3+3 Consensus Meeting

Introducing Model Based Dose Escalation in a Pharmaceutical Environment

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Agenda

- Background
- Challenge
- Actions
- Outcome

Background

- The objective of a SAD study is to find range of safe doses for further investigation in MAD studies
  - Low starting doses
  - Dose escalation in small cohorts
  - Logarithmic increases in dose
- Traditional oncology 3+3 studies provide a simple, practical, quick rule for escalation to the next planned dose and definition of MTD

3+3 Traditions

- Practical
  - Boiler plate text for protocol
  - No statistician needed at Safety Review Meetings
  - No understanding of statistics needed
- Simple
  - Simple dose escalation rules
  - Allows clinical interpretation of ‘tolerated’
- Quick
  - Everybody understands the design

Other Options

- Other options have been looked into due to the inefficiency of the 3+3 design
  - Continuous Reassessment Model (CRM)
  - Modified Therapeutic Probability Interval (mTPI)
  - Bayesian Logistic Regression Model (BLRM)
  - Bivariate modelling of toxicity and efficacy (Thall and Simon approach)
  - Many other themes
- A “Practical CRM” approach based on BLRM

Practical CRM Approach

- Keep the practical nature of the N+N approach
  - Low starting doses
  - Dose escalation in small cohorts
  - Logarithmic increases in dose
- Choosing a level of toxicity that is relevant to the indication, eg, TD20, TD05
- Decide the next dose based on an updated estimate of the toxicity response curve

Bayesian Logistic Regression Model

- We can model the toxicity response curve using a logistic model relating the P(toxicity), p_i , to the dose x_i

$$\text{logit}(p_i) = \alpha + \beta \ln(x_i)$$

- Using a Bayesian approach we can
  - use informative priors for α and β
  - predict the P(toxicity) after each cohort
  - use this to choose the next dose

Example Practical CRM Study

- Choose a set of “nominal” doses for escalation and the cohort size
  - 25, 50, 100, 200, 400
  - Cohort size = 3
- Choose a set of “possible” doses that could be used
  - 25, 50, 100, 150, 200, 250, 300, 350, 400
- Choose a level of toxicity to estimate
  - Dose at which 20% of patients experience toxicity (TD20)
- Provide some prior information about the toxicity response curve from previous or pre-clinical work
  - Estimated TD20= 100 and TD50 = 300

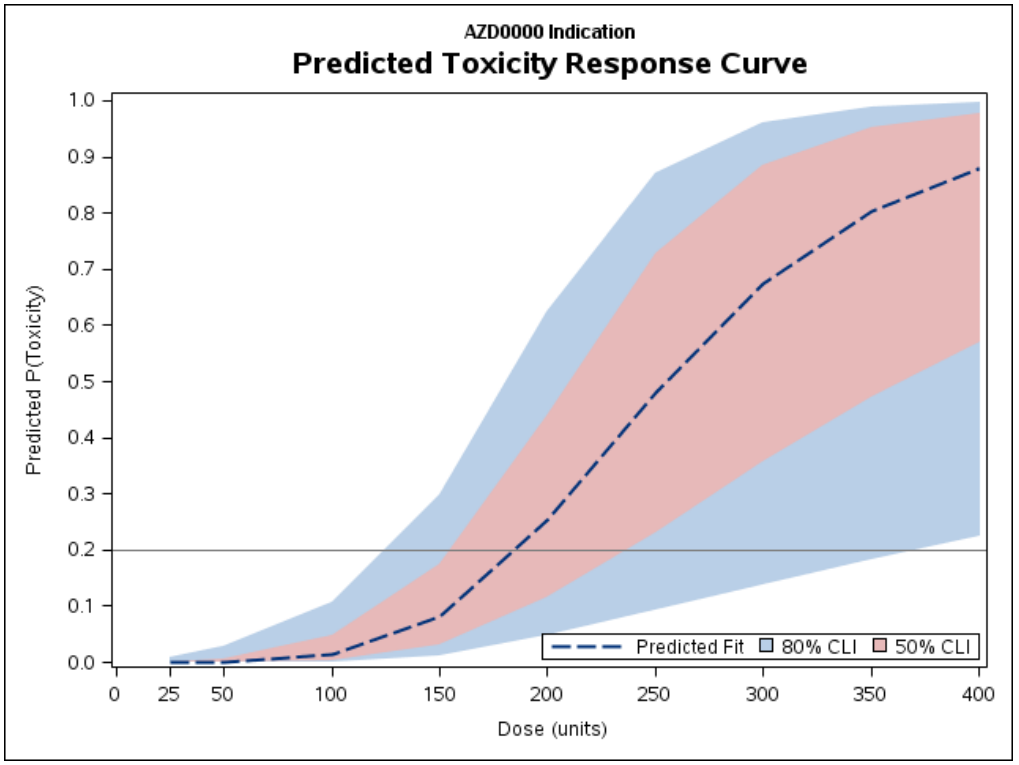
Example Practical CRM Study

- Initiate the study, if no DLTs, escalate through the “nominal” doses
- After seeing the first DLT in a cohort
  - update the toxicity response curve
  - predict the P(tox) at each “possible” dose
  - choose the next dose from the set of “possible” doses based on the predicted P(tox)
    - Variance gain
    - Patient gain
    - Determinant gain (D-Optimality)
    - Other loss functions

Example Practical CRM Study

Data so far

Dose	N	DLTs
25	3	0
50	3	0
100	3	0
200	3	1

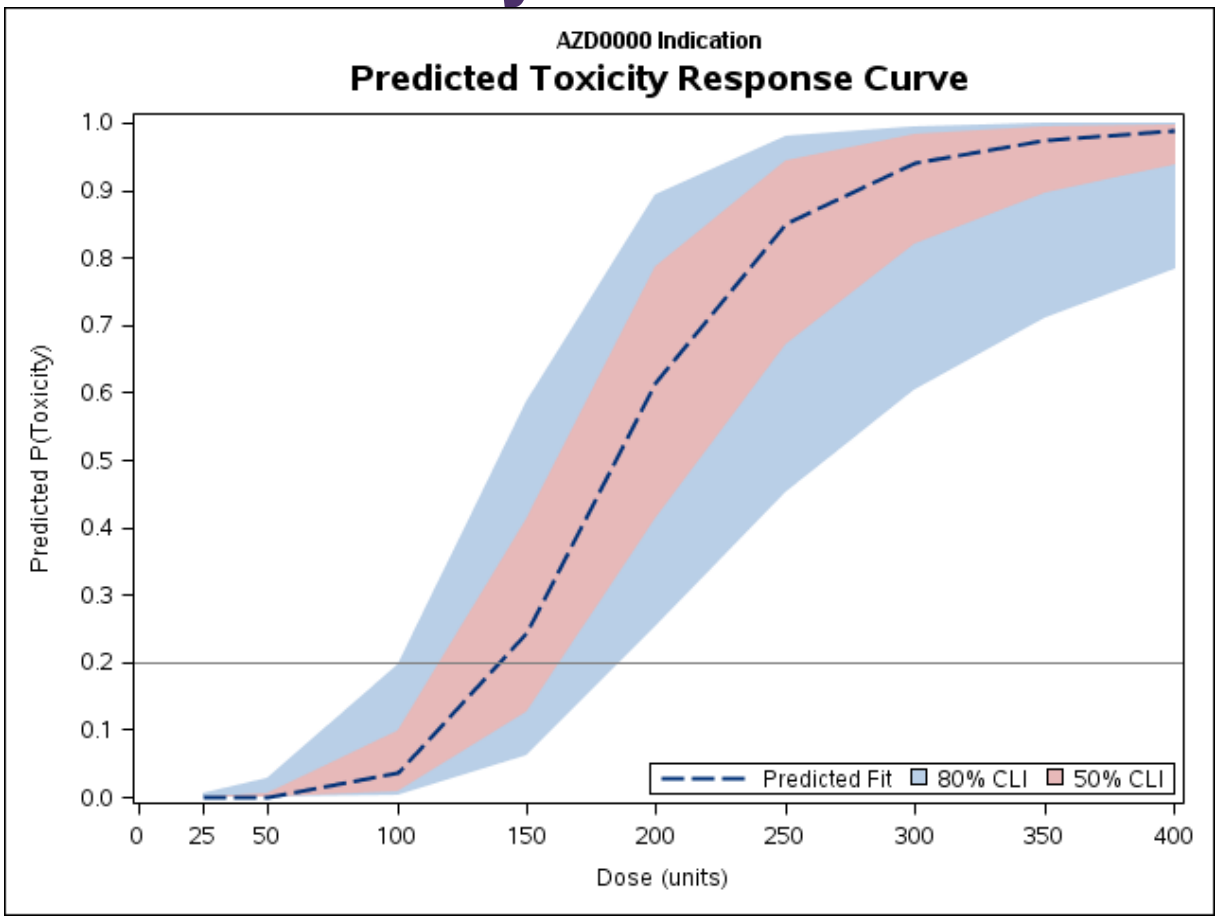


Estimated TD20=188 (95%CrI: 95 - 2232)
Next dose = 200

Example Practical CRM Study

Data so far

Dose	N	DLTs
25	3	0
50	3	0
100	3	0
200	3	2



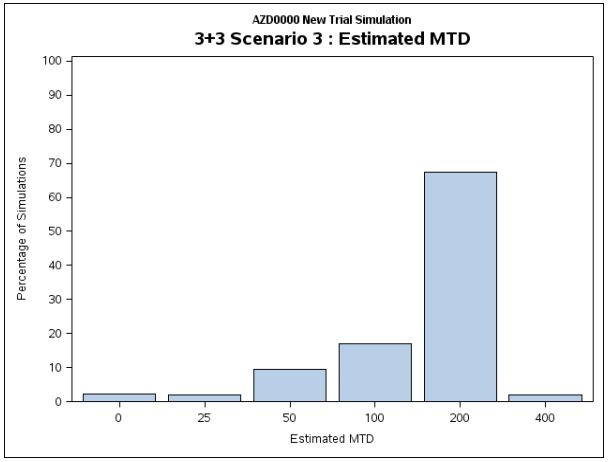
Estimated TD20=143 (95%CrI: 76 - 235)
Precision reached

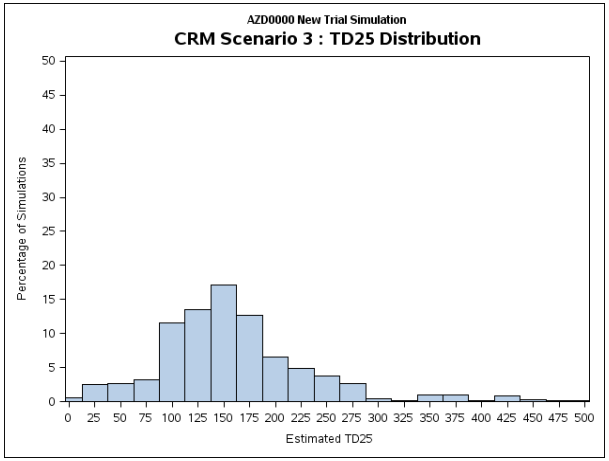
Practical CRM Safety Rules

- We need some additional rules for safe dose escalation
  - Never choose a dose more than double the previous dose
  - Never choose a dose where the current estimate of P(Tox) > 0.50
  - Do not repeat a dose more than once
- Stop escalation when
  - maximum dose or maximum sample size has been reached
  - TD20 precision has been reached (eg Ucl/Lcl < 5.0)

Performance

- The Practical CRM has improved performance
  - More precise estimation of MTD
  - More patients at tolerable doses
  - Sample size
  - Increased flexibility of dosing, when needed
- It can be generalised
  - Different definitions of MTD can be used
  - N per cohort can be altered
  - It can be altered to a model for efficacy e.g. Bayesian EMax Model





Concerns

- Some staff do not like this move away from tradition
  - investigators
  - ethics committee
  - regulators
  - journal reviewers
- Some welcome the move
  - benefit to patients
  - quicker trials
  - better estimates of MTD
- All are concerned with
  - more work in study design stage
  - slowing down study starts
  - involving statisticians during the study

Addressing the Concerns

- Protocols are specified as before, but with a change to the dose escalation rule section (template text provided)
- Simple approach to setting prior distributions
- No waiting for statisticians
  - We can generate a “playbook” for each cohort for each possible outcome.
- Designs can be simulated to show benefits compared to 3+3 design
- We can choose the best based on operating characteristics

Current Status

- Communicating the science
  - presentation at internal symposia
  - retro-fitted a previous study
  - Practical CRM workshop at internal symposia
- Demonstrating the practicality
  - software for simulation and analysis
  - three studies currently piloting new approach
  - compare performance at design stage

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