

# Defining Clinically Meaningful Effect for the Design and Interpretation of RCTs: A Health Care Economist's Perspective

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From Thought Leadership to Clinical Practice

# Cost-Effectiveness Analysis

## Primary Assumption:

- 'For any given level of resources available, society wishes to maximize the total aggregate health benefits conferred'\*

$$\text{ICER} = \frac{C_{ExpTrx} - C_{StdCare}}{E_{ExpTrx} - E_{StdCare}}$$

- Case detected
- Event avoided
- LYS
- QALYs

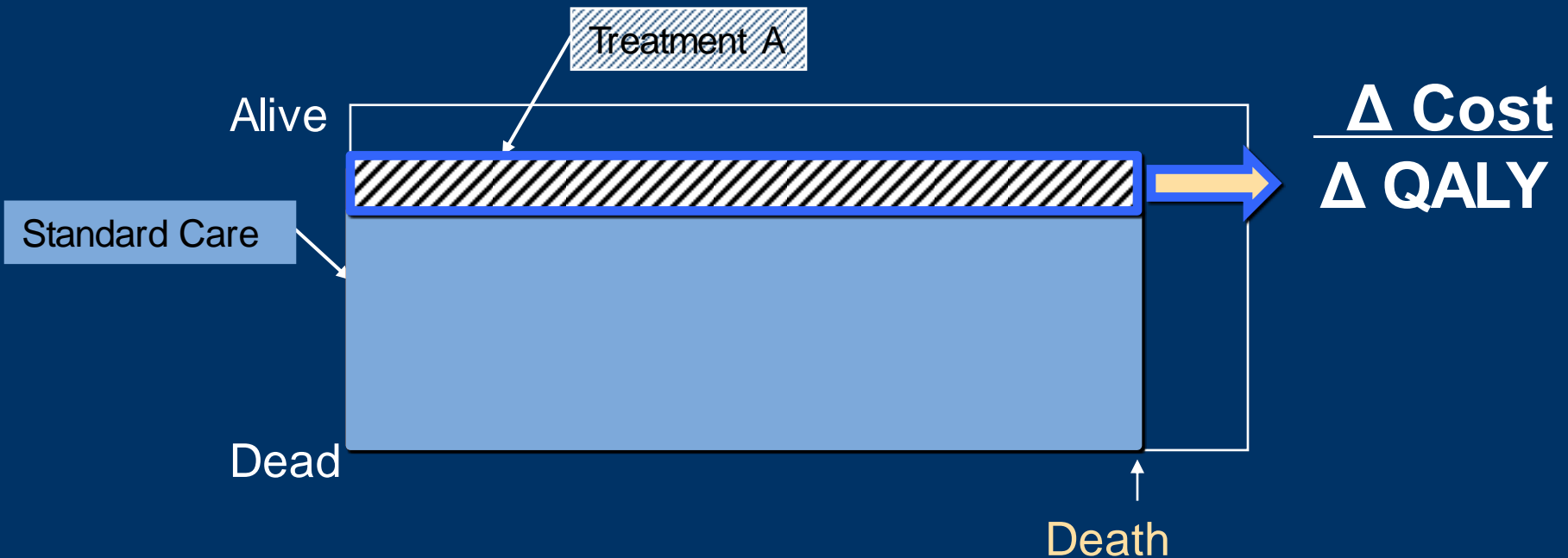
- To implement decision rules for therapies for different conditions,...

*outcomes must be measured using the same units.*

# Cost-Effectiveness Analysis

## Cost-Utility Analysis (CUA):

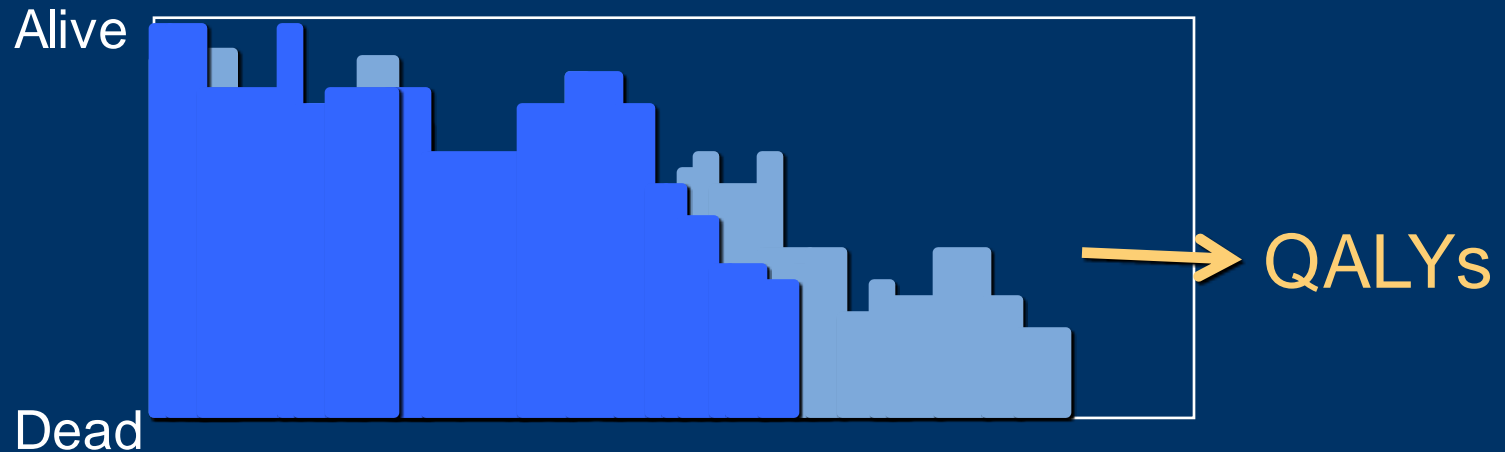
- A form of cost-effectiveness analysis that incorporates patient preferences or utilities for a set of health outcomes.
- Reported as cost per quality-adjusted unit of effectiveness:



# Cost-Effectiveness Analysis

## Cost-Utility Analysis (CUA):

- A form of cost-effectiveness analysis that incorporates patient preferences or utilities for a set of health outcomes.
- Reported as cost per quality-adjusted unit of effectiveness:



# Critical Considerations

Perspective

Time horizon

The comparator

$$\text{ICER} = \frac{C_{ExpTrx} - C_{StdCare}}{E_{ExpTrx} - E_{StdCare}}$$

# Payer Perspective

If private payers  $\approx$  employers

AND

If employment  $\propto$  insurance coverage

AND

If employment  $\propto$  1/mental health issues  $\times$  severity<sup>2</sup>

AND

IF costs  $\propto$  severity

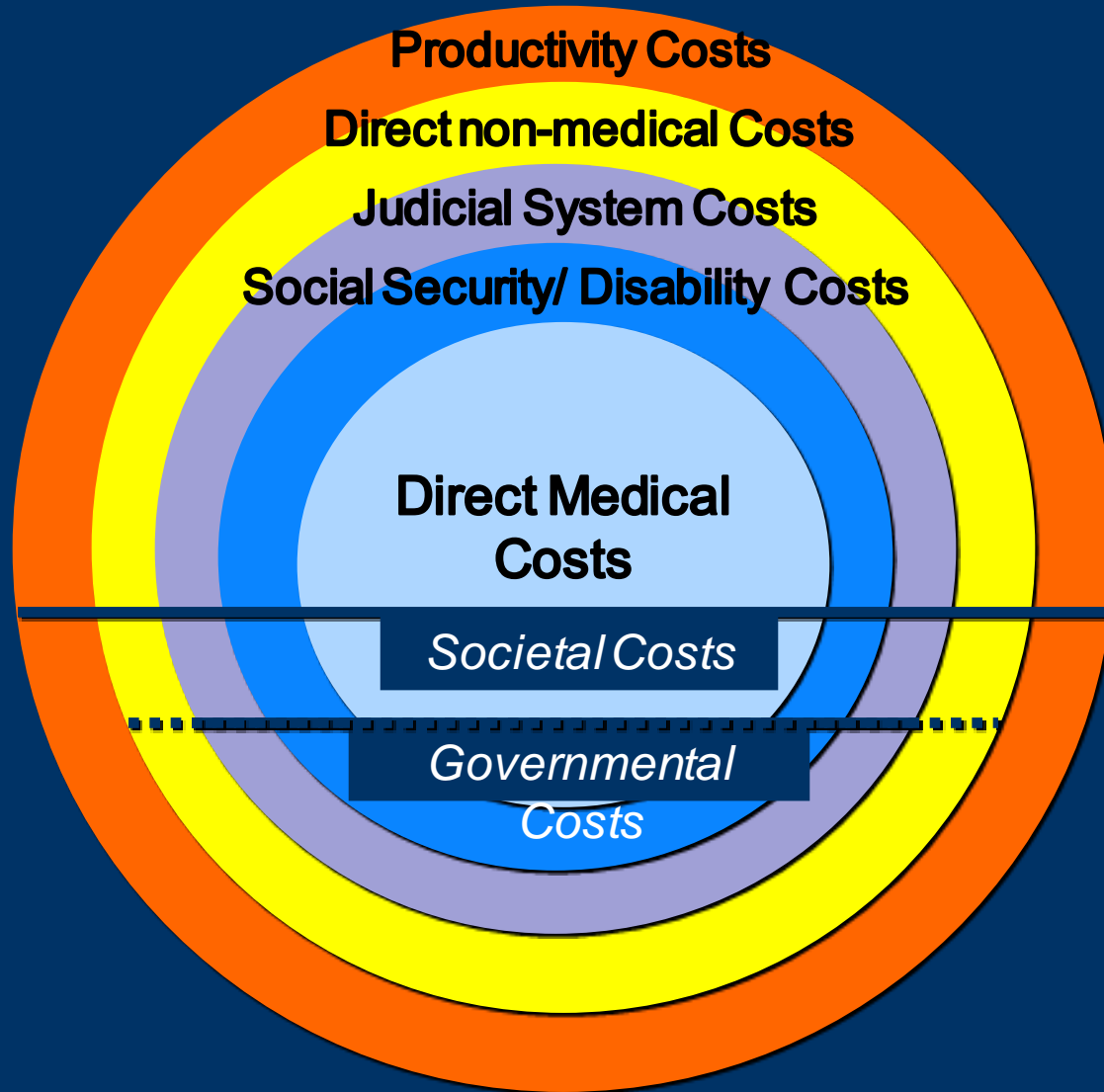
THEN

Private payers cover a fraction of mental health care costs.

# Perspective

- Government payers are dominant in mental health.
  - **Medicare**- Alzheimer's disease, depression
  - **Medicaid**- Alzheimer's disease, depression, schizophrenia, substance abuse
  - **VA**- Alzheimer's disease, PTSD, substance abuse, depression

# Perspective



# Cost-Benefit Analysis

- All costs and effects are measured in monetary units.
- Decision rules are simple:

$$B - C > 0$$

$$\frac{B}{C} > 1$$

Implement  
Intervention

Broader perspectives typically enhance the value of effective mental health interventions.

# Perspective

Productivity Costs  
Social Security/ Disability Costs



# Time Horizon

Long enough to capture:

- ▣ Downstream costs
- ▣ Downstream health consequences



- What effect size is necessary for an intervention to be cost-effective?

# Treatment Effect for Cost-Effectiveness

## A vs. B for 24 weeks

Cost assumptions: Trx A: \$100/wk, Tx B: \$25/wk

Trx A: response rate: 32.5%, adverse events: 0%

Trx B: response rate: 32.5%, adverse events: 0%

*“Cost-minimization analysis”*

# Treatment Effect for Cost-Effectiveness

## A vs. B for 24 weeks

Cost assumptions: Trx A: \$100/wk, Tx B: \$25/wk

Trx A: response rate: 40%

Trx B: response rate: 30%

33% higher  
response rate

Time horizon

24 weeks, assume no extended benefit after D/C trx.

Perspective

Limit to treatment costs.

Measure of  
Effectiveness

Apply utility weights for responders and non-responders.

# 3-Level EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

## Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

## Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

## Usual Activities *(e.g. work, study, housework, family or leisure activities)*

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

## Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

## Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

# EQ-5D Utility Weights

MOBILITY	SELF-CARE	USUAL ACTIVITIES	PAIN/DISCOMFORT	ANXIETY/DEPRESSION	EQ-5D index(US_D1)
1	1	1	1	1	1
1	1	1	1	2	0.8438
1	1	1	1	3	0.5498

# Treatment Effect for Cost-Effectiveness

## A vs. B for 24 weeks

Cost assumptions: Trx A: \$100/wk, Tx B: \$25/wk

Trx A: response rate: 40%

Trx B: response rate: 30%

33% higher  
response rate

$$QALY_{\text{Trx A}} = [(0.4 \times 1) + (0.6 \times 0.844)] \times (24/52) = 0.4183$$

$$QALY_{\text{Trx B}} = [(0.3 \times 1) + (0.7 \times 0.844)] \times (24/52) = 0.4111$$

$$\Delta = 0.0072$$

$$ICER = (\$2400 - \$600) / 0.0072 = \$249,680 \text{ per QALY}$$

# Treatment Effect for Cost-Effectiveness

## A vs. B for 24 weeks

Cost assumptions: Trx A: \$100/wk, Tx B: \$25/wk

Trx A: response rate: 40%

Trx B: response rate: 30%

Assume treatment costs for 24 weeks,  
but vary duration of effectiveness.

Time Horizon	ICER (\$ per QALY)
24 Weeks	\$269,700
1 Year	\$115,200
3 Years	\$38,400
5 Years	\$23,000

# EQ-5D Utility Weights

MOBILITY	SELF-CARE	USUAL ACTIVITIES	PAIN/DISCOMFORT	ANXIETY/DEPRESSION	EQ-5D index(US_D1)
1	1	1	1	1	1
1	1	1	1	2	0.8438
1	1	1	1	3	0.5498

# Treatment Effect for Cost-Effectiveness

## A vs. B for 24 weeks

Cost assumptions: Trx A: \$100/wk, Tx B: \$25/wk

Trx A: response rate: 40%

Trx B: response rate: 30%

$$QALY_{\text{Trx A}} = [(0.4 \times 0.844) + (0.6 \times 0.550)] * (24/52) = 0.3080$$

$$QALY_{\text{Trx B}} = [(0.3 \times 0.844) + (0.7 \times 0.550)] * (24/52) = 0.2945$$

$$\Delta = 0.0136$$

$$ICER = (\$2400 - \$600) / 0.0072 = \$132,653 \text{ per QALY}$$

# EQ-5D Utility Weights

MOBILITY	SELF-CARE	USUAL ACTIVITIES	PAIN/DISCOMFORT	ANXIETY/DEPRESSION	EQ-5D index(US_D1)
1	1	1	1	1	1
1	1	1	1	2	0.8438
1	1	1	1	3	0.5498
1	2	1	1	1	0.8247
1	3	1	1	1	0.5288
1	2	1	1	2	0.7973
1	3	1	1	3	0.3546

# Treatment Effect for Cost-Effectiveness

## A vs. B for 24 weeks

Cost assumptions: Trx A: \$100/wk, Tx B: \$25/wk

Trx A: response rate: 40%

Trx B: response rate: 30%

$$QALY_{\text{Trx A}} = [(0.4 \times 0.797) + (0.6 \times 0.355)] * (24/52) = 0.2454$$

$$QALY_{\text{Trx B}} = [(0.3 \times 0.797) + (0.7 \times 0.355)] * (24/52) = 0.2250$$

$$\Delta = 0.0204$$

$$ICER = (\$2400 - \$600) / 0.0204 = \$88,096 \text{ per QALY}$$

# Treatment Effect for Cost-Effectiveness

- Assuming continued treatment is necessary for continued effect, varying the time horizon has no impact on ICERs.
- However, cost-effectiveness of Trx A could be more attractive under various scenarios.

# Treatment Effect for Cost-Effectiveness

## A vs. B for 24 weeks

Cost assumptions: Trx A: \$100/wk, Tx B: \$25/wk

### Subgroups with differential response

Trx A: response rate: 60% in G1; 20% in G2

Trx B: response rate: 20% in G1; 40% in G2

### With G1:G2 at 1:1:

Trx A: response rate: 40%

Trx B: response rate: 30%

$$QALY_{Trx A} [(0.5 \times 0.6 \times 1) + (0.5 \times 0.2 \times 1) + (0.5 \times 0.4 \times 0.844) + (0.5 \times 0.8 \times 0.844)] \times (24/52) = 0.4183$$

$$QALY_{Trx B} [(0.5 \times 0.2 \times 1) + (0.5 \times 0.4 \times 1) + (0.5 \times 0.8 \times 0.844) + (0.5 \times 0.6 \times 0.844)] \times (24/52) = 0.4111$$

$$\Delta = 0.0072$$

$$ICER = (\$2400 - \$600) / 0.0072 = \$249,680 \text{ per QALY}$$

# Treatment Effect for Cost-Effectiveness

## A vs. B for 24 weeks

Cost assumptions: Trx A: \$100/wk, Tx B: \$25/wk

If subgroups can be pre-identified

### Limit to G1:

Trx A: response rate: 60%

Trx B: response rate: 20%

300% higher  
response rate!

$$QALY_{\text{Trx A}} = [(0.6 \times 1) + (0.4 \times 0.844)] * (24/52) = 0.4327$$

$$QALY_{\text{Trx B}} = [(0.2 \times 1) + (0.8 \times 0.844)] * (24/52) = 0.4039$$

$$\Delta = 0.0288$$

$$ICER = (\$2400 - \$600) / 0.0288 = \$62,420 \text{ per QALY}$$

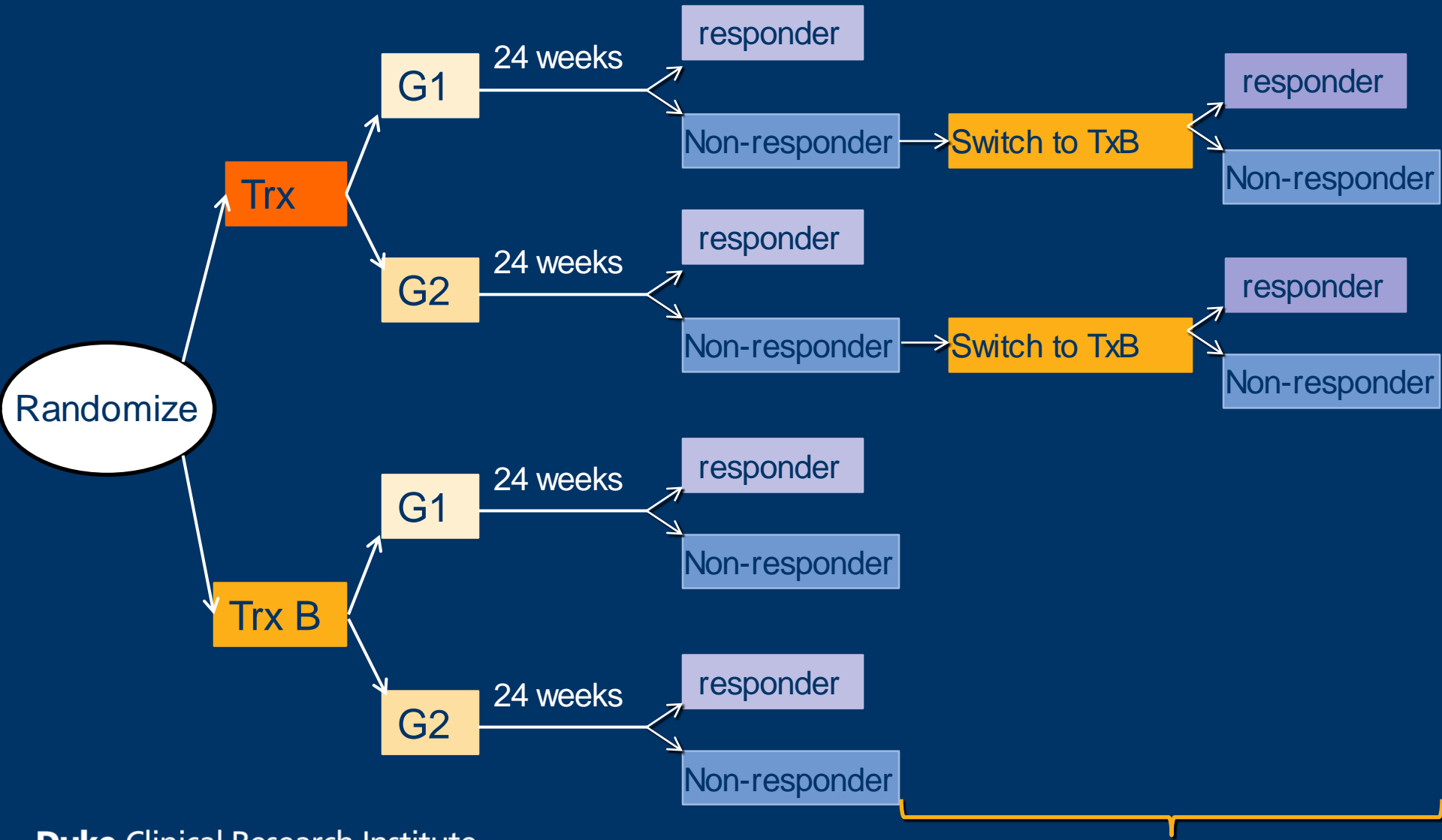
# Treatment Effect for Cost-Effectiveness

Enrich G1 G1:G2	Response on TxA:TxB	ICER (\$/QALY)
1:1	40%:30%	\$249,700
2:1	47%:27%	\$124,800
3:1	50%:25%	\$99,900
1:0	60%:20%	\$62,400



# Treatment Effect for Cost-Effectiveness

Treatment A Withdrawn at 24 weeks if no response



# Treatment Effect for Cost-Effectiveness

A vs. B for 24 weeks

Then, require TxA non-responders to switch to TxB for 24 weeks.

With G1:G2 at 1:1

Trx A: response rate: 40%

Trx B: response rate: 30%

$$\text{ICER} = (\$3720 - \$1200) / (0.851 - 0.822) = \$87,400 \text{ per QALY}$$

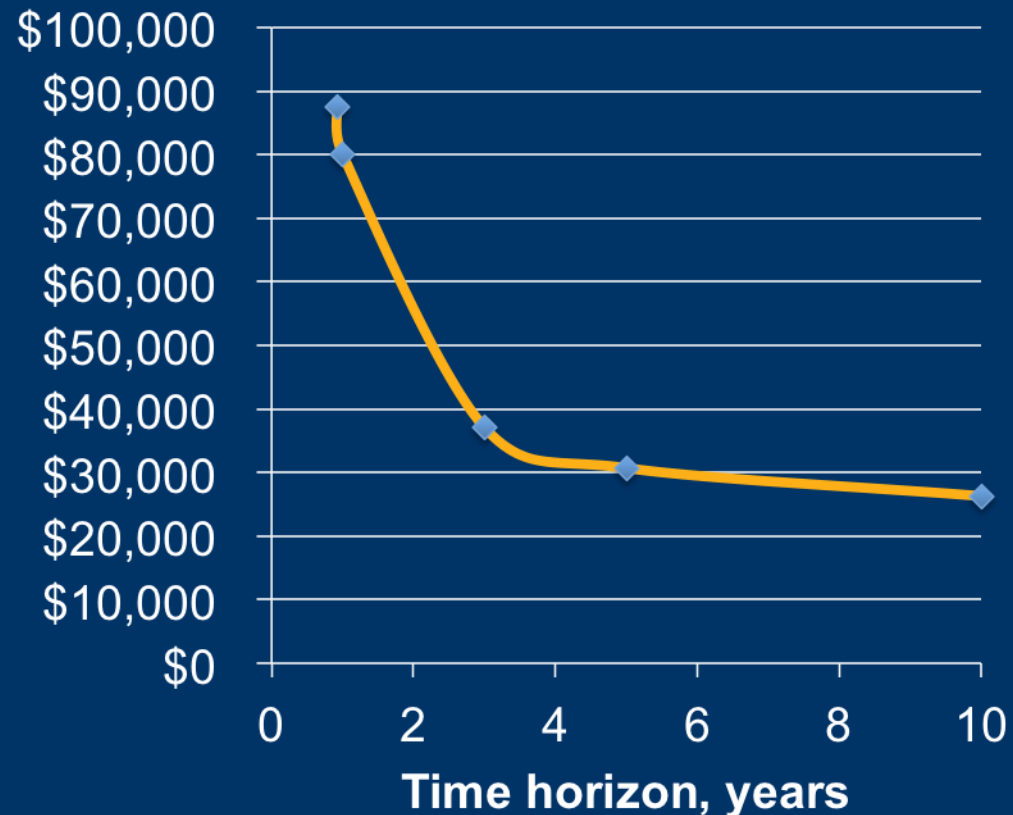
# Treatment Effect for Cost-Effectiveness

With G1:G2 at 1:1:

Trx A: response rate: 40%

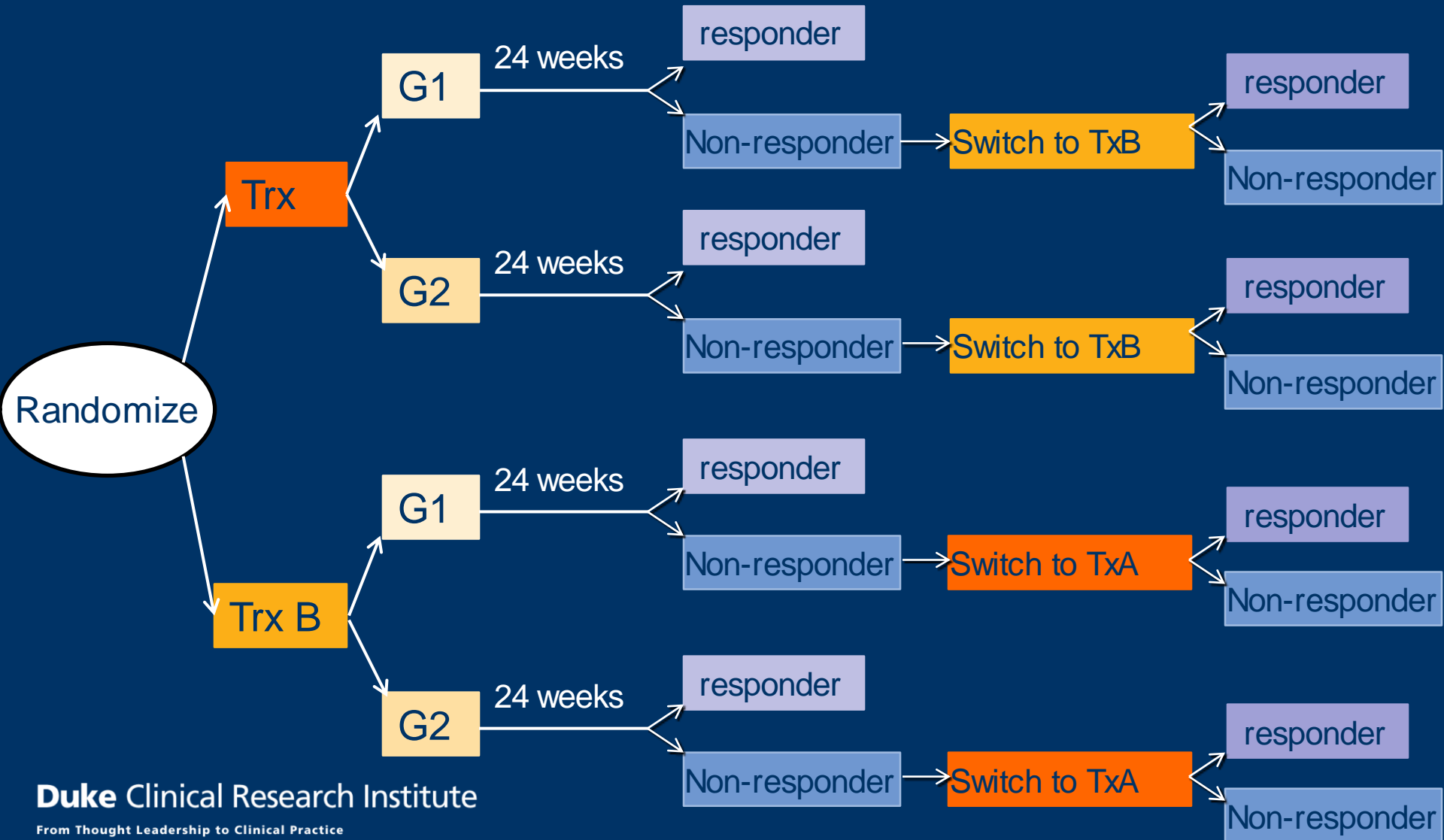
Trx B: response rate: 30%

Time horizon	ICER (\$/QALY)
48 weeks	\$87,400
1 Year	\$80,100
3 Years	\$37,100
5 Years	\$30,700
10 Years	\$26,300



# Treatment Effect for Cost-Effectiveness

Initiate Therapy with TxA or TxB. Non-responders switch to alternative tx



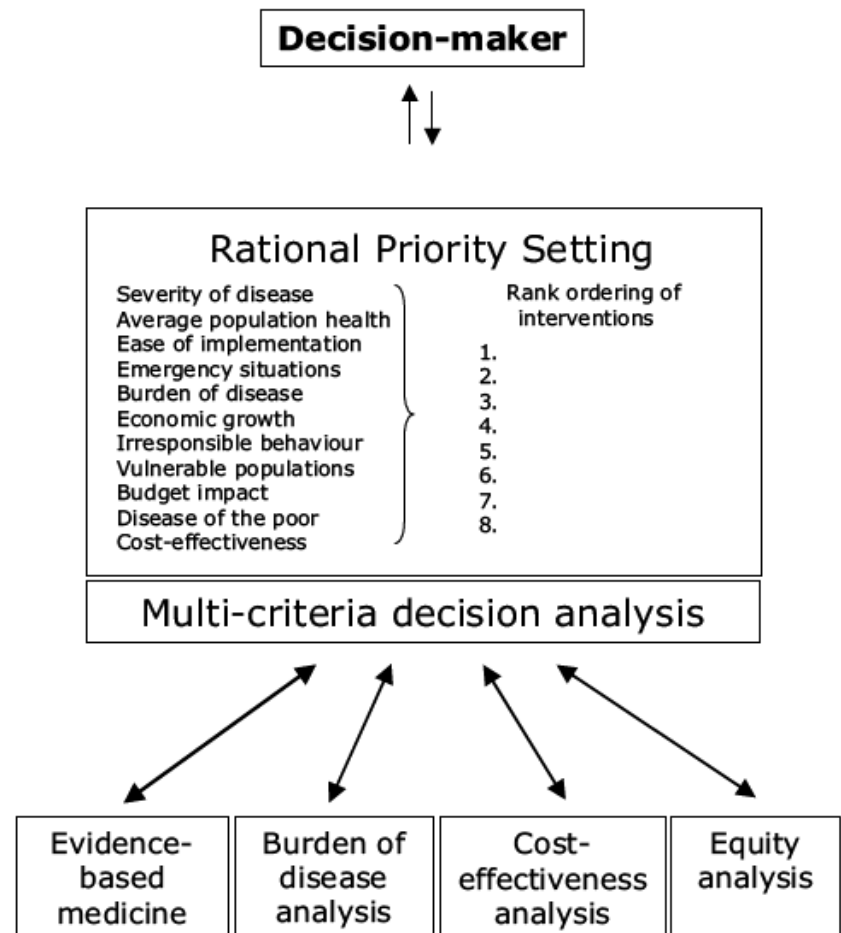
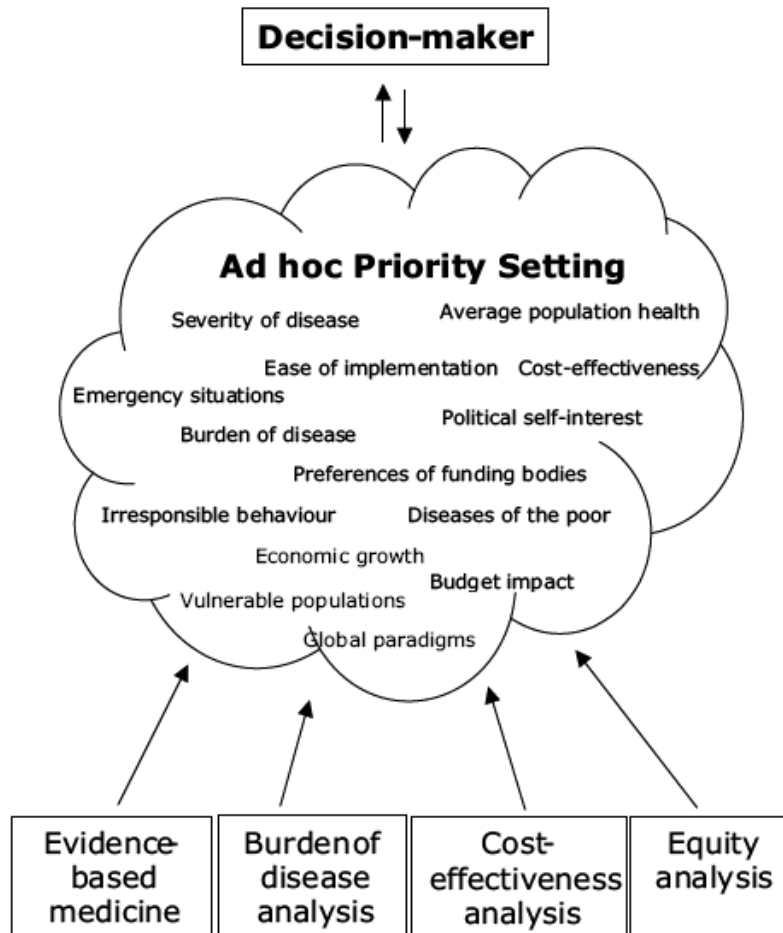
# Treatment Effect for Cost-Effectiveness

## Cost-Effectiveness of Initiating Treatment with Tx A vs. Tx B

Time Horizon	ICER (\$/QALY)
48 weeks	\$174,800
3 Years	\$287,100
5 Years	\$395,300
10 Years	\$665,800

Response rates are 60% with both strategies. QALY gains due to more patients acquiring initial response with Tx A.

# Multi-criteria Decision Analysis



Baltussen R and Niessen L. *Cost Eff Resour Alloc.* 2006.

# Hypothetical Example

Adapted from Baltussen and Niessen 2006

## Performance Matrix





Options	Cost-effectiveness	Severity of disease	Disease of the poor	Age
Tx of depression	\$28,000 per QALY	× × ×		18 years and older
Antiretroviral treatment of HIV/AIDS	\$2000 per QALY	× × × ×	✓	18 years and older
Tx of childhood pneumonia	\$1,000 per QALY	× × × ×	✓	0-17 years
Inpatient trx for acute schizophrenia	\$20,000 per QALY	× × ×	✓ ✓	18 years and older
Plastering for simple fractures	\$10,000 per QALY	×		all

## Scoring Options

Options	Cost-effectiveness	Severity of disease	Disease of the poor	Age	Total
Tx of depression	0	50	0	0	50
Antiretroviral treatment of HIV/AIDS	100	100	50	0	250
Tx of childhood pneumonia	100	100	50	100	350
Inpatient trx for acute schizophrenia	50	50	100	0	200
Plastering for simple fractures	50	0	0	50	100
Total	300	300	200	150	

# Summary

Cost-effectiveness of an intervention is dependent on:

- Absolute effect size **RCT Implications**
  - Comparator  Placebo vs. active comparator
  - Disease severity  Eligibility criteria
- Time horizon  Duration of follow-up
- Perspective  Data collection
  - Medical resource use
  - Employment
  - Informal caregiving
  - Housing
  - Judicial system
  - Other...