Considering economics in assessing biomedical interventions: Cost-effectiveness analysis

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Big 6 Epi-Biostat Methods … plus 2 Choice Methods: Decision & Cost-Effectiveness Analysis

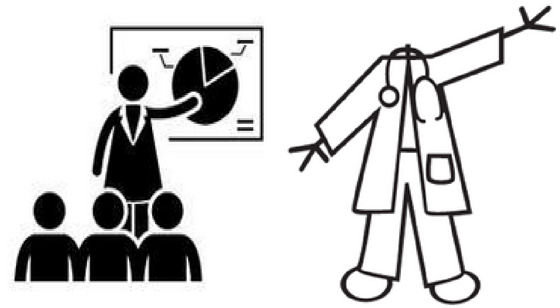
- **Description**
  - How frequent are risk factors/exposures/conditions/diseases?
- **Causation**
  - What are the causal relationships among environmental, behavioral, and biological factors within humans? Does X affect Y? Does intervening on X change Y?
- **Attribution**
  - What fraction of disease Y is eliminated if causal exposure X is eliminated or reduced?
- **Mediation**
  - Mechanisms of causation. How does X cause Y?
- **Interaction**
  - When and for whom does X cause / predict Y?
- **Prediction**
  - Do A, B, and C predict concurrent / future Y? (diagnosis or prognosis)
- **Decision Analysis**
  - What are the **consequences** (primary & secondary, short & long-term) of **alternate health-related actions** (tests or treatments)? Which action optimizes health outcomes?
- **Cost-Effectiveness Analysis**
  - What are the **projected improvements in health** with **increased spending** on health interventions (tests, treatments)? What is the **net added cost per unit of health gain**?

A More Relevant Definition of Epidemiology & Biostatistics

Why care?

Roles

Generate knowledge



Apply knowledge

Benefit from knowledge

Titles

Researcher; Scientist

Public health practitioner; Clinical practitioner (e.g., physicians)

Patient; Community resident

Tools

Biology
Chemistry
Physiology
Engineering
Pharmacology
Toxicology, etc.
.

Epidemiology

Biostatistics

C
E
A

Health promotion; Diagnostic tests; Behavioral, Surgical & Pharmaceutical interventions

Compliance with interventions; live everyday life

Opportunity Costs: Definition

- **Use of resources for one purpose precludes their use for another purpose.**

- **Concerned with real resource consumption.**

- **Resources usually quantified in dollars.**

The value of thinking in terms of opportunity costs

- **Counteracts the tendency to unthinkingly continue this year what worked last year.**

- **Stimulates creativity about the best use of resources given current needs and alternatives.**

The Reality -- Resource Allocation

- **The problem: Resources are always limited.**

- **The challenge: To allocate resources to achieve a maximum benefit.**

Alternative ways of making decisions

- Dogmatism. *All aneurysms should be surgically clipped.*
- Policy. *At UCSF we clip all aneurysms.*
- Experience. *I've referred a number of aneurysm patients for surgery and they have done well.*
- Whim. *Let's clip this one.*
- Nihilism. *It really doesn't matter.*
- Defer to experts. *Vascular neurosurgeons say clip*.
- Defer to patients. *Would you rather have surgery or live with your aneurysm untreated?*

OR

Decision Analysis (incl CEA)

The role of CEA

- **It doesn't decide the goals (value neutral)**

- **CEA helps to maximize reaching a goal with available resources (most efficient)**

CEA = Measuring trade-off between cost and effectiveness

Cost-Effectiveness Analysis: When to use it?

When selecting among 2+ courses of action with different effects and costs.

- ***HIV Prevention*:**
  - **Intervention vs. no intervention?**
  - **One intervention vs. another?**
  - **Universal vs. targeted interventions?**
  - **Group counseling vs. individual counseling?**

Trading off cost and effectiveness for an intervention vs. status quo

	Lower Cost	Higher Cost
Lower Effectiveness	A	B
Higher Effectiveness	C	D

CEA is a method for systematically quantifying the trade-off, *when there is a trade-off*

	Lower Cost	**Higher Cost**
Lower Effectiveness		**Dominated**
Higher Effectiveness	**Dominant**	

Structure of a CEA

- Inputs
- Outcomes
- Analytic Approach

Three broad inputs into CEA

- **Costs of intervention**
- **Health effects of disease & intervention**
- **Costs of health care**

Input: Intervention costs

Standard cost-accounting categories for input resources

- **Personnel** (aka staff) eg doctors, nurses, counselors, lab techs, drivers, guards, etc.
- **Supplies** (aka commodities, consumables) eg drugs
- **Services** (e.g., PR or cleaning)
- **Capital goods** (e.g., vehicle, lab machine)
- **Training** (esp specific to the program)
- **Physical space** (i.e., rent)

Input: Health effects

- **Consequences of the disease** portrayed
  (e.g., mortality and morbidity risks)

- **Intended effect of interventions**
  (e.g., reduced risk of mortality)

- **Side effects of interventions**
  (e.g., adverse events, incl long-term)

Input: Cost of health care

For the disease being modeled,
and due to treatment side effects

- Outpatient (visits)
- Hospitalizations (days)
- Diagnostics (e.g., lab, xray)
- Therapeutic procedures
- Pharmaceuticals

CEA Outcomes

- **Health:**
  - intermediate effects (eg physiological)
  - Clinical: morbidities, mortality

- **DALYs or QALYs:** Inclusive standard metric

- **Net costs**, i.e., intervention cost *adjusted for* offsetting savings or added induced costs

- Incremental CE ratio (ICER!)

QALYs & DALYs

- **QALY – Quality-Adjusted Life Year**
  - Measure of **health** – longevity and health status
  - More is better
  - Health status measured in “health state utility” (1 = perfect health, 0 = death)
  - Years of life adjusted for for imperfect health
  - Dominant metric in US and Europe CEAs

- **DALY – Disability-Adjusted Life Year**
  - Measure of **disease burden** – lost years of life and compromised health
  - Less is better.
  - Health status measured in “disability weight” (0 = perfect health, 1 = death)
  - Years of life lost (YLL) plus disability adjustment (DA) when alive.
  - Dominant metric in global disease policy and for CEAs in LMIC

- **Opposite & equal**
  - For any intervention, QALY gained = DALY averted. Really.
  - Health state utility = 1 minus disability weight, and vice-versa.
  - Theoretical difference but not in practice (as measured).

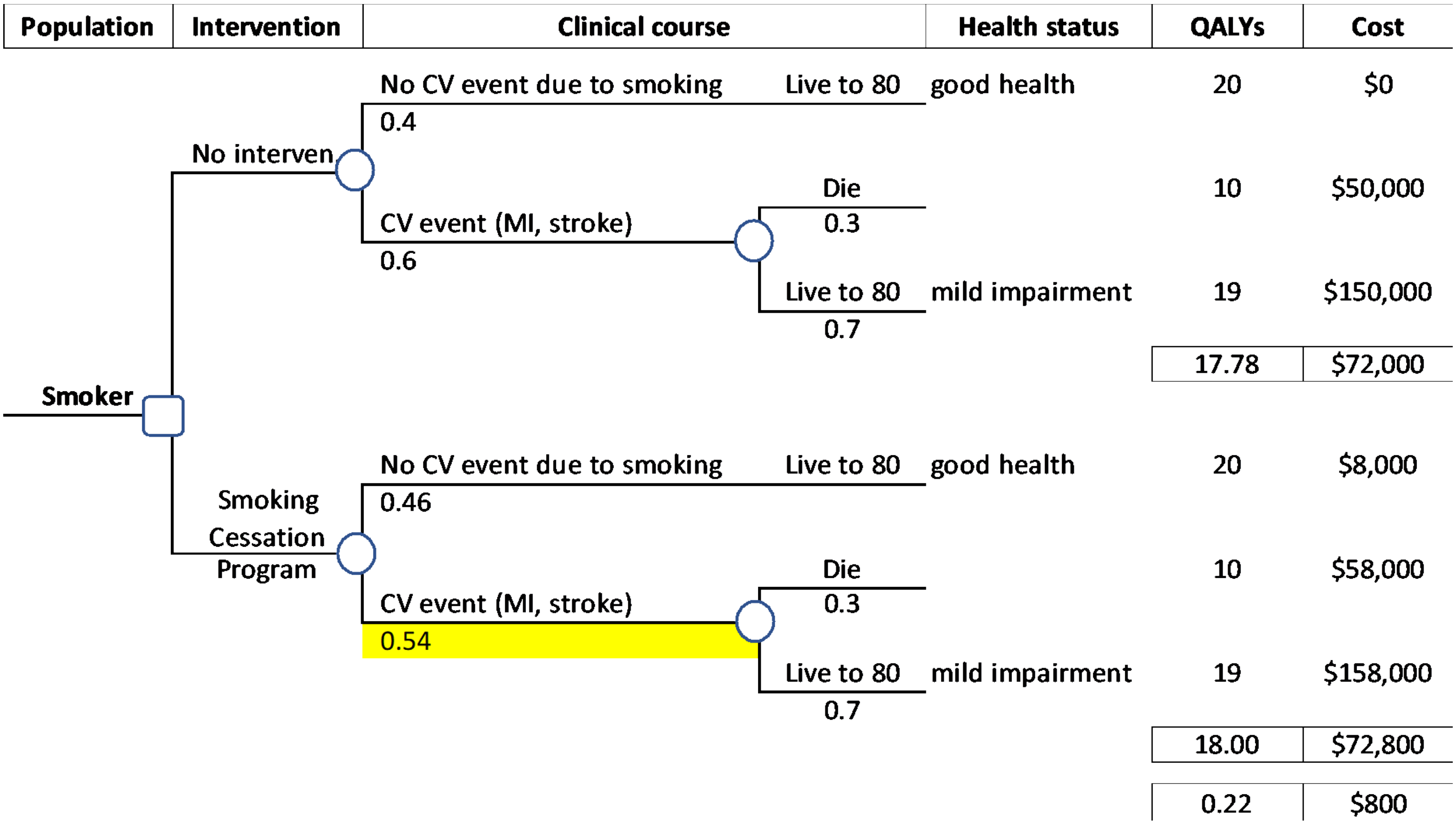
Using decision trees in CEA

- What is a decision tree?
- When should I use a decision tree?
- How to construct a decision tree
- How to analyze a decision tree
- Software options

What is a decision tree?

- A branching structure that leads from a **choice** (among competing courses of action) through a probability net of possible **consequences** (temporary and final) …
- … in which each path of consequences has an associated **probability** and set of **outcomes** of interest (e.g., cost and health status) such that …
- … each course of action can be assigned **expected values** for the outcomes (as the weighted mean of relevant paths) that can be compared and used to **guide decisions** among the actions.

A Very Simple Decision Tree



The CE Ratio (ICER)

Difference in costs between two courses of action

divided by

Difference in health outcomes

The ICER, deeper dive:

$$\frac{\text{Net cost with intervention} - \text{Net cost with no intervention}}{\text{QALYs with intervention} - \text{QALYs with no intervention}}$$

$$\frac{\Delta\ \textbf{Net Cost}}{\Delta\ \textbf{QALYs}}$$

$$\frac{\Delta \text{ Net Cost}}{\Delta \text{ QALYs}}$$

$$\frac{\$800}{0.22}$$

$$= \$3{,}604 \; / \; \text{QALY}$$

When should I use a decision tree?

- **Conceptualizing: Almost always.** Extremely useful to develop and portray the structure of a cost-effectiveness analysis … clarify thinking, tighten logic, avoid omissions of possible paths. Can be used in conjunction with other visual portrayals of model dynamics.

- **Operationalizing: Often.** Assures that conceptual approach is reflected in implementation. Often used in conjunction with other calculation tools. Balance of tree & other calculation structures is personal preference.

- **Presenting: Sometimes.** Some analyses done with trees are presented with trees, some not.

How to construct a decision tree

- **Population & context**
- **Decision node (square)** – the question under study, 2 or more action options – all plausible (judgment call). Later decisions brought to front.
- **Chance nodes (circles)** – in each node probabilities sum to 100%. Mutually exclusive & exhaustive. Dichotomous easiest to manipulate. Markov can be incorporated.
- **Terminal node utilities = outcomes** – health, costs (direct, time)
- **Expected values** for health and costs, for each action option as weighted mean of paths.
- **Iterative revision** – unlike RCTs, the approach can (and nearly always does) change with early results and better understanding. The trick is knowing when to stop refining, and balancing completeness with transparency.

How to analyze a decision tree

- **Comparisons across options** – compare expected values for costs and health outcomes … ordered (least to most expensive) & step-wise incremental … then incremental cost-effectiveness ratios (ICERs)

	Cost	Δ Cost	DALYs	Δ DALYs (averted)	ICER	
Option A	$1,000		10			
Option C	$1,500	$500	8	2.0	$250	
Option B	$1,700	$200	8.5	-0.5	Dominated	
Option D	$2,500	$800	7.5	1.0	$2,000	[vs C]

- **Sensitivity analyses** – 1-way, 2-way, scenarios, thresholds, multivariate (eg Monte Carl0).

Software

- **Excel** – familiar, generic, flexible (eg incorporate epidemic and cost models), has sensitivity analysis add-ons (Crystal Ball, @Risk). My favorite. Consider starting with template.

- **TreeAge** – newer, specialized, efficient for set CEA tasks, learning curve.

- **@Risk** – newer, specialized, efficient for set CEA tasks, powerful, complex, narrow market. Can use for SAs with Excel.

Why the "I" in ICER is important

- The "I" is "Incremental"
- When considering multiple plausible interventions, *must* examine incrementally.

Example:

	No Rx	**Drug A (generic)**	**Drug B (brand)**	**Drug C (biologic)**
Drug cost	$0	$1,000	$10,000	$75,000
Care cost	$10,000	$7,000	$5,000	$3,000
Net Cost	$10,000	$8,000	$15,000	$78,000
QALYs	10	12	12.5	13
Incremental				
△ Net cost	-	($2,000)	$7,000	$63,000
△ QALYs	-	2	0.5	0.5
ICER	Dominated	Dominant	**$14,000**	**$126,000**
Not Incremental				
△ Net cost	-	($2,000)	$5,000	$68,000
△ QALYs	-	2	2.5	3
CE Ratio	Dominated	Dominant	**$2,000**	**$22,667**

CEA examples

Example 1: New antivirals for HCV, U.S.

(Chahal et al JAMA IM 2015)

Treating all fibrosis stages vs stages F3/F4

adds 0.73 QALYs and $28 899

ICER of $39 475 per QALY gained.

Example 2: Adult Male Circumcision in S. Africa

(Kahn, Marseille, Auvert PLoS Medicine 2006)

$181 per HIV infection averted (unadjusted for HIV care)

Adjusted: $2.4 million ***saved*** for 1,000 MCs

Dominant! Cheaper + Better. No ICER needed

Cost and cost-effectiveness results for HCV antivirals by treatment initiation timing

Combined Sofosbuvir and Ledipasvir Treatment Strategy[a]	Base-Case Results: Costs, $: Total Treatment	Base-Case Results: Costs, $: Incremental	Base-Case Results: QALYs: Total	Base-Case Results: QALYs: Incremental Gain	Base-Case Results: ICER, $ per QALY Gained[b]
Treat all vs treat at stages F3 and F4					
Treat at stage F3 or stage F4[c]	60 906	NA	14.09	NA	NA
Treat all[d]	89 804	28 899	14.82	0.73	39 475
By fibrosis stage					
No treatment	46 107	NA	11.82	NA	NA
Treat at stage F4	57 616	11 509	12.85	1.02	11 252
Treat at stage F3	60 906	14 798	14.09	2.27	6522
Treat at stage F2	71 913	11 007	14.65	0.55	19 833
Treat at stage F1	83 594	11 682	14.79	0.14	81 165
Treat all	89 804	6210	14.82	0.03	187 065

Chahal HS, Marseille E, Tice JA, Pearson SD, Ollendorf DA, Fox R, Kahn JG. Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population. *JAMA Intern Med*, 2015.

Analytic Approach – a few issues

- **Time Frame** – Over how many years are you measuring costs and outcomes?
  - Trade off between accuracy and relevance
- **Empirical** data versus **modelled**
- **Economic perspective**
  - Medical system? Patient? Society?
  - Payer(s) eg insurers

Analytic Perspective, Cost-Effectiveness and Policy Implication

		SOCIETAL	
		Cost-effective	Not cost-effective
PAYER	Cost-effective	“No brainer” (Yes)	Realign incentives? (Should be “No”)
	Not cost-effective	Subsidy (Should be “Yes”)	“Non-starter” (No)

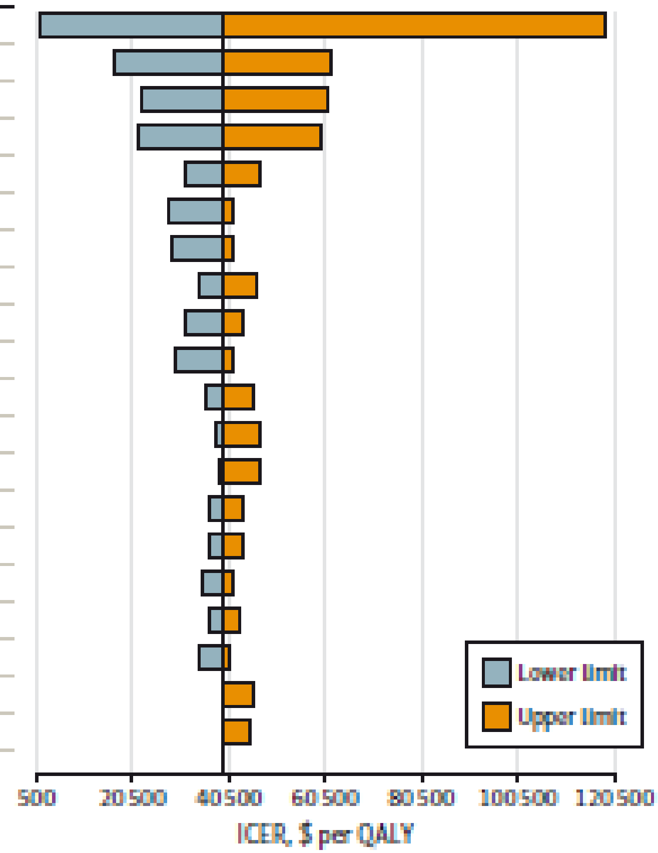
Uncertainties

- A "base case" analysis incorporates best estimates for input values.
- Use **<u>sensitivity analyses</u>** to explore how results change with uncertainty in input values.
  - 1-way – each input value alone (summarize in Tornado)
  - 2-way – eg drug price & efficacy
  - Scenarios – eg most or least favorable circumstances
  - Multi-variate (probabilistic) – all variables at once

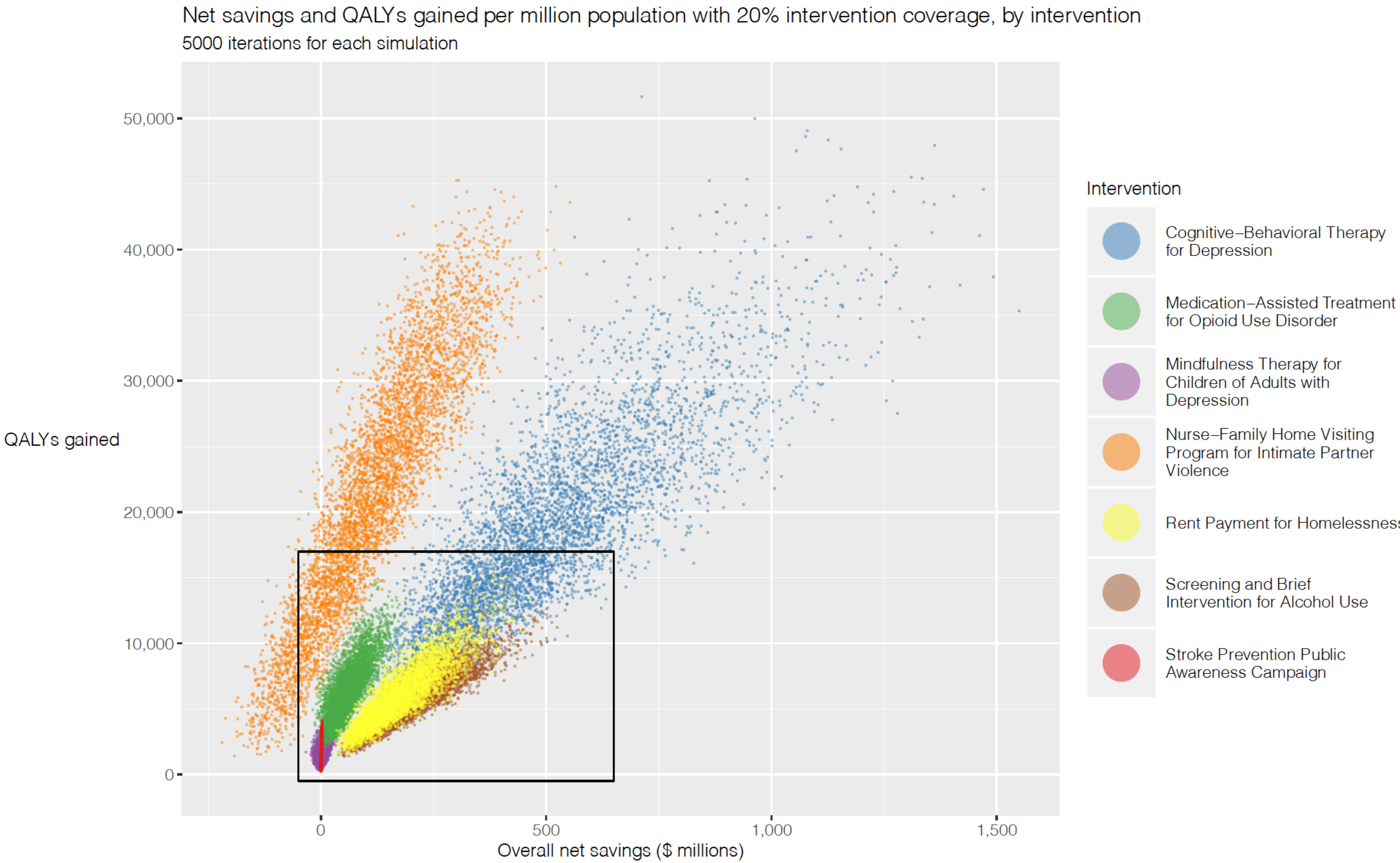
Sensitivity Analysis – an example
One-way, tornado

Figure 2. Sensitivity Analyses of Incremental Cost-effectiveness Ratios (ICERs) for Combined Sofosbuvir and Ledipasvir Treatment for All Stages of Fibrosis vs Stages F3 and F4

		ICER, $ per QALY	
Input	Base Case (Range)	Lower Limit	Upper Limit
Cohort age, y	60 (20-70)	999	118 881
Weekly cost of sofosbuvir-ledipasivir, $	7875 (3937.5-11 812.5)	17 096	61 854
Discount rate	0.03 (0.01-0.05)	22 077	61 112
Utility value in stage F2, no SVR	0.92 (0.72-1)	21 487	59 347
Mortality rate increase in stage F3, after SVR	1.4 (2.5-1)	31 498	46 607
Overall regression proportion	1 (0-1.2)	28 197	41 334
Annual cost of stage F1, no SVR, $	810 (405-3240)	28 905	41 236
Regression proportion from stage F3 to F2, with SVR	0.46 (0.23-0.69)	34 217	46 285
Utility in stage F1, no SVR	0.98 (0.92-1)	31 305	43 236
Annual cost of stage F2, no SVR, $	810 (3240-405)	29 304	41 170
Patients eligible for the 8-wk drug therapy, %	0.67 (0.9-0.3)	35 420	45 864
Annual cost of stage F1 after SVR, $	405 (202.5-1620)	38 180	47 243
Annual cost of stage F0 after SVR, $	405 (202.5-1620)	38 219	47 011
Regression proportion from stage F2 to F1, with SVR	0.58 (0.87-0.29)	36 102	43 519
Regression proportion from stage F3 to F1, with SVR	0.24 (0.12-0.36)	36 327	43 149
Utility in stage F0, no SVR	0.98 (0.92-1)	35 030	41 218
Annual probability of stage F2 to F3 transition (age ≥50)	0.089 (0.103-0.077)	36 557	42 565
Annual cost of stage F0, no SVR, $	810 (3240-405)	34 336	40 331
Utility in stage F1, after SVR	1 (1-0.98)	39 475	45 262
Utility in stage F0, after SVR	1 (1-0.98)	39 475	45 066



Sensitivity Analysis – an example
Multi-variate (stochastic)



Critiquing Published CEAs

Six “tires to kick” before buying:

- What is the **comparison** of options? Is it appropriate & complete?
- **Perspective:** Whose costs and benefits?
- **Analytic approach** explicit and reasonable?
- **Appropriate use of data** on health outcomes, intervention effects, costs? Any gaps or bias?
- Comparison **increments** appropriate?
- **Uncertainties**: Fully explored?