CPRC Initial Full Review Application

Appendix A: Phase I Trial Operating Characteristics

CONTENTS

Overview

1. The purpose of this appendix is to document the operating characteristics of Phase I trials with dose-escalation designs. If operating characteristics are described in the protocol, this appendix is not required and the application submitter should indicate the location of the description of operating characteristics in the CPRC application (section 4).
2. Background:
   To evaluate the performance of the dose escalation design, CPRC biostatistical reviewers require documentation of operating characteristics for the study design under one or more sets of hypothesized toxicity proportions associated with each dose level, in order to determine how likely it is that this design will select a dose in the desired toxicity range. **The CPRC is not requiring revision to the protocol document to include this information.**
3. Software:
   Examples of programs that can be used to calculate operating characteristics are listed below. They are provided as references only; other programs and/or designs may be used.
   a. Trialdesign.org calculates operating characteristics for several common dose escalation designs including BOIN, CRM, and Keyboard. This is usually found on the simulation tab for each design. The BOIN program has an option to calculate 3+3 operating characteristics (https://www.trialdesign.org/one-page-shell.html#BOIN).
   b. The R package "UBCRM" has functions ssimCrm and ssim3p3 that calculate operating characteristics for the CRM and 3+3 designs, respectively.

Example

The following text represents an excellent example of a response to this documentation request.

The operating characteristics of the BOIN design were assessed via clinical trial simulations under various assumed true dose-toxicity relationships. Simulations were performed under 5 different dose-toxicity scenarios. Table 2 gives the true DLT probability at each study drug dose level under each simulation scenario.

The scenarios represent a range of locations for the true MTD. For each scenario, the DLT probability for the true MTD is bolded. Note that all dose levels exceed the true MTD for scenario 1.

Table 2. True DLT Probability at Each Dose Level for Simulation Scenarios

	Study Drug Dose (mg)		
Scenario	**200**	**400**	**800**
1	0.480	0.600	0.700
2	**0.285**	0.480	0.600
3	0.085	**0.285**	0.500
4	0.050	0.100	**0.285**
5	0.050	0.100	**0.150**

To assess the operating characteristics of the BOIN design, 1000 trials were simulated for each of the 5 scenarios shown in Table 2. For simplicity, the following conventions were implemented for all simulations:

- The initial cohort assigned to a dose level consisted of exactly 6 subjects, and subsequent cohorts (if any) assigned to the same dose level consisted of exactly 3 subjects
- The maximum sample size was 24 subjects
- If the starting dose level (200 mg) was eliminated by the dose escalation rule, the trial was terminated early for excessive toxicity (and no MTD was selected)
- If the dose escalation rule indicated allocation to a dose level for which 9 subjects had previously been allocated, the trial was stopped to declare the MTD (i.e., the maximum sample size at any dose level was 9 subjects)

If the lowest dose level did not meet the MTD criteria at the conclusion of the trial, no MTD was selected (i.e., the lowest dose level required de-escalation per the BOIN decision rule, such that all dose levels exceeded the MTD.)

The simulated trials were summarized to obtain the following operating characteristics of the BOIN design under each dose-toxicity scenario:

- MTD selection percentage (% of trials which select each dose level as the MTD)
- Average number of subjects allocated per dose level
- Average total number of subjects allocated per trial
- Average number of DLTs observed per dose level
- Average total number of DLTs observed per trial

Tables 3 through 7 display the operating characteristics for each simulation scenario. The results indicate that the BOIN design correctly selects the true MTD more frequently than other dose levels, and generally selects a dose level at or near the true MTD. Note that for scenario 1, the BOIN design correctly selects no MTD (i.e., all doses exceed the true MTD) with high probability.

Table 3. Operating Characteristics for Scenario 1

Dose (mg)	True Prob (DLT)	MTD Selection %	Avg N	Avg DLT
200	0.480	12.5	8.1	3.8
400	0.600	0.3	1.2	0.7
800	0.700	0.0	0.1	0.1
		No MTD = 87.2%	9.4	4.6

Table 4. Operating Characteristics for Scenario 2

Dose (mg)	True Prob (DLT)	MTD Selection %	Avg N	Avg DLT
200	0.285	48.2	8.7	2.4
400	0.480	6.6	4.5	2.1
800	0.600	0.1	0.6	0.4
		No MTD = 45.1%	13.8	4.9

Table 5. Operating Characteristics for Scenario 3

Dose (mg)	True Prob (DLT)	MTD Selection %	Avg N	Avg DLT
200	0.085	44.6	7.8	0.6
400	0.285	46.8	8.4	2.3
800	0.500	5.5	4.3	2.2
		No MTD = 3.1%	20.5	5.2

Table 6. Operating Characteristics for Scenario 4

Dose (mg)	True Prob (DLT)	MTD Selection %	Avg N	Avg DLT
200	0.050	5.1	6.5	0.3
400	0.100	46.9	7.9	0.8
800	0.285	47.5	8.1	2.3
		No MTD =0.5%	22.5	3.5

Table 7. Operating Characteristics for Scenario 5

Dose (mg)	True Prob (DLT)	MTD Selection %	Avg N	Avg DLT
200	0.050	5.0	6.5	0.3
400	0.100	12.9	6.9	0.7
800	0.150	81.6	8.3	1.2
		No MTD =0.5%	21.6	2.3