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.

Types of Uncertainty

- First order Monte Carlo simulation (FOMCS)
  - If probability is 50%, then in each "trial" there is a 50% chance that event (e.g., 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, the probability is 48%, in some 50%, in some 52%.
First Order Monte Carlo Simulation

- HIV tree

FOMCS Like a Pachinko Machine

Pachinko Machine Analogy

- Pins in machine represent chance nodes
- Balls (trials) represent individuals running through chance nodes
  - Representations of people, not of clinical trials
  - Probability that individuals "bounce" one way or other at a chance node is 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

* hiv.2015.variables.trex
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

No Prophylaxis Probability Ranges

<table>
<thead>
<tr>
<th>Random Draw # 1</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>0.0 to &lt;0.997</td>
<td>0.997 to 1.0</td>
</tr>
</tbody>
</table>
### Sample Run of 5 People Through No Prophylaxis Arm of Tree

<table>
<thead>
<tr>
<th>Person</th>
<th>Draw #1</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.473</td>
<td>No HIV</td>
</tr>
<tr>
<td>2</td>
<td>0.976</td>
<td>No HIV</td>
</tr>
<tr>
<td>3</td>
<td>0.364</td>
<td>No HIV</td>
</tr>
<tr>
<td>4</td>
<td>0.998</td>
<td>HIV</td>
</tr>
<tr>
<td>5</td>
<td>0.279</td>
<td>No HIV</td>
</tr>
</tbody>
</table>

### Prophylaxis Probability Ranges

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Draw # 1</td>
<td>0.0 to &lt;0.5</td>
<td>0.5 to 1.0</td>
</tr>
<tr>
<td>Side Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random Draw # 2</td>
<td>0.0 to &lt;0.999976</td>
<td>0.999976 to 1.0</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Sample Run of 5 People Through Prophylaxis Arm of Tree

<table>
<thead>
<tr>
<th>Person</th>
<th>Draw #1</th>
<th>Draw #2</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>0.759</td>
<td>No SE, No HIV</td>
</tr>
<tr>
<td>2</td>
<td>0.33</td>
<td>0.99998</td>
<td>No SE, HIV</td>
</tr>
<tr>
<td>3</td>
<td>0.76</td>
<td>0.251</td>
<td>SE, No HIV</td>
</tr>
<tr>
<td>4</td>
<td>0.40</td>
<td>0.333</td>
<td>No SE, No HIV</td>
</tr>
<tr>
<td>5</td>
<td>0.83</td>
<td>0.657</td>
<td>Se, No HIV</td>
</tr>
</tbody>
</table>
Running a First Order Monte Carlo Simulation

- TreeAge refers to first order Monte Carlo simulation as "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: 99,999

Seeding the Random Number Generator

- If you want to be able to reproduce your results, set "seed" for random number generator, e.g.,
  \Seed\Seed random number generator: 1
- Begin

Roll Back (Numbers)
First Order Monte Carlo Simulation Results, Utilities

<table>
<thead>
<tr>
<th></th>
<th>No Prophylaxis</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>99.7239</td>
<td>97.4348</td>
</tr>
<tr>
<td>Std Dev</td>
<td>5.0839</td>
<td>2.2305</td>
</tr>
<tr>
<td>Minimum</td>
<td>6.1000</td>
<td>95.3000</td>
</tr>
<tr>
<td>2.5%</td>
<td>100.000</td>
<td>95.3000</td>
</tr>
<tr>
<td>10%</td>
<td>100.000</td>
<td>95.3000</td>
</tr>
<tr>
<td>Median</td>
<td>100.000</td>
<td>99.6000</td>
</tr>
<tr>
<td>90%</td>
<td>100.000</td>
<td>99.6000</td>
</tr>
<tr>
<td>97.5%</td>
<td>100.000</td>
<td>99.6000</td>
</tr>
<tr>
<td>Maximum</td>
<td>100.000</td>
<td>99.6000</td>
</tr>
</tbody>
</table>

FOMCS Standard Deviations

- First order Monte Carlo simulation adds uncertainty into model (we can estimate both means and variances)
- Uncertainty does not come from the 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 N½ to obtain SE
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 the 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

Equations (Continuous Variables)

\[ \text{Var} = \frac{\sum (x_i - \bar{x})^2}{N - 1} \]
\[ \text{SD} = \sqrt{\text{Var}} \]
\[ \text{SE} = \frac{\text{SD}}{\sqrt{N}} \]
\[ \text{SE}_{\text{diff12}} = \sqrt{\text{SE}_1^2 + \text{SE}_2^2} \]
\[ \text{SE}_{\text{corr12}} = \sqrt{\text{SE}_1^2 + \text{SE}_2^2 - 2 \text{COV}} \]

SD vs SE

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obs</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>cost</td>
<td>1000</td>
<td>10000</td>
<td>1000</td>
<td>7183.365</td>
<td>12988.41</td>
</tr>
</tbody>
</table>

• 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obs</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>mcost</td>
<td>1000</td>
<td>9999.67</td>
<td>31.72</td>
<td>9882.69</td>
<td>10108.95</td>
</tr>
</tbody>
</table>
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

Sampling Uncertainty

- Sampling uncertainty includes more than variability due to coin flip (binomial variation)
  - Can’t simply divide SDs by N½ 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%

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 instead of 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"
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 the 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

Example: 4 Random Draws from 9 Distributions

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

Expected Values from 4 Roll Backs

<table>
<thead>
<tr>
<th></th>
<th>No Prophylaxis</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost</td>
<td>Utilities</td>
</tr>
<tr>
<td>Draw #1</td>
<td>1257</td>
<td>99.65544</td>
</tr>
<tr>
<td>Draw #2</td>
<td>746</td>
<td>99.7953</td>
</tr>
<tr>
<td>Draw #3</td>
<td>1201</td>
<td>99.6486</td>
</tr>
<tr>
<td>Draw #4</td>
<td>981</td>
<td>99.7235</td>
</tr>
</tbody>
</table>

Data available from:
\Analysis\monte carlo simulation\sampling (probabilistic)\begin\text reports\Reports-Flat\Values, Dists, Trackers

Hivse.2015.trex; N = 10000; seed = 1
Distributions

<table>
<thead>
<tr>
<th>Probabilities (2 outcomes) (avoid distributions that can yield probabilities &lt;0 and &gt;1)</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probabilities (3+ outcomes) (avoid distributions that can yield probabilities &lt;0 and &gt;1)</td>
<td>Dirichlet</td>
</tr>
<tr>
<td>Relative Risks (odds ratios)</td>
<td>Log normal</td>
</tr>
<tr>
<td>Continuous Variables</td>
<td>Normal; Gamma; Log normal</td>
</tr>
</tbody>
</table>

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

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)
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

Getting Started in TreeAge

- Step 1. Construct your tree

Step 2. Define Your Probability Distributions

- 2 probabilities represented by beta distributions

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>pdHIV</td>
<td>20 / 6202</td>
<td>CDC Prospective Cohort Study</td>
</tr>
<tr>
<td>pdSE</td>
<td>5892 / 11,784</td>
<td>CDC Surveillance Hospitalization Study</td>
</tr>
</tbody>
</table>
Defining pdHIV

- Open distribution window (e.g., \lvalues\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: use real numbered parameters
    - $\alpha = \# \text{ successes} = 20; \beta = \# \text{ failures} = 6182$
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
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

\[
\begin{array}{c}
\text{HIV} \\
\text{No HIV} \\
\hline
\text{pHIV} \\
\text{No Proph} \\
\text{HIV} \\
\text{No HIV} \\
\hline
\text{Side Effects} \\
\text{pSE} \\
\text{No Proph} \\
\text{HIV} \\
\text{No HIV} \\
\hline
\text{No Side Effects} \\
\text{pSE} \\
\text{No Proph} \\
\text{HIV} \\
\text{No HIV} \\
\end{array}
\]

Relative Risk, HIV (reduce)

- Hypothetical experimental data (virtual sample size)

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>No Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>.6 (a)</td>
<td>72 (b)</td>
</tr>
<tr>
<td>No HIV</td>
<td>24,999.3 (c)</td>
<td>22,857 (d)</td>
</tr>
<tr>
<td>Total</td>
<td>24,999.9 (a+c)</td>
<td>22,929 (b+d)</td>
</tr>
</tbody>
</table>

- 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)
- \( \text{se}[\ln(RR)] = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{a+c} + \frac{1}{b+d}} \)
- RR distributed log normal (2 parameters)
  - \( \mu \) (ln RR):
    - ln(.6)+ln(22929)-ln(72)+ln(24999.9) = -4.8740
  - \( \sigma \) (sigma (see ln(RR))):
    - ((1/.6)+(1/72)-(1/24999.9)+(1/22929))^*.5 = 1.2963302
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 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

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

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
    - $\mu = -4.8740; \sigma = 1.2963302$
    - sampling rate (resample per EV)
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 reduce in Variable Properties window
Add Relative Risk (RR) to the Tree

Log Odds Ratio

- Log(OR) and SE Log(OR)
  \[ \ln(\text{OR}) = \ln(a) + \ln(d) - \ln(b) - \ln(c) \]
  \[ \text{se}[\ln(\text{OR})] = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d} \]
- OR distributed log normal (2 parameters)
  \[ \mu (\ln \text{OR}): \ln(0.6)+\ln(22857)-\ln(72)+\ln(24999.3) = -4.8771 \]
  \[ \sigma \text{ (se ln(OR))}: \approx 1.2964 \]
- NOTE: As with RR, mean and median differ

Using Odds Ratios in Trees

- Probability after intervention with a given OR
  \[ p_{\text{int}} = \frac{\text{OR}_{\text{int}} \times p_{\text{no}}}{(\text{OR}_{\text{int}} \times p_{\text{no}}) + (1 - p_{\text{no}})} \]
- Equivalent formula using built-in Treeage functions:
  - ProbToOdds
  - OddsToProb
  - e.g., \[ p_{\text{int}} = \text{OddsToProb}(\text{OR}_{\text{int}} \times \text{ProbToOdds}(p_{\text{no}})) \]
Define Payoffs

<table>
<thead>
<tr>
<th>Cost</th>
<th>Disutility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>HIV</td>
<td>326,500</td>
</tr>
<tr>
<td>Drug</td>
<td>1000</td>
</tr>
<tr>
<td>SE</td>
<td>100</td>
</tr>
</tbody>
</table>

* N = 14 respondents

Step 3. Define Payoff Distributions

- 3 normal distributions for cost (simplification)
- 3 normal distributions for utilities
- 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

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)
Add cHIV to Tree

Assign cdHIV to cHIV
Gamma Distributions for Cost

- Alternatively, we can use gamma distributions to incorporate right-tails that are common to cost distributions
- Treeage gamma distributions:
  - $\alpha = \text{mean}^2 / \text{se}^2$
  - $\lambda = \text{mean} / \text{se}^2$
- e.g.,
  - cdHIV = 326,500; 32,650: gamma = 100; .00030628
  - cdDrug = 1000; 100: gamma = 100; .1
  - cdSE = 100; 15: gamma = 44.4444, .4444
Log Normal Distributions for Cost

- We can also use log normal distributions to incorporate right-tails that are common to cost distributions
- Treeage lognormal distributions:
  - $\mu = \log \left( \frac{\text{mean}^2}{\text{mean}^2 + \text{se}^2} \right)^{0.5}$
  - $\sigma = \left( \log \left( 1 + \frac{\text{se}^2}{\text{mean}^2} \right) \right)^{0.5}$
- e.g.,
  - cdHIV = 326,500; 32,650: lgn = 12.69006; .11068615
  - cdDrug = 1000; 100: lgn = 6.9027801; .09975135
  - cdSE = 100; 15: lgn = 4.5940449; .14916638

### SEs for Normal and Gamma Distributions

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Gamma</th>
<th>Log Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prophylaxis</td>
<td>257.6</td>
<td>256.2</td>
<td>262.6</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>107.4</td>
<td>107.2</td>
<td>107.6</td>
</tr>
</tbody>
</table>

- Means of 5 PSAs for each set of distributions, 10,000 draws per PSA, seeds of 1000, 2000, 3000, 4000, and 5000
Add Utile Payoffs

- 

Gamma Distributions for QALY Scores
- Gamma and log normal distributions are for right-skewed data
- QALY scores usually left skewed rather than right skewed
- 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).
- Define means and SD and use formulas for gamma distribution
- In model, we subtract distribution from original highest possible score (e.g., 1)

Roll Back (Numbers)
Roll Back Tree w/Distributions (Point Estimates) *

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

Sampling

- More like multiple "roll backs" than like pachinko machine
- For each roll back we draw from each distribution to obtain a point estimate for each of probability and outcome parameters

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
Two-Dimensional (Sampling+trials)

- Combines sampling and trials
  - For each sample, draw point estimates for probabilities and outcomes as in sampling; within each sample, 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"

"Sampling" Monte Carlo C-E Statistics

<table>
<thead>
<tr>
<th></th>
<th>No Prophylaxis</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost</td>
<td>Utilities</td>
</tr>
<tr>
<td>Mean</td>
<td>1048</td>
<td>99.70</td>
</tr>
<tr>
<td>SD</td>
<td>258</td>
<td>0.0677</td>
</tr>
<tr>
<td>Min</td>
<td>317</td>
<td>99.42</td>
</tr>
<tr>
<td>2.5%</td>
<td>610</td>
<td>99.55</td>
</tr>
<tr>
<td>10%</td>
<td>732</td>
<td>99.61</td>
</tr>
<tr>
<td>Median</td>
<td>1024</td>
<td>99.70</td>
</tr>
<tr>
<td>90%</td>
<td>1391</td>
<td>99.78</td>
</tr>
<tr>
<td>97.5%</td>
<td>1614</td>
<td>99.82</td>
</tr>
<tr>
<td>Max</td>
<td>2227</td>
<td>99.90</td>
</tr>
</tbody>
</table>

* Reported S.D. is actually the S.E.

Results

- Charts
  - Output distributions
    - Incremental cost
    - Incremental effect
  - CE Analysis
  - CE Acceptability
  - Scatter plots
### Incremental Cost

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>ATTRIBUTE</th>
<th>STATISTIC</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Cost</td>
<td>Mean</td>
<td>19.85</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Cost</td>
<td>SD (SE)</td>
<td>276</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Cost</td>
<td>Min</td>
<td>-1159</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Cost</td>
<td>2.5%</td>
<td>-581</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Cost</td>
<td>Median</td>
<td>41</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Cost</td>
<td>97.5%</td>
<td>504</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Cost</td>
<td>Max</td>
<td>982</td>
</tr>
</tbody>
</table>

### Incremental Effect

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>ATTRIBUTE</th>
<th>STATISTIC</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Eff</td>
<td>Mean</td>
<td>-2.26</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Eff</td>
<td>SD (SE)</td>
<td>1.11</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Eff</td>
<td>Min</td>
<td>-6.13</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Eff</td>
<td>2.5%</td>
<td>-4.39</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Eff</td>
<td>Median</td>
<td>-2.29</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Eff</td>
<td>97.5%</td>
<td>-0.07</td>
</tr>
<tr>
<td>Strategy 2 v. 1</td>
<td>Incr Eff</td>
<td>Max</td>
<td>1.75</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Increments</th>
<th>Cost</th>
<th>Utilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>19.85</td>
<td>-2.26</td>
</tr>
<tr>
<td>SD (SE)</td>
<td>276</td>
<td>1.11</td>
</tr>
<tr>
<td>Minimum</td>
<td>-1159</td>
<td>-6.13</td>
</tr>
<tr>
<td>2.5%</td>
<td>-581</td>
<td>-4.39</td>
</tr>
<tr>
<td>Median</td>
<td>41</td>
<td>-2.29</td>
</tr>
<tr>
<td>97.5%</td>
<td>504</td>
<td>-0.07</td>
</tr>
<tr>
<td>Maximum</td>
<td>982</td>
<td>1.75</td>
</tr>
</tbody>
</table>
Step 5. Parametric Tests of Significance

<table>
<thead>
<tr>
<th>Increments</th>
<th>Cost</th>
<th>Utilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>19.85</td>
<td>-2.26</td>
</tr>
<tr>
<td>SD (SE)</td>
<td>276</td>
<td>1.11</td>
</tr>
<tr>
<td>T statistic</td>
<td>0.0719</td>
<td>2.04</td>
</tr>
<tr>
<td>P-value</td>
<td>0.94</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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

Cost-Effectiveness Report (Numbers)

- Cost-effectiveness analysis text report

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incr Cost</th>
<th>Eff Incr Eff</th>
<th>Incr CE</th>
<th>Dominance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Proph</td>
<td>980</td>
<td>--</td>
<td>99.7183</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proph</td>
<td>1058</td>
<td>78</td>
<td>97.4477</td>
<td>-2.2706</td>
<td>-35</td>
</tr>
</tbody>
</table>

Monte Carlo Sampling Cost-Effectiveness Report

- Charts CE Analysis CE graph text report

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incr Cost</th>
<th>Eff Incr Eff</th>
<th>Incr CE</th>
<th>Dominance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Proph</td>
<td>1047.61</td>
<td>--</td>
<td>99.6987</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Proph</td>
<td>1067.46</td>
<td>19.84</td>
<td>97.4228</td>
<td>-2.2560</td>
<td>-9</td>
</tr>
</tbody>
</table>
Good and Bad Value

Monte Carlo Sampling Strategy Selection (Normal)
- Charts: CE Acceptability/Strategy Selection (Net Benefit)
- "Copy to clipboard" option

Monte Carlo Sampling Strategy Selection (Gamma)
- Charts: CE Acceptability/Strategy Selection (Net Benefit)
- "Copy to clipboard" option

Appropriate W for utilities?
Monte Carlo Sampling Strategy Selection (Log normal)

- Charts/CE Acceptability/Strategy Selection (Net Benefit) (*Copy to clipboard* option)

Monte Carlo Strategy Selection
(WTP: 50000.0)

Hivse.2015lognorm.trex; N = 5000; seed = 1

Monte Carlo Sampling Acceptability Curve

- Charts/CE Acceptability/Acceptability Curve (*Copy to clipboard* option)

CE Acceptability Curve

Hivse.2015.trex; N = 5000; seed = 1

Cost-Effectiveness Plane

- Difference in Cost (-)
- Difference in Effect (+)

Hivse.2015.trex; N = 5000; seed = 1
Monte Carlo CE Scatter Plot

- 'charts\Scatter Plots\ICE Scatter + Ellipses...\Proph v. No Proph

ICE Report

- 'charts\ICE Scatter + Ellipses...\Proph v. No Proph\ICE Report *

<table>
<thead>
<tr>
<th>QUAD-</th>
<th>INCR</th>
<th>INCR</th>
<th>COST</th>
<th>FREQ</th>
<th>PORTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANT</td>
<td>EFF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>IV</td>
<td>IE&gt;0</td>
<td>IC&lt;0</td>
<td>Superior</td>
<td>46</td>
</tr>
<tr>
<td>C2</td>
<td>I</td>
<td>IE&gt;0</td>
<td>IC&gt;0</td>
<td>ICER&lt;50k</td>
<td>61</td>
</tr>
<tr>
<td>C3</td>
<td>III</td>
<td>IE&lt;0</td>
<td>IC&lt;0</td>
<td>ICER&gt;50k</td>
<td>1</td>
</tr>
<tr>
<td>C4</td>
<td>I</td>
<td>IE&gt;0</td>
<td>IC&gt;0</td>
<td>ICER&gt;50k</td>
<td>0</td>
</tr>
<tr>
<td>C5</td>
<td>III</td>
<td>IE&lt;0</td>
<td>IC&lt;0</td>
<td>ICER&lt;50k</td>
<td>2168</td>
</tr>
<tr>
<td>C6</td>
<td>II</td>
<td>IE&lt;0</td>
<td>IC&gt;0</td>
<td>Inferior</td>
<td>2724</td>
</tr>
<tr>
<td>Indiff</td>
<td>origin</td>
<td>IE=0</td>
<td>IC=0</td>
<td>0/0</td>
<td>0</td>
</tr>
</tbody>
</table>

TreeAge Acceptability Quadrants

- (+) Difference in Costs (+)
- (-) Difference in Effects (+)
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 $915

What are the Major Sources Of Uncertainty

• The goal of quantifying uncertainty is to provide the audience with a measure of confidence about the results
• The 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 the SEs include:
  – Excessively large correlations that shrink the SEs
  – Failure to address potential bias?
  – Failure to address modeling uncertainty

Excessively Large Correlations

• Results of the trees (e.g., costs and effects) generally will show correlations, but unless we explicitly model the correlations -- which generally isn’t done -- the observed correlations may not be of the right magnitudes
  – We don’t see it in this example, but in some instances, the SE of the difference is much smaller than $(SE_0^2 + SE_1^2)^{1/2}$
  – If we observe this shrinkage, should probably use separate draws for each arm of the tree
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 the error in the problem under consideration
- Accounting for sampling uncertainty doesn’t address whether we are using a biased estimator
- Not clear that the measure of sampling uncertainty from another population/clinical problem will be appropriate for the current population/clinical problem

Major Sources of Uncertainty (cont.)

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