bCRM – Running A Trial

Tessella Project Number 3760

System User Guide

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Issue	Author	Date	Description
V1.R1.M0	Geraint Lloyd	15-Mar-05	1st version written for release v1.0.0
V1.R2.M0	Robert Nelson	27-Jul-2005	Version for release v1.0.1

References

Ref.	Document	Date	Details and Version
[Goodman]	"Some practical improvements in the continual reassessment method for phase I studies", S.N.Goodman, M.L.Zahurak, S.Piantadosi	Statistics in Medicine 14:1149-1161, 1995	Paper describing a practical application of the CRM to phase I studies
[Braun]	"The bivariate continual reassessment method: extending the CRM to phase I trials of two competing outcomes", T.M.Braun	Controlled Clinical Trials 23:240-256, 2002	Original paper describing the bivariate continual reassessment method
[SUG-S]	"bCRM – Defining and Running Simulations" – System User Guide	11-Mar-05	NPD/3670/SUG "bCRM – Defining and Running Simulations" V1.R1.M0

Table of Contents

1 Introduction

1.1 Purpose of this document

This document describes how to use the bCRM application graphical user interface. It is intended for all end users of the system. Users are encouraged to read the 1995 [Goodman] paper and the original bCRM paper [Braun] before using the bCRM application.

1.2 Scope of this document

This guide only describes using the bCRM graphical interface and the bCRM facilities accessible via that interface for running a trial; it does not cover all the statistical details of the model and method that it uses for dose allocation and simulation.

1.3 Context of this Issue

This issue documents version 1.0.1 of the system.

1.4 Definition of Terms

bCRM	refers to the computer programs that implement the bivariate continual reassessment method dose-finding algorithm, simulate and run phase 1 clinical trials using the bivariate continual reassessment method design and provide charts and graphs of the results.
A Simulation Series	is comprised of a 'Design' for a trial using the bCRM algorithm, a set of one or more 'Scenarios' – possible probabilities of toxicities and efficacies – and one or more 'Variants' where some of the Design parameters can be varied to explore the effect of the variation on the operating characteristics of a Trial. A Simulation Series creates a number of Runs = (number of Scenarios) * (number of Variants).
A Design	is a set of parameters that define a trial design to be carried out using the bCRM algorithm. This consists of: the specific drug dose strengths that can be used during the trial; the 'alpha' value of the modelling logistic curve along with a set of estimated toxicity and efficacy probabilities which are used to define the set of curves to model the response; the start dose and maximum dose level increment allowed during the trial; and the trial size details – the number of subjects assigned in each cohort used in the trial, the maximum number of subjects and the trial termination conditions.
A Scenario	is a set of fixed values of the probability of toxicity and efficacy for each of the dose strengths to be used in the trial. These define the 'true' drug response during a simulation.
A Variant	is a small modification to a Design – for example a different cohort size, study sample size or value of alpha.
A Run	A run is a set of all the parameters required to simulate a trial, it is the combination of a Design and a Scenario. A Simulation Series creates one or more runs. Each run is organised as a separate folder, all the parameters for a run are held in a single file called 'init.bcrm' and all the outputs for the simulations of the run are held in the folder in '.csv' files. (Plain text files with one record per line, individual values separated by commas – this format of file is readily imported into many other programs such as Excel, Access, SAS and Oracle). bCRM can have at most one run directory open at any one time and it is the files in this directory that provide the source data for the parameter values and visualisation.

Simulation	A simulation is the result of probabilistically generating a single clinical trial using bCRM. bCRM creates data for subjects and their responses by randomly selecting from the relevant probability distributions of the scenario defined in the bCRM input file. A particular run may be simulated a number of times, indeed to accurately analyse the characteristics of a particular Design it must be simulated usually ~10,000 times over a range of scenarios.
Trial	A trial is a real clinical trial, where the user enters subjects' data and responses. The bCRM Algorithm is run to determine the doses to allocate and to analyse the results. This facility allows bCRM's adaptive allocation to be used on small (single centre) trials.
MTD	The maximum tolerable dose. This is the strongest of the doses in the trial that has a toxicity below the target toxicity.
MED	The minimum efficacious dose. This is the weakest of the doses in the trial that has an efficacy below the target efficacy.

2 Quick Guide

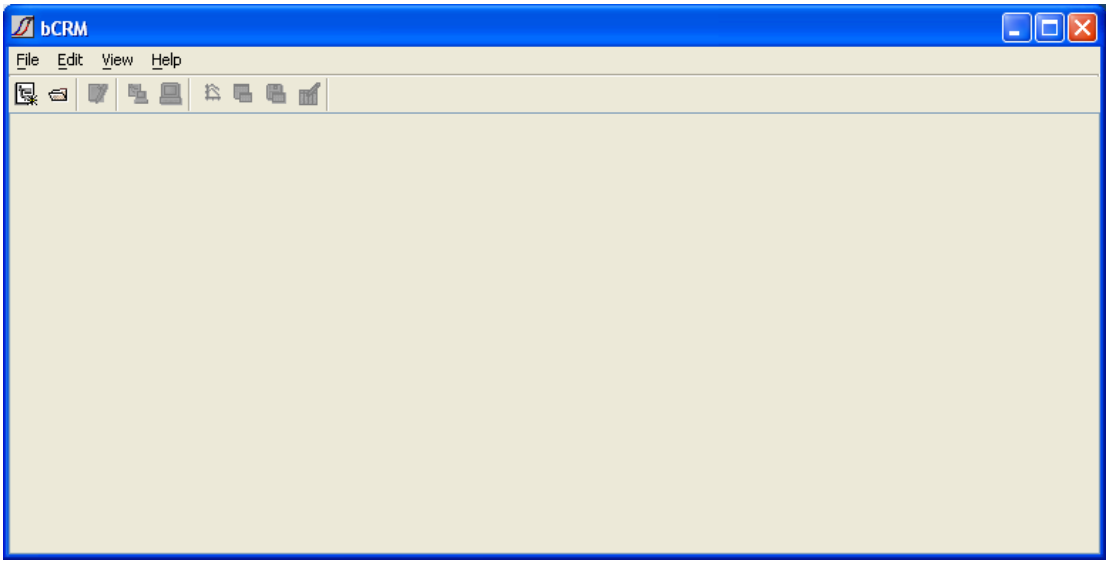
2.1 Starting bCRM

To start bCRM, double-click the bCRM icon that is installed on your computer desktop.

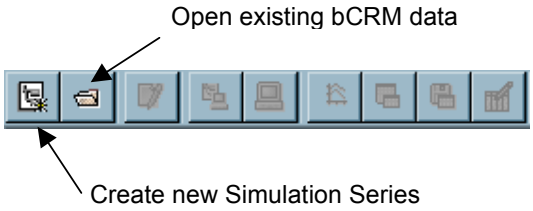
After bCRM has started, the main window will be displayed.

2.2 Main Window

The main window is displayed after bCRM has started and is present until bCRM exits. It is used to open and create designs and to access other parts of the application.



Initially the only enabled buttons are:



These commands are also available from the **File** menu.

2.3 Exiting bCRM

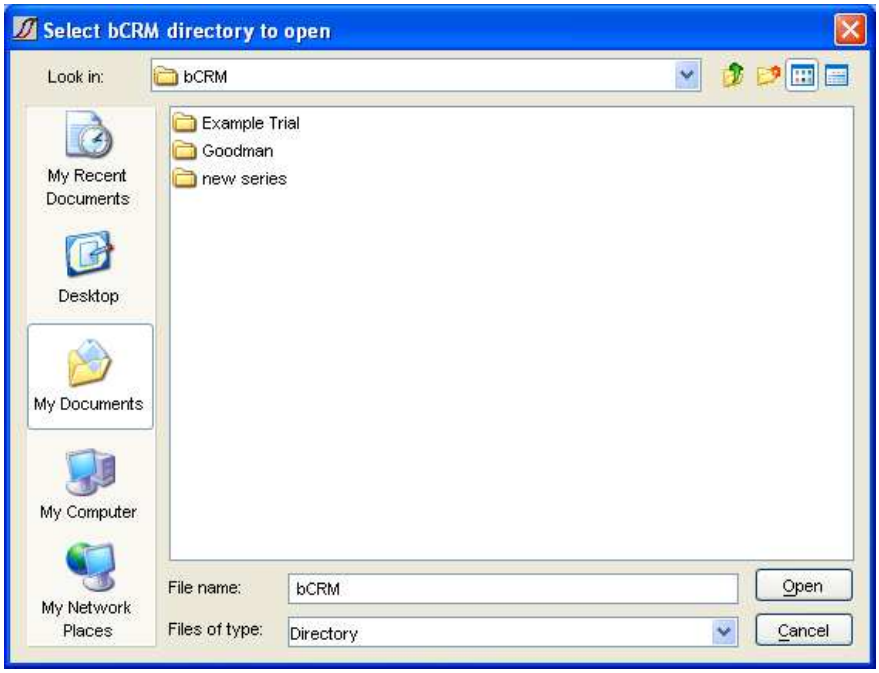
To exit bCRM, select **Exit** from the **File** menu of the main window.

2.4 Displaying Existing Data

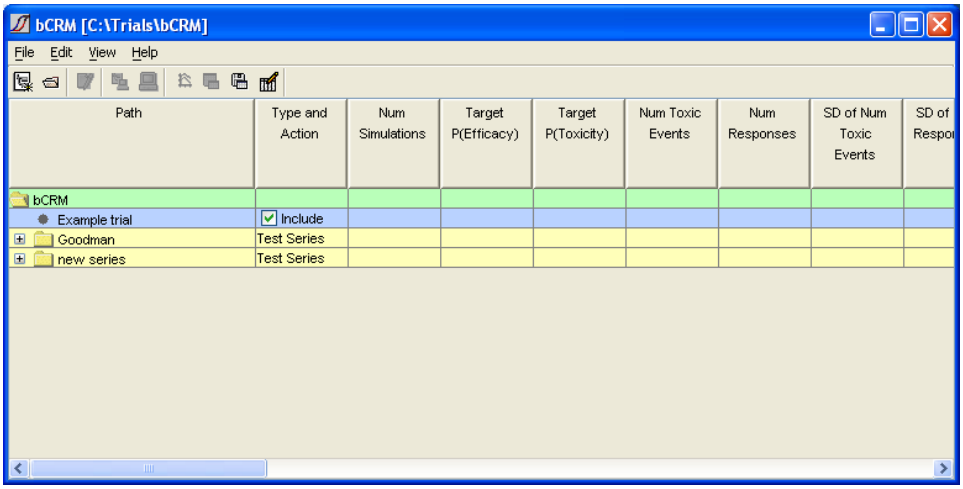
To display existing bCRM Data, select **Open** from the **File** menu, click the tool button or press the `ctrl-o` key. If there are currently any open parameter wizard, run manager, Desktop bCRM or visualisation windows, you will be notified that they will be closed before changing the current simulation series and asked if you wish to proceed.

Use the file browser to select the directory to open and then click the **Open** button. If you change your mind about opening a particular directory then click the **Cancel** button. As well as folders, the file browser displays the bCRM input ('init.bcrm') and output files ('*.csv') in each directory to help you locate the correct one.

If the bCRM input files contain any invalid parameter values, then you will be notified via a message box. These values must be corrected in bCRM before bCRM can be run with this design.

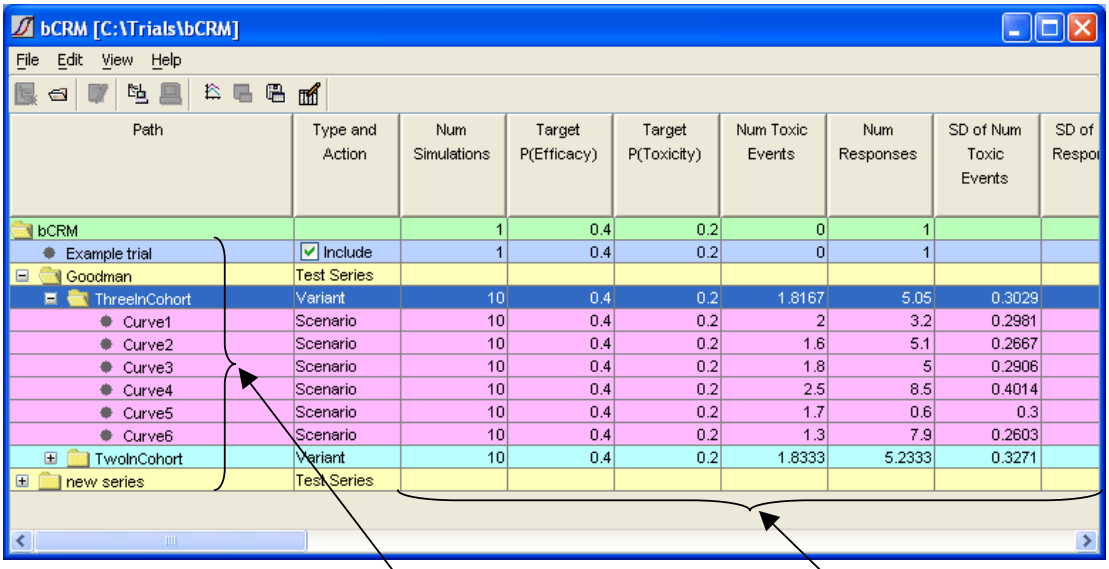


In the folder selected for opening bCRM will display all its folders that contain bCRM data:



2.5 The Toolbar

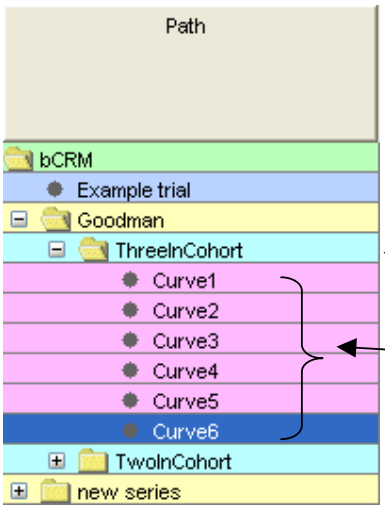
Once a simulation series has been created, or a pre-existing one has been opened, the application's main panel becomes more interesting:



Directory containing the set of Simulation Series & Trials

Simulation Series and Trials

Summary data from simulations or actual trial



A Trial being run by bCRM

A Simulation Series

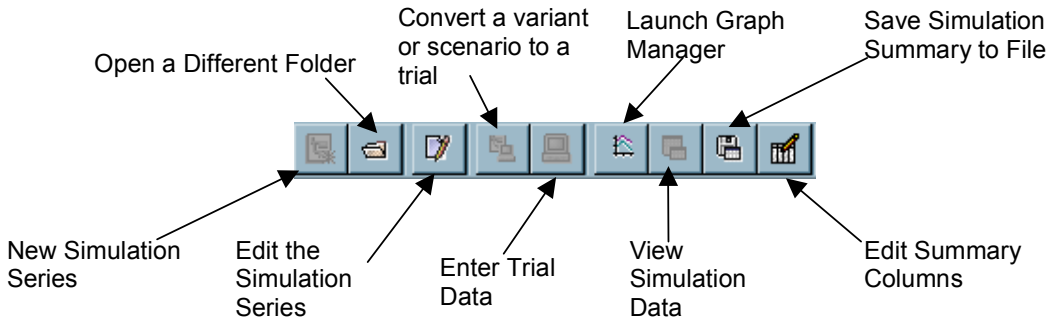
The design variants of the simulation series

The scenarios of design variant "ThreeInCohort", all variants are simulated over the same scenarios.

The currently selected series

Levels can be expanded or hidden by clicking on the '+' or '-' boxes.

Select a simulation series or trial by clicking on its name – the line becomes highlighted. More of the bCRM Toolbar buttons become enabled:



All of these operations are also available from the application's menus.

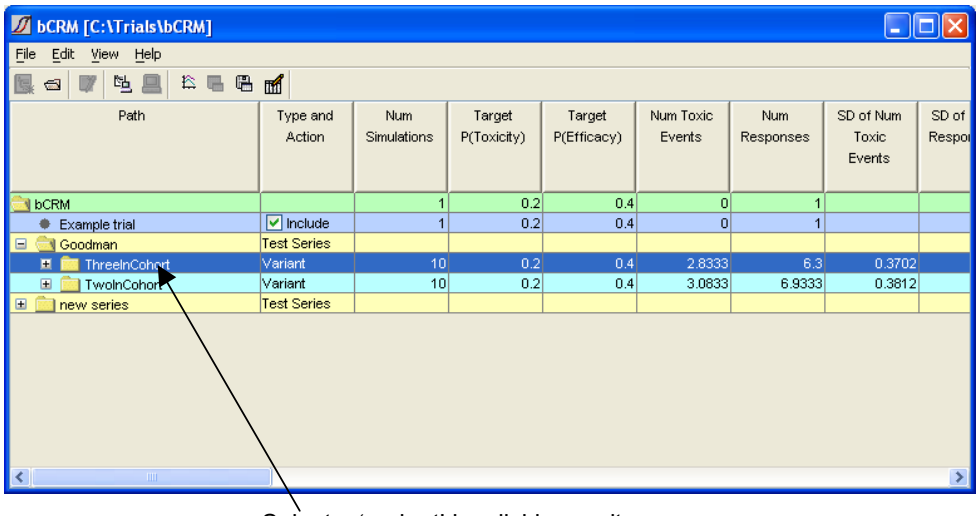
Right clicking on a Trial or Simulation Series selects it and opens a pop-up menu:

This gives short cuts to commands described elsewhere – it also allows the simulation series (the simulation series directory) to be renamed or deleted.

3 Creating A Trial

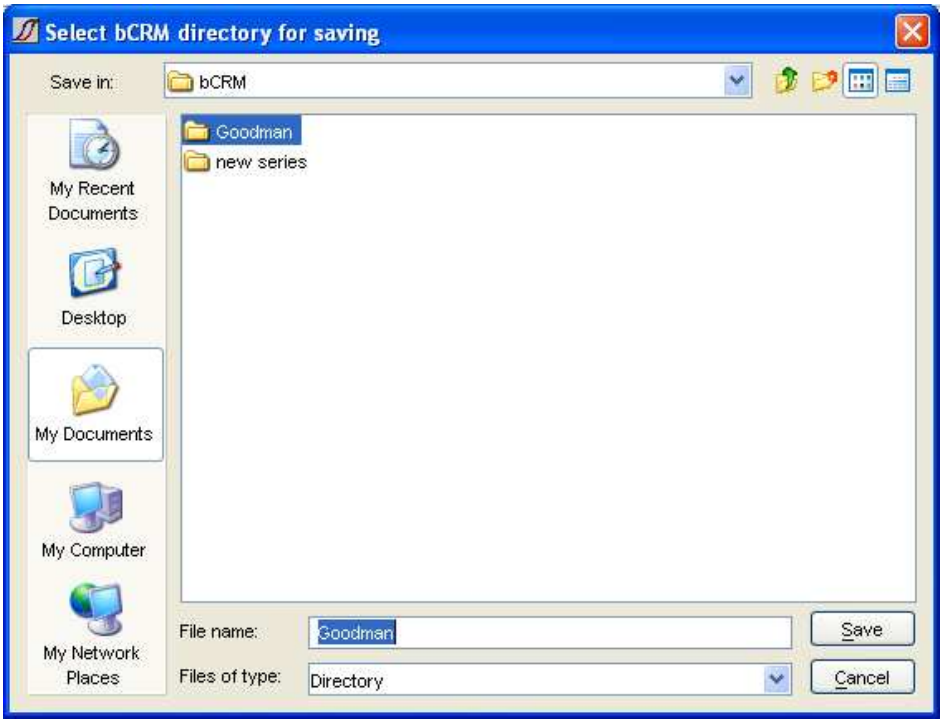
A trial design should be simulated before it is run for real, to check that the operating characteristics of the trial will be acceptable, see [SUG-S] for the facilities in bCRM to support this activity.

At the end of the simulation activity you have a chosen trial design that will be part of a Simulation Series – this will either be one of the variants in the series or the sole, 'default', version of the trial design in that series. To create a trial, simply select this variant in the main screen and click on the 'Convert row to a trial' on the toolbar ( ).



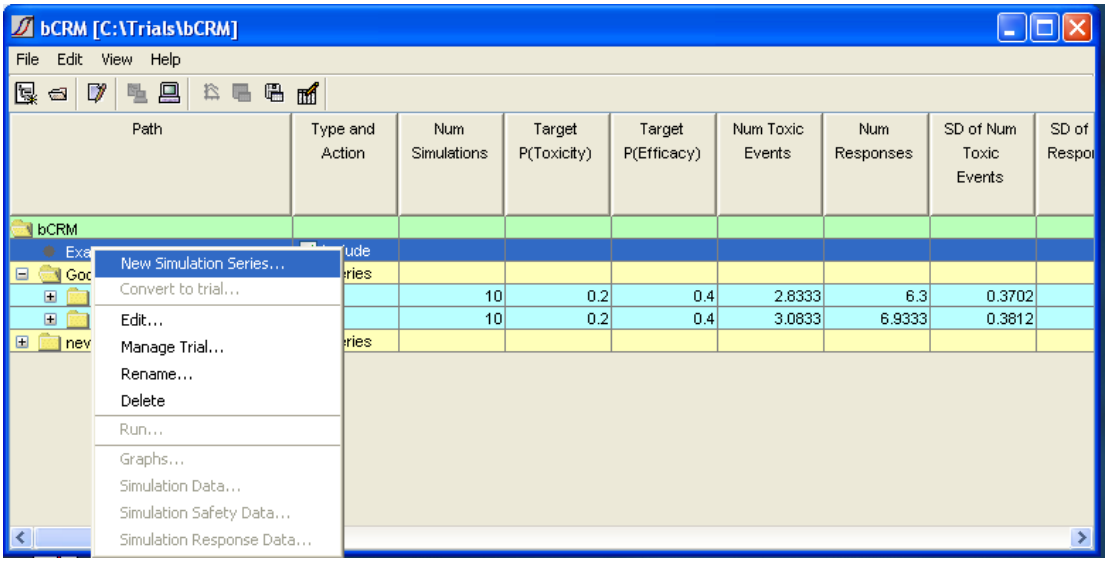
Select a 'variant' by clicking on its name.

You will then be presented with the standard 'save dialog':



This allows you to enter a name for a new directory where the trial definition and the subsequent trial data is to be stored.

Having created the trial you can check, and modify the design by right clicking on the trial name in the main screen and selecting ‘Edit’ from the pop-up menu.

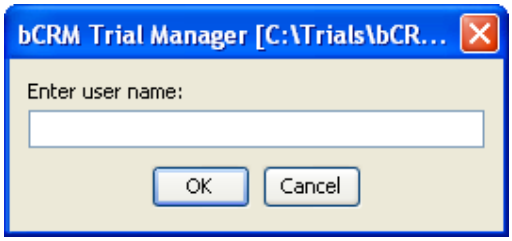


4 Trial Manager

bCRM provides a facility to manage a trial, with subject data and observed toxicities and responses entered manually. The dose allocation is controlled by the bCRM algorithm.

To open the Trial Manager, click the **Manage Trial** button (), or select **Manage Trial** from the **Edit** menu (`Ctrl-t`). These controls are enabled only when a trial row is selected in the summary table.

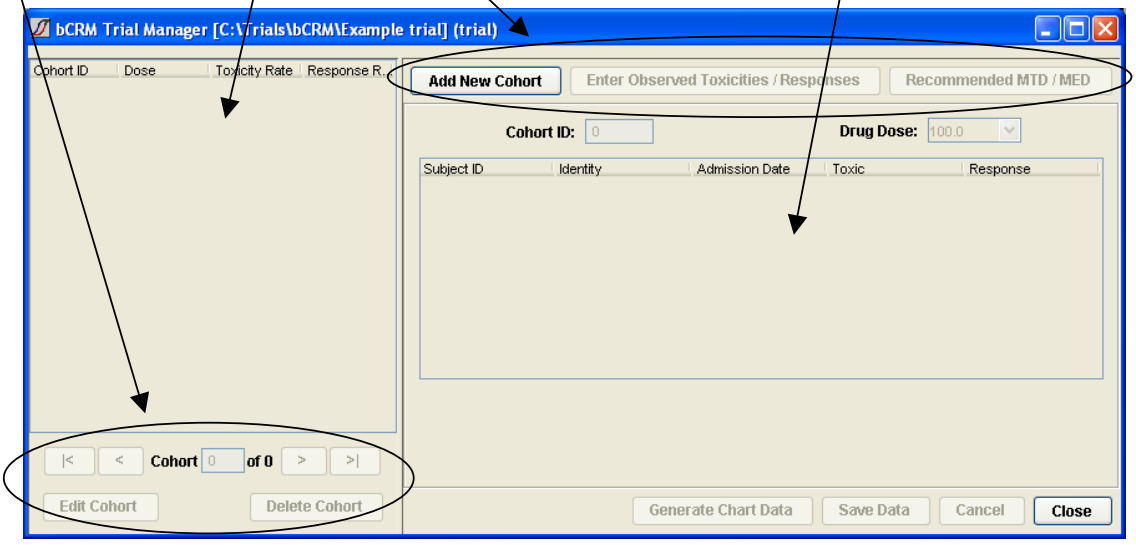
Each time the trial management window is opened, a dialog is displayed requesting a user name. This name ***must not contain space, comma or single quote characters***. Clicking **Cancel** aborts the operation and returns control to the main application window. There is no checking on the name, it is used in the audit log to record who made changes/entered data.



The main Trial Manager window is then displayed.

This is divided into a number of areas:

- general controls for navigating the already entered subject data,
- cohort table that lists all the subjects in the trial,
- a panel displaying information about the currently selected cohort,
- controls to manage a trial.



To select existing cohorts in the trial, the **|<**, **<**, **>** and **>|** navigation buttons may be used or a Cohort ID number may be typed into the **Cohort** text box. Alternatively double clicking a row in the cohort table displays that cohort's details. The currently selected cohort is highlighted in pink.

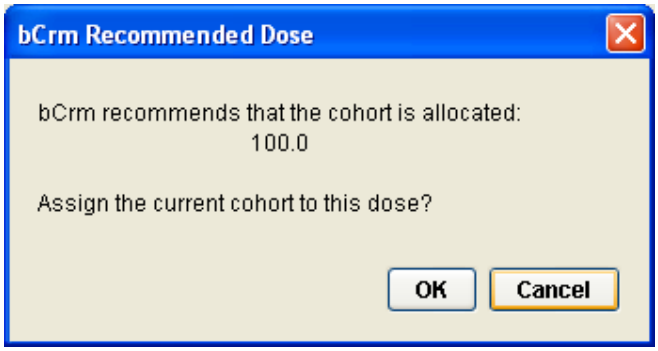
Trail management is divided into 3 steps:

- creation of cohorts and the allocation of doses
- input of observed toxicities
- display of the recommended MTD and MED doses for further study.

4.1.1 Creation of cohorts and the allocation of doses

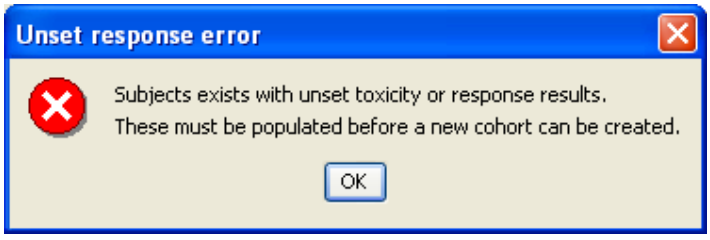
The **Add New Cohort** button creates a new cohort of subjects and executes the bCRM model to recommend a dose to assign them. :

When the calculation finishes the recommended dose strength for this cohort to be allocated is displayed:



Click **OK** to set the cohort **Drug Dose** to this value, otherwise click **Cancel** to ignore the recommendation – the new cohort will be set to the first dose strength.

If there is a cohort that has subjects with an 'unset' observed toxicity or response (efficacy) a warning dialog is displayed and a new cohort may not be added:

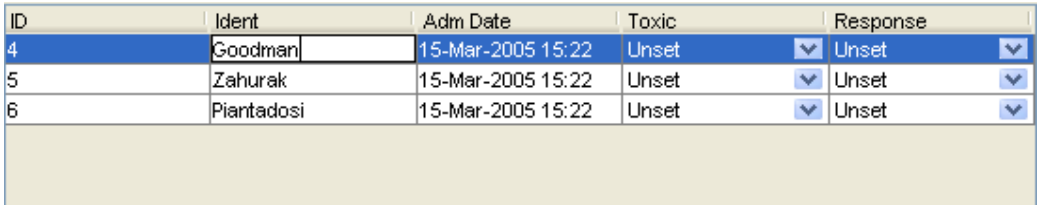


The value in the **Drug Dose** field should be selected manually if the recommended dose is ignored.

The **ID** is a unique number to identify the subject. If the value entered has been repeated a warning is displayed and the value reset. Each subject is automatically assigned an ID one larger than the current maximum, although this may be overridden.

There is a second **Ident** field that may be used to provide something that further identifies the subject (e.g. initials, DoB, patient number). These cannot contain spaces, commas or single quotes.

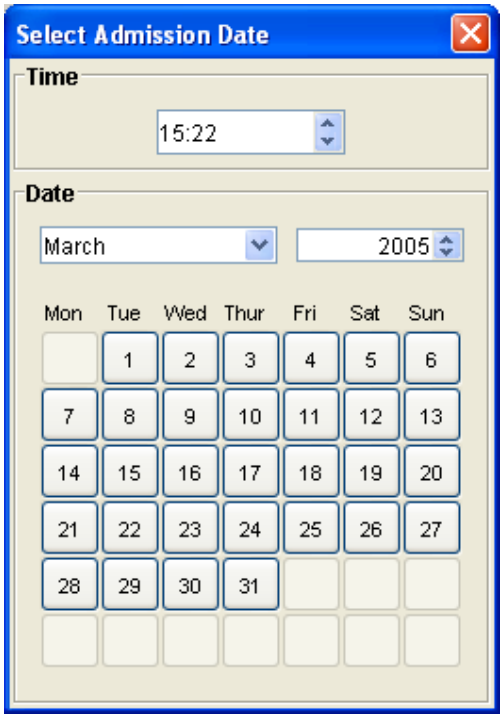
The table lists the subjects associated with the current cohort:



ID	Ident	Adm Date	Toxic	Response
4	Goodman	15-Mar-2005 15:22	Unset	Unset
5	Zahurak	15-Mar-2005 15:22	Unset	Unset
6	Piantadosi	15-Mar-2005 15:22	Unset	Unset

The admission date defaults to the current date. The bCRM algorithm is not time dependent and this field is provided simply to assist cross-checking with subject data recorded elsewhere.

To edit the date or time, click the cell in the table to display a date picker control:



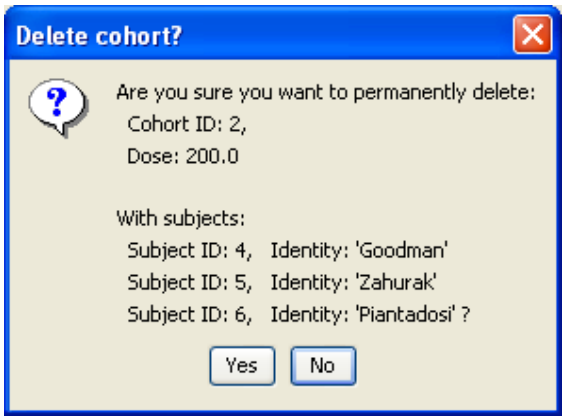
The required time may be set by either typing a new value into the control or selecting the **hours** or **minutes** component and changing it with the up and down arrows at the side of the control.

The required date may be selected picking the **month** from the drop down list, selecting the **year**, either by typing a value into the control or using the up and down controls. Clicking on a **day** button closes the control.

The **Save Data** button writes the current trial subjects to a subject.csv data file. The cohort panel is locked to prevent subject data being edited. **Cancel** locks the record and resets the data to the unedited values.

Click the **Edit Cohort** button to switch the panel into edit mode.

Delete Cohort permanently deletes the currently displayed subject from the trial. A confirmation dialog is displayed to ensure subjects are not deleted in error.

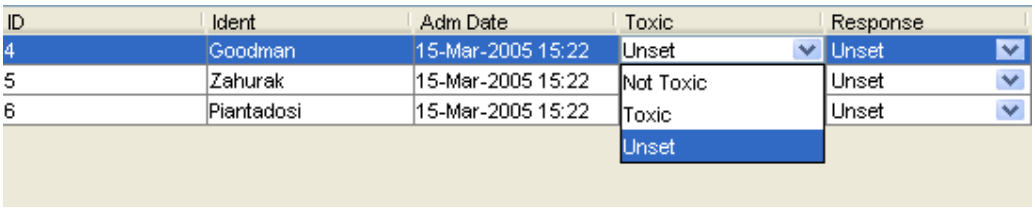


4.1.2 Input of observed toxicities and responses

To enter toxicity results, select the cohort in the cohort table. Initially all the data is locked.

Pressing the **Enter Observed Toxicities / Responses** button unlocks the 'Toxic' and 'Response' columns of the current cohort to allow the observed toxicity or response results to be entered. The remaining controls on the panel remain locked. Alternatively, pressing the **Edit Cohort** button unlocks all controls on the panel.

Clicking a cell in the 'Toxic' column reveals a list of three values that may be set. If no observed toxic responses are available for a subject the value should be 'Unset'; such subjects are ignored when dose recommendations are made. If a toxic event has been observed the toxicity should be set to 'Toxic', if no toxic event was observed it should be set to 'Not Toxic'.



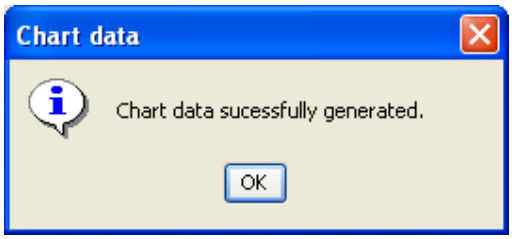
Clicking on cells in the 'Response' column gives a similar set of choices, entitled 'Unset', 'Response' and 'No Response' to mark whether or not efficacy has been observed.

The **Save Data** button writes the updated trial subjects data to a subject.csv data file and the cohort panel is locked to prevent subject data being edited. If the information from the cohort causes the trial early termination conditions to be met, then a message will be displayed to indicate that the trial should now be considered complete.

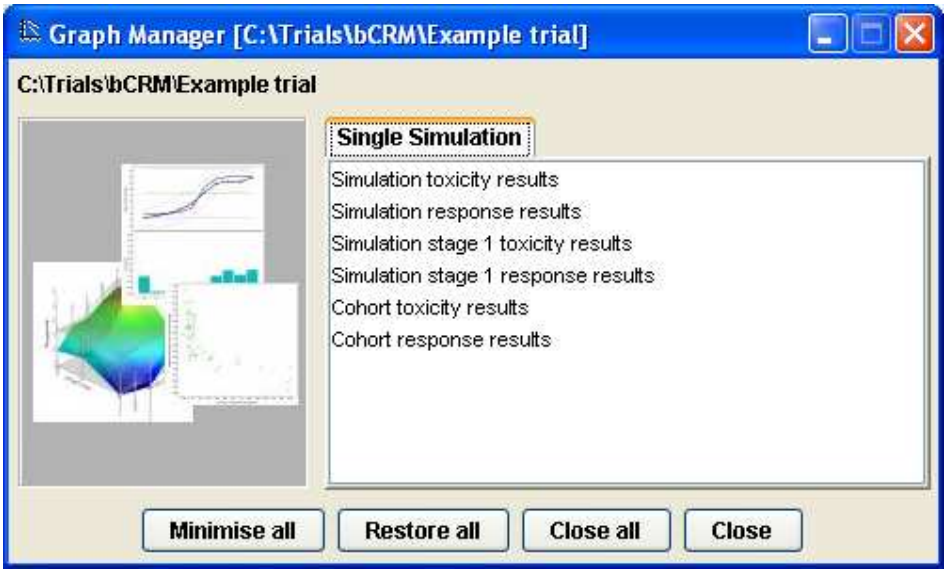
Once toxicity and efficacy information is input for each subject in a cohort, a new cohort may be created (see above). The **Add New Cohort** button is disabled once the final cohort, i.e. the cohort that brings the total number of subjects in the trial to the maximum study size, has been admitted to the trial.

4.1.3 Generate Chart Data

In order to be able to use bCRM's charting facilities (see [SUG-S] for details), the bCRM model must be run on the entered trial data. To do this simply click on the **Generate Chart Data** button. After a few seconds you should see:

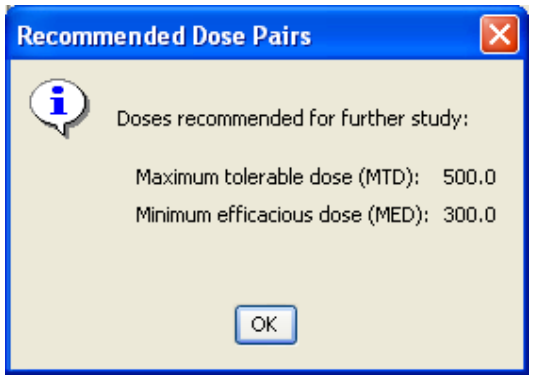


Now when the trial is selected in the main screen, the graph manager button in the toolbar will be enabled and the Graph Manager command in the View menu will be enabled. The Graph Manager will display the subset of graphs applicable to a trial (as opposed to a simulation):



4.1.4 Display of the recommended trio of dose pairs for further study

At any point during a trial, the MTD and MED doses recommended by the bCRM algorithm for a subsequent study, based on the current subject data, may be calculated and displayed by pressing the **Recommended MTD / MED** button.



After the final cohort has been admitted and observed toxicity results entered, the **Recommended MTD / MED** button will calculate the final MTD and MED doses which may be studied in a subsequent randomized trial.

The **Close** button will close the Trial Manager window and display a reminder to resave the trial data if necessary.

4.1.5 Audit Log

All activity is logged in a text file (TrialLog.csv) placed in the trial directory. Each entry is tagged with time, date and user name.

The columns in the log file are:

Column	Description
Date	The date and time of the action.
User	The user name.

Action	A description of the activity, one of: New/Edit/Delete Cohort or New/Edit/Delete Subject.
CohortID	Numeric cohort identity.
Dose	Assigned dose strength.
SubjectID	Numeric subject identity.
Identifier	The subject identifier.
Admission Date	The Admission date of the subject.
Year	The Admission year of the subject.
Time	The Admission time of the subject.
Toxic	The observed toxicity for the subject: 'Toxic', 'Not Toxic' or 'Unset'
Response	The observed response for the subject: 'Response', 'No Response' or 'Unset'

For Cohort actions the subject columns are left empty.

4.2 Reviewing Trial Data

The last MTD / MED doses to be generated, along with the associated P(toxicity) at MTD, P(efficacy) at MED and their uncertainties are displayed in the main application table, and as a single row in the simulation data table.