

## Accelerated Titration

**Perform accelerated titration** - When “Yes” is chosen, accelerated titration will be performed prior to treating patients according to the prespecified cohort size  $m$ , e.g.,  $m = 3$ , as follows. Treat the first patient at the prespecified starting dose (e.g., the lowest dose) and escalate the dose in a one-patient-per-dose-level fashion until:

- [ If the **Cap the titration up to dose level:** is the highest dose level (default) ]: until any of the following events is observed: (i) the first instance of DLT, (ii) the second instance of moderate (grade 2) toxicity, or (iii) the highest dose level is reached. Then, treat  $m - 1$  additional patients at the current dose level. Hereafter, patients are treated in cohorts of size  $m$ .
- [ If the **Cap the titration up to dose level:** is lower than the highest dose level ]: until either of the following events is observed: (i) the first instance of DLT, or (ii) the second instance of moderate (grade 2) toxicity. Then, treat  $m - 1$  additional patients at the current dose level. Hereafter, patients are treated in cohorts of size  $m$ . In the case that the titration reaches the titration dose level upper limit without observing (i) or (ii), patients are treated in cohorts of size  $m$  from the next higher dose level.

This option is useful when the number of dose levels is large (e.g.,  $> 6$ ) and low dose levels are believed to be safe. It accelerates dose escalation and reduces the sample size. The tradeoff is that if the true toxicity probabilities of low dose levels are relatively high, using accelerated titration slightly increases the chance of overdosing patients.

**Note:** If the cohort size is 1, or if the starting dose level is the highest dose level, checking this box has no effect.