# Implementing the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) approach – a case example in HCV therapies

Marlon Graf, PhD[1] • Jacquelyn W. Chou, MPP, MPL[1] • Oliver Diaz Espinosa, PhD[1] • Iris Brewer, MS[1] • Zachary Heim[1] • James Baumgardner, PhD[1]

1. PRECISIONheor, Bethesda, MD, USA.

## BACKGROUND

- Cost-effectiveness analysis (CEA) has been seeing increased usage by healthcare decisionmakers in the United States to assess the comparative economic value of new vs. existing technologies.
- CEAs monetize health benefits and produce incremental cost effectiveness ratios (ICER) to estimate the costs required to gain an additional quality-adjusted life-year (QALY) under a new technology.
- However, application of CEAs as a decision tool to determine whether a new technology represents "value for money" is not without controversy:
  - The validity of QALYs as a decision-making tool in health has been disputed.[1,2]
  - The ability of standard CEA approaches to adequately capture relevant drivers of value for a given treatment has been questioned.[3,4]

## OBJECTIVES

- This study implements a generalized cost-effectiveness analysis (GCEA), including key value drivers of relevance and importance to society, using a class-level GCEA of direct-acting antiviral drugs (DAAs) for the treatment of genotype 1 chronic hepatitis C (HCV) as a case study.
- This study estimates the societal value of DAAs over peginterferon alfa and ribavirin (PEG/riba) considering both novel modeling elements (e.g., transmission, dynamic pricing and genericization) as well as novel aspects of value (e.g., productivity and caregiver burden).[5]
- This poster features this study's implementation of differential valuations of life years vs. quality of life (QoL), disease severity, and insurance value using the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) framework (first introduced by Lakdawalla & Phelps [L&P (2021)]).[6]

## METHODS

### GCEA Methodology

- To provide a comprehensive estimate of societal value for DAAs, we adapted the HCV Transmission and Progression (TaP) model by Van Nuys and colleagues,[7-9] into a GCEA, including additional novel elements and methods for capturing value.
- The HCV TaP model is a discrete time Markov model simulating HCV treatment and progression.[7] The simulation was conducted over a 70-year time horizon, and population outcomes (such as number of people in each disease state) are collected at the end of each cycle.
- This study evaluated the cost-effectiveness of DAAs vs. status quo therapy of PEG/riba in a baseline scenario consistent with a more conventional CEA approach. Additional modeling and value elements were added incrementally in the following order: (1) Disease transmission, (2) Market pricing and competition effect on aggregate efficacy, (3) Genericization after patent expiry, (4) Expanded productivity costs, (5) Caregiver burden and (6) Differential values of life-years vs quality of life, disease severity, and insurance value as accounted for in the GRACE framework.[6]
- Overall study results are presented in Figure 1 and were presented in detail elsewhere.[10]

### GRACE Methodology and Parameter Estimates

- Among the novel elements introduced by the GRACE framework is the idea of a diminishing marginal rate of substitution between life years and health-related QoL, whereby individuals are willing to trade fewer years of survival for improvements in QoL as they near end of life.[6]
- The GRACE framework changes CEA practice with the following three elements incorporated in our analysis:
  1. Willingness to pay (WTP) increases substantially with **untreated illness severity** or **pre-existing permanent disability**, and ends up lower for mild diseases but higher for severe diseases compared with conventional CEA;
  2. There is an adjustment for **uncertainty in treatment effectiveness**; and
  3. The **marginal rate of substitution (MRS) between life expectancy and QoL** varies with health state.
- To apply the GRACE framework, a series of GRACE factors were applied to the baseline model results, following the framework laid-out by L&P (2021)[6] as shown in Table 1:
  - We estimated the marginal rate of substitution (MRS) between life expectancy (LE) and QoL as 1.867, implying that patients with HCV are willing to trade, on average, 36 months in exchange for perfect health.
  - We assumed a coefficient of relative risk aversion of 2.125 and an average HCV health loss of 0.336 to estimate a disease severity ratio of ~1.31, based on L&P (2021).[6]
  - All cost parameters were inflated to 2021 U.S. dollars and future costs and QALYs were discounted at 3% annually.

### Uncertainty Around GRACE Parameters

- The underlying GCEA model was subject to various sensitivity analyses: (1) Adjusting model time horizon (5, 20, 40 years), (2) Implementing an additional health care inflation rate, where healthcare costs have an inflation rate of 2.8% relative to an all-cost inflation rate of 2.5%, (3) Varying generic pricing discounts to 30% and 99.6%.
- Sensitivity of GRACE elements was also tested, applying reasonable ranges suggested by L&P (2021):[6] (1) Certainty equivalence ratio [ε] varied from 1.00 (low) to 1.50 (high), (2) Change in utility (happiness) with health-related QoL [$\omega_h$] varied from 0.75 (low) to 1.00 (high), (3) Rate at which utility changes with income [$\omega_c$] varied from 0.30 (low) to 0.50 (high), (4) Disease severity ratio [R] varied from 1.09 (low) to 1.56 (high), (5) Societal WTP / cost-effectiveness threshold [$\frac{C_0}{H_0}$] varied from $50,000 to $150,000, as these thresholds are commonly used by HTA organizations.
- To assess uncertainty around the GRACE parameter estimation, we then estimated model results separately for the base case, as well as the low and high scenarios outlined above.

Table 1: GRACE framework formulas and components

| GRACE-adjusted ICER: | ≤ | GRACE-adjusted WTP threshold |
|---|---|---|
| $\frac{\Delta Cost}{\Delta S * \delta + S * (\Delta Q * \varepsilon)}$ | | in terms of cost per QALY: $\frac{\omega_h}{\omega_c} * R * \frac{C_0}{H_0}$ |

**ΔCost and ΔQ** are changes in costs and QALYs respectively, obtained as outputs from our baseline model.

**ΔS** is the change in life expectancy obtained from the literature as the gap between life expectancy for people with and without HCV, where $LE_{noHCV} - LE_{HCV} = 12.5\ yrs$.[11]

**δ** $= \frac{(1-QoL_{HCV})}{WTP_{LE\ vs\ QoL}} = \frac{33.6\%}{18\%} = 1.867$ represents the marginal rate of substitution (MRS) between life expectancy and quality of life,[6] where we estimate weighted average QoL as 0.664[12] and, given a geometric mean time trade-off (TTO) score of 0.819 and an estimated remaining life expectancy of 71.1-54.5=16.6 years,[11] that patients with HCV are willing to trade, on average, $WTP_{LEvsQoL} = (1 - 0.819) * 199\ months = 36\ months\ or\ 18\%$ in exchange for perfect health.[13]

For the certainty equivalence ratio **ε**, we assume a value of 1.25 due to lower expected variance of outcomes with DAAs compared to PEG/riba.[6]

$\frac{\omega_h}{\omega_c}$ is the change in willingness to pay with risk aversion in utility and cost, assumed to be $\frac{0.85}{0.4} = 2.125$, based on L&P (2021).[6]

**R** is the disease severity ratio, assumed to be $R$~1.31 based on Table 1 in L&P (2021)[6] and a combination of average HCV health loss $\iota^* = (1 - 0.664) = 0.336$ and relative risk aversion over QoL $r_H^* = 1$.

$\frac{C_0}{H_0} = \$174{,}781\ \text{per QALY}$ represents the WTP for QALYs, as calculated by L&P (2021),[6] where $C_0$ =$73,277 GDP per capita * (1- 0.143 share of HC expenditures) =$62,786 and $H_0$ was assumed to be 1.[14,15]

## RESULTS

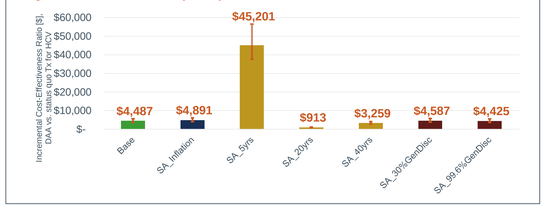
- A traditional CEA model of DAAs compared to PEG/riba yields an ICER of $64,512/QALY.
- Expanding the model into a GCEA with the addition of transmission dynamics, dynamic price and efficacy, genericization, productivity loss, and caregiver spillover leads to an improved ICER of $5,609/QALY
- Incorporating disease severity, insurance value and differential valuations of LYs v QoL through the GRACE framework, in addition to the novel model and value elements, results in an ICER of $4,487/QALY (Figure 1).
- The GRACE-adjusted WTP threshold, accounting for per-capita health expenditures, suggests DAAs would be cost-effective at $171,781/QALY.
- Model results remained consistent across a wide range of assumptions and sensitivity analyses, both on traditional and GRACE-specific model parameters (Table 2 and Figure 2).

Figure 1. Incremental Cost-Effectiveness Ratio of DAA Treatments vs. peginterferon alfa and ribavirin (PEG/riba) for Hepatitis C


Table 2. GRACE sensitivity analysis results

| Model | GRACE Parameter Assumptions | | |
|---|---|---|---|
| | **Base Model** $\varepsilon$=1.25; $\omega_h$=0.85; $\omega_c$=0.40; $R$=1.31 | **Low Model** $\varepsilon$=1.00; $\omega_h$=0.75; $\omega_c$=0.30; $R$=1.09 | **High Model** $\varepsilon$=1.50; $\omega_h$=1.00; $\omega_c$=0.50; $R$=1.56 |
| **Base** | $4,487 | $5,609 | $3,739 |
| **SA_Inflation** (2.8% medical vs. 2.5% all-cost inflation rate) | $4,891 | $6,114 | $4,076 |
| **SA_5yrs** (5-year model time horizon) | $45,201 | $56,500 | $37,668 |
| **SA_20yrs** (20-year model time horizon) | $913 | $1,141 | $760 |
| **SA_40yrs** (40-year model time horizon) | $3,259 | $4,074 | $2,716 |
| **SA_30%GenDisc** (30% generic pricing discount) | $4,587 | $5,734 | $3,823 |
| **SA_99.6%GenDisc** (99.6% generic pricing discount) | $4,425 | $5,532 | $3,688 |

Figure 2. GRACE sensitivity analysis results




## CONCLUSIONS

- Our study provides a roadmap of a potential approach for estimating needed parameters to incorporate GRACE model elements as described by L&P (2021).[6]
- Relative to the ICER of $5,609 in our GCEA model, adding the GRACE elements led to an additional 20% decrease in ICER values and implied that societal WTP for DAAs compared to PEG/riba as a treatment for HCV is $174,781.
- Combining GRACE with novel value aspects (e.g., productivity and caregiver burden) and modeling elements (e.g., transmission, dynamic pricing and genericization) in the context of a full GCEA results in a 93% decrease in ICER values compared to a traditional cost-effectiveness model, underscoring the importance of these additional modeling and value components along with GRACE framework elements in reflecting the comprehensive treatment value.
- Modeling guideline organizations, such as ISPOR, should consider developing best practices and recommendations for broader applications of a GCEA or elements of a GCEA, such as the elements found in the GRACE framework, to ensure appropriate valuation of medicines.

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