Alexia Iasonos, Elyn R. Riedel, David R Spriggs

Background:
Bayesian Phase I designs have received increased attention. The objective is to determine if the Continual Reassessment Method (CRM) is superior to the standard 3+3 dose escalation scheme (SM) in terms of sample size, precision and study duration.

Methods:
Comparisons were carried out through 1000 simulated trials under different scenarios by varying the number of dose levels from 5 to 8 and the location of the true MTD. The hyperbolic tangent was assumed as the dose-toxicity curve and the target toxicity rate was 25%. Four Bayesian designs were evaluated: original CRM; CRM that is restricted in no more than one dose level increase; two-stage CRM that follows an arbitrary escalation plan at the beginning of the trial until a DLT is observed and then switches to CRM; and CRM in cohorts of three patients. CRM was assessed in two alternative schemes: with a fixed sample approach of 20 patients or with a stopping rule that halts the trial when a specified amount of precision around the estimated toxicity rate at the MTD (ETR) is reached. Standard endpoints were evaluated: accuracy, precision, safety, total sample size, and minimum study duration. Results are independent of the increment between dose levels.

Results:
SM found the true MTD on average 20% (range 8-28%) fewer times compared to CRM-based methods in almost all scenarios. All CRM-based methods treated more patients at the MTD compared to SM (42% vs 11%) except when the true MTD is at the second dose level (36 vs 35%). Number of DLTs was the smallest under the SM. CRM and SM are similar in terms of total sample size when testing 5 dose levels, although SM requires shorter duration. As the number of dose levels increases to 8, CRM completes the trial faster than SM when used with a fixed sample of 20 patients; except when the MTD is among the lower levels. Using the stopping rule approach with a maximum of 30 patients, 66-78% of trials have not met the required precision around the ETR.

Conclusions:
All CRM-based methods are an improvement over SM in terms of accuracy and optimal dose allocation, except when the true MTD is among the lower levels. When the number of dose levels is limited (eg 5), a sample of 20 is sufficient by both methods in order to find the MTD. However, a sample size of 20-30 is not sufficient to achieve a narrow confidence interval around the ETR.