EP550 Notes for Lecture 18 (Friday April 1, 2016)  
and  
Homework 7, which Is Due Friday April 8, 2015

The purpose of this exercise is to teach you how to create Markov models using the TreeAge 2016 software program and to use what you’ve created to illustrate additional features of cost-effectiveness analysis. The exercise uses the lupus example that Henry has been using in class.

Step 1. Imagine and create the model
1. Create the decision node
   - Open TreeAge and clear any material from the upper, center panel where decision trees are created and modified.
   - Create a decision node by clicking File/New Decision Tree (Grey highlighting indicates that the command is at the top left of your screen), Click No when the box opens.
   - Label the decision node “Choose” (or “Lupus”), and press Enter on your keyboard.

2. Add nodes to the Choose node and change them to Markov nodes
   - Click on the Choose node, and then click Node/Add Branch until there are 2 new nodes
   - Label the new node at the top “Usual Care,” and label the new node at the bottom “Intervention”
   - Right click one node and then select Change Type/Markov; repeat for the other node
   - Make the display simpler by clicking Edit/Tree Preferences/Display/Variables/Markov info, unselect Show Markov information, and click OK.

3. Add branches to the Usual Care node
   - Right click on the node, select Add Branch, and repeat until there are 4 branches

4. Add branches to the first (uppermost) new node
   - Click on the Usual Care node, which is a Markov node
   - Click Subtree/Select Subtree
   - Click Edit/Copy
   - Click on the first (uppermost) new node, then click Edit/Paste

5. Click the Usual Care node (the Markov node) and label its 4 branches, in order “Remission,” “Active,” “Flair,” and “Death.”

6. Indicate the states that patients can transition to from the Remission branch of the Usual Care node
   - Select the first branch of the Remission node.
   - Change this node to a terminal node (Right click, then click Change Type/Terminal)
   - In the box that appears, click Remission/OK
   - Change the other 3 nodes that branch from the Remission node to terminal nodes and select the appropriate states for them (in order: Active, Flair, and Death)
7. Indicate the states that patients can transition to from the Active branch and the Flair branch of the Usual Care node
   - Click on the Remission node that immediately follows the Usual Care node
   - Click Subtree/Select Subtree
   - Click Edit/Copy
   - Click on the Active node that immediately follows the Usual Care node, then click Edit/Paste
   - Click on the Flair node that immediately follows the Usual Care node, then click Edit/Paste
   - Change the fourth branch of the Markov node (Death) to a terminal node (Right click, then click Change Type/Terminal).

Your tree should look like the tree on the following page. If you want your tree branches to intersect nodes at right angles instead of having curved branches (to decrease the width of your tree), go to Edit/Tree Preferences/Display/Tree Editing/Layout, select Branch lines at right angles, and click OK.
Step 2. Add transition probabilities and initial distributions

Add transition probabilities using the following table from the lecture notes (page 11 middle slide in Henry’s lecture notes titled “EPI550.markovmodels.sp16.pdf”):

<table>
<thead>
<tr>
<th>Transition</th>
<th>Data *</th>
<th>Prob</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission → Remission</td>
<td>59 / 100</td>
<td>0.59</td>
<td>(0.49 to 0.69)</td>
</tr>
<tr>
<td>Remission → Active</td>
<td>41 / 100</td>
<td>0.41</td>
<td>(0.31 to 0.51)</td>
</tr>
<tr>
<td>Remission → Flare</td>
<td>0 / 100</td>
<td>0.00</td>
<td>(0.00 to 0.03)</td>
</tr>
<tr>
<td>Remission → Death</td>
<td>0 / 100</td>
<td>0.00</td>
<td>(0.00 to 0.03)</td>
</tr>
<tr>
<td>Active → Remission</td>
<td>66 / 937</td>
<td>0.07</td>
<td>(0.06 to 0.09)</td>
</tr>
<tr>
<td>Active → Active</td>
<td>806 / 937</td>
<td>0.86</td>
<td>(0.83 to 0.88)</td>
</tr>
<tr>
<td>Active → Flare</td>
<td>56 / 937</td>
<td>0.06</td>
<td>(0.05 to 0.08)</td>
</tr>
<tr>
<td>Active → Death</td>
<td>9 / 937</td>
<td>0.01</td>
<td>(0.00 to 0.02)</td>
</tr>
<tr>
<td>Flare → Remission</td>
<td>0 / 80</td>
<td>0.00</td>
<td>(0.00 to 0.06)</td>
</tr>
<tr>
<td>Flare → Active</td>
<td>22 / 80</td>
<td>0.27</td>
<td>(0.18 to 0.39)</td>
</tr>
<tr>
<td>Flare → Flare</td>
<td>18 / 80</td>
<td>0.23</td>
<td>(0.14 to 0.33)</td>
</tr>
<tr>
<td>Flare → Death</td>
<td>40 / 80</td>
<td>0.50</td>
<td>(0.38 to 0.62)</td>
</tr>
</tbody>
</table>

* Counts are approximations of actual data (not provided in article)

8. Start at the Usual Care node, go to its Remission branch, and go to that node’s Remission terminal branch
   - Click underneath this branch, and type “0.59” followed by Enter. Although you could have typed “0.59” here and it would have worked just as well, having # here facilitates sensitivity analyses.
   - Click underneath the Active terminal branch, and type “0.41” followed by Enter
   - Click underneath the Flare terminal branch, and type “0.00” followed by Enter
   - Click underneath the Death terminal branch and type “#” followed by Enter
   - Add transition probabilities to the terminal nodes of the Active and Flare states. Use # to represent the transition from Active to Death and the transition from Flair to death.
**Add information about the initial distribution of** patients using the following table from the lecture notes (slide 35):

<table>
<thead>
<tr>
<th></th>
<th>Remission</th>
<th>Active</th>
<th>Flare</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission</strong></td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Active</strong></td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flare</strong></td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Click underneath the Remission branch of the Usual Care node and type in “0.10” followed by Enter
   - Add numbers that correspond to the initial states for Active and Flare
   - Use 0 to indicate that no people start in the state of Death

**Step 3. Identify outcome values and add them as transition rewards (not stage rewards)**

Use 2 transition rewards. The first is a cost variable, and the second is a QALY variable. Creating the cost variable begins with the number of hospitalizations, which is described in the following table from the lecture notes (page 5 top slide in Henry’s lecture notes titled “EPI550.markovmodels.sp16.pdf”):

<table>
<thead>
<tr>
<th></th>
<th>Remis.</th>
<th>Active</th>
<th>Flare</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission</strong></td>
<td>0.05</td>
<td>0.25</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Active</strong></td>
<td>0.10</td>
<td>0.20</td>
<td>1.00</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Flare</strong></td>
<td>0.00</td>
<td>0.25</td>
<td>1.25</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Multiply the mean number of hospitalizations times the average cost of hospitalization, which is $10,000 (or cHosp). For example, the cost of hospitalization for the transition from Remission to Remission is 0.05*$10,000 = $500 (or 0.05*cHosp, where cHosp = $10,000).


The second transition award is a QALY reward that takes its values from the hypothetical numbers in the following table from the lecture notes (page 17 top slide in Henry’s lecture notes titled “EPI550.markovmodels.sp16.pdf”):

<table>
<thead>
<tr>
<th>Transition</th>
<th>Preference Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>R to R</td>
<td>0.9</td>
</tr>
<tr>
<td>R to A</td>
<td>(0.9+0.7)/2</td>
</tr>
<tr>
<td>A to R</td>
<td>(0.7+0.9)/2</td>
</tr>
<tr>
<td>A to A</td>
<td>0.7</td>
</tr>
<tr>
<td>A to F</td>
<td>(0.7+0.5)/2</td>
</tr>
<tr>
<td>A to D</td>
<td>0.7/2</td>
</tr>
<tr>
<td>F to A</td>
<td>(0.5+0.7)/2</td>
</tr>
<tr>
<td>F to F</td>
<td>0.5</td>
</tr>
<tr>
<td>F to D</td>
<td>0.5/2</td>
</tr>
</tbody>
</table>

10. To set up the tree to do cost-effectiveness analyses, click Edit/Tree Preferences/Calculation/Calculation Method, select Cost-effectiveness, make sure that in Active Payoffs: C=1 \ E=2, and then click OK. To display the transition rewards you are about to enter, click Edit/Tree Preferences/Display/Variables/Markov info, select Show Definitions at the top and select Show Markov information at the bottom, and then click OK. To begin adding transition rewards to the tree,

- At the top of your screen is a row that has on the extreme left the label TreeAge Pro2016. Underneath this row is a second row with the labels File, Edit, Node, etc. Underneath this row is another row of labels. At the extreme right of this row is the label Views. Click on the down arrow to the right of this label, select Markov info, and note the box labeled Markov Info that opens at the bottom of your screen.
- Start at the Usual Care node, go to its Remission branch, then click on the Remission terminal node to add the rewards for transitioning from the remission to remission.
- In the Markov Info box locate the Rewards (Active Sets), and expand it to reveal two rows (Trans Cost and Trans Effectiveness) underneath it if they are not already visible. In the column labeled Value in the row labeled Trans Cost, type “cHosp*0.05” to indicate the cost of hospitalization for the transition from Remission to Remission.
- When you push Enter, a box will open. In the Description rectangle, type “Cost of Hospitalization.” In the Build Expression rectangle under Root Definition, type 10000.
Click OK.

- In the column labeled Value in the row labeled Trans Effectiveness, type “0.9” to indicate the number of QALYs earned for the transition from Remission to Remission.

- To discount the values you have entered, there are two options. One option is to divide the values you have entered by \((1+r)^\text{stage}\) (note the underline before stage), so they become for example, \((c\text{Hosp}*0.05)/(1+r)^\text{stage}\) and \(0.9/(1+r)^\text{stage}\). When you enter \(r\), a box will open asking you to define the term \((r\text{ is the Discount rate)}\) and to provide its numerical values \((r = 0.03)\). The second option is to use the program’s Discount function. For example, after you enter a value (or you select a row that already has a value in it), note the small box to its right with \(=\text{fx}\) inside. Click on this box, and a larger box will open. The upper part of this box (Build Expression) identifies the variable or value. In the lower part of this box (under Add to Expression) on the left (under Group), click on Functions, and on the right (under Element), find discount (util; rate; time), double click it, and note that it appears in the upper part of the box. Between the parentheses, in order, enter the value you want to discount followed by a semicolon followed by the discount rate, which is \(r\), followed by a semicolon followed by the cycle number, which is \(t\). Alternatively, you can simply type the characters of the discount function. Either way, the result should be \(\text{discount}(c\text{Hosp}*0.05;r;\text{_stage})\) and \(\text{discount}(0.90;r;\text{_stage})\). Click OK when you are finished discounting.

- To add the rewards for transitioning from the remission state to the active state, start at the Usual Care node, go to its Remission branch, click on the Active terminal node, and repeat the steps above to add expressions for the discounted values of cost \((c\text{Hosp}*0.25)/(1+r)^\text{stage}\) or \(\text{discount}(c\text{Hosp}*0.25;r;\text{_stage})\) and effectiveness \((0.8/(1+r)^\text{stage}\) or \(\text{discount}(0.08;r;\text{_stage})\).

- Add expressions for the discounted rewards for transitioning among the remaining states by repeating these steps at the remaining terminal nodes.

- If the boxes that display the Markov information are too narrow to display their contents clearly, widen the box by dragging the tab pointer in the ruler that sits on top of the tree.

To display this and other information in proper format,

- Go to Edit/Tree Preferences/Calculation/Calculation Method, on the right in the section on Active Method select Cost-Effectiveness method, and use payoff one for cost (\(C=1\)) and payoff two for effectiveness (\(E=2\)).

- Set the formats for the payoffs by selecting Numeric Formatting on the left

- For Cost, Decimal Places = zero, Show Numbers exactly, and Units = Currency

- For Effectiveness: Decimal Places = 2, Show Numbers exactly, units = custom suffix, and type “QALYs” for the suffix

- For Cost-Effectiveness, Decimal Places = zero, Show Numbers exactly, Units = Custom Suffix, and type “$/QALY” for the suffix

- Expand Numeric Formatting by clicking on the arrowhead next to it, click Probabilities, set the number of decimal places = 4, select Add trailing zeros, click OK

Even though you are not going to use stage rewards in this exercise, the program requires that there be stage rewards. Check the stage rewards in the tree (open the Markov info box (Go to the top of
the screen, click Views at the extreme right of the third row, and click Markov info) and select each branch of the Usual Care node). Make sure all of the stage rewards have values of zero. If any do not have the value of zero, assign the value of zero as the Initial Reward, Incremental Reward, and Final Reward for Cost and for Effectiveness.

**Tell the program how many cycles it should run**

12. Select the Usual Care Markov node
   - Open the Markov Info box
   - Type “_stage > 99” (or type “_stage > 1999,” if you prefer Henry’s approach)

Your tree should look something like the tree on the following page:
Save this version of your model as a picture, not a workable tree

- Click File/Save Image/All Nodes...
- Name the file with your family name preceded by “MKV” and followed by the number 1, for example, “MKVWilliams1”
- For Type (of format), indicate JPEG
- Click OK

Save this version of your model as a workable tree

- Click File/Save As...
- Name the file with your family name preceded by “MKV” and followed by the number 2, for example, “MKVWilliams2”
- For Save as Type, indicate TreeAge Tree Diagram (*.trex)
- Click Save

**Step 4. Calculate expected values**

**Analyze the model to make sure it works**
13. To determine the average number of QALYs that would be expected for a population of lupus patients who started with this distribution of states
   - Select the Usual Care node
   - Go to Edit/Tree Preferences/Calculation/Calculation Method/Simple and make sure that the Active Payoff is 2. If not, change it, and click OK
   - Go to Analysis/Markov Cohort/Markov Cohort (Full)
   - Select Decimal Probability for Report Probabilities, select Show stage reward only for Rewards, deselect Include per-state rewards column, click OK
   - Wait for the results, which may take a few minutes
   - Click Summary Report

**Save this report**
- The title for this report is Markov Cohort Summary, and it is located at the upper left of the report. At the upper right of the report in the same row is a horizontal line of icons Click on the icon that indicates Export As Tab-Delimited (*.XLS) (third icon from the left).
- Name the file with your family name preceded by “MKV” and followed by the number 3, for example, “MKVWilliams3”
- For Save as Type, indicate Tab-Delimited/Spreadsheet (*.XLS)

**Prepare for a cost-effectiveness analysis that compares the effects of usual care with the effects of a medical intervention.**
14. Create an expanded decision tree by completing the Markov model that describes the outcomes of the medical intervention.
   - Close the Markov Cohort Summary without saving anything
   - To make the model more compact so you can visualize it better, click Edit/Tree Preferences/Display/Variables/Markov Info, at the top select Hide Definitions, and Click OK
   - Click the Usual Care node
   - Click Subtree/Select Subtree
   - Click Edit/Copy
   - Click on the Intervention Markov node, and click Edit/Paste

15. **Change the transition probability that is affected by the intervention**
To set up the tree to do cost-effectiveness analyses, click Edit/Tree Preferences/Calculation/Calculation Method, select Cost-effectiveness, make sure that in Active Payoffs: C=1 \ E=2, and then click OK.

Start with the Intervention Markov node, go to its Remission node, and Click the Active terminal node. Change the transition probability of the Active terminal node by multiplying 0.41 times the effect from the intervention, which is to reduce the frequency of transition from the remission state to the active state. That reduction is represented here by RR, where RR=0.8537. (Click underneath this branch, and type “0.41*RR.” When prompted, define RR as the relative risk corresponding to the effect of the intervention and assign it the value 0.8537)

16. Add the cost of the intervention to the model

- The intervention costs one dollar a day. Think of it as a drug, and one pill has to be taken each.
- Start at the Intervention node, go to its Remission branch, and click on the Remission terminal node to add the reward for transitioning from Remission to Remission
- Open the Markov info box (Click on the down arrow to the right of Views in the third row from the top, select Markov info.
- Go to the Markov Info window, and click the transition reward for cost, which is labeled Rewards (Active Sets)/Trans Costs. Click the white box immediately to the right, type “(cHosp*0.05+365)/(1+r)^stage,” and press Enter. (Alternatively, use the program’s discount function so the white box contains (cHosp*0.05+365;r;stage)”
- Add 365 to each of the remaining cost transitions, except for the transitions with zero probabilities, because no one makes these transitions and thus there is no need to allow for rewards. Be sure to add 365 to all these cost transitions. For some reason, many students neglect to do this.

17. Specify how many cycles the newly expanded Markov node should run

- Click the Intervention Markov node
- Call up the Markov Info window
- For the value under Termination conditions, type “_stage > 99” (or “_stage > 1999”). Check to make sure that the value for termination conditions is identical for the usual care node and the intervention node.

18. Conduct a cost-effectiveness analysis that compares the effects of usual care with the effects of a medical intervention.

- To display more of the model so you can examine more of its contents for errors and for completeness before proceeding, click Edit/Tree Preferences/Display/Variables/Markov Info, select Show Definitions, select Show Markov Information, and Click OK
- Check again to make sure both Markov nodes have the same number of cycles specified for termination

The new part of your tree should look something like the following tree:
Save this version of your model as a workable tree
- Click File/Save As…
- Name the file with your family name preceded by “MKV” and followed by the number 4, for example, “MKVWilliams4”
- For Save as Type, indicate TreeAge Tree Diagram (*.trex)
- Click Save
- Click on the Choose node
- Click Analysis/Cost-Effectiveness… (Wait, the calculations may take a while.)
- Get rid of Console and News Feed, if they appear
- On the right under Actions, click Text Report

Save this report
- The title for this report is Cost-Effectiveness Rankings, and it is located at the upper left of the report. At the upper right of the report in the same row is a horizontal line of icons Click on the icon that indicates Export As Tab-Delimited (*.XLS) (third icon from the left).
- Click on the icon that indicates Export As Tab-Delimited (*.XLS) (third icon from the left).
- Name the file with your family name preceded by “MKV” and followed by the number 5, for example, “MKVWilliams5”
- For Save as Type, indicate Tab-Delimited/Spreadsheet (*.XLS)

Email your saved files to sankey@wharton.upenn.edu. Expect an acknowledgment by return email. If you don’t get an acknowledgment, check to make sure your files were received and not diverted, for example, by a junk mail filter.

The material that follows is optional. It is not part of this homework assignment.

Step 5. Perform Sensitivity Analyses

Conduct deterministic sensitivity analyses
You can change any of the numbers in your tree into algebraic expressions. Once you have made these changes, you can perform deterministic sensitivity analyses, for example, one-way and two-way sensitivity analyses, for the items in the tree represented by algebraic expressions. If you want to do only the deterministic sensitivity analyses that were shown in class, you need to change only the cost of intervention from 365 to cinterv (cost of intervention) and to express the effectiveness of the intervention as rr (relative risk), which you can multiply times the transition probability for remission to active in usual care to represent the transition probability for remission to active in the intervention. You already have made changes like this in Homework 6 and making these changes is tedious, so we have provided you with a tree that has some of these changes already made. It is located in the Handouts/Homework section of Canvas where it is labeled “Lupus Markov model for deterministic sensitivity analyses.trex” and is available for
To reproduce the one-way sensitivity analysis in the slide at the bottom of page 28 in Henry’s notes, select the Choose node, click Analysis/Sensitivity Analysis/1-way. . . . In the box that opens, click on the down arrowhead to the left of Values to reveal a list of all the variables, select cinterv, enter “187.5” in the column Low entry, enter “730” in the column High entry, enter “2” in the column Intervals, and click OK. (Wait for it.) In the box that opens, on the right under Graph Reports, click Cost, Intervention vs ICER (incremental C-E).

To reproduce the one-way sensitivity analysis in the first slide on page 29, select the Choose node, click Analysis/Sensitivity Analysis/1-way. . . . In the box that opens, click on the down arrowhead to the left of Values to reveal a list of all the variables, select rr, enter “0.65” in the column Low entry, enter “0.95” in the column High entry, enter “15” in the column Intervals, and click OK. In the box that opens, on the right under Graph Reports, click Relative risk vs ICER (incremental C-E).

To reproduce the two-way sensitivity analysis that is described in middle slide on page 29, select the Choose node, click Analysis/Sensitivity Analysis/2-way. . . . In the box that opens, click on the down arrowhead to the left of Values to reveal a list of all the variables, select rr in the first row and select cinterv in the second row, accept the values that are listed for these variables, enter “50000” in the box Willingness to pay, make sure Net Monetary Benefits is selected, and click OK.

Conduct probabilistic sensitivity analyses.
You can change any of the numbers or variables in your tree into distributions. For example, change the cost of the intervention from 365 or cinterv to cdInterv (cost distribution for the intervention) and express the effectiveness of the intervention as drr (distribution of relative risk). Once you have made changes like this, you can perform probabilistic sensitivity analyses that can be converted into p-values and confidence intervals, which allow you to make statements about statistical significance and confidence. Making these changes is tedious, so we have provided you with a tree that has these changes already made. It is located in the Handouts/Homework section of Canvas where it is labeled “Lupus Markov model for probabilistic sensitivity analyses.trex” and is available for downloading.

You did not make changes like these in Homework 6, so we also provide you in the material that follows step-by-step directions for making the changes necessary to conduct probabilistic sensitivity analyses. You can either follow the directions described in items 19-24 and then conduct the probabilistic sensitivity analyses described in item 25, or you can download the file we have provided and go directly to item 25.

19. **Define and add distributions for the transition probabilities**

- It will be easier to start with a tree whose numbers for probabilities, transition rewards, and other options have been replaced by variables, for example, the tree that we provided (Lupus Markov model for deterministic sensitivity analyses.trex) or one that you created.
- Click Values/Distributions view, to reveal the Distributions window.
- Click on the green-cross icon (the one without a question mark) to add a new distribution.
- Choose the Dirichlet distribution, Select 1 for Index
• Name the distribution “tRemis,” and describe it as “Transitions from the Remission node.”
• Under Sampling Rate, accept the default, which is Resample per EV/group of trials.
• In the box labeled Alphas, add the following values “List(59;41;0;0),” which come from the middle slide on page 30 (see below), click OK, then close the box.

<table>
<thead>
<tr>
<th>Dirichlet Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dirichlet Distribution is multinomial (more than 2 categories) extension of binomial Beta distribution</td>
</tr>
<tr>
<td>Defined by counts for each of outcomes</td>
</tr>
<tr>
<td>– e.g., For transitions from Remission (tRemiss) List(59;41;0;0) OR List(59;41) OR Beta distribution</td>
</tr>
<tr>
<td>– e.g., For transitions from Active (tActive) List(66;806;56;9)</td>
</tr>
<tr>
<td>– e.g., For transitions from Flare (tFlare) List(0;22;18;40) OR List(22;18;40)</td>
</tr>
<tr>
<td>– e.g., For initial distribution List(100;937;80) (Don’t include count for death)</td>
</tr>
</tbody>
</table>

- For the Usual Care node, click on the value under the Remission terminal node of the Remission subtree, and replace this value with Dist(1;1).
- Make sure the value under the Active terminal node of the Remission subtree is #, which ensures that the probabilities will change correctly when sensitivity analyses are done.
- Click on the value under the Flare terminal node of the Remission subtree, and replace this value with Dist(1;3) (not strictly necessary because the probability is zero).
- Click on the value under the Death terminal node of the Remission subtree, and replace this value with Dist(1;4) (not strictly necessary because the probability is zero).
- Follow the steps above to define and add Dirichlet distributions for the Active subtree and the Flare subtree, using consecutive index numbers and appropriate names and descriptions, and substituting the appropriate list values from the slide above; however, in the Active and Flare subtrees put the pound sign (#) in the transition to Death, not the transition to Remission.
- For the Intervention node, add identical expressions to the comparable terminal nodes. (Later in this exercise you will modify the transition probability for the transition from Remission to Active in this node.)

20. **Define and add a distribution for the initial distribution**
- Click Values/Distribution view to reveal the Distributions window.
- Click on the green-cross icon to add a new distribution.
Choose the Dirichlet distribution, and select 4 for Index
Name the distribution “initdist,” and describe it as “Initial distribution.”
Under Sampling Rate, accept the default, which is Resample per EV/group of trials
In the box labeled Alphas, add the following values “List(100;937;80),” which come from the middle slide on page 30 (see above), click OK, then close the box.
For both the Usual Care node and the Intervention node, replace the existing initial distribution of the Remission node with Dist(4;1), replace the existing initial distribution of the Active node with Dist(4;2), replace the existing distribution of the Flare node with #, and leave the initial distribution of the Death node unchanged at #.

21. Define a distribution for the relative risk
Click Values/Distribution view to reveal the Distributions window.
Click on the green-cross icon to add a new distribution.
Choose the LogNormal distribution, and select 5 for Index
Name the distribution “drr,” and describe it as “Log normal distribution, relative risk.”
Under Sampling Rate, accept the default, which is Resample per EV/group of trials
In the box labeled LogNormal Distribution parameters, for u (mean of values) type “-1.1582” and for sigma (std. dev. of logs) type “.1816,” which come from slide 84, click OK, then close the box.
You will add the distribution for the relative risk later.

22. Define and add distributions for costs and QALYs
Click Values/Distribution view to reveal the Distributions window
At the top of the Distributions box is a row of icons. The fifth icon from the left has a yellow square in the upper left and a green X in the lower right and reveals a window that reads “Open in New Excel Spreadsheet” when you hold the pointer over it. Click this icon.
- An Excel spreadsheet should open that looks something like the following:

- In your spreadsheet, the first five rows, which are labeled with the Index numbers 1-5, should be filled in, and rows with the Index numbers 6-27 should be blank. You can define all the remaining distributions by typing into the cells defined by rows 6-27 and columns A-F in your spreadsheet the information that is in the spreadsheet above. You should be able to move this information into your tree by clicking Add-Ins (at the top of your screen), which opens a box; clicking TreeAge Pro at the left of the new box, which opens another box; and then clicking Add or Update Distributions. It works for Henry on his machine, but it doesn’t work for me on my machine. If it doesn’t work for you, then you will have to define the remaining distributions by entering the information from the spreadsheet above into your tree using the methods described in items 19, 20, and 21 above.

23. Assign distributions for costs, QALYs, and the relative risk to an appropriate variable.
   - Click Values/Variable Definitions View
   - In the box that opens are the existing variables and the definitions of the existing variables. Make the box full screen by clicking on the full screen icon at the upper right corner of the
• Change the Names and Definitions of the variables so they are the same as the ones in the following figure. Remarks in the Info/Comment space are optional.

24. Add new variables to the tree
   • Change any remaining numbers in the tree to the comparable variables
   • In the Intervention subtree, change the probability of the transition from Remission to Active so it becomes “rr*Dist(1;2)”

25. Conduct a probabilistic sensitivity analysis.
   • To reproduce the results at the top of the slide in the middle of page 36 (“Cost-Effectiveness Analysis vs. Sampling . . .”), select the Choose node, click Analysis/Roll Back. Once you’re finished, click Roll Back again.
   • Click on the Choose decision node, Click Analysis/Monte Carlo Simulation/Sampling (Probabilistic Sensitivity), type “1000” in the white box labeled Number of samples. . . .
   • Click Seeding and check on Seed Random Number Generator, make sure “2” is in the white box. (It’s necessary to have the same seed number when you rerun the analysis if you
want to get identical results, but it doesn’t matter which number you choose – the seed number used for the lecture was 2. If you want results as close as possible to the results in the lecture, you should use the same termination rule for the two Markov nodes that was used in the lecture, which was _stage>1999.) Click OK.

- Click Distributions …, make sure Sample All is selected, and click OK.
- Click Begin. Be prepared to wait. If your wait is too long, decrease the number of cycles; for example, click on the Usual Care Markov node, open Markov info, and change the termination instruction from _stage>1999 to _stage>99. Repeat this process for the Intervention Markov node. Alternatively, decrease the number of samples below 1000.
- Compare your output to the output in the lecture.
  - Start with the results in the main screen which are the source for the information in the slide at the top of page 36, which is titled “Second-Order Monte Carlo Simulation*”.
  - To reproduce the results at the bottom of the slide in the middle of page 36, go to the section titled Data in the upper right of the screen and click Summary Report.
  - To reproduce the results in the slide at the top of page 37, expand the section titled Histograms, expand Output Distributions, Expand Incremental Cost, click Intervention vs. Usual Care, type in 10 when asked how many bars you want, and click OK. Repeat, but expand Incremental Effectiveness instead of Incremental Cost and type in 30 when asked how many bars you want.
  - To reproduce the results for the slide in the middle of page 38, expand PSA Outputs, expand ICE Scatterplot, click Intervention v Usual Care, type in 50000 for the willingness-to-pay value, type in 1 for Start and 1000 for End, and click OK.
  - To reproduce the results for the slide at the bottom of page 38, click ICE Report, type “50000” for willingness to pay, accept the other values, and click OK.
  - To generate an acceptability curve (not shown in the lecture), expand PSA Outputs, click Acceptability Curve. When the box opens, for Willingness to pay enter a low value of zero and a high value of 100000, accept the other values, and click OK.