CLINSYS CLINICAL RESEARCH

Implementing the Continuous Reassessment Method (CRM) in a Phase I Oncology Trial

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Topics

- Background of study
- Statistical Methodology
- Implementation During Study
- Challenges of Implementation
- Discussion

Background of Study

- **Multicenter, Phase 1/2, Open-label, Dose-escalation Study of an Oral Angiogenesis Inhibitor in Patients With Advanced Solid Tumors**
- **Primary objective is to determine the MTD of the treatment in the patient population**
- **Dose-escalation by cohort determined by results of CRM**
- **Primary endpoint- Presence of dose limiting toxicity (DLT) as defined in the protocol**

Statistical Methodology (High Level Overview)

- Continual Reassessment Method
  - Alternative to usual 3+3 method of dose escalation/reduction
- Initial cohort of patients dosed at 100 mg QD
- Determination of DLTs
- Working Dose-Toxicity Model Updated

Working Dose-Toxicity Model

- Based on Two-Parameter Logistic Regression Model

$$\text{Prob(Toxicity|dose j)} = \pi(x_j, \theta) = \frac{\exp\{\mu + \beta x_j\}}{1 + \exp\{\mu + \beta x_j\}},$$

$$\theta = (\mu, \beta), x_j = \log(d_j) - \frac{\left\{\sum_{j=1}^{k} \log(d_j)\right\}}{k}.$$

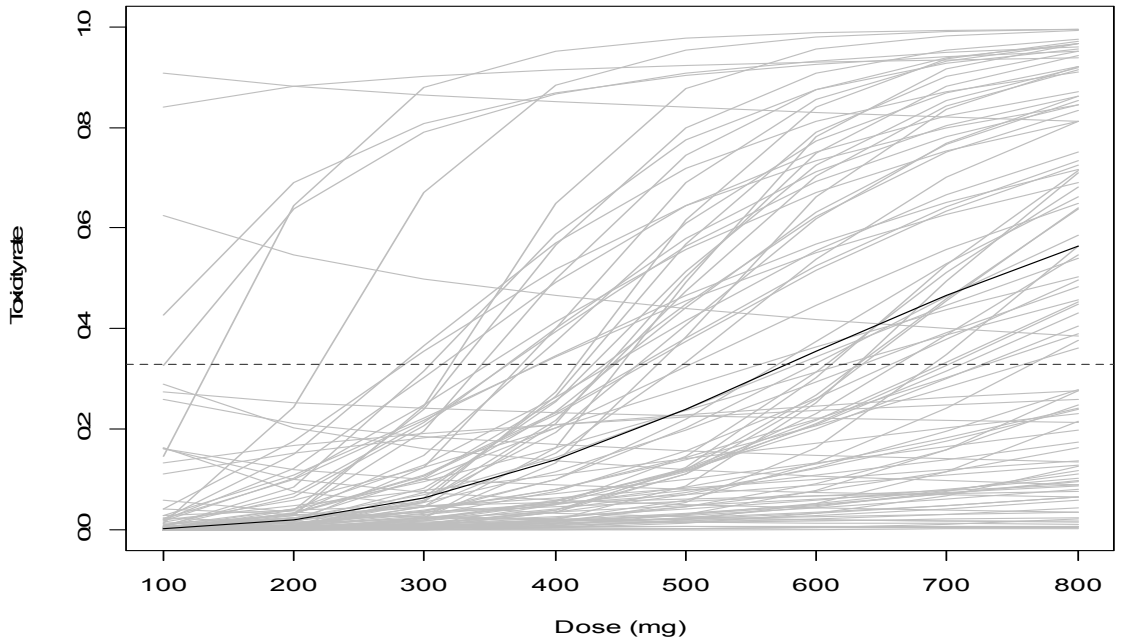
- d_j is a studied dose, and x_j is a recoding of the dose (i.e., a centered log dose, for numerical stability of the algorithm), where k is the number of doses
- $\pi(x_j, \theta)$ is the probability of toxicity of dose j
- μ and β are the two unknown parameters that are updated throughout the study to provide an up to date dose-toxicity model.

Unknown Parameters

- Prior distributions put on μ and β (independent)

$$\mu \sim N(-2, 4)$$
$$\beta \sim N(3, 4)$$

- 100 draws from prior distribution



Updating the Working Dose-Toxicity Model

- Model updated through posterior density of (μ, β), which is determined by multiplying the prior densities together by the likelihood:

$$L(\mathbf{Y} \mid \mu, \beta) = \prod_i \left\{ \pi\left(x_{j(i)}, \mu, \beta\right) \right\}^{Y_i} \left\{ 1 - \pi\left(x_{j(i)}, \mu, \beta\right) \right\}^{1-Y_i}$$

- **Y** is a vector of dichotomous outcomes ($Y_1, \ldots, Y_n$) where 0=no DLT experienced for patient *i* and 1=DLT experienced for patient *i*,
- *j(i)* is the index of the dose given to the *i*th patient
- π, θ, and x_j are all as defined above

Posterior Distribution of Parameters

- Posterior distribution of μ and β given by

$$\pi(\mu,\beta \mid \mathbf{Y}) = \phi\left(\frac{\mu+2}{2}\right)\phi\left(\frac{\beta-3}{2}\right)L\left(\mathbf{Y} \mid \mu,\beta\right)$$

- *L*() is defined as above
- Φ defined as the probability density function of the standard normal distribution
- Next step: Sampling from distribution
- Metropolis within Gibbs sampling using Markov chain length of 1000 samples used to sample from posterior distribution
- Eventually used to update *μ* and *β*

Metropolis within Gibbs algorithm-Programming in SAS

- Start with initial values for μ and β (-2 and 3 from prior distribution)

```
muinit=-2;
betainit=3;
```

- Initiate a loop of 1000 iterations for the MWG sampling
- Define the 8 considered doses (100 to 800 by 100), log adjusted

```
x1=-1.33;
x2=-.63;
x3=-.22;
x4=.06;
x5=.28;
x6=.47;
x7=.62;
x8=.75;
```

- Specify the results of the latest run

```
n1=3;r1=0;n2=0;r2=0;n3=0;r3=0;n4=0;r4=0;n5=0;r5=0;r6=2;n6=2;n7=0;r7=0;n8=0;r8=0;
```

** This signifies that in the first dose of 100 mg, out of three subjects, there were no observed DLTs

Metropolis within Gibbs algorithm-Programming in SAS

- Determine the initial likelihood given the parameters specified in the prior distribution using the current results

```
likelihoodinitmutotal=1;
%do i=1 %to 8;
        probtoxdoseinitmu&i=exp(muinit+betainit*x&i)/(1+exp(muinit+betainit*x&i));
        likelihoodinitmu&i=((probtoxdoseinitmu&i)**(r&i))*((1-probtoxdoseinitmu&i)**(n&i-r&i));
        likelihoodinitmutotal=likelihoodinitmutotal*likelihoodinitmu&i;
%end;
```

- Pull a random number from a normal distribution with mean of the initial mu parameter and variance of 4 (SD=2)
  - This will be considered the next mu parameter value for comparison

```
munext=rand('NORM',muinit,2);
```

- Determine the likelihood given the next value for the mu parameter

```
likelihoodnextmutotal=1;
%do i=1 %to 8;
probtoxdosenextmu&i=exp(munext+betainit*x&i)/(1+exp(munext+betainit*x&i));
likelihoodnextmu&i=((probtoxdosenextmu&i)**(r&i))*((1-probtoxdosenextmu&i)**(n&i-r&i));
likelihoodnextmutotal=likelihoodnextmutotal*likelihoodnextmu&i;
%end;
```

** Note that at this point in the sampling, beta is being held constant

Metropolis within Gibbs algorithm-Programming in SAS

- Calculate the posterior value given the two considered mu values
- Run the comparison per **Metropolis within Gibbs sampling** to determine whether to retain the initial mu parameter value as the current mu or move to the next mu parameter value as the new mu value

```
pdfmuinit=pdf('NORMAL',muinit,-2,2);
pdfbetainit=pdf('NORMAL',betainit,3,2);
pdfmunext=pdf('NORMAL',munext,-2,2);
postdistinitmu=pdfmuinit*pdfbetainit*likelihoodinitmutotal;
postdistnextmu=pdfmunext*pdfbetainit*likelihoodnextmutotal;
```

** The above calculates the posterior value to be used for comparison per MWG sampling; The below programming shows the comparison performed to determine whether to retain the initial value for mu or to use the comparator mu

```
ucompmu=min(1,(postdistnextmu/postdistinitmu));
umu=ranuni(i);
if umu le ucompmu then acceptmu=0;
else acceptmu=1;
if acceptmu=0 then muinit=munext;
else muinit=muinit;
```

Metropolis within Gibbs algorithm-Programming in SAS

- Determine the likelihood given the initial value for the beta parameter (note that the mu value determined in previous step is used here) per Metropolis within Gibbs methodology

```
likelihoodinitbetatotal=1;
%do i=1 %to 8;
probtoxdoseinitbeta&i=exp(muinit+betainit*x&i)/(1+exp(muinit+betainit*x&i));
likelihoodinitbeta&i=((probtoxdoseinitbeta&i)**(r&i))*((1-probtoxdoseinitbeta&i)**(n&i-r&i));
likelihoodinitbetatotal=likelihoodinitbetatotal*likelihoodinitbeta&i;
%end;
```

- Proceed as before to determine the value for beta for this run
- This process provides us with one pair of values for μ and β
- This μ and β is used as the initial starting values for the next iteration in the sampling; 1000 pairs are eventually generated

Updating the Working Toxicity Model

- We have our 1000 pairs of μ and β; now what?
- Substitute the mean values of μ and β (from the 1000 samples) in the formula for Prob(Toxicity|dose j) to determine the updated dose-toxicity model
- Study dose for next cohort will be *suggested as* the study dose with closest estimated toxicity to target toxicity of 0.33 with stipulations

Stipulations for Determining Next Dose

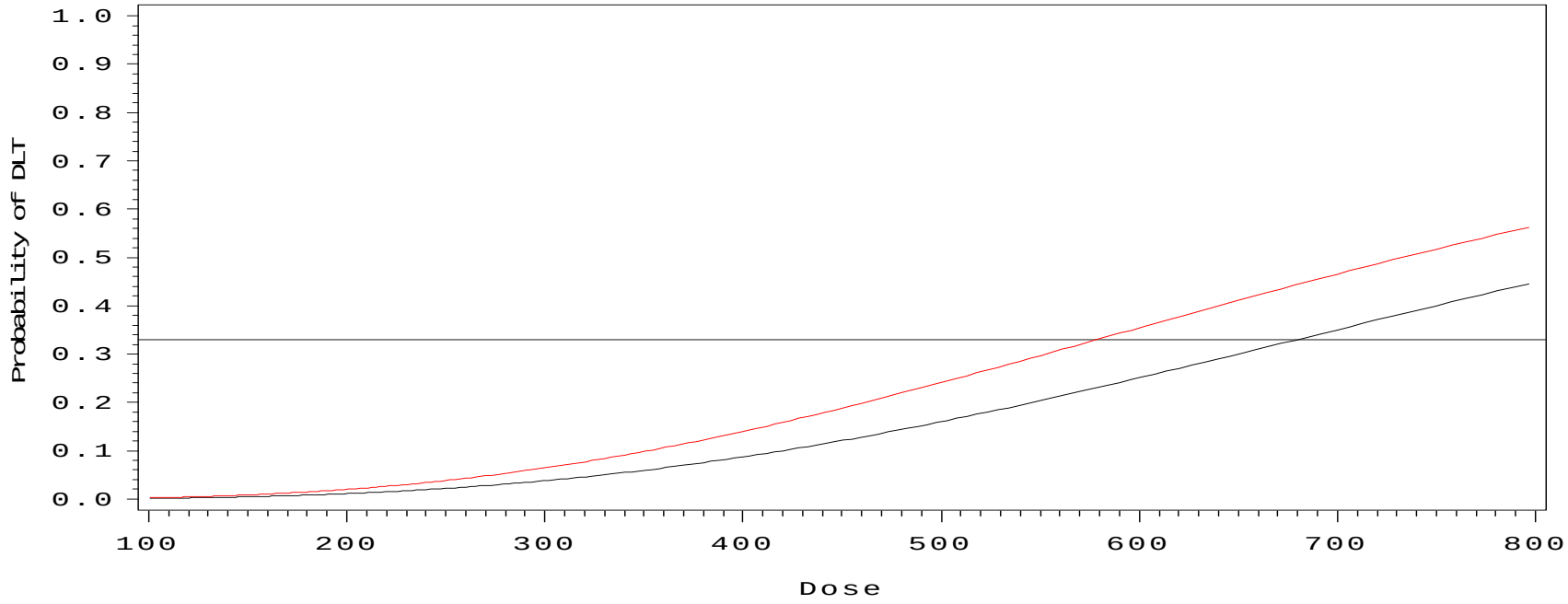
- Next dose cannot be more than twice the current dose
- If posterior probability that 100 mg dose will show at least 33% chance of toxicity is greater than 0.9, the study will stop
  - Determined by calculating the probability of toxicity at each of the 1000 pairs of μ and β at 100 mg and calculating the percentage of times (out of 1000) that the probability of toxicity is greater than 0.33
- Posterior probability of toxicity greater than 33% for the selected dose of next cohort cannot be greater than 0.35
  - Determined by calculating the probability of toxicity at each of the 1000 pairs of μ and β at the suggested dose and calculating the percentage of times (out of 1000) that the probability of toxicity is greater than 0.33
- Continues until set number of patients reached (in our case, this was 18)

Study Implementation

- **Statistician responsibilities**
  - **Communicate with clinical personnel regarding presence or absence of DLTs**
  - **Review AE logs to reconcile results from CRF and clinical judgments**
  - **Schedule formal meeting with client to report on results from CRM run**
    - **Meeting scheduled shortly after study day 21 of the last subject in the cohort**
    - **Full report provided**
  - **Preside over telecon regarding selection of dose for next cohort**
  - **Answer questions from clinical staff regarding data analysis and or the “what-ifs”**

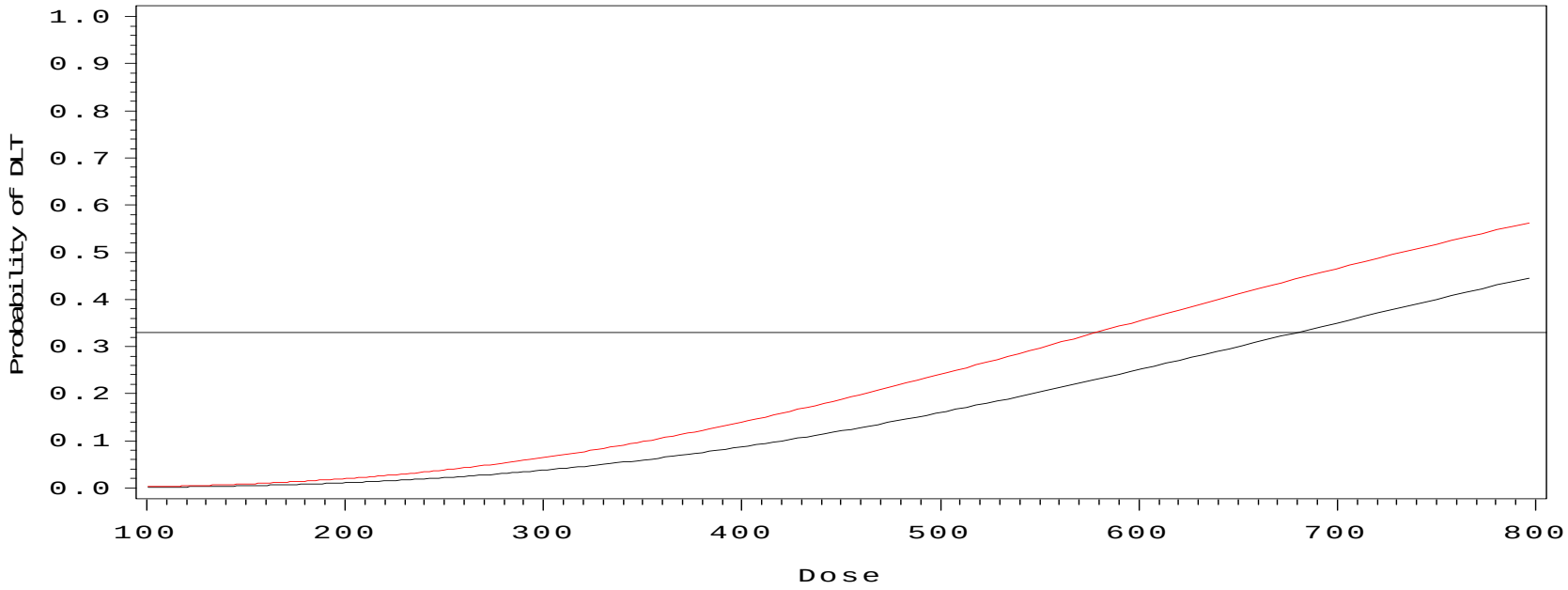
Results after Cohort 1

- Cohort Dose: 100 mg/day (QD)
- Three subjects dosed
- No DLTs
- CRM suggested ~680 mg as next dose
  - 200 mg chosen as next dose due to stipulation that next dose cannot be greater than twice the initial dose
- Posterior probability that 200 mg would have greater than 33% toxicity=0.015
- Black line=new working model; red line=original toxicity model



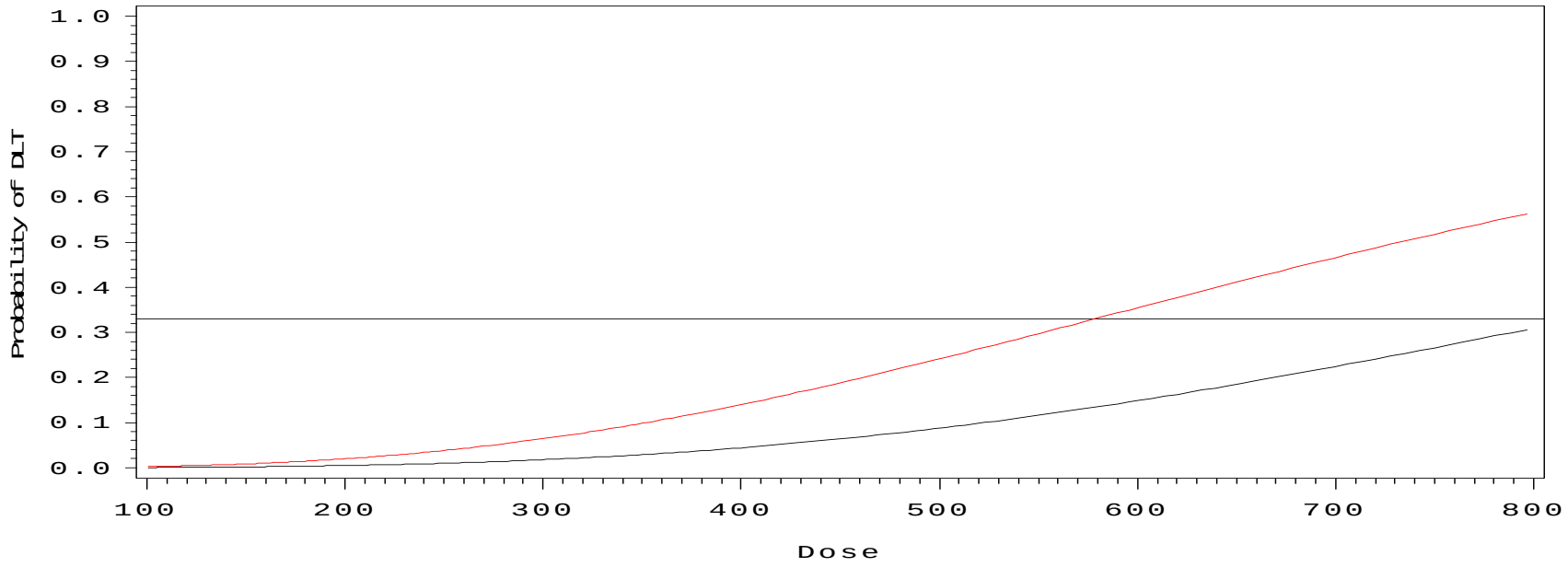
Results after Cohort 2

- Cohort Dose: 200 mg/day (QD)
- Three subjects dosed
- No DLTs
- CRM suggested ~652 mg as next dose
  - 400 mg chosen as next dose due to stipulation that next dose cannot be greater than twice the initial dose
- Posterior probability that 400 mg would have greater than 33% toxicity=0.164
- Black line=new working model; red line=original toxicity model



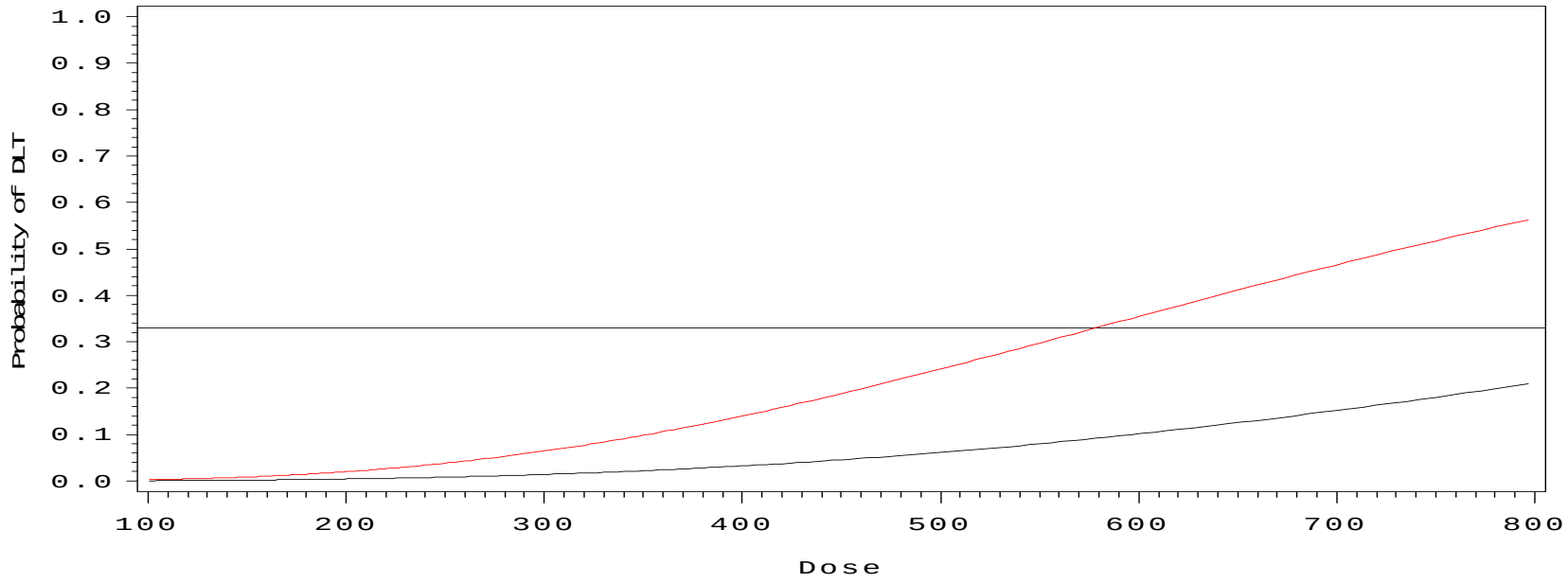
Results after Cohort 3

- Cohort Dose: 400 mg/day (QD)
- Three subjects dosed
- No DLTs
- CRM suggested 800 mg as next dose (max dose in study)
  - Posterior probability of tox was greater than 0.35 (0.485)
  - Lowest study dose with posterior probability less than 0.35 was 600 mg
  - Clinical reviewed tox and PK data and suggested 400 mg/day (200 mg BID) as next dose
- Posterior probability that 600 mg/day would have grater than 33% toxicity=0.338
- Black line=new working model; red line=original toxicity model



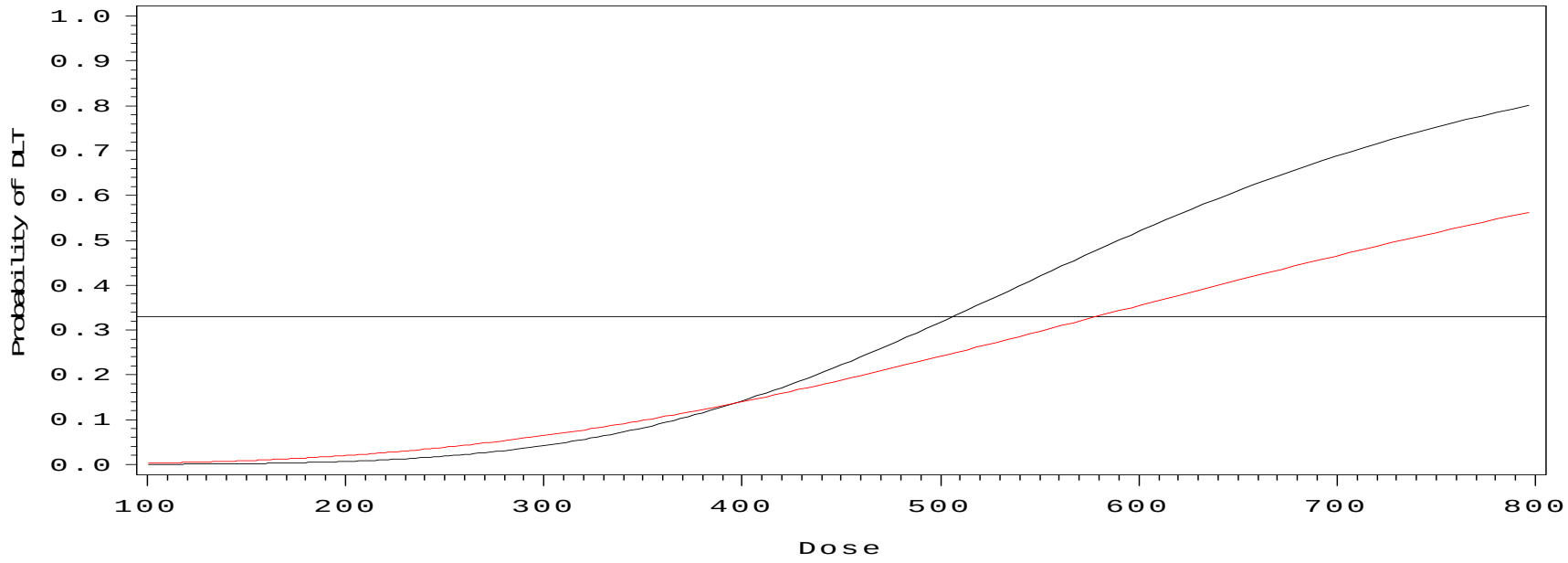
Results after Cohort 4

- Cohort Dose: 400 mg/day (200 mg BID)
- Five subjects dosed; one dropped out of study before day 21, not due to DLT
- No DLTs in other four subjects
- CRM suggested 800 mg as next dose (max dose in study)
  - Posterior probability of tox was greater than 0.35 (0.399)
  - Lowest dose with posterior probability less than 0.35 was 700 mg
  - Clinical reviewed tox and PK data and suggested 600 mg/day (300 mg BID) as next dose
- Posterior probability that 700 mg/day would have greater than 33% toxicity=0.289
- Black line=new working model; red line=original toxicity model



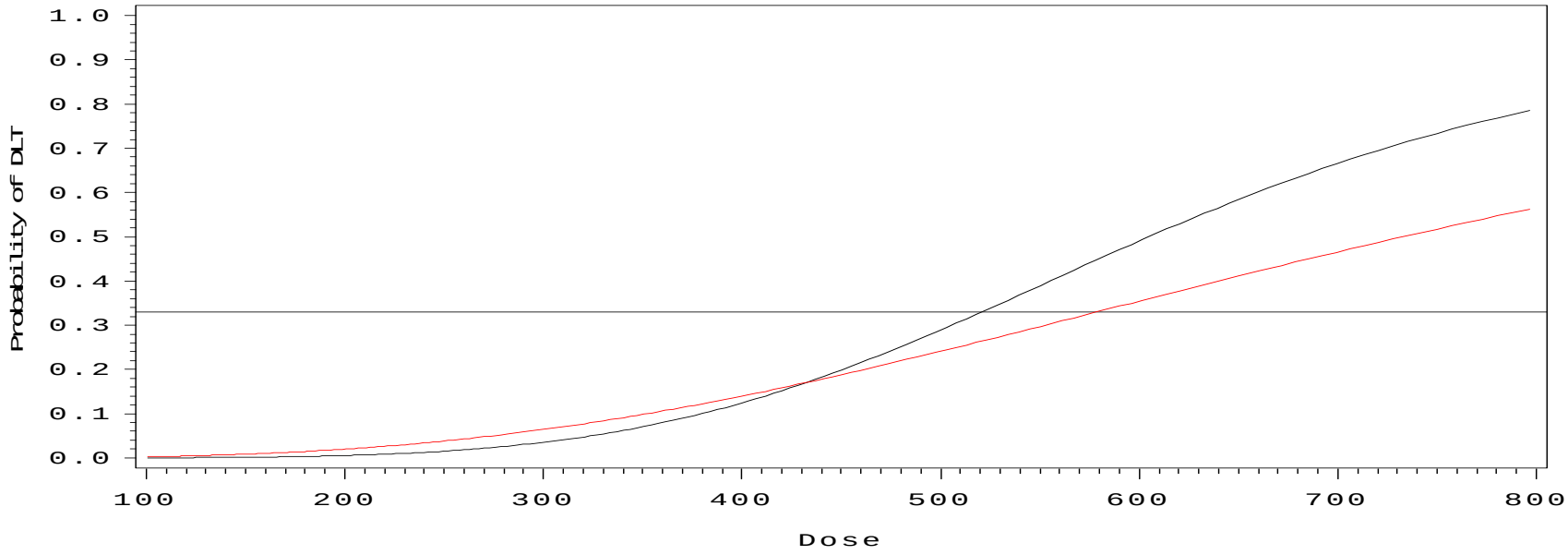
Results after Cohort 5

- Cohort Dose: 600 mg/day (300 mg BID)
- Two subjects dosed
- Both had DLTs
- CRM suggested ~500 mg as next dose
  - Posterior probability of tox was greater than 0.35 (0.458)
  - Lowest dose with posterior probability less than 0.35 was 450 mg
  - Clinical reviewed tox and PK data and suggested 400 mg/day (200 mg BID) as next dose
- Posterior probability that 450 mg/day would have grater than 33% toxicity=0.225
- Black line=new working model; red line=original toxicity model



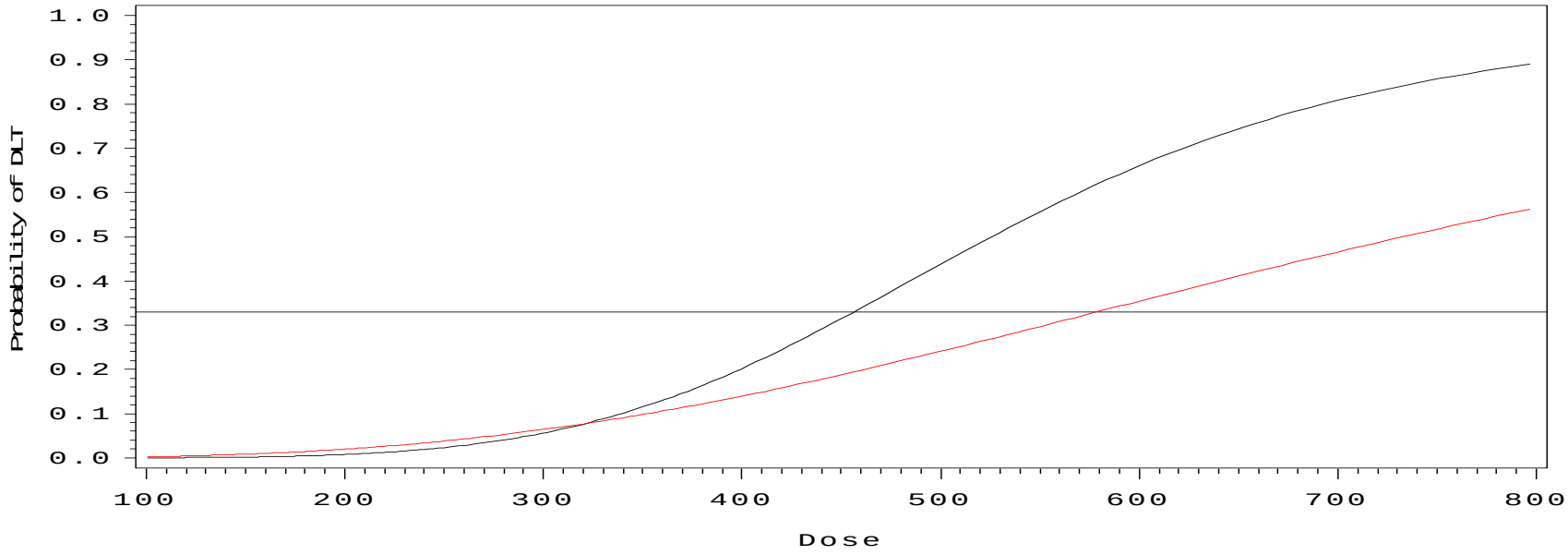
Results after second 200 mg BID cohort- Scenario 1

- Cohort Dose: 400 mg/day (200 mg BID)
- Two subjects dosed
- No DLTs
- CRM suggested 500 mg as MTD (determined final run of CRM)
  - Posterior probability of tox was greater than 0.35 (0.434)
  - Lowest dose with posterior probability less than 0.35 was 450 mg
- Posterior probability that 450 mg/day would have grater than 33% toxicity=0.195
- Two scenarios run due to clinical being “on the fence” on DLT for one of the patients
- Black line=new working model; red line=original toxicity model



Results after second 200 mg BID cohort- Scenario 2

- Cohort Dose: 400 mg/day (200 mg BID)
- Two subjects dosed
- One of two subjects with DLT
- CRM suggested 450 mg as MTD (determined final run of CRM)
  - Posterior probability of tox was greater than 0.35 (0.461)
  - Lowest dose with posterior probability less than 0.35 was 400 mg
- Posterior probability that 400 mg/day would have grater than 33% toxicity=0.190
- Two scenarios run due to clinical being “on the fence” on DLT for one of the patients
- Black line=new working model; red line=original toxicity model



Implementation Challenges

- Working Toxicity Model
  - Bayesian techniques
  - Must trust in prior model
  - Particular model based on “good operating characteristics”; is this appropriate?
- Clinical judgment on DLTs
  - Many times, clinicians were “on the fence”
  - Requests for multiple scenarios
  - Later found that one subject was analyzed in previous cohort who should not have been because lack of 21 days of dosing
- Choice of next dose
  - Many times, a higher dose was chosen, but posterior probability would eliminate that dose
  - Not a negative in my opinion
- No allowance for dosing regimen change
  - Limitation of doing a dose-toxicity model where dose is the independent variable

Discussion

Questions?