\mu, \Sigma)$

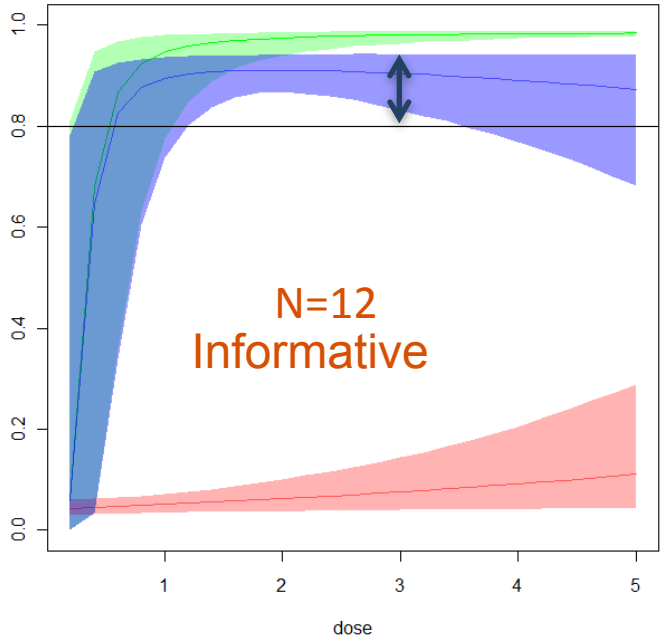
$\varepsilon i \sim N(0, \sigma^2)$

Value of priors

When priors are available and can be justified, their use has a major contribution

- On the sample size (ethics) required to achieve the same decision
- On the decision about the compound





ICH Q8 definition of design space

Design Space is defined as:

> *"The multidimensional combination and interaction of **input variables** (e.g. material attributes) and process parameters that have been demonstrated to provide **assurance** of **quality**."*

- Input Variables (X)
  - Controlled: **Dose**
  - Estimated: **Exposure**
- Quality:= specifications (Y)
  - Clinical end point, minimal improvement defined by MDs
  - Safety measurements and criteria
- Assurance
  - Predictive Probability the improvement and safety will be achieved.

Bayesian Predictive Design Space

Based on the **Predictive Distribution** of future outcomes given the uncertainty of model estimates :

$$p(\tilde{x}|data) = \int_{\theta} p(\tilde{x}|\theta) \times p(\theta|data) d\theta$$

The Bayesian Predictive Design Space is

The **Design Space** is the range of doses such that predictive probability of having efficacy & safety s is greater than a specified minimal Quality level

$$\left\{ dose_0 \in \chi \mid E_{\theta|x,data} \left\{ P\left[O \in \Lambda \right] | x, \theta, data \right\} \geq \pi_{\min} \right\}$$

Design Space graphically

Input Variables

Range of doses

Assurance

That will guarantee

Quality

Efficacy and safety

$$\left\{ dose_0 \in \chi \mid E_{\theta|x,data}\left\{ P\left[O \in \Lambda \right] | x, \theta, data \right\} \geq \pi_{\min} \right\}$$

Conclusions

- Make predictions, unless you're in Phase III
  - That's the very essence of your job.
  - Today's technology/modeling permits it easily.
- Priors have value and are justified in early phases
- Dose ranging studies are a special case of Design Space

  ➔ harmonization of practices
- Bayesian modeling allow you to connect design and results to decision
- In early phase, role of statisticians is to permit decisions

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THANK YOU