DOES LAGGING MEAN LOSING? A CONTINUAL REASSESSMENT METHOD INVESTIGATION

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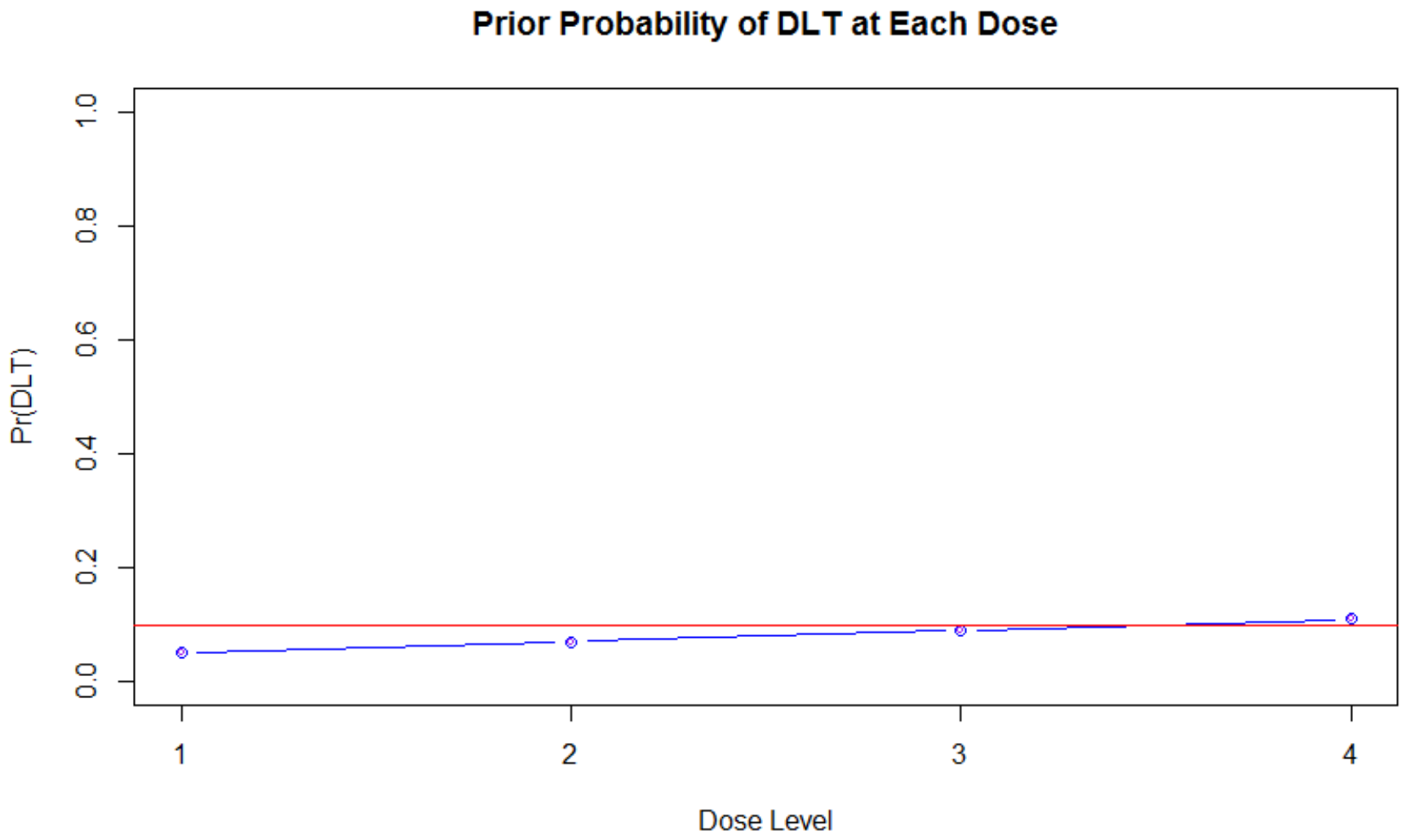
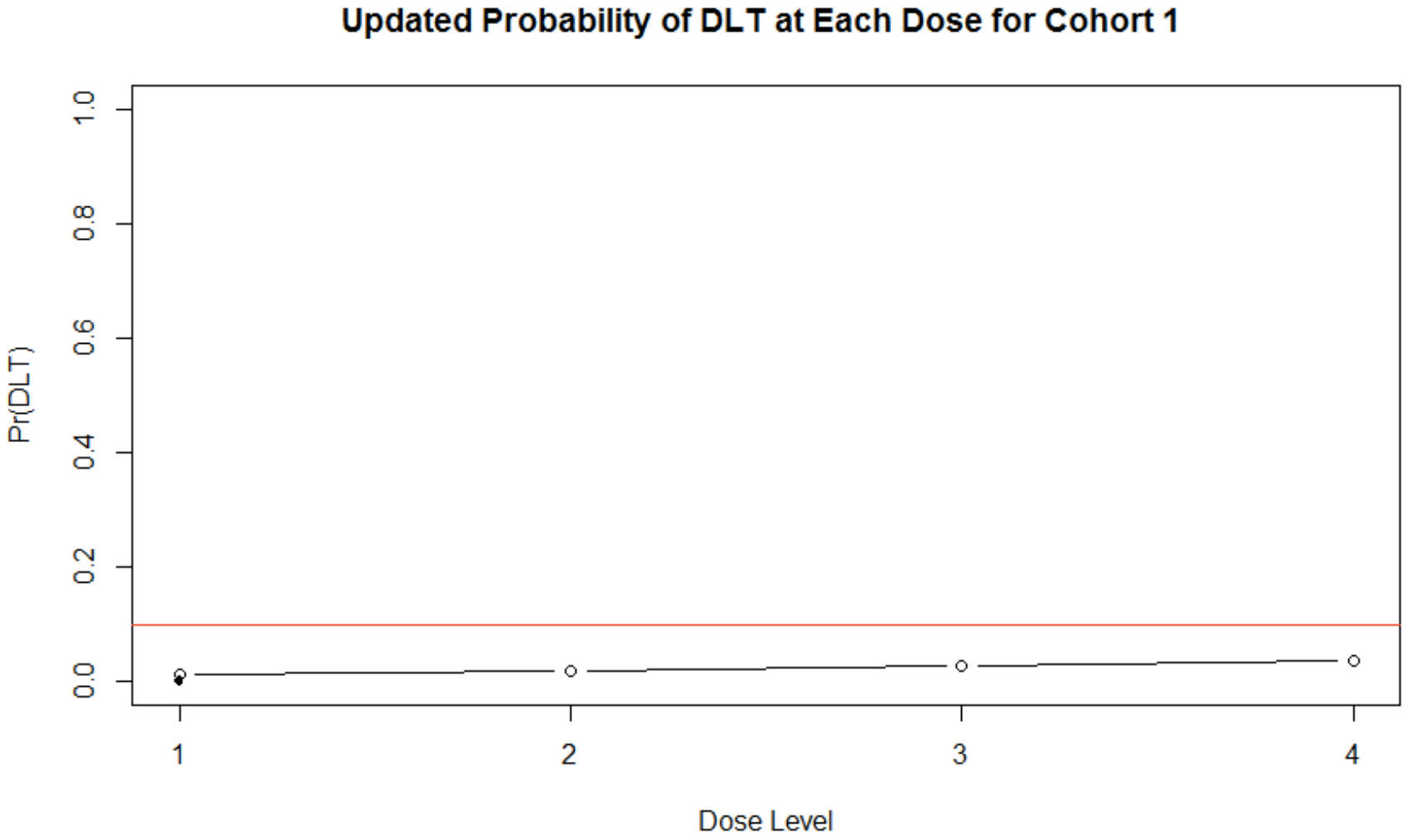
What is the CRM?

- Continual Reassessment Method (CRM)
  - Phase I adaptive dose-finding study design
  - Utilizes previous subjects' results to recommend a dose for the next cohort of subjects
- The dose chosen at the end of the study is the Maximum Tolerated Dose (MTD)
- Prior information gained from physician to produce *A priori* dose-toxicity curve
  - Dose Limiting Toxicities (DLTs)
  - Target toxicity rate
- Curve is continuously updated after data from each cohort is gathered

A Priori Dose-Toxicity Curve



Updated Dose-Toxicity Curve



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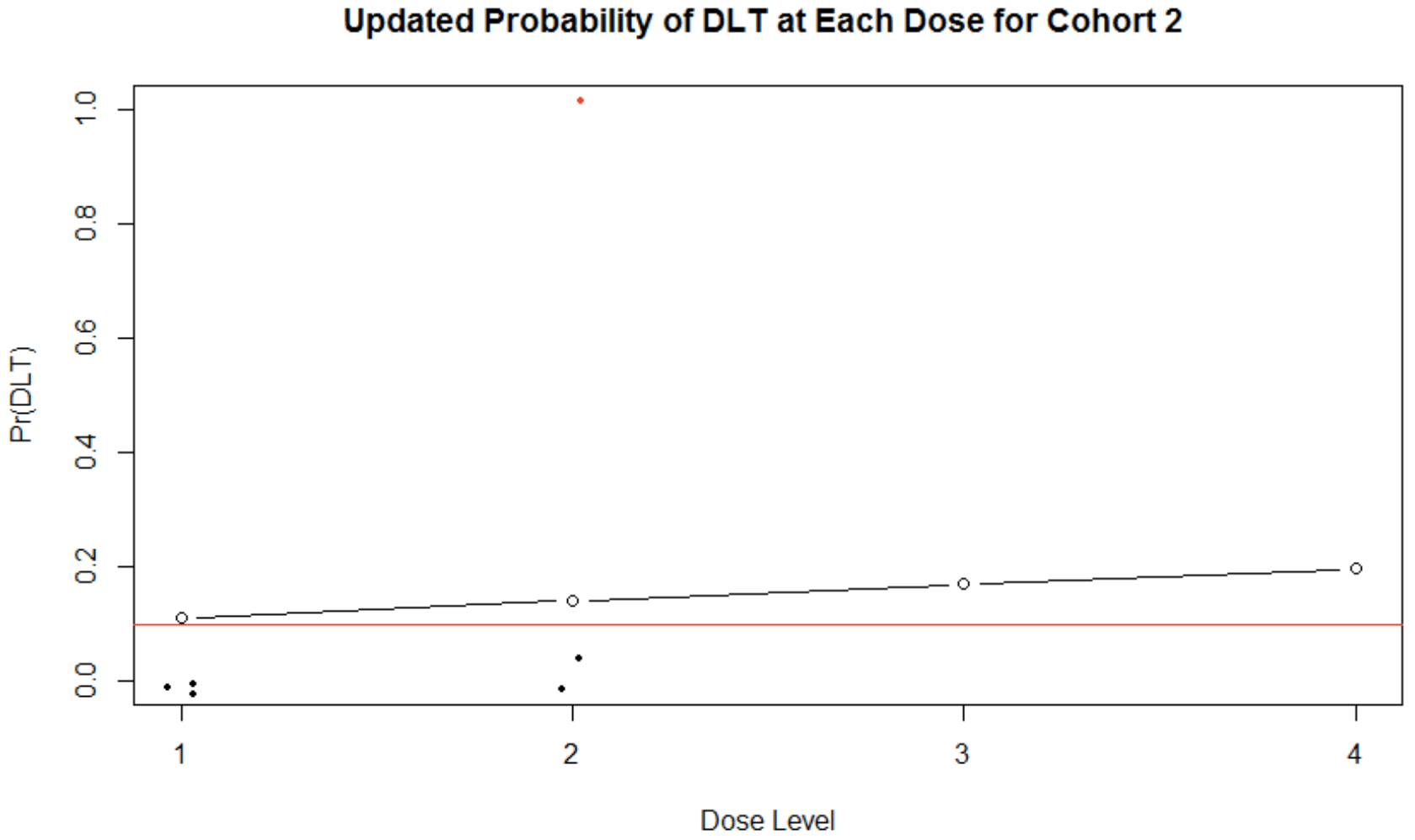

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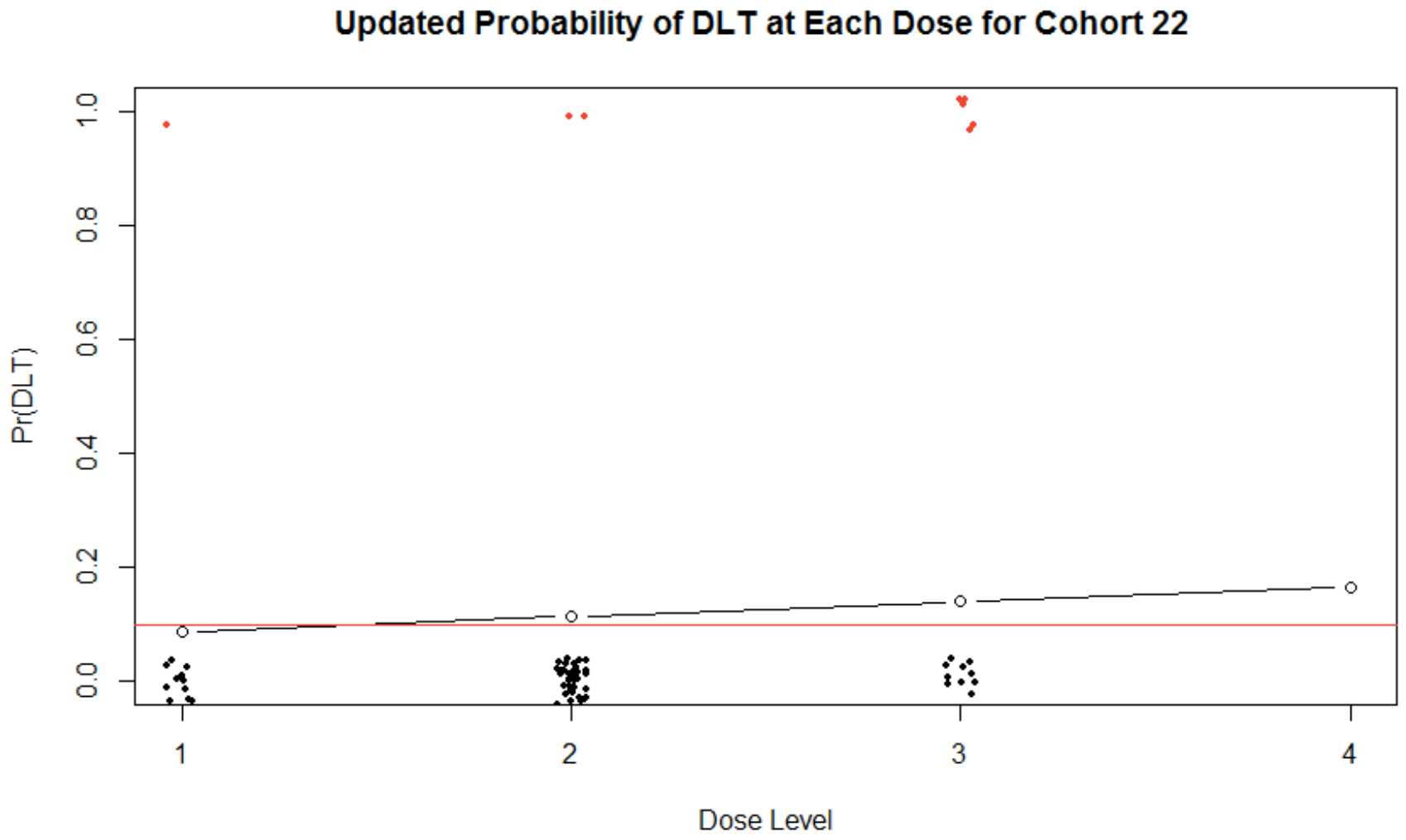
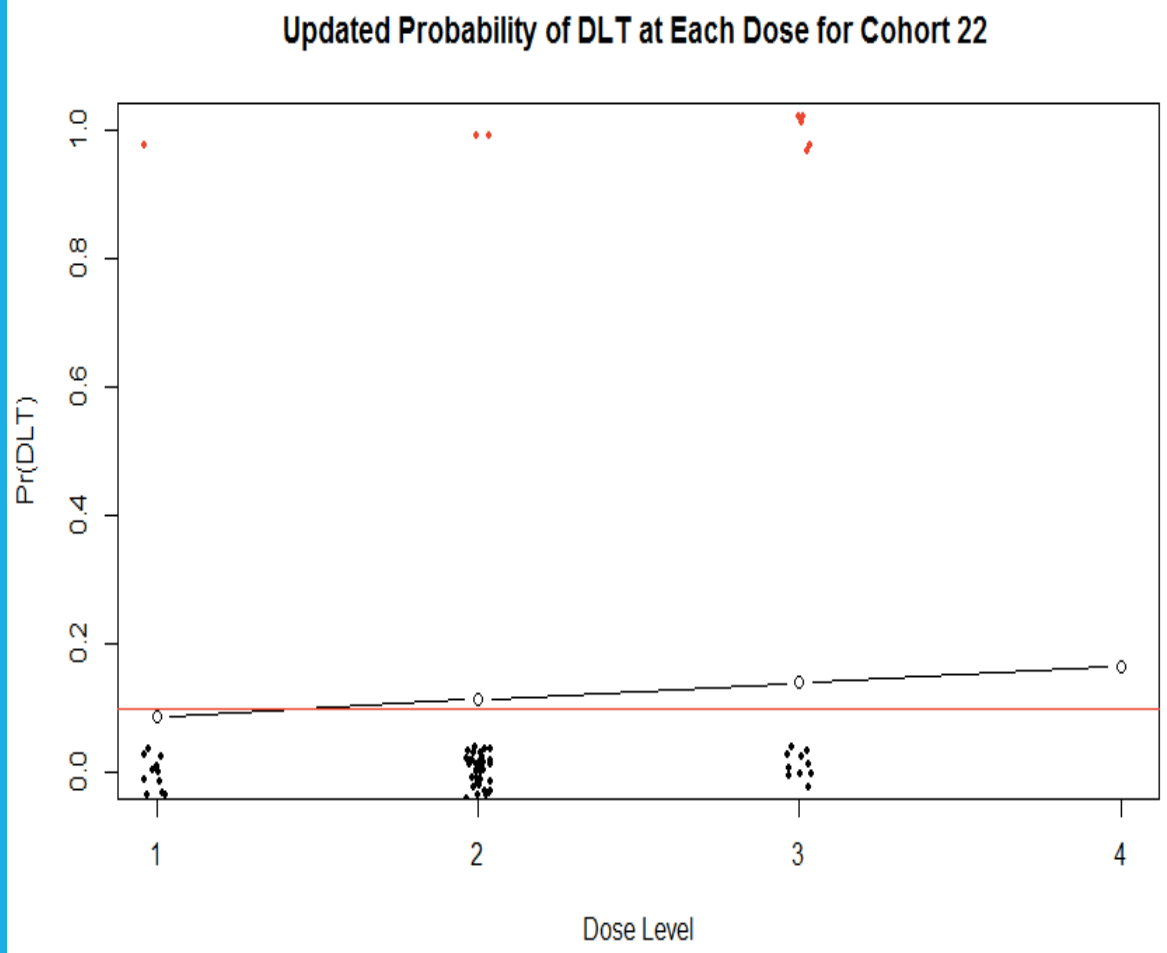
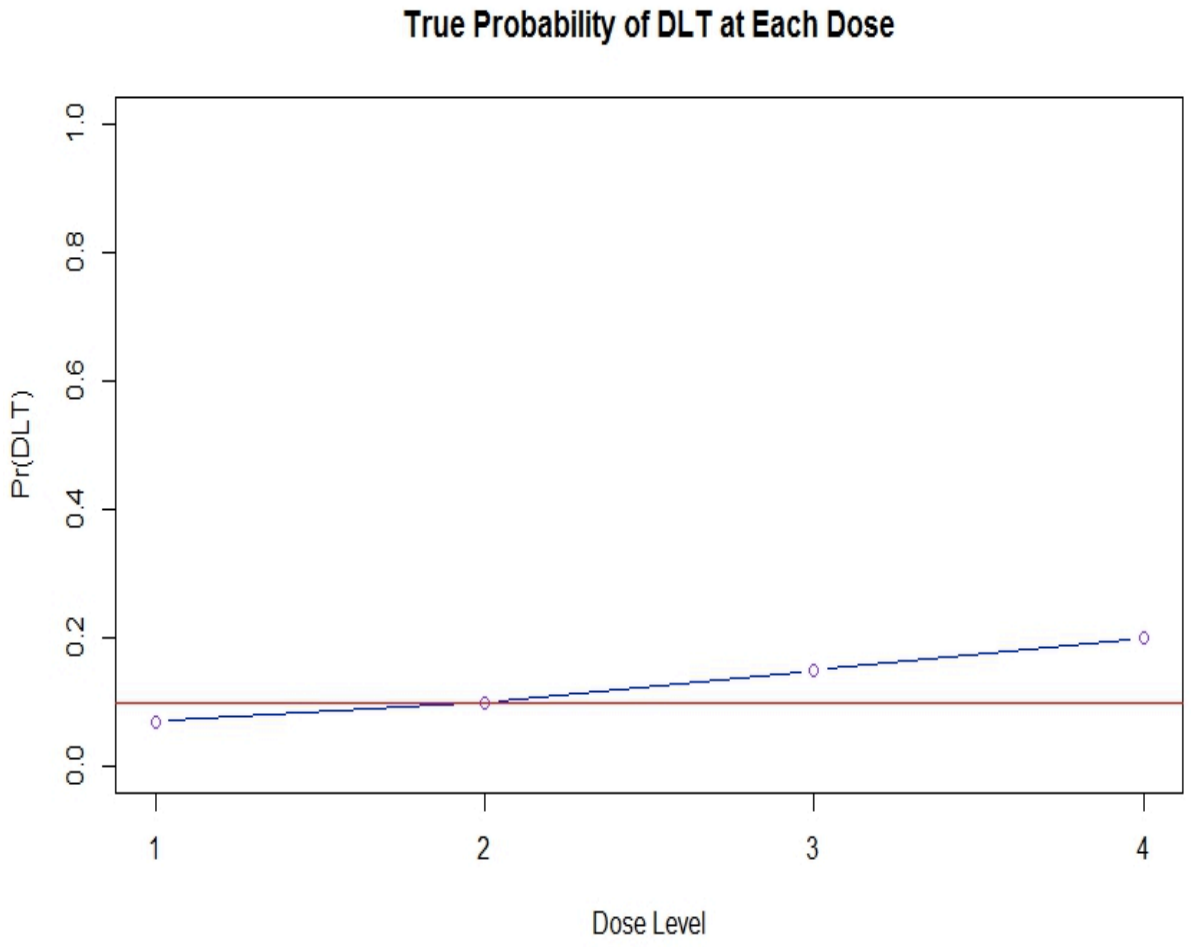


CRM Comparison with True Values





Issue with Traditional CRM Trial

- Dose-finding designs must balance recruitment rates and the length of the DLT observation periods
- What do you do if you planned a traditional CRM dose-finding design but mid-study the recruitment rate drastically changes?

Lagged CRM

- Lagging uses previously completed cohorts' data to update the toxicity curve
- One lag uses all but the previous cohort's data
- Two lags uses all but the previous two cohorts' data
- Similar idea to the Time-To-Event CRM (TITE-CRM), except no weight is given to partial observations
- Goal - Determine whether there is a loss in performance when selecting the MTD when forced to adopt the lagged approach

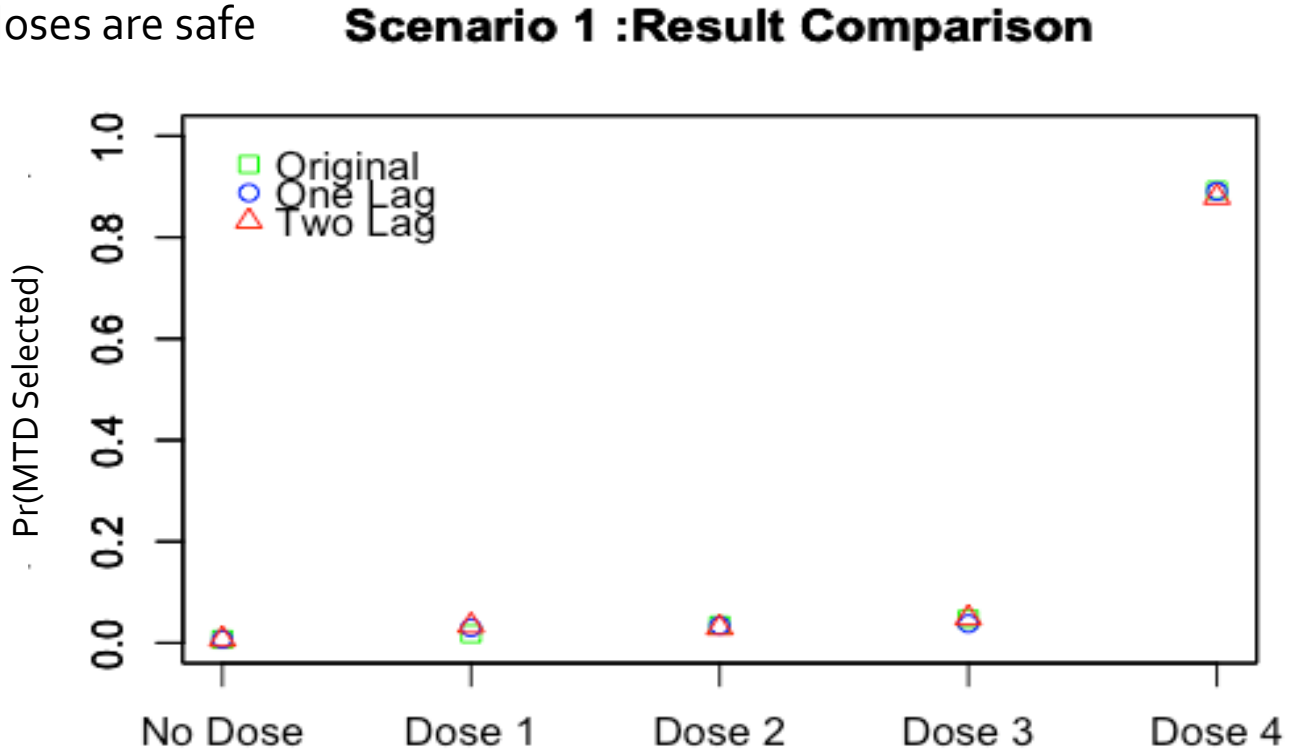
The Simulation

- Three CRM simulations:
  - Originally planned CRM
  - 1 lag CRM
  - 2 lag CRM
- 1000 repetitions for each CRM setting
- Each simulation enrolls a maximum of 66 subjects in cohorts of 3
- Lagging starts once half of the subjects are enrolled

- Maximum Tolerated Dose (MTD)
  - Target toxicity was 10%
  - Can choose "no dose" or dose 1, 2, 3, or 4
- 6 scenarios
  - No doses are toxic
  - All doses are toxic
  - Each dose is an MTD

Simulation Results: Scenario One

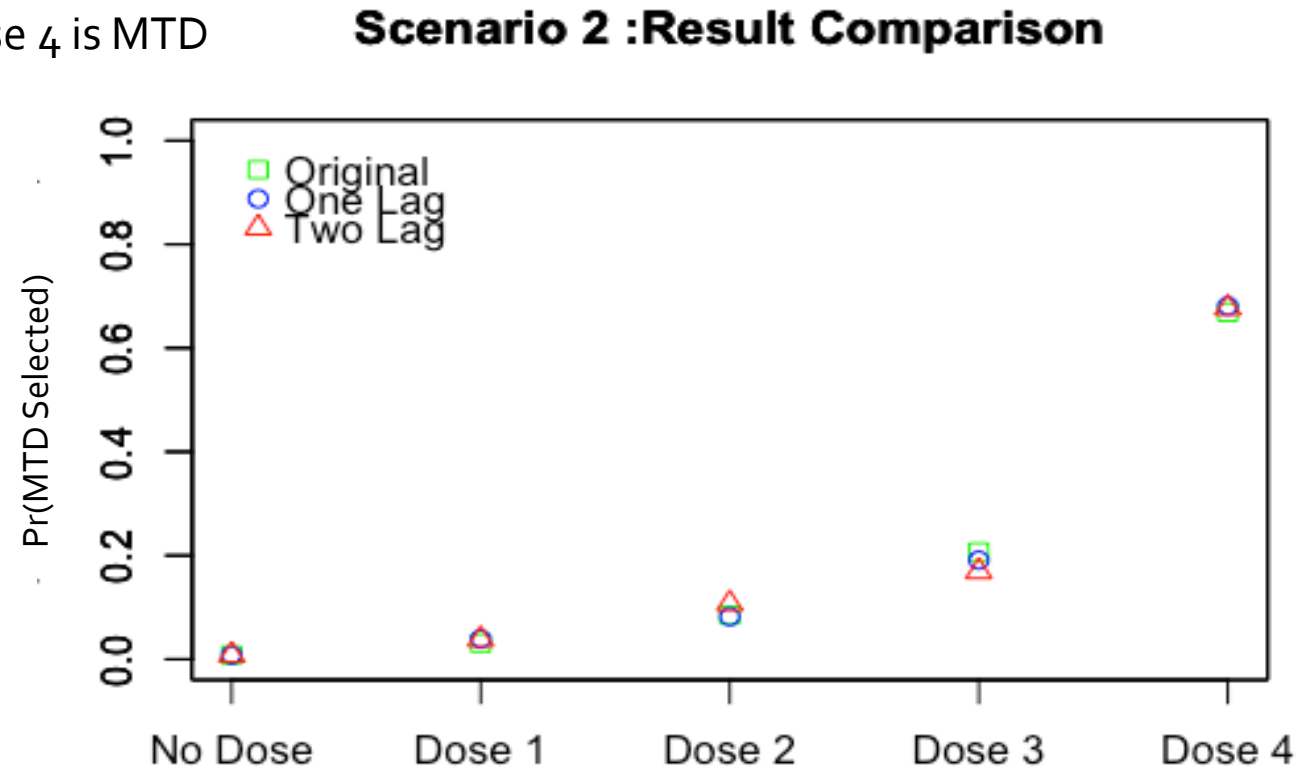
- All doses are safe



	No Dose	Dose 1	Dose 2	Dose 3	Dose 4
Original CRM	0.007	0.018	0.035	0.047	0.893
One Lag	0.007	0.03	0.034	0.038	0.891
Two Lag	0.007	0.034	0.03	0.049	0.879

Simulation Results: Scenario Two

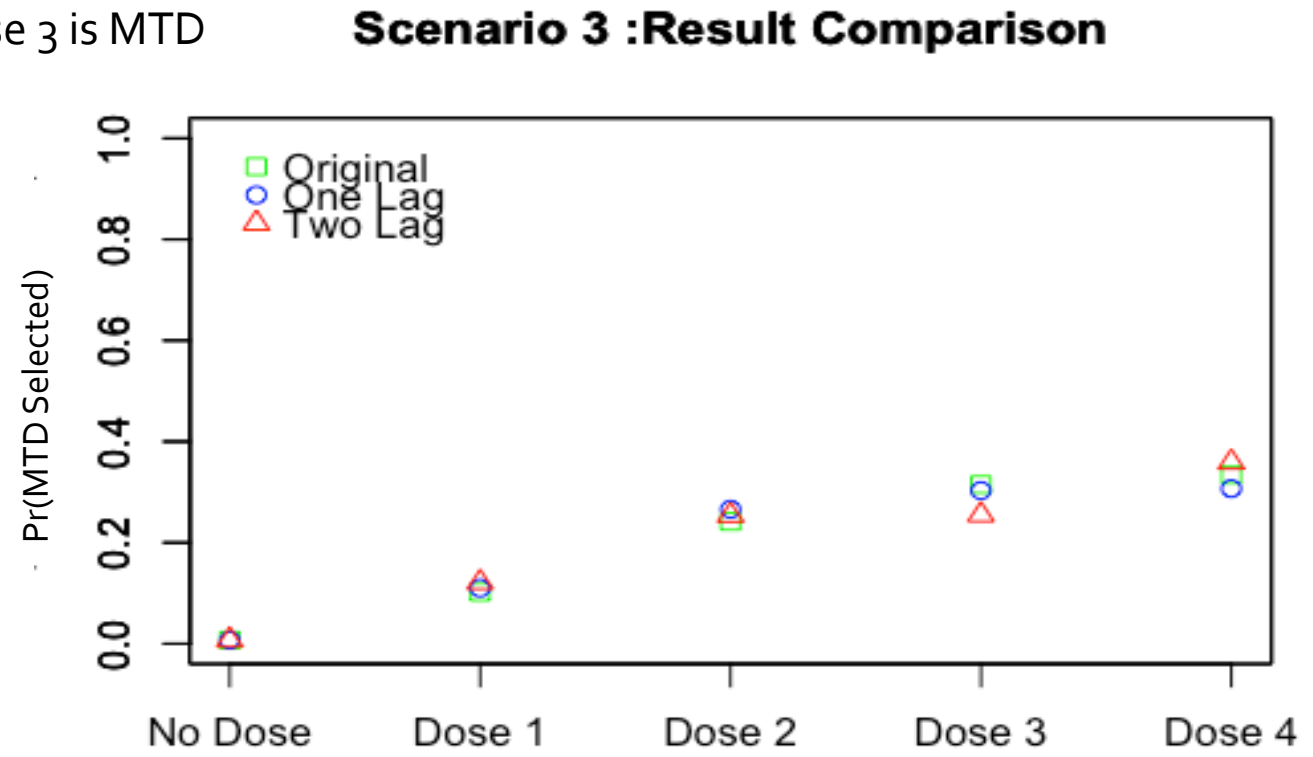
- Dose 4 is MTD



	No Dose	Dose 1	Dose 2	Dose 3	Dose 4
Original CRM	0.008	0.031	0.085	0.207	0.669
One Lag	0.008	0.039	0.082	0.191	0.681
Two Lag	0.008	0.038	0.107	0.169	0.677

Simulation Results: Scenario Three

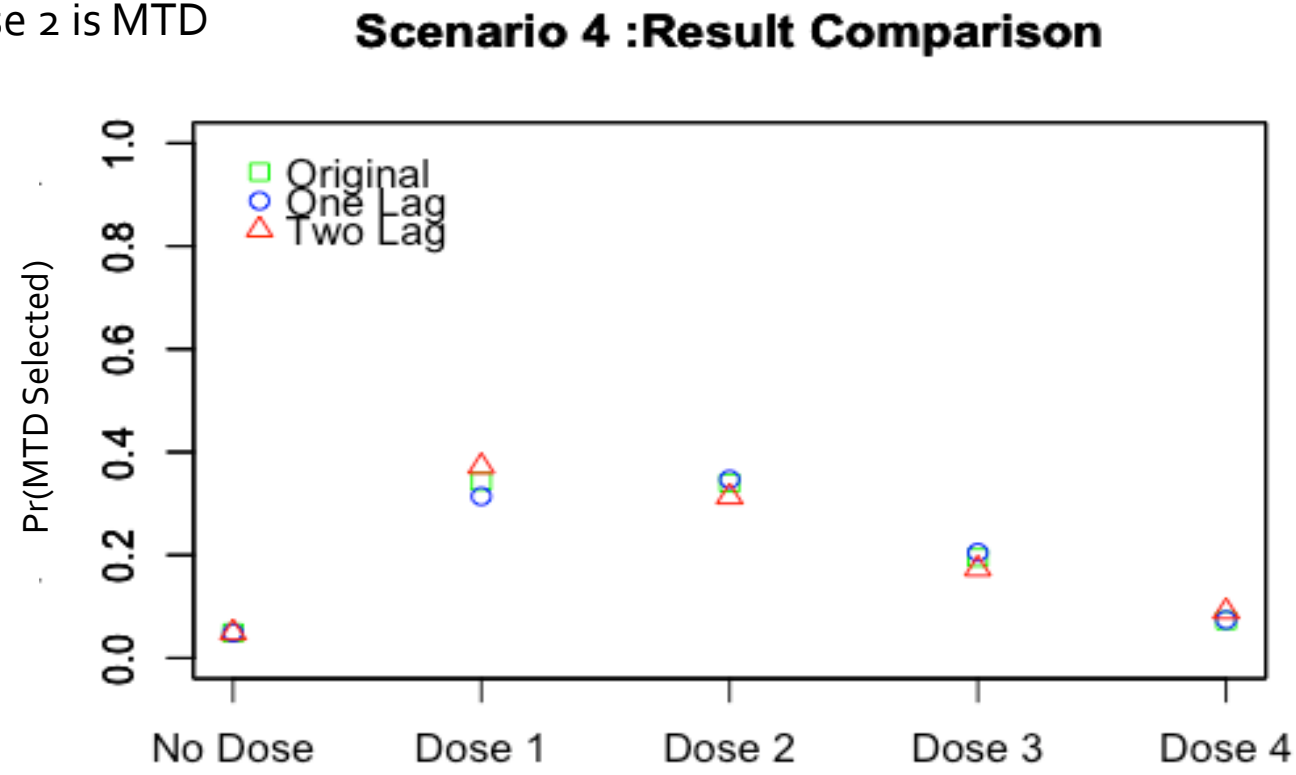
- Dose 3 is MTD



	No Dose	Dose 1	Dose 2	Dose 3	Dose 4
Original CRM	0.007	0.102	0.242	0.315	0.334
One Lag	0.007	0.11	0.266	0.303	0.307
Two Lag	0.007	0.121	0.254	0.255	0.359

Simulation Results: Scenario Four

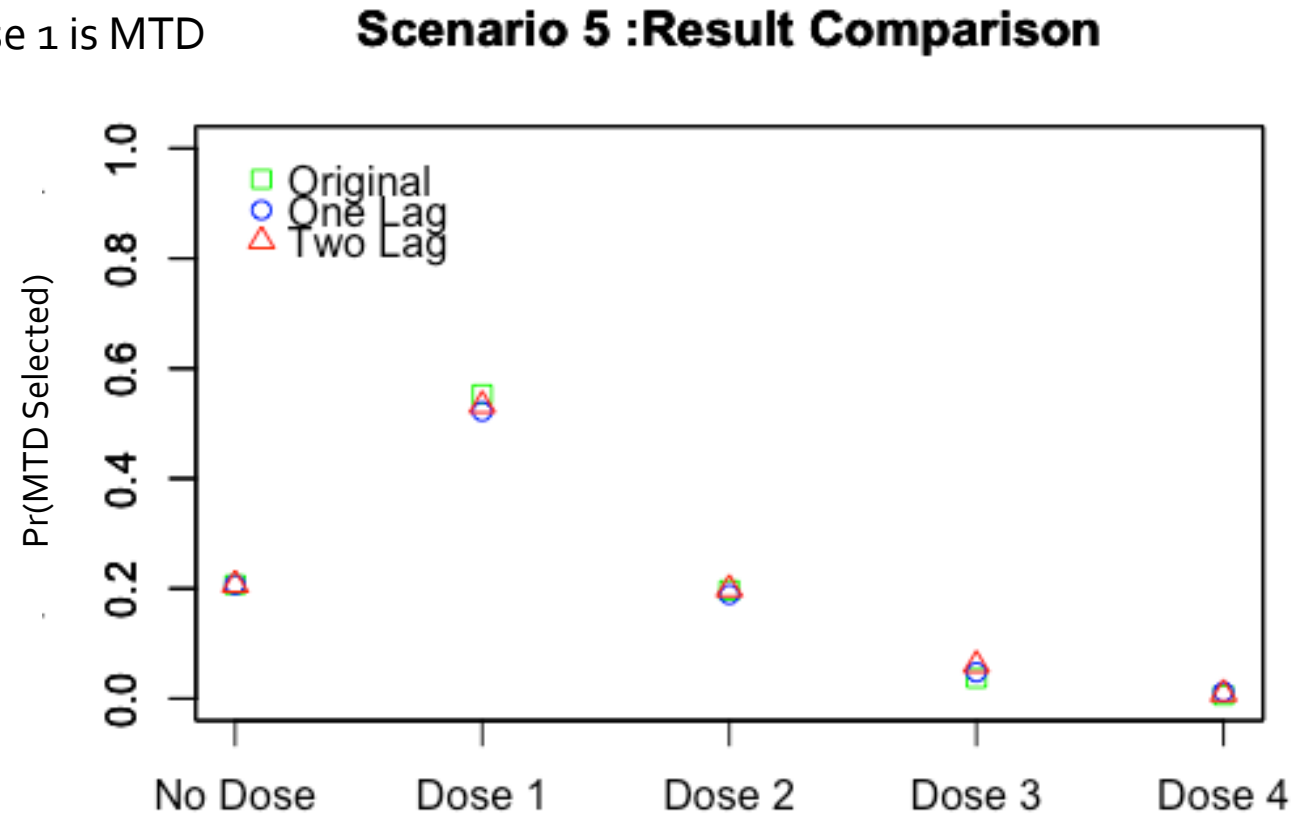
- Dose 2 is MTD



	No Dose	Dose 1	Dose 2	Dose 3	Dose 4
Original CRM	0.049	0.343	0.34	0.195	0.073
One Lag	0.049	0.314	0.347	0.205	0.074
Two Lag	0.049	0.372	0.313	0.173	0.09

Simulation Results: Scenario Five

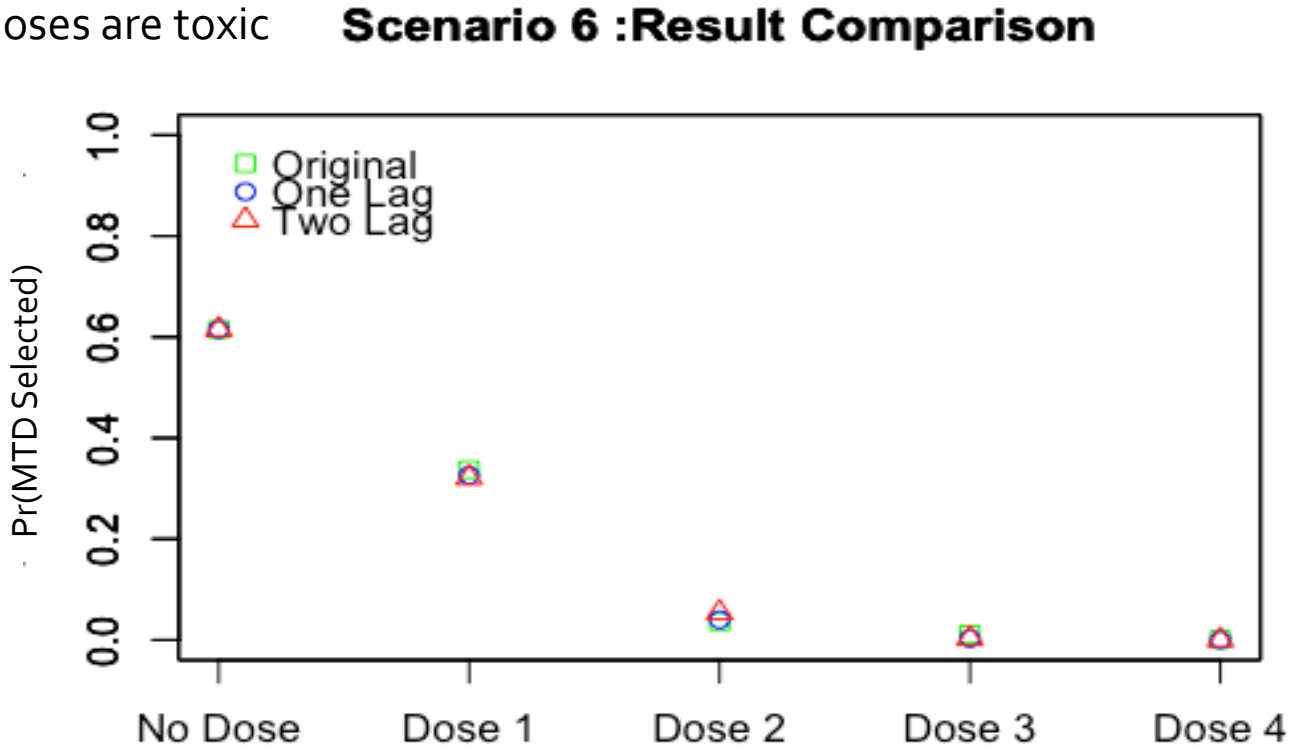
- Dose 1 is MTD



	No Dose	Dose 1	Dose 2	Dose 3	Dose 4
Original CRM	0.207	0.553	0.197	0.037	0.006
One Lag	0.207	0.522	0.189	0.048	0.012
Two Lag	0.207	0.533	0.199	0.061	0.009

Simulation Results: Scenario Six

- All doses are toxic



	No Dose	Dose 1	Dose 2	Dose 3	Dose 4
Original CRM	0.615	0.337	0.036	0.011	0.001
One Lag	0.615	0.326	0.04	0.003	0
Two Lag	0.615	0.321	0.054	0.003	0

Toxic Dose Proportions

Scenario	CRM	One Lag	Two Lag
1	0	0	0
2	0	0	0
3	0.334	0.307	0.359
4	0.268	0.279	0.263
5	0.24	0.249	0.269
6	0.385	0.385	0.385

Investigation Interpretation

- Lagging does not hinder the selection of the correct maximum tolerated dose
- Conclusion: Lagging dose-recommendations for future cohorts is a feasible method for dealing with the change in recruitment rates

Questions?

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Citations

- Garrett-Mayer, Elizabeth. "The continual reassessment method for dose-finding studies: a tutorial." *Clinical Trials* 3.1 (2006): 57-71.
- O'Quigley, John, Pepe Margaret, and Fisher Lloyd. "Continual Reassessment Method: A Practical Design for Phase 1 Clinical Trials in Cancer." *Biometrics* 46.1 (1990): 33-48. Web.

A "Modified" CRM

- What does this mean?
- Safety Measures
  - Dose escalation conditions
    - Increases one dose at a time
  - Stopping conditions
    - Lowest dose has toxicity above threshold and 50% of maximum subjects recruited
    - Observed second consecutive toxicity at lowest dose
    - Failed to observed a toxicity with at least 50% of the maximum subjects recruited
    - Maximum subject recruitment met