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

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

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

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

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

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

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
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

Numeric Results

Solve For: Sample Size
Continuity Correction: Yes

Accuracy		Sample	Dose	Target	Odds Ratio of
Target	Actual	Size	Levels	Toxicity Rate	Toxicity Rates
A	A	N	K	T	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

Report Definitions

A is 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 is the sample size. This is the anticipated number of subjects needed to complete the study.
K is the number of dose levels in the pool of dosages that are being considered.
T is the Target Toxicity Rate or the dose-limiting toxicity rate (DLT) is the proportion of subjects that have a toxic event.
OR is Odds Ratio of toxicity rates between any two adjacent dose levels.

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.

Summary Statements

A sample size of 27 subjects in a CRM design are sequentially assigned to one of 4 dose levels. The study achieves an accuracy level of 0.60068 (the estimated probability of correct MTD selection). The target toxicity rate (DLT) is 0.25. The odds ratio of toxicity rates between all adjacent dosages is 1.8. A continuity correction was used in the calculation.

These reports show that the required sample size increases with the number of levels.

Chart Section

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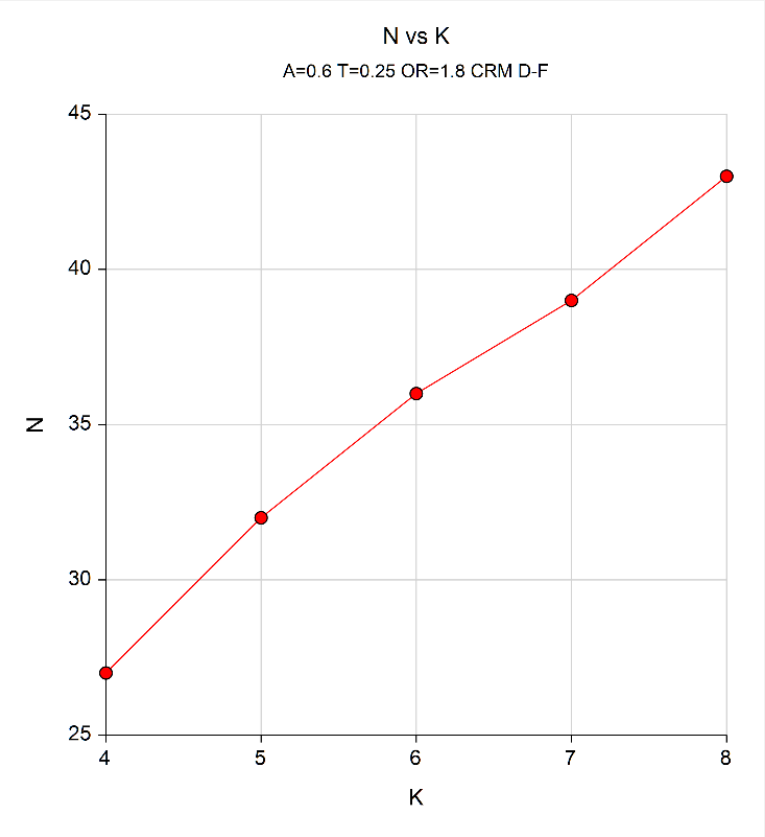

This plot shows that the sample increases steadily with an increasing K.

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
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

Numeric Results

Solve For: Sample Size
Continuity Correction: Yes

Accuracy		Sample	Dose	Target Toxicity	Odds Ratio of Toxicity
Target A	Actual A	Size N	Levels K	Rate T	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.