

TreeAge Software, Inc. presents:

TreeAge Pro 2-Day Healthcare Training Day 1

Using TreeAge Pro for Health Economic Modeling

© 2011 TreeAge Software, Inc.

Course Agenda

Day 1

Agenda & Introduction

Training Modules:

1. Model Structure & Inputs, TreeAge Pro Application Interface
2. Build a Cost-Effectiveness Model
 - Variables, Formula Editor, Clones
3. Roll Back, Cost-Effectiveness Analysis
4. Deterministic Sensitivity Analysis
 - Modeling Exercise
5. Monte Carlo Simulation and Probabilistic Sensitivity Analysis

TreeAge Pro Healthcare Training 2

Course Agenda

Day 2

Training Modules:

6. Markov Models
7. Markov Models & Time Dependence
8. Microsimulation
9. Microsimulation – Decisions & PSA
10. Microsimulation Advanced Techniques
11. Extras

Introduction

- What is TreeAge Pro?
 - Visual tool for building and analyzing models
 - Model types:
 - Decision trees, Markov models, both
 - Analysis features:
 - Expected Value calculations:
 - Roll back, cost-effectiveness analysis, Markov Cohort analysis, etc.
 - Sensitivity analysis:
 - Deterministic and probabilistic
 - Monte Carlo simulation:
 - PSA (sampling), Microsimulation (trials), both, EVPPI

Introduction

- Why use TreeAge Pro?
 - Create models to represent a disease process and possible treatment options
 - Built-in healthcare modeling, analysis and reporting features
 - Compare treatment options on the basis of cost, effectiveness or both
 - Measure effects of uncertainty on treatment strategy selection
 - Build models of nearly unlimited complexity and size
 - Visual tool:
 - Efficient to build and modify models
 - Clear when presenting/sharing models

Model Structure & Inputs, TP User Interface

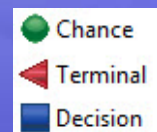
Module Agenda:

1. Examine model structure and inputs
2. Introduce the TreeAge Pro User Interface

Model Structure & Inputs



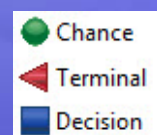
- Model structure is comprised of a collection of nodes
- Root node:
 - Every model starts at the left with a single node
 - Frequently a decision node
- Decision nodes:
 - Branches are alternative strategies
 - Value of each alternative is calculated independently
 - Analysis chooses optimal path/strategy at every decision node

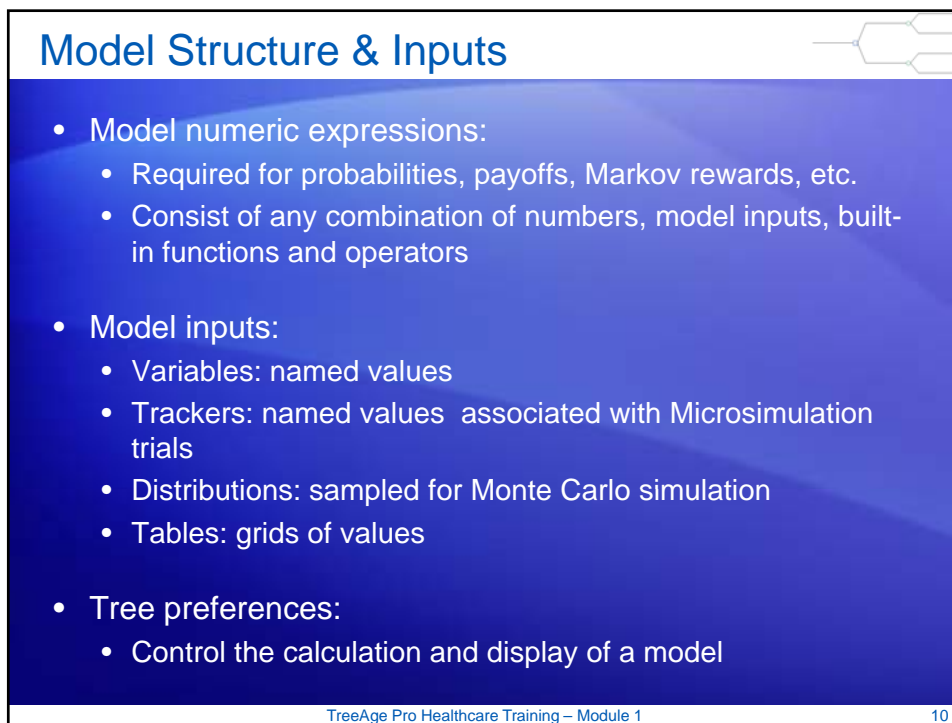
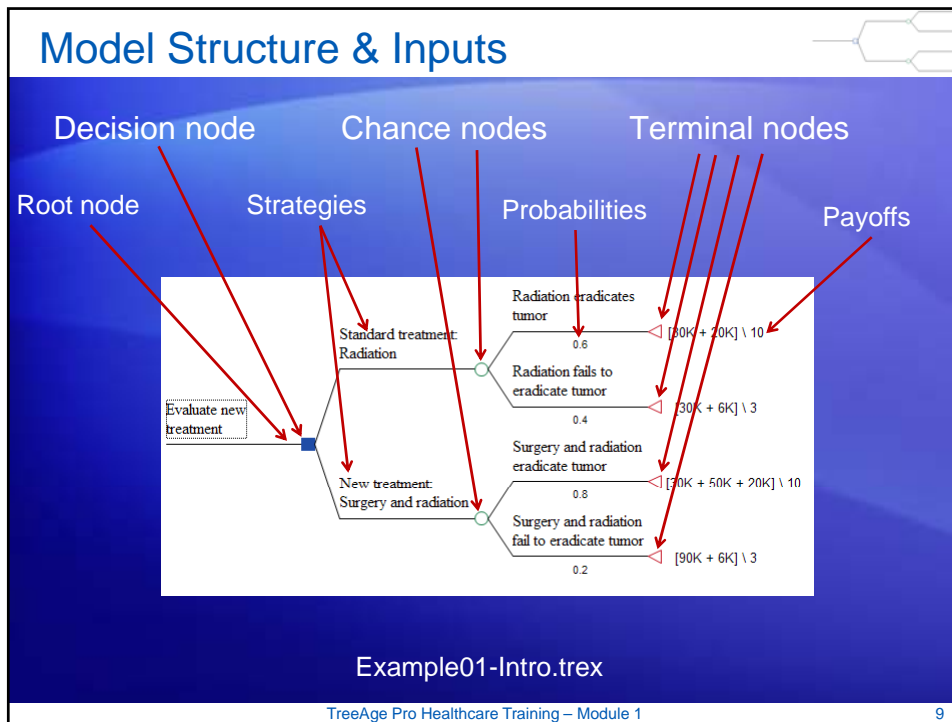


Model Structure & Inputs



- Chance nodes:
 - Branches are possible outcomes
 - Probabilities are associated with each branch
 - Mutually exclusive and exhaustive (“coherence”)
 - Sum of probabilities = 100%
 - Use “#” for complement
- Terminal nodes:
 - Complete the scenario (root to terminal node)
 - Payoffs place a value on all events within that scenario
 - Different for Markov models





TreeAge Pro User Interface

Tree Diagram Editor Perspectives

Projects View Model Input Views

Name	Description	Show in tree	Root Definition	Category
cFollowupAnnual	Cost of followup per year	✓	2K	
cRadiation	Cost of radiation	✓	30K	
cSurgery	Cost of surgery	✓	50K	
effEradicated	Life expectancy if tumor ...	✓	10	

TreeAge Pro Healthcare Training – Module 1 11

TreeAge Pro User Interface

- Tree Diagram Editor
 - Primary modeling window
 - Tabs for multiple models or multiple views of a single model
 - Zoom in/out, multi-select, noteboxes
- Views
 - For editing/viewing components of the model
 - Open via Views toolbar list
 - Move, maximize, minimize, detach
- Perspectives
 - Collection of views' orientation stored when you exit software
 - Can reset to original orientation or overwrite saved orientation

TreeAge Pro Healthcare Training – Module 1 12

TreeAge Pro User Interface







- Model Input Views:
 - Specific view for each model input
 - Some tied to tree (e.g., tree properties, variable properties)
 - Some tied to node (e.g., node properties, variable definitions)
 - Many more
- Other Views:
 - Projects View for managing files
 - Model Overview/Tree Explorer for navigating in large trees
 - Evaluator for testing calculations
 - Context-sensitive help
 - Many more

Build CE Model, Variables, Tree Preferences



Module Agenda:

1. Build a Cost-Effectiveness (CE) Model 
 2. Create and Use Variables
 3. Formula Editor/AutoFill 
 4. Edit Tree Preferences 
 5. Introduce Clones 
- Finally, the training becomes interactive!!!

Build CE Model



- Determining numeric values:
 - All the numeric values you need for this model will be provided
 - In your models, considerable thought will go into determining each value
 - Some will come from medical literature
 - Some will come from trials
 - Some must be estimated
 - Etc.
- TreeAge Pro cannot determine these values for you

Build CE Model



- The current standard is to treat a specific type of tumor with radiation
- We want to study a new treatment that combines surgery and radiation
- We estimate that the new treatment will increase the probability of eradicating the tumor from 60% to 80%
- A person's life expectancy is 10 years if the tumor is eradicated, but only 3 years if not
- The costs associated with radiation and surgery are \$30K and \$50K respectively
- The follow-up costs post-treatment are \$2K per year

Build CE Model



- How do we create a model from the information provided?
 - We will look at each piece of information as we build the tree
- Information:
 - The current standard is to treat a specific type of tumor with radiation
 - We want to study a new treatment that combines surgery and radiation
- Model:
 - Root node is decision with two branches for treatment options

TreeAge Pro Healthcare Training – Module 2

17

Build CE Model



Instructions:

1. Create new model from toolbar icon (blank tree).
2. Drag Decision node from palette to Tree Diagram Editor.
3. Enter node label text.
4. Double-click on root node to add two branches.
5. Enter node label text for each strategy.
6. Adjust width of node as desired for text formatting.

TreeAge Pro Healthcare Training – Module 2

18

Build CE Model

- Information:
 - We estimate that the new treatment will increase the probability of eradicating the tumor from 60% to 80%
- Model:
 - Both strategies are chance nodes with branches for tumor eradicated or tumor not eradicated
 - Different probabilities for each set of branches

TreeAge Pro Healthcare Training – Module 2 19

Build CE Model

Instructions:

1. Double-click on top strategy node to add two branches.
2. Enter node labels.
3. Enter the probability of eradicating tumor under that branch (60% or 0.6 for standard treatment).
4. Enter the complement character (#) under the other branch.
5. Ignore the bottom strategy for now; we will create it later.

TreeAge Pro Healthcare Training – Module 2 20

Build CE Model



- Information:
 - A person's life expectancy is 10 years if the tumor is eradicated, but only 3 years if not
 - The costs associated with radiation and surgery are \$30K and \$50K respectively
 - The follow-up costs post-treatment are \$2K per year
- Model:
 - Each of these numeric values factors into the payoffs (scenario values)
 - However, since they are used in multiple payoffs, it is best to use variables rather than enter the values directly
- We will break from building the model to discuss variables

Variables



- Variables are named values like in algebra
- A variable has a...
 - Name: used as a reference to the variable's value
 - Definition: provides a new value for the variable
- Benefits
 - Transparency - easier for you and your colleagues to understand the meaning of numbers inside a model
 - Efficiency – changing a single variable can affect multiple numeric expressions in the model
 - Consistency – define once use many times
 - Sensitivity analysis – covered later
 - Clones – covered later

Variables



- Variable definitions:
 - Variables are defined at a specific node, so a variable can have a different value for different parts of the model
 - Definition scope is from definition node to the right
 - Shown beneath node in box (to distinguish from probabilities)
 - Useful for clones – covered later
- Variable and other input names:
 - 32 letters/numbers/underscores (no punctuation)
 - Stick to a naming style/convention
 - Not case sensitive
- Now... back to the model!

Build CE Model



Instructions:

1. Right-click on root node and choose Define Variable > New Variable from the context menu.
2. Enter variable name “cFollowupAnnual”.
3. Enter a description and comment if desired.
4. Click OK.
5. Enter definition “2K” in the Define Variable dialog and click OK.
6. You will see the variable definition beneath the root node.
7. Repeat steps 2-5 for the variables below.
 - cRadiation = 30K
 - cSurgery = 50K

Variables



- Variable Properties View:
 - Maintain variables in the tree
 - Options to edit, add, delete, categorize, report variables
 - Edit in Excel available with Excel Module (in TP Suite)

- Variable Definitions View:
 - Maintain variable definitions
 - Contents change with selected node
 - Defined vs. Undefined vs. Inherited
 - Cut/Copy/Paste to copy or move variable definitions to other nodes

Build CE Model



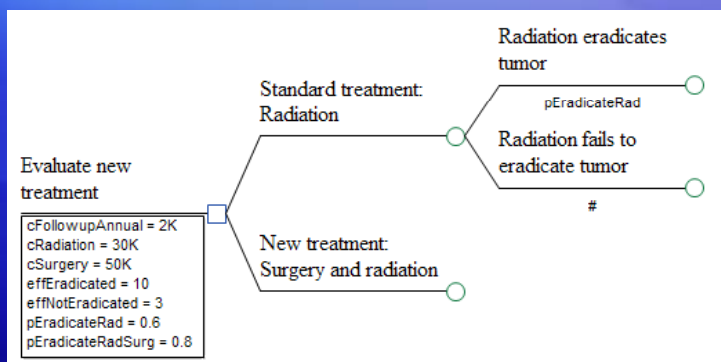
Instructions:

1. Select root node.
2. Select or open the Variable Properties View.
3. Click the “+” icon.
4. Enter the variable name “effEradicated”.
5. Check the box Define numerically at root.
6. Enter 10 in the definition field and click OK.
7. Repeat steps 3-6 for the variable below.
 - $\text{effNotEradicated} = 3$
 - $\text{pEradicateRad} = 0.6$
 - $\text{pEradicateRadSurg} = 0.8$
8. Replace the 0.6 probability value for the Radiation eradicates tumor with the pEradicateRad variable.

Build CE Model



- At this point, our model should look like this...



- We still need to terminate the scenarios for the top strategy and build the bottom strategy

TreeAge Pro Healthcare Training – Module 2

27

Build CE Model



- Information:
 - A person's life expectancy is 10 years if the tumor is eradicated, but only 3 years if not
 - The costs associated with radiation and surgery are \$30K and \$50K respectively
 - The follow-up costs post-treatment are \$2K per year
- Model:
 - Change tree's calculation method to cost-effectiveness
 - Terminate the two scenarios in the top strategies
 - Add the appropriate values for cost and effectiveness
- We will break from building the model to discuss tree preferences

TreeAge Pro Healthcare Training – Module 2

28

Tree Preferences

- Control calculation and display of model
 - Many categories
 - Menu: Tree > Tree Preferences to open dialog
- Calculation Method:
 - Determines which payoff sets will be used to evaluate the model and determine the optimal strategy
 - Usually either simple or cost-effectiveness
- Numeric Formatting:
 - Controls display of outputs (calculated payoffs and EVs)
 - Set for units, decimal places, labels, etc.

TreeAge Pro Healthcare Training – Module 2 29

Tree Preferences

- Simple Calculation Method:
 - Enter a single payoff at each terminal node
 - Single expected value (EV) calculated at all other nodes
 - Either maximize or minimize EVs to pick optimal strategy at decision nodes
- Cost-effectiveness Calculation Method:
 - Enter separate payoff values for cost and effectiveness at each terminal node
 - Cost and effectiveness EVs calculated at all other nodes
 - To select optimal strategy, must balance cost and effectiveness, looking at efficiency & tradeoffs
 - Will examine further when analyzing finished model

TreeAge Pro Healthcare Training – Module 2 30

Tree Preferences



- Not limited to two payoffs (but only two are active)
- Can use extra payoffs for different cost, utility/effectiveness, other outcomes
 - Same model can then be used to analyze problem with different outcome measurements
 - Change active payoffs for different measurements and repeat analyses
- Cost: Total cost vs. patient cost vs. insurer cost, etc.
- Health/Utility: LY, QALY, etc.
- Other: Positive tests, cases avoided, cases identified, etc.
- Advanced techniques allow for reporting on multiple outcomes for certain analyses (terminal columns with Node function, calc extra payoffs preference)

TreeAge Pro Healthcare Training – Module 2

31

Build CE Model



Instructions:

1. Choose Tree > Tree Preferences from the menu.
2. Select the category Calculation > Calculation Method.
3. Select Cost-effectiveness (note active payoffs).
4. Select the category Calculation > Numeric Formatting.
5. Enter settings as seen below.

For cost	Sample	For effectiveness	Sample
Decimal places: 0		Decimal places: 2	
<input checked="" type="checkbox"/> Add trailing zeros		<input checked="" type="checkbox"/> Add trailing zeros	
<input checked="" type="checkbox"/> Use thousands separator	\$1,234,568	<input checked="" type="checkbox"/> Use thousands separator	1,234,567.89 LY
Show numbers: Exactly		Show numbers: Exactly	
Units: Currency		Units: Custom suffix	
Prefix/suffix:		Prefix/suffix: LY	

6. Click OK to save the changes.

TreeAge Pro Healthcare Training – Module 2

32

Build CE Model




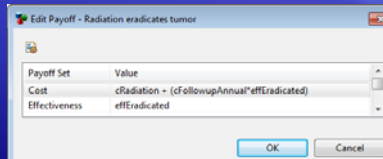
- Terminal nodes terminate the scenario
- Must account for all values that contribute to that scenario on the path from the root node to the terminal node
- For cost-effectiveness model, enter separate values for cost and effectiveness
- For top terminal node...
 - Costs:
 - Initial Treatment Cost: cRadiation
 - Followup Cost: cFollowupAnnual * effEradicated
 - Effectiveness:
 - effEradicated
- For second terminal node...
 - Same except using effNotEradicated

Build CE Model




Instructions:

1. Right-click on top node.
2. Choose Change Type > Terminal.
 - Edit Payoff dialog opens.
3. Enter expression for Cost:
 1. Click ellipsis button to open formula editor for Cost payoff. 
 2. Select variables to enter the following expression...
 - $cRadiation + (cFollowupAnnual * effEradicated)$
4. Enter expression for Effectiveness
 1. Type the following expression...
 - effEradicated
5. Click OK.
6. Repeat steps 2-5 for second terminal node (effNotEradicated).



Formula Editor/Autofill



- The formula editor is available anywhere you see the ellipsis button 
- Helps create expressions by providing lists of
 - Model inputs (variables, trackers, tables, distributions)
 - Built-in functions (Discount, Round, ProbToProb, etc.)
 - Operators (+, -, &&, etc.)
 - Keywords (_stage, _trial, _sample, etc.)
- Auto-fill
 - Press CONTROL+SPACEBAR to automatically complete an element of an expression (as listed above)

Build CE Model



- The two strategies are very similar...
- Rather than build the entire bottom strategy from scratch, we can copy/paste the top strategy's subtree
- Then we will need to make the appropriate changes to the values for the new treatment strategy

Build CE Model



Instructions:

1. Select top strategy node.
2. Choose Subtree > Select Subtree from the menu.
3. Choose Edit > Copy from the menu.
4. Select bottom strategy node.
5. Choose Edit > Paste from the menu.

An exact duplicate of the top strategy's subtree will be copied to the bottom strategy.

Build CE Model

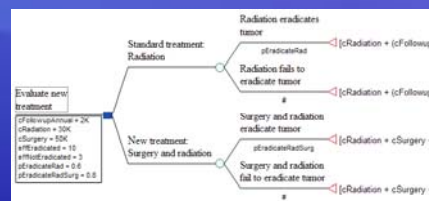


Instructions:

1. Change the node labels in bottom strategy from “Radiation...” to “Surgery and radiation...”.
2. Change the probability for “Surgery and radiation eradicate tumor” node to use pEradicateRadSurg.
3. Change the payoff expressions to include the cost cSurgery.

- The model is now complete!

- Training model: Example02-Variables.trex
- Training model: Example01-Intro.trex – same but without variables



Variables and Clones



- Before analyzing the model, we will introduce clones
- In our example, we copied the subtree from one strategy to the other
- What if the subtree was extremely complex and required significant revision?
- Clones create exact duplicates of a subtree that stay consistent even as the subtree is updated
- We will rebuild the second strategy of our tree using clones

Variables and Clones

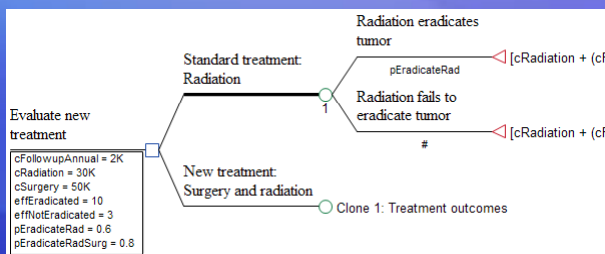


Instructions:

1. Open the Example 2 model.
2. Select the New treatment node.
3. Choose Subtree > Select Subtree from the menu.
4. Choose Subtree > Delete from the menu.
5. Select the Standard treatment node.
6. Choose Subtree > Create Clone Master from the menu.
7. Enter the name "Treatment outcomes".
8. Select the New treatment node.
9. Choose Subtree > Attach Clone.
The clone copy will be attached.

Variables and Clones

- You have now created a clone master and attached a clone copy



- The clone master is identified by a dark node line and a clone index number beneath the node marker
- The clone copy is identified with a reference to the clone master

TreeAge Pro Healthcare Training – Module 2

41

Variables and Clones

- The Clones View allows you to view and edit the clone masters and copies

Clone Masters/Copies window showing the following data:

Index	Clone Name	Node Label
1	Treatment outcomes	Standard treatment:R...

Index	Node ID	Node Label
1	Node5	New treatment:S...

- When a clone master is destroyed, all clone copies are also destroyed
- When a clone copy is destroyed, you can replace it with an independent copy of the clone master

TreeAge Pro Healthcare Training – Module 2

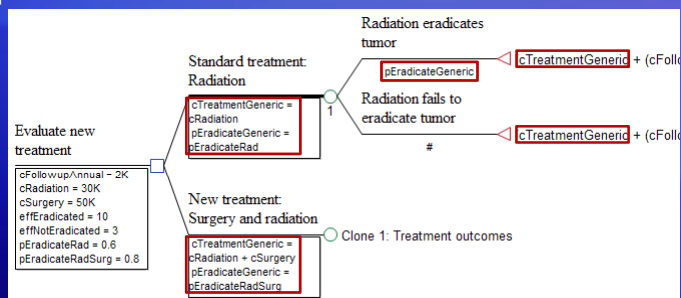
42

Variables and Clones

- But we're not done...
 - The values in the clone copy and master are the same, so how can we really compare strategies?
- Create generic variables in the clone master
- Redefine those generic variables to the left of the clone master and clone copies
- This is done in the example 3 model

Variables and Clones

- The only two values that need to be different for the clone master and clone copy are the probability of eradicating the tumor and the cost of treatment
- Note that the clone master now uses generic variables
 - pEradicateGeneric and cTreatmentGeneric

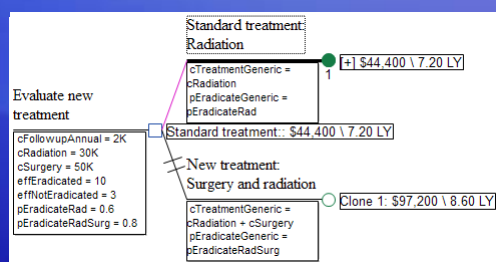


- Those variables are redefined at the strategy nodes

Variables and Clones



- Roll back generates the same values for the strategies as before the clones (next module)
- Now the treatment outcomes subtrees are linked



- A Tree Preferences option will eventually allow you to expand the clone copy subtree

Analyze CE Model



Module Agenda:

1. Run Back and Expected Value Calculations
2. Cost-Effectiveness Analysis (CEA)
3. Dominance in CEA
4. Net Benefits Calculations

Analyze CE Model

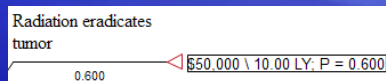


- Expected Value is defined as...
 - The sum of: the probability of each possible outcome of the experiment multiplied by that outcome's value (i.e., payoff)
- Best estimate for the overall value of the strategy
- For CE model, cost and effectiveness EVs are calculated separately
- Roll back calculates EVs at terminal nodes then calculates remaining EVs from right to left

Analyze CE Model



- Terminal nodes:
 - Calculate the payoff expressions
- Top terminal node...
 - Cost: $c_{\text{Radiation}} + (c_{\text{FollowupAnnual}} * \text{effEradicated})$
 $= 30K + (2K * 10) = \mathbf{50K}$
 - Eff: $\text{effEradicated} = \mathbf{10}$

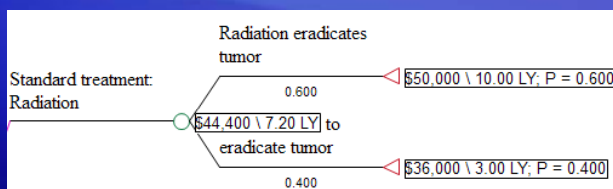


- Path probability:
 - Probability of reaching that node within the scenario
 - $P = 0.600$
 - Only displayed for optimal strategy

Analyze CE Model



- Chance nodes:
 - Weighted average of the node's branches
- Top strategy/chance node...
 - Cost: $(0.6 * 50K) + (0.4 * 36K) = 30K + 14.4K = 44.4K$
 - Eff: $(0.6 * 10) + (0.4 * 3) = 6 + 1.2 = 7.2$



TreeAge Pro Healthcare Training – Module 3

49

Analyze CE Model



- Decision nodes:
 - Compare strategies and take optimal path
 - In a CE tree, this selects the lowest cost value unless CE parameters entered in Tree Preferences
 - Standard treatment costs less, so it is selected
- CE parameters can place weight on effectiveness relative to cost
- However, we will compare the strategies using Cost-Effectiveness Analysis (CEA)

TreeAge Pro Healthcare Training – Module 3

50

Analyze CE Model



- Cost-Effectiveness Analysis (CEA):
 - Standard health economic theory
 - Two goals:
 - Optimize effectiveness (maximize usually)
 - Optimize cost (minimize)
 - CEA context:
 - Efficient use of limited resources
 - Recommend interventions if additional effectiveness comes at a reasonable cost
- Calculate Incremental Cost-Effectiveness Ratio (ICER) and compare to a willingness-to-pay threshold (efficiency)
- Also sometimes compare to ceiling cost value and eliminate strategy if cost exceeds ceiling

TreeAge Pro Healthcare Training – Module 3

51

Analyze CE Model



- ICER = IC/IE

$$= (C_{\text{comparator}} - C_{\text{baseline}}) / (E_{\text{comparator}} - E_{\text{baseline}})$$
- In our model...
 - ICER = $(\$97.2\text{K} - \$44.4\text{K}) / (8.6\text{LY} - 7.2\text{LY})$
 $= (\$52.8\text{K}) / (1.4\text{LY})$
 $= \sim \$37.7\text{K/LY}$
 - To switch from the standard treatment to the new treatment, it costs $\sim \$37.7$ for each extra LY
 - If we are willing to pay at least that much per extra LY, we can recommend the new treatment
- Now, let's run CEA in TreeAge Pro

TreeAge Pro Healthcare Training – Module 3

52

Analyze CE Model



Instructions:

1. Select root node.
2. Choose Analysis > Cost-Effectiveness Analysis from the menu.
3. Click Yes.
A Cost-Effectiveness Analysis graph will be created.
4. Click the Text Report link.
The cost-effectiveness calculations are displayed.

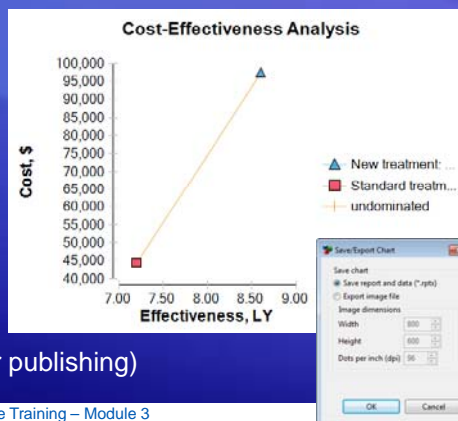
TreeAge Pro Healthcare Training – Module 3

53

Analyze CE Model



- Cost-Effectiveness Analysis graph:
 - Plots strategies on cost and effectiveness axes
 - Best options are lower and to the right
 - When higher and to the right, compare on basis of efficiency (ICER)
 - Slope of line segment is the ICER (IC/IE)
 - Will show dominance next
 - Edit Chart link allows you to modify the appearance of the graph
 - File > Save allows you to save either...
 - The report and data
 - An image of the graph (for publishing)



TreeAge Pro Healthcare Training – Module 3

Analyze CE Model

- Cost-Effectiveness Rankings report:
 - Shows IC, IE, ICER calculations

subset	Strategy	Eff	IncrEff	Cost	IncrCost	IC/IE	Dominance	Avg CE
undominated	Standard treatment: Radiation	7.2	0	44400	0	0		6166.666666667
	New treatment: Surgery and radiation	8.6	1.4	97200	52800	37714.2857142857		11302.3255813954
all	Standard treatment: Radiation	7.2	0	44400	0	0		6166.666666667
	New treatment: Surgery and radiation	8.6	1.4	97200	52800	37714.2857142857		11302.3255813954

- Will show dominance next

TreeAge Pro Healthcare Training – Module 3 55

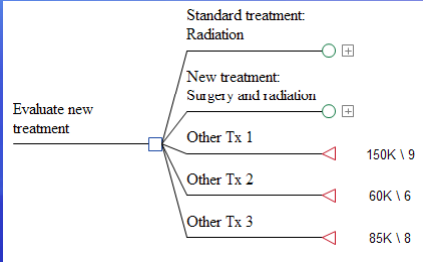
Analyze CE Model

- Dominance:
 - Some strategies may be dominated when other strategies provide better cost-effectiveness
 - Dominated strategies are then rejected as treatment options
- Absolute Dominance:
 - The dominated strategy is both...
 - Less effective
 - More costly
- Extended Dominance:
 - The dominated strategy is both...
 - Less effective
 - Less efficient
 - As measured by an ICER that exceeds an efficiency threshold – Willingness-to-Pay (WTP)

TreeAge Pro Healthcare Training – Module 3 56

Analyze CE Model

- Example 4 model demonstrates both types of dominance

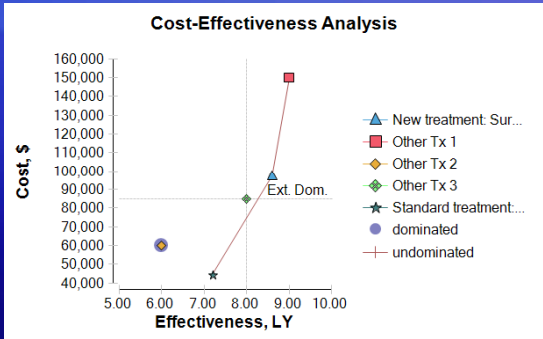


- Same as the tree we built but with three new strategies to evaluate
- Top two strategies collapsed via...
 - Subtree > Collapse Subtree

TreeAge Pro Healthcare Training – Module 3 57

Analyze CE Model

- CEA with dominance
- Line segments create **cost-effectiveness efficiency “frontier”**
- Rejected strategies are not on the frontier




Cost-Effectiveness Analysis

Strategy	Effectiveness (LY)	Cost (\$)	Status
Standard treatment...	~7.2	~45,000	dominated
Other Tx 2	~6.2	~60,000	dominated
Other Tx 3	~8.0	~85,000	undominated
New treatment: Sur...	~9.0	~95,000	undominated
Other Tx 1	~9.2	~150,000	undominated

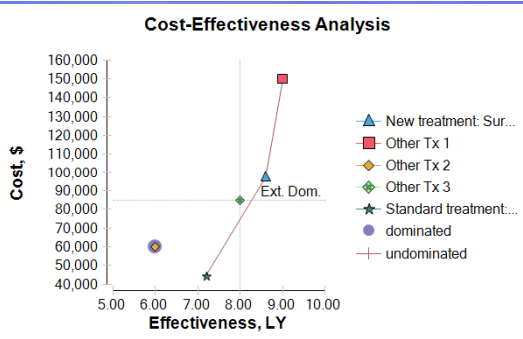
TreeAge Pro Healthcare Training – Module 3 58

Analyze CE Model




- Other Tx 2 rejected by absolute dominance
 - Less effective and more costly than Standard Treatment
- Other Tx 3 rejected by extended dominance
 - More efficient to move from ... Standard treatment to New Treatment (lower ICER/slope) than from ... Standard treatment to Other Tx 3 (higher ICER/slope)

Cost-Effectiveness Analysis



TreeAge Pro Healthcare Training – Module 3 59

Analyze CE Model



- CE Rankings also shows dominance
 - Absolute dominance – negative IE and ICER
 - Extended dominance – ICER declines

subset	Strategy	Eff	IncrEff	Cost	IncrCost	ICER	Dominance	Avg CE
abs. dominated	Other Tx 2	6	-1.2	60000	15000	-13000	(Dominated)	10000
undominated	Standard treatment: Radiation	7.2	0	44400	0	0		6166.666666667
	New treatment: Surgery and radiation	8.6	1.4	97200	52800	37714.2857142857		11302.3255813954
	Other Tx 1	9	0.4	150000	52800	131999.9999999999		16666.6666666667
ext. dominated	Other Tx 3	8	0.8	85000	40000	50750		10625
all	Standard treatment: Radiation	7.2	0	44400	0	0		6166.666666667
	Other Tx 2	6	1.2	60000	15000	13000	(Dominated)	10000
	Other Tx 3	8	0.8	85000	40600	50750		10625
	New treatment: Surgery and radiation	8.6	0.6	97200	12200	20333.3333333333		11302.3255813954
	Other Tx 1	9	0.4	150000	52800	131999.9999999999		16666.6666666667

TreeAge Pro Healthcare Training – Module 3 60

Analyze CE Model

- But which strategy is preferred?
 - Start by rejecting the dominated strategies
 - Then compare the ICERs to the WTP value
 - If $WTP < \$37.7K$, recommend Standard treatment
 - If $\$37.7K < WTP < \$132K$, recommend New treatment
 - If $WTP > \$132K$, recommend Other Tx 1
 - Note that a total cost ceiling could also reject strategies

subset	Strategy	Eff	IncrEff	Cost	IncrCost	IC/IE	Dominance	Avg CE
abs. dominated	Other Tx 2	6	-1.2	60000	15600	-13000	(Dominated)	10000
undominated	Standard treatment: Radiation	7.2	0	44400	0	0		6166.666666667
	New treatment: Surgery and radiation	8.6	1.4	97200	52800	37714.2857142857		11302.3255813954
	Other Tx 1	9	0.4	150000	52800	131999.9999999999		16666.6666666667
ext. dominated	Other Tx 3	8	0.8	85000	40600	50750		10625
all	Standard treatment: Radiation	7.2	0	44400	0	0		6166.666666667
	Other Tx 2	6	-1.2	60000	15600	-13000	(Dominated)	10000
	Other Tx 3	8	0.8	85000	40600	50750		10625
	New treatment: Surgery and radiation	8.6	0.6	97200	12200	20333.3333333333		11302.3255813954
	Other Tx 1	9	0.4	150000	52800	131999.9999999999		16666.6666666667

TreeAge Pro Healthcare Training – Module 3 61

Analyze CE Model

- Note that we can identify the preferred strategy from roll back using CE parameters

- Optimal strategy identified by **Net benefits** calculations
- Change to Invert incremental only if effectiveness should be minimized (e.g., # of infections or # of deaths)

TreeAge Pro Healthcare Training – Module 3 62

Analyze CE Model



- Net Benefits Calculations:
 - Build the threshold ICER (WTP) into calculations, as the weight on effectiveness, or monetary value per unit of additional effect
 - $NMB = (E * WTP) - C$
 $= (LY * \$/LY) - \$ = \$$ monetary scale
 - $NHB = E - (C / WTP)$
 $= LY - (\$ / (\$/LY)) = LY$ effectiveness unit scale
 - Combine cost, effectiveness and WTP into a single measurement which can simply be maximized
 - Easily seen in roll back on prior page
 - Makes graphs that are looking for ICER thresholds much clearer
 - Example: sensitivity analysis graphs

Deterministic Sensitivity Analysis



Module Agenda:

1. Deterministic Sensitivity Analysis
2. Identify Thresholds
3. 2-Way Sensitivity Analysis and Tornado Diagrams
4. Modeling Exercise

Deterministic Sensitivity Analysis

- Sensitivity Analysis studies how a model's outputs are affected by variation in inputs to reflect uncertainty
- Two types of Sensitivity Analysis are supported by TreeAge Pro
 - Deterministic Sensitivity Analysis
 - How parameter VARIABLES (range) affect outputs
 - Covered here
 - Probabilistic Sensitivity Analysis
 - How parameter DISTRIBUTIONS (samples) affect outputs
 - Covered later
- Both are recalculation “loops”, with uncertain parameters changing between recalculations

Deterministic Sensitivity Analysis

Instructions:

1. Open Example 2 tree.
2. Select root node.
3. Choose Analysis > Sensitivity Analysis > 1 Way... from the menu.
4. Enter the sensitivity analysis parameters...
 1. Select the variable pEradicateRadSurg.
 2. Range: 0.5 - 0.9; Intervals: 4.
 3. Click OK.

Deterministic Sensitivity Analysis

- Generates EV calculations for each value of the variable given the range and intervals
 - Cost and effectiveness for each strategy
 - Multiple graph outputs

Example02-Variables.trex *Sensitivity Cost Effectiveness Analysis - Example02-Variables.trex

Sensitivity Cost Effectiveness Analysis

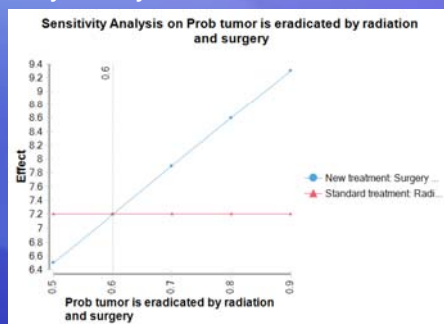
pEradicateRadSurg	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance	Actions
0.5	Standard treatment: Radiation	44400.0	0.0	7.2	0.0	6166.666666667	0.0		(Dominated)
	New treatment: Surgery and radiation	93000.0	48600.0	6.5	-0.7	14307.6923076923	-69428.5714285714		
0.6	Standard treatment: Radiation	44400.0	0.0	7.2	0.0	6166.666666667	0.0		(Dominated)
	New treatment: Surgery and radiation	94400.0	50000.0	7.2	0.0	13111.1111111111	0.0		
0.7	Standard treatment: Radiation	44400.0	0.0	7.2	0.0	6166.666666667	0.0		(Dominated)
	New treatment: Surgery and radiation	95800.0	51400.0	7.9	0.7	12126.582278481	73428.5714285714		
0.8	Standard treatment: Radiation	44400.0	0.0	7.2	0.0	6166.666666667	0.0		
	New treatment: Surgery and radiation	97200.0	52800.0	8.6	1.4	11302.325813954	37714.2857142857		
0.9	Standard treatment: Radiation	44400.0	0.0	7.2	0.0	6166.666666667	0.0		
	New treatment: Surgery and radiation	98600.0	54200.0	9.3	2.1	10602.1505376344	25809.5238095238		

Graph Reports

- Cost-Effectiveness (animated)
- Cost-Effectiveness (animated) x vs Avg. Cost
- x vs Incremental Cost
- x vs Avg. Eff.
- x vs Incremental Eff.
- x vs ICER (Incremental C-E)
- x vs Avg. C-E
- Net Benefits

Deterministic Sensitivity Analysis

- x vs. Avg. Eff. shows sensitivity analysis on effectiveness only
 - Variable on x-axis
 - Effectiveness on y-axis



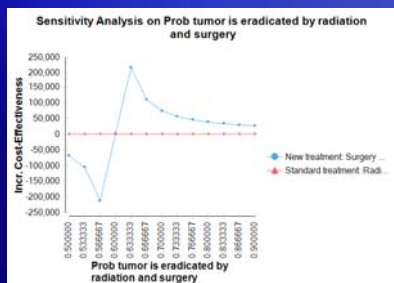
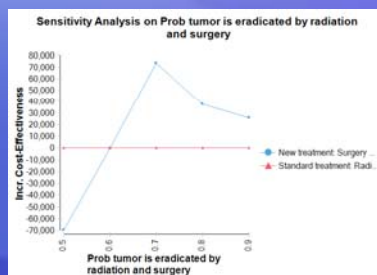
- Standard treatment unaffected
- Threshold at pEradicateRadSurg value 0.6
 - Thresholds Report
 - Beneath 0.6, New treatment is rejected by absolute dominance

Deterministic Sensitivity Analysis

- Sensitivity analysis on cost-effectiveness is more complex
 - Need to consider cost, effectiveness and WTP
 - Change in relative cost-effectiveness
 - Change in dominance and/or efficiency
 - Changes in cost and/or effect ordering
 - WTP is our ICER threshold
- How to identify thresholds visually?
 - x. vs. ICER graph has challenges
 - Net Benefits graph – clearest

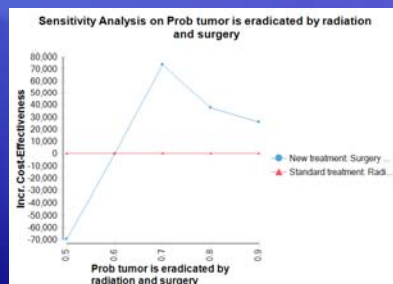
Deterministic Sensitivity Analysis

- x vs. ICER shows how ICER changes with variable
- Output looks odd
 - IE at 0.6 is 0
 - ICER value is undefined, presented as zero
- With more intervals, see asymptote better



Deterministic Sensitivity Analysis

- Suppose we wanted to identify a threshold for the variable based on a WTP of \$50K
 - We could limit the range and add intervals to get more precise values
 - We could add horizontal & vertical lines to the graph to pinpoint the threshold (Edit Chart)
 - Even those options would be problematic with more than two strategies
- Use Net Benefits calculations to combine cost, effectiveness and WTP
 - Net Benefits link

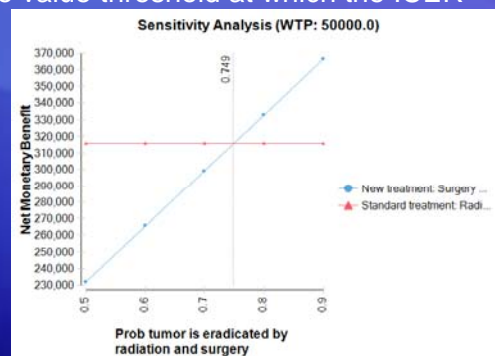
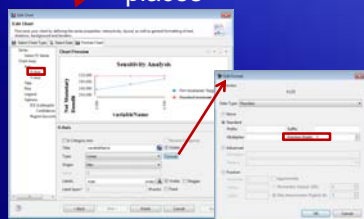


TreeAge Pro Healthcare Training – Module 4

71

Deterministic Sensitivity Analysis

- Net Benefits:
 - When prompted for WTP, enter 50K
 - Net Benefits calculations combine cost, effectiveness and WTP... just look for the max value
 - Graph shows the variable value threshold at which the ICER is \$50K
 - Edit Chart to change numeric formatting to show more decimal places



TreeAge Pro Healthcare Training – Module 4

72

Deterministic Sensitivity Analysis

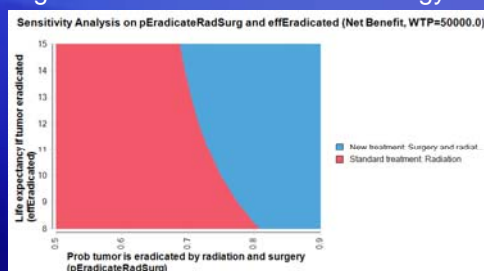
- Net Benefits:
 - Thresholds Report also shows the threshold

1-Way Sensitivity Analysis Thresholds						
Attribute	Variable	Var. Value	Strategy 1	Strategy 2	Exp. Value	Willingness-to-pay
NMB	pEradicateRadSurg	0.7488095238	Standard treatment: ...	New treatment: ...	315600.0	50000.0

- Interpretation:
 - Based on WTP \$50K ...
 - At variable values below ~0.749, Standard treatment is the most cost-effective
 - At variable values above ~0.749, New treatment is the most cost-effective

Deterministic Sensitivity Analysis

- 2-way sensitivity analysis:
 - See how changing two uncertainties affects recommended strategy
 - Requires Net Benefits
 - Each axis taken by a variable
 - Regions show recommended strategy



- New treatment favored more with increased difference between life expectancy for eradicated vs. not eradicated

Deterministic Sensitivity Analysis



Instructions:

1. Open Example 2 tree.
2. Select root node.
3. Choose Analysis > Sensitivity Analysis > 2 Way... from the menu.
4. Enter the sensitivity analysis parameters...
 1. Select the variables:
 1. pEradicateRadSurg; Range: 0.5 - 0.9; Intervals: 4.
 2. effEradicated; Range 8 - 15; Intervals 7
 2. Click OK.

Deterministic Sensitivity Analysis



- Tornado Diagram:
 - See which variables have the largest impact on EV through a series of 1-way sensitivity analyses
 - Uses Net Benefits with additional option for ICER
 - Be careful:
 - Do not overanalyze these graphs
 - Details from 1-way sensitivity analyses are not fully presented in tornado diagram

Modeling and Analysis Exercise



- Model description:
 - Evaluate a new arthritis drug vs. an existing drug
 - Root decision node
 - Both drugs are effective; however, the existing drug is highly effective in 70% of cases while the new drug is expected to be highly effective in 82% of cases
 - Unknown event in each strategy with probabilities
 - The cost of the existing drug is \$1,000 per year, while the planned price of the new drug is \$1,500 per year
 - Component of cost payoffs
 - The utility value for cases treated highly effectively is 0.9, but only 0.8 for cases treated effectively
 - Component of effectiveness payoffs
 - The life expectancy for the cohort is 15 years
 - Component of both payoffs

TreeAge Pro Healthcare Training – Module 4

77

Modeling and Analysis Exercise



- Analysis Questions:
 - Can we recommend the new drug based on a WTP of \$50K?
 - Cost-effectiveness analysis
 - What is the minimum percentage of cases that are treated highly effectively such that we can recommend the new drug?
 - Sensitivity analysis
 - What is the maximum price that could be charged where the new drug could still be recommended?
 - Sensitivity analysis

TreeAge Pro Healthcare Training – Module 4

78

Probabilistic Sensitivity Analysis



Module Agenda:

1. Monte Carlo Simulation
2. Distributions
3. Probabilistic Sensitivity Analysis

Probabilistic Sensitivity Analysis - MC



- Monte Carlo Simulation:
 - TreeAge Pro supports several forms of simulation
 - Probabilistic Sensitivity Analysis
 - Samples: 2nd-order, parameter uncertainty
 - Microsimulation
 - Trials: 1st-order, individual variability
 - Two-Dimensional
 - Samples & Trials
 - Three-Dimensional
 - Partial EVPI
 - Stored analyses can run simulations in batches
 - Analysis > Stored Analyses → Tree Preferences
 - We will focus on Probabilistic Sensitivity Analysis within this training module

Probabilistic Sensitivity Analysis



- Probabilistic vs. Deterministic Sensitivity Analysis

Deterministic Sensitivity Analysis	Probabilistic Sensitivity Analysis
Variables	Distributions
Calculate EV based on range/intervals for uncertain inputs	Calculate EV based on random samples for uncertain inputs
Repeating gives same results	Repeating yields different results from different sampled input values
Usually only 1 uncertainty at a time (2 and 3 available)	All uncertainties sampled simultaneously

TreeAge Pro Healthcare Training – Module 5

81

Probabilistic Sensitivity Analysis



- Advantages of PSA over Deterministic SA
 - More robust
 - More parameters
 - More recalculations
 - More interpretation
 - Confidence intervals, value of information, etc.
- Non-PSA applications of Monte Carlo simulation with sampling:
 - Non-linear models, parameters
 - Roll back EVs (using distribution means), might not be the same as simulation mean results (due to non-linearity)...
 - In this case, the mean from the sampling simulation is a better estimate of EV than rollback using estimates/means
 - If distribution means are not the same as original estimates, EV calculations will be different

TreeAge Pro Healthcare Training – Module 5

82

Probabilistic Sensitivity Analysis



- Requires defining parameters using probability distributions instead of simple variables
 - Only parameters you want to study via PSA need distributions
- Calculation Loop:
 - Sample parameter value from each distribution
 - Calculate expected value for tree using sampled values
 - Repeat for predefined number of samples
- Examine set of resulting EVs
 - Mean/median of EVs
 - Distribution of EVs
 - High/low EVs
 - Confidence intervals

TreeAge Pro Healthcare Training – Module 5

83

Probabilistic Sensitivity Analysis



- We will start with the Example 02 model
 - Open and save under new name
- We will introduce distributions to measure parameter uncertainty for...
 - Probability of eradicating tumor with standard treatment
 - Probability of eradicating tumor with new treatment
 - Cost of surgery

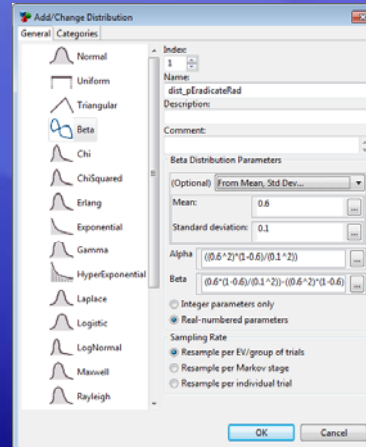
TreeAge Pro Healthcare Training – Module 5

84

Probabilistic Sensitivity Analysis - Distributions

Instructions:

1. Choose Views > Distributions from the toolbar.
2. Click the “+” icon in the Distributions View to create a new distribution.
3. Enter the distribution information as seen at right:

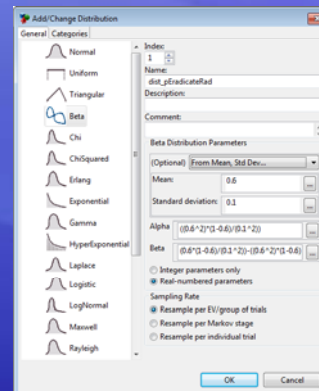


TreeAge Pro Healthcare Training – Module 5

85

Probabilistic Sensitivity Analysis - Distributions

- Distribution type and parameters define the shape of the distribution
- Each distribution type requires specific parameters
 - Example: normal type has a mean and standard deviation
- Analysis required to determine appropriate and parameters for your model's uncertainties
 - This can be difficult



TreeAge Pro Healthcare Training – Module 5

86

Probabilistic Sensitivity Analysis - Distributions

- Common distribution types:
 - Normal
 - Standard bell curve
 - Uniform
 - Equal likelihood of all values in range
 - Option to limit to integers
 - Beta
 - Frequently used for probabilities
 - Restricted to between 0 and 1
 - Triangular
 - Provide min, max and most likely
 - Dirichlet
 - Sample multiple complementary probabilities, like interrelated betas
 - Table
 - Sample from “empirical” data:
 - Table with columns for “values” and corresponding probability
 - Will cover in detail during Microsimulation

TreeAge Pro Healthcare Training – Module 5

87

Probabilistic Sensitivity Analysis - Distributions

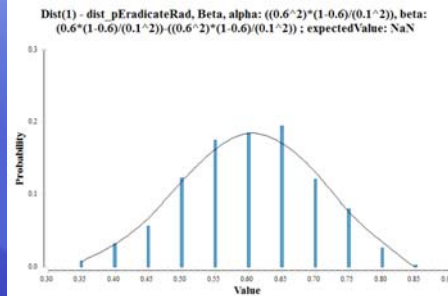
- Distribution index and name:
 - Can reference distribution in the model by either
 - Recommend references by name
 - Certain distribution functions require reference by index
 - Example: DistForce(index), DistTrim(index; min; max)
- Parameter approximation:
 - Certain distribution types’ parameters can be approximated from other statistics
 - In our first distribution, we estimated the Alpha and Beta parameters from the mean and standard deviation
- Sampling rate:
 - Use Resample per EV/group of trials for PSA *parameter uncertainty*; parameter affects entire cohort
 - Other options for *individual variability* among trials

TreeAge Pro Healthcare Training – Module 5

88

Probabilistic Sensitivity Analysis - Distributions

- Graph distribution to test: 
- Mimics sampling that will be performed during PSA



- Samples centered around mean (0.6) with variation
 - Beta is not a normal bell curve

Probabilistic Sensitivity Analysis - Distributions

Instructions:

1. Open/select the Distributions View.
2. Click the “+” icon in the Distributions View to create a new distribution.
3. Create two more distributions...
 1. dist_pEradicateRadSurg
 - Beta parameters approximated from mean 0.8 and std dev 0.1
 2. dist_cSurgery
 - Normal distribution with mean 50,000 and std dev 10,000

Probabilistic Sensitivity Analysis - Distributions

- Distributions created, but they need to be integrated into the model
- Two options...
 - Replace references to variables with references to distributions
 - Define variables using distributions rather than numeric values
 - Can still run deterministic sensitivity analysis

Probabilistic Sensitivity Analysis - Distributions

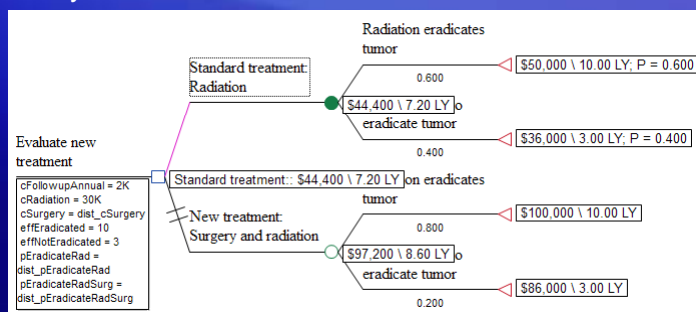
Instructions:

1. Select the root node.
2. Open/select the Variable Definitions View.
3. Redefine the following three variables...
 1. $cSurgery = dist_cSurgery$
 2. $pEradicateRad = dist_pEradicateRad$
 3. $pEradicateRadSurg = dist_pEradicateRadSurg$

---Defined @ Evaluat	
cFollowupAnnual	2K
cRadiation	30K
cSurgery	dist_cSurgery
effEradicated	10
effNotEradicated	3
pEradicateRad	dist_pEradicateRad
pEradicateRadSurg	dist_pEradicateRadSurg
---Undefined @ Evaluat	

Probabilistic Sensitivity Analysis - Distributions

- Non-PSA calculations will use mean values for distributions (no sampling)
- Since we setup our distributions with means equal to the original numeric estimates, our roll back and CEA results will not change
- This is not always the case, so be careful with non-PSA analysis



TreeAge Pro Healthcare Training – Module 5

93

Probabilistic Sensitivity Analysis - Distributions

Instructions:

1. Select the root node.
 2. Choose Analysis > Monte Carlo Simulation > Sampling.
 3. Enter 1000 samples.
 4. Click Begin.
- We ran 1000 iterations
 - How many do you need?
 - Depends on number of distributions and complexity of model
 - If successive simulations generate same mean and std dev for each strategy → enough iterations

TreeAge Pro Healthcare Training – Module 5

94

Probabilistic Sensitivity Analysis - Distributions

- After PSA simulation completes...
 - Statistics are displayed for each strategy
 - Cost, effectiveness, and NMB (using WTP from prefs)
 - Links to a series of reports and graphs
 - We will look at a few
- How do we interpret results?
 - We now have N separate EV calculations
 - Need to review these EV calcs balancing each strategy's cost and effectiveness with our overall WTP

Attribute	Statistic	Standard treatment: Pac...	New treatment...
Cost	Mean	44342.3876551724	87993.86693348...
	Std Deviation	1329.6578079511	8753.1717529514
	Minimum	40744.8778613389	69464.626309...
	2.5%	41394.6918143091	78963.55879602...
	10%	42611.1892381556	84218.10029647...
	Median	44405.6584762385	87386.17905717...
	90%	46035.8777466702	109518.3648474...
	97.5%	48774.2487808885	138100.3983706...
	Maximum	47681.4339392252	128144.5126406...
	Size (n)	1000	1000
Variance	1767990.0988843265	95124398.25331...	
Variance of M...	1767990.0988843	95124398.25331...	
Std Error of M...	42.0474743461	308.4224347438	
EQ	Mean	7.2711888276	8.6535323478
	Std Deviation	0.664828844	0.6623511262
	Minimum	5.3799388406	6.3837548219
	2.5%	5.7974958072	7.288493861
	10%	6.3059951102	7.66881479
	Median	7.2003082383	8.701433646
	90%	8.0179388710	9.405833815
	97.5%	8.367242659	9.702880786
	Maximum	8.8417081653	9.823384512
	Size (n)	1000	1000
Variance	0.4418975287	0.483000085	
Variance of M...	0.0004418975	0.000438769	
Std Error of M...	0.021027772	0.0209453815	
NMB	Mean	354217.5437741386	333456.7511846...
	Std Deviation	31911.7893088075	32053.48476782...
	Minimum	327695.9648423853	231282.213037...
	2.5%	248272.6039434175	284121.3188723...

TreeAge Pro Healthcare Training – Module 5

95

Probabilistic Sensitivity Analysis - Distributions

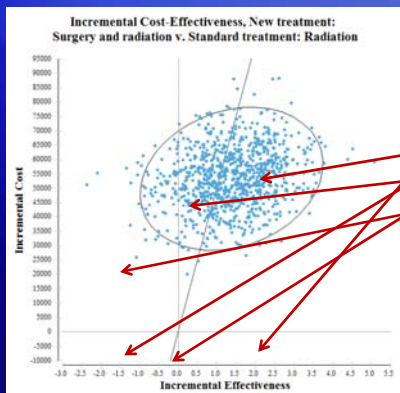
- Monte Carlo simulation output can be saved as *.rptx file for review later
- Selected PSA output options...
 - Values, Dists, Trackers: Shows each strategy's EV calculations and distribution samples for each iteration
 - Output Distributions: Shows distribution of EV outputs for each strategy or for incrementals
 - ICER distribution can be interesting, but also can be difficult in cases where IE can be zero (wild fluctuation in ICER)
 - CE Analysis: CEA from simulation means
 - ICER may not match regular non-PSA CEA ICER
 - CE Scatterplot: Shows scatter of each iteration's cost and effectiveness values for each strategy
 - More...

TreeAge Pro Healthcare Training – Module 5

96

Probabilistic Sensitivity Analysis - Distributions

- Selected PSA output options (continued)...
 - ICE Scatterplot: Compares a pair of strategies showing IC and IE on graph
 - Edit graph to change y-axis scale to include zero

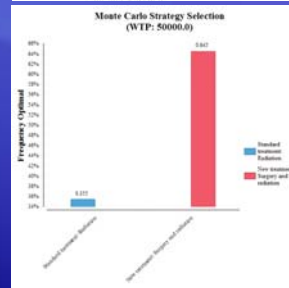
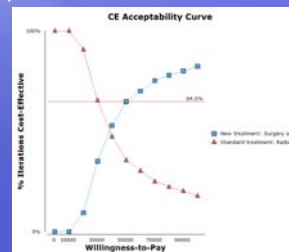


COMPONENT	QUADRANT	INCREFF	INCRICOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE=0	IC>0	Superior	0	0
C2	I	IE=0	IC>0	ICER<50000.0	645	0.645
C3	III	IE=0	IC>0	ICER>50000.0	0	0
C4	I	IE=0	IC>0	ICER<50000.0	278	0.278
C5	III	IE=0	IC>0	ICER>50000.0	0	0
C6	II	IE=0	IC=0	Inferior	77	0.077
Indiff	origin	IE=0	IC=0	0/0	0	0

- Want to be below and to the right of the WTP line
- Components 1, 2, 5 recommend new treatment
- Overall 64.5% of iterations recommend new strategy
- Measure of our confidence in recommendation

Probabilistic Sensitivity Analysis - Distributions

- Selected PSA output options (continued)...
 - CE Acceptability Curve: Shows the percentage of iterations that favor each strategy over WTP range
 - Shows same percentage as ICE scatterplot, but easier to see using Net Benefits
 - Added line via Edit Chart options
 - Strategy Selection Frequency: Shows the percentage of iterations that favor each strategy for a single WTP
 - Should change y-axis to start at 0, looks misleading as is



Course Agenda

Day 1 is complete!!!

Day 2

1. Markov Models
2. Time Dependence & Tables in Markov Models
3. Extra Markov Options
4. Microsimulation & Trackers
5. Bootstrapping with Patient Data
6. Decision Trees & Microsimulation Models
7. Two-Dimensional Simulations
8. Getting Help