**Notation**

Consider the situation where there is a fixed ordered set of dose levels *dj*, *j{1,...,K}.* Let k be a categorical random variable with i response categories denoting the possible levels of viral load reduction. Without loss of generality we assume 3 different levels of viral load reduction given no toxicity; between 0% and 20 (category 1), between 20% and 50% (category 2) and greater than 50% (category 3), and regard toxicity as category 0. Modifying these definitions or adding new intervals is conceptually straightforward. Let be the probability of toxicity at *dj*, be the probability of no or little efficacy at *dj*, be the probability of medium efficacy at *dj*, and be the probability of high efficacy at *dj*, . Let be the maximum tolerable level of toxicity.

The probability of encountering at level *dj* is assumed to increase monotonically with dose. We may also assume a mono tonicity property to hold across the doses with regard to the conditional probability of achieving efficacy in terms of viral load reduction given toxicity. Whether or not we make this assumption, overall success, being the absence of toxicity together with viral load reduction, is not necessarily monotonic.



Isotonic regression is used to estimated .

**The rapid enrollment design to find the optimal dose**

Let {1 ..., k} be the set of doses with at least one patient assigned.

(1)  *Initial escalation.* Do not change the dose unless at least m patients are assigned to the dose and their toxicity outcomes are observed (except when the safety rule is invoked). We recommend using cohorts of m= 3. Assigning at least three patients prevents making a decision based on insufficient information.

(2)  If > and at least m patients have been assigned to dose level k, the next patient is assigned to dose level k + 1 (or k if k = K).

(3)  If < and if there is a dose s such that = , the next patient is assigned to dose level s. Otherwise, let s, , be such that > and < . That is, given the data, the optimal dose is somewhere between dose levels s and s+1. If , the next patient is assigned to dose level s. Otherwise, the next patient is assigned to dose level s+1.

(4)  *Safety rule.* Do not assign patients to the dose with . If , reduce dose level to k' until .

(5) *Sufficient efficacy rule.* For , if and , that is bose doses s\*-1 and s\* have sufficient efficacy, assigned the next patient to dose s\*-1. Otherwise, assign to s\*.

(6) *Estimation of the optimal dose at the end of the trial.* The unconditional expectation of efficacy is referred to as the centre of mass (CM) of dose k.

At the end of trial, the dose with highest estimated CM and estimated probability of toxicity less than is declared the optimal dose.

**Table 1**

*dose levels = 3, sample size = 30, ,*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | K=0 | K=1 | K=2 | K=3 | CM | - | results | -- | results |
| Scenario 1 | | | | | | | | | |
| d1 | 0.1 | 0.72 | 0.09 | 0.09 | 1.17 | -0.62 | 0.05 | -0.71 | 0.05 |
| d2 | 0.2 | 0.32 | 0.24 | 0.24 | 1.52 | **-0.12** | 0.19 | -0.36 | 0.24 |
| d3 | 0.3 | 0.07 | 0.07 | 0.56 | **1.89** | 0.23 | **0.76** | **0.16** | **0.71** |
| Scenario 2 | | | | | | | | | |
| d1 | 0.15 | 0.6375 | 0.17 | 0.0425 | 1.10 | -0.49 | 0.26 | -0.6575 | 0.21 |
| d2 | 0.3 | 0.42 | 0.21 | 0.07 | 1.05 | **-0.12** | 0.22 | -0.33 | 0.26 |
| d3 | 0.45 | 0.0275 | 0.11 | 0.4125 | **1.48** | 0.42 | **0.52** | **0.3125** | **0.53** |
| Scenario 3 | | | | | | | | | |
| d1 | 0.2 | 0.56 | 0.16 | 0.08 | 1.12 | -0.36 | 0.24 | -0.52 | 0.25 |
| d2 | 0.4 | 0.06 | 0.18 | 0.36 | **1.50** | **0.34** | **0.53** | **0.16** | **0.58** |
| d3 | 0.7 | 0.03 | 0.03 | 0.24 | 0.81 | 0.67 | 0.23 | 0.64 | 0.17 |

**Table 2**

*dose levels = 4, sample size = 30, ,*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | K=0 | K=1 | K=2 | K=3 | CM | - | results | -- | results |
| Scenario 1 | | | | | | | | | |
| d1 | 0.1 | 0.72 | 0.09 | 0.09 | 1.17 | -0.62 | 0.03 | -0.71 | 0.03 |
| d2 | 0.2 | 0.32 | 0.24 | 0.24 | 1.52 | **-0.12** | 0.12 | -0.36 | 0.18 |
| d3 | 0.3 | 0.07 | 0.07 | 0.56 | **1.89** | 0.23 | **0.48** | **0.16** | **0.49** |
| d4 | 0.4 | 0.06 | 0.06 | 0.48 | 1.62 | 0.34 | 0.37 | 0.28 | 0.29 |
| Scenario 2 | | | | | | | | | |
| d1 | 0.15 | 0.6375 | 0.17 | 0.0425 | 1.10 | -0.49 | 0.20 | -0.6575 | 0.16 |
| d2 | 0.3 | 0.42 | 0.21 | 0.07 | 1.05 | **-0.12** | 0.17 | -0.33 | 0.20 |
| d3 | 0.45 | 0.0275 | 0.11 | 0.4125 | **1.48** | 0.42 | **0.37** | **0.3125** | **0.40** |
| d4 | 0.6 | 0.02 | 0.06 | 0.32 | 1.10 | 0.58 | 0.26 | 0.52 | 0.23 |
| Scenario 3 | | | | | | | | | |
| d1 | 0.2 | 0.56 | 0.16 | 0.08 | 1.12 | -0.36 | 0.24 | -0.52 | 0.25 |
| d2 | 0.4 | 0.06 | 0.18 | 0.36 | **1.50** | **0.34** | **0.53** | **0.16** | **0.58** |
| d3 | 0.7 | 0.03 | 0.03 | 0.24 | 0.81 | 0.67 | 0.13 | 0.64 | 0.08 |
| d4 | 0.8 | 0.02 | 0.02 | 0.16 | 0.54 | 0.78 | 0.10 | 0.76 | 0.09 |

**Table 3**

*some weird scenarios*

*dose levels = 4, sample size = 30, ,*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | K=0 | K=1 | K=2 | K=3 | CM | - | results | -- | results |
| Scenario 1 | | | | | | | | | |
| d1 | 0.1 | 0.00 | 0.45 | 0.45 | **2.25** | 0.1 | **0.77** | -0.35 | **0.62** |
| d2 | 0.2 | 0.32 | 0.24 | 0.24 | 1.52 | -0.12 | 0.08 | -0.36 | 0.13 |
| d3 | 0.3 | 0.07 | 0.28 | 0.35 | 1.68 | 0.23 | 0.13 | **-0.05** | 0.24 |
| d4 | 0.4 | 0.4 | 0.10 | 0.10 | 0.9 | **0.00** | 0.01 | -0.1 | 0.01 |
| Scenario 2 | | | | | | | | | |
| d1 | 0.15 | 0.55 | 0.20 | 0.10 | 1.25 | -0.40 | 0.11 | -0.6 | 0.13 |
| d2 | 0.3 | 0.00 | 0.35 | 0.35 | **1.75** | -0.3 | **0.73** | **-0.05** | **0.74** |
| d3 | 0.45 | 0.20 | 0.20 | 0.15 | 1.05 | 0.25 | 0.14 | **0.05** | 0.11 |
| d4 | 0.6 | 0.4 | 0.00 | 0.00 | 0.4 | **0.2** | 0.03 | 0.2 | 0.02 |
| Scenario 3 | | | | | | | | | |
| d1 | 0.0 | 0.6 | 0.4 | 0.00 | **1.40** | -0.6 | **0.72** | -1 | **0.64** |
| d2 | 0.1 | 0.7 | 0.2 | 0.00 | 1.10 | -0.6 | 0.27 | -0.8 | 0.35 |
| d3 | 0.7 | 0.1 | 0.1 | 0.1 | 0.60 | 0.6 | 0.00 | **0.5** | 0.02 |
| d4 | 0.8 | 0.2 | 0.00 | 0.00 | 0.20 | 0.6 | 0.01 | 0.6 | 0.00 |

**Table 4**

*some weird scenarios*

*dose levels = 6, sample size = 30, ,*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | K=0 | K=1 | K=2 | K=3 | CM | - | results | -- | results |
| Scenario 1 | | | | | | | | | |
| d1 | 0.1 | 0.5 | 0.4 | 0.0 | 1.3 | -0.4 | 0.03 | -0.8 | 0.02 |
| d2 | 0.2 | 0.3 | 0.3 | 0.2 | 1.5 | **-0.1** | 0.12 | -0.4 | 0.17 |
| d3 | 0.3 | 0.1 | 0.25 | 0.35 | 1.65 | 0.2 | 0.25 | **-0.05** | **0.28** |
| d4 | 0.4 | 0.0 | 0.1 | 0.5 | **1.7** | 0.4 | **0.28** | 0.3 | 0.23 |
| d5 | 0.5 | 0.0 | 0.0 | 0.5 | 1.5 | 0.5 | 0.21 | 0.5 | 0.19 |
| d6 | 0.6 | 0.0 | 0.0 | 0.4 | 1.2 | 0.6 | 0.12 | 0.6 | 0.11 |
| Scenario 2 | | | | | | | | | |
| d1 | 0.0 | 1.0 | 0.0 | 0.0 | 0.1 | -1 | 0.01 | -1 | 0.01 |
| d2 | 0.1 | 0.9 | 0.0 | 0.0 | 0.9 | -0.8 | 0.03 | -0.8 | 0.02 |
| d3 | 0.2 | 0.7 | 0.1 | 0.0 | 0.9 | -0.5 | 0.08 | -0.6 | 0.07 |
| d4 | 0.3 | 0.4 | 0.2 | 0.1 | 1.1 | **-0.1** | 0.18 | -0.3 | 0.20 |
| d5 | 0.4 | 0.1 | 0.2 | 0.3 | 1.4 | 0.3 | 0.31 | **0.1** | **0.36** |
| d6 | 0.5 | 0.0 | 0.0 | 0.5 | **1.5** | 0.5 | **0.39** | 0.5 | 0.34 |
| Scenario 3 | | | | | | | | | |
| d1 | 0.15 | 0.4 | 0.35 | 0.1 | 1.4 | -0.25 | 0.25 | -0.6 | 0.24 |
| d2 | 0.3 | 0.3 | 0.25 | 0.15 | 1.25 | **0.0** | 0.17 | -0.25 | 0.22 |
| d3 | 0.45 | 0.1 | 0.15 | 0.3 | 1.3 | 0.35 | 0.18 | **0.2** | 0.19 |
| d4 | 0.5 | 0.0 | 0.0 | 0.5 | **1.5** | 0.5 | **0.31** | 0.5 | **0.27** |
| d5 | 0.75 | 0.0 | 0.0 | 0.25 | 0.75 | 0.75 | 0.07 | 0.75 | 0.06 |
| d6 | 0.9 | 0.0 | 0.0 | 0.1 | 0.3 | 0.9 | 0.02 | 0.9 | 0.02 |
| Scenario 4 | | | | | | | | | |
| d1 | 0.3 | 0.3 | 0.2 | 0.2 | 1.3 | **0.0** | 0.17 | -0.2 | 0.18 |
| d2 | 0.35 | 0.3 | 0.2 | 0.15 | 1.15 | 0.05 | 0.09 | -0.15 | 0.11 |
| d3 | 0.4 | 0.15 | 0.15 | 0.3 | 1.35 | 0.25 | 0.16 | **0.1** | 0.16 |
| d4 | 0.45 | 0.05 | 0.1 | 0.4 | 1.45 | 0.4 | 0.19 | 0.3 | 0.16 |
| d5 | 0.5 | 0.0 | 0.0 | 0.5 | **1.5** | 0.5 | **0.20** | 0.5 | 0.17 |
| d6 | 0.55 | 0.0 | 0.0. | 0.45 | 1.34 | 0.55 | **0.20** | 0.55 | **0.21** |