Decision Tree Sampling Uncertainty

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Sampling Uncertainty

- Traditionally, decision tree analysis has expressed uncertainty by use of one- and two-way sensitivity analysis
- More recently, Monte Carlo simulation has been used to evaluate more traditional measures of "sampling uncertainty"
  - Sampling Uncertainty: Degree to which results from a specific sample represent actual results in population from which sample was drawn
- One of several types of uncertainty
  - e.g., doesn't address biased sampling

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Types of Sampling Uncertainty

- First order Monte Carlo simulation (FOMCS)
  - If probability is 50%, then in each "trial" there is a 50% chance that event such as a side effect occurs
- Second order Monte Carlo simulation (SOMCS)
  - Also referred to as probabilistic analysis
  - Uncertainty about whether "true" probability is 50% or 48% or 52%
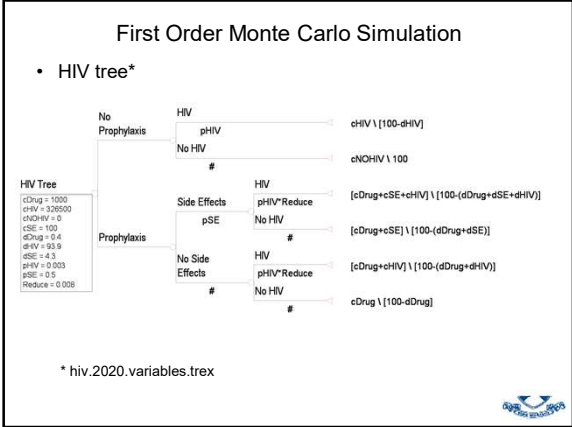   - In some trials, 48% chance of occurrence, in some 50%, in some 52%

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First Order Monte Carlo Simulation

- HIV tree*

HIV Tree
cDrug = 1000
cHIV = 326500
cNOHIV = 0
cSE = 100
dDrug = 0.4
dHIV = 93.9
dSE = 4.3
pHIV = 0.003
pSE = 0.5
Reduce = 0.008

No Prophylaxis → HIV: pHIV → cHIV \ [100-dHIV]
No HIV: # → cNOHIV \ 100

Prophylaxis:
Side Effects: pSE
 HIV: pHIV*Reduce → [cDrug+cSE+cHIV] \ [100-(dDrug+dSE+dHIV)]
 No HIV: # → [cDrug+cSE] \ [100-(dDrug+dSE)]
No Side Effects:
 HIV: pHIV*Reduce → [cDrug+cHIV] \ [100-(dDrug+dHIV)]
 No HIV: # → cDrug \ [100-dDrug]

* hiv.2020.variables.trex

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FOMCS Like a Pachinko Machine

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Pachinko Machine Analogy

- Pins in machine represent chance nodes
- Balls (trials) represent individuals running through chance nodes
  - Each ball represents an individual in a (clinical) trial
    - Don't represent (clinical) trials, each with many individuals
- Probability that individuals "bounce" one way or other at a chance node based on probability for node
  - e.g., if pHIV equals 0.003, then on average 3 in 1000 individuals will bounce into HIV "bin" and 997 in 1000 individuals will bounce into No HIV "bin", but any one individual ends up in either HIV or No HIV bin
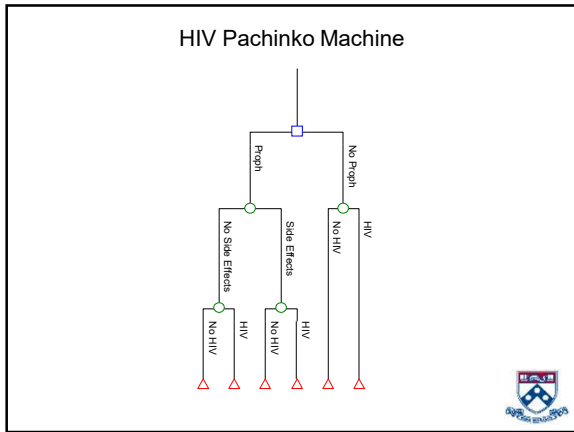
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HIV Pachinko Machine

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Movement in First Order Monte Carlo Simulation

- FOMCS models movement of multiple individuals through tree using results of random number generation (e.g., between 0 and 1) and probabilities
- Path through tree based on probabilities
  - No Prophylaxis: final outcome based on 1 random number
  - Prophylaxis: final outcome based on two random numbers

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No Prophylaxis Probability Ranges

	No	Yes
Random Draw # 1		
HIV	0.0 to <0.997	0.997 to 1.0

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Sample Run of 5 People Through No Prophylaxis Arm

Person	Random Draw #1	Outcome
1	0.473	No HIV
2	0.976	No HIV
3	0.364	No HIV
4	0.998	HIV
5	0.279	No HIV

Prophylaxis Probability Ranges

	No	Yes
Random Draw # 1 Side Effects	0.0 to <0.5	0.5 to 1.0
Random Draw # 2 HIV	0.0 to <0.999976	0.999976 to 1.0

Sample Run of 5 People Through Prophylaxis Arm

Person	Random Draw #1	Random Draw #2	Outcome
1	0.25	0.759	No SE, No HIV
2	0.33	0.99998	No SE, HIV
3	0.76	0.251	SE, No HIV
4	0.40	0.333	No SE, No HIV
5	0.83	0.657	Se, No HIV

Running a First Order Monte Carlo Simulation

- TreeAge refers to first order Monte Carlo simulation as "Trials (Microsimulation)"

  \Analysis\Monte Carlo Simulation\Trials (Microsimulation)

- Identify number of trials you want TreeAge to run (number of individuals run through tree)

  – Monte Carlo simulation does not give exact answers to decision problem

  – Number of trials should be sufficiently large that central limit theorem works

     (In what follows:) Number of trials: 50,000

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Seeding Random Number Generator

- If you want to be able to reproduce your results, set "seed" for random number generator, e.g.,

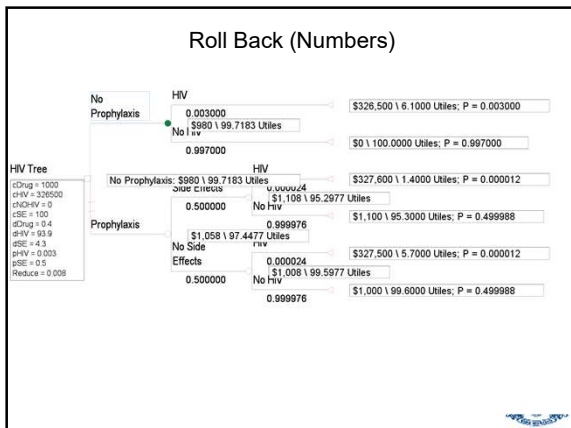   \Seeding\Seed random number generator: 1

- Begin

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Roll Back (Numbers)

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First Order Monte Carlo Simulation Results, Utiles

- Copy to Clipboard button

	No Prophylaxis	Prophylaxis
Mean	99.7239	97.4348
Std Devi…	5.0839	2.2305
Minimum	6.1000	95.3000
2.5%	100.000	95.3000
10%	100.000	95.3000
Median	100.000	95.3000
90%	100.000	99.6000
97.5%	100.000	99.6000
Maximum	100.000	99.6000

hiv.2020.variables.trex; N = 50000; seed = 1

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First Order Monte Carlo Simulation Results, Cost

- Copy to Clipboard button

	No Prophylaxis	Prophylaxis
Mean	959.91	1063.33
Std Dev	17,677.36	2065.53
Minimum	0	1000
2.5%	0	1000
10%	0	1000
Median	0	1100
90%	0	1100
97.5%	0	1100
Maximum	362500	327,600

hiv.2020.variables.trex; N = 50000; seed = 1

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FOMCS Standard Deviations

- First order Monte Carlo simulation adds uncertainty into model (we can estimate both means and variances)
- Uncertainty does not come from parameter estimates themselves
  - Point estimates for pHIV, cHIV, dHIV assumed to be known with certainty
- Reported standard deviations result from "random walks" – pachinko ball "bounces" – that leave people in different terminal bins, each with different payoffs
  - Referred to as "binomial variation"
- FOMCS SDs not sufficient for interval estimation or statistical tests
  - Can't divide reported SD by $N^{\frac{1}{2}}$ to obtain SE

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Standard Deviation vs Standard Errors

- As noted by Altman and Bland:
  - Standard deviation of sample used to estimate variability in population from which sample was drawn
    - For all distributions (normal or otherwise) ~95% of observations usually have values that are within 2 standard deviations of mean
  - Generally estimate sample mean to learn about mean in population from which sample was drawn
    - Sample mean varies from sample to sample and variability is described by sampling distribution
    - Standard deviation of sampling distribution is called standard error
  - Confidence intervals / inferences derived using means and SEs, not means and SDs

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Equations (Continuous Variables)

$$Var = \frac{\sum_i (x_i - \bar{x})}{N - 1}$$

$$SD = \sqrt{Var}$$

$$SE = \frac{SD}{\sqrt{N}} \quad \text{Reason why sample size matters}$$

$$SE_{Diff12} = \sqrt{SE_1^2 + SE_2^2}$$

$$SE_{CorrDiff12} = \sqrt{SE_1^2 + SE_2^2 - 2\,COV}$$

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SD Vs SE, Age

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21	Mean	25.75
25	SD	3.615443
26	N^0.5	2.8284271
27	SE	1.2782
28		
29		
30		

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SD vs SE (2)

- Summary of data from 1000 normally distributed observations with mean 10,000 and SD 1000

```
Variable |  Obs   Mean   Std. Dev.      Min       Max
---------+-------------------------------------------
    cost | 1000  10000       1000   7183.365  12988.41
```

- Calculated SE, $1000 / 1000^{0.5} = 31.62$
- Result of bootstrap of mean of distribution with 1000 observations with a mean of 10,000 and SD of 1000

```
Variable |  Obs    Mean   Std. Dev.     Min       Max
---------+-------------------------------------------
   mcost | 1000  9999.67     31.72   9882.69  10108.95
```

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Why Do We Need to Know?

- TreeAge doesn't know whether data represent individuals or means of groups of individuals, so it doesn't know if it is calculating SDs or SEs
  - Stata, also has no idea if a variable contains observations of individuals ("summarize" command yields mean and SD) OR
  - if it contains observations of means ("summarize" command yields mean of means and SE)
- TreeAge doesn't calculate parametric p-values or CI for outcomes of interest
- If we provide TreeAge with correct data, it yields results **WE CAN USE** to calculate p-values and CI
- Thus need to know correct data to enter into program and how to use results that come out

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Sampling Uncertainty

- Sampling uncertainty includes more than variability due to coin flip (binomial variation)
  - Can't simply divide SDs by $N^{\frac{1}{2}}$ and interpret results as SEs
- Must take into account that had probabilities (or mean costs or mean QALYs) been derived from a different sample, point estimates would have differed
  - Sankey reported that pHIV equaled 0.28% in CDC Prospective Cohort Study and when combined with 22 smaller studies equaled 0.32%

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Second Order Monte Carlo Simulation: Addressing Sampling Uncertainty

- SOMCS incorporates sampling uncertainty by using distributions rather than point estimates to define variables
  - E.g., drawing from distribution of probability of pHIV with a mean of 0.003 rather than using point estimate of .003
- Implication: Allows statistical statements such as:
  - "No prophylaxis yields significantly greater utility than does prophylaxis" OR
  - "Utility for no prophylaxis and prophylaxis are not significantly different from one another"

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Second Order Monte Carlo Simulation: Addressing Sampling Uncertainty (2)

- Second-order (parameter uncertainty): Mean and standard error
  - Sample means/proportions from each distribution drawn once per trial; roll back to obtain expected values for trial
    - pdHIV, pdSE, reduce, cdHIV, cdDrug, cdSE, ddHIV, ddDrug, ddSE
- If all data not derived from a single dataset (e.g., registry or trial), may lose some of correlation structure in sampling
  - Software allows drawing from correlated normal distributions

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Example: 4 Random Draws from 9 Distributions

	Draw #1	Draw #2	Draw #3	Draw #4
pHIV	.0036	.0022	.0037	.0030
pSE	.5048	.5031	.5020	.4925
reduce	.0065	.0009	.0099	.0095
cHIV	345,751	340,751	320,707	328,625
cDrug	1018	995	996	1186
cSE	81	73	96.7	104
dHIV	95.00	93.49	93.79	92.60
dDrug	.145	.491	-.578	1.948
dSE	3.946	2.566	3.573	1.986

Data available from "All Data Report"

Hivse.2020.trex; N = 10000; seed = 1

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Expected Values from 4 Roll Backs

	No Prophylaxis		Prophylaxis	
	Cost	Utiles	Cost	Utiles
Draw #1	1257	99.6544	1067	97.8604
Draw #2	746	99.7953	1032	98.2176
Draw #3	1201	99.6486	1056	98.7817
Draw #4	981	99.7235	1247	97.0709

Data available from:
\Analysis\monte carlo simulation\sampling (probabilistic)\
begin\All Data Report

hivse.2020.trex; N = 10000; seed = 1

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Distributions

Probabilities (2 outcomes) (avoid distributions that can yield probabilities <0 and >1)	Beta
Probabilities (3+ outcomes) (avoid distributions that can yield probabilities <0 and >1) AND those that don't sum to 1.0	Dirichlet
Relative Risks (odds ratios)	Log normal
Continuous Variables	Normal; Gamma; Log normal

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Primary Changes in Defining Trees Using TreeAge

- Define probabilities and pay-offs (by use of distributions)
- Analyze tree by use of Monte Carlo Simulation
  - Simple roll back (generally) gives point estimate for tree, by use of mean values for each distribution used in tree
- Because some point estimates represent medians rather than means (e.g., OR and RR), point estimate from roll back can differ from point estimate from Monte Carlo

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Steps in Performing Probabilistic Cost-Effectiveness Analysis

- Step 1. Construct your tree
- Step 2. Define your probability distributions
  - Select a distribution for variable of interest (e.g., for pdHIV, distribution that defines pHIV
  - Define distribution (e.g., pdHIV)
  - Label distribution (e.g., Probability of HIV)
  - Add variable that is defined by distribution (e.g., pHIV) where ever it appears in tree
  - Assign distribution to variable (e.g., assign pdHIV to pHIV)

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Steps in Performing Probabilistic Sensitivity Analysis (cont.)

- Step 3. Define your payoff distributions
- Step 4. Analyze "stochastic" tree
- Step 5. Calculate a significance test or confidence interval and perform sensitivity analysis

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Getting Started in TreeAge

- Step 1. Construct your tree
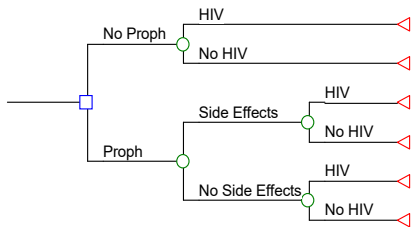
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Step 2. Define Your Probability Distributions

- 2 probabilities represented by beta distributions

pdHIV	20 / 6202	CDC Prospective Cohort Study
pdSE	5892 / 11,784	CDC Surveillance Hospitalization Study

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Defining pdHIV

- Open distribution window (e.g., \values\distributions view OR \views\distributions)
- Create new distribution (green cross)
- Identify:
  - type of distribution (beta)
  - sampling rate (resample per EV)
  - name of distribution (pdHIV)
  - description of distribution (Probability distribution, HIV)
  - distribution parameters: for Beta distribution use real numbered parameters
    - Total observations = 6202;
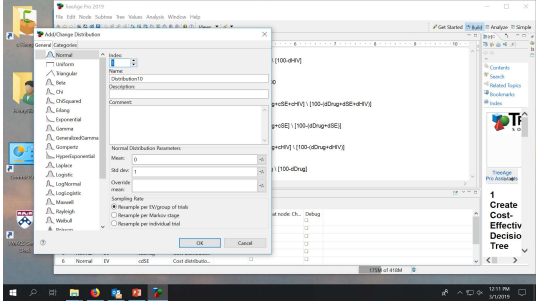 α= # successes = 20; β = # failures = 6182

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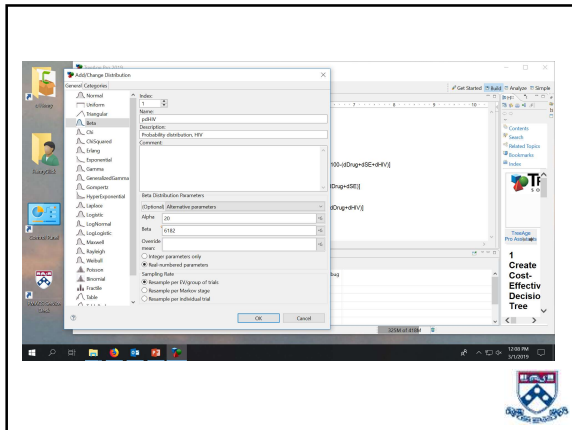
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Create pHIV Variable and Set Equal to pdHIV

- Open Variable Properties window (e.g., \values\variable properties view OR \views\variable properties)
- Create new variable (green cross): opens Add/Change Variable window
- Identify:
  - name of variable (pHIV)
  - description of variable (Probability of HIV)
  - show definitions in tree
  - (do NOT define numerically at root)
- Close Add/Change Variable window
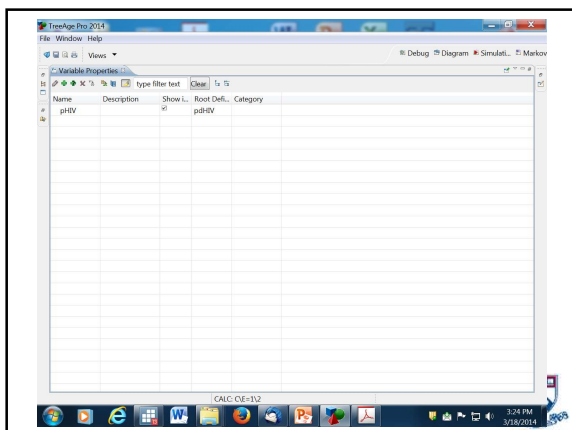- Add pdHIV to pHIV Root Definition in Variable Properties window

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Step 2d. Add pHIV to Tree

No Proph — HIV — pHIV
No HIV

pHIV = pdHIV

Proph — Side Effects — HIV — pHIV
No HIV

No Side Effects — HIV — pHIV
No HIV

Define pdSE; Assign It to pSE; Add to Tree

• Use beta distribution and "Real-numbered parameters" option (5892 / 5892) to define pdSE
• Identify value for pSE

No Proph — HIV — pHIV
No HIV — #

pHIV=pdHIV
pSE=pdSE

Proph — Side Effects — HIV — pHIV
pSE — No HIV — #

No Side Effects — HIV — pHIV
— No HIV —

Relative Risk, HIV (reduce)

• Hypothetical experimental data (virtual sample size)

	Prophylaxis	No Prophylaxis
HIV	.6 (a)	72 (b)
No HIV	24,999.3 (c)	22,857 (d)
Total	24,999.9 (a + c)	22,929 (b + d)

• Relative risk: 0.000024/.003140 = .007643
• Relative risk modeled as a log normal distribution (log(RR) and SE(log(RR))

Log Relative Risk

- Log(RR) and SE Log(RR)

$$\ln(RR) = \ln(a) + \ln(b+d) - \ln(b) - \ln(a+c)$$

$$se[\ln(RR)] = \sqrt{\frac{1}{a} + \frac{1}{b} - \frac{1}{a+c} - \frac{1}{b+d}}$$

- RR distributed log normal (2 parameters)
  - μ (ln RR):
    $\ln(.6)+\ln(22929)-(\ln(72)+\ln(24999.9)) = -4.8740$
  - sigma (se ln(RR)):
  $((1/.6)+(1/72)-((1/24999.9)+(1/22929)))^.5 = 1.2963302$

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Log Relative Risk (2)

- Point estimate of relative risk represents median of RR
- In many situations, median RR ≈ mean RR
- Use of log normal distribution for THIS RR provides example where median (0.0076) ≠ mean (0.0184)
  - Difference may be exacerbated by use of 0.6 for HIV|prophylaxis cell, but mean is still twice median if we substitute 1.0 for 0.6
  - Tends to occur when probabilities are close to 0, distribution is truncated, and log normal not a good representation of distribution of RR
- In current example, simulation suggests square root or normal distributions are better fits to data

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Log Relative Risk (3)

- When using a log normal to represent RR, results of rollbacks and Monte Carlo simulations reflect MEAN of RR, not median
- Judge extent of bias from use of log normal distribution by comparing results to rollback that substitutes numeric values for means and medians for distributions

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Define Relative Risk Distribution

- Open distribution window (e.g., \values\distributions view)
- Create new distribution (green cross)
- Identify:
  - type of distribution (log normal)
  - name of distribution (pdRR)
  - description of distribution (relative risk, HIV given drug)
  - distribution parameters
    - μ = -4.8740
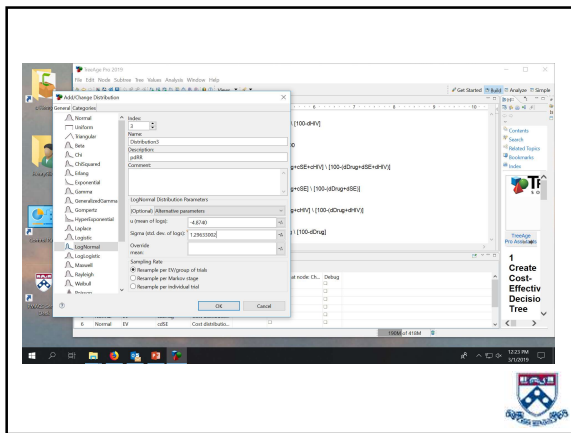   - sigma = 1.2963302
  - sampling rate (resample per EV)

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Create RR Variable and Set Equal to pdRR

- Open Variable Properties window (e.g., \values\variable properties view OR \views\variable properties)
- Create new variable (green cross): opens Add/Change Variable window
- Identify:
  - name of variable (RR)
  - description of variable (Relative risk, HIV)
  - show definitions in tree
  - do NOT define numerically at root
- Close Add/Change Variable window
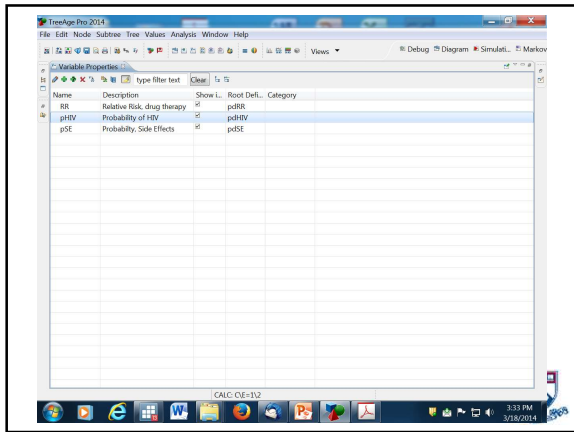- Add pdRR to Root Definition of RR in Variable Properties window

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Add Relative Risk (RR) to Tree

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Distribution of LR VS OR
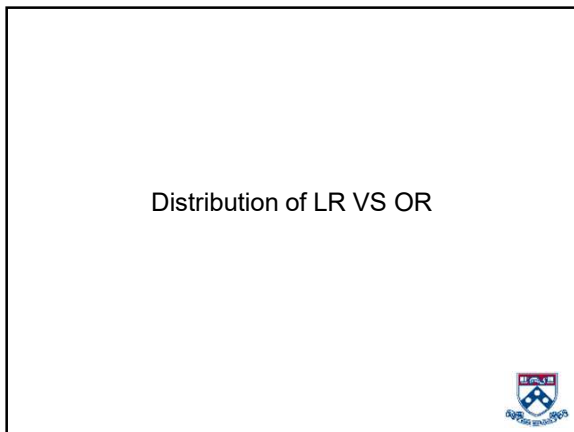
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(Recap) Log Relative Risk

- Log(RR) and SE Log(RR)

$$ln(RR) = ln(a) + ln(b+d) - ln(b) - ln(a+c)$$

$$se[ln(RR)] = \sqrt{\frac{1}{a} + \frac{1}{b} - \frac{1}{a+c} - \frac{1}{b+d}}$$

- RR distributed log normal (2 parameters)
  - μ (ln RR):
    ln(.6)+ln(22929)-(ln(72)+ln(24999.9)) = -4.8740
  - sigma (se ln(RR)):
    ((1/.6)+(1/72)-((1/24999.9)+(1/22929)))^.5 = 1.2963302

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Log Odds Ratio

- Log(OR) and SE Log(OR)

$$ln(OR) = ln(a) + ln(d) - ln(b) - ln(c)$$

$$se[ln(OR)] = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

- OR distributed log normal (2 parameters)
  - μ (ln OR):
    ln(0.6)+ln(22857)-(ln(72)+ln(24999.3)) = -4.8771
  - sigma (se ln(OR)):
    ((1/0.6)+(1/72)+(1/24999.3)+(1/22857))^.5 = 1.2963947
- NOTE: As with RR, mean and median differ

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Using Odds Ratios in Trees

- Probability after intervention with a given OR

$$p_{int} = \frac{OR_{HIV} \times p_{HIV}}{(OR_{HIV} \times p_{HIV}) + (1 - p_{HIV})}$$

- Equivalent formula using built-in Treeage functions:
  - ProbToOdds
  - OddsToProb
    e.g., p_{int} = OddsToProb(OR$_{HIV}$ * ProbToOdds(p$_{HIV}$))

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Step 3. Define Payoff Distributions

- 3 normal distributions for cost (simplification)
- 3 normal distributions for utiles
- Use mean and SE where program asks for mean and SD, in part because TreeAge doesn't ask for N, and thus can't calculate an SE if we enter an SD

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Define Payoffs

	Cost		Disutility	
	Mean	SE	Mean	SE *
HIV	326,500	32,650	93.9	1.566
Drug	1000	100	0.4	0.918
SE	100	15	4.3	1.203

* N = 14 respondents

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Define cHIV Distribution

- Open distribution window (e.g., \values\distributions view)
- Create new distribution (green cross)
- Identify:
  - type of distribution (normal)
  - name of distribution (cdHIV)
  - description of distribution (cost distribution, HIV)
  - distribution parameters (mean = 326,500; std dev = 32,650)
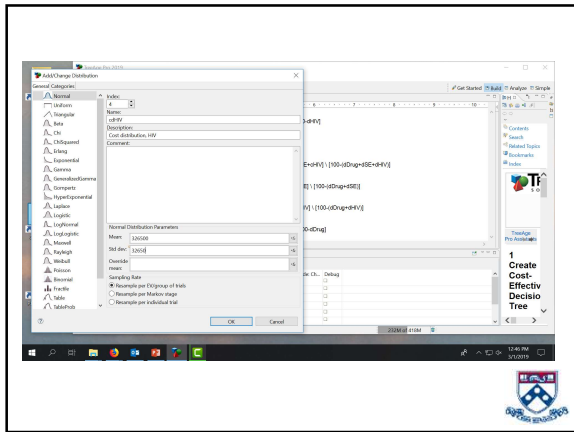 - sampling rate (resample per EV)

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Add cHIV to Tree

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Assign cdHIV to cHIV

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Add Remaining Cost Payoffs
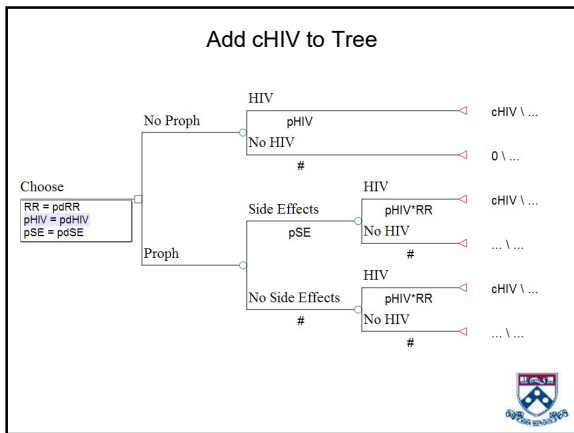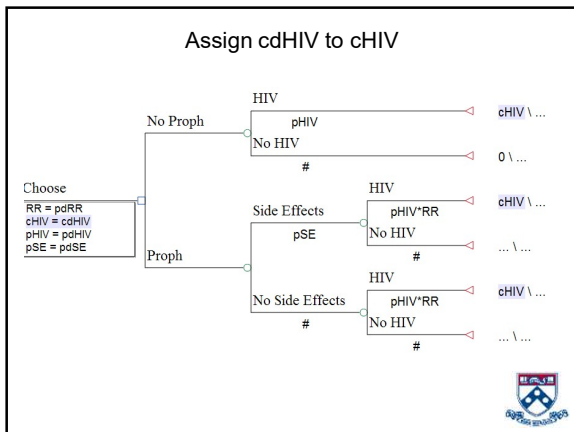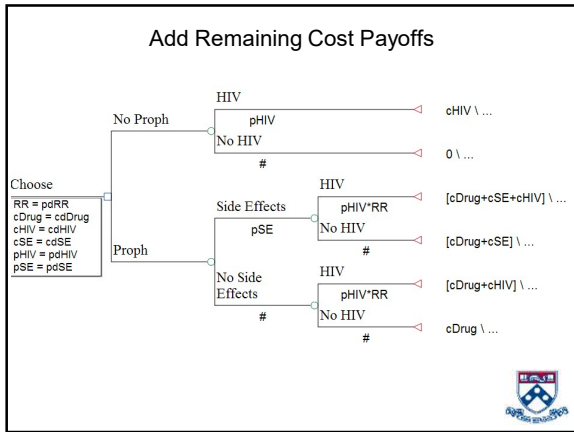
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Concerns About Normal Distributions
(Not shared by me)

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Gamma Distributions for Cost

- Even though we use distributions of means (thus central limit theorem applies), some worry that raw costs aren't typically normally distributed
- One typical response is to represent cost data as distributed gamma
  - Gamma distribution defined by two parameters, alpha and lambda

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Treeage Parameterization of Gamma Distributions

$$\text{Alpha} = \frac{\text{mean}_{RS}^2}{s_{RS}^2}$$

$$\text{Lamba} = \frac{\text{mean}_{RS}}{s_{RS}^2}$$

where RS = raw or untransformed scale

- e.g.,
  - cdHIV = 326,500; 32,650: gamma = 100; .00030628
  - cdDrug = 1000; 100: gamma = 100; .1
  - cdSE = 100; 15: gamma = 44.4444, .4444

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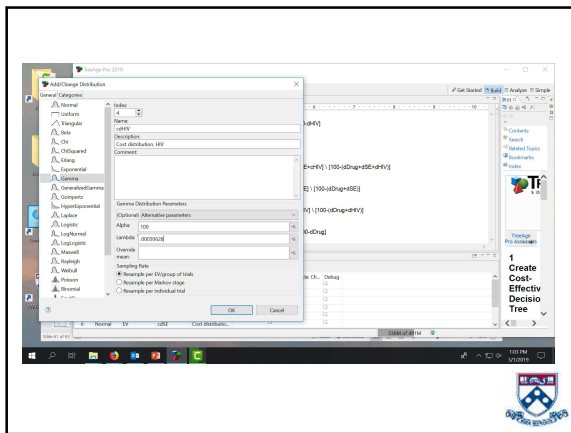
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More General Gamma Distribution Parameterization

- Gamma defined by a shape and a scale parameter
- At least 3 parameterizations exist, and each uses a different notation
  - E.g., K and Θ (theta), α and inverse scale parameter β, and K and μ=α/β
- Briggs et al. warn that TreeAge and his book (chapter in readings) don't use same parameterization
  - Treeage uses α and β which it refers to as α and λ
- In simulation can be shown that TreeAge parameterization returns correct mean, sd or se, and skewness ($2/\alpha^{0.5}$) on raw/untransformed scale
  - Less clear about Kurtosis ($6/\alpha$) (but random generation of gamma variables not always valid for small values of α)

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Log Normal Distributions for Cost

- A second typical response to concern that raw costs aren't typically normally distributed is to represent them as distributed log normal
- Log normal distribution defined by 2 parameters, μ (mean of logs) and sigma (error term of logs)

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Parameterization of Log Normal Distribution

$$\mu = \ln\left(\frac{mean_{RS}^2}{\left(mean_{RS}^2 + s_{RS}^2\right)^{0.5}}\right)$$

$$sigma = \left(\ln\left(1 + \frac{s_{RS}^2}{mean^{RS\,2}}\right)\right)^{0.5}$$

where RS = raw or untransformed scale

- cdHIV = 326,500; 32,650: lognorm = 12.69121 .09975135
- cdDrug = 1000; 100: lognorm = 6.9027801; .09975135
- cdSE = 100; 15: lognorm = 4.5940449, .14916638

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TreeAge Parameterization of Log Normal Distribution

$$\mu = \ln\left(median_{RS}\right)$$

$$\sigma = \sqrt{2\ln\left(\frac{mean_{RS}}{median_{RS}}\right)}$$

where RS = raw or untransformed scale (TreeAge manual)

- Can be shown in simulation that TreeAge "median" parameterization yields identical parameters as "mean/s" parameterization

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TreeAge Log Normal Distribution Parameterization

- Limitation: if obtaining cost parameters from published sources, median is rarely reported
- Yes, can derive raw scale median from raw scale mean/s

$$\text{median}_{RS} = \frac{\text{mean}_{RS}^2}{\left(\text{mean}_{RS}^2 + s_{RS}^2\right)^{0.5}}$$

where RS = raw or untransformed scale (TreeAge manual)

- But if already have mean/s why go through extra steps to use median?

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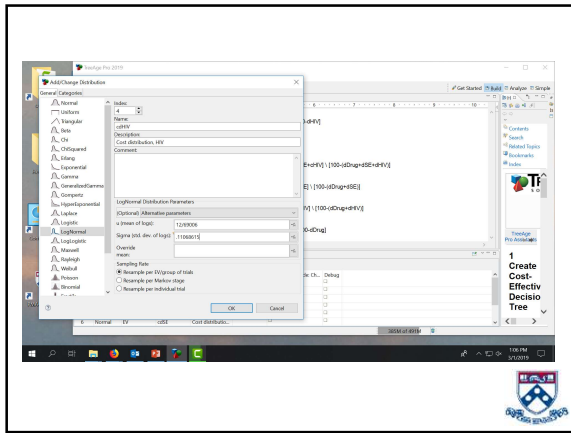
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Monte Carlo SEs: Normal, Gamma, and Log Normal Cost Distributions

	Normal	Gamma	Log Normal
No Prophylaxis	258.99	258.98	258.99
Prophylaxis	108.72	110.11	108.16
Difference	277.25	277.12	277.24

- Means of 5 PSAs for each set of distributions, 10,000 draws per PSA, seeds of 1, 2, 3, 4, and 5
- Central limit theorem: distributions of means derived from variables with normal, gamma, and log normal distributions are themselves normal

Hivse.2020.trex; HIVSE.2020gamma.trex; HIVSE.2020lognorm.trex

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Gamma Distributions in Simulation Nearly Symetric

- Changed mean and SE of cost of side effects to 10,000 and 15,800 respectively
  - Made gamma distribution substantially more skewed and kurtotic

	No Proph	Proph	Diff	SE
Normal	1054	6032	4979	7909
Gamma	1052	6021	4969	7918

- Means, differences in means, and SE of differences derived from normal and gamma distributions remained similar
- Averaged data from 10 PSAs for normal and gamma distributions, 10,000 draws per PSA, seeds of 1 to 10

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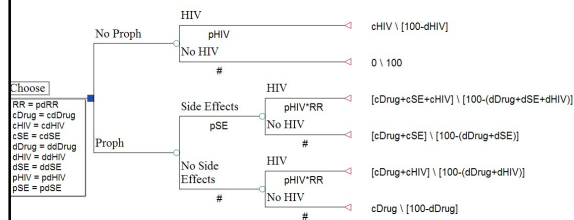## Create Disutility Distributions and Add Disutility Payoffs to Tree


```
                        HIV
            No Proph    pHIV                cHIV \ [100-dHIV]
                        No HIV
                        #                   0 \ 100

Choose
RR = pdRR
cDrug = cdDrug                HIV
cHIV = cdHIV    Side Effects  pHIV*RR       [cDrug+cSE+cHIV] \ [100-(dDrug+dSE+dHIV)]
cSE = cdSE      pSE           No HIV
dDrug = ddDrug                #             [cDrug+cSE] \ [100-(dDrug+dSE)]
dHIV = ddHIV    Proph
dSE = ddSE                    HIV
pHIV = pdHIV    No Side       pHIV*RR       [cDrug+cHIV] \ [100-(dDrug+dHIV)]
pSE = pdSE      Effects       No HIV
                #             #             cDrug \ [100-dDrug]
```

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Are Disutility Scores Normally Distributed?

- As with costs, even though we use distributions of means (thus central limit theorem applies), some worry that raw utility scores aren't normally distributed
- Again, one response is to represent cost data as distributed gamma
- But Gamma (and log normal) distributions are for right-skewed data
- QALY scores typically left skewed rather than right skewed

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Gamma Distributions and Left-Skewed Data

- To define gamma distributions for left-skewed data, we usually subtract scores from highest possible value for distribution (e.g., if QALY score varies between 0 and 1, we subtract all scores from 1)
  - Represent disutility scores
- Define means and SD of disutility scores and use formulas for gamma distribution
- Without adjustment, result represents sum of disutility scores and thus requires retransformation in tree
  - Payoff = 100-disutility score (if 0-100 scale) OR
  - Payoff = 1-disutility score (if 0-1 scale)

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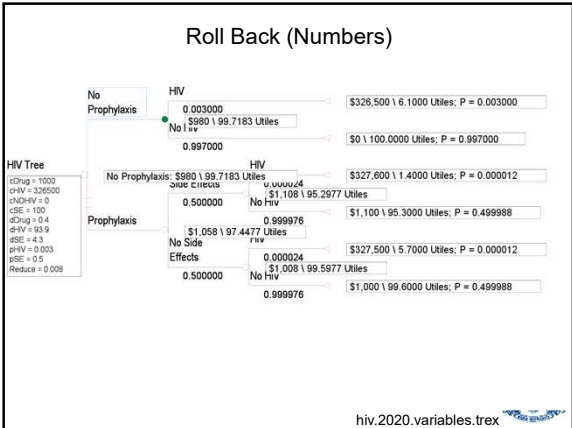## Analyze the Tree

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Roll Back (Numbers)

HIV Tree
cDrug = 1000
cHIV = 326500
cNOHIV = 0
cSE = 100
dDrug = 0.4
dHIV = 93.9
dSE = 4.3
pHIV = 0.003
pSE = 0.5
Reduce = 0.008

No Prophylaxis
HIV
0.003000
$980 \ 99.7183 Utiles
No HIV
0.997000
$326,500 \ 6.1000 Utiles; P = 0.003000
$0 \ 100.0000 Utiles; P = 0.997000

No Prophylaxis: $980 \ 99.7183 Utiles
Side Effects
0.500000
HIV
0.000024
$1,108 \ 95.2977 Utiles
No HIV
0.999976
$1,058 \ 97.4477 Utiles
$327,600 \ 1.4000 Utiles; P = 0.000012
$1,100 \ 95.3000 Utiles; P = 0.499988

Prophylaxis
No Side Effects
0.500000
HIV
0.000024
$1,008 \ 99.5977 Utiles
No HIV
0.999976
$327,500 \ 5.7000 Utiles; P = 0.000012
$1,000 \ 99.6000 Utiles; P = 0.499988

hiv.2020.variables.trex

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Roll Back Tree w/Distributions (Point Estimates) *

* Small differences between stated probabilities and distribution parameters lead to observed differences in expected values

hivse.2020.trex

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Sampling

- More like multiple "roll backs" than like pachinko machine
- For each roll back typically draw from each distribution to obtain a point estimate for each of probability and outcome parameter
  - Able to limit number of distributions from which draws are made
    - Generally useful for identifying how much variability comes from each distribution

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Sampling in TreeAge

- \Analysis \ Monte Carlo Simulation \ Sampling (Probabilistic Sensitivity....)
- Identify number of samples (e.g., 5000)
- (optional) Seeding
  - Check "Seed random number generator box" and select seed (counting number)
- (optional) identify Distributions to be sampled (typically "sample all")
- Begin

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Two-Dimensional (Sampling+trials)

- Combines sampling and trials
  - For each sample
    - Draw point estimates for probabilities and outcomes as in sampling
    - Run multiple people through "pachinko" machine
- For decision trees, not clear if there are any advantages over "Sampling" alone
- For Markov models, may allow us to probabilistically account for "history"

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"Sampling" Monte Carlo C-E Statistics

	No Prophylaxis		Prophylaxis	
	Cost	Utiles	Cost	Utiles
Mean	1049	99.70	1067	97.45
SD *	253	0.07	108	1.09
Min	368	99.36	722	93.94
2.5%	626	99.56	861	95.30
10%	747	99.61	934	96.04
Median	1025	99.70	1064	97.45
90%	1382	99.78	1200	98.62
97.5%	1611	99.81	1285	99..55
Max	2430	99.88	1966	**101.63**

* Reported Std Dev. is actually S.E.

hivse.2020.trex; N = 5000; seed = 1

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(Selected) Monte Carlo Simulation Sampling Results

- Actions
  - Data
    - **Summary report**: means, **ses**, etc. of costs, effects, NMB and probability distributions
    - **All Data Report**: Point estimates of means, ses, etc. of cost, effects,and probability distributions by iteration
    - **All Data Report Export**: Exports All Data Report
  - Other
    - **Expected Values**: 1st 4 columns of Summary report
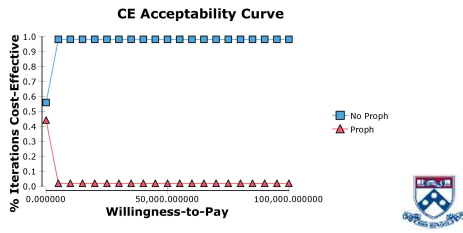   - **Distributions by name and order**: Other columns

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Selected Monte Carlo Simulation Sampling Results (2)

- Actions (Continued)
  - PSA Outputs
    - **Acceptability Curve**: Draws acceptability curves and offers text report of fraction of each therapies iterations that are acceptable for values of WTP
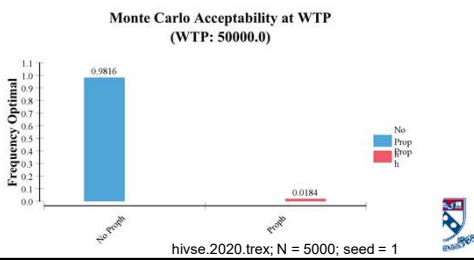

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Selected Monte Carlo Simulation Sampling Results (3)

- Actions (Continued)
  - PSA Outputs
    - **Acceptability at WTP**: Creates bar chart of fraction acceptable for a specified WTP

hivse.2020.trex; N = 5000; seed = 1

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Acceptability at WTP

- Gamma

- Log Normal

hivse.2020gamma.trex; N = 5000; seed = 1
Hivse2020lognorm.trex; N = 5000; seed =1

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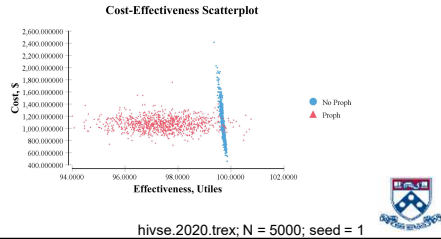## Selected Monte Carlo Simulation Sampling Results (4)

- Actions (Continued)
  - PSA Outputs
    - **CE Scatter plot**: Graphs and reports distribution of each therapy's C/Q points (by iteration) on cost-effectiveness plane **[UNHELPFUL]**

Cost-Effectiveness Scatterplot

hivse.2020.trex; N = 5000; seed = 1

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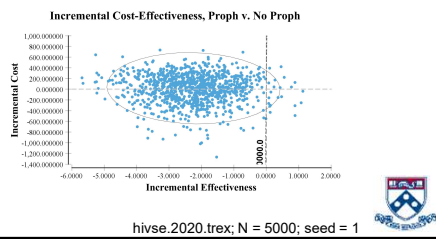## Selected Monte Carlo Simulation Sampling Results (5)

- Actions (Continued)
  - ICER Scatter Plot: Graphs ΔC/ΔQ points (by iteration) on cost-effectiveness plane **(Classic cost-effect-tiveness plane);** provides text file of detailed results AND **reports fractions of point in 6 regions on plane**

Incremental Cost-Effectiveness, Proph v. No Proph

hivse.2020.trex; N = 5000; seed = 1

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Good and Bad Value

C4: New Therapy Bad value

C6: Alternative Dominates

C2: New Therapy Good Value

C5: Alternative Good Value

C1: New Therapy Dominates

C3: Alternative Bad Value

(-) Difference in Cost (+)

(-) Difference in Effect (+)

Ratios refer to alt Rx   Ratios refer to new Rx

Maximum Willingness to Pay

Appropriate W for utiles?

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ICE Report

- \ICE Scatterplot\Proph v. No Proph\ICE Report (WTP=50000)

	QUAD-RANT	INCR EFF	INCR COST		FREQ	PRO-PORTION
C1	IV	IE>0	IC<0	Superior	48	0.0096
C2	I	IE>0	IC>0	ICER<50k	42	0.0084
C3	III	IE<0	IC<0	ICER>50k	2	0.0004
C4	I	IE>0	IC>0	ICER>50k	1	0.0002
C5	III	IE<0	IC<0	ICER<50k	2154	0.4308
C6	II	IE<0	IC>0	Inferior	2753	0.5506
Indiff	origin	IE=0	IC=0	0/0	0	0

hivse.2020.trex; N = 5000; seed = 1

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Monte Carlo Simulation Sampling Results (6)

- Actions (Continued)
  - ICER Distributions: Histogram of distribution of ICERs with stats report that assumes ICER is a continuous variable with a mean and SD (SE) **[IT'S NOT]**

STRATEGY	ATTRIBUTE	STATISTIC	VALUE
Strategy 2 v. 1	ICER	Mean	5
Strategy 2 v. 1	ICER	SD (SE) *	1958
Strategy 2 v. 1	ICER	2.5%	-477
Strategy 2 v. 1	ICER	Median	-18
Strategy 2 v. 1	ICER	97.5%	502

* SE FOR ICER undefined; 95% CI ≠ +/- 1.96*SE

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Monte Carlo Simulation Sampling Results (6)

- Actions (Continued)
  - CE Outputs
    - **CE Graph**: Graphs each therapy's cost/effect pair **[Same Unhelpful Graph As CE Scatter plot; Additional Text Report identical to CE Rankings below]**
    - **CE Rankings**: Provides cost-effectiveness "Text Report" with incremental and single treatment ratios **[Classic cost-effectiveness table (except for individual therapy c/e ratios)]**

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Cost-Effectiveness Report (Rollback With Numbers)

- \Cost Effectiveness\Text Report

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr CE	Dominance
No Proph	980	--	99.7183	0	0	
Proph	1058	78	97.4477	-2.2706	-35	Dominated

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Monte Carlo Sampling Cost-Effectiveness Report

- \CEA Outputs\CE Rankings *

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr CE	Dominance
No Proph	1049.22	--	99.6980	--	--	
Proph	1066.88	17.66	97.4521	-2.2459	-8	Dominated

* Also \CEA Outputs\CE Graph\Text Report

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Monte Carlo Simulation Sampling Results (7)

- Actions (Continued)
  - Incremental INMB and WTP: Draws NMB curve reporting WTP on X axis and NMB on Y axis

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Monte Carlo Simulation Sampling Results (8)

- Actions (Continued)
  - Histograms
    - Output Distributions
      - Cost, incremental cost, effect, incremental effect, NMB
        - Incremental Cost: Histogram and stats report that provides statistics for ΔC **[Very important for reporting sampling uncertainty]**
        - Incremental Effect: same as above for ΔE

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Distribution of Incremental Cost

\Histograms\Output Distributions\Incremental Cost\ Proph v. No Proph\Stats Report

STRATEGY	ATTRIBUTE	STATISTIC	VALUE
Strategy 2 v. 1	Incr Cost	Mean	17.66
Strategy 2 v. 1	Incr Cost	SD (SE)	272
Strategy 2 v. 1	Incr Cost	Min	-1372
Strategy 2 v. 1	Incr Cost	2.5%	-557
Strategy 2 v. 1	Incr Cost	Median	38
Strategy 2 v. 1	Incr Cost	97.5%	491
Strategy 2 v. 1	Incr Cost	Max	856

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Incremental Effect

\Histograms\Output Distributions\Incremental Eff\ Proph v. No Proph\Stats Report

STRATEGY	ATTRIBUTE	STATISTIC	VALUE
Strategy 2 v. 1	Incr Eff	Mean	-2.25
Strategy 2 v. 1	Incr Eff	SD (SE)	1.09
Strategy 2 v. 1	Incr Eff	Min	-5.80
Strategy 2 v. 1	Incr Eff	2.5%	-4.40
Strategy 2 v. 1	Incr Eff	Median	-2.24
Strategy 2 v. 1	Incr Eff	97.5%	-0.13
Strategy 2 v. 1	Incr Eff	Max	1.99

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Step 5. Nonparametric Tests of Significance (p<.05)

Incrementals	Cost	Utiles
Mean	17.66	-2.25
SD (SE)	272	1.09
Minimum	-1372	-5.80
2.5%	**-557**	**-4.40**
Median	38	-2.24
97.5%	**491**	**-0.13**
Maximum	856	1.99

- For cost, nonparametric 95% CI includes 0; for Utiles both limits are negative
- Statistical significance?

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Step 5. Parametric Tests of Significance

Incrementals	Cost	Utiles
Mean	17.66	-2.25
SD (SE)	272	1.09
T statistic	0.06	2.06
P-value *	0.95	0.04

* 2*(1-normal(17.66/272)); 2*ttail(1000,19.85/276)
2*(1-normal(2.25/1.109)); 2*ttail(1000,2.26/1.11)
T-test calculations assume 1000 DOF

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Cost-Effectiveness Ratios

Point estimate: No prophylaxis dominates prophylaxis
95% Lower limit: No prophylaxis dominates prophylaxis
95% Upper limit: No prophylaxis costs more and does more, and it's c/utile ratio equals $679 *

* Based on ΔC=17.66; Sec= 272; ΔU=-2.25; Seq=1.09; and rho=0

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What are Major Sources Of Uncertainty?

- Goal of quantifying uncertainty is to provide audience with a measure of confidence about results
- Audience will be misled (i.e., overly confident) if we present measure of uncertainty that is smaller than it should be
- Sources of shrinkage in SEs include:
  - Excessively large correlations that shrink SEs
  - Failure to address potential bias?
  - Failure to address modeling uncertainty

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Excessively Large Correlations

- Results of trees (e.g., costs and effects) generally will show correlations, but unless we explicitly model correlations -- which generally isn't done -- observed correlations may not be of right magnitudes
  - We don't see it in this example, but in some instances, SE of difference is much smaller than $(SE_0^2 + SE_1^2)^{0.5}$
  - If we observe this shrinkage, should probably use different distributions for each arm of tree

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Focusing on Sampling Uncertainty

- When we borrow data from multiple sources and combine them, we assume:
  - Point estimate is appropriate (unbiased)
  - Sampling error observed in another setting is a good measure of error in problem under consideration
- Accounting for sampling uncertainty doesn't address whether we are using a biased estimator
- Not clear that measure of sampling uncertainty from another population/clinical problem will be appropriate for current population/clinical problem

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Major Sources of Uncertainty (cont.)

- Possibly most important: We have not accounted for "Model" uncertainty

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