**Supplementary materials**

**Dose-Outcomes models for the EffTox design**

Denotes by Y= ( the pair of toxicity and activity outcomes. A joint probability of toxicity and activity is modelled with the two marginal probabilities of activity and toxicity. Denotes the vector of recoded dose. The marginal probability of activity is based on a quadratic dose-activity relationship to take into account non-monotonic dose-activity relationships:

The marginal probability of toxicity is defined as follows:

and = () the vector of models parameters where and defined the parameters of models for the marginal probabilities of activity and toxicity.

Finally, the joint probability is modelled by:

Where is an association parameter.

**Supplementary tables**

**Table S1.** Parameters tested for the simulation study.

|  |
| --- |
| **Simulations for C1** |
| **Designs** | **Parameters** | **Correct dose decision if,** |
| **DE-EC** | Ensign design |  = 0.05, = 0.25, = 9, = 1, = 9, = 2, = 8, = 26, = 3 | P(toxicity) ≤ 0.33 and P(activity) ≥ 0.15 |
| **DE-ECext** | Ensign design |  = 0.05, = 0.25, = 9, = 1, = 9, = 2, = 8, = 26, = 3 |
|  | Fleming design | = 17 and = 2 |
| **EffTox** | , (, = 40 |
| **Simulations for C2** |
| **Designs** | **Parameters** | **Correct dose decision if,** |
| **DE-EC** | Ensign design |  = 0.10, = 0.25, = 18, = 1, = 10, = 3, = 12, = 40, = 7 | P(toxicity) ≤ 0.33 and P(activity) ≥ 0.20 |
| **DE-ECext** | Ensign design |  = 0.10, = 0.25, = 18, = 1, = 10, = 3, = 12, = 40, = 7 |
|  | Fleming design  | = 39 and = 6 |
| **EffTox** | , (, = 60  |
| **Simulations for C3** |
| **Designs** | **Parameters** | **Correct dose decision if,** |
| **DE-EC / DE-ECext** | CRM |  = (0.02,0.04,0.07,0.11,0.16,0.25,0.37,0.48) |  |
| **DE-EC** | Ensign design |  = 0.10, = 0.30, = 10, = 1, = 9, = 3, = 7, = 40, = 5 | P(toxicity) ≤ 0.33 and P(activity) ≥ 0.20 |
| **DE-ECext** | Ensign design |  = 0.10, = 0.30, = 10, = 1, = 9, = 3, = 7, = 40, = 5 |
|  | Fleming design  | = 24 and = 4 |
| **EffTox** | , (, = 50  = (0.02,0.04,0.07,0.11,0.16,0.25,0.37,0.48) |

**Table S2.** Additional results focused on the DE-ECext design. **CD**: correct dose decision. No correct dose decision was specified for Scenarios 3 and 5.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | % trials revising the MTD | Average total patients for trials revising the MTD | # of patients treated at CD | Average total patients |
| **Sc. 1** | 13.5 | 46.8 | 27.4 | 35.5 |
| **Sc. 2** | 17.5 | 46.6 | 17.7 | 34.8 |
| **Sc. 4** | 15.4 | 46.5 | 27.0 | 34.1 |
| **Sc. 6** | 15.0 | 46.4 | 17.1 | 34.2 |
| **Sc. 7** | 3.1 | 50.3 | 16.6 | 33.9 |

**Table S3.** Operating characteristics of each design. Correct dose decisions are bolded. The values highlighted in light gray correspond to the PCS (percentage of correct MTD selection). The values highlighted in dark gray correspond to the POS (percentage of optimal dose selection) at the recommended optimal dose (dose with the highest desirability, i.e the dose with the better trade-off between toxicity and activity). Q1-Q3: interquartile ranges. For EffTox, no interquartile range is provided as the sample size was fixed (except in the uncommon case of early stopping). #: number. The average total number of toxicity and patient are provided. **Parameters: = 0.05 / = 0.25 / = 0.15**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Dose level% selection |  | # of toxicity |  # of patients(Q1-Q3) | Percentage of Correct dose Decision |
|  | -1 | 1 | 2 | 3 | 4 | None |
| **Sc. 1** |  |  |  |  |  |  |  |  |  |
| DE-EC | **2.1** | **20.5** | **50.1** | 25.4 | 1.9 |  | 7.9 | 34.3 (32-36) | 72.1 |
| DE-ECext | **0.2** | **11.2** | **67.2** | 20.1 | 1.3 |  | 7.7 | 33.9 (31-36) | 81.0 |
| EffTox | **8.0** | **55.0** | **35.0** | 2.0 | 0.0 | 1.0 | 6.4 | 39.8 | 98.0 |
| **Sc. 2** |  |  |  |  |  |  |  |  |  |
| DE-EC | 2.4 | 20.8 | **51.1** | 22.9 | 2.8 |  | 7.7 | 32.6 (32-36) | 58.6 |
| DE-ECext | 1.4 | 15.7 | **62.0** | 20.1 | 0.8 |  | 7.6 | 32.3 (31-36) | 67.0 |
| EffTox | 4.0 | 47.0 | **42.0** | 3.0 | 0.0 | 3.0 | 7.2 | 38.7 | 42.0 |
| **Sc. 3** |  |  |  |  |  |  |  |  |  |
| DE-EC | 1.1 | **20.3** | **53.3** | 22.7 | 2.6 |  | 7.1 | 30.6 (30-36) | 54.9 |
| DE-ECext | 0.2 | **13.0** | **66.9** | 18.7 | 1.2 |  | 7.2 | 30.9 (29-36) | 48.2 |
| EffTox | 8.0 | **47.0** | **37.0** | 2.0 | 0.0 | 3.0 | 6.9 | 37.7 | 84.0 |
| **Sc. 4** |  |  |  |  |  |  |  |  |  |
| DE-EC | **1.9** | **19.8** | **53.4** | 21.8 | 3.1 |  | 7.6 | 32.9 (31-36) | 69.8 |
| DE-ECext | **0.2** | **10.6** | **68.2** | 20.5 | 0.5 |  | 7.4 | 32.7 (31-37) | 68.4 |
| EffTox | **13.0** | **49.0** | **33.0** | 2.0 | 0.0 | 4.0 | 6.7 | 38.7 | 95.0 |
| **Sc. 5** |  |  |  |  |  |  |  |  |  |
| DE-EC | 1.9 | 20.8 | 50.9 | 23.8 | 2.6 |  | 5.3 | 22.9 (15-30) | 81.3 |
| DE-ECext | 2.0 | 16.1 | 59.8 | 20.3 | 1.8 |  | 5.5 | 23.5 (16-32) | 93.6 |
| EffTox | 1.0 | 16.0 | 45.0 | 9.0 | 1.0 | 28.0 | 7.3 | 31.0 | 28.0 |
| **Sc. 6** |  |  |  |  |  |  |  |  |  |
| DE-EC | 1.3 | **23.7** | **51.6** | 21.5 | 1.9 |  | 7.7 | 32.8 (31-36) | 70.8 |
| DE-ECext | 1.2 | **13.6** | **64.3** | 19.5 | 1.4 |  | 7.3 | 32.1 (31-36) | 68.1 |
| EffTox | 5.0 | **52.0** | **37.0** | 2.0 | 0.0 | 4.0 | 6.7 | 38.2 | 89.0 |
| **Sc. 7** |  |  |  |  |  |  |  |  |  |
| DE-EC | 0.2 | **1.4** | **8.7** | **27.8** | 61.9 |  | 4.7 | 33.9 (33-38) | 80.3 |
| DE-ECext | 0.0 | **0.3** | **2.9** | **24.4** | 72.4 |  | 4.6 | 33.6 (32-37) | 74.8 |
| EffTox | 2.0 | **7.0** | **26.0** | **41.0** | 25.0 | 0.0 | 4.8 | 39.8 | 74.0 |

**Table S4.** Operating characteristics of each design. Correct dose decisions are bolded. The values highlighted in light gray correspond to the PCS (percentage of correct MTD selection). The values highlighted in dark gray correspond to the POS (percentage of optimal dose selection) at the recommended optimal dose (dose with the highest desirability, i.e the dose with the better trade-off between toxicity and activity). Q1-Q3: interquartile ranges. For EffTox, no interquartile range is provided as the sample size was fixed (except in the uncommon case of early stopping). #: number. The average total number of toxicity and patient are provided. **Parameters: = 0.10 / = 0.25 / = 0.20**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Dose level% selection |  | # of toxicity | # of patients (Q1-Q3) | Percentage of Correct dose Decision |
|  | -1 | 1 | 2 | 3 | 4 | None |
| **Sc. 1** |  |  |  |  |  |  |  |  |  |
| DE-EC | **0.0** | **13.8** | **63.7** | 22.0 | 0.5 |  | 14.1 | 57.3 (53-61) | 77.4 |
| DE-ECext | **0.0** | **7.1** | **76.9** | 15.7 | 0.3 |  | 12.6 | 53.6 (47-57) | 85.6 |
| EffTox | **5.0** | **56.0** | **37.0** | 1.0 | 0.0 | 1.0 | 9.8 | 59.4 | 98.0 |
| **Sc. 2** |  |  |  |  |  |  |  |  |  |
| DE-EC | 0.2 | 13.9 | **63.3** | 21.3 | 1.3 |  | 13.8 | 56.9 (53-61) | 70.8 |
| DE-ECext | 0.0 | 6.1 | **78.3** | 15.3 | 0.3 |  | 12.7 | 53.2 (47-57) | 72.2 |
| EffTox | 3.0 | 39.0 | **50.0** | 4.0 | 0.0 | 4.0 | 11.4 | 57.5 | 50.0 |
| **Sc. 3** |  |  |  |  |  |  |  |  |  |
| DE-EC | 0.2 | 11.1 | 65.7 | 21.4 | 1.6 |  | 13.6 | 56.1 (53-60) | 30.0 |
| DE-ECext | 0.1 | 7.2 | 74.9 | 17.7 | 0.1 |  | 12.1 | 51.2 (46-56) | 57.8 |
| EffTox | 7.0 | 41.0 | 34.0 | 3.0 | 1.0 | 15.0 | 9.5 | 50.9 | 15.0 |
| **Sc. 4** |  |  |  |  |  |  |  |  |  |
| DE-EC | **0.0** | **13.9** | **63.0** | 22.1 | 1.0 |  | 13.8 | 56.9 (53-61) | 74.1 |
| DE-ECext | **0.0** | **5.9** | **76.3** | 17.6 | 0.2 |  | 12.5 | 52.8 (47-58) | 69.8 |
| EffTox | **14.0** | **45.0** | **31.0** | 2.0 | 1.0 | 7.0 | 9.2 | 55.5 | 90.0 |
| **Sc. 5** |  |  |  |  |  |  |  |  |  |
| DE-EC | 0.1 | 12.1 | 65.3 | 21.2 | 1.3 |  | 11.1 | 45.2 (31-55) | 96.6 |
| DE-ECext | 0.3 | 11.8 | 69.8 | 17.7 | 0.4 |  | 9.7 | 40.0 (32-48) | 98.7 |
| EffTox | 1.0 | 4.0 | 19.0 | 17.0 | 5.0 | 55.0 | 8.8 | 32.5 | 55.0 |
| **Sc. 6** |  |  |  |  |  |  |  |  |  |
| DE-EC | 0.3 | 15.6 | **64.8** | 18.7 | 0.6 |  | 13.9 | 56.6 (53-61) | 71.7 |
| DE-ECext | 0.0 | 8.8 | **74.1** | 16.6 | 0.5 |  | 12.4 | 52.6 (47-57) | 76.2 |
| EffTox | 2.0 | 52.0 | **36.0** | 2.0 | 1.0 | 8.0 | 9.9 | 55.4 | 36.0 |
| **Sc. 7** |  |  |  |  |  |  |  |  |  |
| DE-EC | 0.0 | 0.3 | **2.4** | **21.7** | 75.6 |  | 9.2 | 57.3 (55-61) | 41.9 |
| DE-ECext | 0.0 | 0.0 | **0.6** | **16.4** | 83.0 |  | 8.1 | 51.5 (49-56) | 63.1 |
| EffTox | 3.0 | 2.0 | **19.0** | **41.0** | 28.0 | 7.0 | 7.4 | 56.0 | 60.0 |

**Table S5.** Scenarios investigated for the sensitivity simulation study. Pairs of toxicity and activity rates in bold correspond to a correct dose decision. The desirability represents the trade-off between the toxicity and the activity provided by EffTox.

|  |  |
| --- | --- |
|  | **Doses level** |
|  | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| **Scenario S1** |  |  |  |  |  |  |  |  |
|  True Toxicity | 0.01 | 0.01 | **0.03** | **0.08** | **0.13** | **0.25** | 0.35 | 0.50 |
|  True Activity (desirability) | 0.10 (0.00) | 0.15 (0.06) | **0.25 (0.17)** | **0.38 (0.30)** | **0.45 (0.35)** | **0.56 (0.20)** | 0.62 (0.08) | 0.71 (-0.26) |
| **Scenario S2** |  |  |  |  |  |  |  |  |
|  True Toxicity | 0.01 | 0.01 | 0.03 | 0.08 | 0.13 | **0.25** | 0.35 | 0.50 |
|  True Activity (desirability) | 0.03 (0.00) | 0.05 (0.06) | 0.08 (0.17) | 0.11 (0.30) | 0.15 (0.35) | **0.27 (0.27)** | 0.38 (0.08) | 0.54 (-0.26) |
| **Scenario S3** |  |  |  |  |  |  |  |  |
|  True Toxicity | 0.01 | 0.01 | 0.03 | 0.08 | **0.13** | **0.25** | 0.35 | 0.50 |
|  True Activity (desirability) | 0.05 (-0.06) | 0.05 (-0.06) | 0.11 (0.01) | 0.15 (0.05) | **0.21 (0.10)** | **0.25 (0.04)** | 0.32 (-0.05) | 0.38 (-0.33) |

**Table S6.** Operating characteristics of each design. Correct dose decisions are bolded. The values highlighted in light gray correspond to the PCS (percentage of correct MTD selection). The values highlighted in dark gray correspond to the POS (percentage of optimal dose selection) at the recommended optimal dose (dose with the highest desirability, i.e the dose with the better trade-off between toxicity and activity). Q1-Q3: interquartile ranges. For EffTox, no interquartile range is provided as the sample size was fixed (except in the uncommon case of early stopping). #: number. The average total number of toxicity and patient are provided.Dose levels -1 and 1 were never recommended in this set of simulations. Results for these two levels were not presented.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Dose level**% selection |  | # of toxicity | # of patients (Q1-Q3) | Percentage of Correct dose Decision |
|  | 2 | 3 | 4 | 5 | 6 | 7 | None |
| **Sc. S1** |  |  |  |  |  |  |  |  |  |  |
| DE-EC | **0.0** | **1.4** | **14.0** | **49.8** | 32.2 | 2.5 |  | 9.7 | 45.5 (43-48) | 65.3 |
| DE-ECext | **0.0** | **0.2** | **11.4** | **62.6** | 24.5 | 1.3 |  | 9.4 | 44.7 (40-48) | 76.9 |
| EffTox | **3.0** | **21.0** | **54.0** | **20.0** | 1.0 | 0.0 | 1.0 | 7.3 | 49.6 | 98.0 |
| **Sc. S2** |  |  |  |  |  |  |  |  |  |  |
| DE-EC | 0.2 | 1.8 | 15.1 | **51.6** | 27.7 | 3.6 |  | 9.4 | 43.7 (42-48) | 56.5 |
| DE-ECext | 0.1 | 1.4 | 14.9 | **52.3** | 28.9 | 2.4 |  | 9.2 | 43.7 (39-48) | 59.7 |
| EffTox | 0.0 | 11.0 | 42.0 | **38.0** | 4.0 | 0.0 | 5.0 | 8.7 | 47.2 | 38.0 |
| **Sc. S3** |  |  |  |  |  |  |  |  |  |  |
| DE-EC | 0.0 | 1.0 | **15.2** | **49.3** | 31.5 | 3.0 |  | 9.6 | 44.4 (42-48) | 55.5 |
| DE-ECext | 0.0 | 0.3 | **12.6** | **61.6** | 23.4 | 2.1 |  | 10.2 | 43.7 (40-48) | 48.2 |
| EffTox | 1.0 | 11.0 | **49.0** | **28.0** | 4.0 | 0.0 | 6.0 | 8.2 | 46.7 | 77.0 |

**Supplementary figures**



**Figure S1.** Family of trade-offs contours (grey lines) and target of equidesirable pairs of activity-toxicity contour (bold and black line). Blue triangle to the three target probabilities pairs defined.



**Figure S2.** Supplementary scenarios investigated.