Bridging the gap with the non-statistical community - what sort of information should we be communicating and discussing?

Alun Bedding PhD., Principal Statistical Scientist

Roche

Background and what the Clinician really wants

N-CRM (Brief)

Example Study

Doing the analysis

Conclusions

Background - 3+3 vs N-CRM

- Many CRM methods have been proposed
  - N-CRM is a good one (ref below)
  - We know this is better than 3+3!
- Implementation of N-CRM is the challenge
  - 3+3 or modified 3+3 used for a long time
  - Investigators may be wary
  - Statistician has short time to turn around model for dose escalation decision

Beat Neuenschwander, Michael Branson and Thomas Gsponer, 'Critical aspects of the Bayesian approach to phase I cancer trials', *Statistics in Medicine*, 27:2420-2439 (2008)

What is Important to the Non-Statistician?

- 3+3 has poor statistical properties
  - Tends to treat patients at low and inefficacious doses
  - Not model based
  - Underestimates the MTD
  - But a statistician is not needed

- Can I escalate to the doses of interest quicker while maintaining safety?
- Do I get a good estimate of my MTD (maybe with smaller numbers)?
- Can it be implemented easily?
- Don't like a black box
- Show me the benefit Mr. Statistician !!!!!

Managing Change

- What-if scenarios:
  - Compare actual trial decisions from 3+3 to CRM dose recommendations
- Simulations
  - To understand how CRM performs under various scenarios in comparison to 3+3
- Have easy to use software to do the implementation

Roche

Background and what the Clinician really wants

N-CRM (Brief)

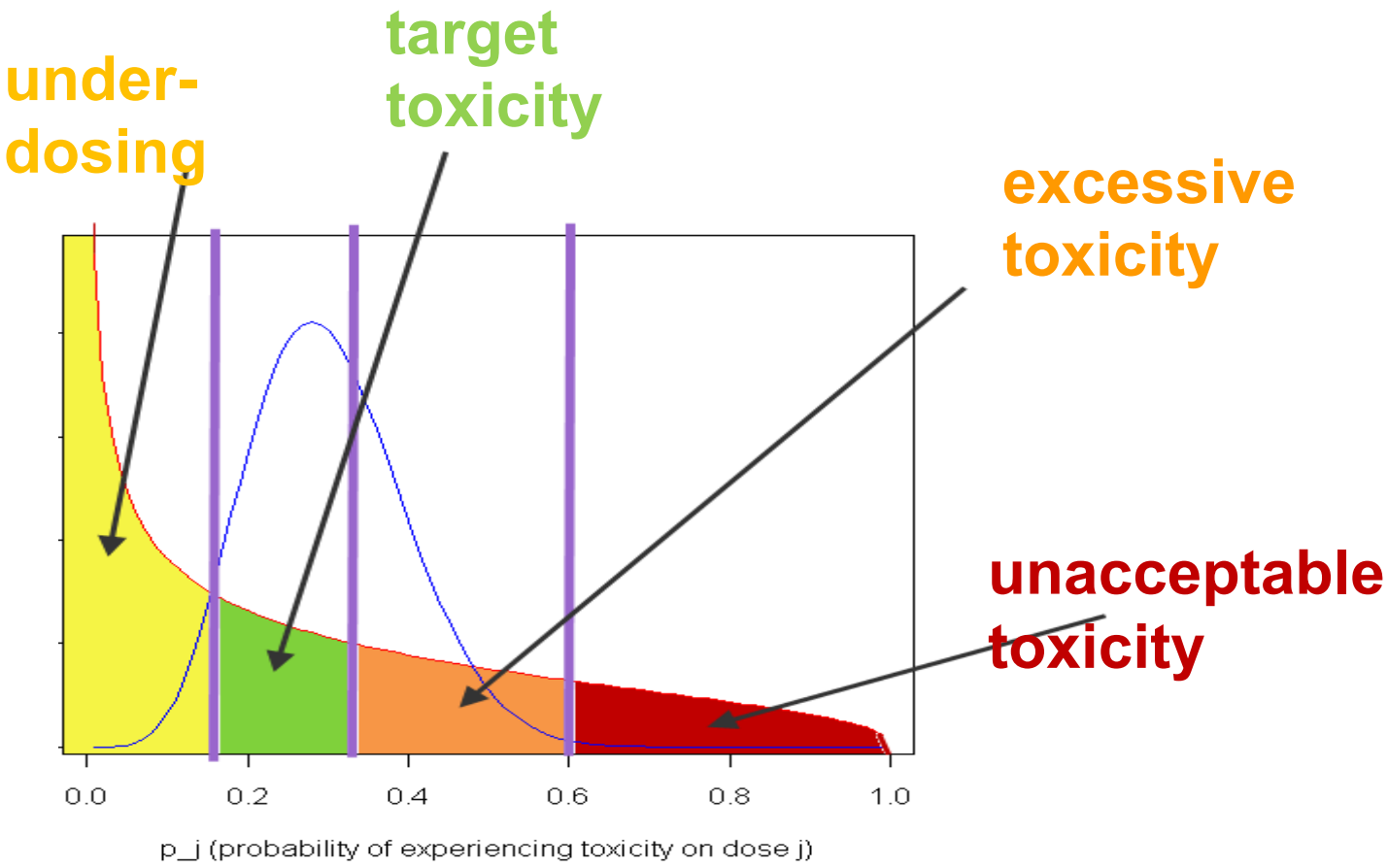
Example Study

Doing the analysis

Conclusions

N-CRM: Expectation of toxicity

For each dose, we evaluate the probability that the true toxicity of a dose rate lies in one of 4 toxicity intervals ….



Background and what the Clinician really wants

N-CRM (Brief)

Example Study

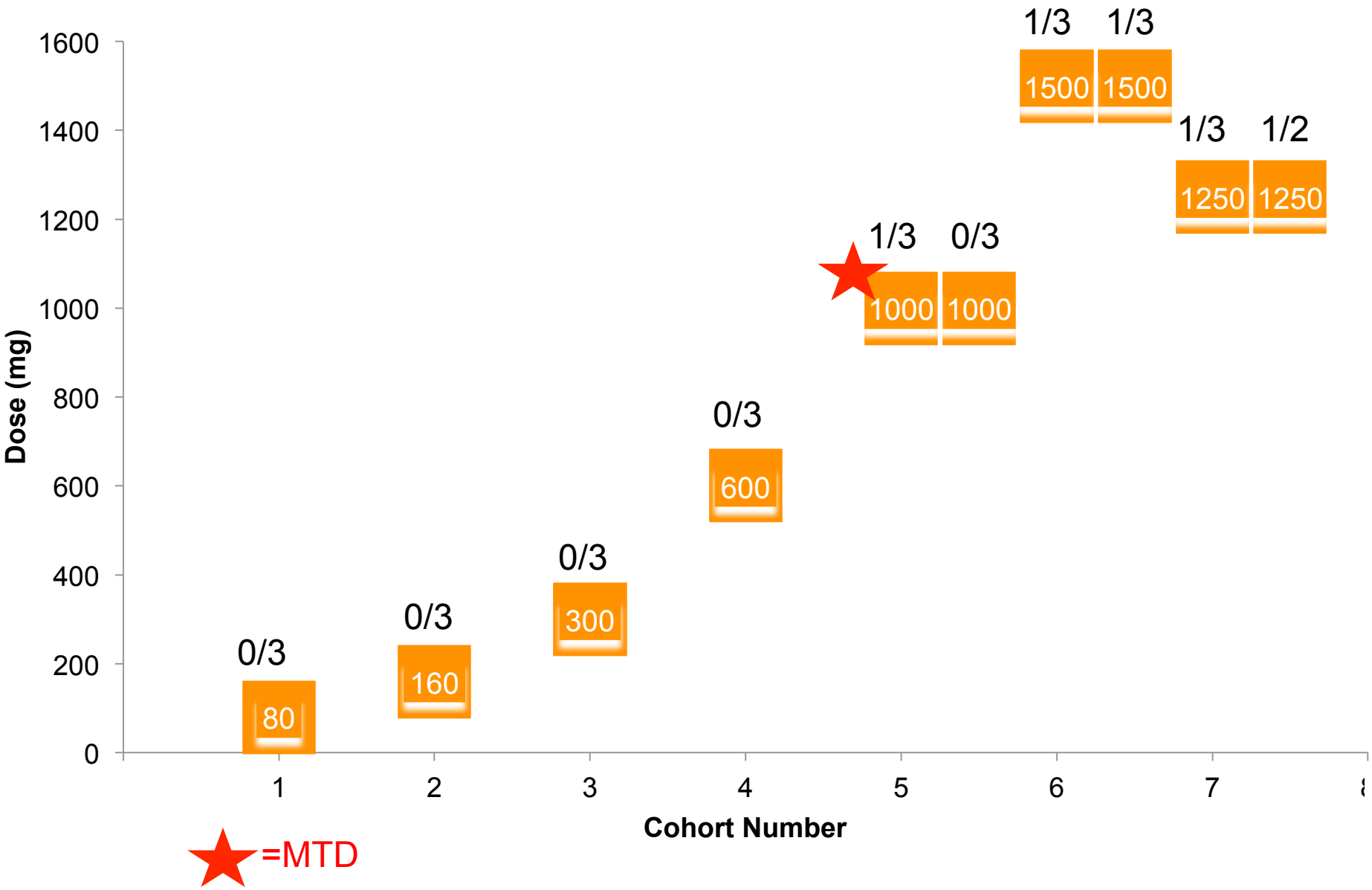
Doing the analysis

Conclusions

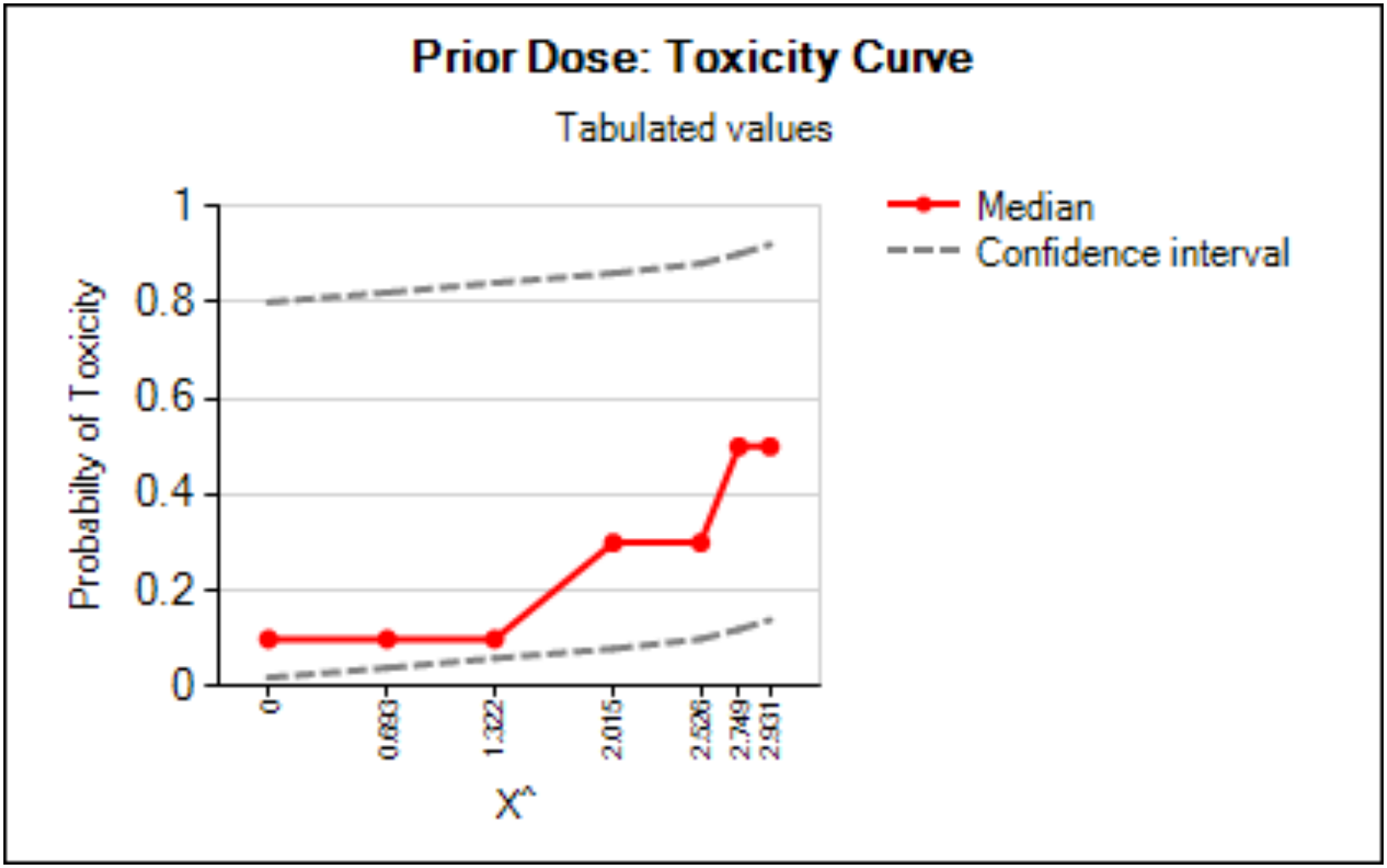
Example Study

- Phase I oncology study
- 7 doses (6 initial but with one added)
- Doses used in the trial
  - 80, 160, 300, 600, 1000, 1500 (1250 added) mg BID
- Objective – find the MTD
- Allow CRM to allow skipping of doses

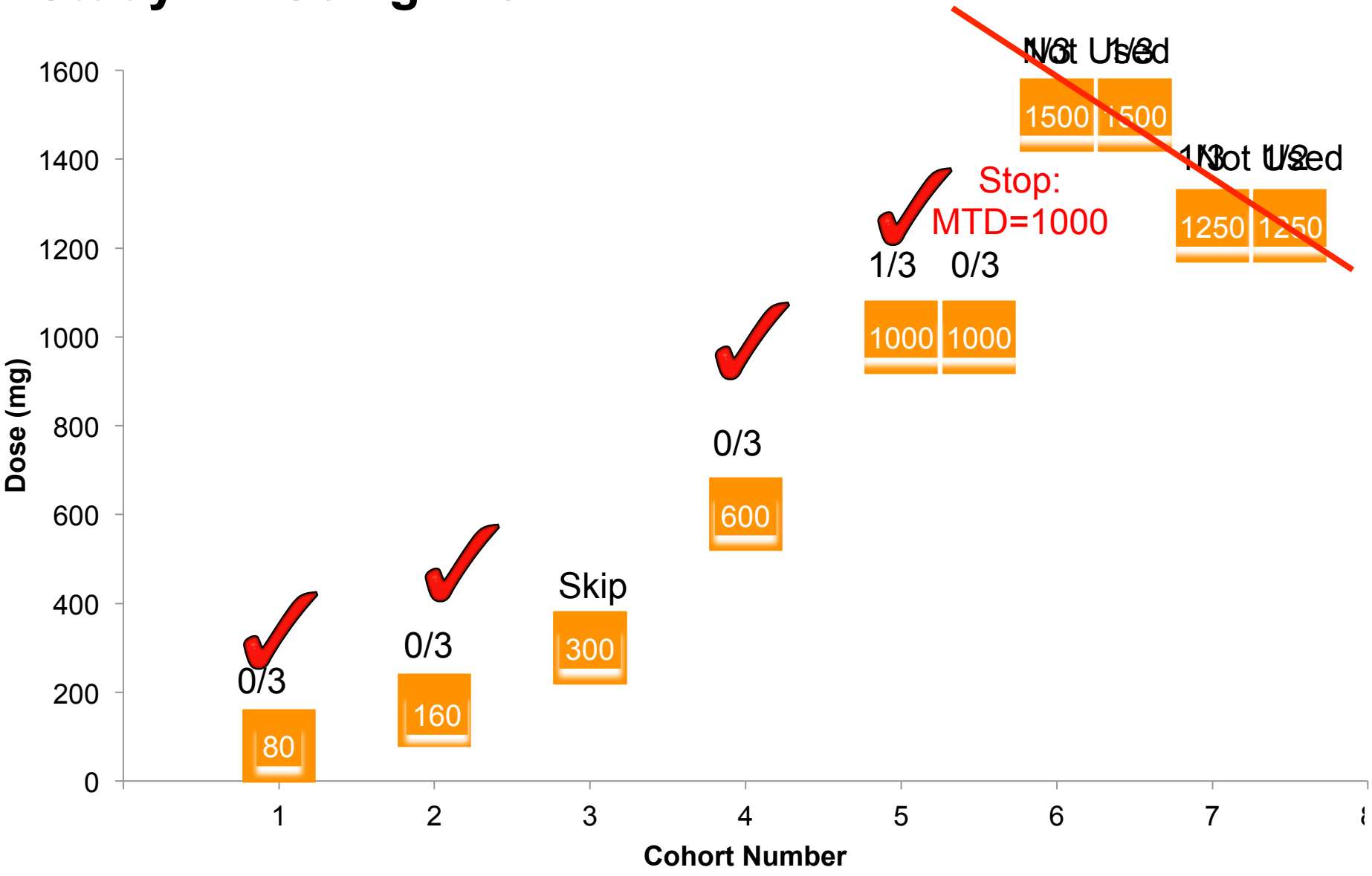
Actual Study – Actual Decisions



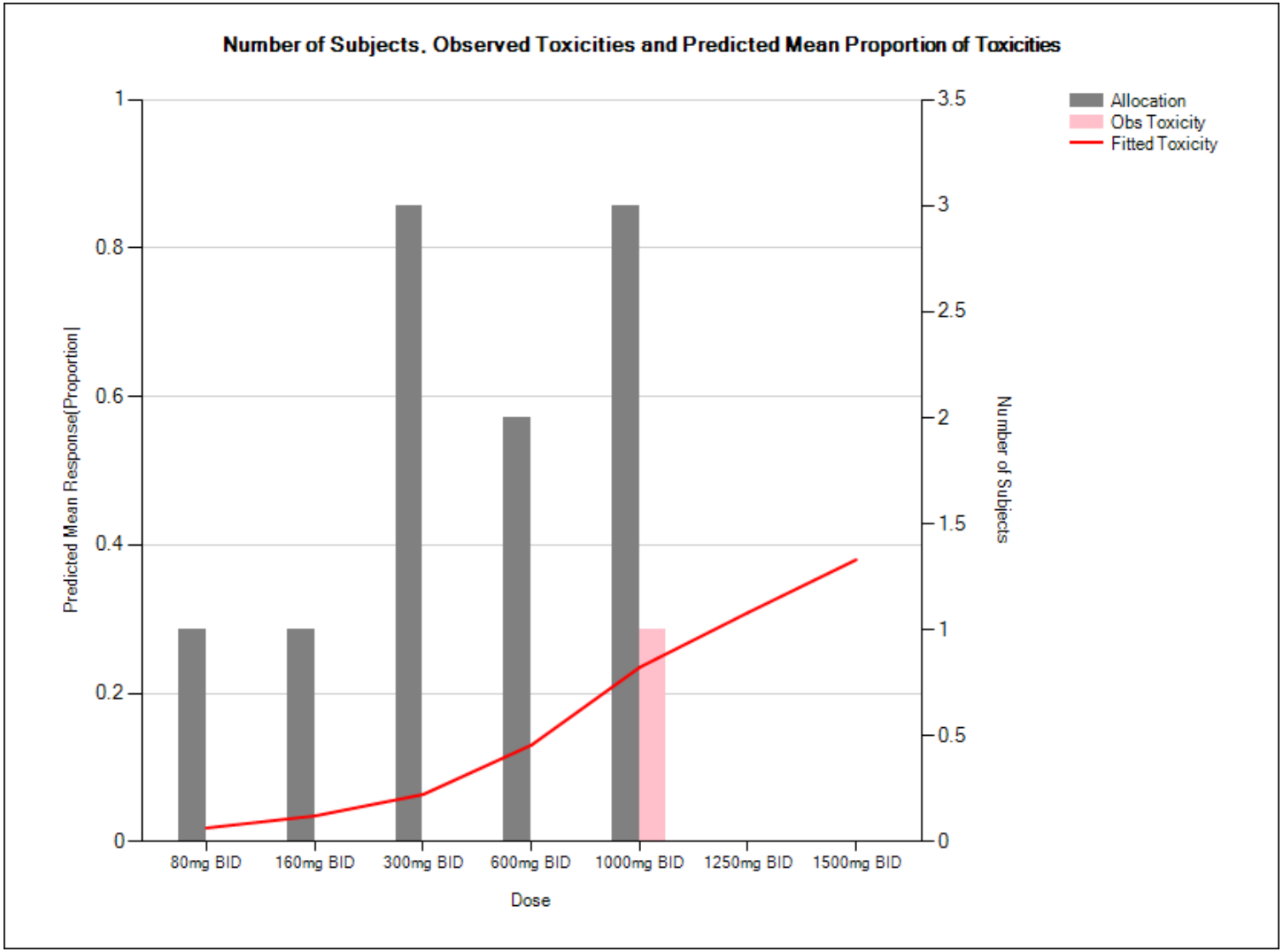
Prior Expectation of the Probability of Toxicity



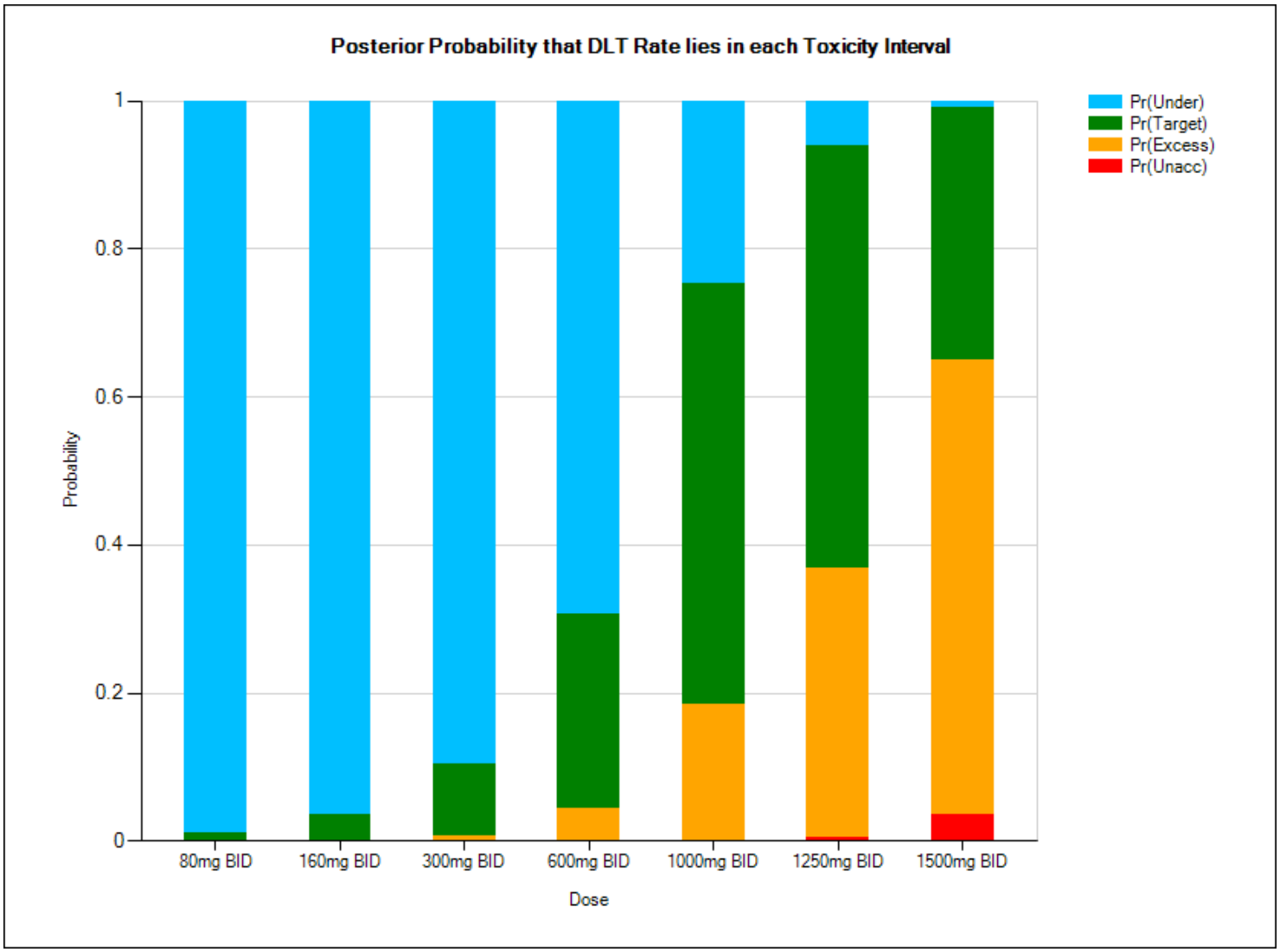
Study 1 – Using N-CRM



Estimated Toxicity Curve after 3 Patients Dosed at 1000mg(1/3 DLT's)

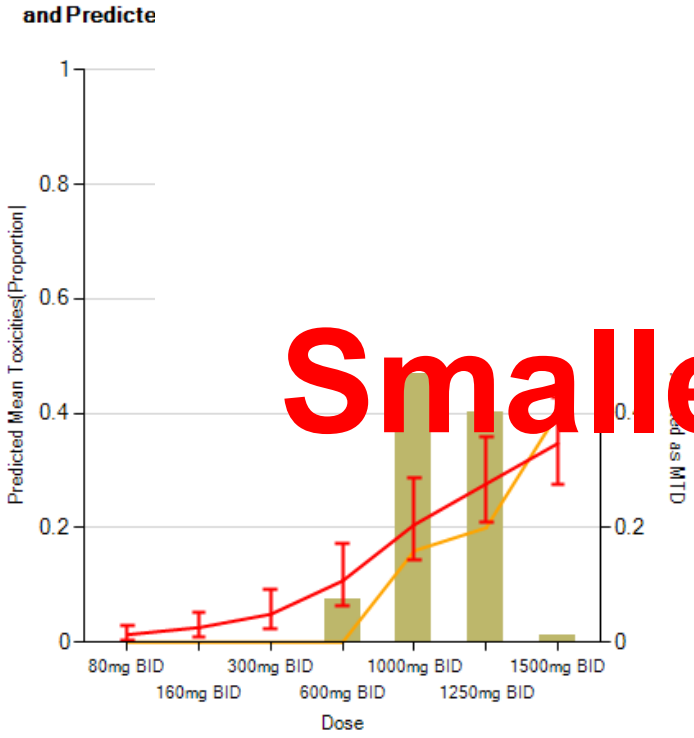


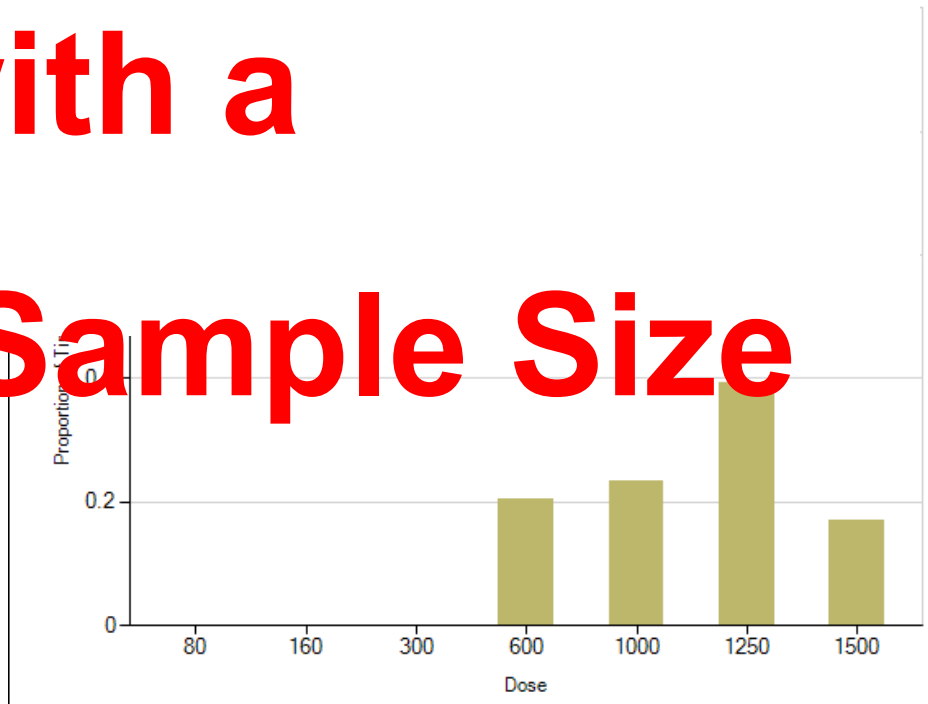
Probabilities of falling into toxicity bands after cohort 5a (1/3 DLT's at the 1000 mg BIDdose)



Simulations under Observed Tox Profile

Better Estimation with a Smaller Sample Size





Background and what the Clinician really wants

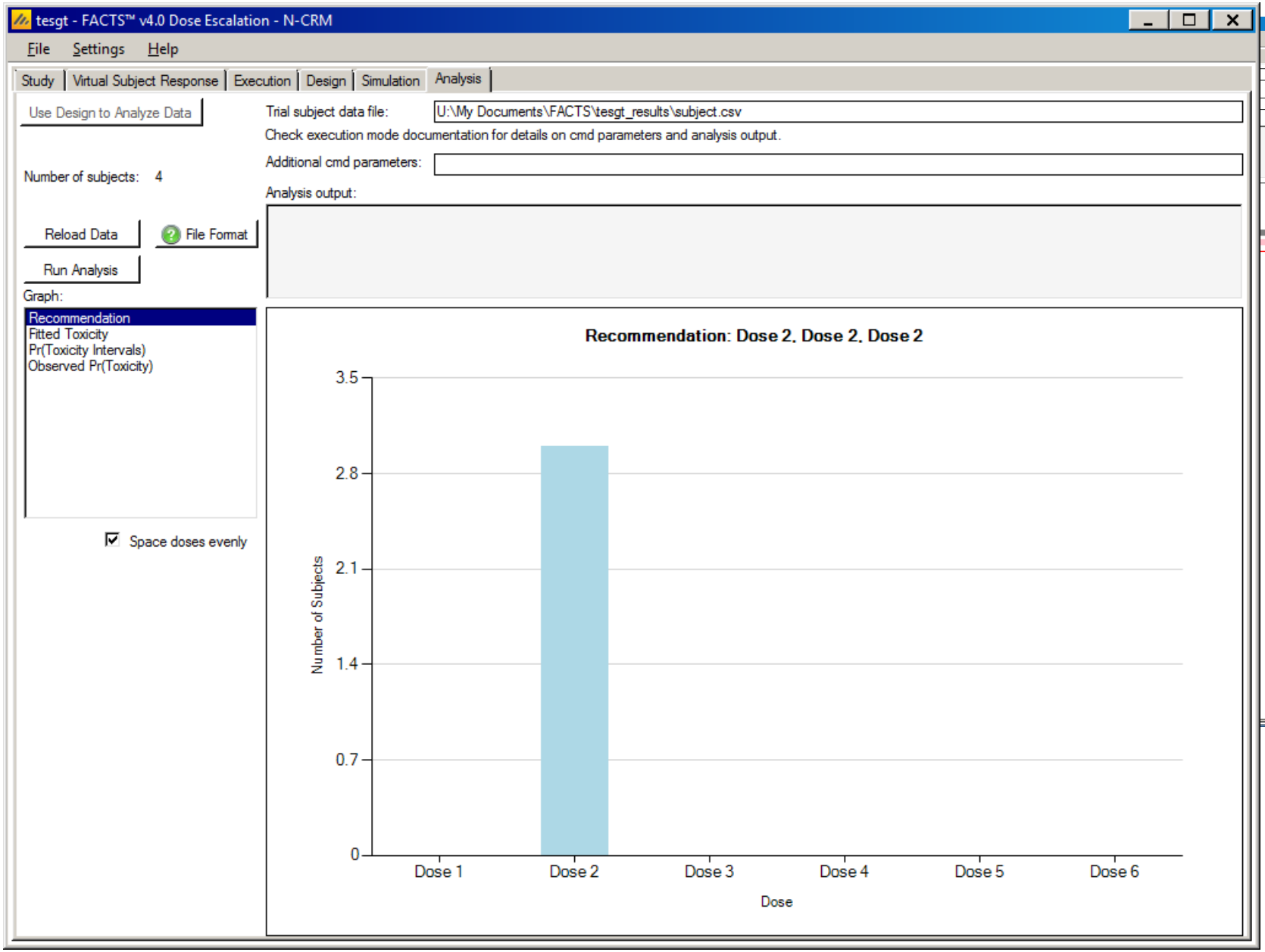
N-CRM (Brief)

Example Study

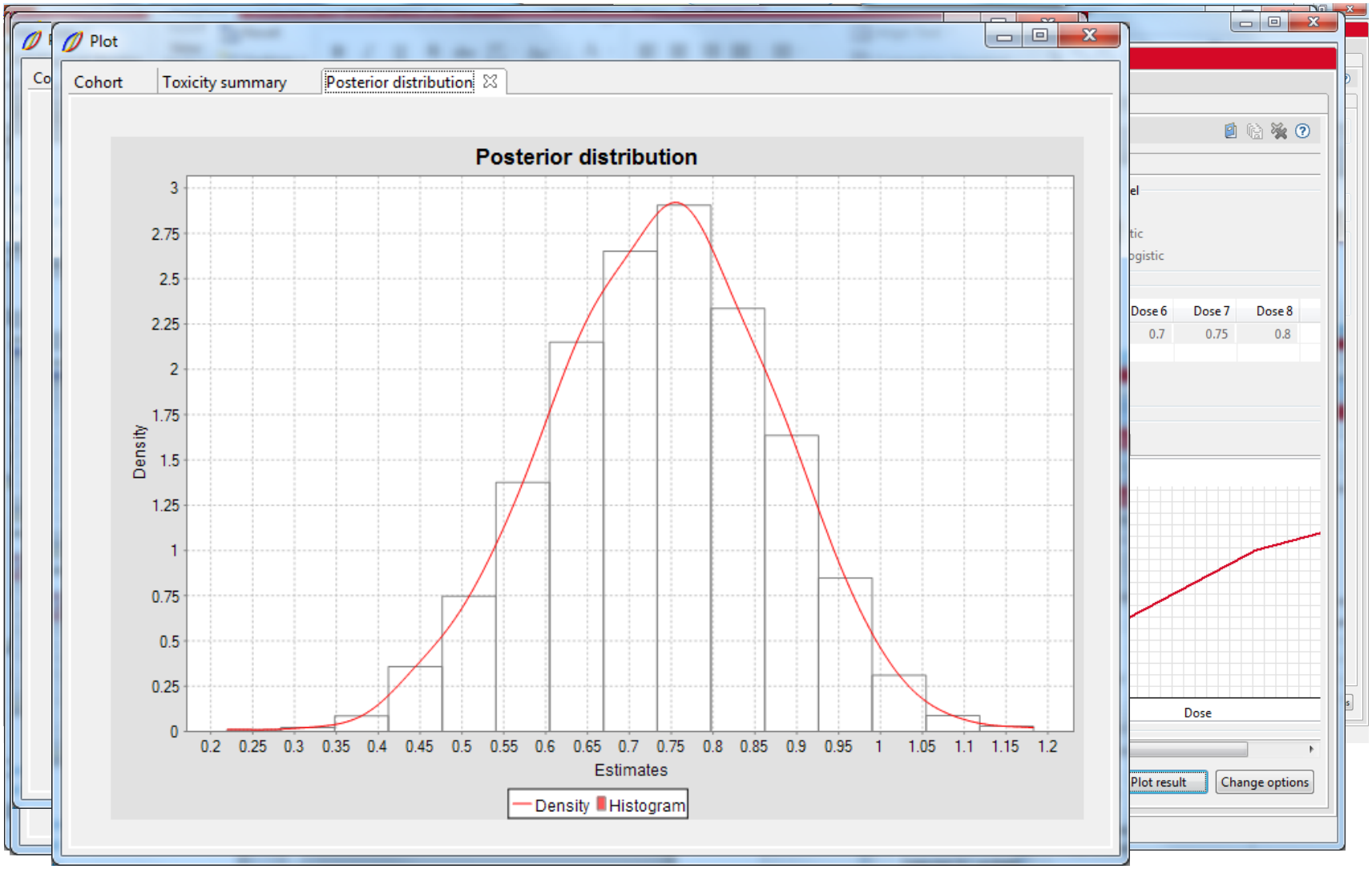
Doing the analysis

Conclusions

Analysis Can be Done in FACTS and Addplan



Analysis Can be Done in FACTS and Addplan



Roche

Background and what the Clinician really wants

N-CRM (Brief)

Example Study

Doing the analysis

Conclusions

Conclusions – Change Management

- To successfully switch to N-CRM, clinicians and statisticians need to feel comfortable with it
  - Show what would have happened in past studies
  - Simulations
  - Show example graphs for dose escalation decisions
  - Allow for clinical knowledge to override the statistical recommendation
- Statisticians need to feel comfortable too
  - Give statisticians time and tools for doing simulations and working with the prior
- Upper management support critical

Doing now what patients need next