Frequency of ICER Miscalculation and Misinterpretation in Published Cost-Effectiveness Analyses Comparing More Than Two Alternatives

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Overview

- Study Context and Research Questions
- Background: Incremental Cost Effectiveness Ratio (ICER) calculation and interpretation
- Methods
- Results
- Conclusions
- Recommendations

Study Context and Research Questions

- Study Context
  - The correct method for calculating ICERs for Cost-Effectiveness Analyses (CEAs) that examine more than two alternatives is well-established.
  - Despite that, "it seems remarkably easy to find articles to critique for seminar…"

Research Questions

- What proportion of CEA articles **that examine more than two alternatives** contain errors in ICER calculation or interpretation?
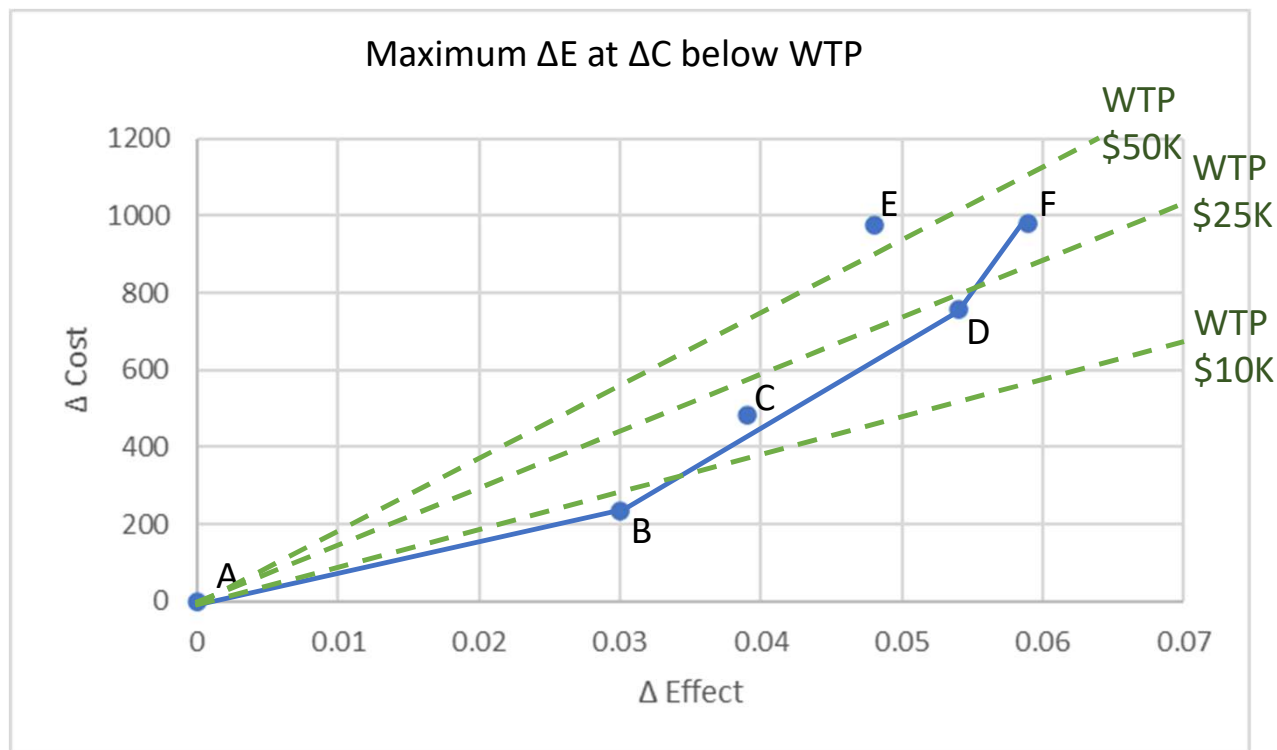- What are the specific types of errors observed?

ICER calculation: two alternatives

$$\frac{Cost_A - Cost_B}{Effect_A - Effect_B} = \frac{\Delta C}{\Delta Q}$$
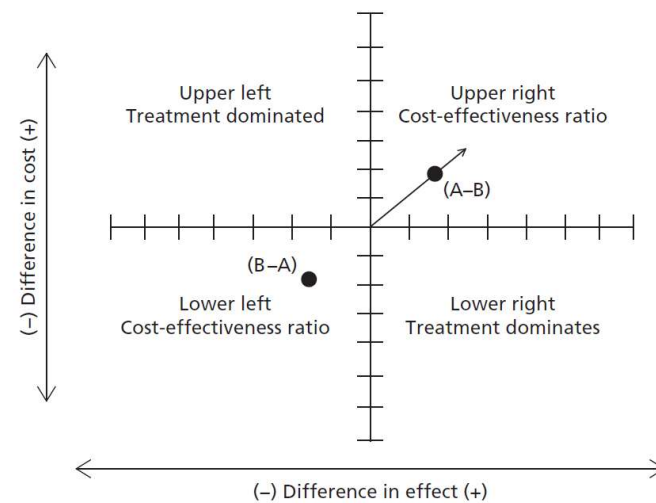
Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. 2nd ed. Oxford University Press; 2015.

ICER calculation: more than two alternatives

Most cost-effective option depends on willingness to pay (WTP) per unit of health gain.

WTP $10,000/QALY: Choose B

WTP $25,000/QALY : Choose D

WTP $50,000/QALY : Choose F

Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. 2nd ed. Oxford University Press; 2015.

Methods: Study Overview

|		
■	Conduct search in PubMed database	Create sample of cost-effectiveness analyses published in 2017
■	Screen articles for Inclusion/Exclusion criteria	First screening based only on title and abstract Second screening and review based on full text
📈	Review articles to determine if ICER calculated and interpreted correctly	Follow sequential protocol to evaluate ICER calculation and interpretation Classify based on first type of error found
✓	Analyze data	Calculate proportion of articles with errors in ICER calculation or interpretation

Methods: Search and Sample Creation

- PubMed search for cost effectiveness articles published in 2017
- 815 articles retrieved
    - Abstracts and Titles screened by two reviewers
        - Exclusion criteria
            - Lacking abstract
            - Not a CEA
            - Only 2 interventions
- 152 articles met criteria

Methods: Sequential Evaluation Protocol

- Screened for errors in the order defined by protocol
  - Full text screened by two reviewers
  - Differences resolved by discussion
- Presence of one error removes article from consideration for assessing additional errors
- Initial Set of Errors
  - Error 1: Average Cost Effectiveness Ratio (ACER)
  - Error 2: All compared to single comparator (All to One)
  - Error 3: Aggregated/overlapping populations or interventions
  - Error 4: Incorrect or multiple options below single WTP identified as cost effective
  - Error 5: Missing WTP
- Other Errors emerged during review
  - Reviewers could not reproduce numbers
    - Not within 5% of Correct, ACER, or All to One)
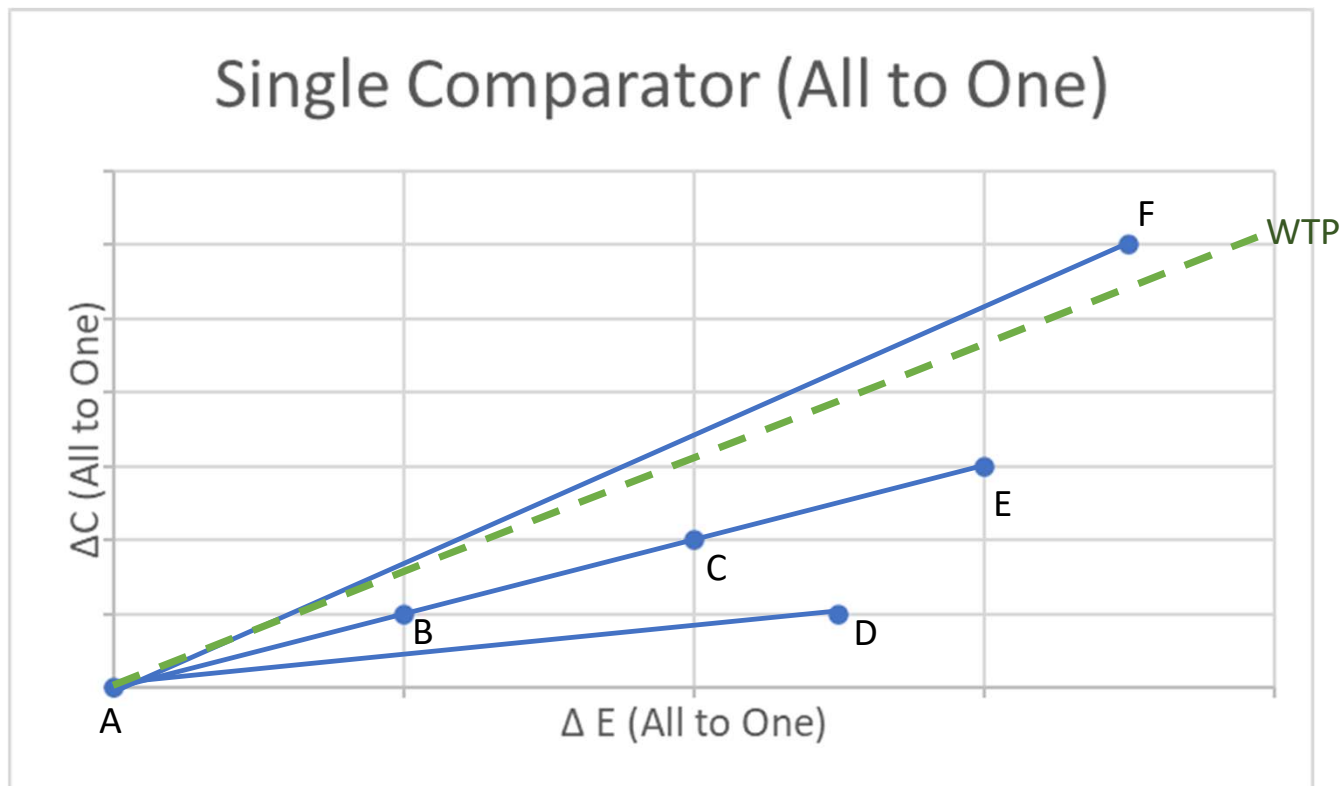 - Other (unique errors)

Miscalculation

Misinterpretation
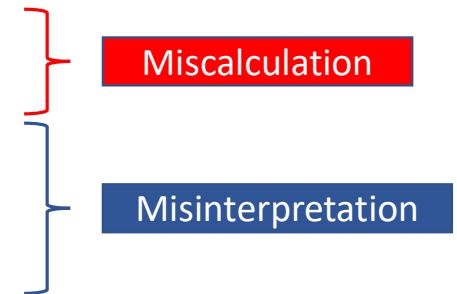
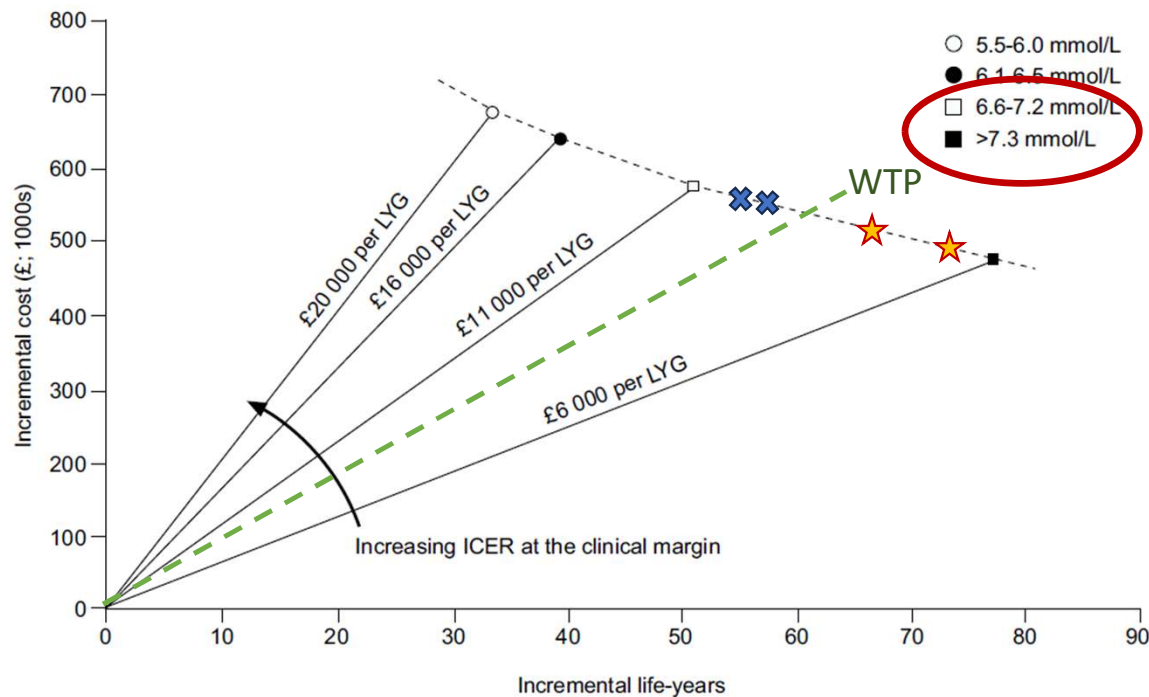# Example of Error 1: ACER Calculation
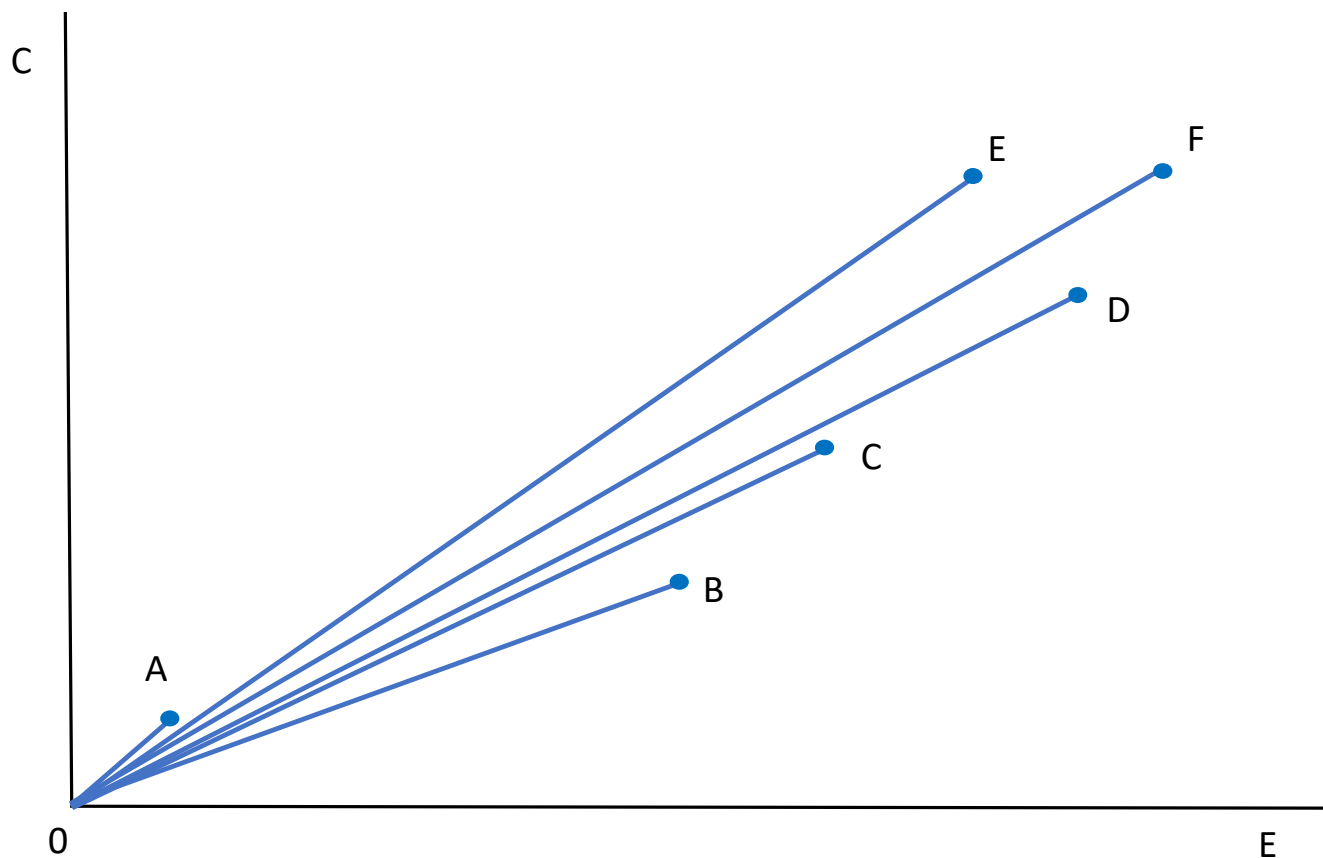
- Average Cost Effectiveness Ratio (ACER): **Cost** (**not ΔC)** of treatment divided by **Effect** (**not ΔE)** of treatment

- Comparison to zero cost and zero effect at origin

Example of Error 2: Single Comparator (All to One)

Single Comparator (All to One)

- Compare to single alternative (usually Standard of Care or Placebo)

- Points B, C, and E all have the same (meaningless) "ICER"!

- Incremental differences between <u>adjacent</u> options are what creates the Cost Effectiveness Frontier

Example of Error 3: Aggregated/Overlapping Populations

Fig. 2. Changing incremental cost effectiveness at the clinical margin on the cost-effectiveness plane (the dotted line represents the estimated cholesterol level production function) [1995 values].[30] **ICER** = incremental cost-effectiveness ratio; **LYG** = life-year gained.

Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000 May;17(5):479-500. doi: 10.2165/00019053-200017050-00006.
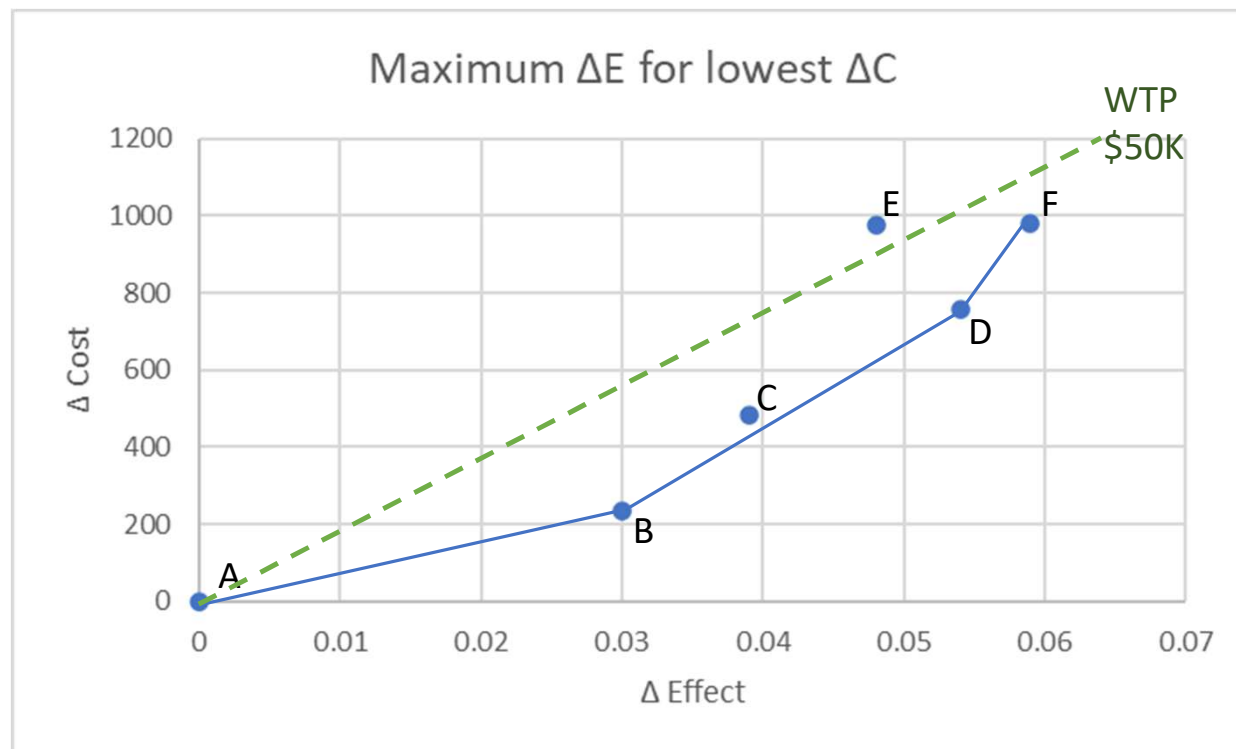
If two subgroups of patients are combined, the possible weighted averages are points in between the black and white squares

This average of 2 subgroups may be CE (★) or not CE (✖) at a given WTP

Heterogeneity! Aggregating populations may obscure important differences

Example of Error 4: Incorrect or Multiple "CE" Options
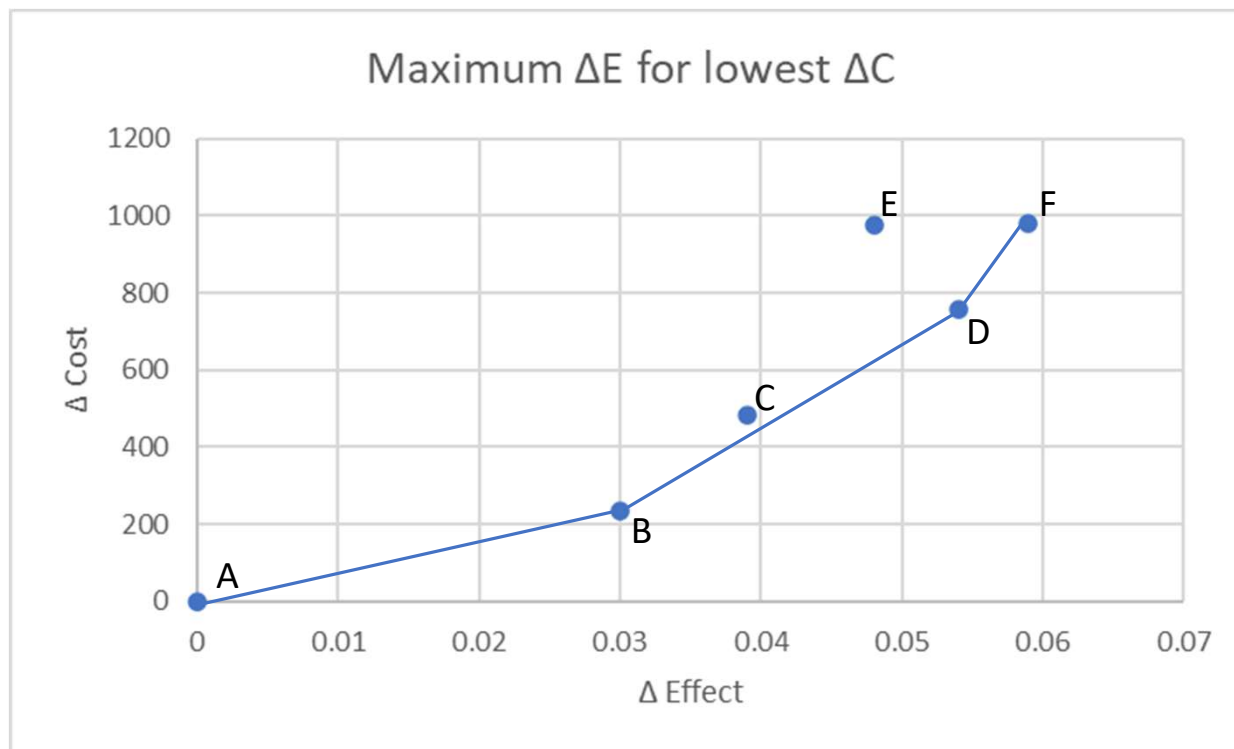

Maximum ΔE for lowest ΔC

Two ways to be incorrect:

"Option B is the Cost-Effective option because it has the lowest ICER below the WTP."

"Options B, D, and F are all Cost-Effective because they are all below the WTP."

Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. 2nd ed. Oxford University Press; 2015.

Example of Error 5: Missing Willingness To Pay

Maximum ΔE for lowest ΔC

Impossible to determine which option is most cost-effective if no WTP is specified!

Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. 2nd ed. Oxford University Press; 2015.

Results

- A **minority** of published articles that met our inclusion criteria were unambiguously correct

**Frequency and Type of ICER Errors,
CEAs published in 2017 that examined >2 alternatives**

Correct 27.6%

Uncertain 7.2%

Errors 65.1%

All to One 35.5%

Other 2.0%

Aggregated Groups 1.3%

Incorrect or multiple options identified as CE 3.3%

Missing WTP 3.9%

Numbers not reproducible 5.3%

ACER 13.8%

14
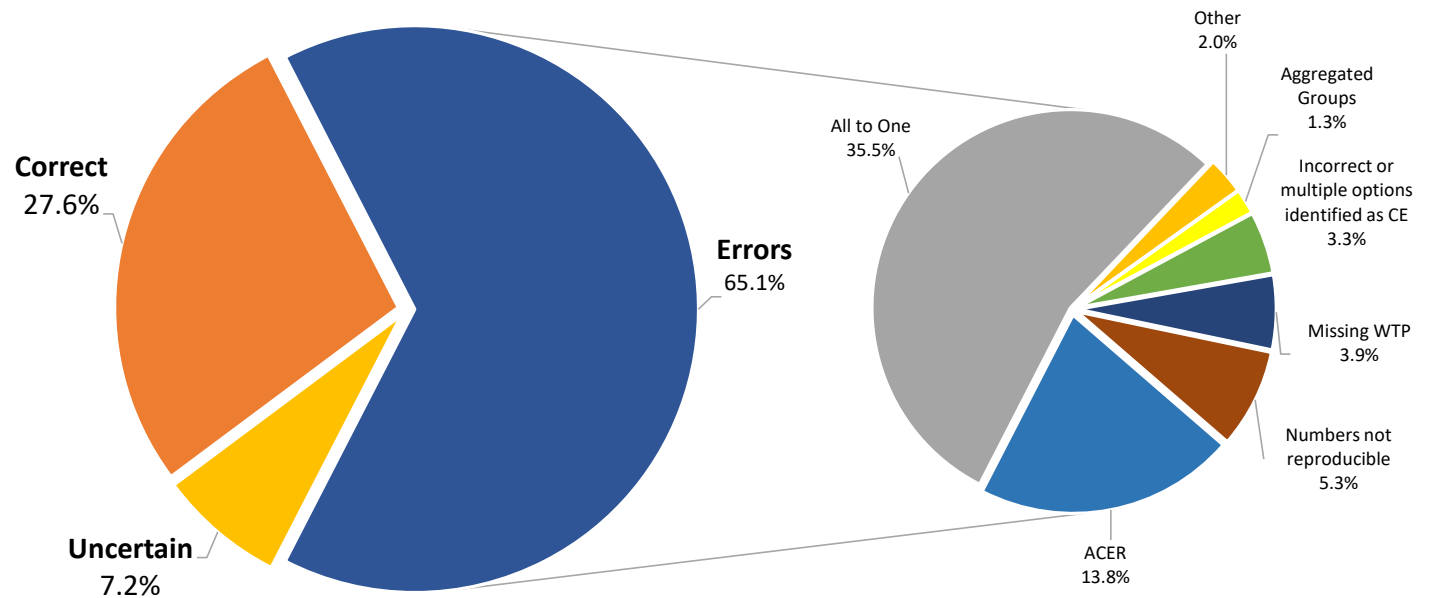
Results

- For articles with more complex ICER calculation (>2 alternatives):
  - 27.6% Correct
  - 7.2% Uncertain (not enough information provided)
  - 65.1% had errors in ICER calculation or interpretation
    - Even if the 5.3% of "Numbers not reproducible" moved to "Uncertain", still have error rate of nearly 60%!
- The majority of errors were "All to One" errors, followed by ACERs
  - These are Error 2 and Error 1 in our protocol
  - Sequential process—articles potentially could have multiple errors

Conclusions

- **Most CEAs that examine more than two therapeutic alternatives use incorrect methods for ICER calculation and interpretation.**

- We saw no acknowledgements or attempts to justify the incorrect approaches as deviations from accepted practice.

- Checklists exist, yet some authors who claimed to follow them still had errors in their articles.

Conclusions: Study Limitations

- **Only considered one error "family" (ICERs)**
  - Other error types exist, e.g. sensitivity analyses, inclusion of all relevant clinical options, errors in cost/effect models

- **Potential for bias exists—all reviewers make judgement calls**
  - Mitigation strategies in this study: multiple reviewers, clear exclusion criteria, clear error definitions, set protocol

- **Search was not exhaustive**
  - We believe it unlikely that articles sourced from PubMed would have more errors than usual

- **Examined methods, not conclusions**
  - Some articles may identify the correct option, by luck rather than rigor

Recommendations and closing thoughts

- If asked to be a reviewer, say yes!
  - You can be part of the solution!
- Carefully review final versions of submitted manuscripts where you are a co-author
- Rethink existing checklists
  - Presenter's opinion: Correct ICER calculation and interpretation in a manuscript is a "need to have", not a "nice to have"
  - Errors should be considered fatal flaws, not just a decrement in points
- Is it time to retire ICERs entirely and move to Net Monetary Benefit (NMB) calculations?
  - Correctly done ICER and NMB calculations yield the same conclusions

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  - Second reader for full-text review
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Questions?

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