

# Sampling Uncertainty and Patient-Level Cost-Effectiveness Analysis (Part 2)

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EPI 550

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## Concerns with CI for ICER

- If every experiment was pattern 1, probably wouldn't have seen development of net monetary benefit and acceptability curves
- But experiments can occur in which CI for ICER have "odd properties" that most people at least initially find counter-intuitive
  - CI can be undefined
    - Referred to as Pattern 3
  - On real number line, either  $PE > LL > UL$  or  $LL > UL > PE$ 
    - Referred to as Pattern 2



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## Second Example:

Replicates in all 4 quadrants

Naïve ordering DOESN'T work

Smart ordering EXTREMELY UNLIKELY TO / DOESN'T work



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Consider confidence intervals for following experiment:

$\Delta C=400$ ;  $SEC=325$ ;  $\Delta Q=.02$ ;  $SEQ=.02$ ;  $\rho=0.25$ ;  
 $DOF=498$




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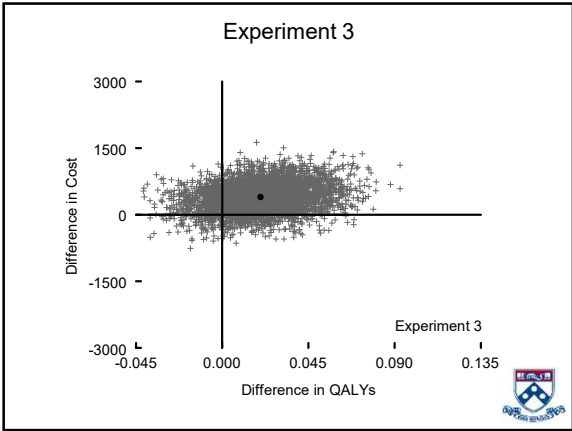
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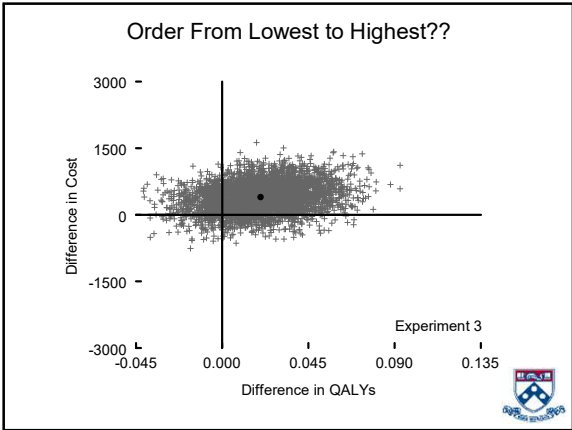
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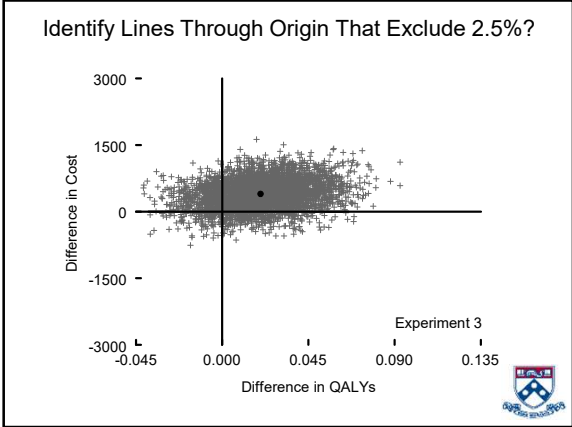
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Implications for Acceptability curve?

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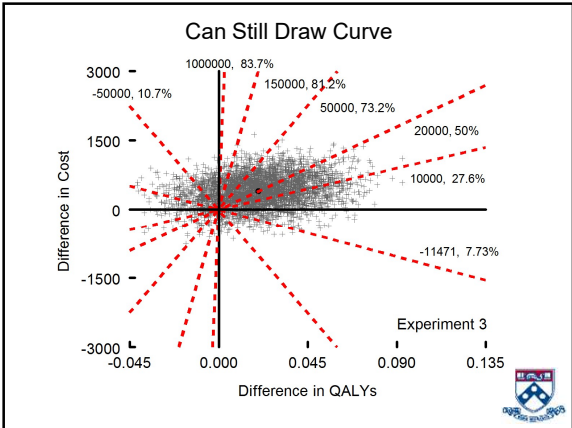
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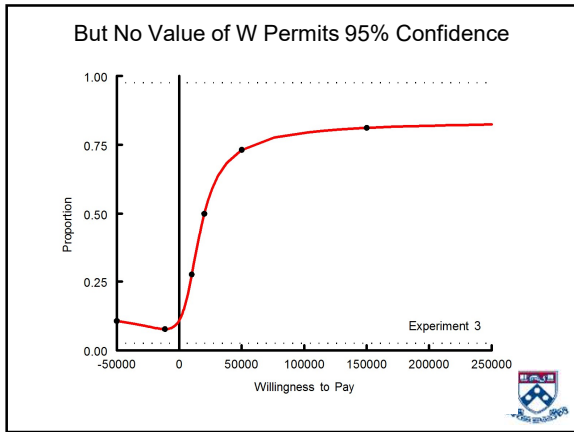
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Implications for CI for ICER?

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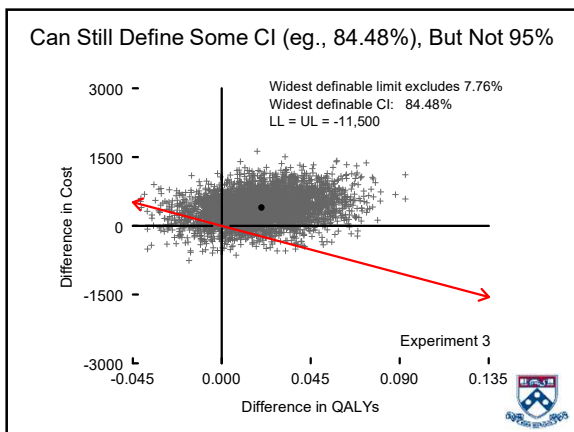
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Implications for CI for NMB for Particular W?



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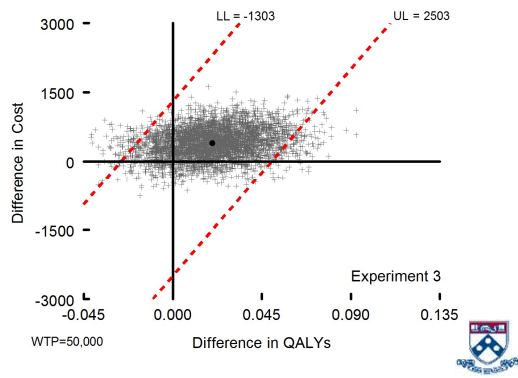
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95 CI for NMB for Particular W Always Defined



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Implications for NMB Graph?



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Can Still Draw, But....



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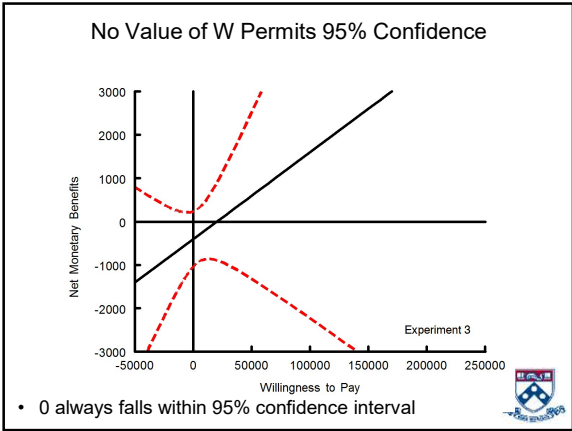
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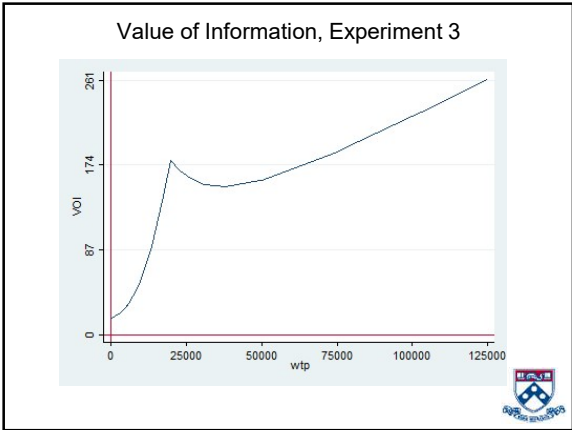
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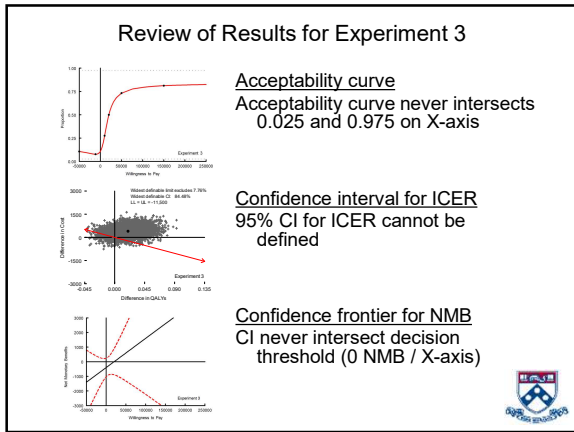
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- ### Pattern 3 Findings
- Refer to findings like those in experiment 3 as pattern 3 findings
  - 1 of 2 patterns that occur only when difference in effect is not significant
    - $P > 0.05$  for cost necessary but not sufficient condition
  - Know we are observing a pattern 3 finding when:
    - Acceptability curve never intersects horizontal lines drawn at either 0.025 or 0.975 on Y axis
    - Confidence interval for the ICER is undefined
    - Neither NMB confidence limit curve intersects decision threshold (0 NMB / X axis)
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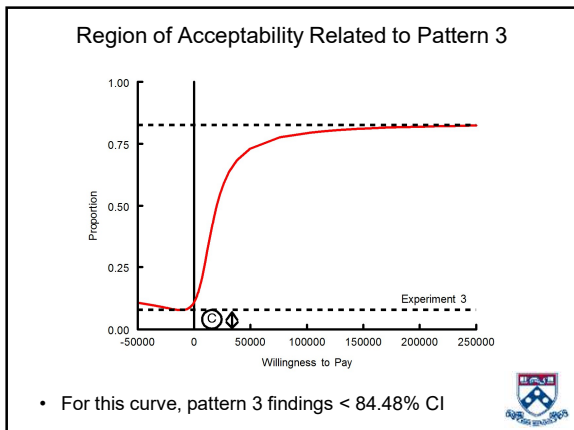
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Pattern 3 Findings (2)

Not confident value of two therapies differs

$-\infty$  ← Willingness to Pay →  $\infty$




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Third Example:

Some replicates on both sides of Y-axis, but primarily in 2 or 3 quadrants

Naïve ordering doesn't work, but smart ordering generally does




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Consider a third experiment that doesn't have either pattern 1 or pattern 3 findings

$\Delta C=35$ ;  $SEC=777.06$ ;  $\Delta Q=.04$ ;  $SEQ=.0224$ ;  
 $\rho=0.70625$ ;  $DOF=498$

P value for cost, 0.96  
P value for QALYs, 0.07  
(NEITHER SIGNIFICANTLY DIFFERENT)




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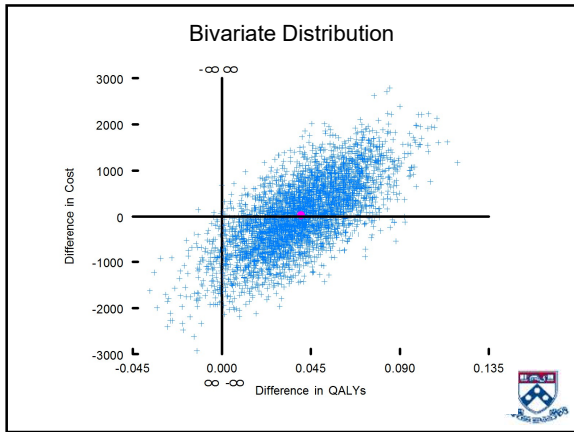
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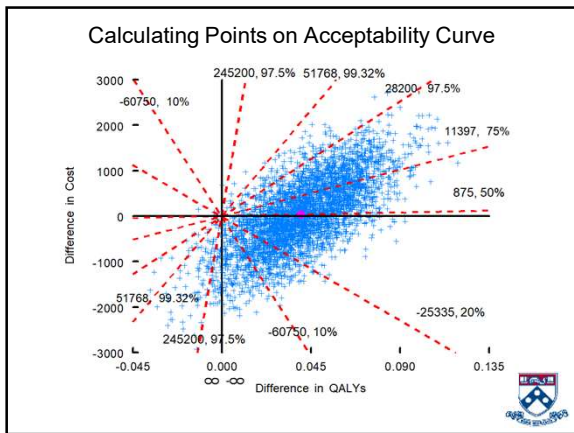
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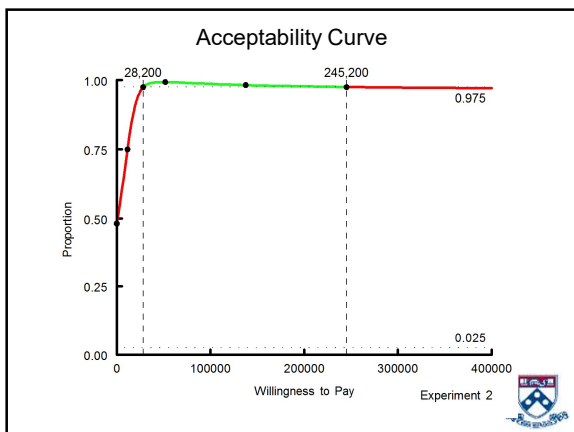
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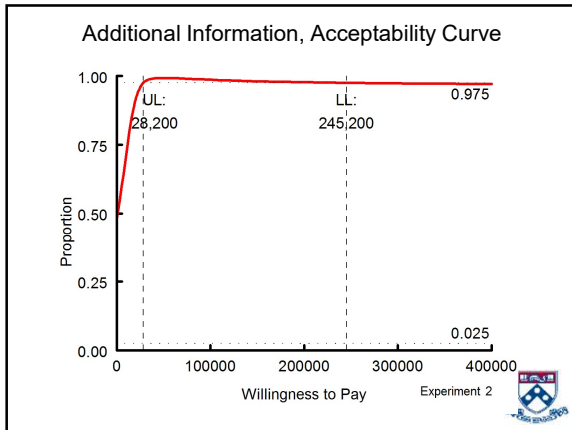
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Neither  $\Delta C$  nor  $\Delta Q$  significant, but can be 95% confident of value for  $W$  between 28,200 and 245,200

For all other values of  $W$  can't be 95% confident

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CI for ICER When Some Replicates Fall on Each Side of Y Axis?

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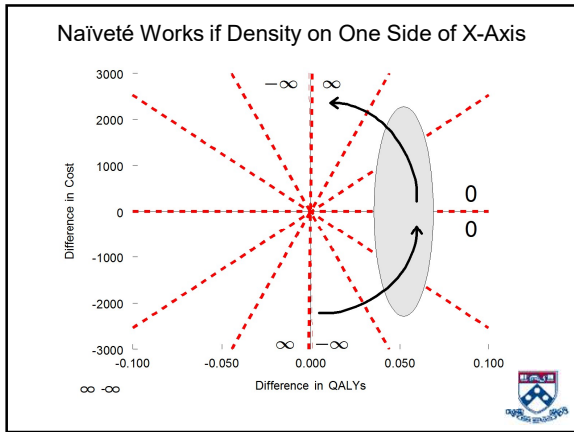
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- ### Pluses and Minuses of Ordering for CI for ICER
- Previously said that naïve ordering can work
    - e.g., when all replicates fall on one side of X axis
  - But conditions when it fails are well defined (e.g., for  $\Delta Q$ ,  $p > .05$ )
  - CI for CER technically **NOT** an “order statistic”
    - Instead defined by lines through origin of CE plane that each exclude  $\alpha/2\%$  of joint distribution
  - **Independent of whether lower limit is a larger or smaller number than upper limit, on CE plane, interval stretches counter-clockwise from lower (clockwise) limit to upper (counter-clockwise) limit**

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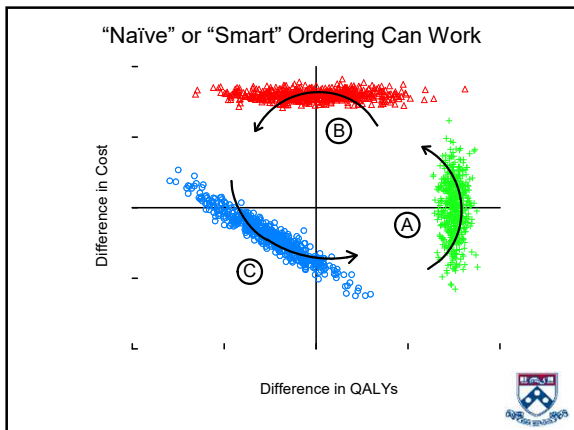
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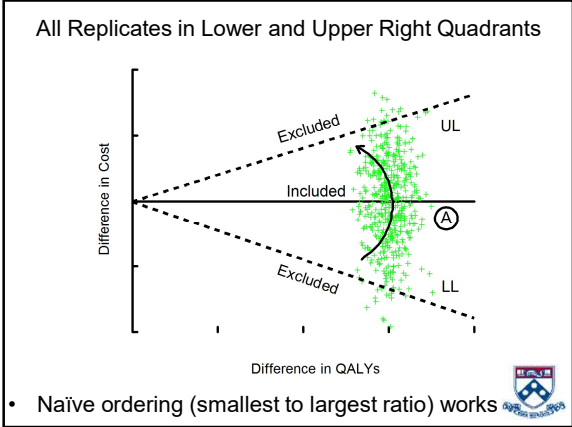
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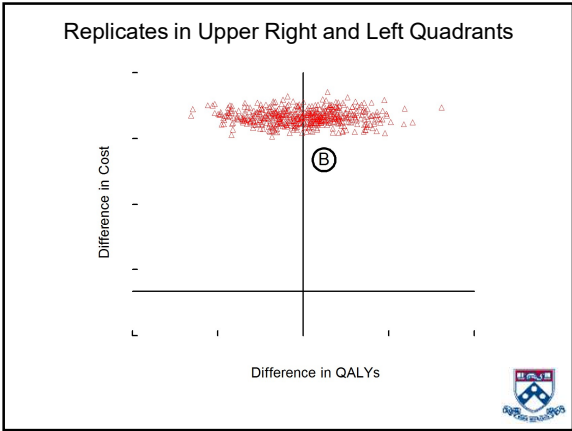
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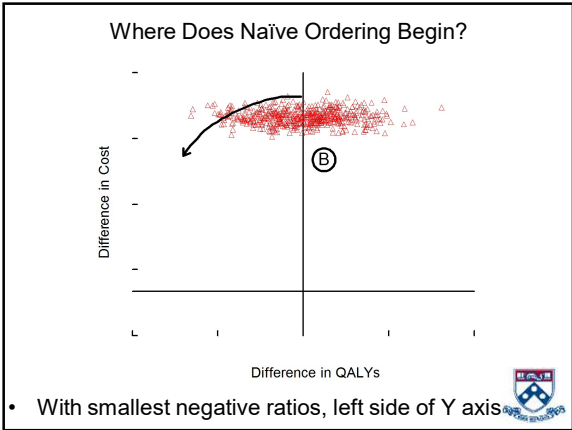
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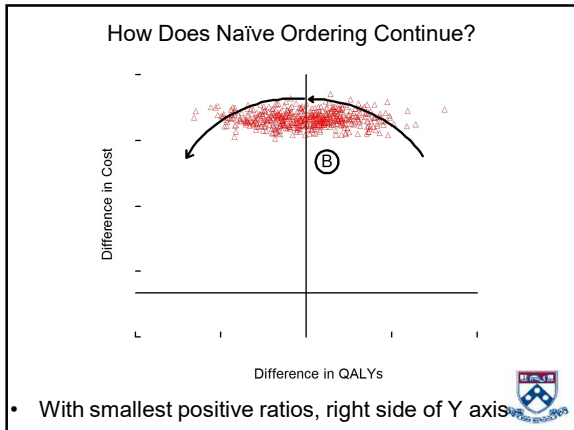
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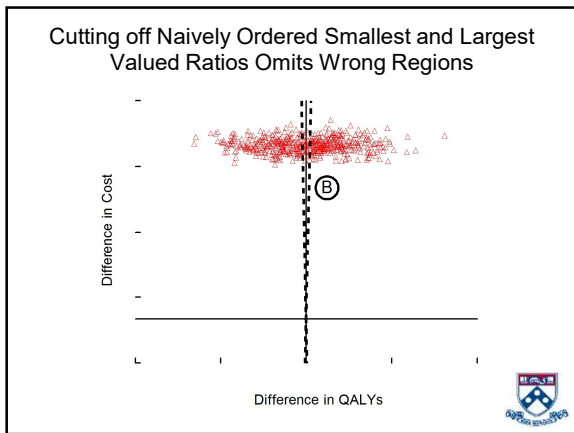
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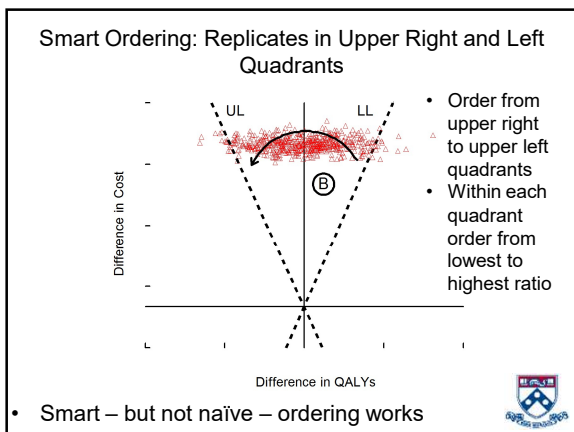
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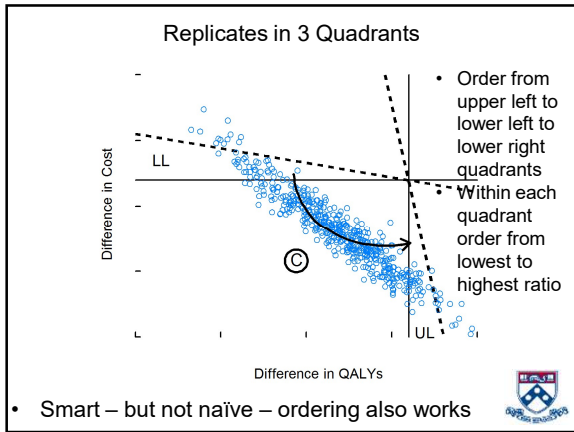
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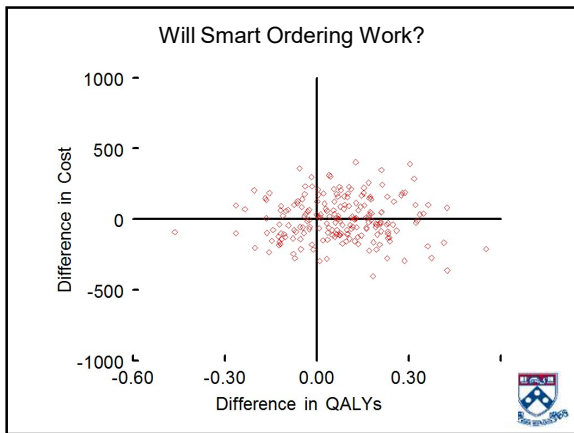
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Back to CI for CER for experiment #2

$\Delta C=35$ ;  $SEC=777.06$ ;  $\Delta Q=.04$ ;  $SEQ=.0224$ ;  
 $\rho=0.70625$ ;  $DOF=498$

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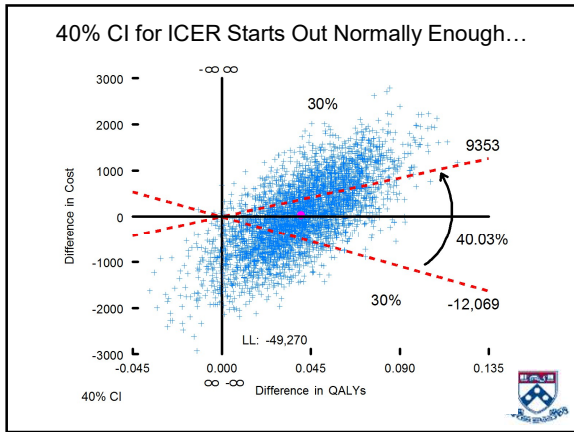
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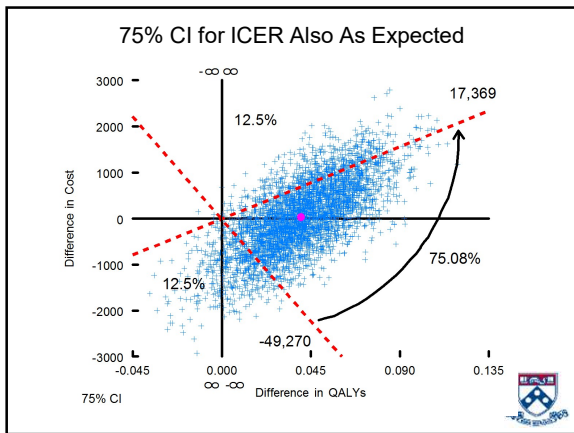
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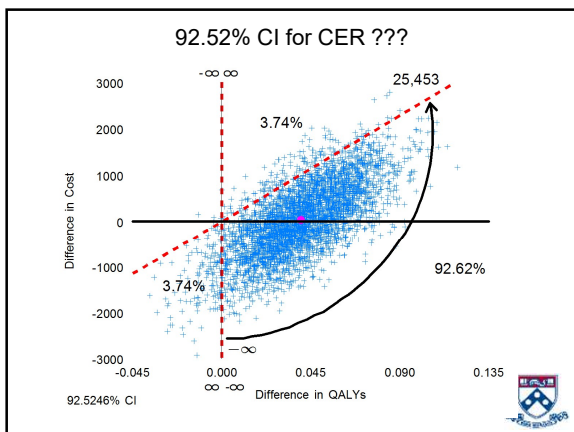
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92.52% lower limit equals  $-\infty^*$

Is 92.52% interval widest that can be defined?  
i.e., is it possible to find lines through origin that  
omit less than 3.74%

(\* Technically, lower and upper parametric limits equal  $\pm\infty$ )



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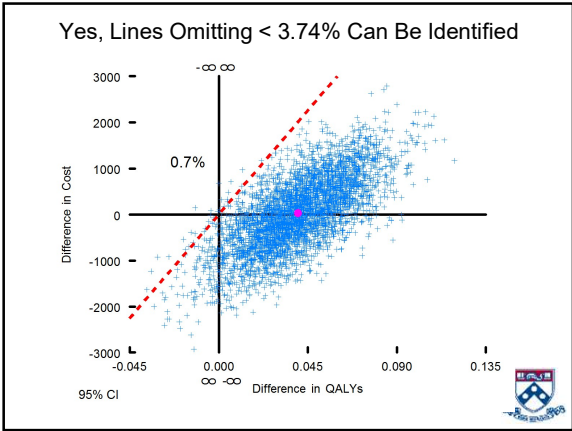
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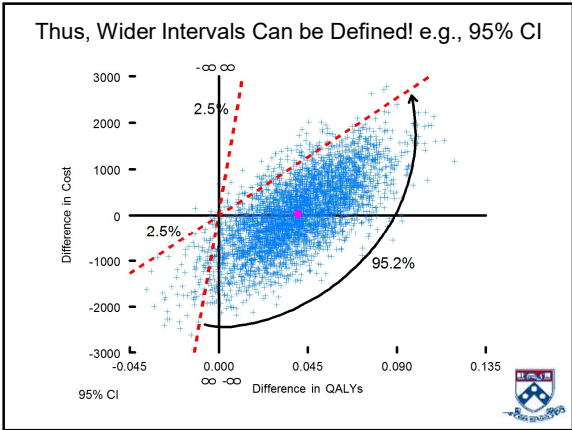
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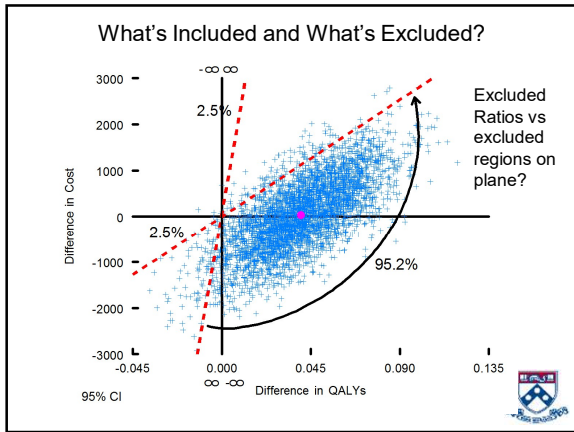
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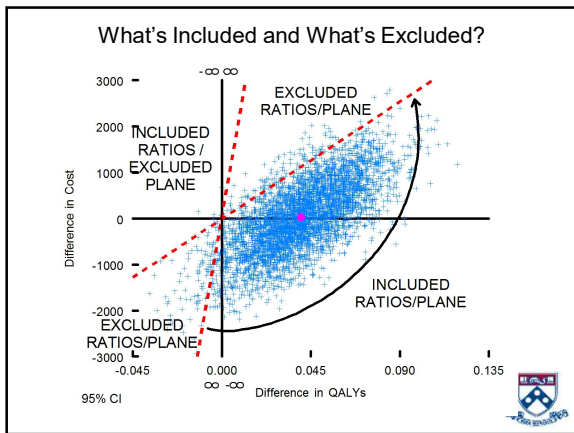
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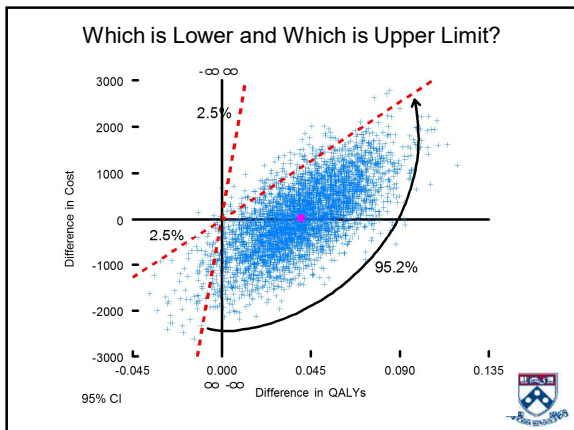
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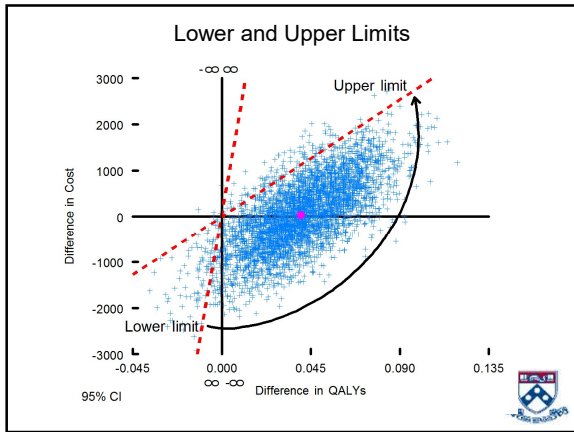
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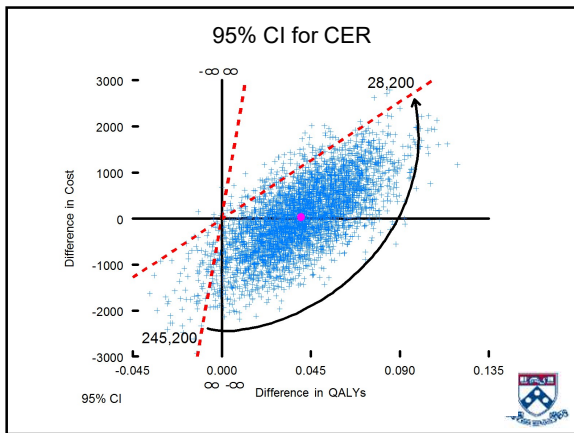
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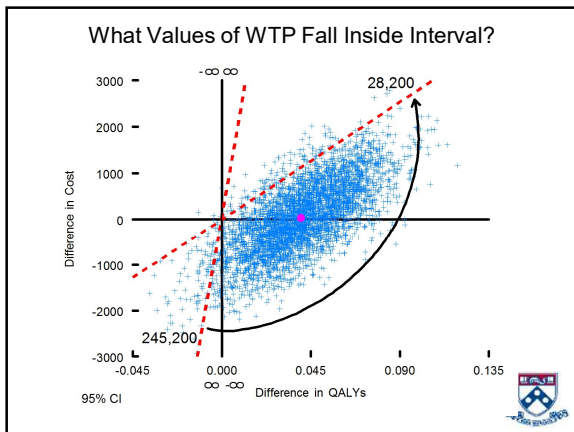
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-∞ to 0 (lower right quadrant)  
 0 to 28,200 (part of upper right quadrant that falls below / to right of upper limit)  
 245,200 to ∞ (part of lower left quadrant that falls below / to right of lower limit)  
 Interval: -∞ to 28,200 and 245,200 to ∞




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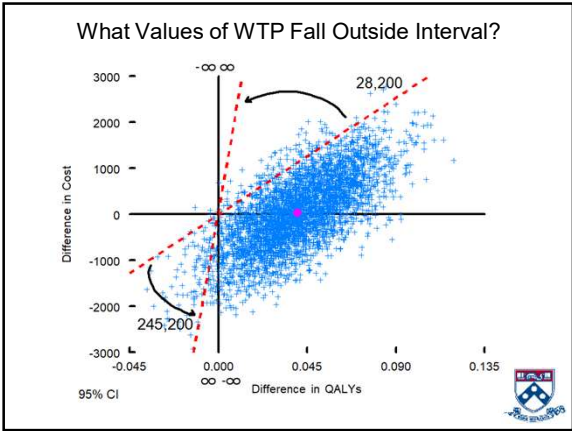
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28,200 to 245,200 fall outside interval

For what values of WTP can we be 95% confident of value?

If  $W = 50,000$ , can we be confident of value?




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### Confidences Statements for CI for CER

- Confident of value if:
  - P1:  $LL < UL < W$  (confident of good value)
  - P1:  $W < LL < UL$  (confident of bad value)
  - P2:  $UL < W < LL$  (confident of good value if  $PE < W$ ; confident of bad value if  $PE > W$ )
- Not confident of value if:
  - P1:  $LL < W < UL$
  - P2/P3: CI is undefined
  - P2:  $W < UL < LL$
  - P2:  $UL < LL < W$




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### Counter-Intuitive Relationships for CI for ICER

- When more than  $\alpha/2\%$  of replicates fall on both sides of Y-axis, yet CI is defined:
  - Lower limit (e.g., 245,200) is a larger number than upper limit (e.g., 28,200)
  - ICER point estimate is either a smaller number (e.g., 875 (35/.04)) than both limits or a larger number than both limits
  - Values of WTP included in interval range from  $-\infty$  to upper limit and from lower limit to  $\infty$ 
    - e.g.,  $-\infty$  to 28,200 and 245,200 to  $\infty$
  - Values of WTP that are excluded from interval range from (smaller) upper limit to (larger) lower limit
  - Confident of value if  $WTP \geq$  upper limit and  $\leq$  lower limit




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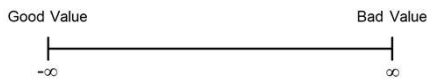
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### SOURCE OF COUNTER-INTUITIVE RELATIONSHIPS?



On real number line,  $-\infty$  and  $\infty$  as far apart as can be




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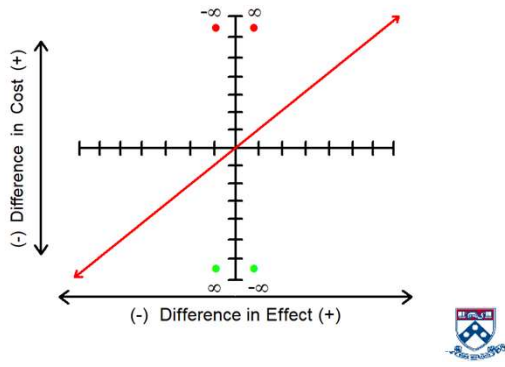
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But Infinitesimally Different On Cost-Effectiveness Plane



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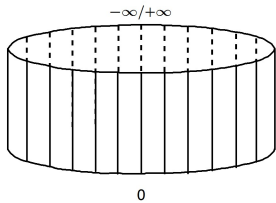
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One way to replicate this relationship on real number line would be to tape its ends together



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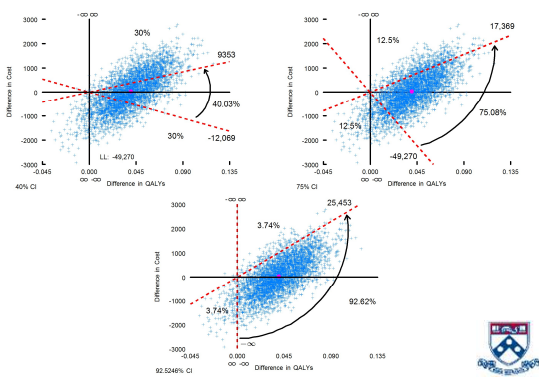
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40%, 75% and 92.5% CI on Cost-Effectiveness Plane



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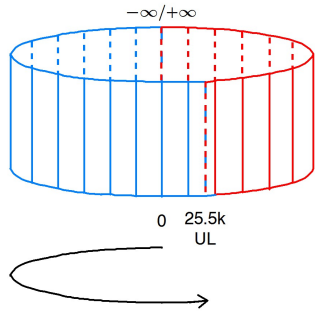
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What Happens if We Tape Ends of Real Number Line Together to Form a Ring (92.52% CI)



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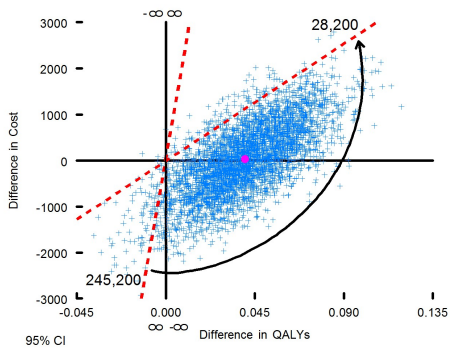
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What Happens on Plane When 95% CI Defined?



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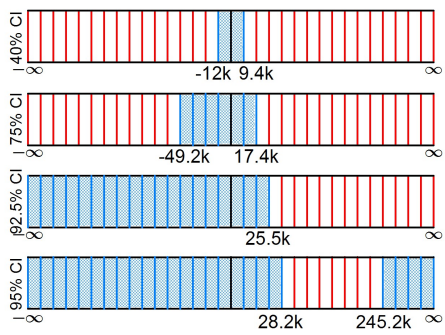
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What Happens on Real Number Line?



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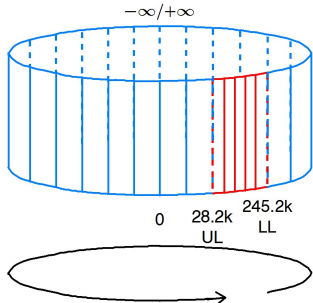
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What Happens if We Tape Ends of Real Number Line Together to Form a Ring (95% CI)?



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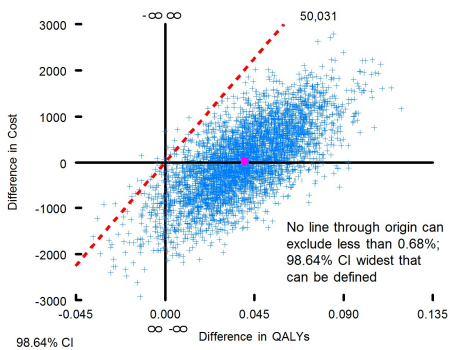
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Widest Definable Interval



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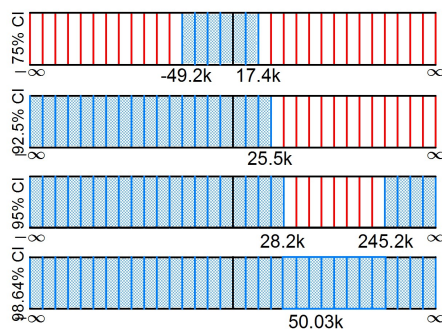
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What Happens on Real Number Line?



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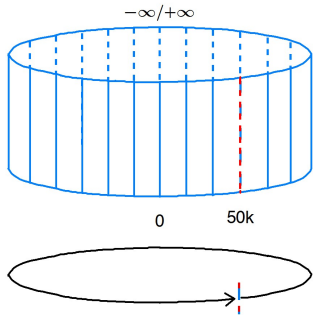
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What Happens if We Tape Ends of Real Number Line Together to Form a Ring (98.64% CI)?



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Widest Definable Interval

- Can find no line through origin that excludes a smaller proportion of replicates
- Includes all values of WTP from  $-\infty$  to  $+\infty$
- Represents maximum level of confidence where we can conclude one therapy is better value than another
- Conclusion for all greater levels of confidence (pattern 3):  
 "Can't be confident that therapies differ"



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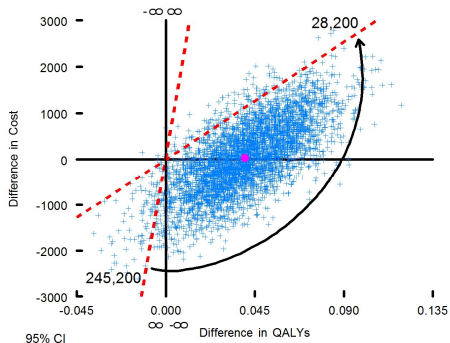
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95% CI for CER Recap



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When Lower Limit is "Larger" # than Upper Limit

- One of limits indicates that one of therapies may be delivering more health at increased or decreased cost
- Other limit indicates that alternative therapy may be delivering more health at increased or decreased cost
- Q is not statistically significant at  $\alpha$  level represented by interval
- Interval thus includes y axis



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When Lower Limit is "Larger" than Upper Limit (2)

- Point estimate is either larger than both limits or is smaller than both limits, but does what we expect for one of limits
  - If point estimate and lower limit are on same side of Y axis, point estimate is larger than lower limit (which is larger than upper limit)
  - If point estimate and upper limit are on same side of Y axis, point estimate is smaller than upper limit (which is smaller than lower limit)



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77

Example of Mistakes from Published Literature



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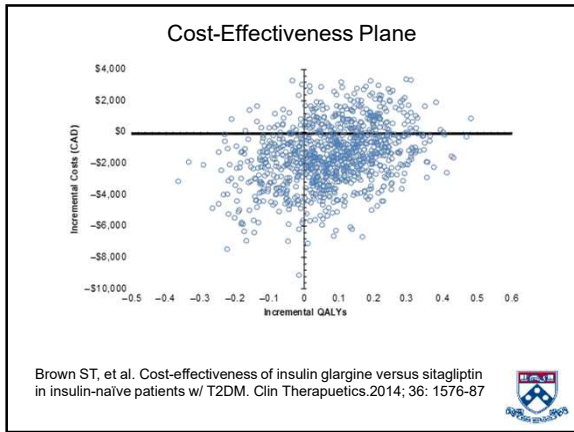
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### Brown Table 5

Outcome	Mean	95% CI
Incremental Cost	-1418	-1540 to -1295
Incremental QALYs	0.074	0.066 to 0.082
ICER	-19511	-23,815 to 2044

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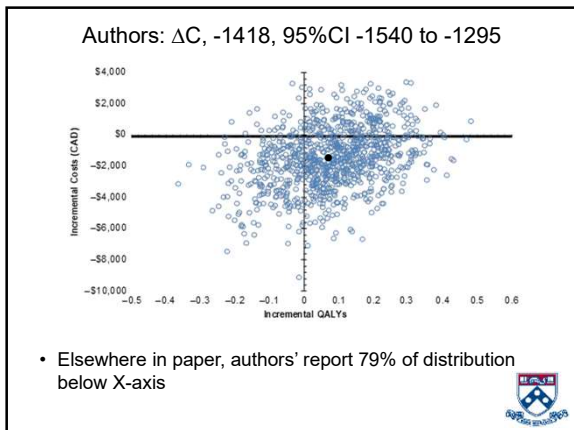
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81

Too much density on both sides of X-axis  
to conclude  $\Delta C$  significantly  
differs from 0

(If 21% above X-Axis,  $p=0.58$ )

95% CI cannot equal -1540 to -1295



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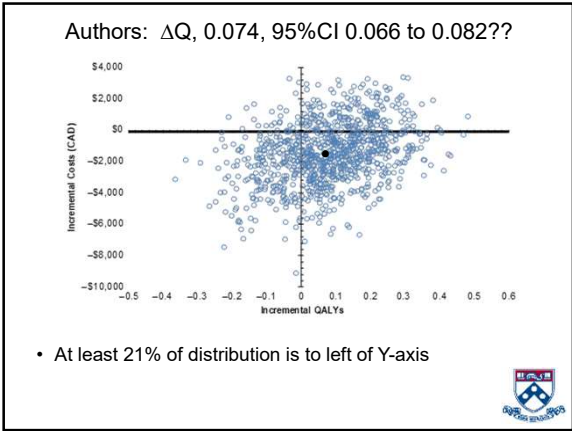
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83

Too much density on both sides of Y-axis  
to conclude  $\Delta Q$  significantly  
differs from 0

(If 21%+ to left of Y-Axis,  $p>0.58$ )

95% CI cannot equal 0.066 to 0.082



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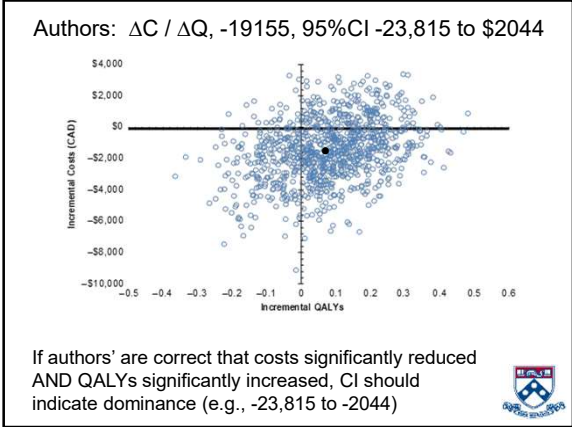
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85

Based on scatter plot, cannot identify line through origin that excludes 2.5%

No 95% CI can be defined!

When  $p > 0.05$  for  $\Delta Q$ , lower limit of CI for CER can never be smaller number than upper limit




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Conclusion

Something very wrong with either Brown et al.'s data plotted on CE plane or with Brown's reported statistics (Probable)

Probably mistakenly divided SE by  $N^{1/2}$

CE Plane does not confirm any statistical conclusions reported in their Table V




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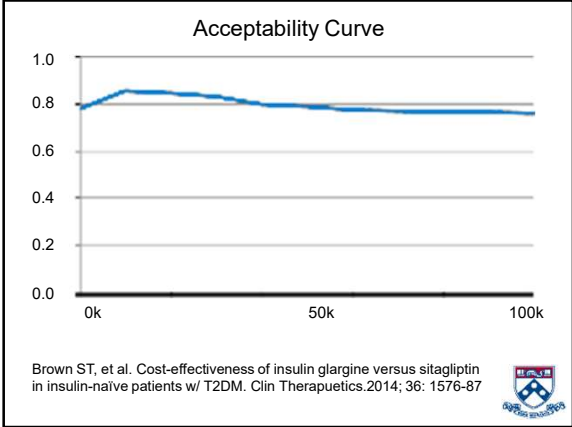
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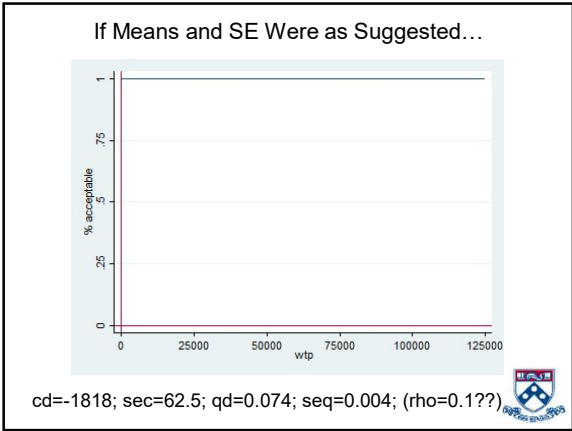
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### Unique Features of CI for ICER

- Role of  $\infty$ 
  - For OR and RR, widest imaginable limits equal:  $1/\infty$  to  $\infty$
  - For difference, widest imaginable limits equal:  $-\infty$  to  $\infty$
  - Do  $-\infty$  and  $+\infty$  bound the widest CI for an ICER?

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### Unique Features (2)

- What's inside and outside the interval?
  - For differences – e.g., NMB, OR, and RR, – what's inside interval ALWAYS falls somewhere in middle of real number line
  - What's outside interval always falls on left and right sides of real number line

Outside interval    Inside interval    Outside interval



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### 2) What's Inside and Outside Interval?

- For CI for CER, what's inside interval CAN fall somewhere in middle of real number line

Outside interval    Inside interval    Outside interval

- But can also fall on left and right sides of real number line

Inside interval    Outside interval    Inside interval



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### Unique Features (3)

- Reserved numbers for each Rx
  - For differences – e.g., NMB, OR, RR, and acceptability curve – CI has separate ranges of numbers reserved for when one therapy is larger/more effective/more acceptable than alternative versus when it isn't
    - Difference >0, larger than alternative; <0 smaller than alternative
    - OR,RR <1, more effective than alternative; >1, less effective (or vice versa)
    - % acceptable > 0.5 greater likelihood of being good value; <0.5 smaller likelihood of being good value



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### 3) Reserved Numbers

- Numbers reserved for each therapy
  - Not true for CI for ICER
    - When  $\Delta Q > 0$ , CI can include all values between  $-\infty$  and  $\infty$



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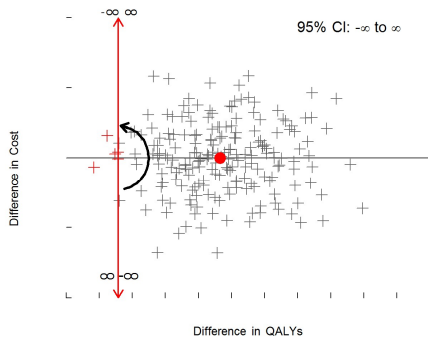
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$\Delta Q > 0$ ; 95% CI,  $-\infty$  to  $\infty$



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### ??? Misperceptions About Value When $W = \infty$ ???

- If Rx deemed good value when  $WTP = 50k$ , must it also be good value when  $WTP = 100k$ ? When  $WTP$  approaches  $\infty$ ?
- When designing a study, if power is 50% for  $WTP = 50k$  and 80% for  $WTP = 100k$  must power be approaching 100% as  $WTP$  approaches  $\infty$ ?



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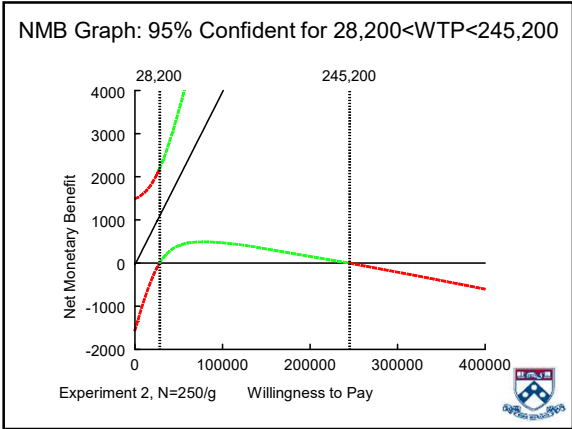
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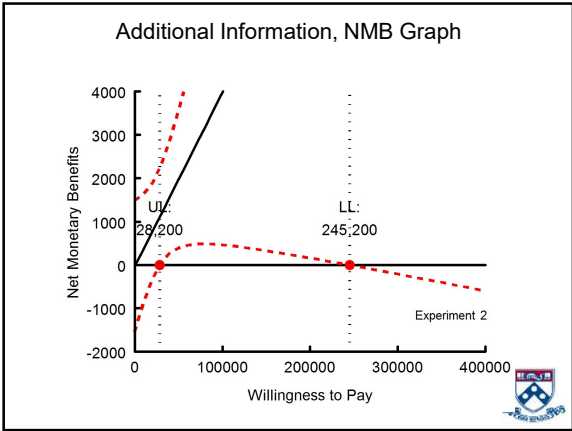
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Confidences Statements for CI for NMB

- If both confidence limits negative, 95% confident therapy is bad value
  - In this experiment, does not occur
- If both confidence limits positive, 95% confident therapy is good value
  - i.e., for values of  $WTP \geq 28,200$  and  $\leq 245,200$
- If one confidence limit positive and one negative, cannot be 95% confident value of 2 therapies differs
  - i.e., for values of  $WTP < 28,200$  and  $> 245,200$

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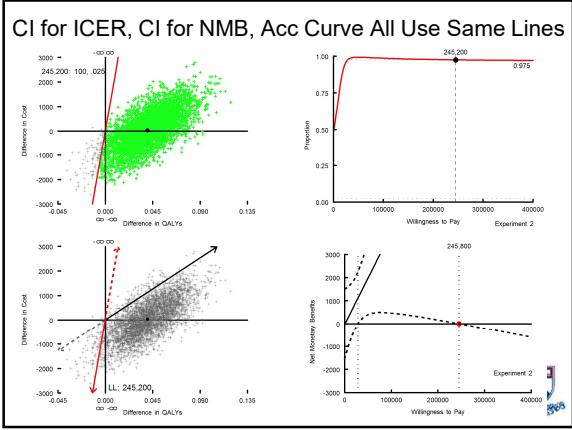
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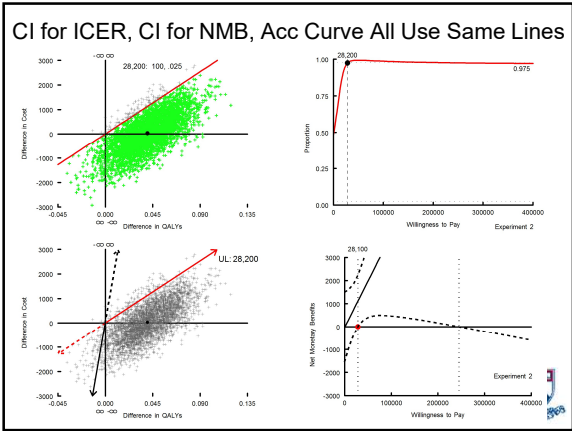
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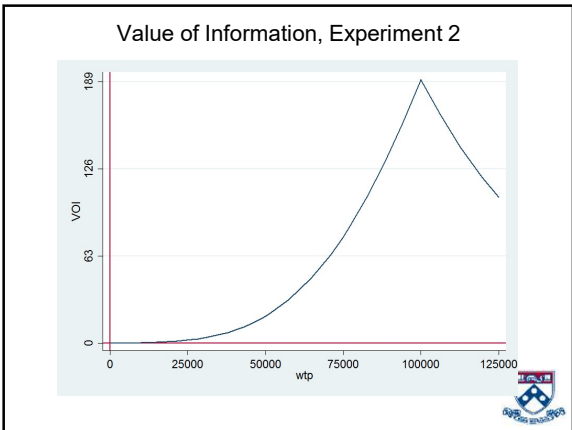
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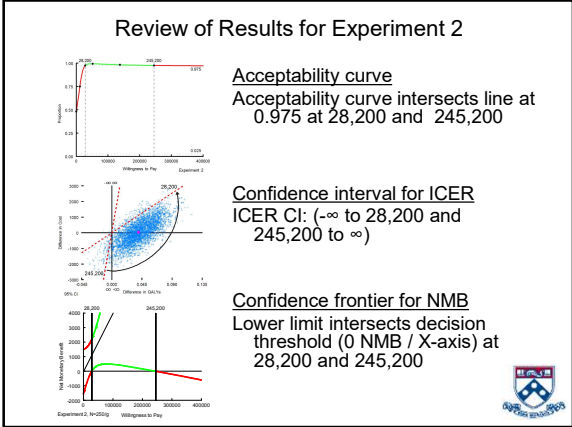
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- ### Pattern 2 Findings
- Refer to findings like these as pattern 2 findings
  - 1 of 2 patterns that occur only when difference in effect is not significant
  - Know we are observing a pattern 2 finding when:
    - Confidence interval for ICER includes Y axis (i.e.,  $LL > UL > PE$  OR  $PE > LL > UL$ )
    - One NMB confidence limit curve intersects decision threshold (0) twice; other limit never intersects decision threshold
    - Acceptability curve intersects a horizontal line drawn at either 0.025 and 0.975 on Y axis twice and never intersects other line
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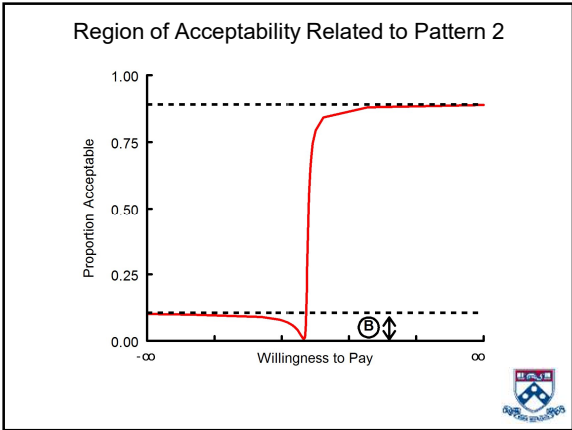
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### 3 Ranges of WTP for Pattern 2 Findings

- In cases where some of boundaries between regions occur at negative values of willingness to pay, may not always observe all 3 regions on acceptability curve or NMB plot

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### Conclusions (1)

- For any given W, an experiment **ALWAYS** supports one of three conclusions:
  - Confident one therapy good value compared to alternative
  - Confident alternative therapy good value compared to first
  - Cannot be confident that two therapies differ in economic value

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### Conclusions (2)

- If goal is to identify which of 3 statements holds for a given W, confidence intervals for cost-effectiveness ratios, confidence intervals for NMB, and acceptability curves **ALWAYS** provide same answer
  - e.g., if W included within CI for CER, then:
    - CI for NMB that is calculated by use of W will include 0, and
    - Fraction of distribution that is acceptable at W will fall between horizontal lines that define decision threshold (e.g., between 0.025 and 0.975)

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### Conclusions (3)

- Confidence intervals for cost-effectiveness ratios provide concise information (i.e., 0, 1, or 2 numbers) that allows determination – based on a particular  $W$  – of confidence about a therapy's value
- Acceptability curves provide added advantage of allowing decision makers to assess alternate levels of confidence if such alternate levels are of interest



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