ToxFinder – Running A Trial

Tessella Project Number 3760

System User Guide

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Issue	Author	Date	Description
V1.R1.M0	Nick Battam, Tom Parke	14-Oct-04	1st version written for Alpha release v0.2.6
V1.R2.M0	Nick Battam	03-Dec-04	Updated for release v1.0.0
V1.R2.M1	Tom Parke	08-Jun-2005	Incorporated minor updates from Peter Thall

References

Ref.	Document	Date	Details and Version
[TMML]	"Dose Finding with Two Agents in Phase I Oncology Trials" Peter F. Thall, Randall E. Milikan, |Peter Mueller, Sang-Joon Lee	Biometrics 59:487-496, 2003	Original paper describing the algorithm.
[SUG-S]	"ToxFinder – Defining and Running Simulations" – System User Guide		NPD/3670/SUG "ToxFinder – Defining and Running Simulations" V1.R3.M0

Table of Contents

1 Introduction

1.1 Purpose of this document

This document describes how to use the ToxFinder graphical user interface. It is intended for all end users of the system. Users are strongly encouraged to read the 2003 Biometrics Paper [TMML] before using ToxFinder.

1.2 Scope of this document

This guide only describes using the ToxFinder graphical interface and the ToxFinder facilities accessible via that interface for running a trial; it does not cover the low level details of the ToxFinder model.

1.3 Context of this Issue

This issue documents version 1.0.0 of the system released to MD Anderson for review.

Note:

- **This release has not been approved by the author's of the [TMML] algorithm as a correct implementation of that algorithm.**
- **This release has been specifically prepared to allow the author's of the [TMML] algorithm to review the current state of the implementation.**

1.4 Definition of Terms

ToxFinder — is a pair of computer programs that implement the TMML dose-finding algorithm, simulate and run clinical trials using the TMML design and provide charts and graphs of the results.

A Simulation Series — is comprised of a 'Design' for a trial using TMML, a set of one or more 'Scenarios' – possible probabilities of toxicities – 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 set of parameters that define a trial design to be carried out using the TMML method. This consists of: the two dose ranges to be used, lambda - the relative cancer killing potential of the two drugs, the prior distribution of the parameters that characterise the probability of toxicity as a function of the dose pair of the two agents, the cohort size, the sample sizes of the two stages of the trial, the fixed line L1 used in the first stage of the trial and the first set of doses to use on L1.

A Scenario — is a set of fixed values of the probability of toxicity as a function of the two agents' doses, $\mathbf{x} = (x_1, x_2)$. We denote this probability by $\pi(\underline{\mathbf{x}})$. As $\mathbf{x}$ varies over the two-dimensional domain of the dose pairs $\pi(\mathbf{x})$ forms a surface that may be illustrated graphically. ToxFinder does this, providing a graphical representation of each scenario specified by the user.

A Variant — is a small modification to a Design – e.g. different prior, cohort size or study sample size.

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 consists of 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.tmml' 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 file format is readily imported into many other programs such as Excel, Access, SAS and Oracle). ToxFinder 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 ToxFinder. ToxFinder creates data for subjects and their responses by randomly selecting from the relevant probability distributions of the scenario defined in the ToxFinder 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 1,000-10,000 times over a range of scenarios.

Trial — A trial is a real clinical trial, where the user enters subjects' data and responses. The ToxFinder Algorithm is run to determine the doses to allocate and to analyse the results. This facility allows ToxFinder's adaptive allocation to be implemented to conduct small (single centre) trials.

2 Quick Guide

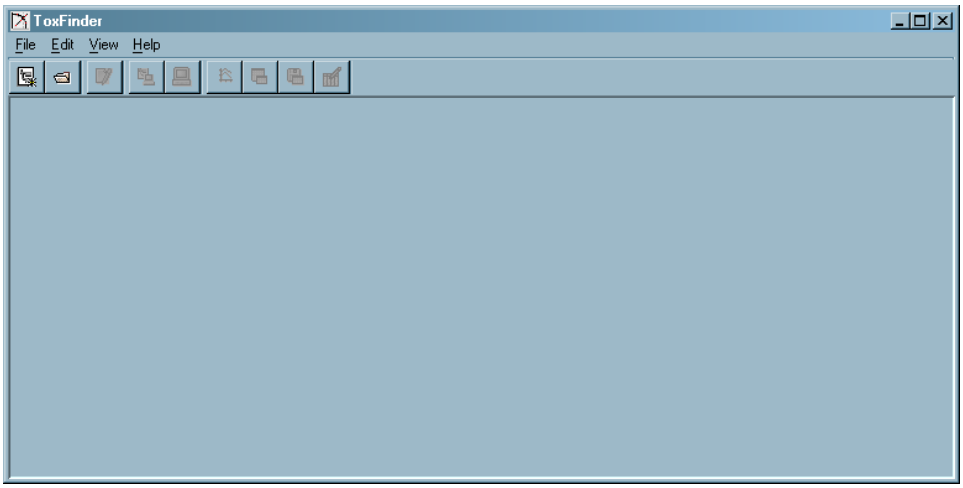
2.1 Starting ToxFinder

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

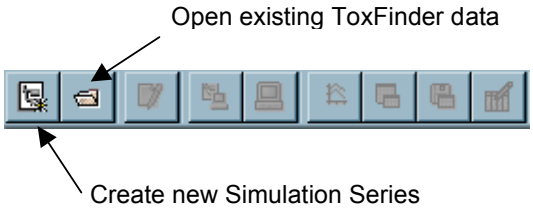
After ToxFinder has started, the main window will be displayed.

2.2 Main Window

The main window is displayed after ToxFinder has started and is present until ToxFinder 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 (along with 'new trial').

2.3 Exiting ToxFinder

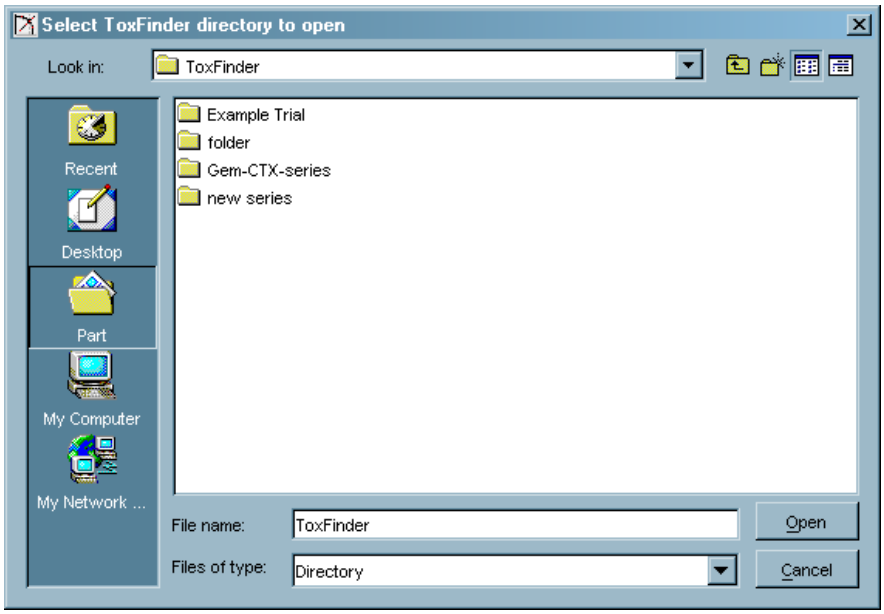
To exit ToxFinder, select **Exit** from the **File** menu of the main window. You will be prompted to save any unsaved changes that you have made to parameter values.

2.4 Displaying Existing Data

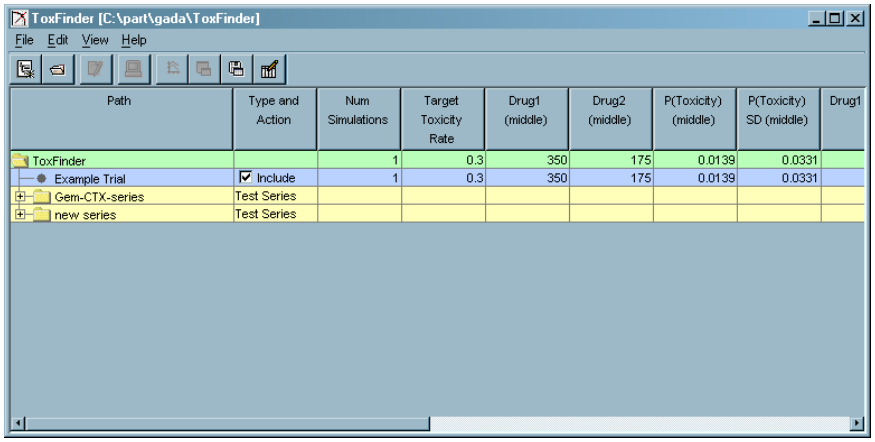
To display existing ToxFinder Data, select **Open** from the **File** menu, click the tool button or press the `ctrl-o` key. If there are currently any open parameter wizard, run manager, Desktop ToxFinder or visualisation windows, you will be notified that they will be closed before changing the current 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 ToxFinder input ('init.tmml') and output files ('*.csv') in each directory to help you locate the correct one.

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

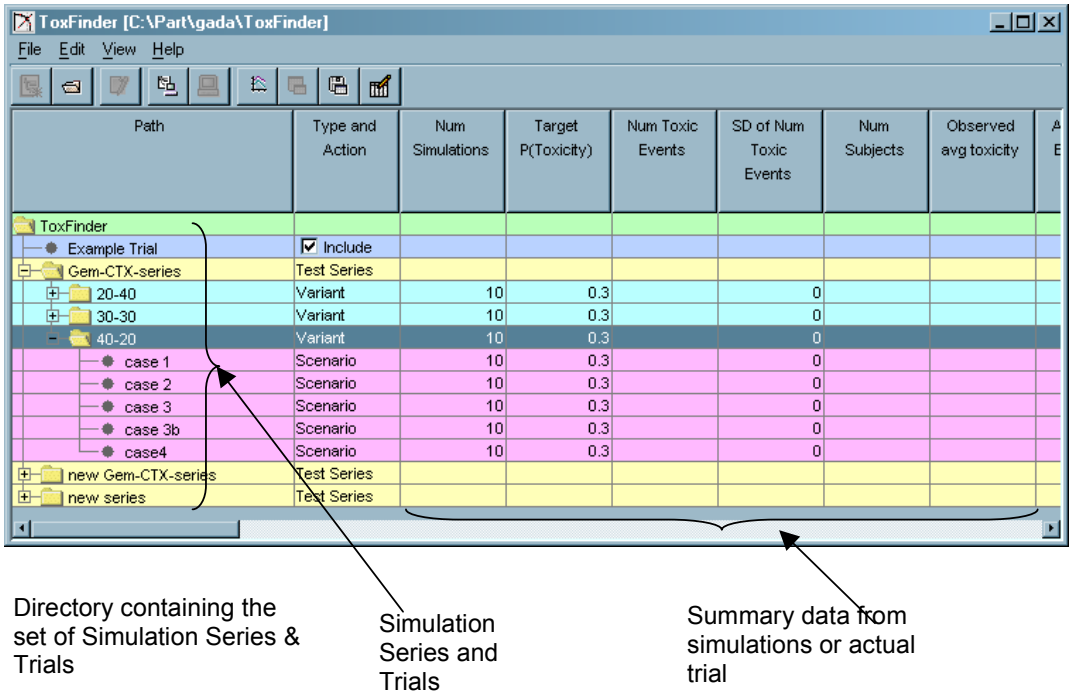


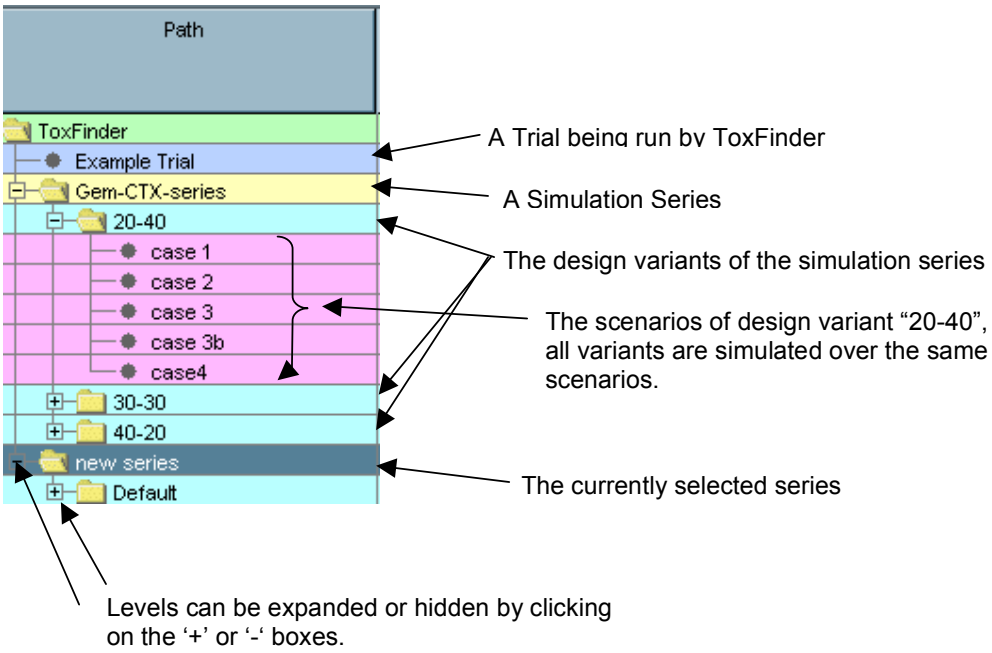
In the folder selected for opening ToxFinder will display all its folders that contain ToxFinder data:



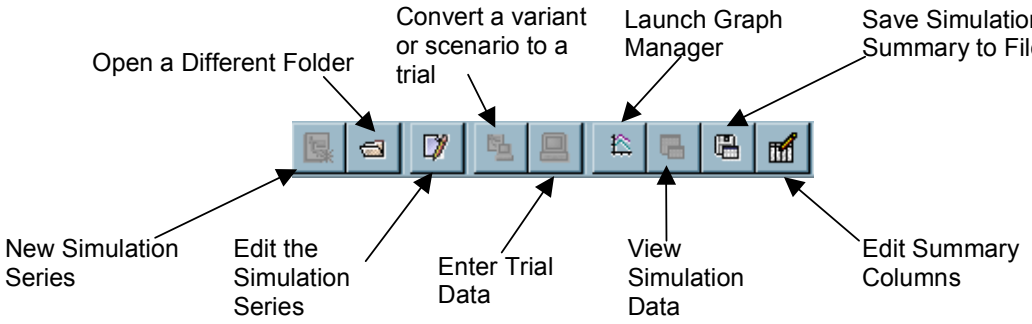
2.5 The Toolbar

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



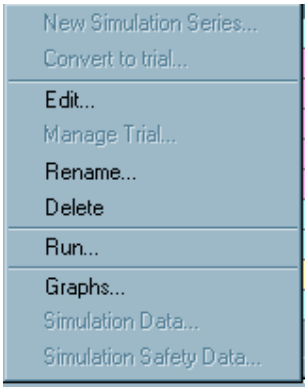


Select a simulation series or trial by clicking on its name – the line becomes highlighted. More of the ToxFinder Toolbar buttons become enabled:



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:

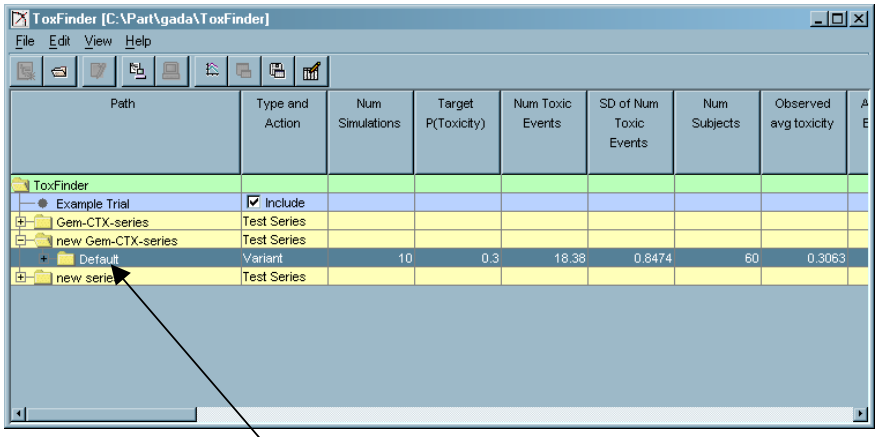


This gives short cuts to commands described elsewhere – it also allows the simulation series (the simulation series directory) to be renamed or deleted.

3 Creating A Trial

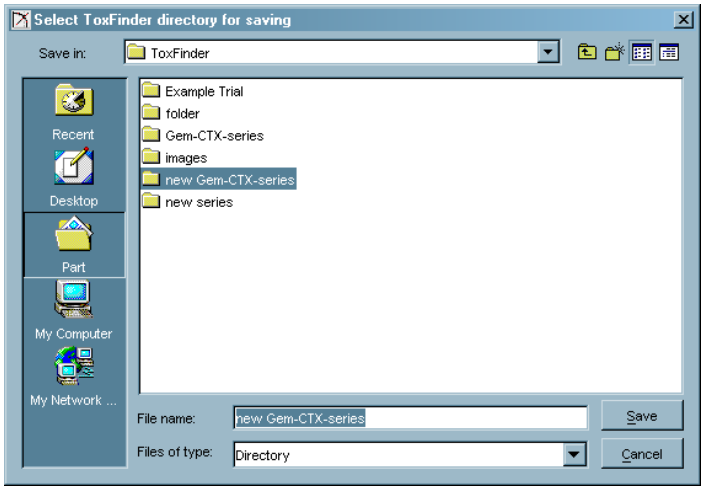
A trial design should be simulated before it is run for real, to check that the operating characteristics of the trial will be acceptable, see [SUG-S] for the facilities in ToxFinder to support this activity.

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 ().



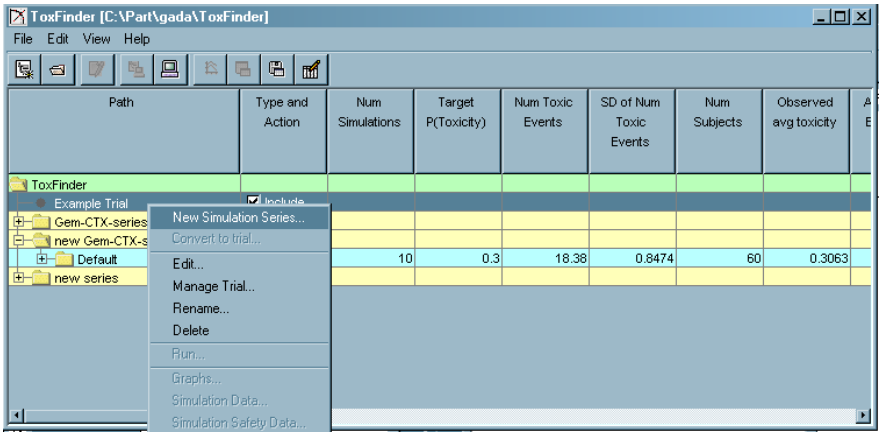
Select a 'variant' by clicking on its name.

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.

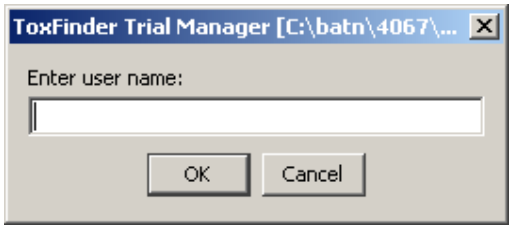


4 Trial Manager

ToxFinder provides a facility to manage a trial, with subject data and observed toxicities entered manually. The dose allocation being controlled by the TMML algorithm.

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

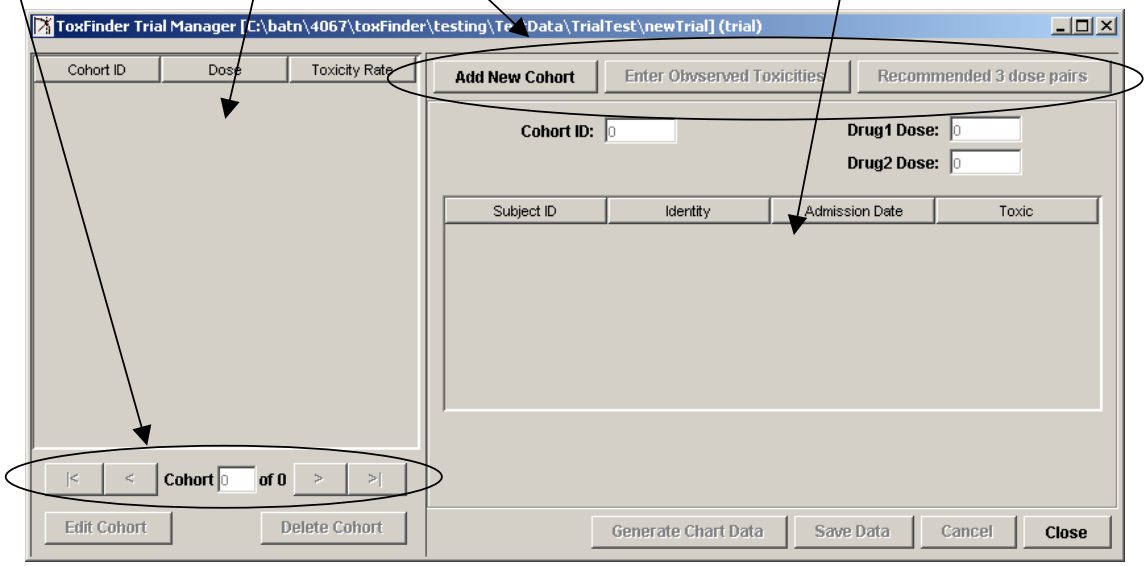
Each time the trial management window is opened, a dialog is displayed requesting a user name. This name ***must not contain space, comma or single quote characters***. Clicking **Cancel** aborts the operation and returns control to the main application window. There is no checking on the name, it is 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 DI 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.

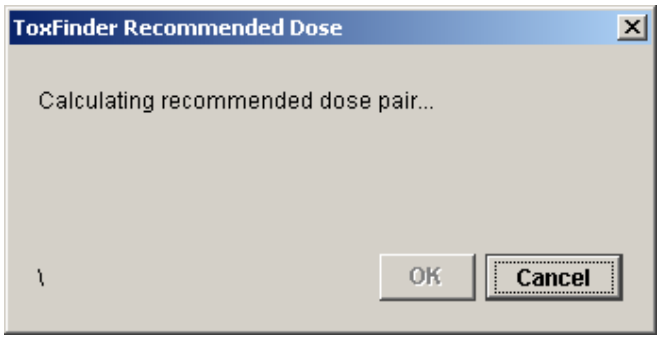
Trail management is divided into 3 steps:

- creation of cohorts and the allocation of doses

- input of observed toxicities
- display of the recommended trio of dose pairs 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 TMML method to recommend a dose to assign them.



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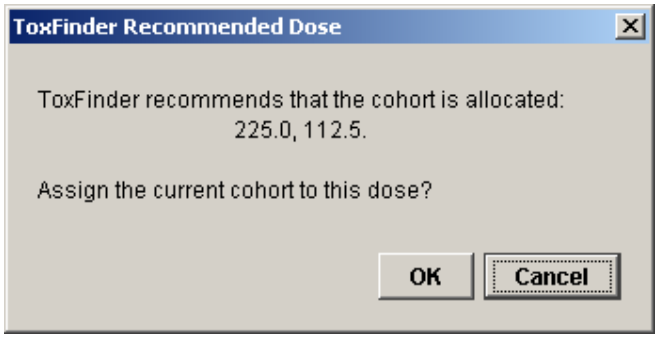
Whilst the program that computes the recommended dose is running (this may take up to a minute) an animated ticker is displayed on a dialog. At any time during the execution clicking **Cancel** will stop the process and return control to the Trial Manager.

When the calculation finishes the message is updated and the recommended dose pair is displayed:



Click **OK** to set the cohort **Dose** to these values, otherwise click **Cancel** to ignore the recommendation – the new cohort will be set a dose of (0, 0).

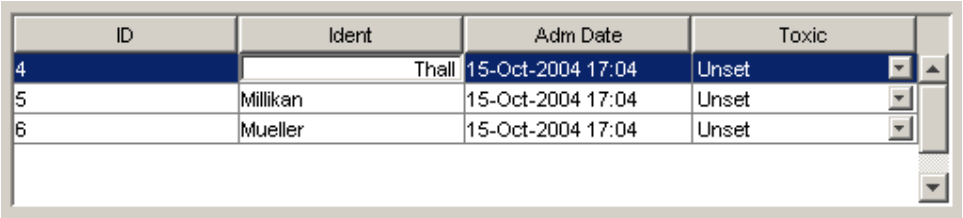
If there is a cohort that has subjects with an 'unset' observed toxicity a warning dialog is displayed and a new cohort may not be added:

The values in the **Dose** field must be entered 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.

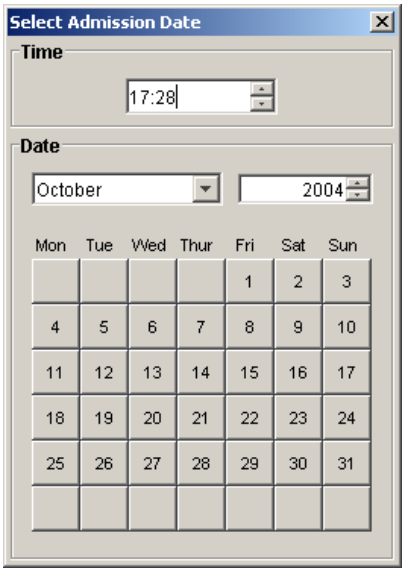
There is a second **Ident** field that may be used to provide something that further identifies the subject (e.g. initials, DoB, patient number). These cannot contain spaces, commas or single quotes.

The table lists the subjects associated with the current cohort:



The admission date defaults to the current date. The TMML 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:



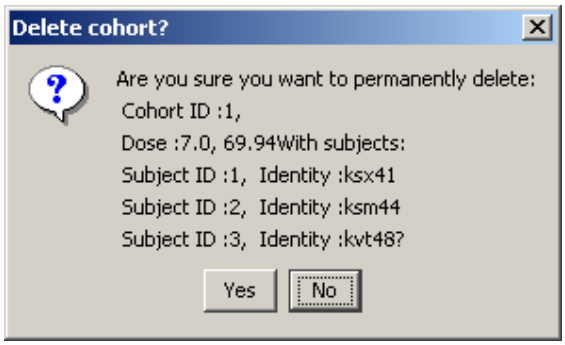
The required time may be set by either typing a new value into the control or selecting the **hours** or **minutes** component and changing it with the up and down arrows at the side of the control.

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.

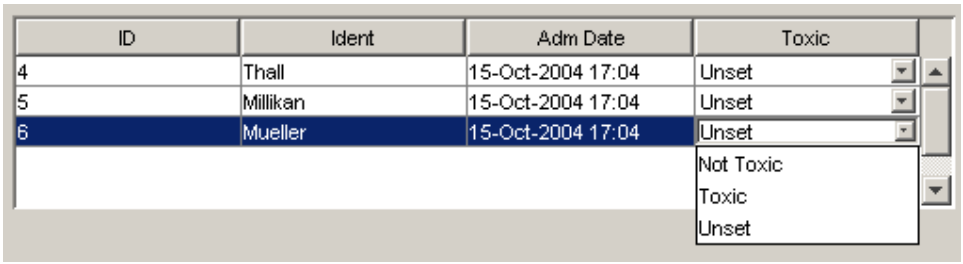


4.1.2 Input of observed toxicities

To enter toxicity results, select the cohort in the cohort table and double click it or press **Edit Cohort**. Initially all the data are locked.

The **Enter Observed Toxicities** button unlocks the 'Toxic' column of the current cohort to allow the observed toxicity results to be entered. The remaining controls on the panel remain locked.

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



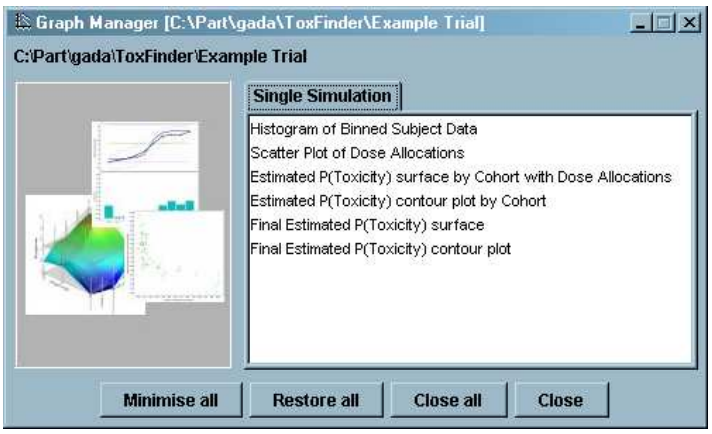
The **Save Data** button writes the updated trial subjects data to a subject.csv data file and the cohort panel is locked to prevent subject data being edited.

Once toxicity 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 to total number of subjects in the trial to the maximum study size (n_1+n_2), has be admitted to the trial.

4.1.3 Generate Chart Data

In order to be able to use ToxFinder's charting facilities (see [SUG-S] for details), the ToxFinder 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):

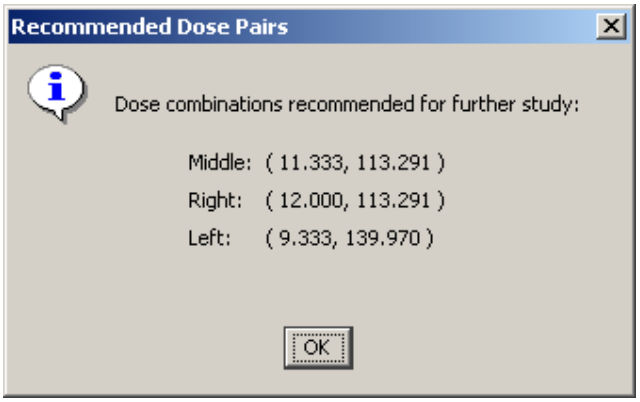


When new cohort data are added the graph manager button and menu command will be disabled again until the chart data is re-generated using the **Generate Chart Data** on the Trial Manager dialog as before.

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

At any point during a trial, the 3 dose pairs recommended by the TMML algorithm for a subsequent study, based on the current subject data, may be calculated and displayed by pressing the **Recommended 3 dose pairs** button.

During the first phase of the trial only a single 'middle' value is returned. Once the second phase of the trial is reached three dose pairs are recommended:



Middle (x_n^{middle})	Lies on the L1 line and contains substantial quantities of both agents
Right ($x_n^{\downarrow right}$)	Contains more of agent 1 and less agent 2
Left ($x_n^{\uparrow left}$)	Contains more of agent 2 and less agent 1

This process may take some seconds to complete if the response data have been updated since the last cohort was added.

After the final cohort has been admitted and observed toxicity results entered, the **Recommended 3 dose pairs** button will calculate the final trio of doses (x_N^{middle} , $x_N^{\downarrow right}$, $x_N^{\uparrow left}$) 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 scenario 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 pair.
SubjectID	Numeric subject identity.
Identifier	The subject identifier.
Admission Date	The Admission date of the subject.
Time	The Admission time of the subject.
Toxic	The observed toxicity for the subject: 'Toxic', 'Not Toxic' or 'Unset'

For Cohort actions the subject columns are left empty.

4.2 Reviewing Trial Data

The last trio of recommended doses to be generated (by either the addition of a new cohort or displaying the recommended doses), along with the associated P(toxicity) and is uncertainty are displayed in the main application table, and as a single row in the simulation data table.

During the first phase of a trial nothing is shown for the 'left' and 'right' recommended dose pairs or their associated P(toxicity) information. These dose pairs are not defined during the initial phase of the trial.