MTD is estimated by fitting a non-decreasing dose-DLT rate curve using linear ordering isotonic (monotonic) regression.

Algorithms: PAVA(Pool-Adjacent-Violator Algorithm)

Extend PAVA for mono/combo parallel trials: 2-Dimensional PAVA (2D PAVA)
- Monotonic on both dose level dimension and the mono/combo arm dimension
- Alternately applying PAVA to each dimension to satisfy the constraints on both (convergence proof in R.L. Dykstra, 1982)

MDT Selection Probabilities – Comparison of PAVA's

Operating Characteristics

Conclusions
- Our in-house 2D PAVA outperforms others in MTD identification probability for almost all cases by 1%-4% percent.
- Our modified BOIN: 1) improves MTD selection when mono and combo toxicities are similar, but not as good when toxicities differ a lot; 2) dramatically reduces early termination while maintaining similar safety characteristics.