A modified Hierarchical Continuous Reassessment Method (CRM) applied to a first-in-man study.

BAYES2010
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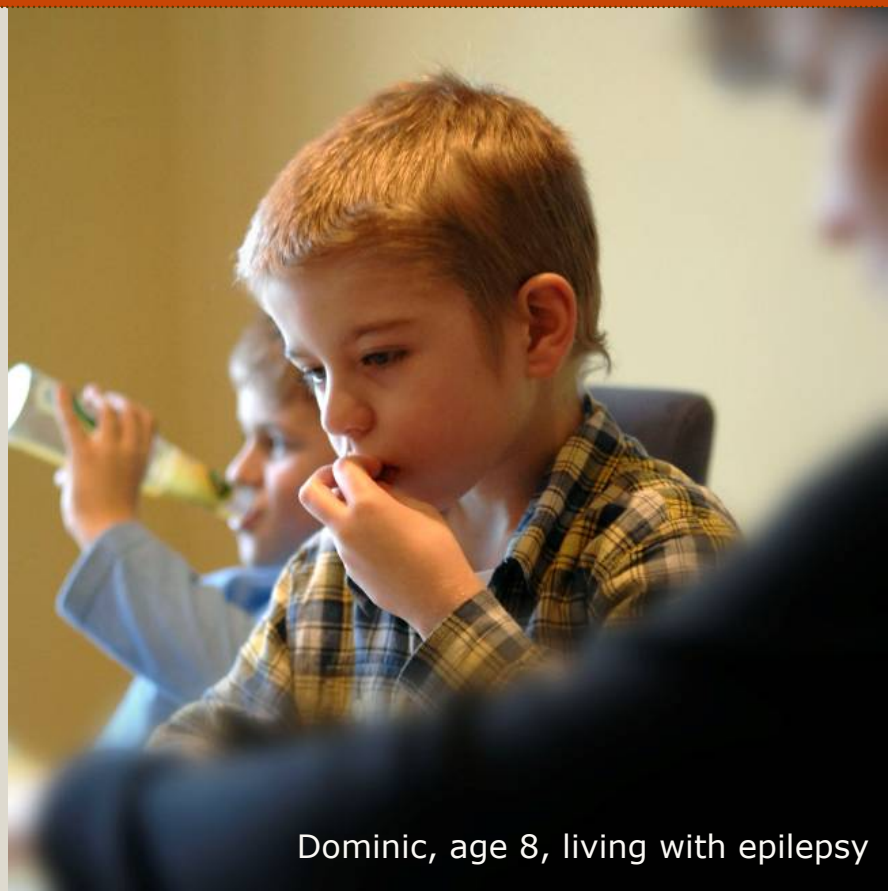
Tom Jacobs



Dominic, age 8, living with epilepsy

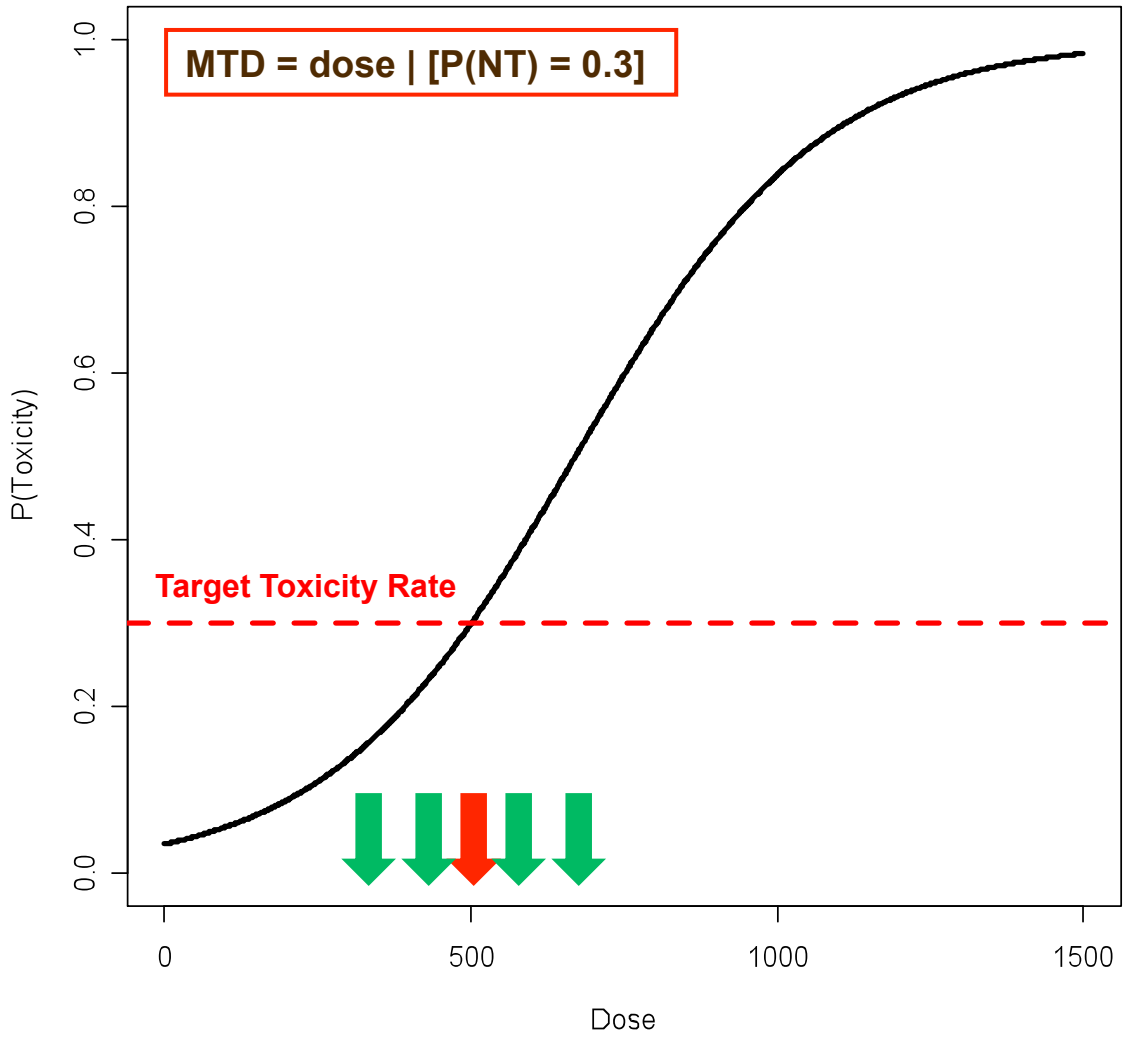
Outline

- First in Human Trial
- Dose escalation designs:
  - Classical
  - CRM
  - mCRM
- Hierarchical Logistic model
- Multinomial model

First in Human Trial

- Primary objective: information on safety
- Population:
  - Patients
    - Eg. Oncology
    - Goal: Administration of the most efficacious yet safe dose (Target Toxicity Rate/ MTD)

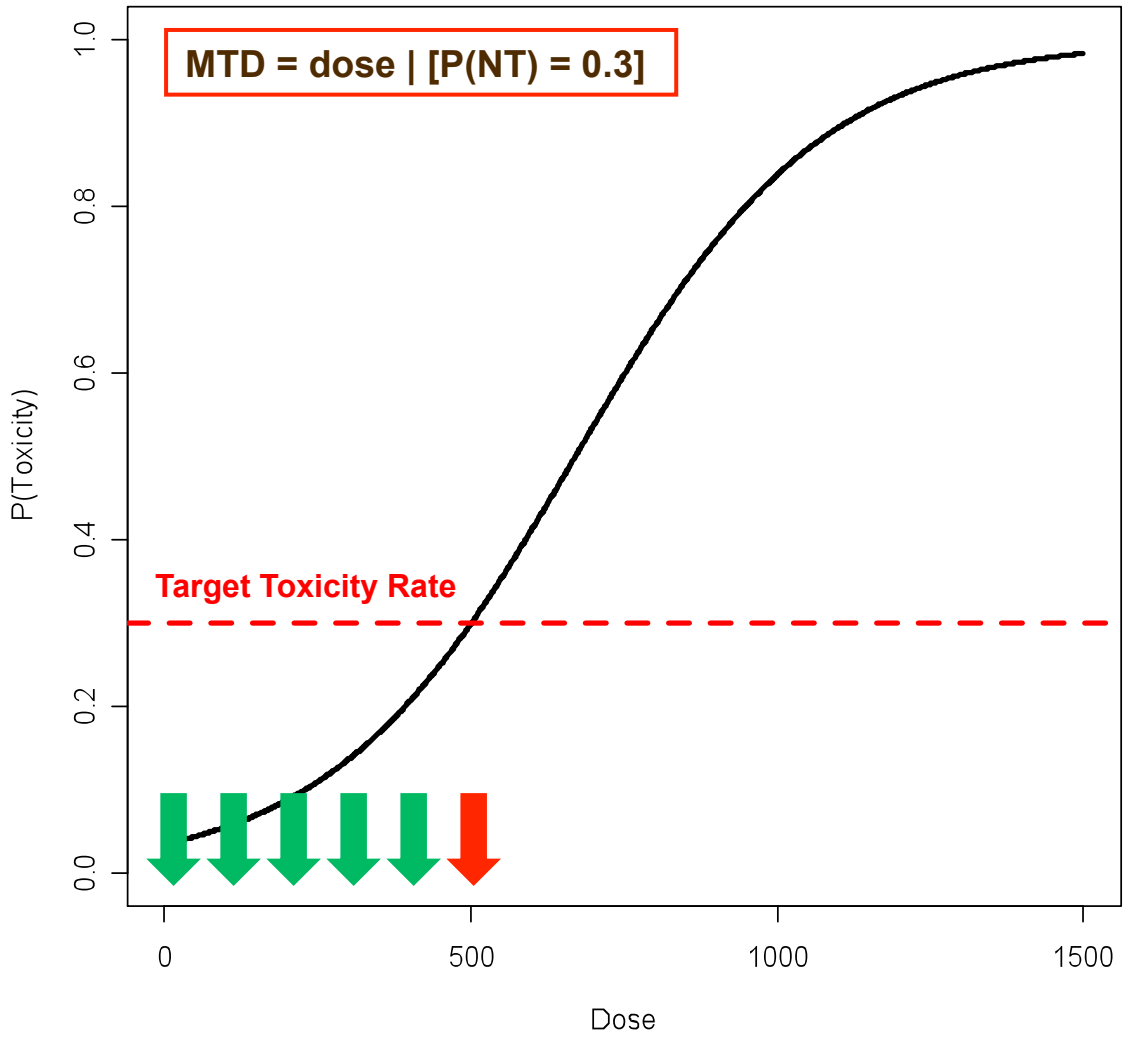
First in Human Trial



First in Human Trial

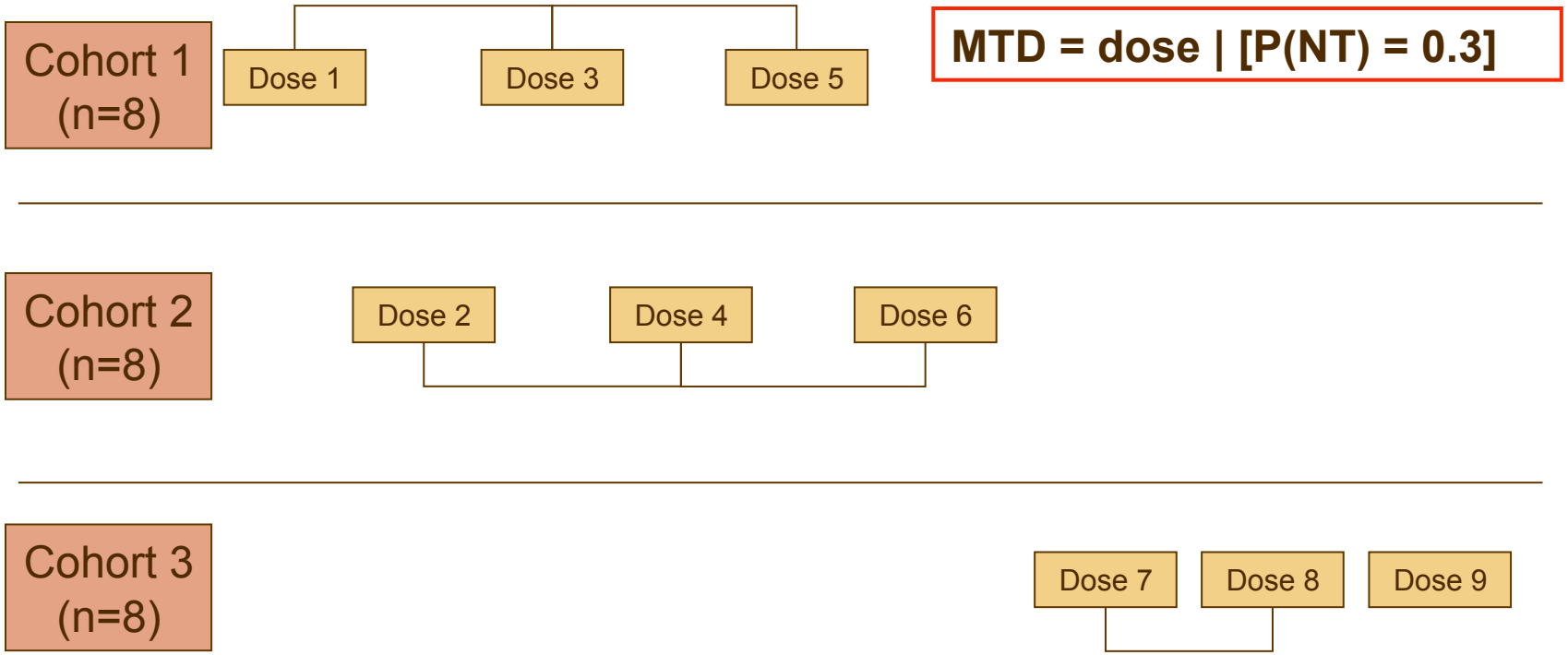
- Primary objective: information on safety
- Population:
  - Patients
    - Eg. Oncology
    - Goal: Administration of the most efficacious yet safe dose (Target Toxicity Rate/ MTD)
  - Healthy volunteers
    - Eg. Epilepsy
    - Goal: Escalating up to the highest safe dose (Target Toxicity Rate / MTD)

First in Human Trial

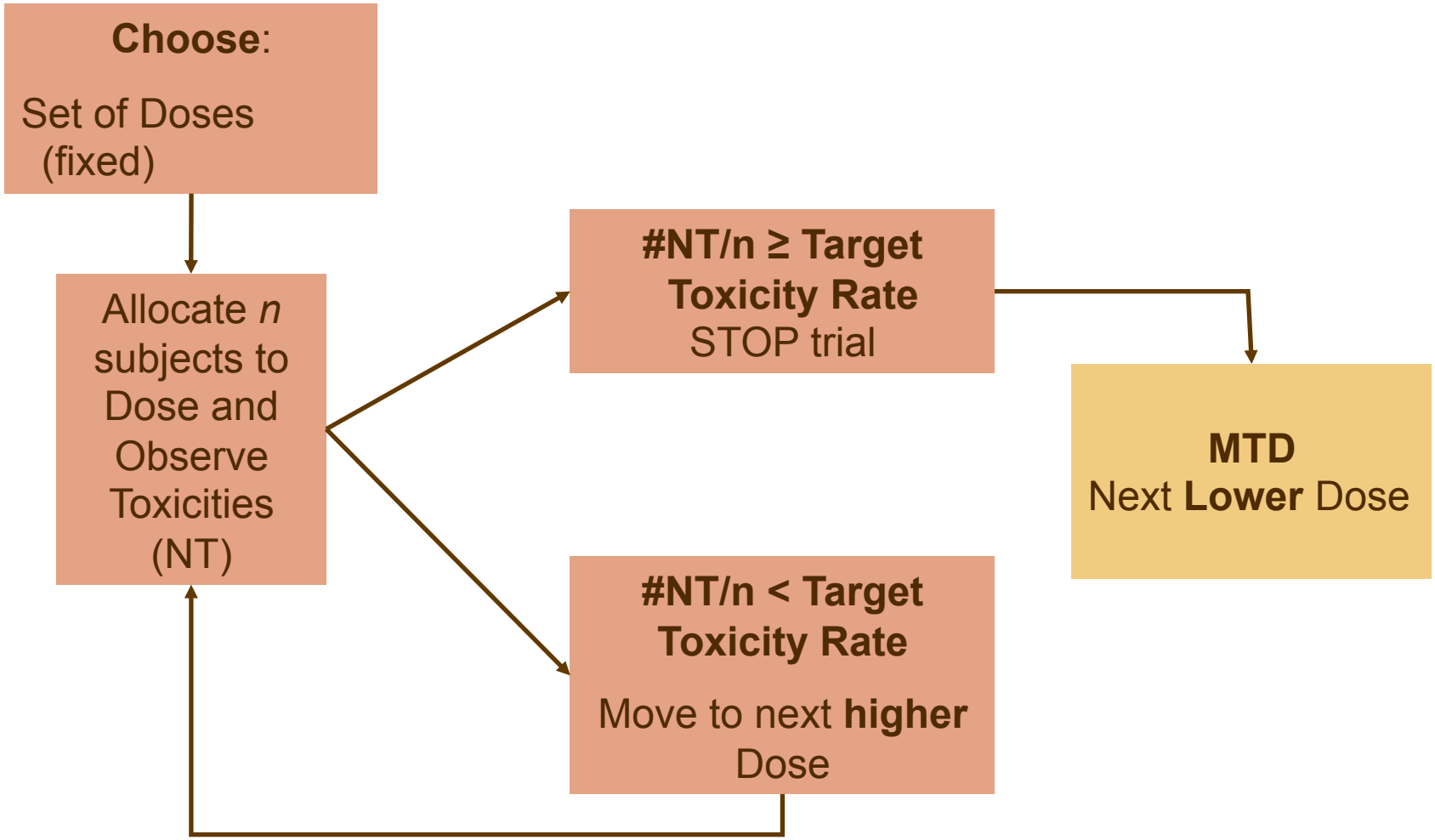


Dose Escalation

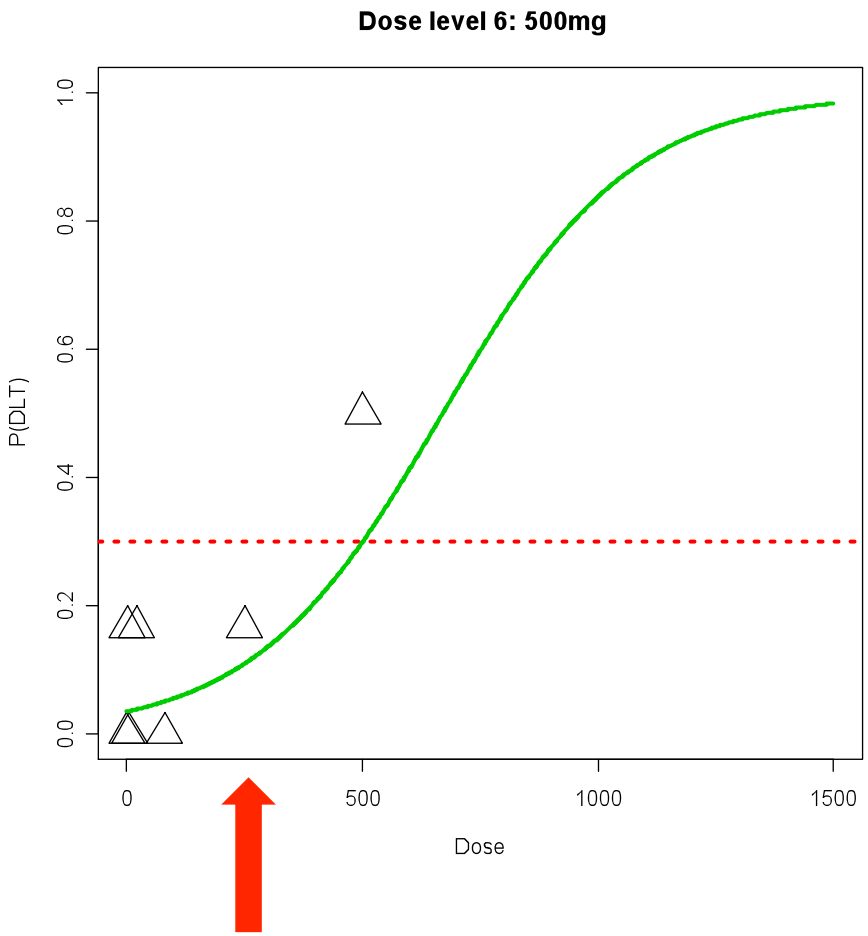
- Alternating dose escalation design
- Healthy volunteers



Dose Escalation: Classical Design



Dose Escalation: Classical Design



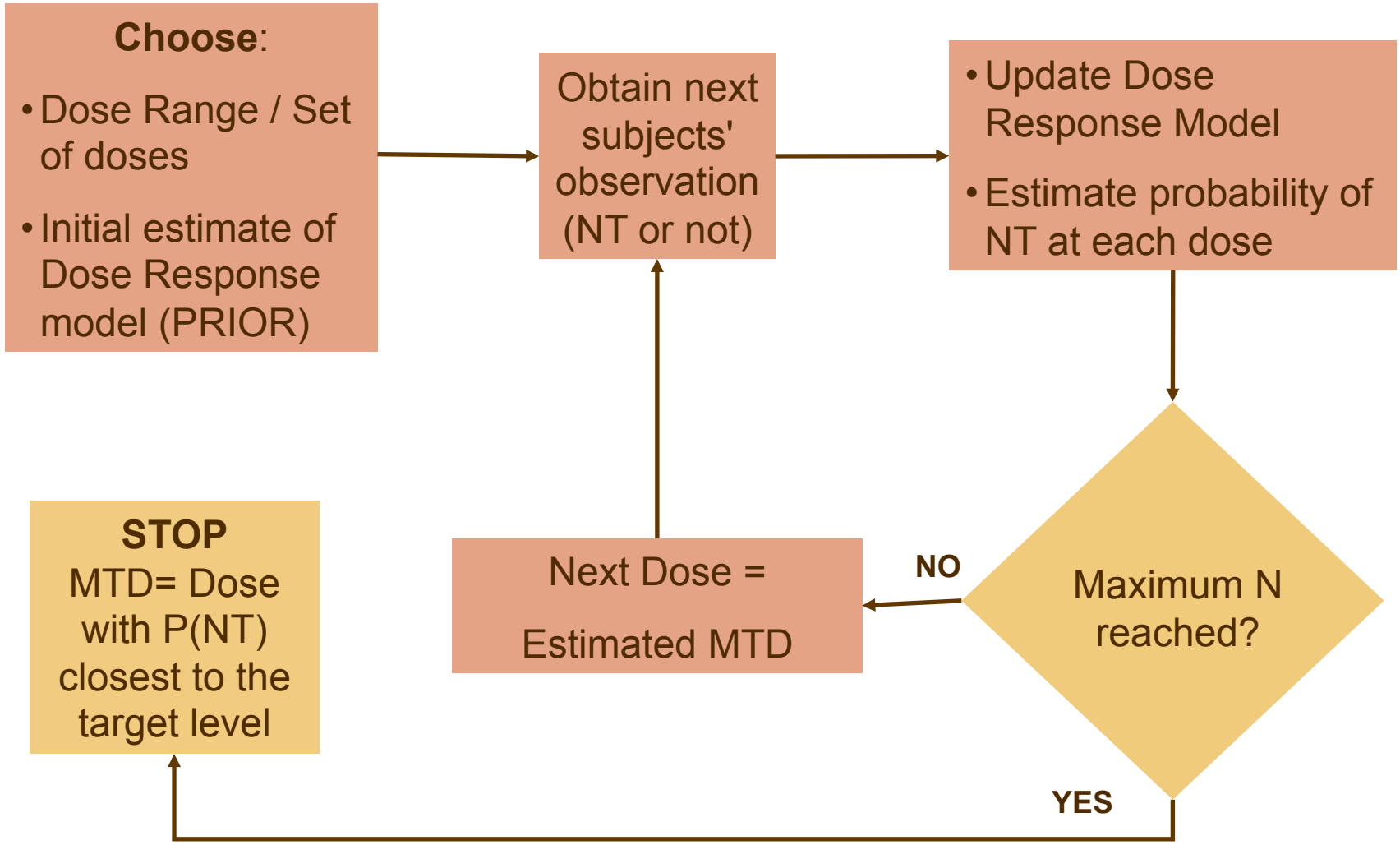
Dose Escalation: Classical Design

- Pros:
  - Fixed Doses
  - Easy trial conduct
- Cons:
  - Lack of flexibility:
    - Fixed Doses
    - Can Only Increase the Dose
  - Uses only information from current dose
  - Underestimation of the MTD

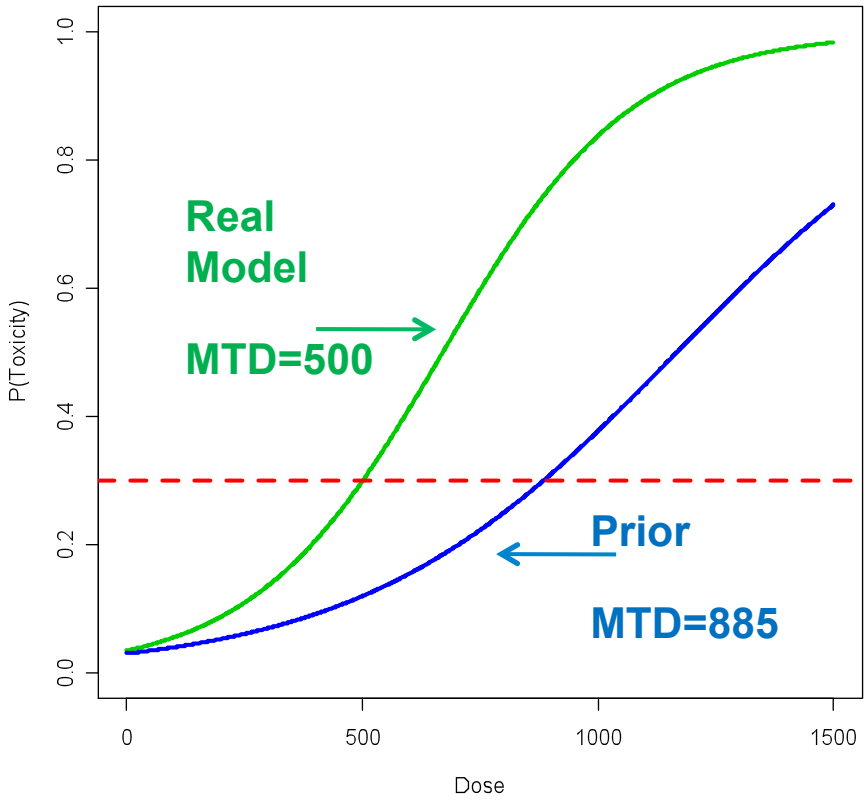
Dose Escalation: CRM

- Adaptive design developed by O'Quigley et al., (1990) for oncology studies
- Goal: allocate most patients to MTD (most efficacious "safe" dose)
- Well known method (plenty of literature)

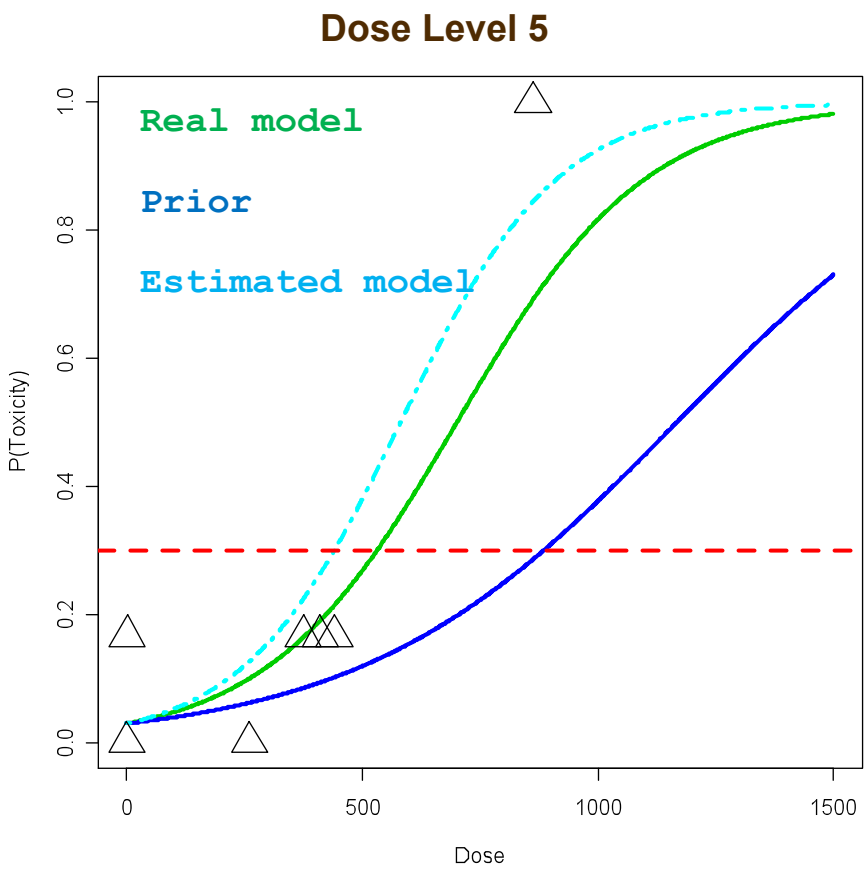
Dose Escalation: CRM



Dose Escalation: CRM



Dose Escalation: CRM



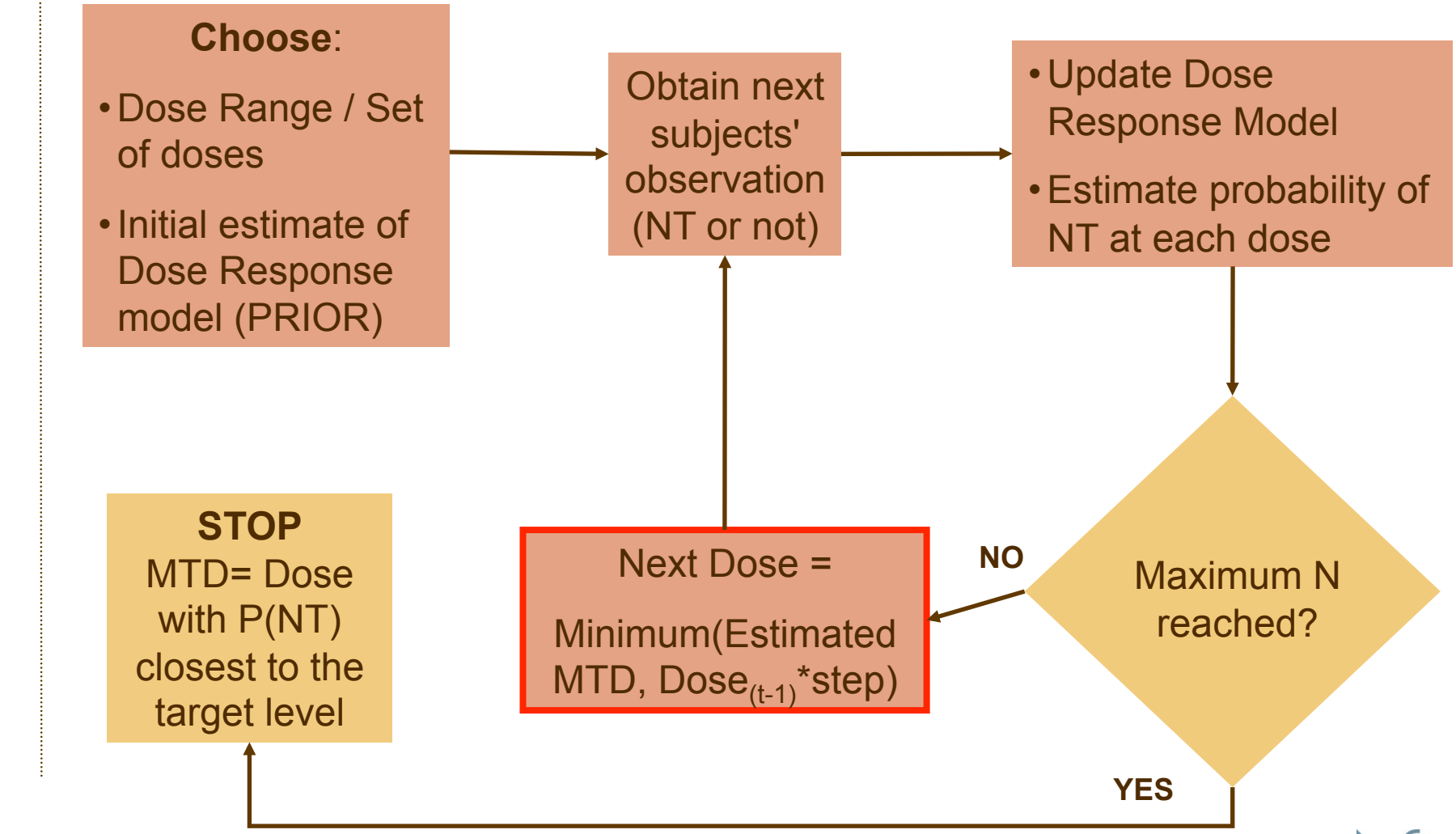
MTD.model=440mg

Cohort	Sub	Per	Dose	DLT
1	1	3	410	1
1	2	3	410	0
1	3	3	0	0
1	4	3	410	0
1	5	3	410	0
1	6	3	410	0
1	7	3	0	0
1	8	3	410	0

Dose Escalation: CRM

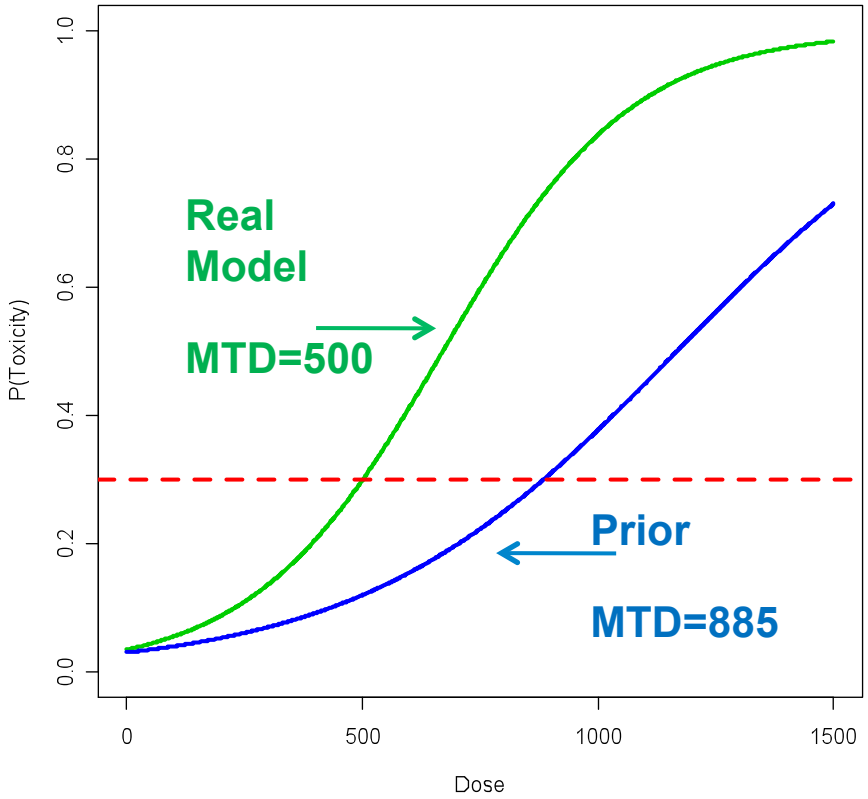
- PROS:
  - Flexibility during the trial
  - Decisions about next doses are made based on information from all tested doses and previous knowledge
  - Estimation of the complete dose-response curve on the doses range considered
    - MTD not necessary a tested dose
    - Idea of precision of the estimators
- CONS:
  - Potentially large dose increases are allowed
  - More difficult to put in place
  - A lot of thinking needed ahead

Dose Escalation: mCRM

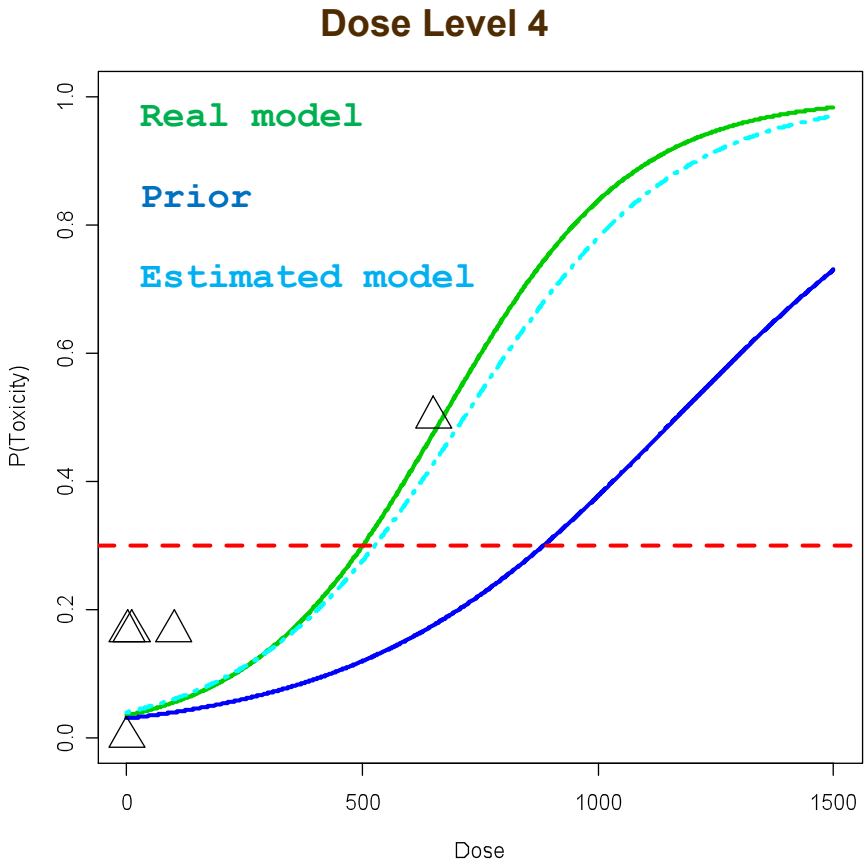


Dose Escalation: mCRM

Maximum step=10



Dose Escalation: mCRM



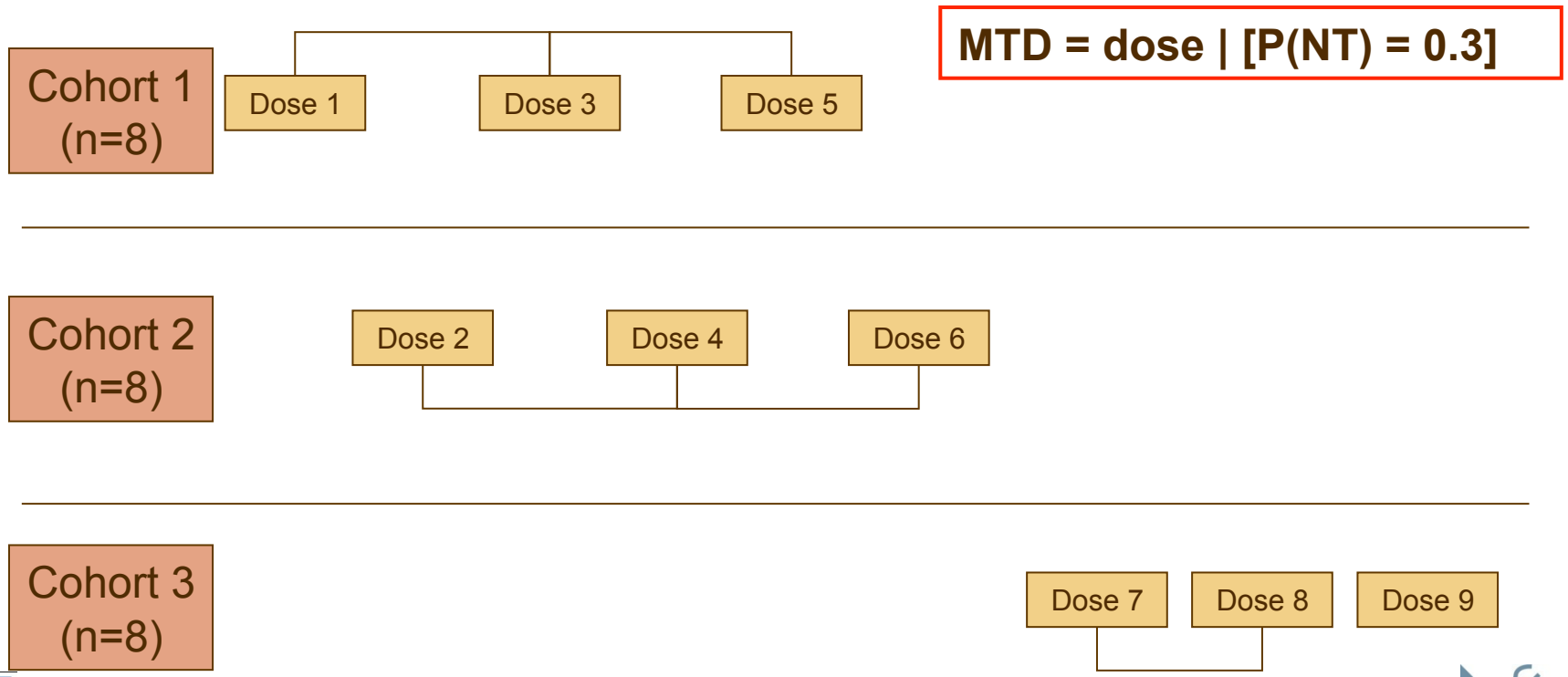
MTD.model=526mg

Dose Escalation: mCRM

- PROS:
  - Flexibility during the trial
  - Decisions about next doses are made based on information from all tested doses and previous knowledge
  - Estimation of the complete dose-response curve on the doses range considered
    - MTD not necessary a tested dose
    - Idea of precision of the estimators
  - Conservative dose increase
- CONS:
  - More difficult to put in place
  - A lot of thinking needed ahead

Dose Escalation: Case study

- Alternating dose escalation design
  - Same subject can receive up to 3 doses (including placebo)



Dose Escalation: Case study

- Alternating dose escalation design
  - Same subject can receive up to 3 doses (including placebo)
- CSE: AE at least of moderate intensity and treatment related
- Predefined set of escalation steps

1. Estimation of population and individual dose-toxicity curves
2. Use of all AEs to predict the CSE

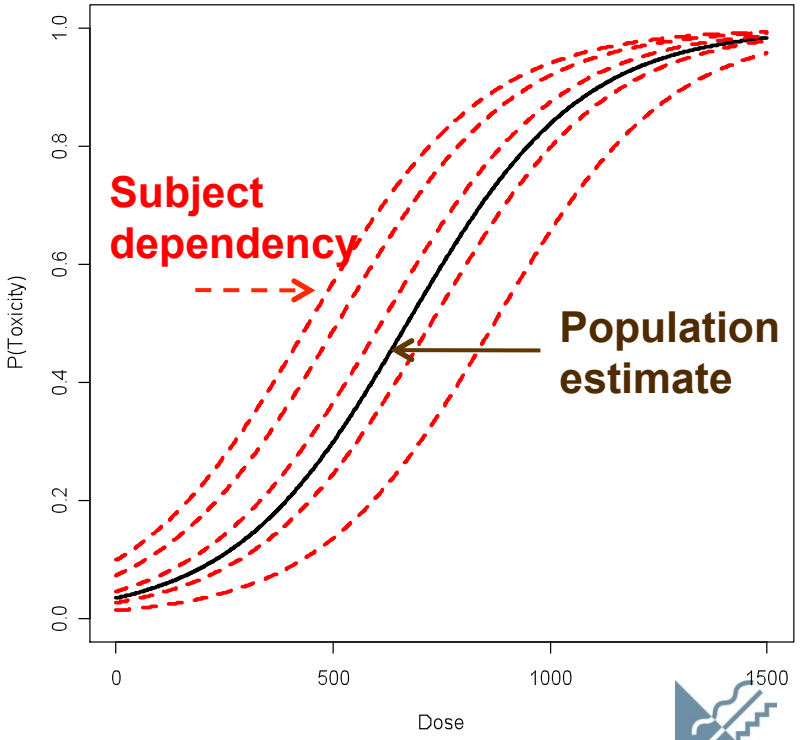
Hierarchical mCRM

- The model:
  - Logistic model
  - p_{ij} : probability that a patient *i* who receives dose *j* experiences NT

$$\text{logit}(p_{ij}) = \alpha_{0i} + \alpha_1(\text{dose}_j)$$

α_{0i} = Individual intercept parameter → define P (NT) under placebo

α_1 = slope parameter → define effect of 1 unit of product on P(NT)



mCRM (non Hierarchical)


```
model
{
     for(j in 1:n.doses)
     {
      logit(p[j]) <- alpha0.p+alpha1.p*dose[j]
      n.events[j] ~ dbin(n.subjects[j], p[j])
     }
alpha0.p ~ dnorm(alpha0.m.prior ,alpha0.v.prior)
alpha1.p ~ dnorm.trunc(alpha1.m.prior, alpha1.v.prior)
}
```

Dose Loop

Parameters common for all doses

Hierarchical mCRM


```
model
{
    for (i in 1:n.subjects)
     {
          for(j in 1:n.doses[i])
          {
          logit(p[i, j]) <- alpha0[i]+alpha1.p*dose[i, j]
          n.events[i, j] ~ dbern(p[i, j])
          }
     rand[i]~ dnorm(0, theta0)
     alpha0[i]<- alpha0.p + rand[i]
     }
theta0 ~ dlnorm(theta0.m.prior, theta0.v.prior)
alpha0.p ~ dnorm(alpha0.m.prior ,alpha0.v.prior)
alpha1.p ~ dnorm.trunc(alpha1.m.prior, alpha1.v.prior)
}
```

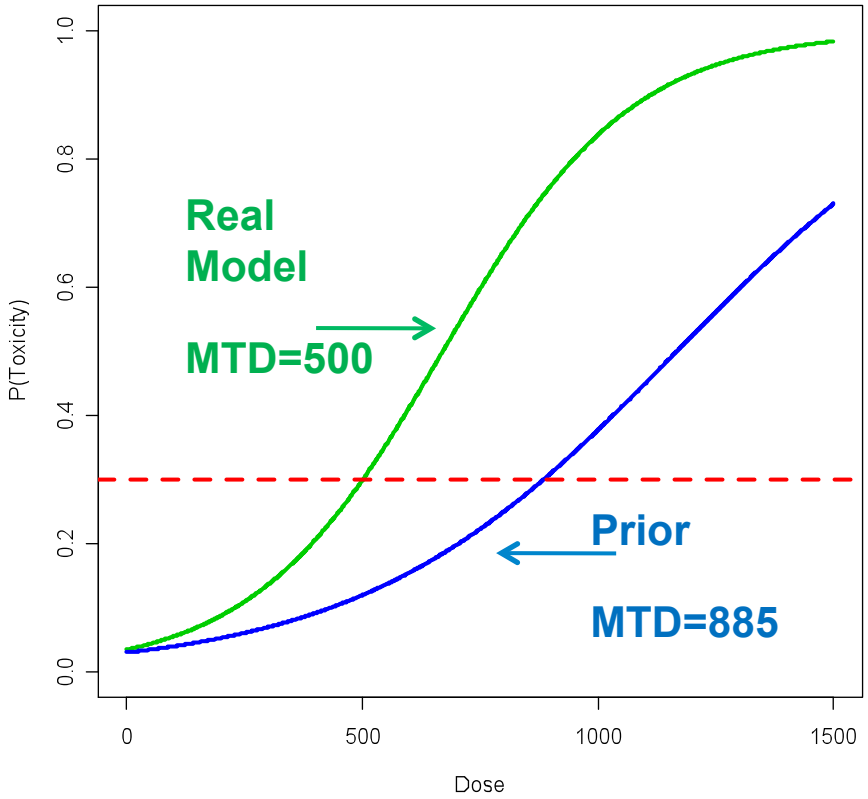
Subject Loop

Dose Loop

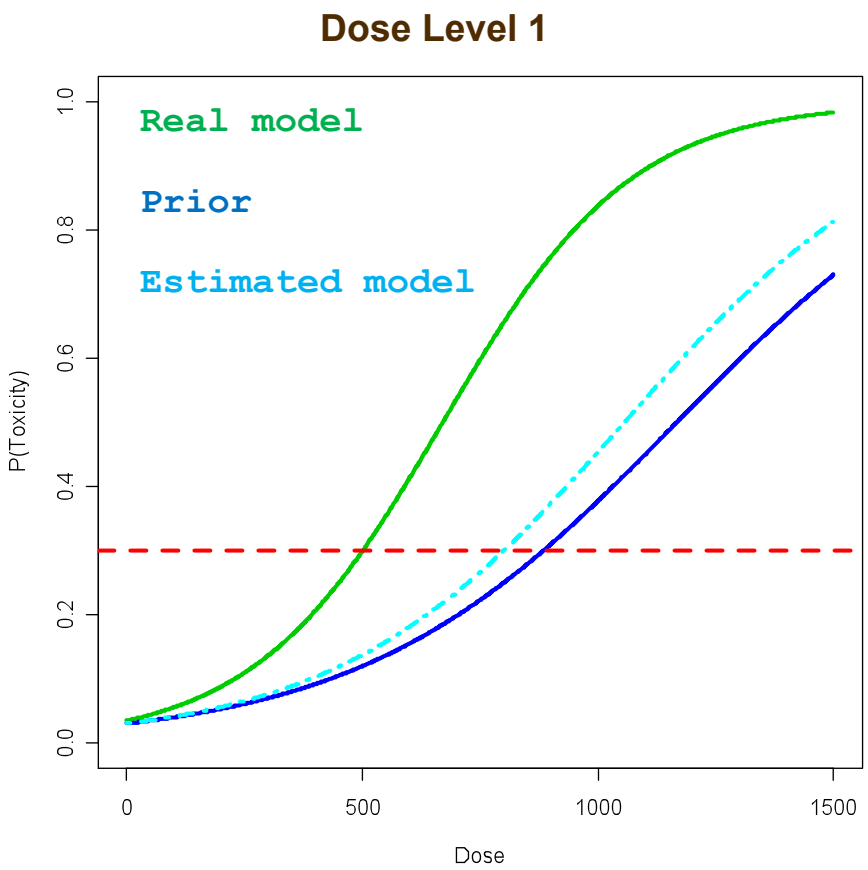
Parameters common for all doses

Hierarchical mCRM

Maximum step=10



Hierarchical mCRM

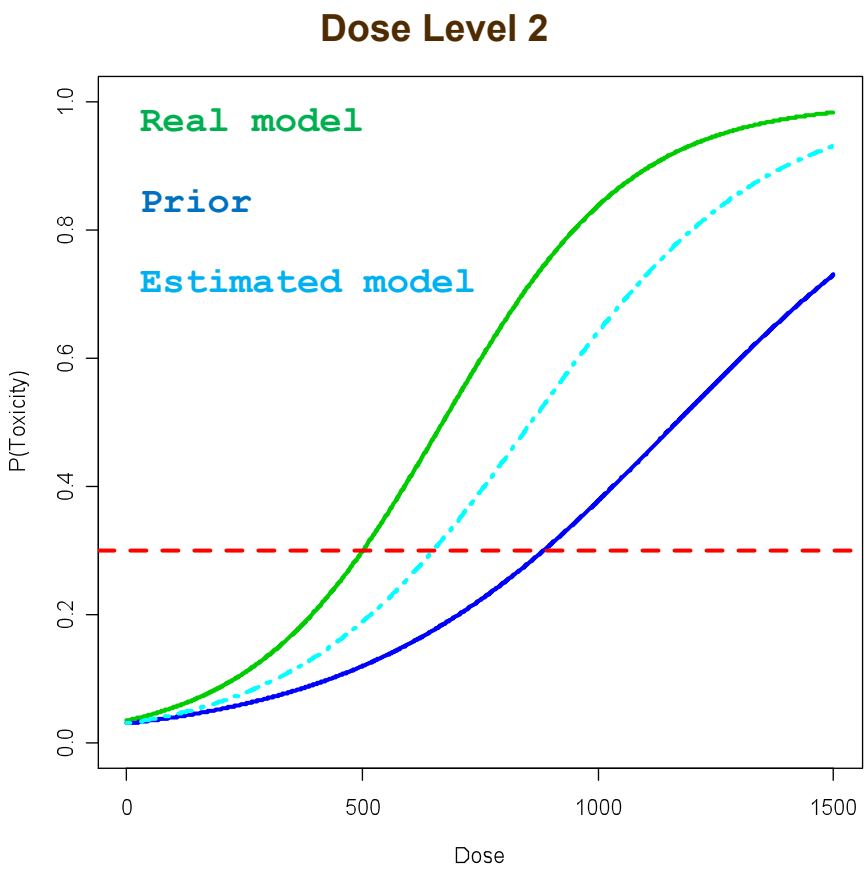


MTD.model=800mg

→ next dose=min(10*1mg, 800mg)

Cohort	Sub	Per	MTD	Dose	DLT
1	1	1	NA	1	0
1	2	1	NA	0	0
1	3	1	NA	1	1
1	4	1	NA	1	0
1	5	1	NA	1	0
1	6	1	NA	1	0
1	7	1	NA	1	0
1	8	1	NA	0	0

Hierarchical mCRM

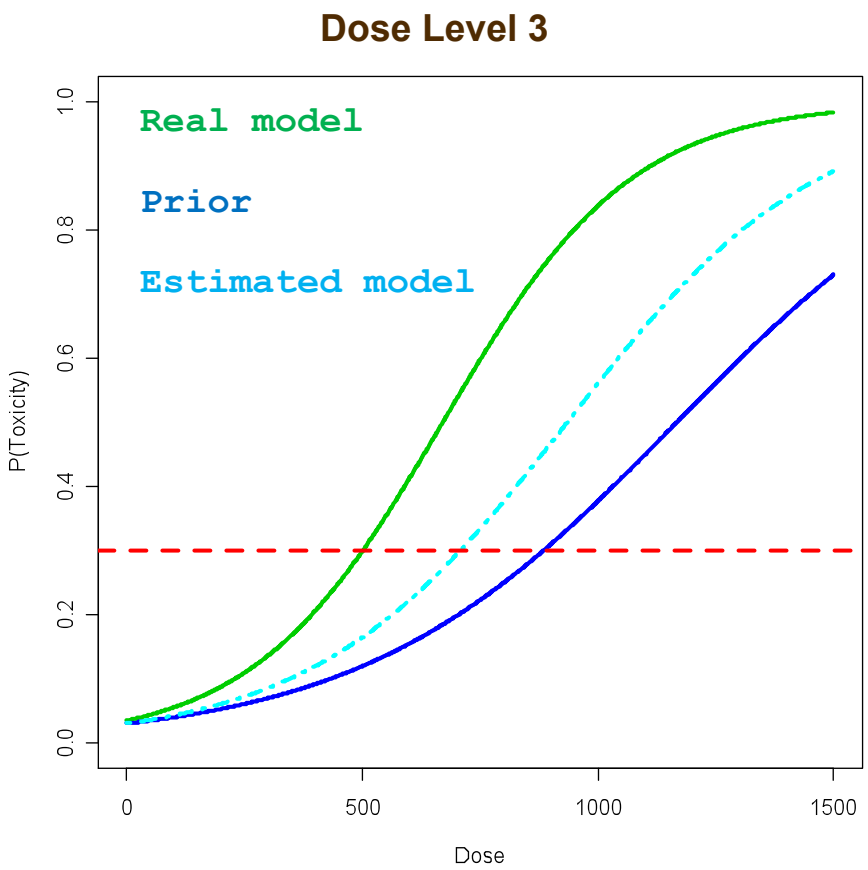


MTD.model=650mg

→ next dose=min(10*10mg, 650mg)

Cohort	Sub	Per	MTD	Dose	DLT
2	9	1	NA	10	0
2	10	1	NA	0	0
2	11	1	NA	10	0
2	12	1	NA	0	0
2	13	1	NA	10	0
2	14	1	NA	10	0
2	15	1	NA	10	1
2	16	1	NA	10	0

Hierarchical mCRM

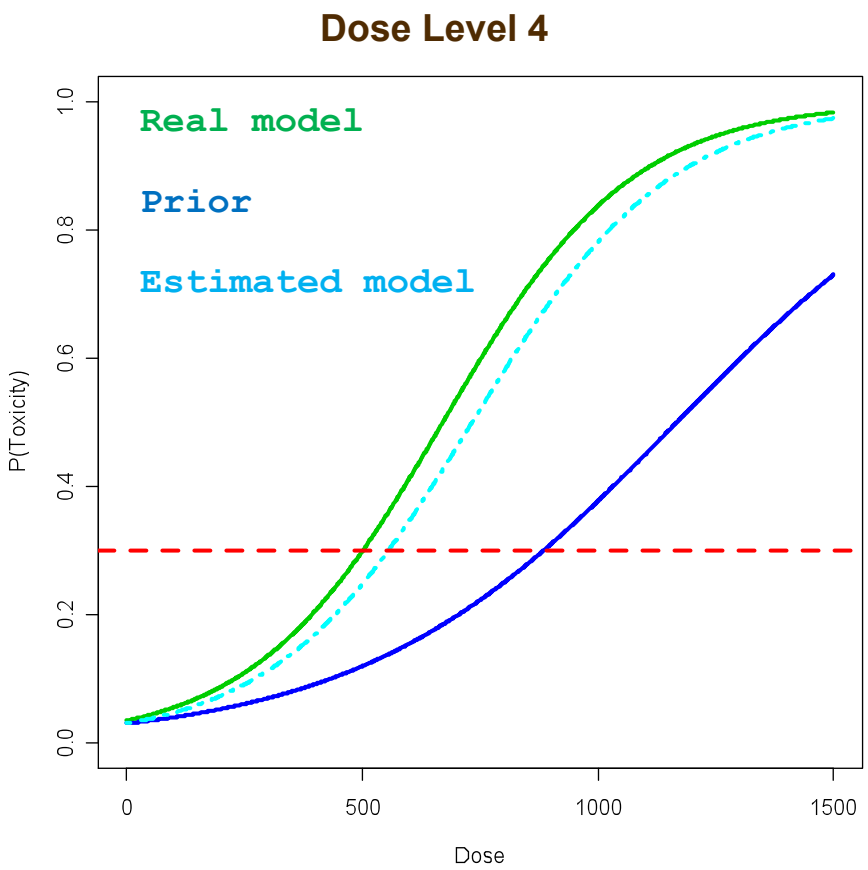


MTD.model=708mg

→ next dose=min(10*100mg, MTD.ind)

Cohort	Sub	Per	MTD	Dose	DLT
1	1	2	NA	0	0
1	2	2	NA	100	0
1	3	2	NA	100	0
1	4	2	NA	100	0
1	5	2	NA	0	0
1	6	2	NA	100	0
1	7	2	NA	100	0
1	8	2	NA	100	1

Hierarchical mCRM

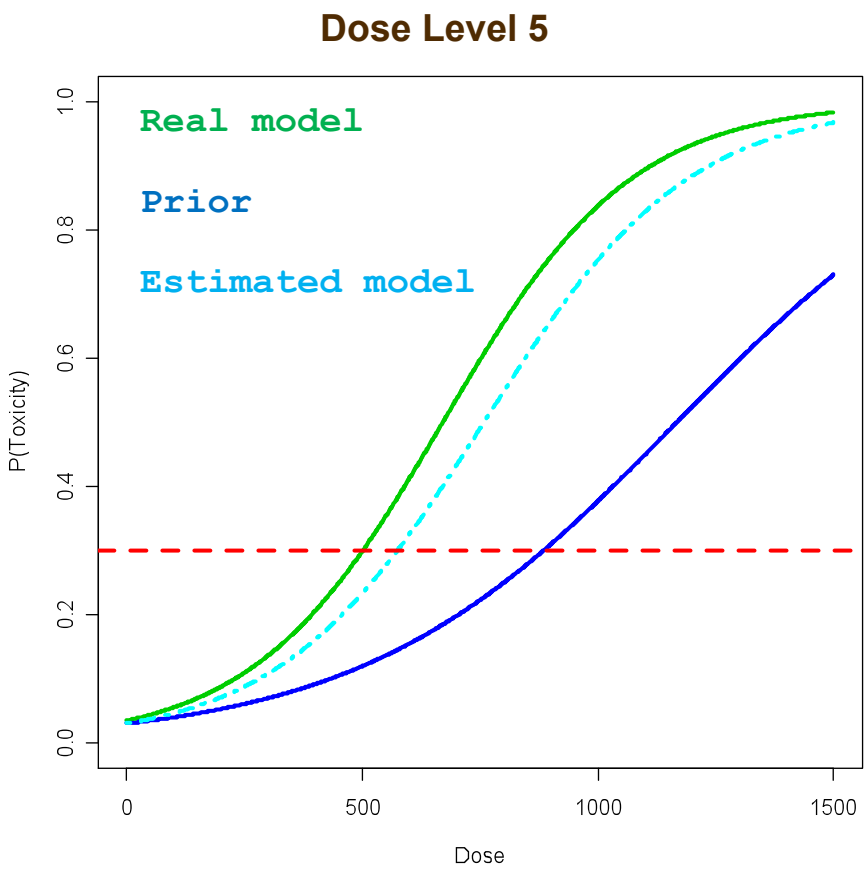


MTD.model=555mg

→ **next dose=min(10*700mg, MTD.ind)**

Cohort	Sub	Per	MTD	Dose	DLT
2	9	1	769	769	0
2	10	1	763	763	0
2	11	1	790	790	1
2	12	1	765	765	1
2	13	1	775	775	1
2	14	1	770	0	0
2	15	1	508	508	0
2	16	1	773	0	0

Hierarchical mCRM



Cohort	Sub	Per	MTD	Dose	DLT
1	1	2	566	0	0
1	2	2	564	564	0
1	3	2	450	450	0
1	4	2	573	573	0
1	5	2	565	0	0
1	6	2	565	565	1
1	7	2	568	568	0
1	8	2	474	474	1

Simulations

- Still ongoing
- Less CSE observed
- No impact on the parameters estimates

→ More ethical at no statistical cost

Hierarchical mCRM

- PROS:
  - Same as mCRM
  - Subjects who experienced NT(s) have smaller predicted MTDs → smaller doses in the trial
  - Possible to use info (model) for future trial and / or labeling.

ICH Topic E 4
Dose Response Information to Support Drug Registration

In adjusting the dose in an individual patient after observing the response to an initial dose, what would be most helpful is knowledge of the shape of individual dose-response curves, which is usually not the same as the population (group) average dose-response curve. Study designs that allow estimation of individual dose-response curves could therefore be useful in guiding titration, although experience with such designs and their analysis is very limited.

Hierarchical mCRM

- CONS:
  - Same as mCRM
  - More difficult to put in place, especially if we want to adjust the dose to the subject during the trial.
  - Variability only on intercept parameter
  - Objective: modeling of something we don't want to observe, i.e., toxicities
    - Many mild AEs observed
    - Not considered as toxicities
    - Easy to imagine that they are related (graduation)

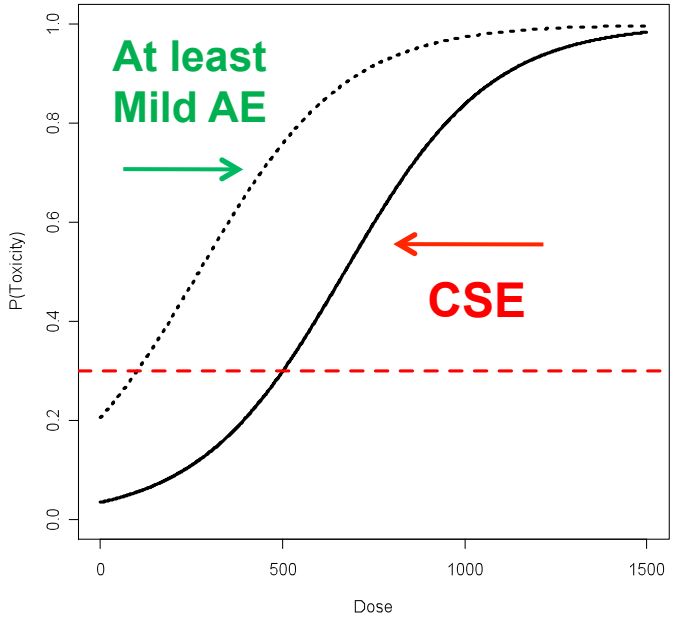
    → Use intensity information to build the model

Multinomial mCRM

- The model:
  - Logistic multinomial model
  - p_{jk} : probability that a patient who receives dose *j* experiences AE of intensity at least *k (→ ordinal)*
  - α1 common to all curves → <u>proportionality</u>

$$\sum_{k=1}^{k=2} pr(AE_k \mid dose_j) = 1$$

$$\text{logit}(p_{jk}) = \alpha_{0_k} + \alpha_1(\text{dose}_j)$$



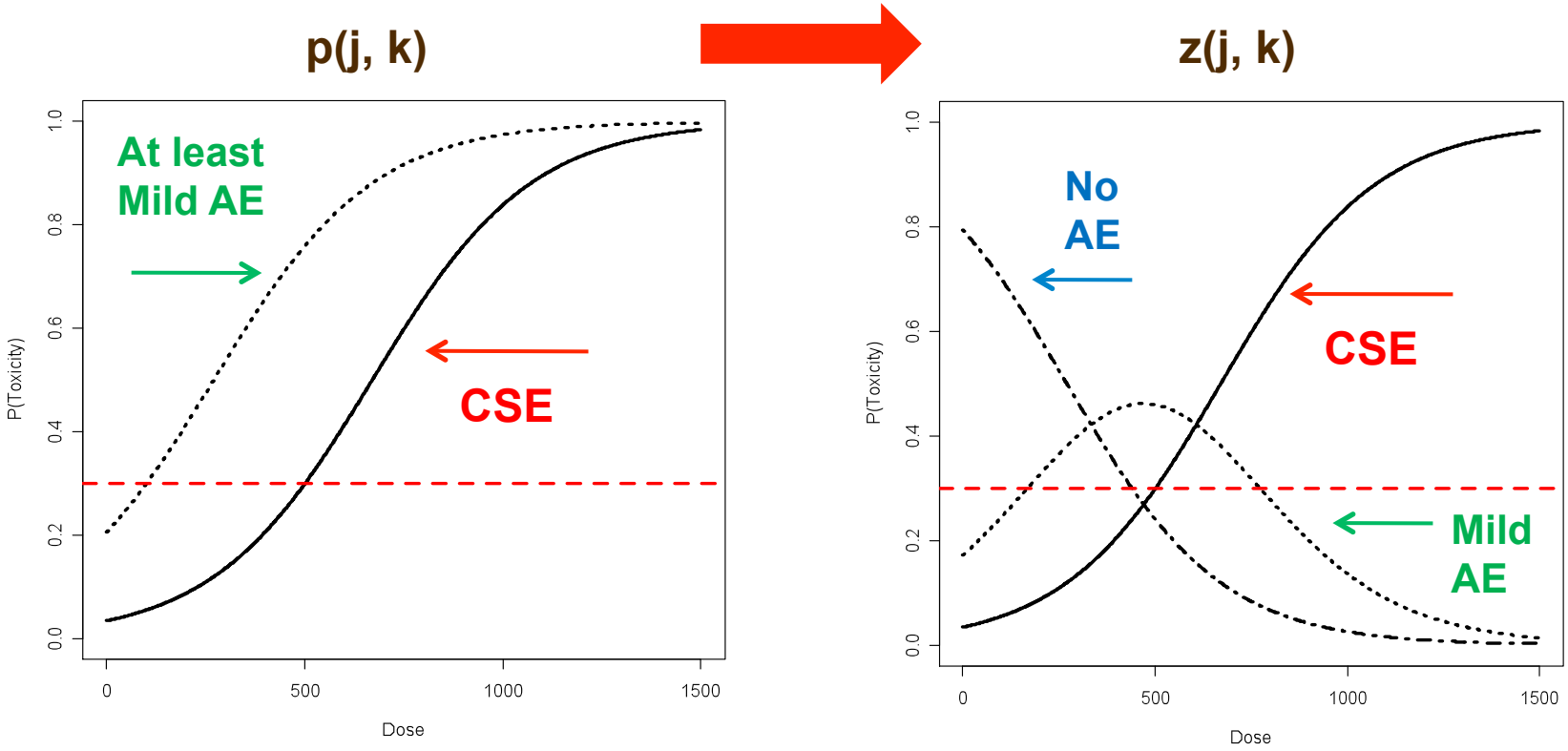
Multinomial mCRM


```
model{
for(j in 1:n.doses) {
   z[j,1]<- 1- p[j,2]          Probability of no AE
   z[j,2]<- p[j,2]-p[j,1]      Probability of mild AE
   z[j,3]<- p[j,1]             Probability of CSE

   n.events[j, 1:3] ~ dmulti(z[j,1:3], n.subject[j])

   logit(p[j, 1]) <- alpha0 + alpha1.p * dose[j]
                                Probability of at least CSE
   logit(p[j, 2]) <- (alpha0 + alpha0bis) + alpha1.p * dose[j]
                                Probability of at least mild AE
 }
alpha0.p ~ dnorm(alpha0.m.prior ,alpha0.v.prior)
alpha1.p ~ dnorm.trunc(alpha1.m.prior, alpha1.v.prior)
alpha0bis ~ dlnorm(alpha0bis.m.prior, alpha0bis.v.prior)
```

Dose Loop

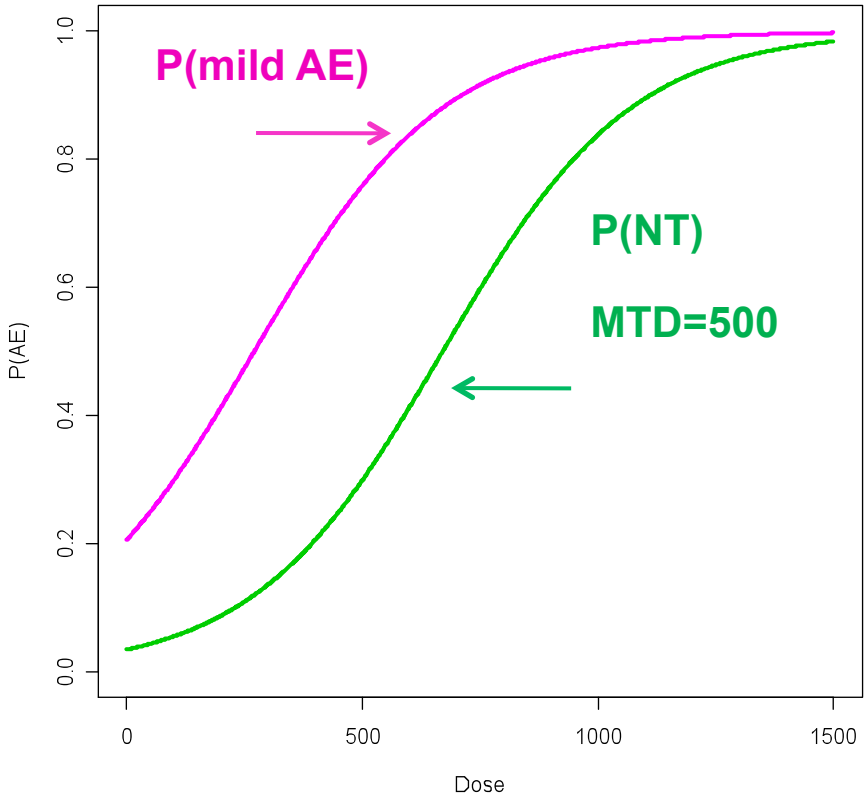
Parameters common for all doses

Multinomial mCRM

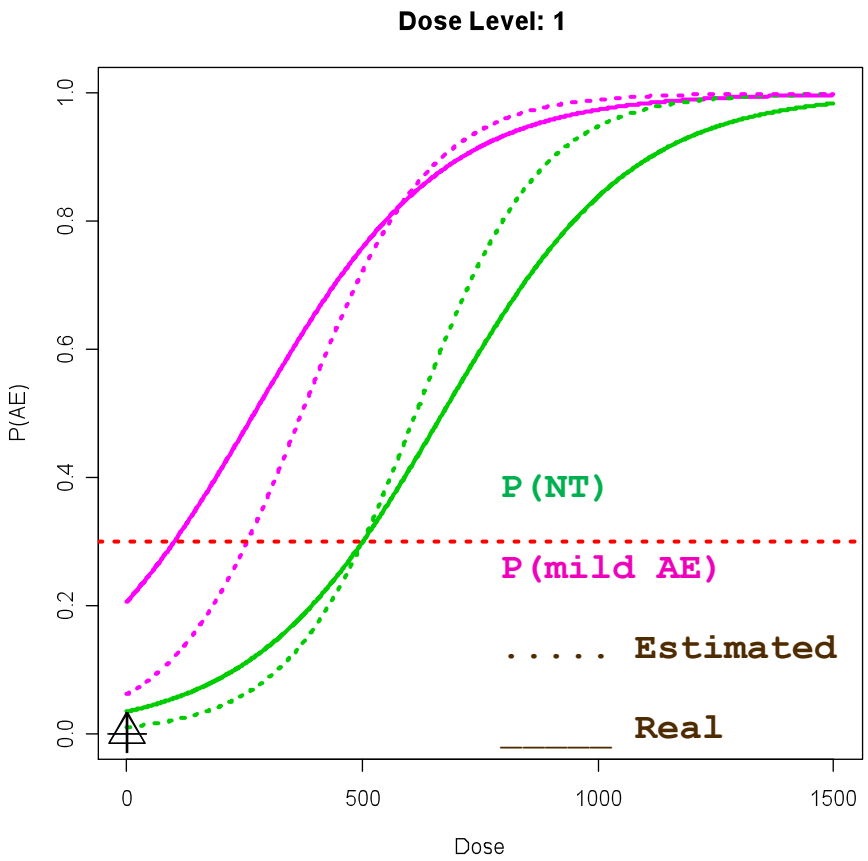


Multinomial mCRM

Maximum step=10



Multinomial mCRM

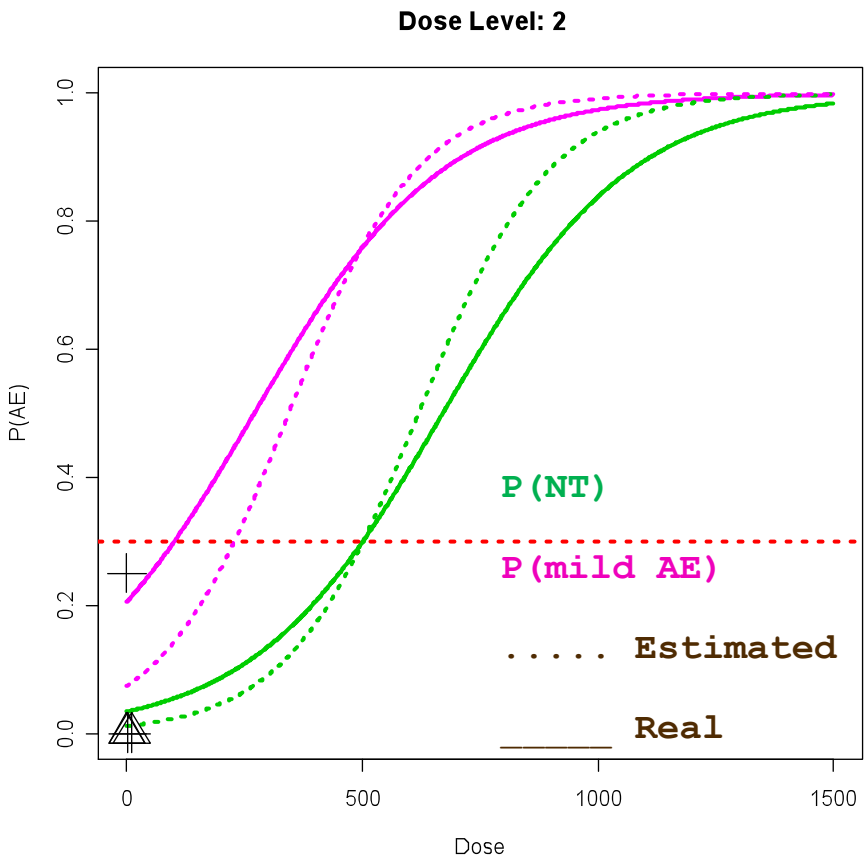


MTD.model=500mg

→ next dose=min(10*1mg, 500mg)

Cohort	Sub	Per	Dose	AE
1	1	1	1	0
1	2	1	0	0
1	3	1	1	0
1	4	1	1	0
1	5	1	1	0
1	6	1	1	0
1	7	1	1	0
1	8	1	0	0

Multinomial mCRM

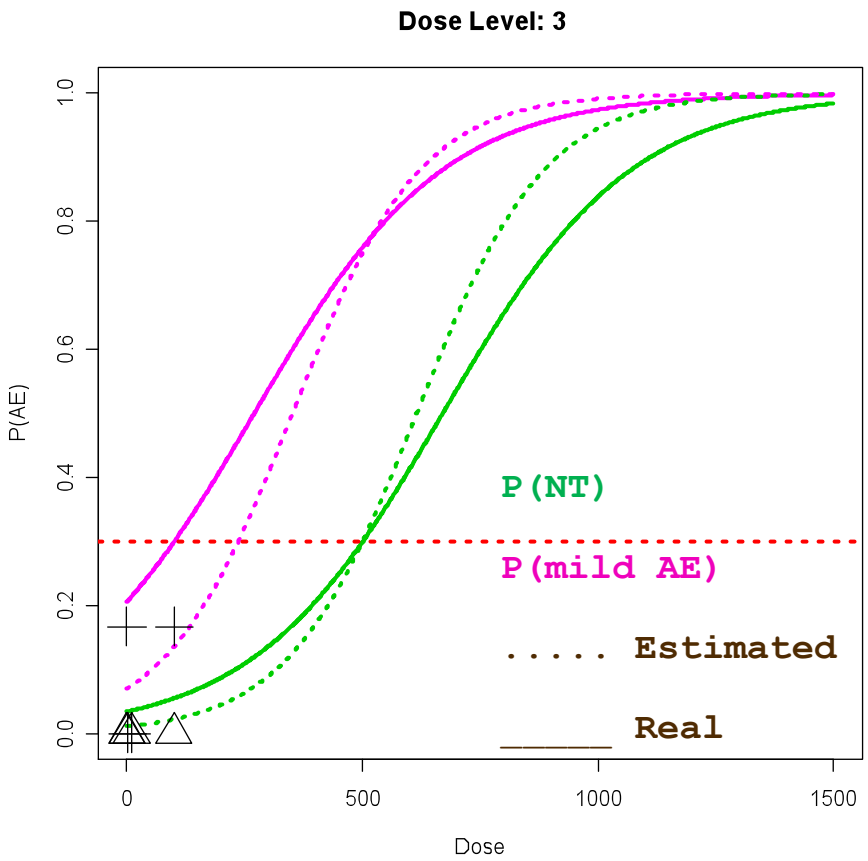


MTD.model=500mg

→ next dose=min(10*10mg, 500mg)

Cohort	Sub	Per	Dose	DLT
2	9	1	10	0
2	10	1	0	mild
2	11	1	10	0
2	12	1	0	0
2	13	1	10	0
2	14	1	10	0
2	15	1	10	0
2	16	1	10	0

Multinomial mCRM

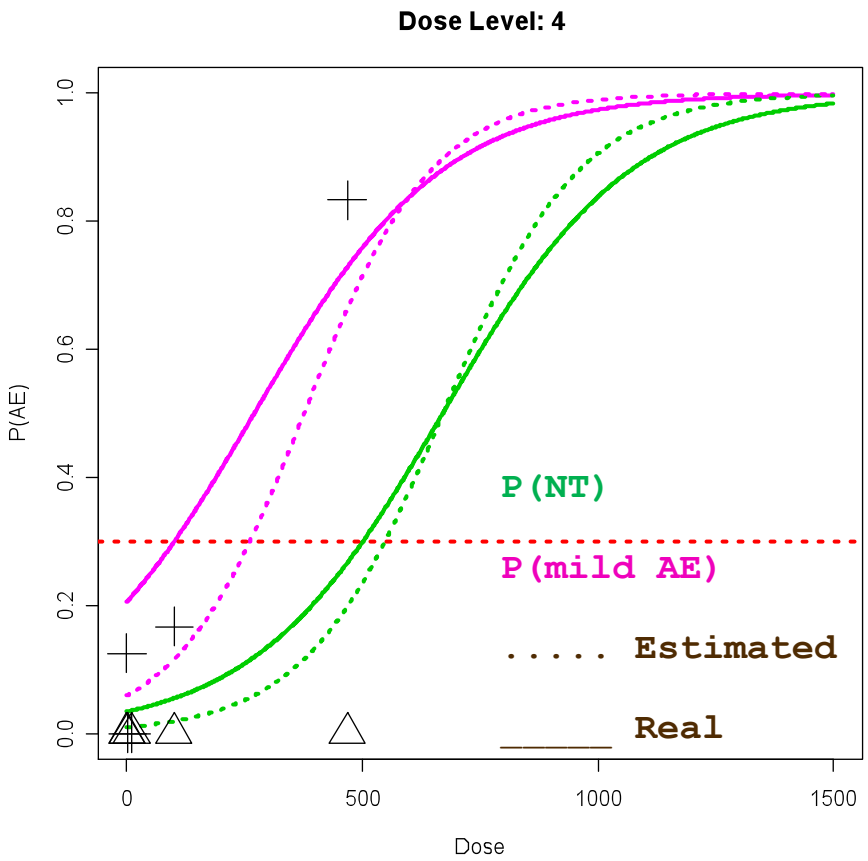


MTD.model=500mg

→ next dose=min(10*100mg, 500mg)

Cohort	Sub	Per	Dose	DLT
1	1	2	0	0
1	2	2	100	0
1	3	2	100	0
1	4	2	100	0
1	5	2	0	0
1	6	2	100	mild
1	7	2	100	0
1	8	2	100	0

Multinomial mCRM

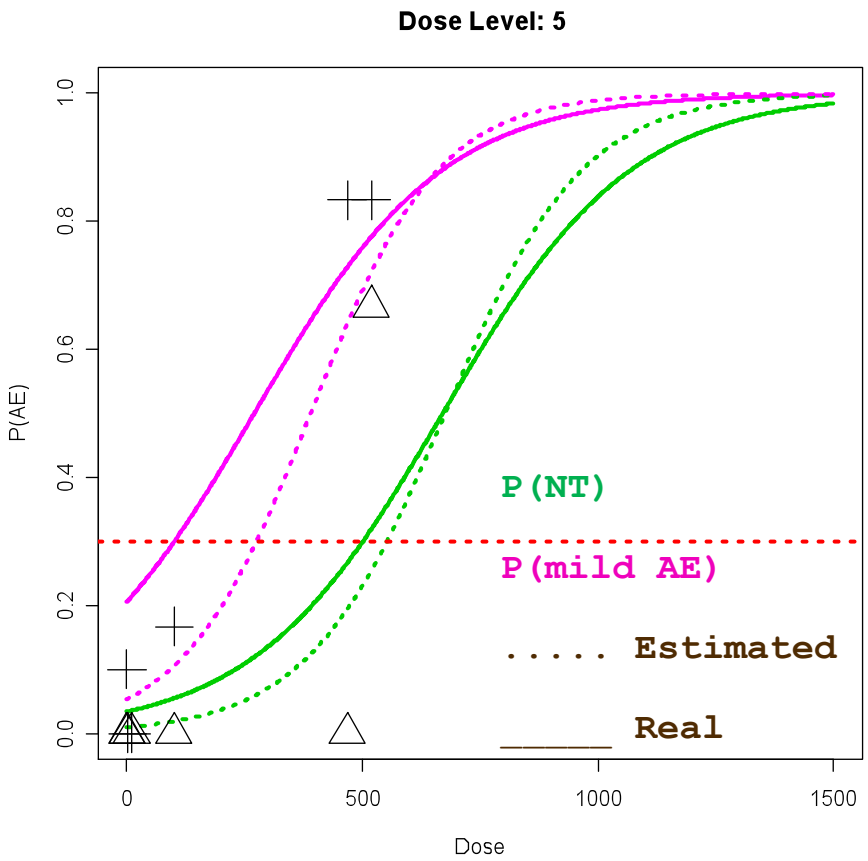


MTD.model=520mg

→ next dose=min(10*100mg, 525mg)

Cohort	Sub	Per	Dose	DLT
2	9	2	500	mild
2	10	2	500	mild
2	11	2	500	mild
2	12	2	500	mild
2	13	2	500	mild
2	14	2	0	0
2	15	2	500	0
2	16	2	0	0

Dose Escalation: mCRM



MTD.model=525mg

Cohort	Sub	Per	Dose	DLT
1	1	3	520	mod
1	2	3	520	mod
1	3	3		0
1	4	3	520	0
1	5	3	520	mod
1	6	3	520	Mod
1	7	3	0	0
1	8	3	520	mild

Multinomial mCRM

- PROS:
  - Same as mCRM
  - Use of all information on AE (from mild to moderate)
- CONS:
  - Strong hypothesis of proportionality
  - Impact of proportionality assumption? (very few NTs)

Conclusions

- Estimation possible of MTD
- With sufficient accuracy
- More ethical method by approaching the MTD while limiting the subject's risk
  - Individualize dose-adjustment possible
  - Use of « tolerable » AEs to learn about non tolerable ones
- To do: risk assessment (what adjustment combination have the best impact) via trial simulations

References

- O'Quigley & al., Continual Reassessment Method: A Practical Design for Phase I Clinical Trials in Cancer Biometrics. 1990 Mar, 46(1):33-48.
- Garret-Mayer E., Understanding the Continual Reassessment Method for Dose Finding Studies: An Overview for Non-Statisticians. Johns Hopkins University, Dept. of Biostatistics Working Papers. 2005, Working Paper 74.
- Tibaldi F., Beck B. & Bedding A., Implementation of a Phase 1 Adaptive Clinical Trial in a Treatment of Type 2 Diabetes. Drug information journal. 2008, 42(5): 455-465.