Decision Modeling

David L. Veenstra, PharmD, PhD
University of Washington
Seattle, WA

Bio

- Professor in the Pharmaceutical Outcomes Research and Policy Program in the Department of Pharmacy
- Member of the Institute for Public Health Genetics
- Primary research interests are the clinical, economic, and policy implications of genomics

Today’s Lecture Outline

I. Errors in decision making
II. Framing a study
III. How to perform a decision analysis
IV. ‘In-class’ exercise
V. Sensitivity analysis, model validation
VI. Software
I. Errors in Decision Making

Judgment under Uncertainty: Heuristics and Biases

- Uncertainty: “I think that...”
- Sometimes expressed as probabilities
- How do people quantify uncertainty?
  - They rely on a limited number of heuristic principles
    1. Representativeness
    2. Availability
    3. Adjustments and Anchoring
  - Can be useful, but can lead to errors

Heuristics: Representativeness

- Is A related to B? People evaluate how representative B is of A
- Example: “Steve is very shy and withdrawn, invariably helpful, but with little interest in people, or in the world of reality. A meek and tidy soul, he has a need for order and structure, and a passion for detail”
- What is his most likely profession?
  - Farmer, salesman, airline pilot, librarian, or physician

Tversky and Kahneman, Science 1974 185:1124
Heuristics: Representativeness

- Error: **Insensitivity to prior probabilities**
- There are many more farmers than librarians. Does this revise your estimate?
- Experiments have shown that people utilize prior probabilities when given no other information, but will ignore this information if they are able to use representativeness.

Heuristics: Availability

- People assess frequency of an event based on ability to recall such events
- Error I: Biases due to retrievability (celebrity names)
- Error II: Effectiveness of a search set (letter “r” in words)
- Error III: Biases of imaginability
- Error IV: Illusory correlation (causation)

Heuristics: Adjustment and anchoring

- “Starting point bias”
- Conjunctive event: probability of a specific sequence of events (probability of success/failure)
- Usually overestimated when each event fairly likely -> project planning too optimistic (drug development)
Heuristics: Adjustment and anchoring

- Disjunctive event: probability of one specific event in a sequence of events (evaluation of risk)
- Usually underestimated when each event fairly unlikely -> underestimate risk of failure of a complex system (e.g. nuclear reactor, healthcare)

Heuristics: Adjustment and anchoring

- Subjective probability distributions usually too narrow, i.e. uncertainty is underestimated because people tend to “anchor” toward their central estimate

Framing decisions

- A disease outbreak is expected to kill 600 people in the U.S. You need to choose an intervention:
- Program A: 200 people will be saved
- Program B: There is a 1/3 probability that 600 people will be saved, and a 2/3 probability that no people will be saved
- Which do you favor?

Framing decisions

- A disease outbreak is expected to kill 600 people in the U.S. You need to choose an intervention:
- Program C: 400 people will die
- Program D: There is a 1/3 probability that no one will die, and a 2/3 probability that 600 people will die
- Which do you favor?
- Over 70% of students chose A, then D

Prospect theory

- Response to losses is greater than response to gains
- Low probabilities are over-weighted
- Moderate and high probabilities are underweighted

In summary:

- People evaluate uncertainty
  - based on similarities
  - ability to recall examples
  - with starting-point bias and adjustments
- Thus, utilizing decision analysis to make decisions under uncertainty explicit can help to avoid potential errors or misconceptions
II. Framing a Study

1) Objectives of analysis

• Inform policy makers about the value of a health care program
  – what are the incremental costs?
  – what are the incremental benefits - both clinical and humanistic?
  – what are to opportunity costs? e.g., what are the alternatives?
  – is the program worth the additional cost?

Objectives of analysis

• Needs of policy makers
  – clearly defined question
  – relevant intervention, population
  – costs only
  – benefits only
  – short-term
  – transparent assumptions
  – implications of assumptions
• May conflict with your goals
2) Audience

- Specific audience
  - guidelines - e.g., PBAC (Austr.), CCOHTA (Can.), NICE (UK), AMCP Format (managed care), PHS
- Clinical audience
  - influence opinion (e.g., KOL’s, national guidelines)
- Secondary audience
  - patients, press, individual providers

3) Types of analyses

- Economic evaluation: which one and why?
  - cost-minimization
  - cost-consequences
  - cost-effectiveness
  - cost-utility
  - cost-benefit
  - budget impact
  - financial incentives

4) Perspective

- Societal perspective is “recommended”
  - not a “governmental” perspective
  - “should” include *all* costs
  - in practice, often does not
- Health care institution
- Third-party payer
- Patient and family
- Multiple perspectives
5) Define the intervention

• Frequency or intensity
• Patient population
  – age, sex, disease severity, comorbidities
• Applicability for policy makers
• Delivery of program
  – e.g., NP’s vs. Physicians
  – inpatient vs. outpatient

6) Target population

• Population should reflect audience’s needs
• Sub-group analyses
  – statistically significant differences?
  – difficulty obtaining clinical data (loss of precision)
• Sub-groups should be feasible
  – Baseline risk key driver in CEA
  – Note limitations, assess implications

Example: Hypercholesteremia

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Cost per year of life saved</th>
<th>Low-risk patient</th>
<th>All patients</th>
<th>High-risk patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;300</td>
<td></td>
<td>$1,500,000</td>
<td>$195,000</td>
<td></td>
</tr>
<tr>
<td>Women 35-44</td>
<td></td>
<td>$58,000</td>
<td></td>
<td>$15,000</td>
</tr>
<tr>
<td>Men 55-64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;250</td>
<td></td>
<td>$4,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women 35-44</td>
<td></td>
<td>$1,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men 55-64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Goldman et al, JAMA 1991;265:1145
7) Comparison program

- One of the most important aspects of an economic evaluation
- Include “do-nothing” option?
- Common practice or existing guidelines?
- May be a variety of comparators
  - select each one
  - use as mixture
- But...supporting data?

Comparator cont’d

- Use next less-intensive program as comparator
  - e.g., annual BrCA screening vs. biannual screening
- Include intensities that are feasible
  - also can inform future studies
- Sequential therapy?
  - 1st line, 2nd line, salvage tx.

8) Boundaries

- Individuals included
- How far do “spillover” effects go?
  - E.g., smoking cessation
- Examples
  - childhood illness affects parents
  - infectious diseases can affect many
  - debilitating diseases affect families
- Magnitude of effect should dictate inclusion/exclusion – as well as effort required
Boundaries

- Health outcomes
  - QoL domains: physical, mental, emotional
- Non-health
  - costs of providing care for disabled
  - income effects

9) Time Horizon

- Need to capture the major health and economic outcomes, both intended and unintended
- Lifetime analyses common
- Discounting

10) Conceptual model

- What is the decision being faced?
- What are the potential alternative actions?
- What are the (clinical) events that follow the decision?
- ...and what is your hypothesis?
### III. Decision Analysis

#### What is Decision Analysis?

- Decisions have to be made
- How will they be made?
- Decision analysis is a **systematic**, **quantitative**, and **explicit** approach for assessing the relative value of different decision options

#### Why use Decision Analysis?

- Making real-world decisions often involves assessing the probability and value of multiple outcomes
- It is difficult to evaluate complex decisions
- Decision analysis allows for the incorporation of data from **multiple sources**, makes assumptions explicit, and quantifies the decision parameters
- Highlights data strengths and deficiencies
Example

Are Antiseptic-impregnated Central Venous Catheters Cost-effective?


Catheter-related bloodstream infection (CR-BSI)

- 3 million central lines used per year in U.S.
- 3-7% of central lines lead to CR-BSI
- Approx. 150,000 cases per year in U.S.
- Increased mortality
- Increased hospitalization and costs
Antiseptic-impregnated catheters

- Chlorhexidine
  - broad spectrum antiseptic used for disinfection, irrigation
- Silver sulfadiazine
  - bactericidal and fungicidal action, used for prolonged periods in burn treatment

Are antiseptic catheters effective?

- Meta-analysis indicated an approximately 50% reduction in the risk of CR-BSI

Are antiseptic catheters cost-effective?

- Additional cost of $20-$25
- Risk of hypersensitivity reaction
- Reduction in healthcare costs?
- Reduction in patient mortality?
Patient cohort

- Reflective of those enrolled in RCTs
- Hospitalized patients at high-risk for CR-BSI (e.g. ICU, TPN patients)
- Catheters:
  - central lines
  - short-term
  - multi-lumen

Clinical probabilities: Infection

- Standard catheters: pooled from trials
  - colonization: 23.6%
  - CR-BSI: 5.2%
- Antiseptic catheters: pooled risk ratio
  - colonization: 0.57
  - CR-BSI: 0.58
Clinical probabilities: Mortality

- Pittet et al: case-control study (N=86) in ICU
  - 25% attributable mortality for CR-BSI
- Other studies:
  - 28% in critically ill patients
  - 10-25% hospital-wide
- Our estimate:
  - 15% attributable mortality due to CR-BSI*

*newer data suggest closer to 5%

Clinical probabilities: Adverse events

- No reports of adverse events in U.S.
- 13 cases of hypersensitivity in Japan
- Used incidence in Japan for base-case analysis (~1:10,000)

Economic parameters: CR-BSI

- Pittet: $33,268 attributable cost
  - 8 ICU days, 6 hospital days
- UW per diem room costs
  - $1,152 ICU, $375 hospital
- Estimated cost: $11,466
Summary of key data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base-case</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR-BSI</td>
<td>5.2%</td>
<td>3.9-6.5%</td>
</tr>
<tr>
<td>RR for CR-BSI</td>
<td>0.58</td>
<td>0.40-0.85</td>
</tr>
<tr>
<td>Cost of CR-BSI</td>
<td>$11,466</td>
<td>$5,733-22,392</td>
</tr>
<tr>
<td>Cost of catheter</td>
<td>$25</td>
<td>$20-30</td>
</tr>
<tr>
<td>Mortality</td>
<td>15%</td>
<td>5-25%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1:10,000</td>
<td>1:20,000-1:5,000</td>
</tr>
</tbody>
</table>

Results: Base-case analysis

<table>
<thead>
<tr>
<th></th>
<th>Costs</th>
<th>CR-BSI</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiseptic Catheter</td>
<td>$383</td>
<td>3.0%</td>
<td>0.45%</td>
</tr>
<tr>
<td>Standard Catheter</td>
<td>$616</td>
<td>5.2%</td>
<td>0.78%</td>
</tr>
<tr>
<td>Difference</td>
<td>-$233</td>
<td>-2.2%</td>
<td>-0.33%</td>
</tr>
</tbody>
</table>

Summary

- Antiseptic-impregnated catheters likely save lives and money under a wide variety of assumptions.
- For approximately every 300 catheters used, $70,000 will be saved, 7 cases of CR-BSI avoided, and 1 death prevented.
Steps in Conducting a Decision Analysis

Step 1: Identify and bound the problem
• What is the decision problem; what is the research question?
• What are the potential alternative actions?
• What are the events that follow the decision?

Step 2: Structure the problem
• Draw a picture
• Use a decision tree
• A decision tree depicts graphically the components of the decision problems and relates actions to consequences
Remember - building a model

- Is a dynamic process
- Is driven (unfortunately) as much by data availability/feasibility as natural disease progression
- Investigate different models

Decision tree conventions

- Build left to right
- Nodes
  - decision nodes (squares)
  - chance nodes (circles)
- Event placed above “branch”
- Probability of event placed below “branch”

Decision tree

Choose drug A or B

Drug A

Event
Live

Outcome
1

Die
0.25

0

Drug B

Live
0.75

0.50

Die
0.50

0

Decision node: decision-maker has control of this event only

Probability

Terminal node
Each event at a node must be mutually exclusive.

Thus, the sum of the event probabilities at a node must be 1.0.

Probabilities

Use conditional probabilities for “downstream” nodes:
- \( p(A) = 0.10 \) prob. you’re asleep
- \( p(B) = 0.25 \) prob. you understand DA
- \( p(B|A) = \) prob. you understand DA given that you are asleep = 1.0? 0.0?
Example

- 25% of patients started on a drug experience an adverse drug reaction
- 10% of patients discontinue drug

A Few Rules

a) Tree should be ‘fair and balanced’

What’s missing?

Drug A

- Treat or don’t treat
  - Live 0.75
  - Die 0.25

- No drug
  - Live 0.50
  - Die 0.50

The “Drug A” branch had no risk

b) Prefer only 2 branches per node

Why might this structure be a problem?

Solution

Be sure to use conditional probabilities

\[ p_{\text{Blind|Alive}} = \frac{p_{\text{Blindness}}}{1 - p_{\text{Die}}} \]

\[ p_{\text{Die}} = 0.05 \]

\[ p_{\text{Blind}} = 0.80 \]

\[ p_{\text{Alive}} = 0.15 \]

\[ \text{Sum} = 1.00 \]
c) No embedded decision nodes

Test+/Treat
Test-/No Treat
Treat all
No test
Treat none

Use diagnostic test? If not, treat?

Present all options at first node

Treat all
Test+/Treat
Test-/Don't treat
Treat none

Test

d) Link branches

- Linkage is the explicit relationship among probabilities or outcomes that ought to be related
  - e.g., baseline risk of patients in each arm of tree
- Linkage is achieved by sharing common variables (e.g. prevalence, efficacy (relative risk)) across tree
e) Tree should have symmetry

- Use same subtree structure throughout model when possible
  - (cut and paste!)
How complex should a model be?

- Model should be “disease based”
- Include key factors that impact outcomes
- But an unnecessarily complex model may be an ineffective decision tool (or vice-versa)
- Model structure is often data driven
- Model building is an iterative process
- Complexity/real-world model vs. evidence is likely hardest issue you will face

Step 3: Gathering data

- Conduct systematic search where appropriate
- Can use RCT’s, meta-analysis, expert opinion, etc.
- Use best estimate for “base-case” analysis
- Use 95% CI’s or ranges for sensitivity analysis
Step 4: Analyzing the tree

- Calculate expected value of each strategy
- Also referred to as “rolling back” or taking the average of the tree

1. Start at terminal node and multiply probabilities as you trace tree to origin to get probability of outcome
2. Sum weighted outcomes for each strategy

Analyzing tree

```
<table>
<thead>
<tr>
<th>Drug A</th>
<th>0.375</th>
<th>0.125</th>
<th>0.50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat</td>
<td>Alive</td>
<td>0.75</td>
<td>0.25</td>
</tr>
<tr>
<td>No side effect</td>
<td>Alive</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>No drug</td>
<td>Alive</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Die</td>
<td>0.25</td>
<td>0.75</td>
</tr>
</tbody>
</table>
```

IV. Exercise
Measles vaccination

- In the context of an epidemic of measles in an inner-city population, experts estimate that 20 out of every 100 children age 8-15 will come in contact with an infectious case of measles each year.
- Literature review reveals that the probability of getting measles if exposed to an infectious case is 0.33 in a child who has had only one measles vaccination and 0.05 in a child who is re-vaccinated.
- The probability of getting measles (and of dying of measles) in children not exposed is 0.
- During the current epidemic, the probability of dying from measles if a child gets measles is 23 per 10,000 cases, or 0.0023.

‘In-class’ exercise

- Construct a decision tree comparing the outcomes of the re-vaccinate and don’t re-vaccinate strategies
- Assign probabilities to nodes
- Calculate expected value of each strategy

Remember

- Start with the decision
- Which step in the clinical event pathway is first?
- Symmetry between ‘arms’ as feasible
V. Sensitivity analysis:
Model validation and
Uncertainty assessment

What is sensitivity analysis?

- Group therapy for decision analysts
Simple sensitivity analysis

- One-way
  - One parameter in the model is varied to examine the effect on the results

One-way sensitivity analysis

- Vary parameters
  - probabilities
  - costs
  - outcomes (utilities, LE)
- and evaluate impact on
  - costs
  - effects
  - cost-effectiveness
  - **incremental cost-effectiveness**

1-way sensitivity analysis

![Graph showing sensitivity analysis on Cost of Bloodstream infection (BSI)]

- Use Trained catheter
- Use Standard catheter
- Threshold Values:
  - Cost of BSI $= 690.9$
  - EV $= 61.9$
Sensitivity Analyses: What to do

- Evaluate every parameter in the model
- Use plausible ranges
- Assess impact on differences in clinical outcome(s) first, e.g., events, LYS, QALYs
- Then assess impact on cost differences
- Finally, can evaluate impact on incremental cost effectiveness (ICER)

a) Model Validation

- Face validity
  - does the model make sense clinically?
  - do the results make sense clinically and economically?
- Technical accuracy
  - quality control
  - model testing
    - does model perform well with extreme values?
    - does the model produce expected results for simple cases?

Model validation: Step 1

- Perform 1-way sensitivity analyses on all parameters in the model
  - Results should be logical
- To de-bug tree;
  - Vary probabilities from 0 to 1; model should not 'break'
  - Set all costs/outcomes equal; strategies should have same expected value
Model validation: Step 2

- Predictive validity
  - does model reproduce real-world data?
  - does model reproduce results from other models and analyses?
  - did model predict clinical endpoints based on surrogate outcomes?

All models have bugs

- Find the big ones!
- Perform validation steps above before showing anyone your ‘results’

b) Evaluating Uncertainty

- As important as a p-value or 95% CI in frequentist statistics
What are sources of uncertainty?

• Model parameters
  – vary parameters (sensitivity analysis)
• Model structure
  – vary structure (scenario analysis)
• Modeling process
  – vary analyst!

How is uncertainty evaluated?

• Simple sensitivity analysis
• Threshold analysis
• Extreme scenario analysis
• Probabilistic sensitivity analysis
  (Monte Carlo simulation)

Quality of studies in literature

• 1995 Review by Briggs and Sculpher
  – articles published in 1992
  – 24% failed to consider uncertainty at all
  – 38% had inadequate sensitivity analyses
  – only 14% provided a good account of uncertainty

Briggs and Sculpher, Health Economics
1995;4:155
What is a plausible range for 1-way sens. analyses?
• Efficacy estimates:
  – 95% confidence interval from RCT
• Effectiveness estimates:
  – meta-analysis 95% CI
  – range of values reported in literature
  – data from observational studies
  – expert opinion

What is a plausible range?
• Prevalence/incidence estimates:
  – control group(s) in clinical trial(s)
  – observational data
  – effect modification?
  – generalizability?

What is a plausible range?
• Model parameters - Discount rate:
  – use 0%, 3%, 5% for U.S. study (for both costs and effects)
What is a plausible range?

- Costs:
  - use costs from different sources
    - Medicare reimbursement
    - Charges converted to costs
  - costs for medical events often skewed
    - but range should reflect uncertainty about population mean cost, not individual costs
  - cost of intervention should always be varied

But what about patient sub-groups?

- Can this be varied in a sensitivity analysis?
- No, not a parameter you are estimating
- Instead, run separate (scenario) analyses for 
  **subgroups**
  - where CE is expected (or does) differ
  - realistic to identify and treat subgroup in clinical practice
  - evidence is ‘reasonable’ for effectiveness in subgroup

Results: Use ‘Tornado’ diagram

- to determine which parameters have greatest impact on your results
- recognize impact is dependent on *your* choice of ranges for parameters
- further evaluate most important parameters in multi-way sensitivity analysis
Tornado diagram:
Outcome = Cost

Parameter
Cost of CR-BSI ($4,869-19,476)
RR for CR-BSI (0.398-0.851)
CR-BSI incidence (3.9%-6.5%)
Additional catheter cost ($20-30)

Parameter threshold
$687
0.970
0.4%
$221

Tornado diagram:
Outcome = Deaths

Parameter
Probability of death due to CR-BSI (5%-25%)
RR for CR-BSI (0.398-0.851)
CR-BSI incidence (3.9%-6.5%)
Probability of hypersensitivity (0.0056%-0.0222%)

Parameter threshold
0.2%
0.99
0.07%
4.2%

Software: TreeAge

- TreeAge (treeage.com)
  - Advantages
    - Easy to build, analyze, modify model
  - Disadvantages
    - 'Black box', others can't use
- Student version available (annual license)
  - 'Limited' version [TreeAge Pro Suite] (125 nodes, $45; full, $150)
Spreadsheet Software

- Spreadsheet (i.e., Excel)
  - Advantages
    - Not a 'Black box'
    - Non-experts can use
    - Quick to analyze
  - Disadvantages
    - Slower to build, more time consuming to modify model
Excel Add-ins

• Treeplan – within Excel
  – http://www.treeplan.com/academic.htm
  – Free trials, academic pricing
  – Build trees
  – Sensit
    • Conduct sensitivity analyses
    • Tornado diagrams

Software

• Excel Add-on for sensitivity analysis
  – Tornado diagrams (R. Myerson, Univ. Chicago)
    • http://home.uchicago.edu/~rmyerson/torndiag.xls
    • TORNDIAG.XLS instructions in workbook file
    • free

Software

• Excel examples
  – Briggs, Claxton, Sculpher textbook
  – http://www.herc.ox.ac.uk/pubs/handbooksoup/material_modelling
  – Although no simple decision models presented

The Laws of Model Building
(adapted from Akin’s Laws of Spacecraft Design, Professor David Akin, University of Maryland)

1. In nature, the base-case is almost always in the middle somewhere. Distrust assumptions that the base-case is at an extreme point. (Use common sense)
2. Not having all the information you need is never a satisfactory excuse for not starting the analysis. (Get going)
3. There is never a single right solution. There are always multiple wrong ones, though. (You’ll never know whether your model is ‘right’)
4. (Edison’s Law) “Better” is the enemy of “good”. (Keep it simple)
5. (Shea’s Law) The ability to improve a model occurs primarily with the data. This is also the prime location for screwing it up. (It’s about the data)
6. The odds are greatly against you being immensely smarter than everyone else in the field. If your model is giving you amazing results, you may have solved the healthcare crisis, but the chances are a lot better that you’ve screwed up. (Can you explain all the results?)
7. A bad model with a good presentation is doomed eventually. A good model with a bad presentation is doomed immediately. (Present good models well)

References & Resources

Thank you