EE192

A Simple and Practical Guide to Implementing Generalized Risk-Adjusted Cost-Effectiveness (GRACE): A Case Study in Non-Small Cell Lung Cancer

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BACKGROUND

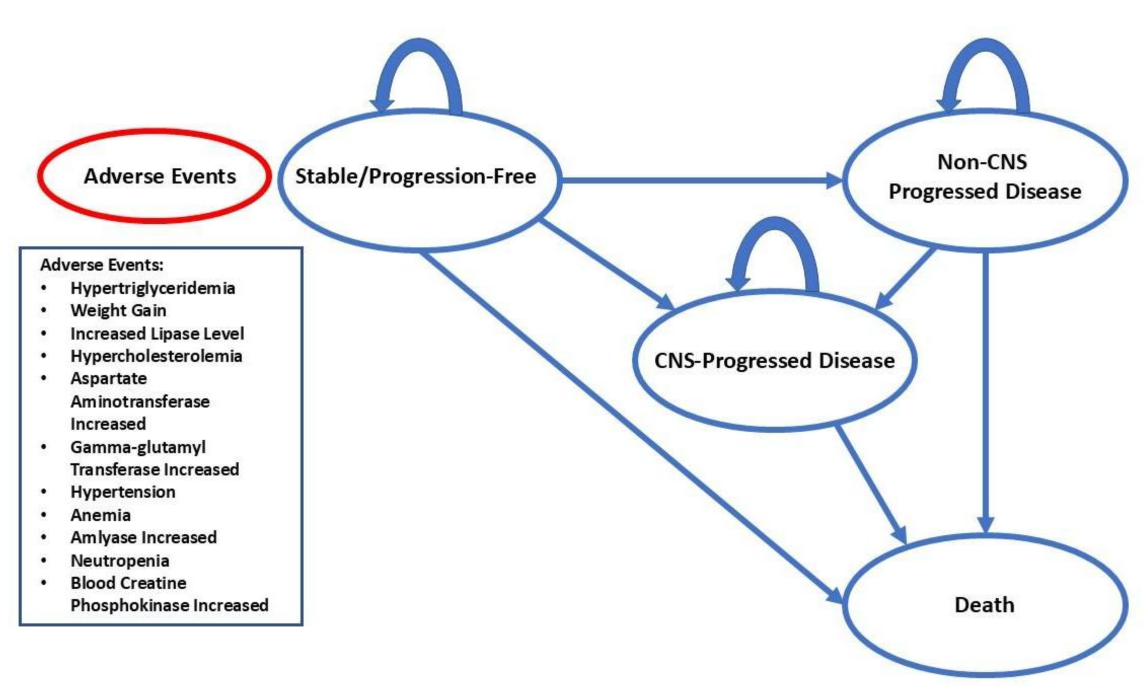
- Traditional cost-effectiveness analysis (CEA) assumes risk-neutrality over health, and omits value elements such as disease severity, value of hope, and equity, **potentially undervaluing treatments for severe illnesses**[1,2]
- Generalized Risk-Adjusted Cost-Effectiveness (GRACE) **relaxes this assumption** by accommodating non-linear returns to health (diminishing returns) within current framework, also factoring these omitted value elements[2]
- As such, GRACE promises a more **comprehensive, equitable, and accurate** approach to value assessment
- However, perceived complexity limits its uptake and may lead to shortcuts resulting in flawed execution

OBJECTIVE

- This study aims to outline a simplified process for implementing GRACE and demonstrates its application by extending a traditional cost-effectiveness analysis (CEA) of three therapies for advanced non-small cell lung cancer (NSCLC) into a GRACE analysis

METHODS (OVERVIEW)

- A traditional CEA model (Mudumba et al. 2025) evaluating alectinib, brigatinib, and lorlatinib in advanced anaplastic lymphoma kinase (ALK)-positive NSCLC was extended into GRACE[3]
- Comparisons were made between traditional CEA and GRACE results, examining the effects of societal versus patient-derived risk preferences and potential shortcuts in implementation
- Statistical significance was assessed at the 5% level using Monte Carlo simulations over 10,000 iterations



*CNS central nervous system

METHODS (STEP-BY-STEP GRACE EXTENSION GUIDE)

Step 1: Health State Mapping to Align Health Indexes

- If the analyst has visual analog scale (VAS)-based health-related quality-of-life (HRQoL) values for each modeled health state, they can be directly input into VAS-based GRACE utility functions (e.g., Mulligan et al., 2024) — no mapping required
- However, if the HRQoL values and the utility function' health index do not align (e.g., using EQ-5D values), a mapping step will be required to ensure alignment of health indexes and subsequent accuracy of GRACE (e.g. map EQ-5D value to VAS)
  - Current implementation relies on VAS-based utility functions
  - Time trade-off (TTO)-based GRACE functions are forthcoming, and will allow analysts to bypass mapping for EQ-5D-style inputs

Step 2: Estimation of Risk-Adjusted Utilities

- Insert VAS-based health values (or mapped equivalents) resulting from step 1 into GRACE utility functions to calculate risk-adjusted utility for each health state
  - Available functions under expected utility theory include constant relative risk aversion (CRRA), hyperbolic absolute risk aversion (HARA), and 1 and 2-parameter expo power (EP-1 and EP-2), estimated in Mulligan et al. 2024; patient-derived TTO-based functions forthcoming
- These utility functions capture non-risk-neutrality over health, allowing for inclusion of risk aversion, diminishing returns, and value of hope—which traditional CEA ignores

Step 3: Replacement of Traditional HRQoL Values

- Once risk-adjusted utility values have been estimated via step 2, they will replace the HRQoL values used in the CEA model
- The resulting model will calculate GRA-QALYs (Generalized Risk-Adjusted QALYs), which factor in health status (disease severity) and non-linear returns to health, satisfying the following equations to extend CEA into a GRACE analysis

What needs to be changed for GRACE? (Spoiler: Not much!)

The following represents a **traditional QALY**, where t indicates time (model cycles), β is the discount factor, Q is the HRQoL/health, and S is expected survival (e.g., life years). T signifies treatment (intervention), while Soc indicates comparator:

$$\Delta QALYs \equiv \sum_{t=0}^{\infty} \beta^t Q_T \cdot S(t)_T - \sum_{t=0}^{\infty} \beta^t Q_{Soc} \cdot S(t)_{Soc}$$

The following depicts a **generalized risk-adjusted QALY (GRA-QALY)**, where HRQoL/health is simply replaced by utility (W) as a function of health (H), while the rest (e.g., survival, discounting, time, costs) remains the same:

$$\Delta GRA-QALYs \equiv \sum_{t=0}^{\infty} \beta^t W(H_T) \cdot S(t)_T - \sum_{t=0}^{\infty} \beta^t W(H_{Soc}) \cdot S(t)_{Soc}$$

Since incremental GRA-QALYs in this approach represent change in utility as opposed to HRQoL, K (WTP) is not adjusted

PRELIMINARY RESULTS

	Traditional CEA		GRACE		Comparison
	Mean ICER	95% CI	Mean ICER	95% CI	Paired T-Test P-Value
Alectinib vs. Brigatinib	$245,622 /QALY	$237,448 - $253,796 /QALY	$229,716 /GRA-QALY	$222,083 - $237,348 /GRA-QALY	<0.0001
Lorlatinib vs. Brigatinib	$483,259 /QALY	$475,646 - $490,871 /QALY	$420,761 /GRA-QALY	$414,142 - $427,379 /GRA-QALY	<0.0001

*Based on 10,000 Monte Carlo simulations; GRACE analysis was based on implementation shortcut of skipping step 1, while using EP-2 utility function from Mulligan et al. 2024

PRELIMINARY RESULTS & NEXT STEPS

- GRACE analysis, based on societal utility functions and implementation shortcuts, demonstrated systematic shifts in incremental cost-effectiveness ratios (ICERs) over 10,000 iterations
- For alectinib vs. brigatinib, the median ICER decreased from $248,990/quality-adjusted life year (QALY) under the traditional model to $232,568/QALY under GRACE ($p < 0.001$), representing a 7% reduction
- Similarly, the median ICER for lorlatinib vs. brigatinib decreased from $481,635/QALY to $420,038/QALY ($p < 0.001$), a 13% reduction
- Across both comparisons, GRACE adjustments showed consistent effects over iterations
- Results incorporating patient-centric preferences will be presented following completion of an ongoing study

CONCLUSIONS

- GRACE analyses can significantly shift cost-effectiveness conclusions and accommodate both societal and patient-centered risk preferences
- This study provides a step-by-step guide to extending traditional CEA models into GRACE, demonstrating its feasibility and flexibility in advancing more accurate, comprehensive, and equitable value assessments

SCAN ME

← Scan QR code for downloadable excel file with programmed utility functions for step 2 adjustment

REFERENCES

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