Chapter 108

Dose-Finding using the Bayesian Continual Reassessment Method (CRM)

Introduction

This procedure provides sample size calculations for a phase I dose-finding trial that uses the continual reassessment method.

These calculations are based on Cheung (2013) which provides closed form formulae for sample size requirements for the Bayesian continual reassessment method (CRM). This procedure was described in O'Quigley *et al.* (1990) with more details given in Piantadosi *et al.* (1998).

Sample Size Calculation

In a typical phase I study, each additional patient is treated at a dose selected from a set of *K* doses. The binary outcome of interest is whether the patient experiences a toxicity event. The objective of the study is to estimate the maximum tolerated dose (MTD) which will then be used in a phase II trial.

The benchmark index, A, of the CRM design assuming a logistic dose-toxicity configuration is probability of a correct selection of the MTD. This probability, *A*(*N, T, K, OR*), is defined in terms of four parameters: *N* (sample size), *T* (target toxicity rate), *K* (number of doses levels), and *OR* (odds ratio of toxicity rates between any two adjacent dose levels).

The formula for *B*(*N, T, K, OR*), given as (7) on page 855 of Cheung (2013), is

$$B(N,T,K,OR) = \frac{1}{K} + \left(\frac{K-1}{K}\right)\left\{\Phi\left(\Delta_L\sqrt{N}\right) + \Phi\left(\Delta_U\sqrt{N}\right) - 1\right\}$$

where

$$p_1 = \frac{T}{T + OR - T(OR)}$$

$$p_2 = \frac{T(OR)}{1 - T + T(OR)}$$

$$c = \frac{1}{2N}$$

$$\Delta_L = \frac{T - p_1 + c}{\sqrt{T(1-T) + p_1(1-p_1) + 2p_1(1-T)}}$$

$$\Delta_U = \frac{p_2 - T - c}{\sqrt{T(1-T) + p_1(1-p_1) + 2p_1(1-T)}}$$

The optional quantity *c* is called the continuity correction. Cheung (2013) uses *c* in all of calculations. The relationship between *A*(*N, T, K, OR*) and *B*(*N, T, K, OR*) is

$$\text{logit}\{A(N,T,K,OR)\} = 2.26 + 0.854\,\text{logit}\{B(N,T,K,OR)\} - 0.00235K^2 - 0.7(OR) - \frac{1.903}{OR}$$

Finally, using the inverse of the *logit*, the desired value of $A(N,T,K,OR)$ is given by

$$A(N,T,K,OR) = \frac{\exp[\text{logit}\{A(N,T,K,OR)\}]}{1 + \exp[\text{logit}\{A(N,T,K,OR)\}]}$$

Again, note that *A* is the probability of the correct selection of the MTD. This is called the *accuracy* of the study and is analogous to power.

Based on the above formula, a simple search beginning at *N* = 2 is conducted by increasing *N* by one at each iteration until the computed value of *A* is greater than the designated value.

Parameter Restrictions

The above formulation is based on a simulation study that was restricted to the following constraints:

$$0.1 \le T \le 0.3$$

$$4 \le K \le 8$$

$$1.25 \le OR \le 2.5$$

$$20 \le N \le 40$$

Validation simulations were conducted within these limits, with the exception that some values of *N* were allowed from 9 to 60.

Example 1 – Sample Size across Number of Dose Levels

Researchers are planning a phase I trial to find the appropriate dose level for a phase II trial. They want to understand the relationship between the number of dose levels and the required sample size. The parameter settings will be A = 0.6; K = 4, 5, 6, 7, 8; T = 0.25; and OR = 1.8. The continuity correction factor will be applied. The value of N will be determined.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Sample Size**
A (Accuracy Level)	**0.6**
K (Number of Dose Levels)	**4 5 6 7 8**
T (Target Toxicity Rate)	**0.25**
OR (Odds Ratio of Toxicity Rates)	**1.8**
Continuity Correction	**Checked**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: Sample Size
Continuity Correction: Yes

Accuracy					
Target A	Actual A	Sample Size N	Dose Levels K	Target Toxicity Rate T	Odds Ratio of Toxicity Rates OR
0.6	0.60068	27	4	0.25	1.8
0.6	0.60137	32	5	0.25	1.8
0.6	0.60230	36	6	0.25	1.8
0.6	0.60063	39	7	0.25	1.8
0.6	0.60434	43	8	0.25	1.8

A The Actual Accuracy level desired. This is the probability of a correct selection of the MTD (maximum tolerated dose). It is analogous to power.
N The sample size. This is the anticipated number of subjects needed to complete the study.
K The number of dose levels in the pool of dosages that are being considered.
T The Target Toxicity Rate or the dose-limiting toxicity rate (DLT) is the proportion of subjects that have a toxic event.
OR The Odds Ratio of toxicity rates between any two adjacent dose levels.

Summary Statements

A continual reassessment method (CRM) design with sequential assignment to 4 dose levels will be used to estimate the maximum tolerated dose (MTD). A continuity correction will be used in the calculation of the study accuracy. The target toxicity rate is 0.25. To achieve an accuracy level of 0.6 (the estimated probability of correct MTD selection) with an odds ratio of toxicity rates between all adjacent dosages of 1.8, 27 subjects will be needed.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	27	34	7
20%	32	40	8
20%	36	45	9
20%	39	49	10
20%	43	54	11

Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N	The evaluable sample size at which the confidence interval is computed. If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated confidence interval.
N'	The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula N' = N / (1 - DR), with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)
D	The expected number of dropouts. D = N' - N.

Dropout Summary Statements

Anticipating a 20% dropout rate, 34 subjects should be enrolled to obtain a final sample size of 27 subjects.

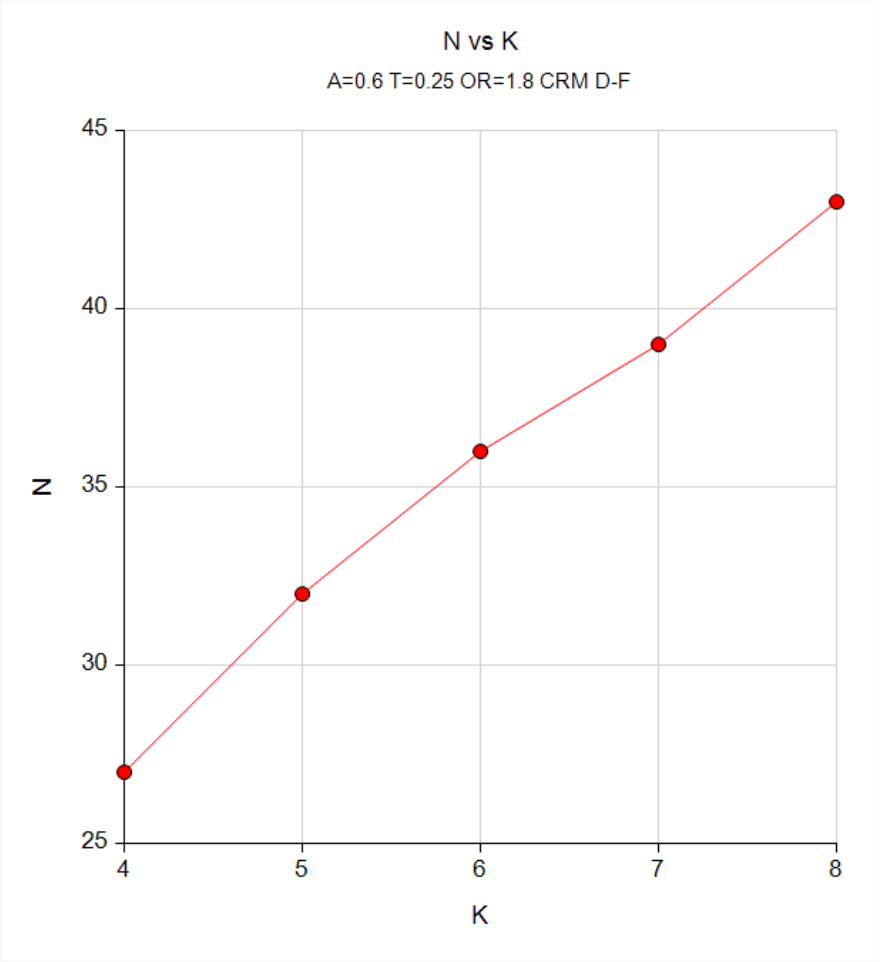
References

Cheung, Ying Kuen. 2013. 'Sample size formulae for the Bayesian continual reassessment method.' Clinical Trials, Volume 10, 852-861.

O'Quigley, J, Pepe, M, Fisher, L. 1990. 'Continual reassessment method: A practical design for phase I clinical studies in cancer.' Biometrics, Volume 46, 33-48.

Piantadosi, S, Fisher, JD, Grossman, S. 1998. 'Practical implementation of a modified continual reassessment method for dose-finding trials.' Cancer Chemotherapy Pharmacology, Volume 41, 429-436.

Plots



This plot shows that the sample increases steadily with an increasing K.

Example 2 – Validation using Cheung (2013)

Cheung (2013) page 858 Table 6 provides results that may be used to validate the procedure. The parameter settings we will use for validation are A = 0.6; K = 5; T = 0.25; and OR = 1.8. The continuity correction factor is applied. The value of N is found to be 32.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Sample Size**
A (Accuracy Level)	**0.6**
K (Number of Dose Levels)	**5**
T (Target Toxicity Rate)	**0.25**
OR (Odds Ratio of Toxicity Rates)	**1.8**
Continuity Correction	**Checked**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: Sample Size
Continuity Correction: Yes

Accuracy					
Target A	Actual A	Sample Size N	Dose Levels K	Target Toxicity Rate T	Odds Ratio of Toxicity Rates OR
0.6	0.60137	32	5	0.25	1.8

PASS also calculated the sample size to be 32, which validates the procedure.