EP550 Notes for the Continuation of Lecture 16 (Wednesday April 8, 2020)
and
Homework 9, which Is Due Wednesday April 15, 2020

The purpose of this exercise is to teach you how to create Markov models and how to understand additional features of cost-effectiveness analysis. The exercise uses the lupus example from class. If you get stuck, send the tree you have (.trex format) to sankey@wharton.upenn.edu and explain what the problem is. I'll do what I can to get you unstuck.

Step 1. 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"
   - Make the display simpler by clicking Edit/Tree Preferences/Display/Variables/Markov info, unselect Show Markov information, and click Apply and Close.

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

4. **Add branches to the first (uppermost) new node**
   - Click on the Usual Care node
   - Click Subtree/Select Subtree
   - Click Edit/Copy
   - Click on the first (uppermost) new node, then click Edit/Paste
   - Right click the Usual Care node and then select Change Type/Markov; repeat for the Intervention node

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

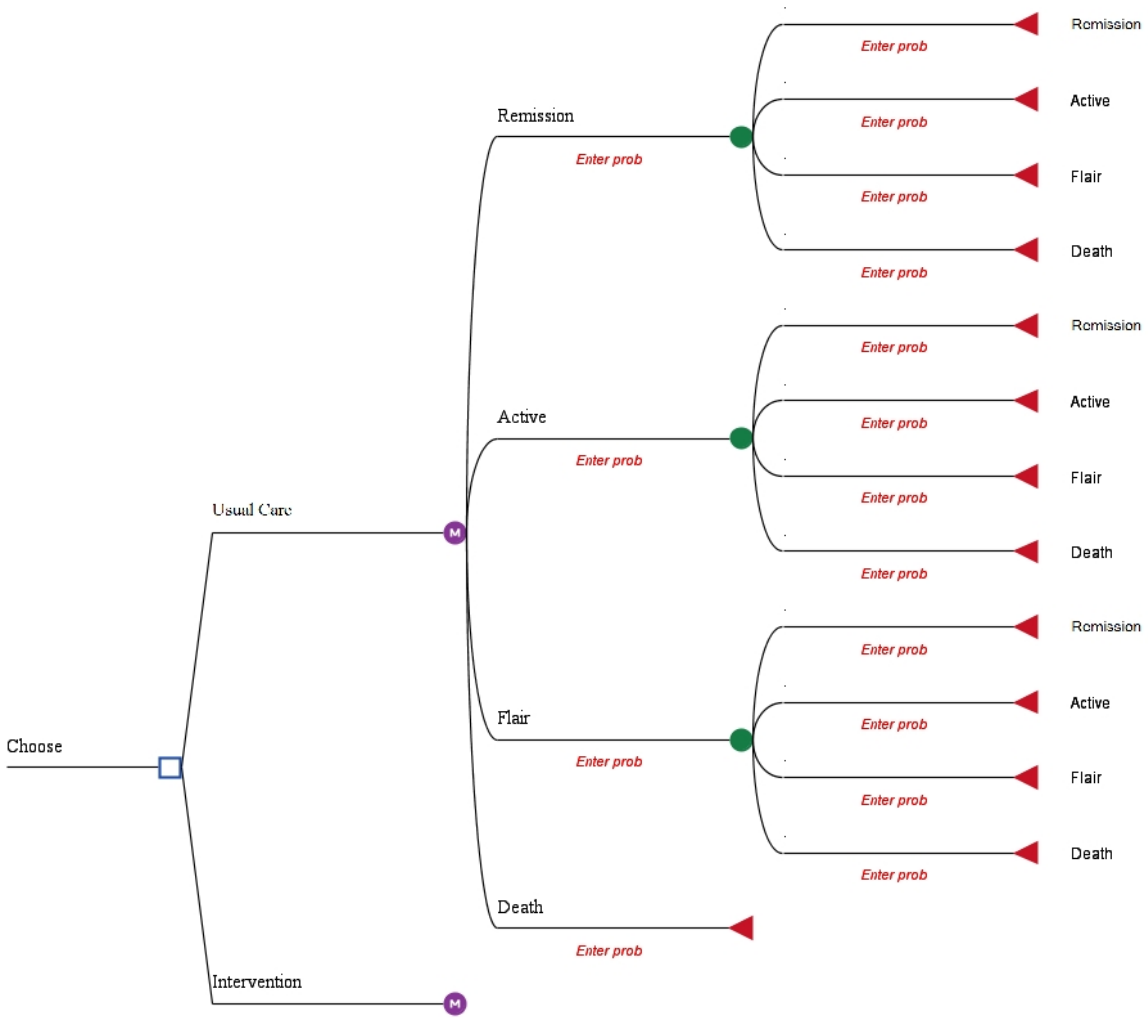
the appropriate states for them (in order: Active, Flair, and Death)

- If you want to get rid of the red text (Enter label) above each branch, you have to replace it with different text, although this text does not affect how the model works. You can enter text that repeats the text to the right of the triangle. Alternatively, you can enter a period, which provides no information and minimizes the distraction.

7. Indicate the states that patients in the Active branch and the Flair branch of the Usual Care node can transition to

- 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 something like the following tree:



Step 2. Add transition probabilities and the initial distribution

Add transition probabilities using the following table from the lecture notes (page 11 bottom slide in Henry's lecture notes titled "16epi550.markovmodels.sp20.pdf"):

Transition	Data *	Prob	95% CI
Remission ➔ Remission	59 / 100	0.59	(0.49 to 0.69)
Remission ➔ Active	41 / 100	0.41	(0.31 to 0.51)
Remission ➔ Flare	0 / 100	0.00	(0.00 to 0.03)
Remission ➔ Death	0 / 100	0.00	(0.00 to 0.03)
Active ➔ Remission	66 / 937	0.07	(0.06 to 0.09)

Active ➔ Active	806 / 937	0.86	(0.83 to 0.88)
Active ➔ Flare	56 / 937	0.06	(0.05 to 0.08)
Active ➔ Death	9 / 937	0.01	(0.00 to 0.02)
Flare ➔ Remission	0 / 80	0.00	(0.00 to 0.06)
Flare ➔ Active	22 / 80	0.27	(0.18 to 0.39)
Flare ➔ Flare	18 / 80	0.23	(0.14 to 0.33)
Flare ➔ Death	40 / 80	0.50	(0.38 to 0.62)

* 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 "#" followed by Enter. Although you could have typed "0.59" here and it would have worked just as well, having # here facilitates steps you will take later on.
- 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 "0.00" 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.

9. Add information about the initial distribution of patients using the following table from the lecture notes (page 13 of Henry's notes, bottom slide):

Remission:	0.10
Active:	0.85
Flare:	0.05

- 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 0.00 to indicate that no people start in the state of Death

Now would be a good time to save a temporary copy of the working tree (File/Save as "Temp.trex") in case you inadvertently delete your tree or make some other mistake.

Step 3. Identify outcome values and add them as transition 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 16, middle slide):

	Remis.	Active	Flare	Death
Remission	0.05	0.25	0.00	0.00
Active	0.10	0.20	1.00	0.50
Flare	0.00	0.25	1.25	0.75

Multiply the mean number of hospitalizations times the average cost of hospitalization, which is $10,000. To facilitate later parts of this exercise, use the variable cHosp to represent the cost of hospitalization. For example, the cost of hospitalization for the transition from Remission to Remission is 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 middle slide):

Transition	Preference Score
R to R	0.9
R to A	(0.9+0.7)/2
A to R	(0.7+0.9)/2
A to A	0.7
A to F	(0.7+0.5)/2
A to D	0.7/2

F to A	(0.5+0.7)/2
F to F	0.5
F to D	0.5/2

10. Enter the transition rewards. Begin by setting up the tree to do cost-effectiveness analyses. Click Edit/Tree Preferences/Calculation/Calculation Method, select Cost-effectiveness, make sure that in Active Payoffs the Cost payoff =1 and the Effectiveness payoff=2. Click CE Parms. For Willingness to pay, enter "50000," and then click Apply and Close. 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/For active payoffs only at the bottom, and then click Apply and Close. You are now ready to add transition rewards to the tree.

- Click on 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.
- At the very top of your screen is a row that has on the extreme left the label TreeAge Pro Healthcare 2020. Underneath this row is a second row with the following labels: File, Edit, Node, etc. Underneath this row is another row that is mostly icons. At the right near the end of this row is the label Views. Click on the down arrow to the right of this label, select Markov info. A box labeled Markov Info should open at the bottom or to the right of your screen. The information it provides depends on where you are in the tree.
- Locate Rewards (Active Sets), and expand it to reveal two rows that are labeled Trans Cost and Trans Effectiveness (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." Under Root Definition and Build Expression is a box, where you should type in "10000," which is the number of dollars that corresponds to the variable cHosp. Click Apply and Close.
- 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.
- If you are having trouble seeing what you need, use the slider underneath the tree or change the box size by going to the top row, clicking on an edge, and dragging.
- Add expressions for the rewards for transitioning among the remaining states in this node. You do not need to add transition rewards when the probability of making the transition is zero (unless you plan to conduct probabilistic sensitivity analyses that could include non-zero probabilities).
- Add expressions for the rewards for transitioning among the states in the remaining nodes. When you are finished, click the x at the top of the box next o Markov info.
- If the boxes that display the Markov information are too narrow to display their contents clearly, widen the box by clicking on the corresponding tab pointer in the ruler that sits on top of the tree and dragging it to the desired position..
- To discount the values you have entered, you have options. The easiest and the recommended option is to click Edit/Tree Preference/Calculation/Payoffs/Discounting. Select Use Global Discounting. For Markov cycle length (in years) and for DES time unit (in years), click the arrow in the grey box and select Annual. In the white box below this

material, type “0.03” as the discount rate for Cost and again as the discount rate for Effectiveness. Click Apply and Close.

- The other two options work just as well but they are more difficult to enable. However, they are necessary in the uncommon situation where some payoffs have different discount rates than other payoffs. These options are described in the following material, in case you ever need them. One option is to divide the values you have entered by (1+r)^_stage (note the underline before stage), so they become for example, (cHosp*0.05)/(1+r)^_stage and 0.9/(1+r)^_stage. When you enter r, a box will open asking you to define the term (r is the Discount rate) and to provide its numerical values (r = 0.03). The other 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 =*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 discount(cHosp*0.05;r;_stage) and discount(0.90;r;_stage). Click OK when you are finished discounting.

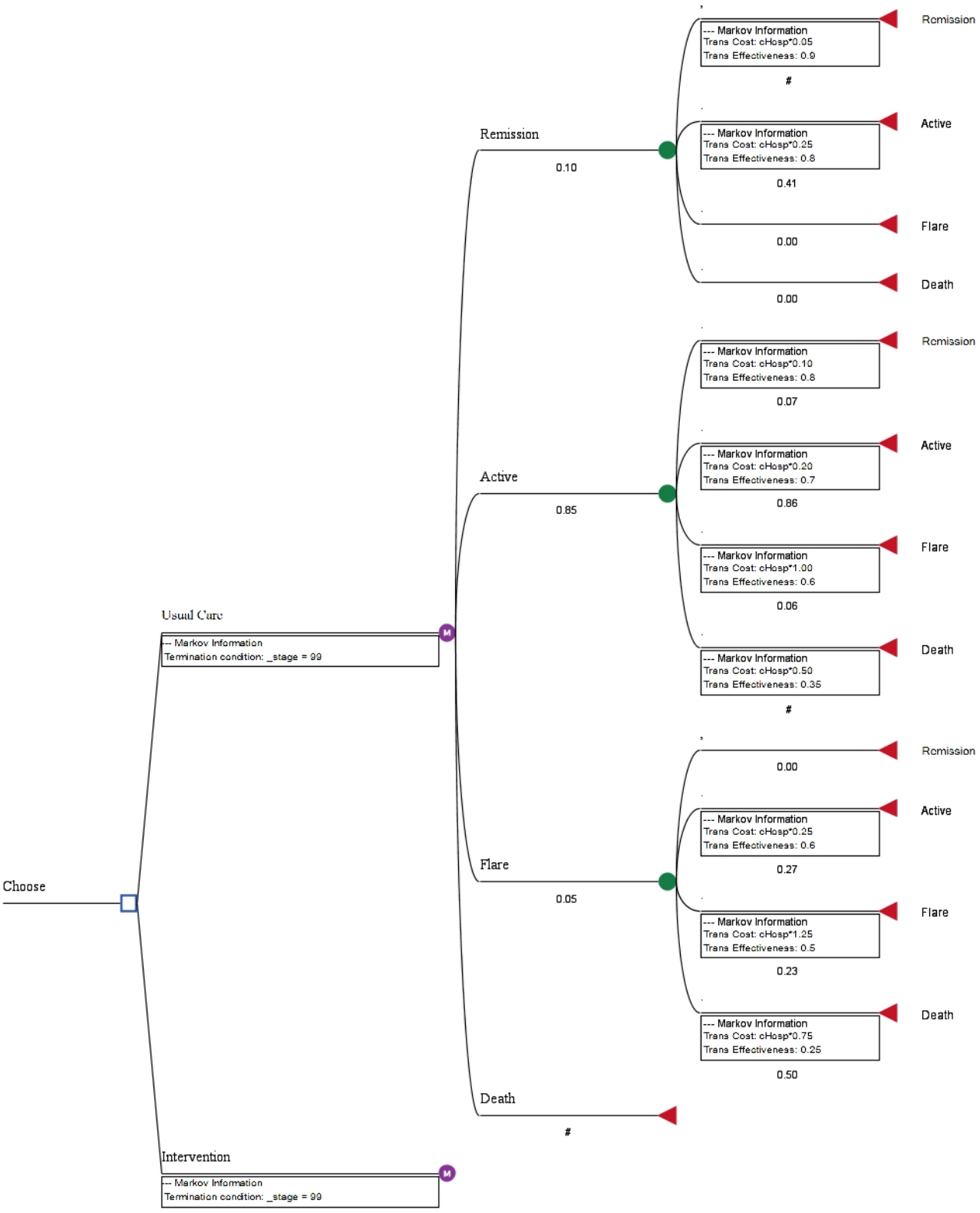
- To display this and other information in proper format, go to Edit/Tree Preferences/Calculation/Calculation Method, on the right in the section on Active Method select Cost-Effectiveness method, and use payoff 1 for Cost payoff and payoff 2 for Effectiveness payoff.
- Set the formats for the payoffs by selecting Numeric Formatting on the left
- For Cost, Decimal Places = zero, Use thousands separator, 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, Add thousands separator, 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 Apply and Close

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 the arrow next to Views at the right of the third row, and click Markov info). Select each branch of the Usual Care node (not the terminal branches). 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.

12. Tell the program how many cycles it should run

- Select the Usual Care Markov node
- Open the Markov Info box.
- The default number of cycles is 120. Henry likes to use 1999 because it decreases the population to zero (almost). I like to use 99 because some clinicians think the other 2 values are unrealistic. Use whatever number you like. For example, if you want the cycle number to be 100, type "_stage > 99" or "_stage = 100."
- When the program asks if you want to use the same number of cycles in all Markov nodes, click Yes.

Your tree should look something like the tree on the following page:


Choose
Usual Care
--- Markov Information
Termination condition: _stage = 99
Intervention
--- Markov Information
Termination condition: _stage = 99
Remission
0.10
Active
0.85
Flare
0.05
Death
#
--- Markov Information
Trans Cost: cHosp*0.05
Trans Effectiveness: 0.9
#
Remission
--- Markov Information
Trans Cost: cHosp*0.25
Trans Effectiveness: 0.8
0.41
Active
0.00
Flare
0.00
Death
--- Markov Information
Trans Cost: cHosp*0.10
Trans Effectiveness: 0.8
0.07
Remission
--- Markov Information
Trans Cost: cHosp*0.20
Trans Effectiveness: 0.7
0.86
Active
--- Markov Information
Trans Cost: cHosp*1.00
Trans Effectiveness: 0.6
0.06
Flare
--- Markov Information
Trans Cost: cHosp*0.50
Trans Effectiveness: 0.35
#
Death
0.00
Remission
--- Markov Information
Trans Cost: cHosp*0.25
Trans Effectiveness: 0.6
0.27
Active
--- Markov Information
Trans Cost: cHosp*1.25
Trans Effectiveness: 0.5
0.23
Flare
--- Markov Information
Trans Cost: cHosp*0.75
Trans Effectiveness: 0.25
0.50
Death

Save this version of your model as a workable tree

- **Click File/Save As…**
- **Name the file with your family name followed by the number 7, for example "Williams7" If your family name is Lee, include the first letter of your first name.**
- **For Save as Type, indicate TreeAge Tree Diagram (*.trex)**
- **Click Save**

Step 4. Calculate expected values

13. Analyze the model to make sure it works

- 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 Apply and Close
- Go to Analysis/Markov Cohort/Basic Report (or Extended Report)
- 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 Report, and it is located at the upper left of the report. At the upper right of the report in the same row as the title is a horizontal line of icons. Click on the icon at the extreme right, which is the icon for Open in a New Excel Spreadsheet.**
- **Name the file with your family name followed by the number 8, for example, "Williams8"**

14. Expand the decision tree so you can conduct a cost-effectiveness analysis that compares the effects of usual care with the effects of a medical intervention.

- To complete the Markov model that describes the outcomes of the medical intervention, exit the Excel spreadsheet and 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 Apply and Close
- 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 the Cost payoff =1 and the Effectiveness payoff =2, and then click Apply and Close. Click yes

if you are asked if you want to active cost-effectiveness analysis.

- 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 clicking underneath the branch that leads to this terminal node and changing 0.41 to "0.41*rr." When prompted, define rr as the "Relative benefit of the intervention" and assign it the value 0.8537). This change reduces the frequency of going from the remission state to the active state.

16. Add the cost of the intervention to the model

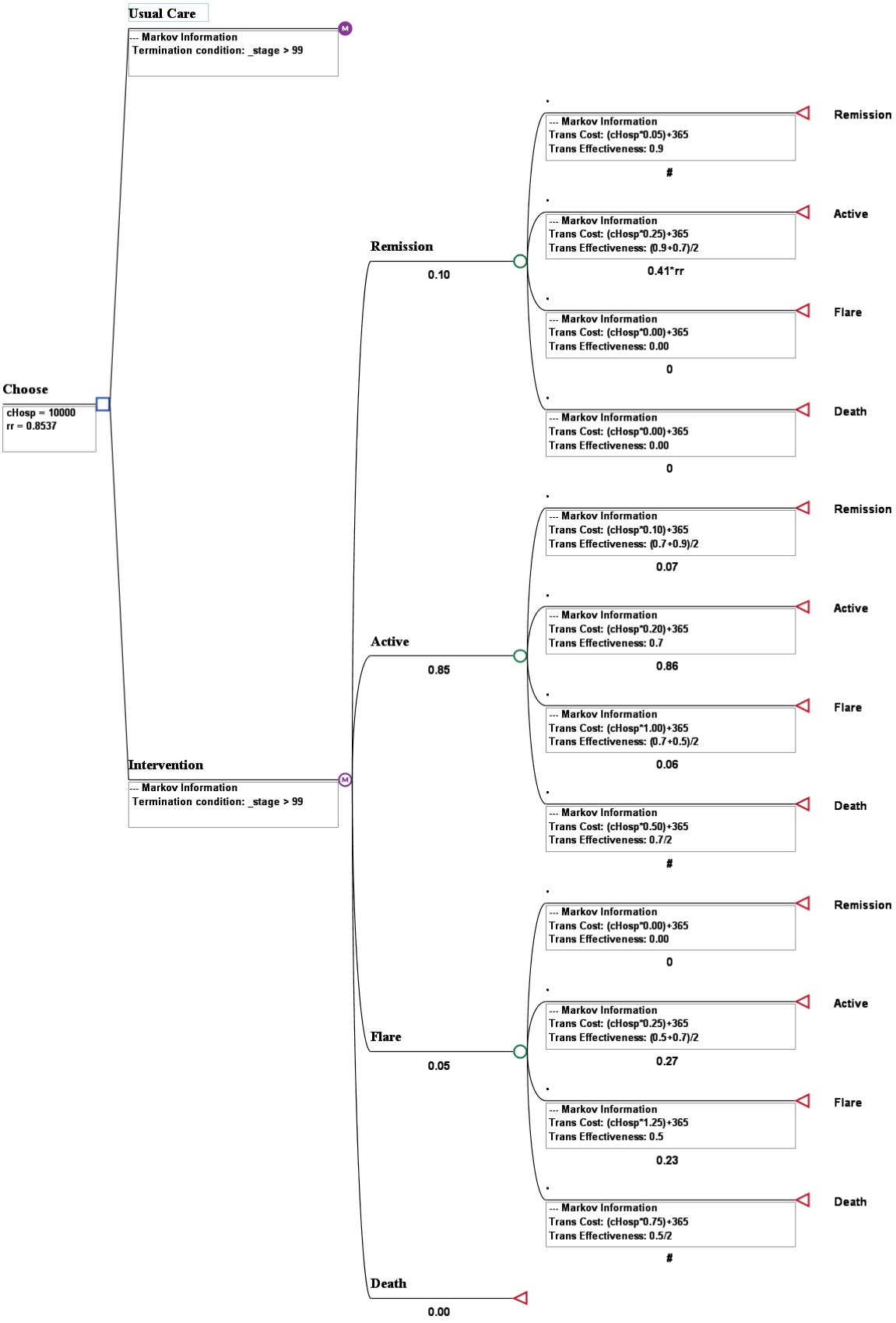
- The intervention costs one dollar a day. Think of it as a drug, and one pill has to be taken each day.
- Start at the Intervention node, go to its Remission branch, and click on the Remission terminal node to add the drug cost
- Open the Markov info box (Click on the down arrow to the right of Views 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. In the white box immediately to the right, change the entry so it reads "(cHosp*0.05)+365" and press Enter.
- Add 365 to each of the remaining cost payoffs, except for the transitions with zero probabilities (no one makes these transitions and thus there is no need to assign rewards). Be sure to add 365 to all these cost payoffs. Some students neglect to do this.

17. Check to make sure that the value for termination conditions is identical for the two Markov nodes

- Click the Usual Care Markov node, and call up the Markov Info window
- Click the Intervention Markov node, and call up the Markov Info window

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 Apply and Close
- The new part of your tree should look something like the following tree:


Usual Care
--- Markov Information
Termination condition: _stage > 99
Choose
cHosp = 10000
rr = 0.8537
Intervention
--- Markov Information
Termination condition: _stage > 99
Remission
0.10
Active
0.85
Flare
0.05
Death
0.00
--- Markov Information
Trans Cost: (cHosp*0.05)+365
Trans Effectiveness: 0.9
#
Remission
--- Markov Information
Trans Cost: (cHosp*0.25)+365
Trans Effectiveness: (0.9+0.7)/2
0.41*rr
Active
--- Markov Information
Trans Cost: (cHosp*0.00)+365
Trans Effectiveness: 0.00
0
Flare
--- Markov Information
Trans Cost: (cHosp*0.00)+365
Trans Effectiveness: 0.00
0
Death
--- Markov Information
Trans Cost: (cHosp*0.10)+365
Trans Effectiveness: (0.7+0.9)/2
0.07
Remission
--- Markov Information
Trans Cost: (cHosp*0.20)+365
Trans Effectiveness: 0.7
0.86
Active
--- Markov Information
Trans Cost: (cHosp*1.00)+365
Trans Effectiveness: (0.7+0.5)/2
0.06
Flare
--- Markov Information
Trans Cost: (cHosp*0.50)+365
Trans Effectiveness: 0.7/2
#
Death
--- Markov Information
Trans Cost: (cHosp*0.00)+365
Trans Effectiveness: 0.00
0
Remission
--- Markov Information
Trans Cost: (cHosp*0.25)+365
Trans Effectiveness: (0.5+0.7)/2
0.27
Active
--- Markov Information
Trans Cost: (cHosp*1.25)+365
Trans Effectiveness: 0.5
0.23
Flare
--- Markov Information
Trans Cost: (cHosp*0.75)+365
Trans Effectiveness: 0.5/2
#
Death

Save this version of your model as a workable tree

- **Click File/Save As…**
- **Name the file with your family name followed by the number 9, for example, "Williams9."**
- **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 as the title 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 at the extreme right, which is the icon for Open in a New Excel Spreadsheet.**
- **Name the file with your family name followed by the number 10, for example, "Williams10"**

The material that is in Step 5 (Perform Deterministic Sensitivity Analyses) is **NOT** part of this homework assignment. However, some of the material that is in Step 6 (Add distributions to the model in preparation for conducting a probabilistic sensitivity analyses) **IS** part of this homework assignment, including items 19, 20, and 21.

Step 5. Perform 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 4 and making all the possible changes is tedious, so we have provided a tree that has most 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

downloading. You are welcome to use it to conduct deterministic sensitivity analyses that are described below.

- To reproduce the one-way sensitivity analysis in the slide at the top of page 30 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. If the arrowhead is not visible, click on the cell defined by the first row and the column labeled Variable. 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 middle slide on page 30, 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 the bottom slide on page 30, 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.
- To produce a Tornado diagram (not shown in class), Click Analysis/Sensitivity Analysis/Tornado Diagram… (not pre 2017 Tornado Diagram…). In the box that opens, the name of each variable is in the first column and the value for each variable in the base case is in the 7th column (labeled Definitions). For each variable, enter a range (in the white cells, not the grey cells) to be used in the Tornado diagram by entering a low and a high value (try one-half the base value and twice the base value keeping in mind that QALYs cannot be greater than 1). Also for each variable, enter the number of intervals (4 works fine). Click OK. Wait. In the box that opens, select ICER. On the bottom at the left click Open Report. In the upper right, Click Text Report.

The material that is in items 19, 20, and 21 of "Step 6. Conduct probabilistic sensitivity analyses" **IS** part of the homework assignment.

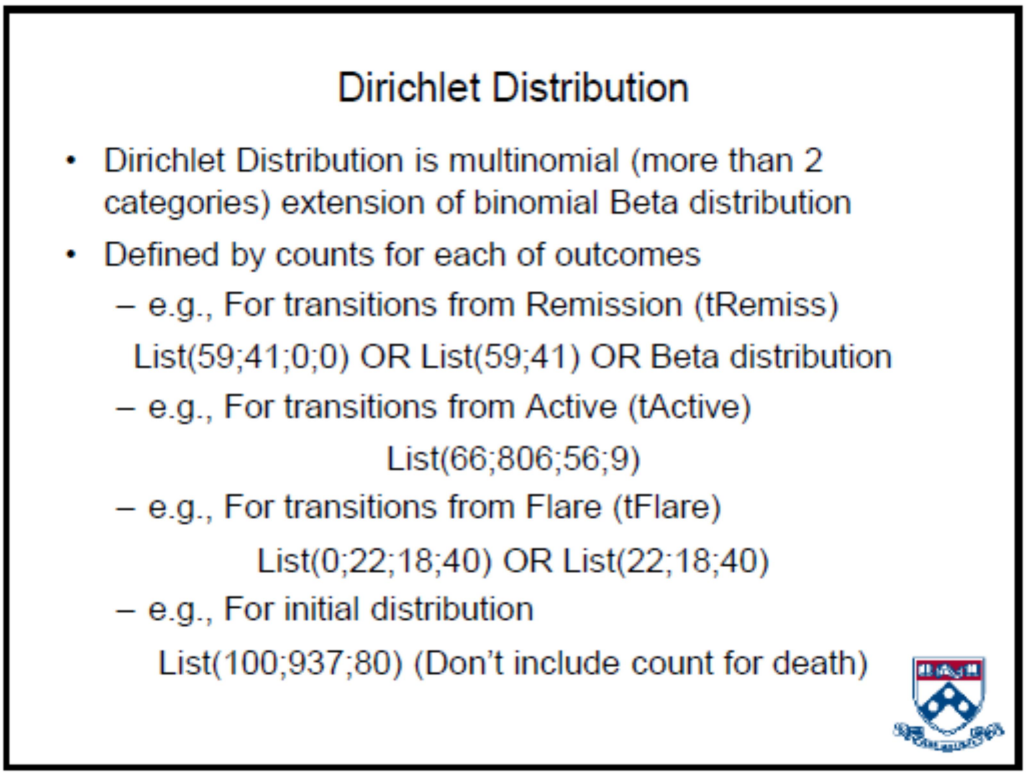
Step 6. Add distributions to the model in preparation for conducting a probabilistic sensitivity analyses.

You can change any of the numbers or variables in your tree into distributions. 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. You made these types of changes in a previous homework, but there are differences between what you did there and what is required for a Markov analysis. Therefore, this assignment requires that you to create some, but not all, of the distributions for this Markov

model, so you will understand the principles.

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. The tree we provide has different values for the number of cycles and uses a different way of discounting, but is otherwise identical to the tree in the earlier part of this exercise.
- 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 list, add the following values "List(59;41;0;0)," which come from the top slide on page 31 (see below), click OK, and then close the box.



- For the Usual Care node, go to the Remission subtree, and then go to the Active terminal node, where you should replace the transition probability, which is 0.41, with the new value Dist(1;2).
- Close the box if it pops up.
- Make sure the value under the Remission terminal node of the Remission subtree is #, which ensures that the probabilities will change correctly when sensitivity analyses are done.
- You could replace the value under the Flare terminal node of the Remission subtree with Dist(1;3), but is not strictly necessary because the probability is zero. Similarly, you could

replace the value under the Death terminal node of the Remission subtree with Dist(1;4), it is 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 make sure the pound sign (#) is in the transition to Death.
- For the Intervention node, add identical expressions to the comparable terminal nodes.
- In the Intervention subtree, change the probability of the transition from Remission to Active so it becomes "rr*Dist(1;2)"

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 list, add the following values "List(100;937;80)," which come from the bottom of the same slide we have been using (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 0.

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 "-.1582" and for sigma (std. dev. of logs) type ".1816," click OK, then close the box.

Save this version of your model as a workable tree

- **Click File/Save As…**
- **Name the file with your family name followed by the number 11, for example, "Williams11"**
- **For Save as Type, indicate TreeAge Tree Diagram (*.trex)**
- **Click Save**

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.

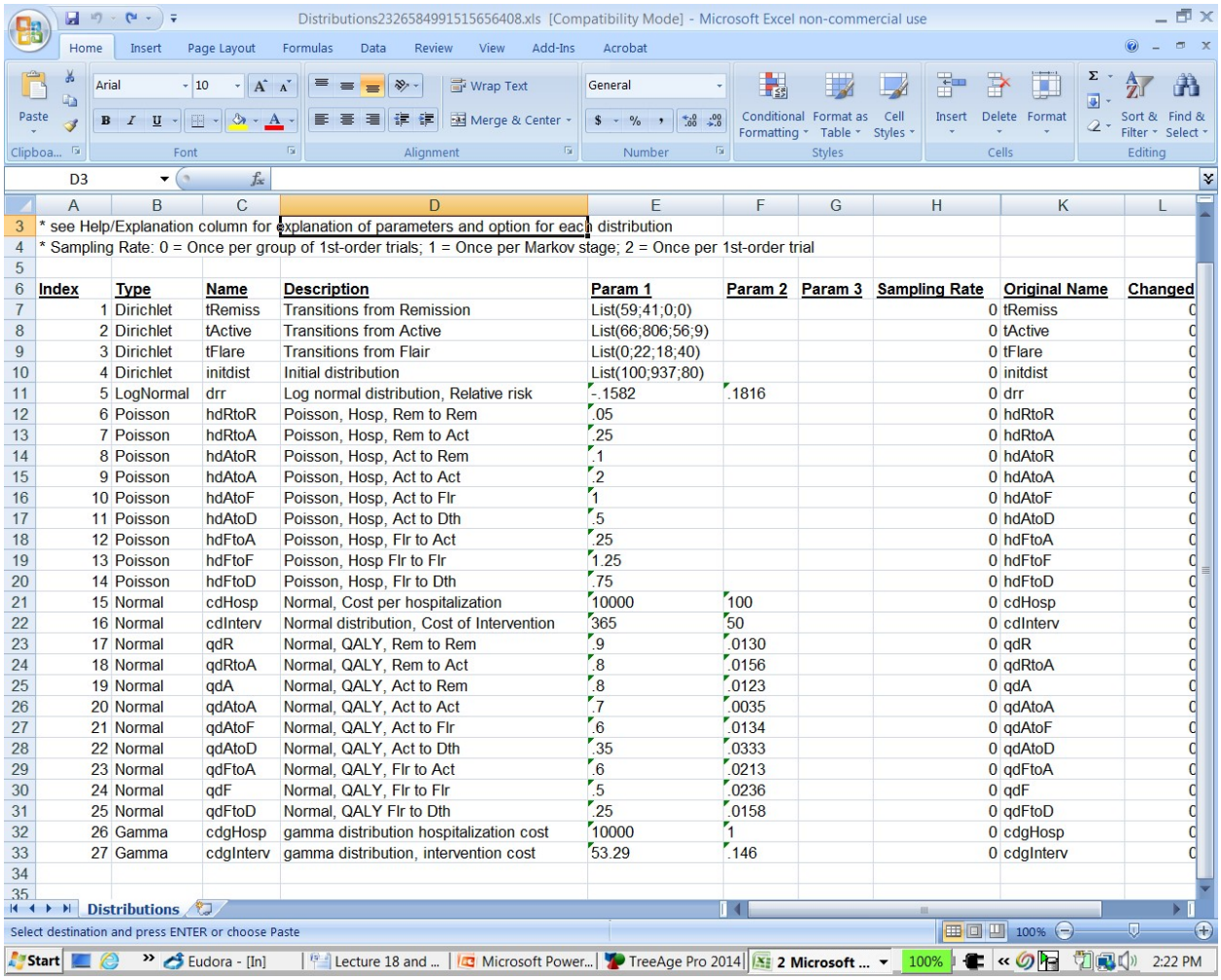
Items 22-24 are **NOT** part of the homework assignment, but item 25 IS part of the homework assignment.

Creating the remaining distributions is tedious, so we have provided you with a tree with 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 can either follow the directions described in items 22-24 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.

22. Define and add distributions for costs and QALYs

- If you do not have the TreeAge feature that allows you to create and edit distributions in an Excel spreadsheet, you can create distributions for costs and QALYs using methods like the ones described in items 19-21 above and using information from the Excel spreadsheet below. Once you have finished, go to item 23.
- If you have the TreeAge feature that allows you to create and edit distributions in an Excel spreadsheet, you can follow the remaining directions in items 22-24.
- Click Values/Distribution view to reveal the Distributions window
- Just beneath the label for this tab (Distributions) is a row of icons (pencil, green plus sign, etc.) Hover your pointer over the 7th icon in this row, and it will read Open in New Excel Spreadsheet. Click this icon.
- An Excel spreadsheet should open that looks something like the figure on the next page. (Note that the names of columns A-G are identical when comparing your figure with the figure on the next page, but the names of the columns to the right of column G are different. That is OK because we will not be using the columns to the right of column F.)



Index	Type	Name	Description	Param 1	Param 2	Param 3	Sampling Rate	Original Name	Changed
1	Dirichlet	tRemiss	Transitions from Remission	List(59;41;0;0)			0	tRemiss	0
2	Dirichlet	tActive	Transitions from Active	List(66;806;56;9)			0	tActive	0
3	Dirichlet	tFlare	Transitions from Flair	List(0;22;18;40)			0	tFlare	0
4	Dirichlet	initdist	Initial distribution	List(100;937;80)			0	initdist	0
5	LogNormal	drr	Log normal distribution, Relative risk	-.1582	.1816		0	drr	0
6	Poisson	hdRtoR	Poisson, Hosp, Rem to Rem	.05			0	hdRtoR	0
7	Poisson	hdRtoA	Poisson, Hosp, Rem to Act	.25			0	hdRtoA	0
8	Poisson	hdAtoR	Poisson, Hosp, Act to Rem	.1			0	hdAtoR	0
9	Poisson	hdAtoA	Poisson, Hosp, Act to Act	.2			0	hdAtoA	0
10	Poisson	hdAtoF	Poisson, Hosp, Act to Flr	1			0	hdAtoF	0
11	Poisson	hdAtoD	Poisson, Hosp, Act to Dth	.5			0	hdAtoD	0
12	Poisson	hdFtoA	Poisson, Hosp, Flr to Act	.25			0	hdFtoA	0
13	Poisson	hdFtoF	Poisson, Hosp Flr to Flr	1.25			0	hdFtoF	0
14	Poisson	hdFtoD	Poisson, Hosp, Flr to Dth	.75			0	hdFtoD	0
15	Normal	cdHosp	Normal, Cost per hospitalization	10000	100		0	cdHosp	0
16	Normal	cdInterv	Normal distribution, Cost of Intervention	365	50		0	cdInterv	0
17	Normal	qdR	Normal, QALY, Rem to Rem	.9	.0130		0	qdR	0
18	Normal	qdRtoA	Normal, QALY, Rem to Act	.8	.0156		0	qdRtoA	0
19	Normal	qdA	Normal, QALY, Act to Rem	.8	.0123		0	qdA	0
20	Normal	qdAtoA	Normal, QALY, Act to Act	.7	.0035		0	qdAtoA	0
21	Normal	qdAtoF	Normal, QALY, Act to Flr	.6	.0134		0	qdAtoF	0
22	Normal	qdAtoD	Normal, QALY, Act to Dth	.35	.0333		0	qdAtoD	0
23	Normal	qdFtoA	Normal, QALY, Flr to Act	.6	.0213		0	qdFtoA	0
24	Normal	qdF	Normal, QALY, Flr to Flr	.5	.0236		0	qdF	0
25	Normal	qdFtoD	Normal, QALY Flr to Dth	.25	.0158		0	qdFtoD	0
26	Gamma	cdgHosp	gamma distribution hospitalization cost	10000	1		0	cdgHosp	0
27	Gamma	cdgInterv	gamma distribution, intervention cost	53.29	.146		0	cdgInterv	0

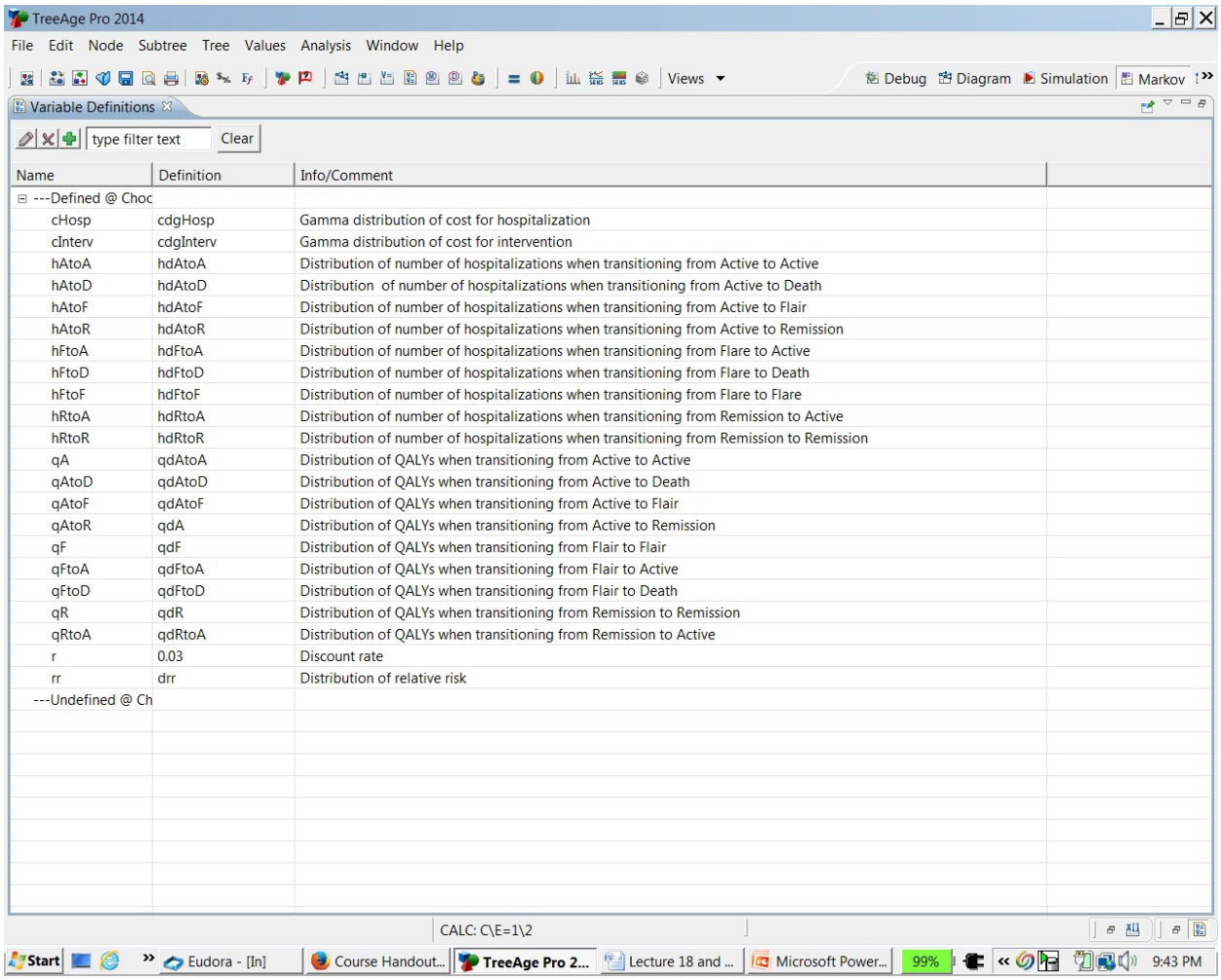
- In this spreadsheet, the first five rows, which are labeled with the Index numbers 1-5, should be filled in, and rows with the Index numbers 6-27 in the figure above should be blank. You can define all the remaining distributions by typing into the cells defined by rows 6-27 and columns A-F the information that is in the spreadsheet above. Be sure to include the index number when you edit a row. After making these changes, click on any empty cell (Important). To move this material back in to your Markov model, at the top of your screen click TreeAge Pro, which opens up a row of boxes. Click the box for Distributions and then click Add or Update Distributions. Ignore any warnings about entries being stored as text and not numbers, as long as that is what you intended. Close Excel and do not save the information in the spreadsheet. Check Values/Distributions View to make sure your changes were properly recorded in TreeAge.

23. Assign distributions for costs, QALYs, and the relative risk to an appropriate variable.

- Click Values/Variable Properties View.
- In the box that opens are the existing variables and the definitions of the existing variables.

The definitions are numbers.

- Make the box full screen by clicking on the full screen icon at the upper right corner of the box.
- Change the Definitions of the variables from numbers to the labels you created for the distributions, which should be the labels in the following figure. Remarks in the Info/Comment space are optional.
- Close this screen by clicking the X next to the tab label (Variable Properties)



24. Add new variables to the tree

- Change any remaining numbers in the tree to the comparable variables

25. Conduct a probabilistic sensitivity analysis.

We made the following material part of the homework because knowing how to conduct and interpret the results of probabilistic sensitivity analyses is important to your understanding about decision analysis. However, we are not asking you to save files and turn them in just so we can document that you did this part of the assignment.

Begin by producing the results for the slide that is in the middle of page 36, which is titled, Roll Back CE Analysis, Numbers vs Distributions. To produce the results at the bottom of this slide, select the Choose node which is labeled Lupus in this version of the model, and click Analysis/Roll Back. The main results will be in the rectangles to the right of each Markov node (purple circle with an M). Once you're finished, click Roll Back again to release the program from Roll Back. (To produce the results at the top of the slide, open the file that you previously saved with your last name followed by 9. Select the Choose node and click Analysis/Roll Back. The main results will be in the rectangles to the right of the Usual care node and the Intervention node. If your numbers are slightly different from the slide numbers, it may be because you used a different number of cycles. If they are substantially, different, it probably is because of a typo in some other part of the model. Once you're finished, click Roll Back again to release the program from Roll Back.)

- To reproduce other slides, start by clicking 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 this type of analysis if you want to get identical results, but it doesn't matter which number you choose. Use the seed number 2 if you want to reproduce the results that are in the lecture slides. If you want results as close as possible to the results in the lecture, you should also use the same termination rule for the two Markov nodes that was used in the lecture, which was _stage>1999.) Click Apply and Close.
- On the right, click Distributions, which brings up the Distribution Sampling box. Make sure Sample All is selected, and click Apply and Close.
- 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. Make sure the Intervention Markov node has the identical termination instructions. Alternatively, decrease the number of samples below 1000.
- Compare your output to the slides in the lecture.
    - Start with the results in the main screen (Monte Carlo Summary Text Report), which are the source for the information in the slide at the top of page 37 (Second-Order Monte Carlo Simulation*). Another way to display this and additional information is to go to the section titled Data in the upper right of this screen and click Summary Report
    - To reproduce the histograms in the slide at the bottom of page 37, close the Summary Report, expand the section titled Histograms, expand Output Distributions, Expand Incremental Cost, click Intervention vs. Usual Care, look at the section for Histogram Parameters, select Custom, change the number of bars to 20, and click OK. Close this material. Repeat what you did, but expand Incremental Effectiveness instead of Incremental Cost and change the number of bars to 30.
    - To reproduce the results for the slide at the top of page 43 (Cost-Effectiveness Plane . . .), close the histogram, expand PSA Outputs, expand ICE Scatterplot, click Intervention v Usual Care, make sure 50000 is the willingness-to-pay value, type in 1 for Start and 1000 for End, and click OK.

- To reproduce the results for the slide in the middle of page 43 (Incremental CE Plot Report . .), in the upper right of this screen click ICE Report, make sure “50000” is the willingness to pay, accept the other values, and click OK.
- To generate an acceptability curve (shown in the left of the slide at the top of p. 40), close this screen and the screen with the scatter plot, 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.