A Guide to Reviewing TreeAge Pro Models

1 Summary

The goals of this guide are to help reviewers with the following:

1. **Understand the Model**

   A reviewer needs to understand how to use TreeAge Pro to explore the model structure and to find the important information.

2. **Reproduce Results**

   A reviewer needs to be able to reproduce the results submitted by a modeller.

3. **Test Values/Assumptions**

   A reviewer may want to test the model by changing parameter values and assumptions.

A Guide to Reviewing TreeAge Pro Models

2 Orientation

2.1 Information Expected From the Modeller

A reviewer should expect a modeller to provide the following information with their model. We call it the “**list of 5”**.

1. Purpose of the model
2. Strategies in the model
3. Outcomes measured by the model
4. Analyses to be run
5. Important outputs to consider

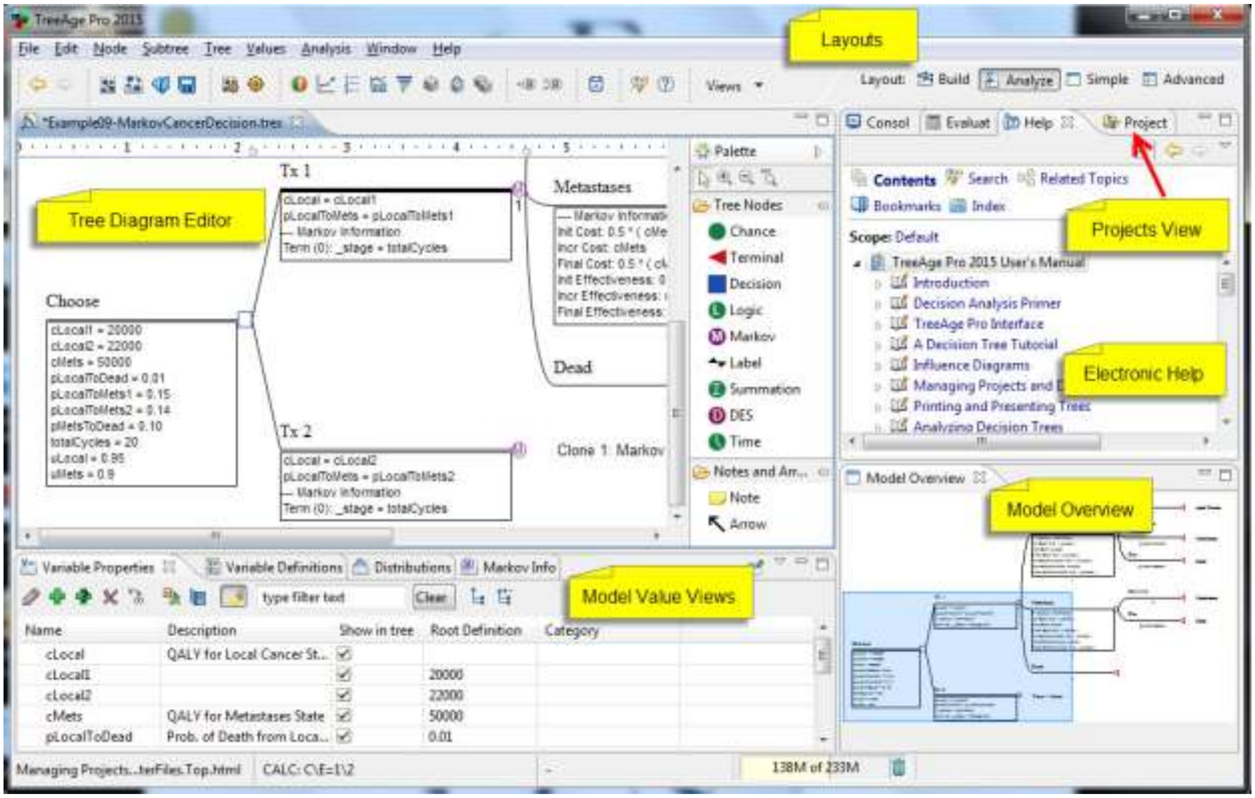
We encourage reviewers to request the above information for any model submitted. However, if this information is not provided, it is sometimes possible to retrieve some of this information directly from the model. More details about this can be found in section 3, *Understand the Model*.

Model files are opened like any document files. A TreeAge Pro model usually has the file extension “.trex”. The most obvious ways to open models are either using the File menu in the software to select the model to open, or by selecting the model file directly and opening via double-click. There may be other files which are associated with the model, and these should be saved into the same folder. For example, a model may contain links to an Excel document. In this case, if the Excel file is saved in the same folder as the model, TreeAge will update the connections between the associated files.

2.2 Navigating the TreeAge Pro User Interface

For users are who unfamiliar with the TreeAge Pro interface, this section gives you some basics to assist you. Figure 1 shows the Analyze Perspective or Layout and includes notes to highlight features of the interface. You may find these things particularly useful:

- The TreeAge Pro workbench is organized into **panes** which can be resized, maximised and minimised as desired to use the space most effectively for any task (Figure 2a).
- **Layouts** (Build, Analyze, Advanced and Simple at top right of the window) present the software components in different ways. We recommend that you use the Analyze layout when reviewing models.
- As you adjust your workbench by **resizing panes** and **opening/closing views**, TreeAge Pro will remember the current layout. To return to the original organization of the layout, right click on the layout button (at the top right hand side) and choose Reset from the context menu.



Name	Description	Show in tree	Root Definition	Category
cLocal	QALY for Local Cancer St...	☑		
cLocal1		☑	20000	
cLocal2		☑	22000	
cMets	QALY for Metastases State	☑	50000	
pLocalToDead	Prob. of Death from Loca...	☑	0.01	

Figure 1: Analyze layout with important components highlighted.
The Model Overview View is opened from the Views menu.

2.2.1 Components of the TreeAge Pro interface

The following Views are useful and open in the Analyze perspective:

- Tree Diagram Editor:
  - Edit/review model structure.
  - Contains the palette which is used to add nodes and labels. Hide the palette using the arrow at the top of the window (Figure 2a, # 1).
  - When analysis output is generated, those results will be presented as additional tabs within this pane.
- Model Value Views:
  - Views for specific values in the model, including variables, distributions, tables, trackers, Markov and Discrete Event Simulation (DES) information.
- Electronic Help:
  - Contains a “User Guide” for TreeAge Pro.
  - Other “helper views”…
    - Console – can be used to output calculations during analyses.
    - Evaluator – acts like a calculator to test expressions with the context of the selected node.

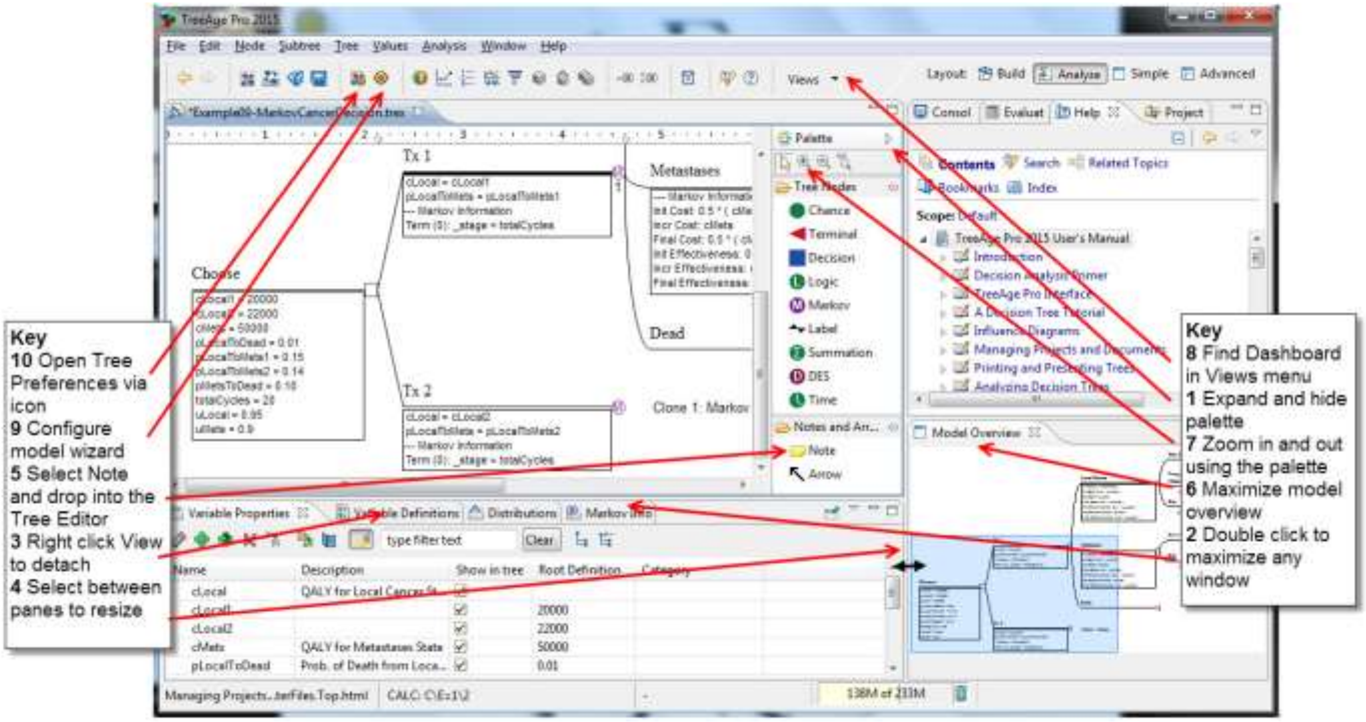
        - Projects View – access files from projects, which act as pointers to file folders with TreeAge Pro files (not necessary to use this).

Views which are not open in the Analyze perspective which can be useful include:

- Model Overview:
    - See entire model structure in compact format and use it to navigate around a large model. This View is opened via Views menu and visible in Figure 1.

2.2.2 Using the TreeAge Pro interface (Quick start)

- To quickly maximize an Editor or View, double-click on its tab. Then double-click on it again to return it to its prior location (Figure 2a, # 2).
- Open and/or activate any View via the Views list in the toolbar.
- Most of the Views have a common toolbar and the functions are highlighted in Figure 2b.
- The Analyze perspective has a toolbar of most commonly used analysis functions. Figure 2c highlights the elements of the toolbar which are available when a model is in the Tree Editor window. The toolbar will change dependent on content of the Editor (i.e. model, graph or text output). By rolling over the toolbar, tooltips describe the function of each icon.
- Any of the Views (other than the Tree Editor) can be detached from the software window to more easily work with the model. Select the tab at the top of the View, right click and select Detach from the menu (Figure 2a, #3). The window will then be floating and can be moved. Repeat the process to re-attach.
- All of the individual panes in the software can be re-sized by selecting the area between them (hove mouse over and wait until a double arrow appears) and then dragging (by holding the left mouse key) to re-size (Figure 2a, # 4).
- The Dashboard View gives an overview of the most important elements of the model. Open the Dashboard from the Views list in the toolbar (Figure 2a, #8).



Name	Description	Show in tree	Root Definition	Category
cLocal	QALY for Local Cancer St...	☑		
cLocal1		☑	20000	
cLocal2		☑	22000	
cMets	QALY for Metastases State	☑	50000	
pLocalToDead	Prob. of Death from Loca...	☑	0.01	

Key
10 Open Tree Preferences via icon
9 Configure model wizard
5 Select Note and drop into the Tree Editor
3 Right click View to detach
4 Select between panes to resize

Key
8 Find Dashboard in Views menu
1 Expand and hide palette
7 Zoom in and out using the palette
6 Maximize model overview
2 Double click to maximize any window

Figure 2a: Guide to find useful functions in the TreeAge Pro interface

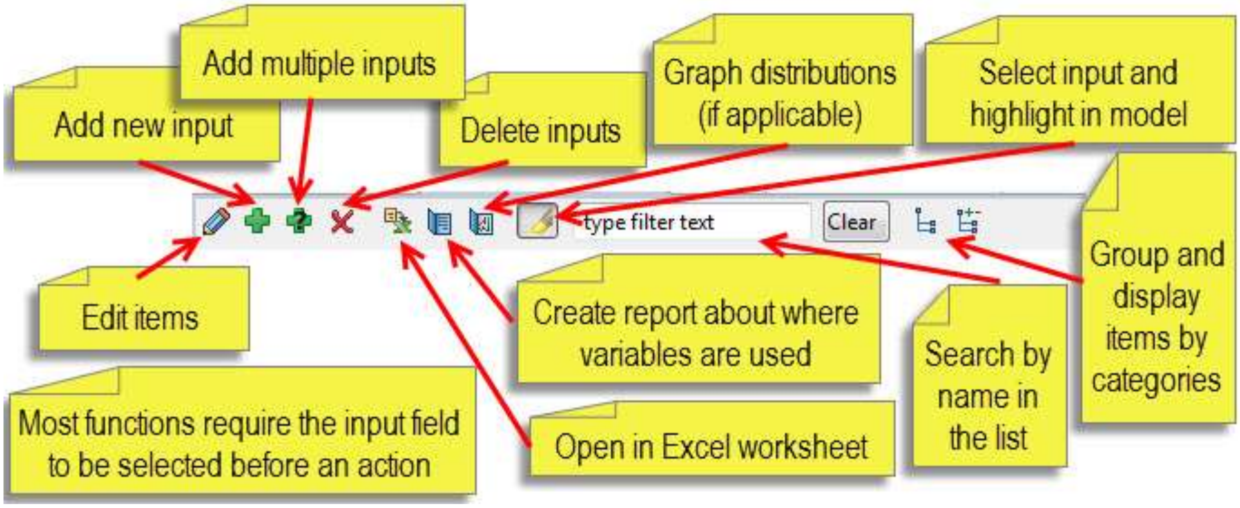


Figure 2b: Toolbar guide highlighting functions common to most Views

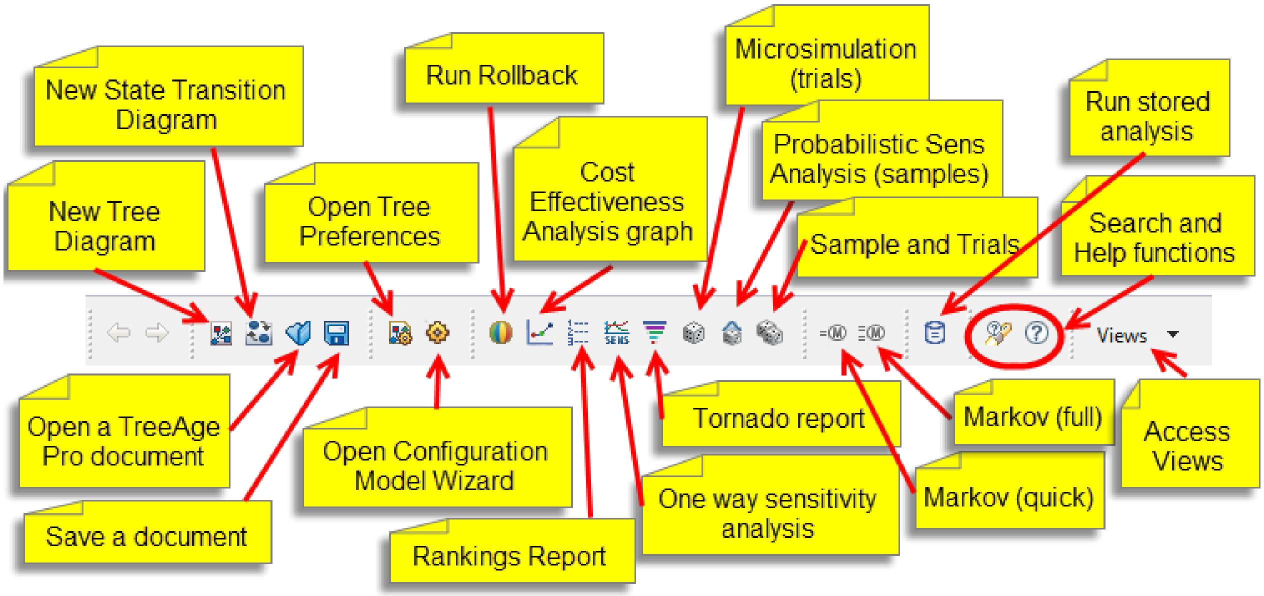


Figure 2c: Toolbar guide highlighting common functions in the Analyze perspective

3 Understand the Model

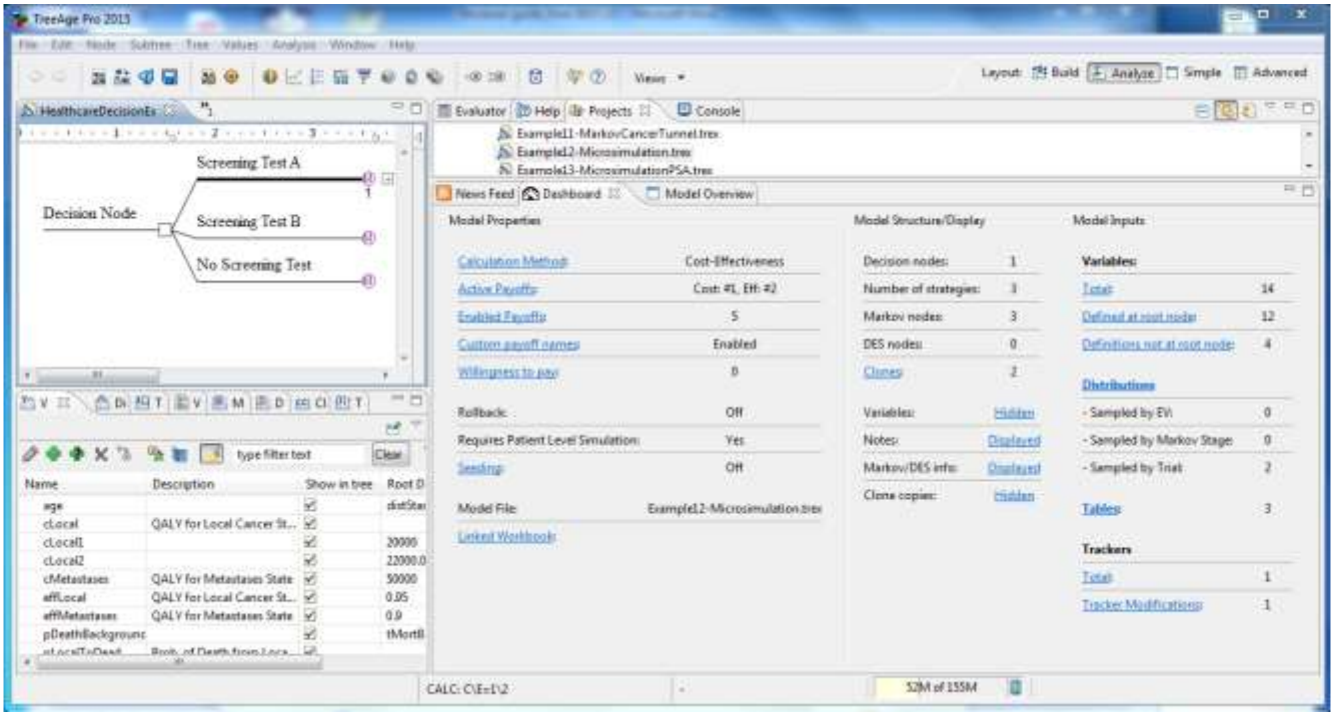
This section is designed to help a reviewer understand how a model is structured and where to find the model parameters and calculated values in TreeAge Pro.

3.1 Identify model purpose and outcome measures

- The Dashboard View (as in Figure 3a) provides an "at-a-glance" overview to all the elements of the model and can help identify model purpose and outcomes. The View is split into three sections:

    1. **Model Properties** – Provides information about the model configuration, including the calculation method. Suggests how to analyse the model (cohort or microsimulation) and indicates whether there are any linked workbooks.
    2. **Model Structure/Display** – Provides information about the number of Decision, Markov and DES nodes as well as clones. Indicates if the model is set to hide or display important information such as displaying variables, notes, Markov/DES info and clones with toggle option to change these settings.
    3. **Model Inputs** – Provides information about the number and location of Variables, Variable Definitions, Distributions, Tables and Trackers in the model.

- Examining the node labels at the root decision node and its branches can be helpful. The root decision node label will often describe the basic question the model is trying to address. Branches off the decision node represent alternative treatment strategies. Normally, each strategy node will be described by its node label (Figure 3b).



Example11-MarkovCancerTunnel.trex
Example12-Microsimulation.trex
Example13-MicrosimulationPSA.trex

Model Properties

Calculation Method	Cost-Effectiveness
Active Payoffs	Cost: #1, Eff: #2
Enabled Payoffs	5
Custom payoff names	Enabled
Willingness to pay	0
Rollback:	Off
Requires Patient Level Simulation:	Yes
Seeding	Off
Model File	Example12-Microsimulation.trex
Linked Workbook	

Model Structure/Display

Decision nodes:	1
Number of strategies:	3
Markov nodes:	3
DES nodes:	0
Clones	2
Variables:	Hidden
Notes:	Displayed
Markov/DES info:	Displayed
Clone copies:	Hidden

Model Inputs

Variables:	
Total	14
Defined at root node	12
Definitions not at root node	4
Distributions	
- Sampled by EV	0
- Sampled by Markov Stage	0
- Sampled by Trial	2
Tables	3
Trackers	
Total	1
Tracker Modifications	1

Name	Description	Show in tree	Root D
age		☑	distStar
cLocal	QALY for Local Cancer St...	☑	
cLocal1		☑	20000
cLocal2		☑	22000.0
cMetastases	QALY for Metastases State	☑	50000
effLocal	QALY for Local Cancer St...	☑	0.95
effMetastases	QALY for Metastases State	☑	0.9
pDeathBackgrounc		☑	tMortB

Figure 3a: Healthcare decision model with Dashboard View expanded to show Model Properties, Model Structure/Display and Model Inputs.

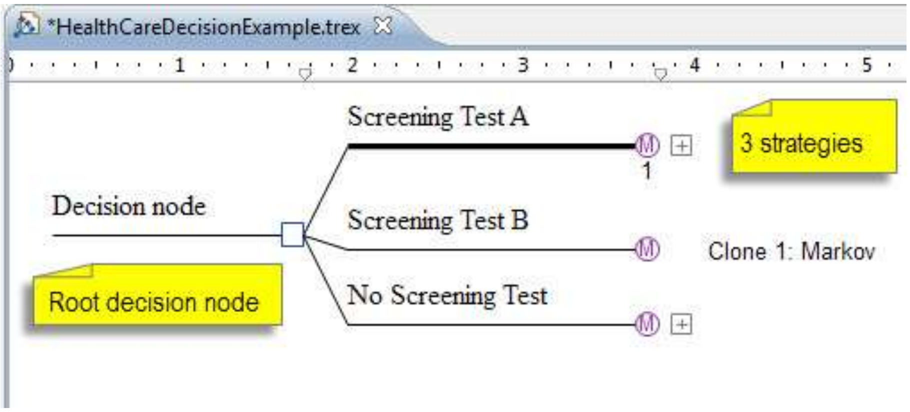
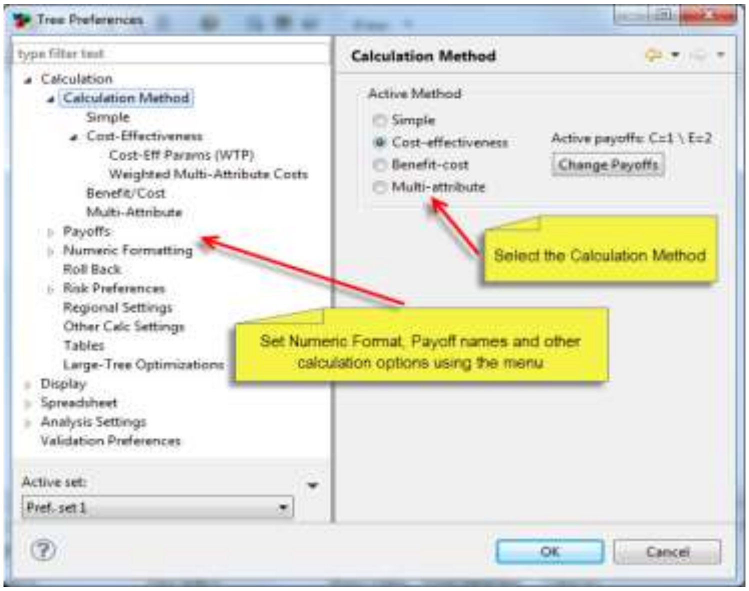


Figure 3b: Healthcare decision model showing node labels

- Outcomes measured can be partially determined by the model's calculation method. You can access the calculation method by selecting Tree > Tree Preferences from the menu, then choose the category Calculation > Calculation Method (Figure 4). Or you can use the Dashboard to observe the Calculation Method.



● Cost-effectiveness

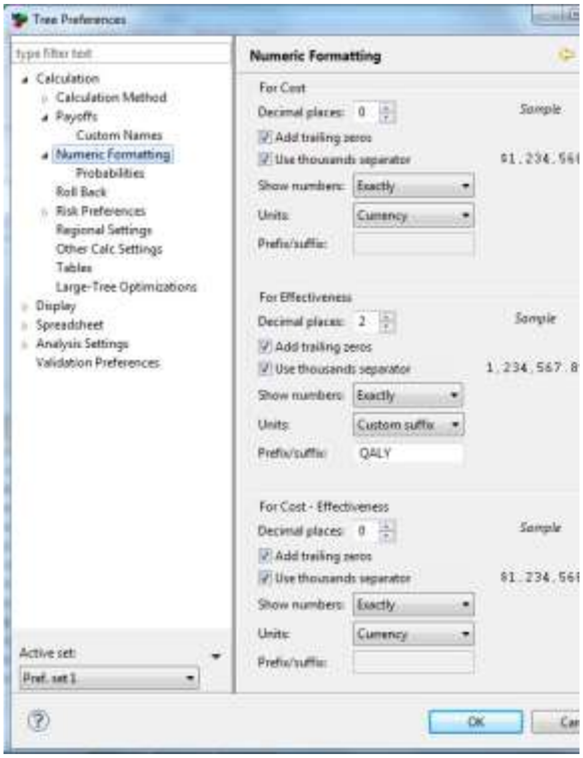
Active payoffs: C=1 \ E=2

Select the Calculation Method

Set Numeric Format, Payoff names and other calculation options using the menu

Figure 4: Tree Preferences dialogue

- A calculation method of cost-effectiveness indicates that treatments should be evaluated on the basis of Cost-Effectiveness Analysis (CEA), which requires separate payoff sets to be used for cost and effectiveness. Cost is nearly always measured in units of currency, and effectiveness is often, but not always measured in Quality Adjusted Life Years (QALYs).
- To find the units for Cost and QALYs, look for any Numeric Formatting used by the modeller; select Tree > Tree Preferences > Calculation > Numeric Formatting and look for the units labelling outputs (Figure 5a). A modeller may use custom payoff names which can be found in Tree Preferences > Calculation > Payoffs > Custom Names. This can be very helpful when non-standard outcomes are used (Figure 5b).
- The Configure Model Wizard is accessible via the toolbar (Figure 2a, # 9). This can be used to access the most commonly accessed Tree Preferences. The Configure Model Wizard will walk you through:
    - Calculation Method;
    - Payoffs (active and extra);
    - Global discounting;
    - Custom payoff names; and
    - Numeric Formatting.
- All Tree Preferences can be accessed via the Tree > Tree Preferences menu, or by selecting the Tree Preferences icon in the toolbar (Figure 2a, # 10).



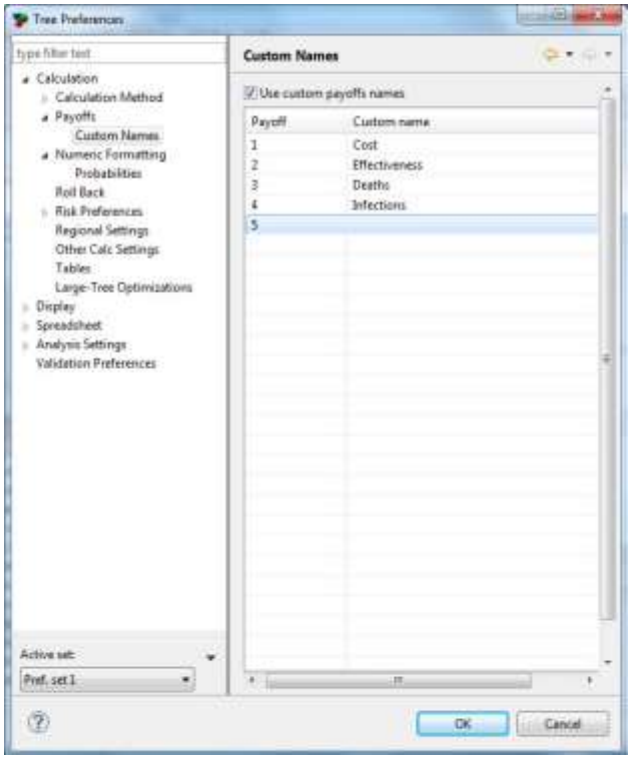
Numeric Formatting

For Cost
Decimal places: 0
☑ Add trailing zeros
☑ Use thousands separator
Show numbers: Exactly
Units: Currency
Prefix/suffix:
Sample $1,234,56

For Effectiveness
Decimal places: 2
☑ Add trailing zeros
☑ Use thousands separator
Show numbers: Exactly
Units: Custom suffix
Prefix/suffix: QALY
Sample 1,234,567.8

For Cost - Effectiveness
Decimal places: 0
☑ Add trailing zeros
☑ Use thousands separator
Show numbers: Exactly
Units: Currency
Prefix/suffix:
Sample $1,234,56

Figure 5a: Numeric Formatting to set units in payoffs



Custom Names

☑ Use custom payoffs names

Payoff	Custom name
1	Cost
2	Effectiveness
3	Deaths
4	Infections
5	

Figure 5b: Enabled payoffs with custom names

- It is difficult to know which analyses should be run without some guidance from the modeller. An important question is whether analyses can be run at the overall cohort level or if the model requires patient-level simulation. If the model contains trackers (refer to Section 3.6 Trackers) and/or distributions with “per trial sampling” (refer to Section 3.5 Distributions), it is very likely that patient-level simulation is required. The Dashboard uses these as indicators that the model likely requires patient-level simulation. Note that this requirement affects all other analyses, including CEA and all sensitivity analyses.

3.2 Look for model documentation

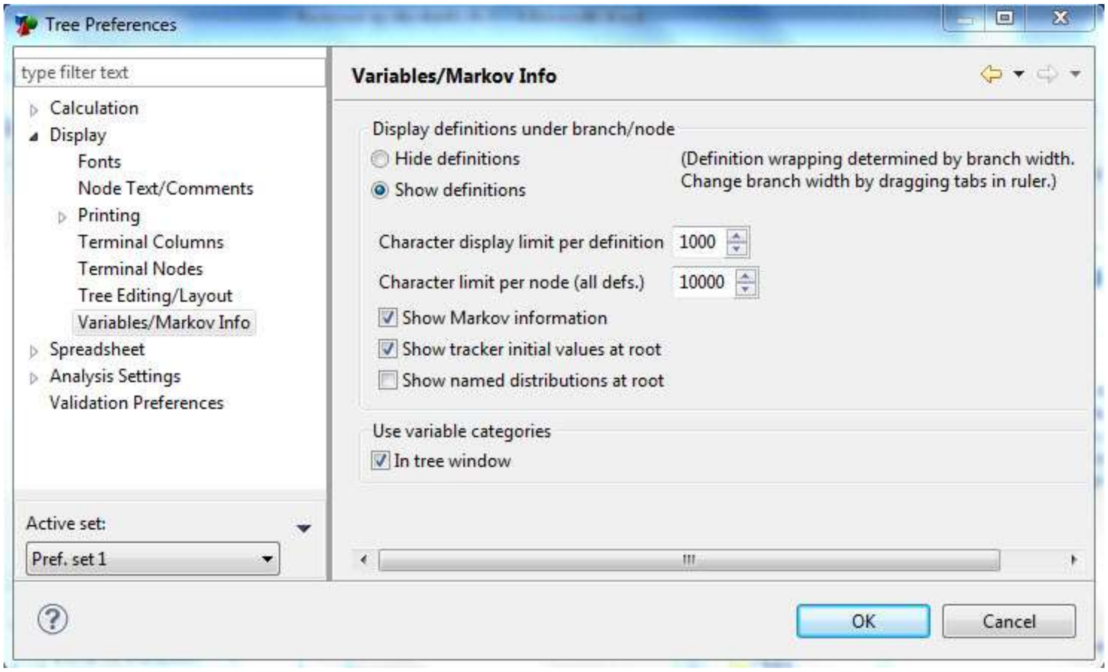
- The modeller should provide the “list of 5” as a minimum.
- Model documentation (if created by modeller) may be either be:
  - Available as a HTML file which came with the original model file, or
  - Accessed by clicking in the Tree Diagram Editor and pressing the F1 key.
  - Alternatively, a modeller can provide the “list of 5” information in a separate document.
- Within most views, there are places for the modeller to enter comments and descriptions for variables and other model inputs.
- Notes can be used to document any model by selecting the Notes icon in the Tree Diagram Editor palette, and then drag/dropping a Note into the editor (Figure 2a, # 5). Notes can

optionally be bound to a node to highlight that area of the model. The modeller may have already added notes as a guide, but you can also add notes as you choose.

3.3 Examine the model structure

- Maximize the Model Overview window to see the entire model structure, double click on the tab to increase and then decrease (Figure 2a, # 6).
- In the Tree Editor window, use the palette to zoom in and out via the "+" and "-" (Figure 2a, # 7). To stop zooming in/out, click on the selection arrow at the top of the palette.
- You can change the Tree Preferences to hide the numeric values displayed within the model structure. This can make it easier to examine the model structure (Figure 6).

    - Choose Tree > Tree Preferences from the menu.
    - Select category Display > Variables/Markov Info > Hide definitions.
    - Select category Display > Node Text/Comments> Hide probabilities.
    - Remember to select "Show definitions" in the Variable/Markov Info to examine model details closely as this will assist with identifying where variables are being defined throughout the model.
    - Note that using the Dashboard you can access and turn on/off elements of the model structure listed above via the Model Structure/Display section.



Variables/Markov Info

Display definitions under branch/node

○ Hide definitions

● Show definitions

(Definition wrapping determined by branch width. Change branch width by dragging tabs in ruler.)

Character display limit per definition 1000

Character limit per node (all defs.) 10000

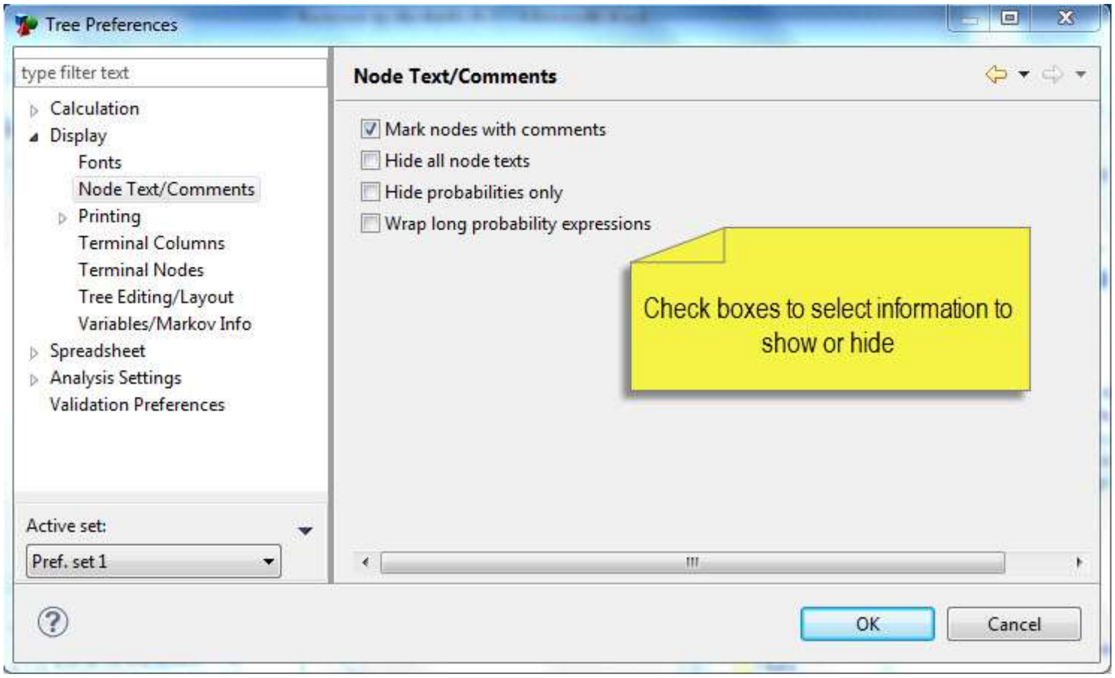
☑ Show Markov information

☑ Show tracker initial values at root

☐ Show named distributions at root

Use variable categories

☑ In tree window



Node Text/Comments

☑ Mark nodes with comments

☐ Hide all node texts

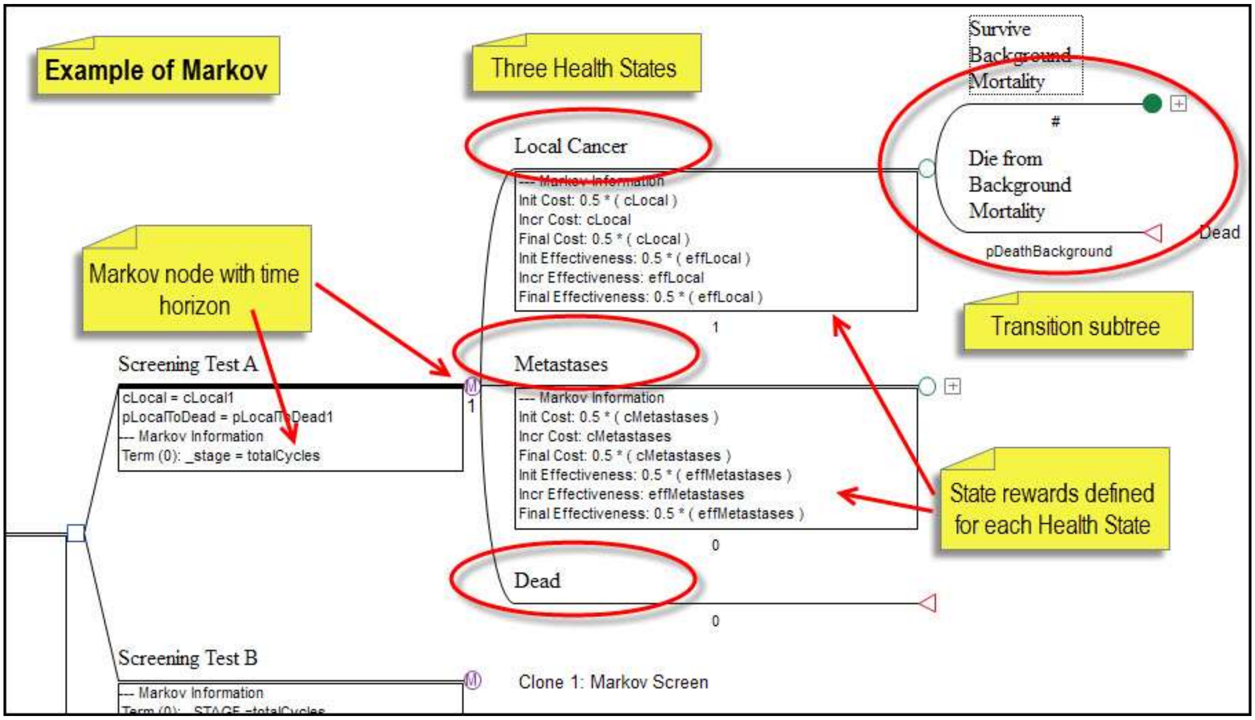
☐ Hide probabilities only

☐ Wrap long probability expressions

Check boxes to select information to show or hide

Figure 6: Hiding definitions and probabilities via Tree Preferences

- Look for Markov and DES nodes within the overall model structure, Figure 7a and b.
  - **Markov structure** will look like (Figure 7a)…..
    - Markov node (purple circle with "M") is the start of a Markov Model. The model time horizon is defined here.
    - Each direct branch from the Markov node is a Health State.
    - All structure to the right of each Health State is a Transition Subtree. Each Transition Subtree describes the events that can occur if starting a cycle in a specific Health State. Each end point within the Transition Subtree is a terminal node which sends flow back to a Health State to start the next cycle.
    - Values (cost, eff, etc.) can be accumulated at any Health State and at any event in a Transition Subtree.


Example of Markov

Three Health States

Markov node with time horizon

Transition subtree

State rewards defined for each Health State

--- Markov Information
Init Cost: 0.5 * (cLocal)
Incr Cost: cLocal
Final Cost: 0.5 * (cLocal)
Init Effectiveness: 0.5 * (effLocal)
Incr Effectiveness: effLocal
Final Effectiveness: 0.5 * (effLocal)

--- Markov Information
Init Cost: 0.5 * (cMetastases)
Incr Cost: cMetastases
Final Cost: 0.5 * (cMetastases)
Init Effectiveness: 0.5 * (effMetastases)
Incr Effectiveness: effMetastases
Final Effectiveness: 0.5 * (effMetastases)

cLocal = cLocal1
pLocalToDead = pLocalToDead1
--- Markov Information
Term (0): _stage = totalCycles

--- Markov Information
Term (0): _STAGE =totalCycles

Figure 7a: Markov model structure

- **DES structure** will look like (Figure 7b)….
  - DES node (purple circle with "D") is the start the DES model. The model time horizon is defined here.
  - Time nodes anywhere to the right of the DES node represent a point where a "trial" (or individual) is waiting for the next event. Time-based values are accumulated here.
  - Branches of time nodes represent each possible event with the time to event beneath each node. Event-based values are normally accumulated here.
  - Time is automatically updated based on the appropriate time-to-event.

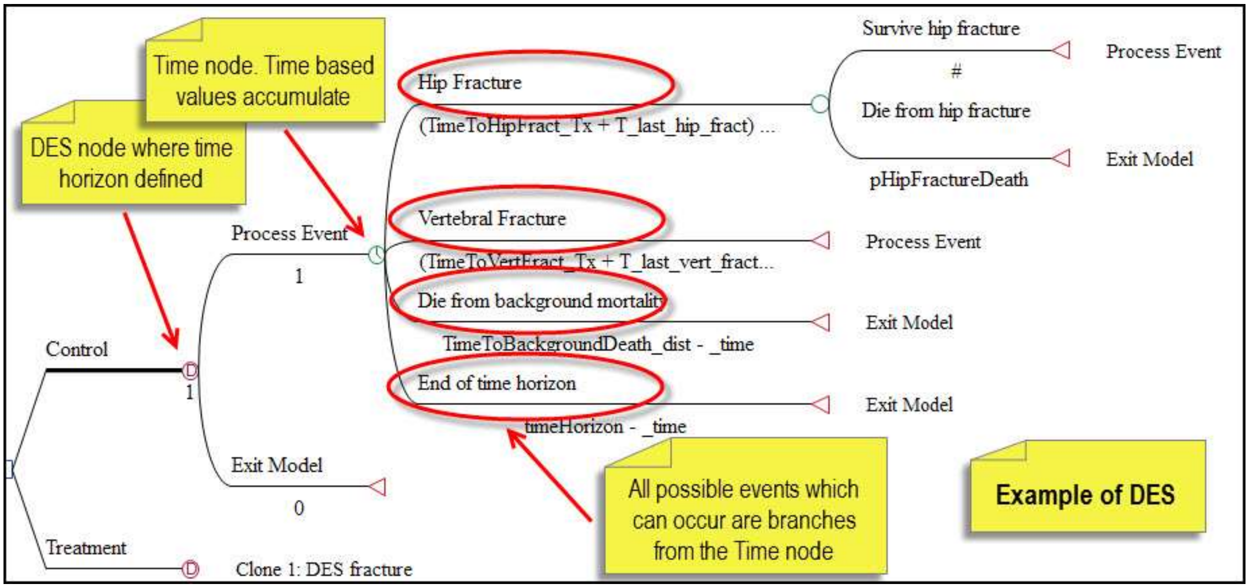
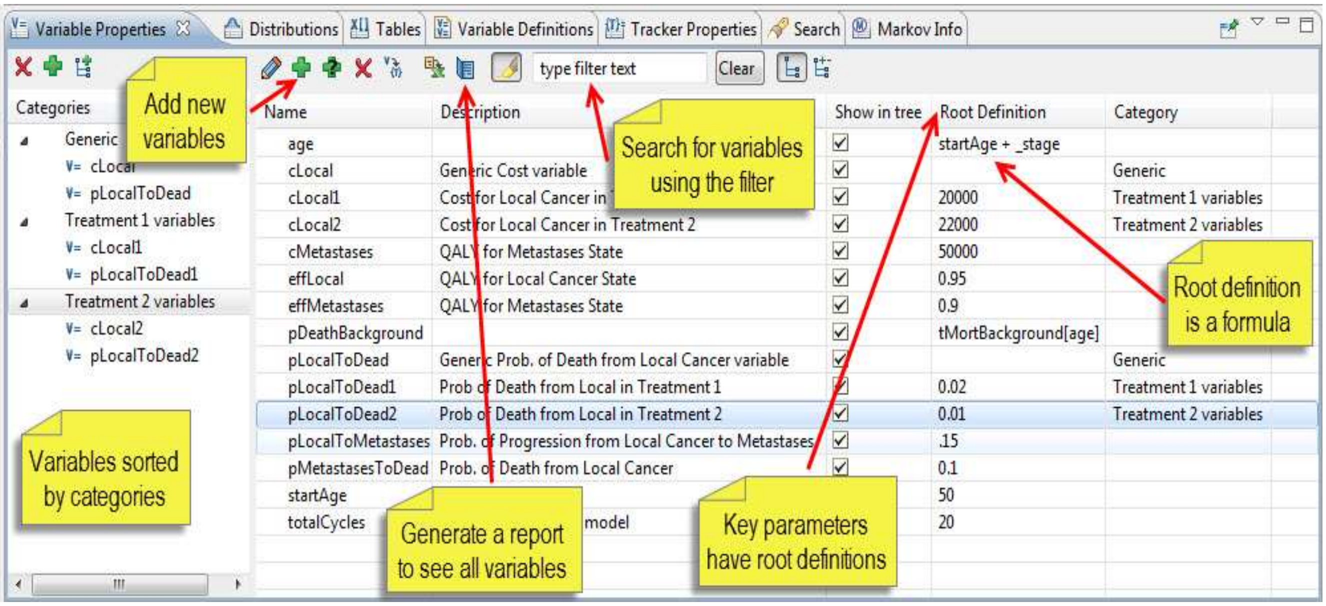


Figure 7b: DES model structure

- Select any node and use the Subtree menu to collapse/expand subtrees to better examine certain portions of the model.

3.4 Variables

- Examine variables via the Variable Properties View (Figure 8).
- Modellers may group variables into logical Categories.
- Look for key parameters (root node definition is a number).
- Look for key formulas (root node definition is a formula expression).
- Look for variable definitions in the model that are not placed at the root node. Such variable definitions may be used to apply different values to the same variable name in different parts of the model.
    - This is useful for Clones where we want variables to have different values dependent on where they are in the tree.
    - The Variable Definitions View will show different variable definitions based on the node selected in the Tree Diagram Editor (Figure 11).



- Generic
    - cLocal
    - pLocalToDead
- Treatment 1 variables
    - cLocal1
    - pLocalToDead1
- Treatment 2 variables
    - cLocal2
    - pLocalToDead2

Name	Description	Show in tree	Root Definition	Category
age		☑	startAge + _stage	
cLocal	Generic Cost variable	☑		Generic
cLocal1	Cost for Local Cancer in	☑	20000	Treatment 1 variables
cLocal2	Cost for Local Cancer in Treatment 2	☑	22000	Treatment 2 variables
cMetastases	QALY for Metastases State	☑	50000	
effLocal	QALY for Local Cancer State	☑	0.95	
effMetastases	QALY for Metastases State	☑	0.9	
pDeathBackground		☑	tMortBackground[age]	
pLocalToDead	Generic Prob. of Death from Local Cancer variable	☑		Generic
pLocalToDead1	Prob of Death from Local in Treatment 1	☑	0.02	Treatment 1 variables
pLocalToDead2	Prob of Death from Local in Treatment 2	☑	0.01	Treatment 2 variables
pLocalToMetastases	Prob. of Progression from Local Cancer to Metastases	☑	.15	
pMetastasesToDead	Prob. of Death from Local Cancer	☑	0.1	
startAge			50	
totalCycles	model		20	

Add new variables

Search for variables using the filter

Root definition is a formula

Variables sorted by categories

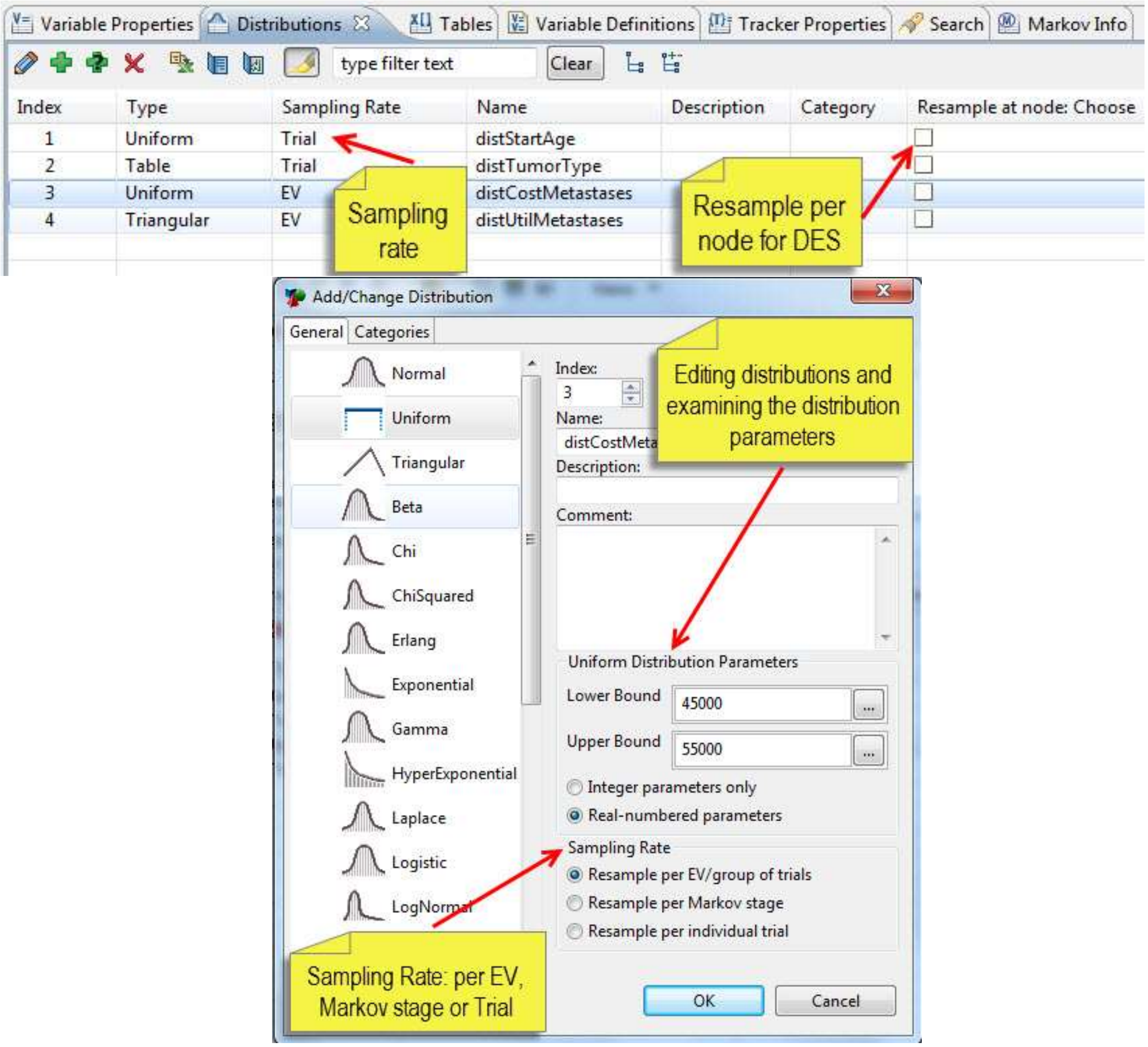
Generate a report to see all variables

Key parameters have root definitions

Figure 8: Variable Properties View

3.5 Distributions

- Examine distributions via the Distributions View (Figure 9).
- The distribution list will include the name (as given by the modeller), distribution type and sampling rate.
    - Distributions with sampling rate "Sample per EV (Expected Value)" are likely parameters for Probabilistic Sensitivity Analysis.
    - Distributions with sample rate "Sample per Trial" are likely individual characteristics for patient-level simulation. Any such distributions suggest a heterogeneous cohort; therefore, the model should most likely be analysed via Microsimulation.
- Double-click on a distribution to edit its properties via the Add/Change Distributions dialogue, including adding Comments and changing the distribution's parameters and sampling rate (Figure 9).



Index	Type	Sampling Rate	Name	Description	Category	Resample at node: Choose
1	Uniform	Trial	distStartAge			☐
2	Table	Trial	distTumorType			☐
3	Uniform	EV	distCostMetastases			☐
4	Triangular	EV	distUtilMetastases			☐

Sampling rate

Resample per node for DES

Index: 3

Name: distCostMeta

Description:

Comment:

Uniform Distribution Parameters

Lower Bound 45000

Upper Bound 55000

○ Integer parameters only

● Real-numbered parameters

Sampling Rate

● Resample per EV/group of trials

○ Resample per Markov stage

○ Resample per individual trial

Editing distributions and examining the distribution parameters

Sampling Rate: per EV, Markov stage or Trial

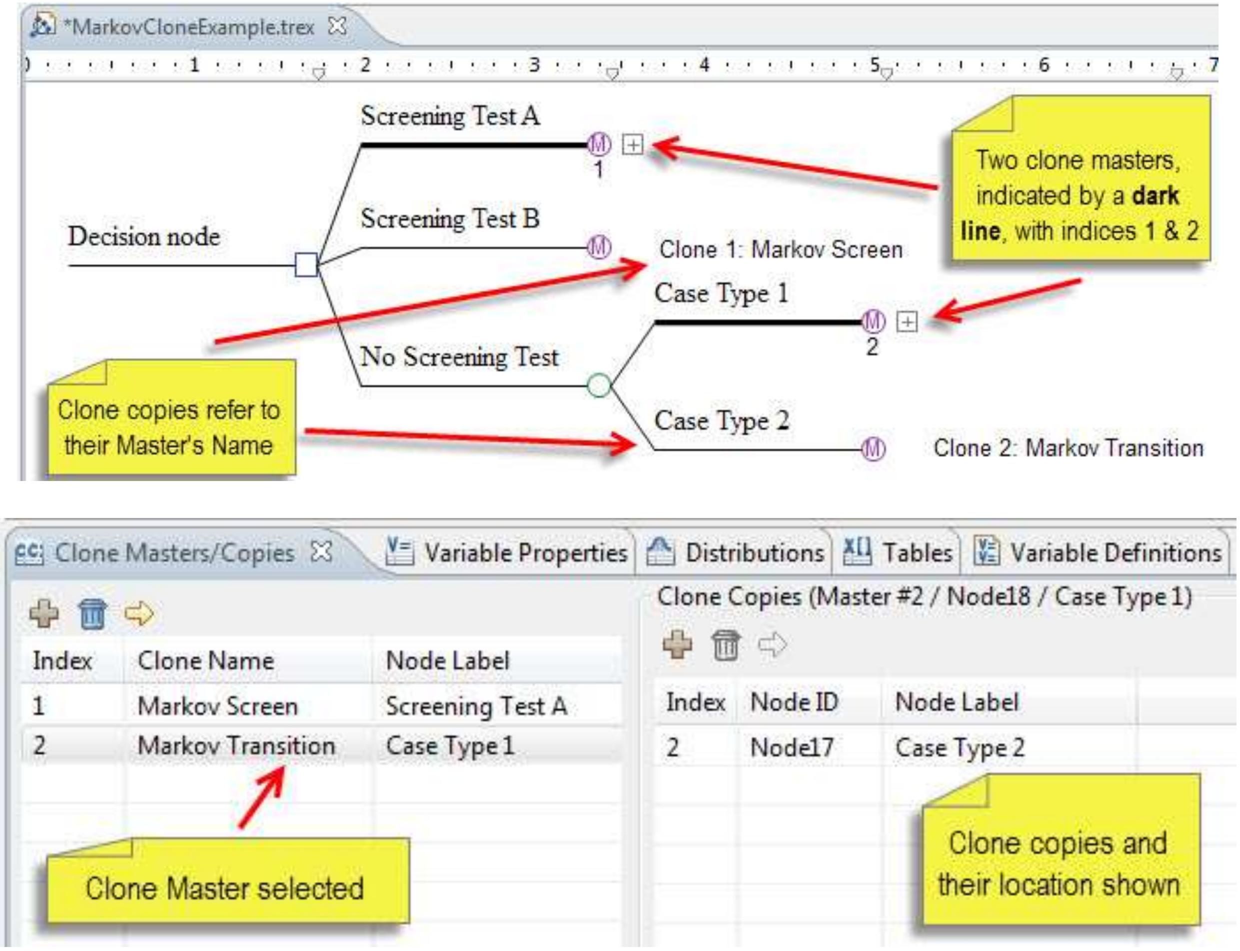
Figure 9: Distributions View and Add/Change Distribution dialog

3.6 Trackers

- Examine trackers using the Tracker Properties View.
  - The Dashboard will indicate if there are Trackers in the model. Additionally, if there are no trackers in the model, then the Tracker View will be blank.
- Trackers are used to record individual patient data values, usually in response to a specific event. The information stored in a tracker can impact any subsequent value in the model.
- In order to collect the individual-level data via trackers, the model must be analysed via Microsimulation.
- Trackers usually indicate that a model must be analyzed via patient-level simulation.

3.7 Clones

- Clones allow modellers to reuse portions of model structure (the “clone master”) in other parts of the model (the “clone copy”). Clone copies are synchronized with the clone master, guaranteeing consistency in model structure and eliminating the need to recreate portions of the model (Figure 10).



Two clone masters, indicated by a **dark line**, with indices 1 & 2

Clone copies refer to their Master's Name

Index	Clone Name	Node Label
1	Markov Screen	Screening Test A
2	Markov Transition	Case Type 1

Clone Master selected

Clone Copies (Master #2 / Node18 / Case Type 1)

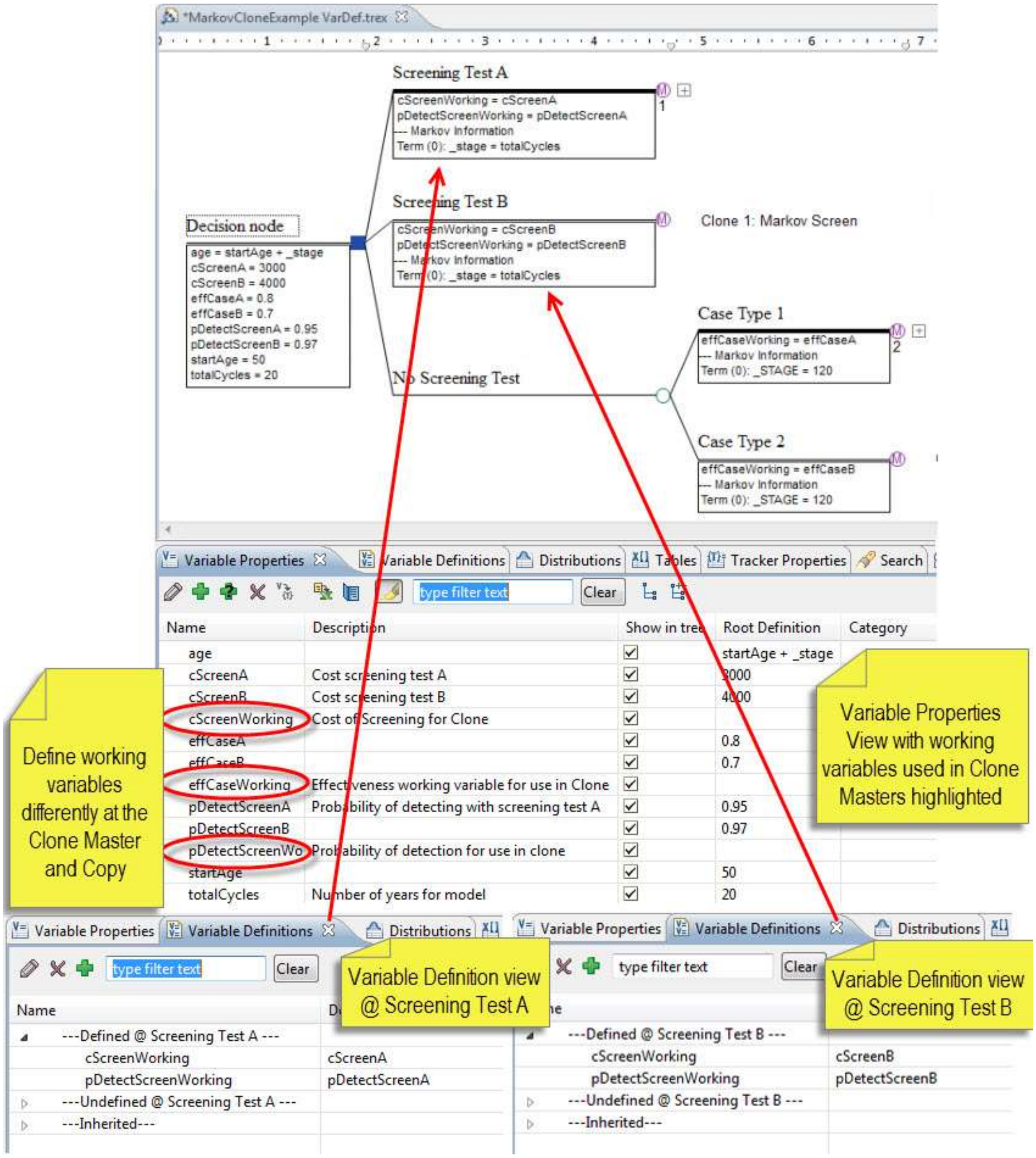
Index	Node ID	Node Label
2	Node17	Case Type 2

Clone copies and their location shown

Figure 10: Clone master and copies in the tree editor and information in the Clones View

- All Clones will appear in the Clone Masters/Copies View. This view lists all the clone masters to the left. When a clone master is selected, all the clone copies associated with that clone master are listed to the right. Select a clone master or copy and then click the yellow arrow in the view's toolbar to "go to" the node associated with the clone within the Tree Editor.
- In the Tree Editor, clones are presented as follows:
    - Clone master anchors are marked by a heavy solid line. The clone master contains the subtree to the right of the anchor node (but not the anchor node itself). The clone master index is presented beneath the node marker of the anchor node.
    - Clone copies can either be displayed or hidden based on a Tree Preference option. Specifically, within the category Display > Tree Editing/Layout, check or uncheck the option "Show clone copy subtrees".
        - When not displayed (as in Figure 10), the clone copy will reference the clone master by index and name.
        - When shown, the clone copy structure is displayed with grey node lines to indicate that the structure cannot be edited.

- Clone masters and copies will always use the same variable references; however, the variables may use different variable definitions. This allows modellers to pass different values into the clone master vs. its clone copies.
    - Variables which are associated with a specific clone master or copy are frequently defined just to the left of the clone master and copies. Figure 11 shows where a common variable has different values in the clone master and the clone copy. We can see two places to look for variables defined at specific nodes:
    - Under the node in the Tree Editor and in the Variable Definitions View.



Decision node:
age = startAge + _stage
cScreenA = 3000
cScreenB = 4000
effCaseA = 0.8
effCaseB = 0.7
pDetectScreenA = 0.95
pDetectScreenB = 0.97
startAge = 50
totalCycles = 20

Screening Test A:
cScreenWorking = cScreenA
pDetectScreenWorking = pDetectScreenA
--- Markov Information
Term (0): _stage = totalCycles

Screening Test B:
cScreenWorking = cScreenB
pDetectScreenWorking = pDetectScreenB
--- Markov Information
Term (0): _stage = totalCycles

Case Type 1:
effCaseWorking = effCaseA
--- Markov Information
Term (0): _STAGE = 120

Case Type 2:
effCaseWorking = effCaseB
--- Markov Information
Term (0): _STAGE = 120

Name	Description	Show in tree	Root Definition	Category
age		☑	startAge + _stage	
cScreenA	Cost screening test A	☑	3000	
cScreenB	Cost screening test B	☑	4000	
cScreenWorking	Cost of Screening for Clone	☑		
effCaseA		☑	0.8	
effCaseB		☑	0.7	
effCaseWorking	Effectiveness working variable for use in Clone	☑		
pDetectScreenA	Probability of detecting with screening test A	☑	0.95	
pDetectScreenB		☑	0.97	
pDetectScreenWo	Probability of detection for use in clone	☑		
startAge		☑	50	
totalCycles	Number of years for model	☑	20	

Define working variables differently at the Clone Master and Copy

Variable Properties View with working variables used in Clone Masters highlighted

Variable Definition view @ Screening Test A

Name	D
---Defined @ Screening Test A ---	
cScreenWorking	cScreenA
pDetectScreenWorking	pDetectScreenA
---Undefined @ Screening Test A ---	
---Inherited---	

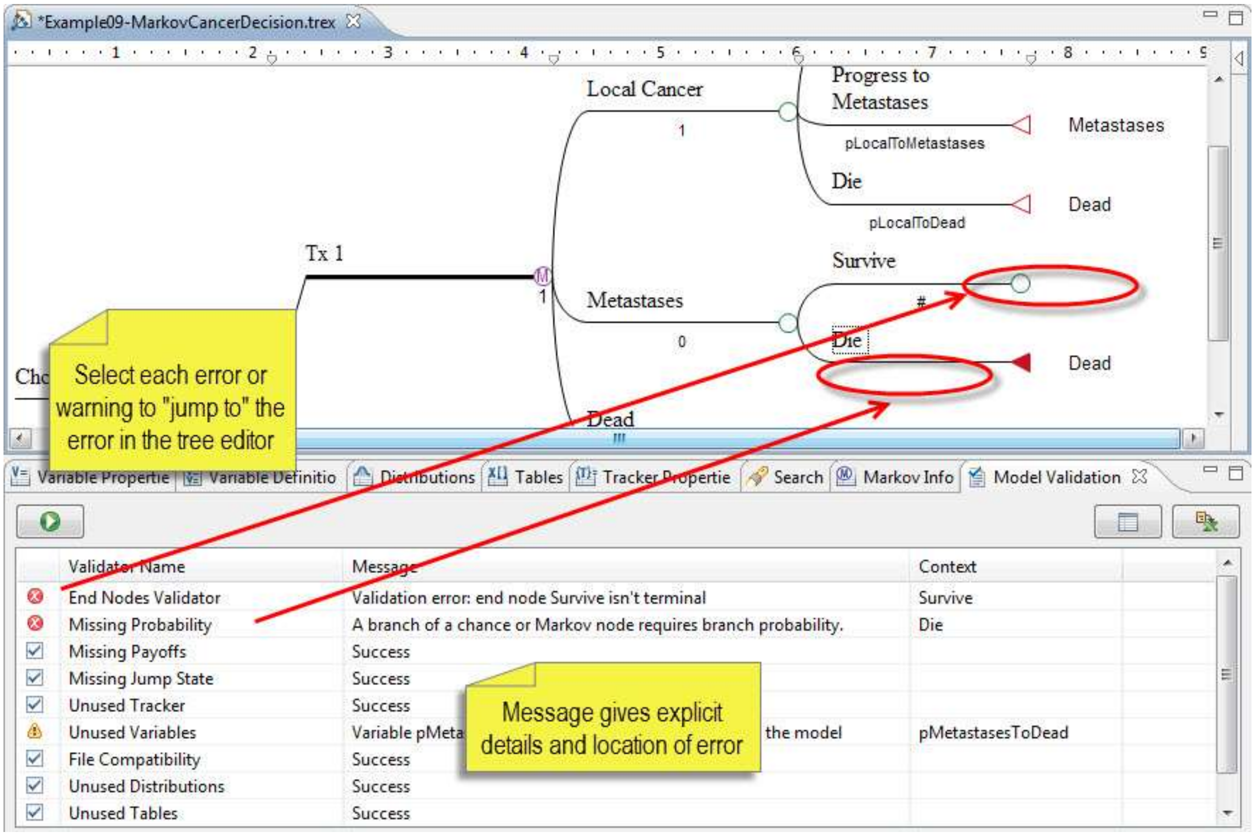
Variable Definition view @ Screening Test B

ne	
---Defined @ Screening Test B ---	
cScreenWorking	cScreenB
pDetectScreenWorking	pDetectScreenB
---Undefined @ Screening Test B ---	
---Inherited---	

Figure 11: Tree Editor, Variable Properties and Variables Definitions Views illustrating how different variables are defined differently at each node

3.8 Model Validation

- The Model Validation View allows you to perform a series of validation checks on the model. This will alert you of common model errors. In the Model Validation View, click the “play” button to see any modelling irregularities found (Figure 12), such as scenarios not terminated, missing probabilities and unused variables. Model Validation cannot validate the data used in the model.



Select each error or warning to "jump to" the error in the tree editor

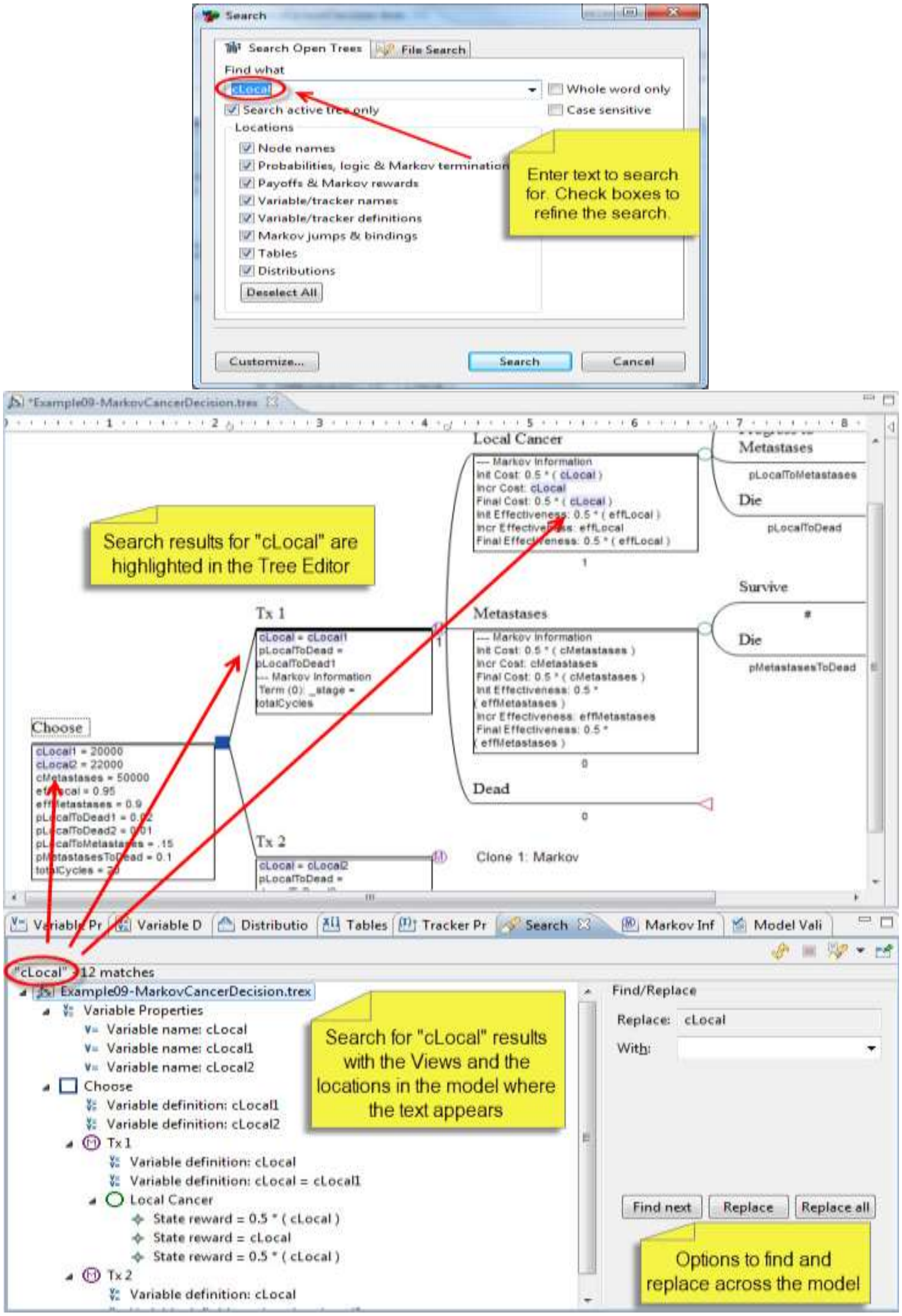
	Validator Name	Message	Context
⊗	End Nodes Validator	Validation error: end node Survive isn't terminal	Survive
⊗	Missing Probability	A branch of a chance or Markov node requires branch probability.	Die
☑	Missing Payoffs	Success	
☑	Missing Jump State	Success	
☑	Unused Tracker	Success	
⚠	Unused Variables	Variable pMeta the model	pMetastasesToDead
☑	File Compatibility	Success	
☑	Unused Distributions	Success	
☑	Unused Tables	Success	

Message gives explicit details and location of error

Figure 12: Validator view showing location of the errors in the tree editor window

3.9 Find, Search, and Replace

- Choose Tree > Find from the menu to search for words or expressions in the model. TreeAge Pro allows you to select the contexts (variables, node labels, etc.) which you wish to search.
- When the search is finished, the results open in a Search View (Figure 13), which allows you to select and/or replace each result as you wish. . When a specific search result is selected, it is also highlighted in the Tree Editor.



Find what: cLocal

☐ Whole word only
☑ Search active tree only
☐ Case sensitive

Locations
☑ Node names
☑ Probabilities, logic & Markov termination
☑ Payoffs & Markov rewards
☑ Variable/tracker names
☑ Variable/tracker definitions
☑ Markov jumps & bindings
☑ Tables
☑ Distributions

Enter text to search for. Check boxes to refine the search.

cLocal1 = 20000
cLocal2 = 22000
cMetastases = 50000
effLocal = 0.95
effMetastases = 0.9
pLocalToDead1 = 0.02
pLocalToDead2 = 0.01
pLocalToMetastases = .15
pMetastasesToDead = 0.1
totalCycles = 20

cLocal = cLocal1
pLocalToDead = pLocalToDead1
--- Markov Information
Term (0): _stage = totalCycles

--- Markov Information
Init Cost: 0.5 * (cLocal)
Incr Cost: cLocal
Final Cost: 0.5 * (cLocal)
Init Effectiveness: 0.5 * (effLocal)
Incr Effectiveness: effLocal
Final Effectiveness: 0.5 * (effLocal)

--- Markov Information
Init Cost: 0.5 * (cMetastases)
Incr Cost: cMetastases
Final Cost: 0.5 * (cMetastases)
Init Effectiveness: 0.5 * (effMetastases)
Incr Effectiveness: effMetastases
Final Effectiveness: 0.5 * (effMetastases)

cLocal = cLocal2
pLocalToDead =

Search results for "cLocal" are highlighted in the Tree Editor

"cLocal" - 12 matches
- Example09-MarkovCancerDecision.trex
  - Variable Properties
    - Variable name: cLocal
    - Variable name: cLocal1
    - Variable name: cLocal2
  - Choose
    - Variable definition: cLocal1
    - Variable definition: cLocal2
    - Tx 1
      - Variable definition: cLocal
      - Variable definition: cLocal = cLocal1
      - Local Cancer
        - State reward = 0.5 * (cLocal)
        - State reward = cLocal
        - State reward = 0.5 * (cLocal)
    - Tx 2
      - Variable definition: cLocal

Search for "cLocal" results with the Views and the locations in the model where the text appears

Find/Replace
Replace: cLocal
With:

Options to find and replace across the model

Figure 13: The search results in the Search View and highlighted in the Tree Editor

4 Reproduce Results

This section provides an overview of how to run some of the most common analyses to reproduce the results submitted by the modeller. Note that it may not be possible to run all these analyses on one model and the “list of 5” should direct you to those analyses which are appropriate.

All analyses can be executed from the Analysis menu, Figure 14. Tree Preferences impact the way the analyses are calculated, the most important being the model’s Calculation Method.

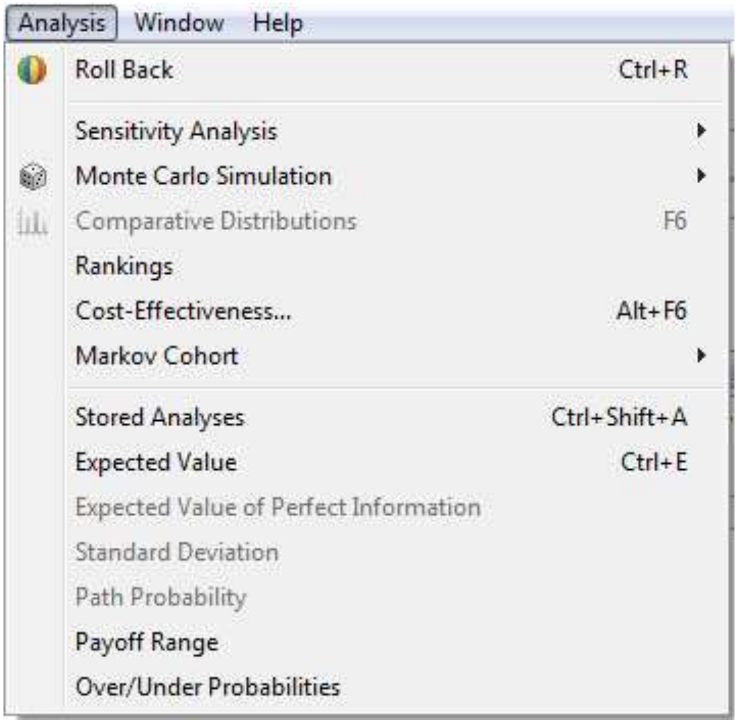
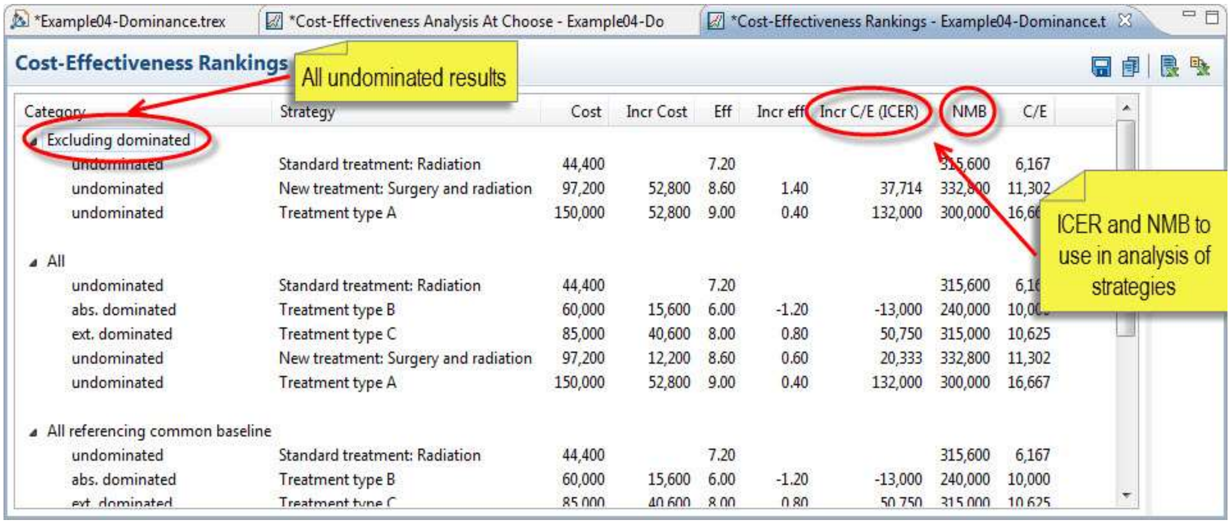


Figure 14: Analysis menu

In addition, some of the most common analyses can be executed from the tool bar when the Analyze perspective is selected. Refer to Figure 2c for a description of the analyses you can run from the toolbar. We will describe how to find the analysis functions using the menus in the remainder of this document, but the toolbar can also be used.

4.1 Cost-Effectiveness Analysis (CEA)

- Use to compare strategies on the basis of cost-effectiveness.
- Select the decision node where CEA should be run. This is usually the left most node in the model.
- Choose Analysis > Rankings from the Analysis menu to generate a text report which will provide the overall expected values for each strategy, along with incremental values. The details include cost, effectiveness, incremental cost-effectiveness ratio (ICER), net monetary benefits (NMB) and dominance (if appropriate) (Figure 15).



All undominated results

Category	Strategy	Cost	Incr Cost	Eff	Incr eff	Incr C/E (ICER)	NMB	C/E
Excluding dominated								
undominated	Standard treatment: Radiation	44,400		7.20			315,600	6,167
undominated	New treatment: Surgery and radiation	97,200	52,800	8.60	1.40	37,714	332,800	11,302
undominated	Treatment type A	150,000	52,800	9.00	0.40	132,000	300,000	16,66
All								
undominated	Standard treatment: Radiation	44,400		7.20			315,600	6,16
abs. dominated	Treatment type B	60,000	15,600	6.00	-1.20	-13,000	240,000	10,00
ext. dominated	Treatment type C	85,000	40,600	8.00	0.80	50,750	315,000	10,625
undominated	New treatment: Surgery and radiation	97,200	12,200	8.60	0.60	20,333	332,800	11,302
undominated	Treatment type A	150,000	52,800	9.00	0.40	132,000	300,000	16,667
All referencing common baseline								
undominated	Standard treatment: Radiation	44,400		7.20			315,600	6,167
abs. dominated	Treatment type B	60,000	15,600	6.00	-1.20	-13,000	240,000	10,000
ext. dominated	Treatment type C	85,000	40,600	8.00	0.80	50,750	315,000	10,625

ICER and NMB to use in analysis of strategies

Figure 15: Cost Effectiveness Rankings

- Choose Analysis > Cost-Effectiveness from the menu to generate the CEA graph, with options to generate the Rankings report and insert a Willingness-To-Pay (WTP) line (Figure 16).

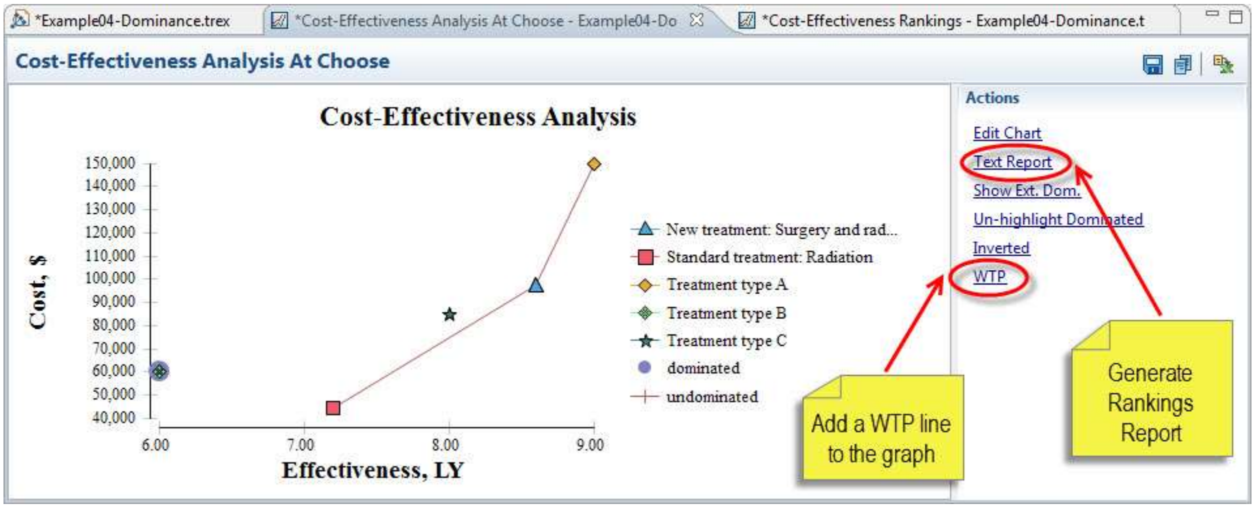
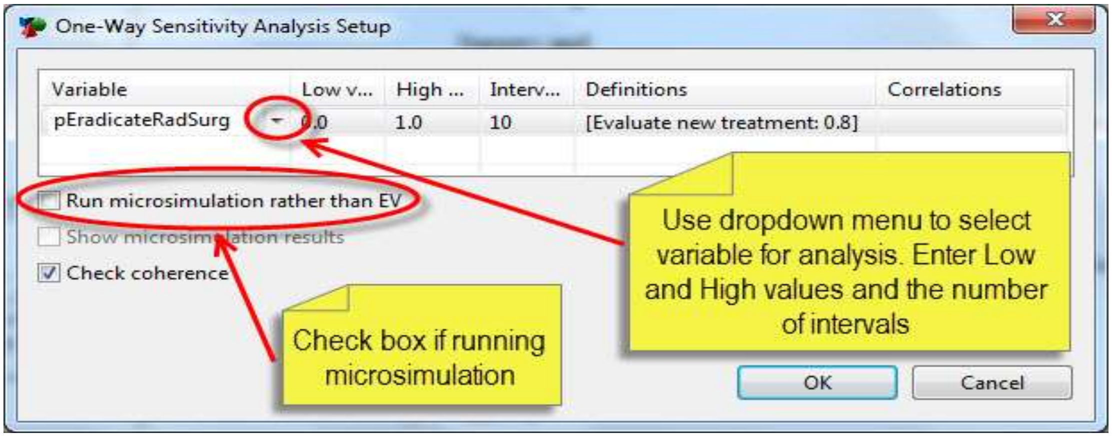


Figure 16: Cost Effectiveness Analysis graph showing options to generate secondary reports and edit the graph

- If a model requires Microsimulation, you must first run Microsimulation first, then use the aggregated results to compare strategies, including CEA. Do not directly choose Analysis > Cost Effectiveness from the menu. See Section 5 below for more details about Microsimulation.

4.2 Sensitivity Analysis (One-way)

- Use to study the impact of uncertainty related to a single parameter across a range.
- Select the decision node.
- Choose Analysis > Sensitivity Analysis > 1-way from the menu and a dialogue box, shown in Figure 17, will appear to prompt the user to select the variable parameter and set its sensitivity analysis range.



Variable	Low v...	High ...	Interv...	Definitions	Correlations
pEradicateRadSurg	0.0	1.0	10	[Evaluate new treatment: 0.8]	

☐ Run microsimulation rather than EV

☐ Show microsimulation results

☑ Check coherence

Use dropdown menu to select variable for analysis. Enter Low and High values and the number of intervals

Check box if running microsimulation

Figure 17: Dialogue for entering details for 1-way sensitivity analysis

- Click the variable column to activate the dropdown menu and select a variable. Then, set the range and number of intervals.
  - Be sure to choose only variables that are used for numeric parameters and not variables that are defined using formula expressions.

- The aggregated output is a set of Rankings, which compare strategies at each parameter value within the uncertainty range (Figure 18).
- Secondary outputs can be useful when looking for thresholds where the recommended strategy changes. Specifically, you might choose the “x versus ICER” and “Net Benefits” graphs which are highlighted in Figure 18.
- If the model requires Microsimulation, check the appropriate box when running one-way sensitivity analysis, as indicated in Figure 17.

Sensitivity Cost Effectiveness Analysis

cLocal	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance
10,000.0								
	Tx 1	383,840	0	10.95	0.00	35,042	0	
	Tx 2	402,106	18,266	11.53	0.58	34,875	31,700	
15,000.0								
	Tx 1	410,104	0	10.95	0.00	37,440	0	
	Tx 2	429,976	19,872	11.53	0.58	37,292	34,488	
20,000.0								
	Tx 1	436,368	0	10.95	0.00	39,837	0	
	Tx 2	457,847	21,479	11.53	0.58	39,709	37,277	
25,000.0								
	Tx 1	462,632	0	10.95	0.00	42,235	0	
	Tx 2	485,717	23,086	11.53	0.58	42,127	40,065	
30,000.0								
	Tx 1	488,895	0	10.95	0.00	44,633	0	
	Tx 2	513,588	24,692	11.53	0.58	44,544	42,853	

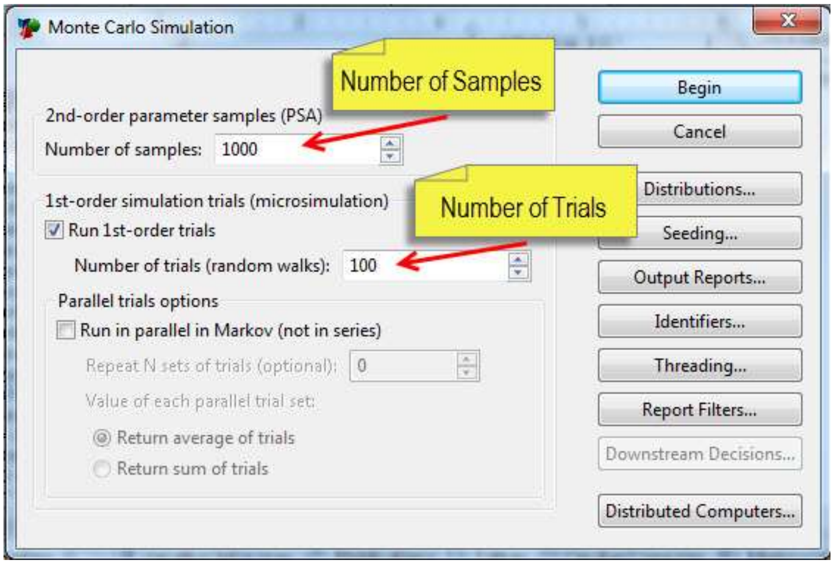
Rankings are given for each value in 1-way analysis range

Secondary graphs. These two useful for thresholds.

Figure 18: One-way sensitivity analysis output

4.3 Probabilistic Sensitivity Analysis (PSA)

- Use to study the impact of combined uncertainty related to a number of parameters represented by distributions.
- Select the decision node.
- If the model does not require Microsimulation:
  - Choose Analysis > Monte Carlo Simulation > Sampling (Probabilistic Sensitivity)… from the menu.
  - Select the number of samples to run, as in Figure 19 except with “Run 1st-order trials” unchecked.
  - Note that the Expected Value (EV) for each set of sampled parameters is generated from a cohort-level analysis.
- If the model requires Microsimulation:
  - Choose Analysis > Monte Carlo Simulation > Samples & Trials… from the menu.
  - Select the number of samples and trials to run, as in Figure 19.
  - Note that the expected value for each set of sampled parameters is generated from the aggregated mean values from a set of trial results.



2nd-order parameter samples (PSA)

Number of samples: 1000

1st-order simulation trials (microsimulation)

☑ Run 1st-order trials

Number of trials (random walks): 100

Parallel trials options

☐ Run in parallel in Markov (not in series)

Repeat N sets of trials (optional): 0

Value of each parallel trial set:

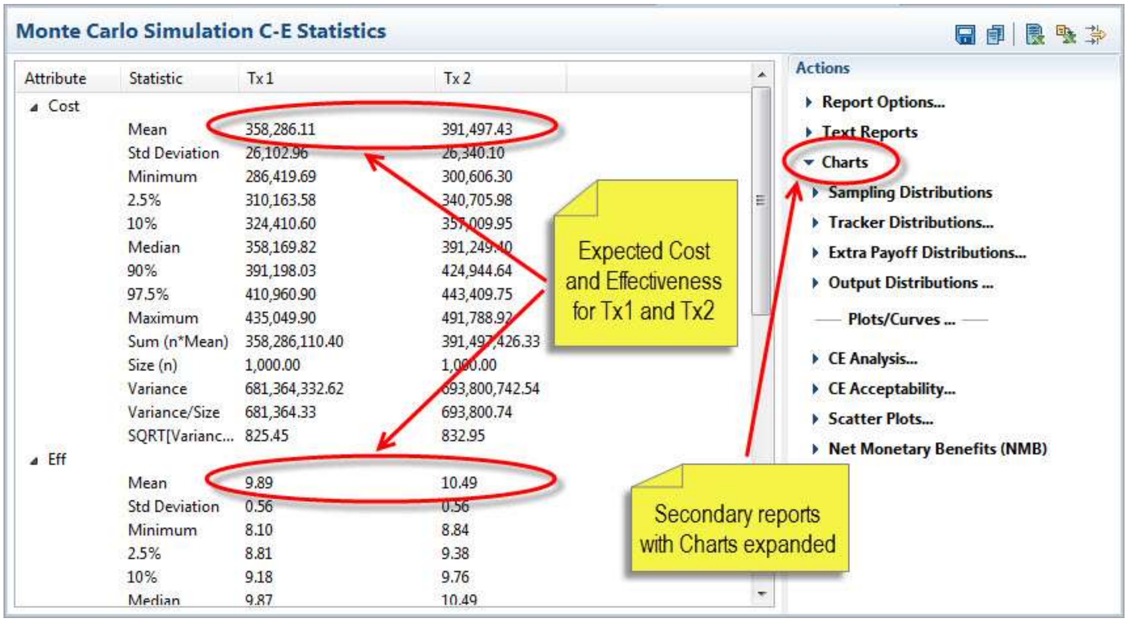
● Return average of trials

○ Return sum of trials

Figure 19: The dialogue for entering number of Samples and Trials for running PSA with Microsimulation

- The number of samples and trials to run:
  - The modeller should provide this advice based on research.
  - Generally for samples, the more distributions being sampled from, the more samples should be taken. You can start with 1,000 samples, but may need more to stabilise results.
  - Generally for trials, a sufficient number need to be run through the model to stabilise the aggregate results. This should be tested prior to running PSA to ensure the number of trials in the microsimulation is generating stable results. You can start with 10,000 trials, but you may need more.

- To cancel a simulation which is in progress, use the “cancel” button in the dialogue box which appears when the simulation is running.
- PSA will sample those distributions which have been created with a sampling rate of “Sample per EV”.
- The outputs from PSA are usually Expected Cost and Effectiveness and the analysis provides statistics around those values.
- Secondary outputs are listed to the right of the aggregated values. They include several text reports and charts (Figure 20). Key secondary reports are…
    - Text Report > Values, Dists, Trackers – a numeric display of the iteration-by-iteration data generated by the analysis.
    - Charts > Scatterplots > ICE Scatterplot – plots incremental cost versus incremental effectiveness when comparing two strategies (Figure 21).
    - Charts > Acceptability > Acceptability Curve – plots the percentage of iterations favouring each strategy as WTP changes (Figure 22).



Monte Carlo Simulation C-E Statistics

Attribute	Statistic	Tx 1	Tx 2
Cost			
	Mean	358,286.11	391,497.43
	Std Deviation	26,102.96	26,340.10
	Minimum	286,419.69	300,606.30
	2.5%	310,163.58	340,705.98
	10%	324,410.60	357,009.95
	Median	358,169.82	391,249.40
	90%	391,198.03	424,944.64
	97.5%	410,960.90	443,409.75
	Maximum	435,049.90	491,788.92
	Sum (n*Mean)	358,286,110.40	391,497,426.33
	Size (n)	1,000.00	1,000.00
	Variance	681,364,332.62	693,800,742.54
	Variance/Size	681,364.33	693,800.74
	SQRT[Varianc...	825.45	832.95
Eff			
	Mean	9.89	10.49
	Std Deviation	0.56	0.56
	Minimum	8.10	8.84
	2.5%	8.81	9.38
	10%	9.18	9.76
	Median	9.87	10.49

Figure 20: The simulation output with secondary reports listed for PSA with Microsimulation

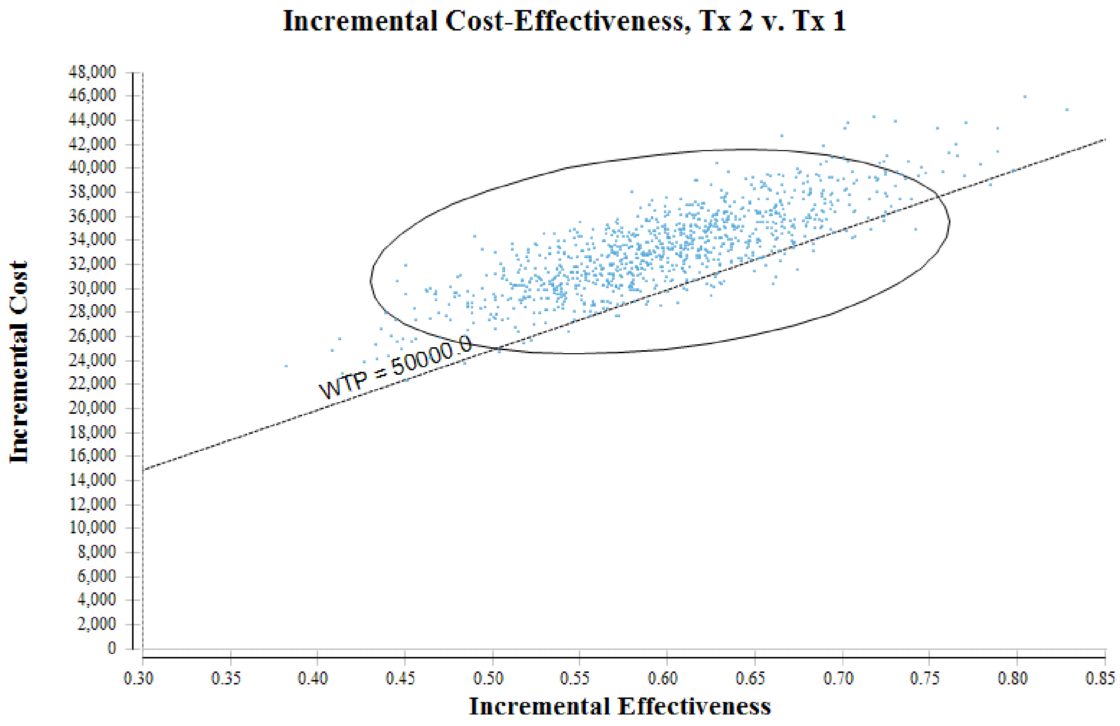


Figure 21: ICE Scatterplot from PSA with Microsimulation

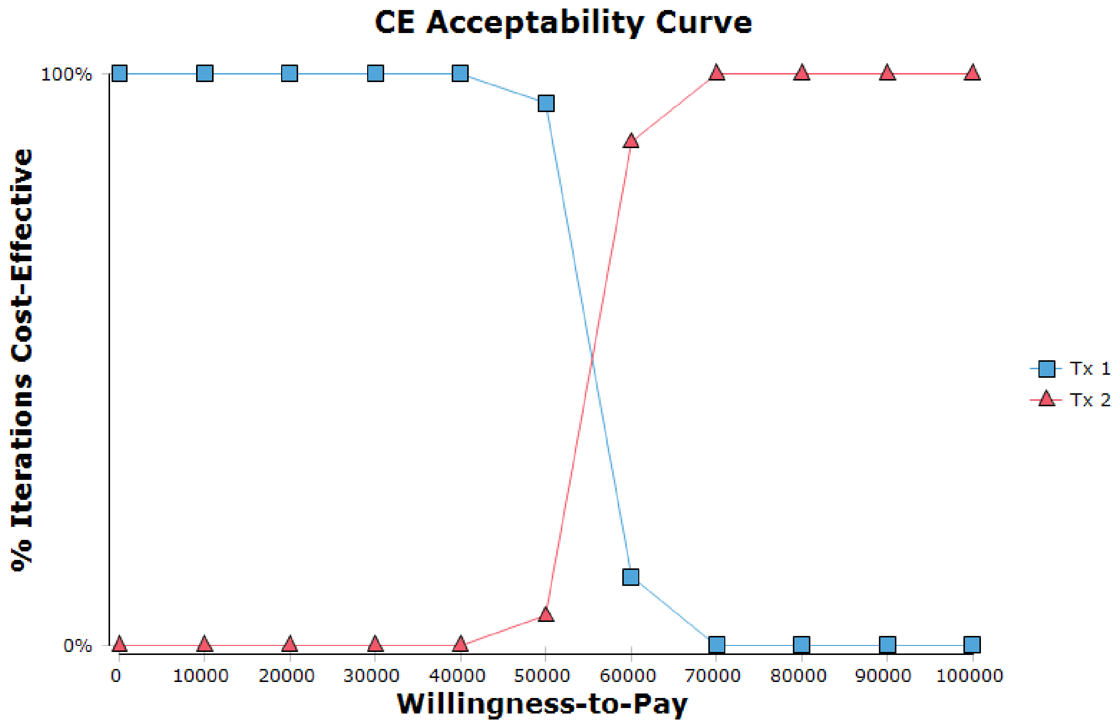
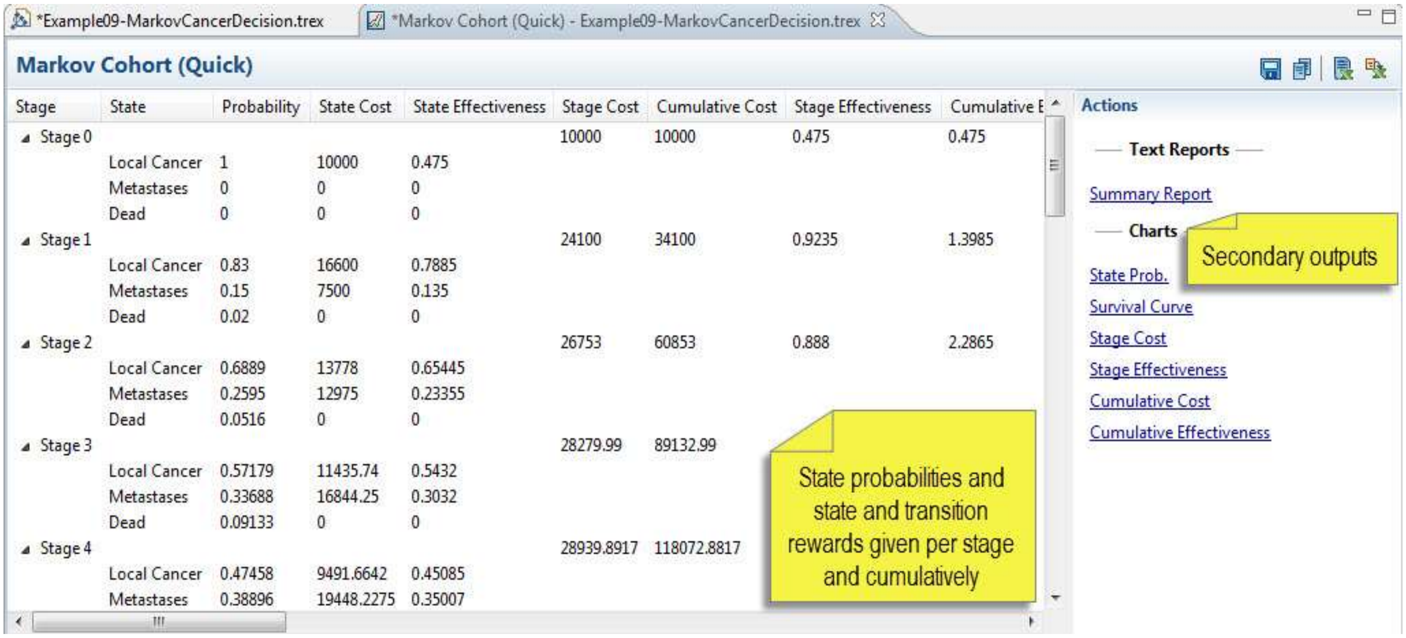


Figure 22: Acceptability Curve as WTP changes from PSA with Microsimulation

4.4 Markov Cohort Analysis

- Use to show the detailed calculations performed when evaluating a Markov model via cohort analysis. This analysis is run for a single Markov model within the overall decision tree.
- Select a Markov node, then choose Analysis > Markov Cohort (quick) or Markov Cohort (full) from the menu, as in Figure 14.
  - The “quick” output shows the states and value accumulated by cycle (Figure 23).
  - The “full” output expands on the quick output by showing the progression of the cohort from each state through its entire transition subtree.



Stage	State	Probability	State Cost	State Effectiveness	Stage Cost	Cumulative Cost	Stage Effectiveness	Cumulative E
Stage 0					10000	10000	0.475	0.475
	Local Cancer	1	10000	0.475				
	Metastases	0	0	0				
	Dead	0	0	0				
Stage 1					24100	34100	0.9235	1.3985
	Local Cancer	0.83	16600	0.7885				
	Metastases	0.15	7500	0.135				
	Dead	0.02	0	0				
Stage 2					26753	60853	0.888	2.2865
	Local Cancer	0.6889	13778	0.65445				
	Metastases	0.2595	12975	0.23355				
	Dead	0.0516	0	0				
Stage 3					28279.99	89132.99		
	Local Cancer	0.57179	11435.74	0.5432				
	Metastases	0.33688	16844.25	0.3032				
	Dead	0.09133	0	0				
Stage 4					28939.8917	118072.8817		
	Local Cancer	0.47458	9491.6642	0.45085				
	Metastases	0.38896	19448.2275	0.35007				

Figure 23: Markov Cohort Analysis (quick) output

- This output is useful for validating that a Markov model is producing the results which are expected, prior to incorporating those results into a larger model.

- To the right of the Markov output, secondary reports graphs are available, including a survival curve (Figure 24).

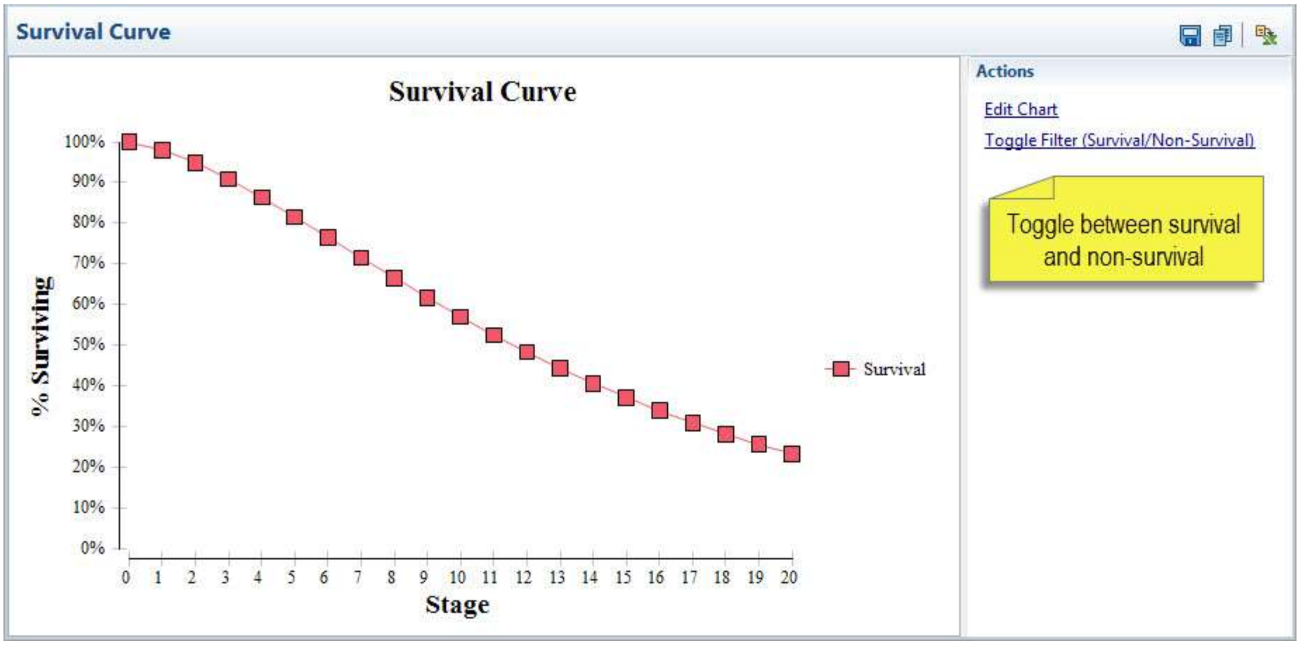
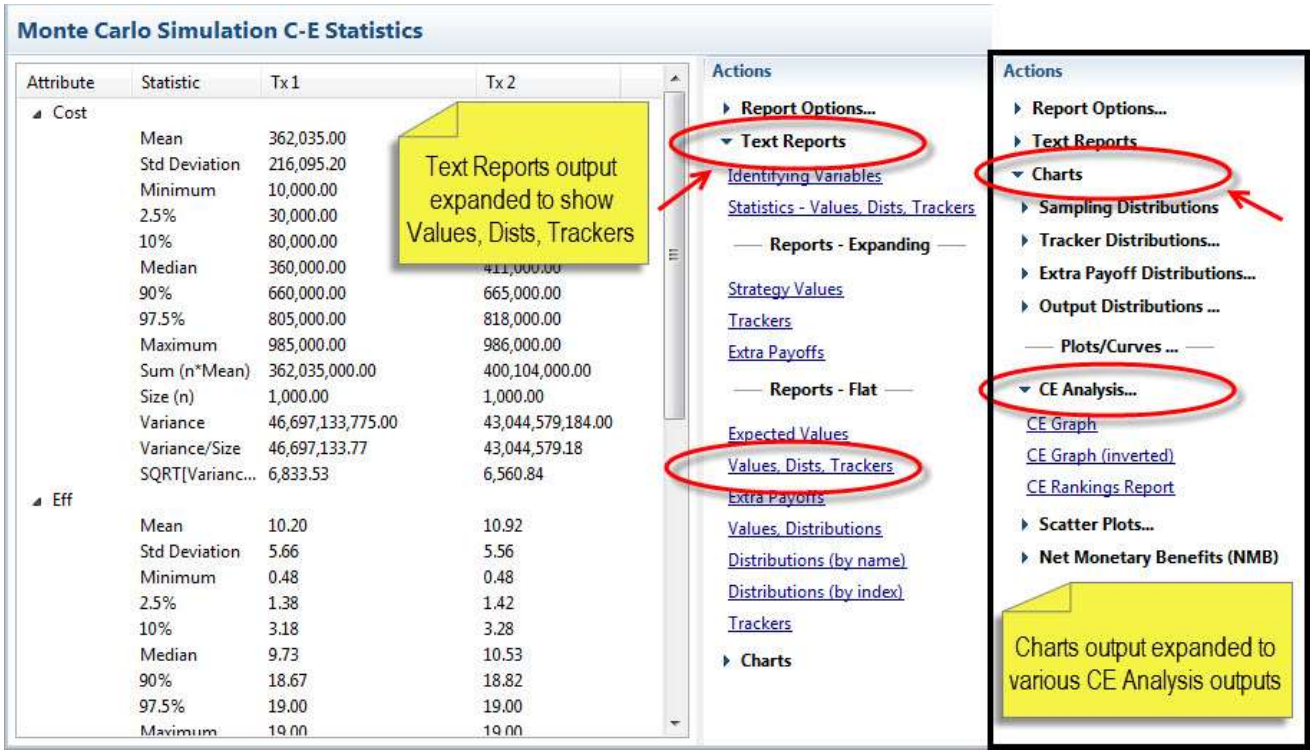


Figure 24: Survival curve: one of the secondary outputs of Markov analysis

- If a model requires Microsimulation, Markov Cohort Analysis should not be used. Microsimulation Markov models are evaluated based on individual-patient simulation rather than overall cohort aggregation.

4.5 Microsimulation

- Use to generate primary analysis results for models that require individual-patient simulation.
- Select the decision node, then choose Analysis > Monte Carlo Simulation > Trials from the menu.
- Set the number of trials required.
    - Note that the more complex the model, the more trials need to be run to stabilize aggregate results.
- Outputs are aggregated EV's for cost and effectiveness for all trials. Statistics around the values are provided.
- Secondary outputs to the right of the aggregated values include several text reports and charts, Figure 25. Key secondary reports are…
    - Text Report > Values, Dists, Trackers – a numeric display of the iteration-by-iteration data generated by the analysis.
    - Graph > CE Analysis > CE Graph and/or CE Rankings – displays the cost-effectiveness analysis as in Section 1 where we considered CEA (Figures 15 and 16). Note that for models that require Microsimulation, this is the primary analysis for comparing strategies.



Monte Carlo Simulation C-E Statistics

Attribute	Statistic	Tx 1	Tx 2
Cost			
	Mean	362,035.00	
	Std Deviation	216,095.20	
	Minimum	10,000.00	
	2.5%	30,000.00	
	10%	80,000.00	
	Median	360,000.00	411,000.00
	90%	660,000.00	665,000.00
	97.5%	805,000.00	818,000.00
	Maximum	985,000.00	986,000.00
	Sum (n*Mean)	362,035,000.00	400,104,000.00
	Size (n)	1,000.00	1,000.00
	Variance	46,697,133,775.00	43,044,579,184.00
	Variance/Size	46,697,133.77	43,044,579.18
	SQRT[Varianc...	6,833.53	6,560.84
Eff			
	Mean	10.20	10.92
	Std Deviation	5.66	5.56
	Minimum	0.48	0.48
	2.5%	1.38	1.42
	10%	3.18	3.28
	Median	9.73	10.53
	90%	18.67	18.82
	97.5%	19.00	19.00
	Maximum	19.00	19.00

Text Reports output expanded to show Values, Dists, Trackers

Charts output expanded to various CE Analysis outputs

Figure 25: Microsimulation output with Expected Values and statistics for Cost and Effectiveness. The Action menus show where to generate key outputs.

4.6 Analysis Seeding

- Seed the random number generator to yield consistent output from any Monte Carlo simulation analysis, which includes PSA and Microsimulation.
  - Note that use of seeding can hide a problem of running too few trials to stabilize aggregate results.
- To set the seed, go to Tree > Tree Preferences > Analysis Settings > Monte Carlo Options > Random Number Seeding.

4.7 Analysis Considerations

In all analyses, important considerations are:

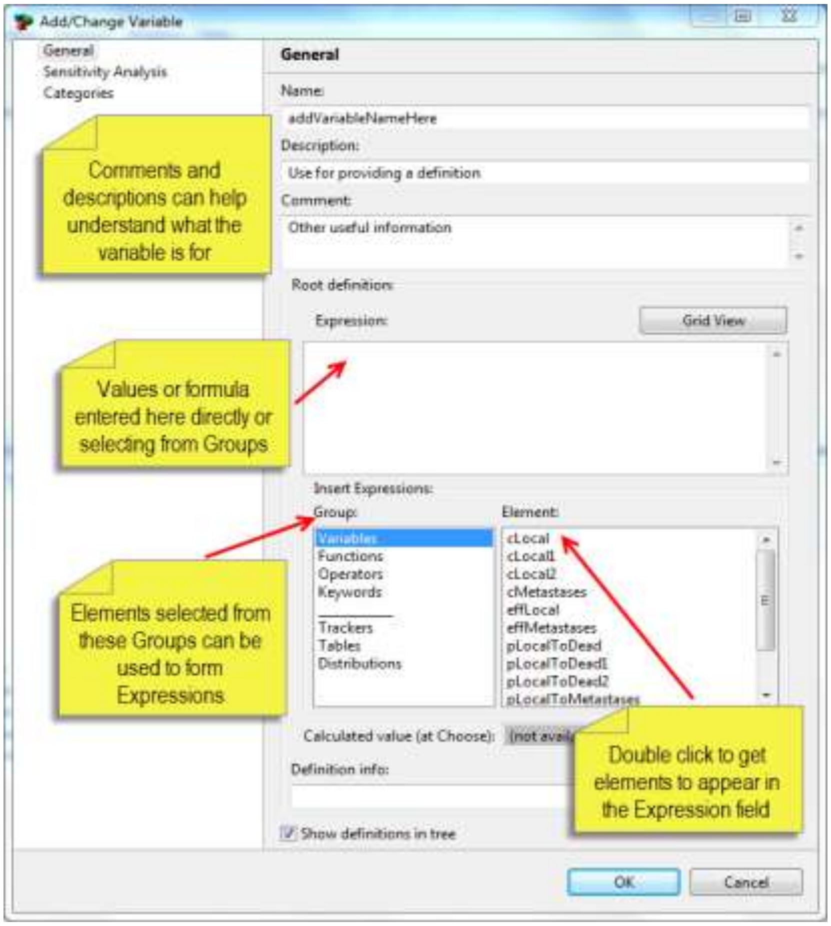
- Are there specific parameters that are good candidates for 1-way sensitivity analysis?
- If some distributions are defined with a Sampling Rate of “Sample per EV”, run PSA.
- If not a Microsimulation model, run Markov Cohort Analysis at specific Markov nodes as desired.
- These details about types of analyses to run should be provided in the “list of 5”.

5 Testing Values/Assumptions

This section provides details to the Reviewer about how to test the model to generate sets of results, other than those provided by the modeller. There are a number of ways that changing the model might be of interest to the Reviewer.

5.1 Change the values of key variables in the model and repeat analyses

- Most parameter variables can be changed via the Variable Properties View. If no definition exists at the root node, you probably should not add one.
- Figure 26 shows the editor which opens once you have selected the variable to change and clicked the pencil in the Views tool bar.
- The Add/Change window provides the options of editing an "Expression".
    - The expression can be a number, entered directly into the "expression" field;
    - The expression can be a formula, entered directly into the "expression" field with elements via the formula editor by selecting individual model elements (variables, functions, etc.) to build the expression.



Name: addVariableNameHere

Description: Use for providing a definition

Comment: Other useful information

Calculated value (at Choose): (not avail

☑ Show definitions in tree

Comments and descriptions can help understand what the variable is for

Values or formula entered here directly or selecting from Groups

Elements selected from these Groups can be used to form Expressions

Double click to get elements to appear in the Expression field

Figure 26: Add/Change Variable dialogue at the root node

5.2 Change the parameters describing key distributions in the model

- In the Distributions View, Distributions in the model can be open by highlighting them and selecting the pencil in the view tool bar.
- Distributions can then be edited by changing the distribution parameters, see Figure 9.
- Dependent on the Resample rate for the distribution, the effect of changing the distribution maybe seen through different analysis.
    - Sample per EV will affect any PSA analysis.
    - Sample per Trial will affect any microsimulation analysis.

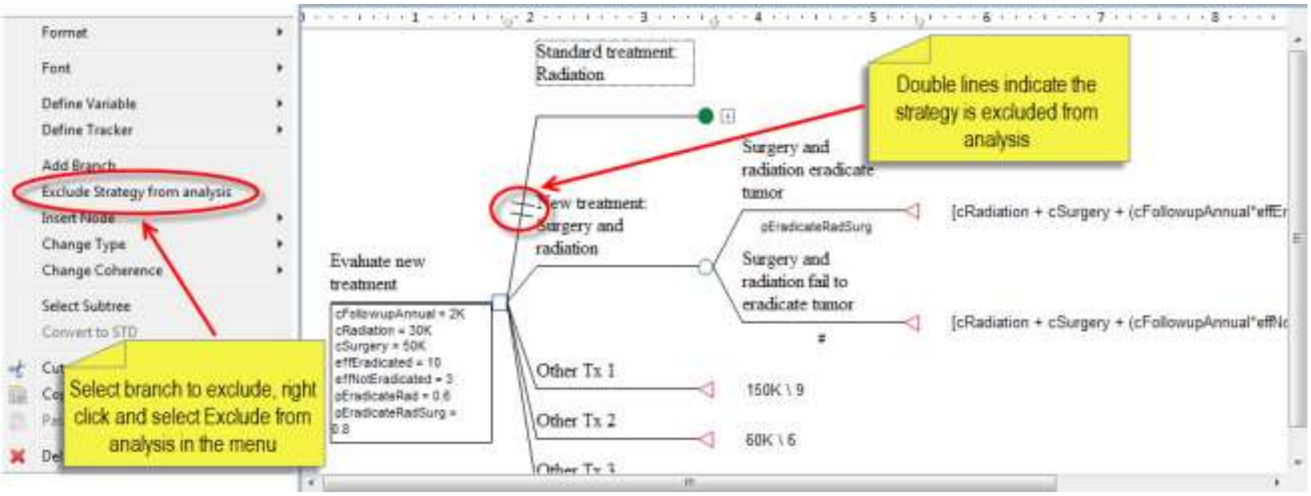
5.3 Testing uncertainty around variables in the model

- If distributions with a Resample rate per EV have been changed, then this will affect PSA. A count of distributions by sampling rate is available in the Dashboard View.
- In addition, testing uncertainty can also be done as per the instructions in the section for reproducing results for 1-way sensitivity analysis and PSA.

5.4 Restrict which strategies to run

- You may wish to select which strategies to include in analyses. You can exclude strategies from analyses using the instructions below.
    - Select a branch/strategy which starts at the root decision node.
    - Right click and a menu will give you the option of “Excluding the Strategy from Analysis”. Once a strategy is excluded, the strategy branch will appear with a double strike the branch to indicate it is excluded from analysis (Figure 27).

When the model is rolled-back, the preferred strategy will be highlighted in green with the other strategies highlighted in red.



cFollowupAnnual = 2K
cRadiation = 30K
cSurgery = 50K
effEradicated = 10
effNotEradicated = 3
pEradicateRad = 0.6
pEradicateRadSurg = 0.8

Double lines indicate the strategy is excluded from analysis

Select branch to exclude, right click and select Exclude from analysis in the menu

Figure 27: Excluding a Strategy from Analysis

6 Contact Us

If you have additional questions, please contact support@treeage.com or call (+1) 413 458 0104.