The impact of Generalized Risk Adjusted Cost-Effectiveness Analysis (GRACE) on value assessment: Formal adoption or global methodological trends?

Yi Y[1], Meiwald A[1], Hirst A[1], Heron L[1]
[1]Adelphi Values PROVE, Bollington, Cheshire SK10 5JB, United Kingdom

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Introduction and objectives

- Traditional cost-effectiveness analysis (CEA) assumes all quality adjusted life years (QALYs) as equal and assumes risk-neutrality. As a result, it may undervalue interventions for patients with severe illness, major disability, or substantial outcome uncertainty.[1,2]
- The generalized risk-adjusted cost-effectiveness (GRACE) framework was proposed to address this limitation by incorporating disease severity, risk aversion, and variation in how people value gains in quality of life versus life expectancy across health states. In principle, GRACE gives greater value to health gains for patients who start from worse baseline health and to interventions that reduce catastrophic risk or uncertainty.[1,2]
- Interest in GRACE has grown alongside wider concern that conventional health technology assessment (HTA) methods may not fully reflect equity, unmet need, or the social preference to prioritize the worst-off.[3] At the same time, major HTA organizations have been exploring severity-sensitive approaches, although direct routine adoption of GRACE remains limited.[3]
- Objective: To review the current status of GRACE applications, summarize reported impacts on value assessment outcomes, assess alignment with major global HTA frameworks, and identify key strengths, critiques, and implementation challenges.

Methods

- A targeted review of HTA agency websites, PubMed / PubMed Central, and ISPOR / Value in Health materials from 2020 to 2026 was conducted.
- Primary GRACE applications were reviewed to identify additional value parameters, data sources and reported impacts on incremental cost-effectiveness ratios (ICERs), willingness-to-pay (WTP) thresholds, and net monetary benefit (NMB).
- HTA methodological guidelines were examined to assess whether agencies adopted GRACE or implicitly applied GRACE-consistent approaches, including severity modifiers, unmet-need weighting, or shortfall-based prioritization.
- Findings were synthesized narratively to identify recurring strengths, critiques, and implementation barriers.

Conclusion

- GRACE represents a promising extension to traditional CEA by offering a continuous, preference-based framework for valuing disease severity and protection again risk and uncertain outcomes, dimensions often addressed through ad hoc thresholds or qualitative deliberation in current HTA practice.
- While GRACE can strongly influence ICERs, WTP thresholds, and NMB in high-burden conditions, full standalone adoption by HTA agencies remains limited, reflecting methodological complexity and evidentiary uncertainty.
- The prevailing global trend is not direct adoption of GRACE, but rather a shift away from strictly flat-QALY valuation toward severity-sensitive and unmet-need-sensitive approaches. In this context, GRACE's greatest near-term contribution may be as a unifying conceptual and analytical framework to help calibrate, validate, and rationalise existing HTA modifiers.
- Future research should prioritise standardising parameter estimation, improve transparency and reproducibility, and directly compare GRACE with severity-weighting mechanisms currently used by HTA bodies to assess its practical added value.

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Results

Review of existing GRACE applications

- A small but growing body of GRACE applications exists across sickle cell disease, non-small cell lung cancer, hepatitis C, and neurological conditions, alongside cross-disease or illustrative analyses (Table 1).
- Published GRACE applications remain concentrated in methodological papers and conference-based case studies rather than HTA submissions.
- All identified GRACE applications were conducted in the United States, indicating limited geographic adoption to date. In most studies, GRACE was implemented by extending an existing traditional CEA model to incorporate additional value elements, including risk preferences, mostly based on .[4] Results were commonly presented by comparing ICERs derived from traditional CEA with those obtained under the GRACE framework.
- Across studies, GRACE consistently assigns higher value to interventions targeting more severe disease relative to traditional CEA, with reported ICERs reductions ranging from 6% to 93% and a corresponding increase in implied WTP thresholds of roughly 10% to 50%, depending on assumptions and parameterisation (Table 1).
- A white paper found that applying GRACE, dynamic pricing, and stacked cohorts changed the proportion of interventions judged to provide value for money from 8/20 under traditional CEA to 17/20 in the benchmark analysis and 18/20 in the sensitivity analysis.[12] As this study applied GRACE across 20 prior ICER case studies, results are therefore not directly comparable with single-disease GRACE-only applications.

Table 1. Empirical GRACE applications

Reference	Type	Disease	Intervention vs Comparator	Additional GRACE parameter values	Impact of GRACE compared to traditional CEA	Key message
Graf et al 2025[5]	Full	SCD	Gene therapies: exa lovo-cel and exa-cel vs SoC	Hu = 0.60; Ht = 0.75; expo-power utility inputs: a = 2.176, b = 2.6152, c = 1; δ = 0.57; CRRA p = 0.2822; ε = 1.76; ω_h = 0.85; R = 1.72	**ICER ↓ ~6%** **WTP ↑ ~50%**	**GRACE assigns greater value to potentially curative therapies in severe disease.**
Kleintjens et al. 2024[6]	Poster	R4	Gene therapies: exa lovo-cel and exa-cel vs SoC	Disease-specific GRACE parameter values were not reported.	**ICER ↓ ~6%** **WTP ↑ ~50%**	**Same as above**
Mudumba et al. 2025[7]	Poster	mNSCLC	Alectinib vs brigatinib; Lorlatinib vs brigatinib	Mean relative risk aversion = 0.680; SD = 1.843; median = 0.350; 95% CI = 0.506–0.855; insurance value share = 80.2%; other disease-specific GRACE parameter values were not reported.	**ICER ↓ 7–13%**	**Severity adjustment can improve oncology value assessment**
Chou et al. 2023[8]	Full	HCV	DAAs vs peginterferon/ribavirin	Hu = 0.664; life expectancy gap = 12.5 years; TTO geometric mean = 0.819; $WTP_{LE\ vs\ QoL}$ = 18%; δ = 1.867; ε = 1.25; ω_h/ω_c = 2.125; R ≈ 1.31;	**ICER ↓ 93%**	**GRACE shows that insurance value and risk reduction can strongly affect value**
Hsu L 2024[9]	Poster	AIS	AI intervention vs usual care	Numerical GRACE-specific parameters were not reported.	**Net benefit 1.4-2.5 times**	**GRACE better captures the value of disability reduction and caregiver burden**
Shafrin et al. 2026[10]	Full	Neurological conditions	Hypothetical treatment delaying mobility impairment vs standard care	Full disease-specific GRACE parameters were not reported.	**NMB ↑ 11.6%** **WTP ↑ 9.7%**	**GRACE increases the assessed value of preventing disability progression.**
Mulligan et al 2025[11]	Full	53 diseases	69 drugs	Power utility; exact utility approach; disease-specific GRACE parameters were not reported	**Mean VBP ↑ 7.5%** **Budget impact ↑ 2%**	**GRACE tends to reallocate value from less severe to more severe conditions.**

AIS, Acute ischemic stroke; DAAs, Direct-acting antivirals; HCV, Hepatitis C virus; ICER, Incremental cost-effectiveness ratio; mNSCLC, metastatic non-small cell lung cancer; SCD, sickle cell disease; SoC, Standard of care; TTO, Time trade-off; VBP, Value-based price; WTP, Willingness to pay; CI, Confidence Interval; SD, Standard deviation
Hu and Ht: Quality of life (QoL); δ, Marginal rate of substitution between life expectancy (LE) and QoL; CRRA p, Constant Relative Risk Aversion utility input; ε, Certainty equivalence ratio; ω_h, Change in utility per health-related QoL gain; ω_h/ω_c, change in WTP with risk aversion in utility and cost; R, Disease severity ratio; $WTP_{LE\ vs\ QoL}$,Willing to treat off between LE and QoL

Current global HTA status

- Direct formal adoption of GRACE remains limited across major HTA agencies. None of the agencies reviewed had adopted GRACE as a full routine quantitative framework incorporating severity, risk preference, and insurance value in one unified model (Table 2).
- ICER (US) has formally signalled strong methodological interest in GRACE and related non-linear approaches to value assessment that relax the assumption of linear QALY valuation. ICER is actively exploring methods to reflect severity, risk aversion, and insurance value through quantitative adjustments to health gains, engaging stakeholders and monitoring international HTA practice. However, ICER considers the evidence base insufficiently mature to adopt a formal severity-weighted metric at present, and therefore continues to rely on transparent, deliberative consideration of these factors, with the possibility of future iterative methodological updates.
- Several HTA agencies show increasing convergence with GRACE-like principles, albeit through distinct mechanisms rather than explicit GRACE adoption (Table 2).
  - Severity is the most aligned GRACE principle: NICE and NOMA (Norway) use more explicit severity-related approaches, while ICER (US), CADTH (Canada), PBAC (Australia), HAS (France), and G-BA / IQWiG (Germany) reflect severity more indirectly through deliberation, added-benefit assessment, or ethical appraisal criteria.
  - Unmet need is commonly considered, but mostly qualitatively, usually incorporated through committee judgment or appraisal rather than formal mathematical weighting.
  - Shortfall-based prioritization shows partial convergence with GRACE: NOMA (Norway) is the clearest example, with NICE (England and Wales) also conceptually related, suggesting movement away from strictly flat QALY valuation toward prioritizing patients with worse baseline health.
  - Risk preference and insurance value remain the least integrated principles as they are not routinely modelled in current HTA practice; even where interest exists, adjustment remains largely qualitative.

Table 2. Alignment of major HTA agencies with GRACE principles

HTA body	Formal severity modifier	Unmet need weighting	Shortfall-based prioritisation	Risk / uncertainty adjustment	Notes on relation to GRACE
ICER (US) (2023)[13]	❌ No formal multiplier	⚠️ Yes, deliberative	❌ No formal shortfall metric	⚠️ Qualitative only	Explicit methodological interest in GRACE and non-linear valuation, but currently addresses severity, unmet need, and insurance value through deliberation rather than quantitative adjustment.
NICE (England and Wales) (2026)[14]	✅ Yes, severity modifier	⚠️ Indirect	⚠️ Conceptually related	❌ No explicit risk adjustment	Closest to GRACE in formal structure but uses categorical modifiers rather than continuous preference-based adjustment.
CDA-AMC (Canada) (2024)[15]	❌ No formal multiplier	⚠️ Yes, committee deliberation	❌ No	❌ No explicit risk adjustment	Conceptual alignment with GRACE through consideration of severity and unmet need, but without quantitative weighting.
NOMA (Norway)[16]	⚠️ Yes, severity criterion used in prioritisation	⚠️ Indirect	✅ Yes	❌ No explicit risk adjustment	One of the clearest examples of convergence with GRACE principles, as higher severity or shortfall can justify greater willingness to pay, although risk aversion and insurance value are not directly modelled.
PBAC (Australia)[17]	❌ No formal multiplier	⚠️ Yes	❌ No formal shortfall metric	❌ No explicit risk adjustment	Considers disease severity, clinical need, and in some cases Rule of Rescue, showing conceptual alignment with GRACE through severity and unmet need, but not through quantitative adjustment.
HAS (France) (2020/updated 2025)[18]	❌ No formal QALY modifier	⚠️ Indirect	❌ No	❌ No explicit risk adjustment	Considers disease severity and clinical added value through SMR/ASMR and deliberative assessment but does not apply GRACE-style quantitative weighting.
G-BA / IQWiG (Germany) (2023)[19]	❌ No formal QALY modifier	⚠️ Indirect	❌ No formal shortfall metric	❌ No explicit risk adjustment	Does not use QALYs as the main basis for value assessment but added-benefit evaluation is sensitive to severity and magnitude of clinical improvement.
TLV (Sweden)[20]	❌ No formal multiplier	⚠️ Yes, through need-solidarity principle	❌ No formal shortfall metric	❌ No explicit risk adjustment	Gives greater priority to patients with greater medical need under its ethical platform, making it conceptually close to GRACE on prioritizing the worse-off, though not mathematically implemented.

Notes: ✅ formal feature; ⚠️ indirect, deliberative, or partial feature; ❌ not formally identified.
ICER (US), Institute for Clinical and Economic Review; NICE, National Institute for Health and Care Excellence; CDA-AMC, Canada's Drug Agency; HAS, Haute Autorité de Santé (French National Authority for Health); G-BA, Gemeinsamer Bundesausschuss (Federal Joint Committee); IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); PBAC, Pharmaceutical Benefits Advisory Committee; TLV, Dental and Pharmaceutical Benefits Agency; NOMA, Norwegian Medical Products Agency.

Strengths, critiques, and challenges

- Across the literature, GRACE's main strengths include providing a mathematically coherent, economic-theory-based framework for incorporating disease severity, valuing reductions in outcome uncertainty (insurance value), and supporting equity-sensitive assessments for severe conditions.[1,2]
- Key critiques and challenges include high methodological complexity and difficulty in reliably estimating core parameters (e.g., relative risk aversion, baseline untreated health) compared with standard CEA. Furthermore, there is a risk of "double counting" if GRACE is layered over existing HTA severity modifiers.[13, 21]
- These limitations complicate interpretation of global methodological convergence, as many HTA reforms are conceptually similar to GRACE without being methodologically equivalent.