EE466

Implementing the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Model for Sickle-Cell Disease – A Case Study

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BACKGROUND

- Sickle cell disease (SCD), one of the most prevalent genetic blood disorders in the United States, significantly impairs quality of life (QoL) and leads to early mortality.[1]
- The Institute for Clinical and Economic Review conducted a health technology assessment (HTA) to assess the cost-effectiveness of two recently approved gene therapies, exa-cel and lovo-cel, for the treatment of SCD.[2]
- Traditional cost-effectiveness analyses (CEAs) do not adequately address health returns by disease state severity, treatment outcome uncertainty, and preference for quality of life over extension of life.[3]
- Generalized Risk-Adjusted Cost Effectiveness (GRACE) is a new approach that modifies standard CEA to account for these elements of value.[4,5]
- The Institute for Clinical and Economic Review has proposed an initiative to pilot the GRACE framework in their HTAs to explicitly reflect individual and/or societal value judgments related to disease severity, outcome uncertainty, and risk aversion.[6]
- To explore feasibility and implications of this proposed approach, we applied the GRACE framework to the former assessment of gene therapies for SCD.[2]

OBJECTIVE

- This study aimed to quantify the societal value of curing SCD by using the GRACE method to adjust the ICER and the WTP thresholds, incorporating disease severity, reduction of uncertainty in treatment outcomes, and preference for quality of life over extension of life.

METHODS

GRACE Framework

- Implementing the GRACE framework alters the existing CEA (Beaudoin et al, 2023)[2] in three ways:[4,5]
  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) An adjustment for **uncertainty** in treatment outcomes is made; and
  3) The **marginal rate of substitution (MRS)** between life expectancy (LE) and QoL varies across different health states.
- The GRACE framework and components are outlined in **Table 1**.

Estimating GRACE parameters

- GRACE parameter estimates were taken from the literature and are briefly described below.

Health state utility:

- First, we derived the expo-power and constant relative risk-aversion (CRRA) utility using estimates from Mulligan et al (2024) and L&P (2023).[3,4]
- Using these measures, we then estimated the MRS based on the utility for the untreated health ($W(H_u)$), the utility resulting from treatment ($W(H_t)$), and the incremental life expectancy (ΔLE).

Risk aversion:

- Relative risk-aversion was calculated using $r_H{}^* = -\frac{W''(H)}{W'(H)}H$ which reveals the cost to consumers from variation in treatment effects.
- We calculated empirical estimates for the relative risk parameters over the full range of health [0-1], according to the pooled utility and risk estimates provided in Mulligan et al (2024).[3]

WTP:

- The GRACE parameter for the adjustment of the traditional WTP was based on the marginal utility for untreated health ($W'((H_u)$) divided by the baseline health inclusive of any permanent disability or other pre-existing conditions ($W(H_D)$).

Measuring cost-effectiveness of lovo-cel and exa-cel

- We estimated GRACE-adjusted incremental cost-effectiveness ratios (ICERs) for lovo-cel and exa-cel for the payer and modified societal perspective. The payer perspective only includes healthcare costs, and the modified societal perspective also accounts for productivity and caregiver costs for the patients. Mean costs and outcomes were the same for lovo-cel and exa-cel.[2]
- We further estimated value-based prices (VBPs) for both therapies.
- The GRACE-adjusted ICERs and VBPs were compared to the existing traditional-style HTA model results.[2]
- We also present results for commonly used traditional CEA WTP thresholds such as K=50,000 and K=150,000.

Table 1. GRACE framework and components

GRACE-adjusted ICER	≤	GRACE-adjusted WTP threshold
$\frac{\Delta Cost}{\Delta LE * \delta + LE * (\Delta Q * \varepsilon)}$ ⇩ $\frac{\Delta Cost}{\Delta LE * \left\{\frac{E[W(H_t)]}{W'(H_u)}\right\} + LE * (\Delta Q * \varepsilon)}$	≤	$\frac{\omega_h}{\omega_c} * R * \frac{C_0}{H_0}$ ⇩ $K\omega_H R$

$\Delta Cost$ and ΔQ are changes in costs and QALYs respectively, obtained from Beaudoin et al (2023) baseline CEA model.[2]

ΔLE is the change in LE before and after receiving a treatment.

δ represents the MRS between LE and QoL. The marginal utility of gains in LE can be interpreted as the expected utility of the level of health experienced after treatment, i.e., $E(W(H_t))$. The marginal utility of gains in average QoL can be expressed as $W'(H_u)$, i.e., the marginal utility of the average value of untreated health. Therefore, an alternative expression of the MRS between LE and QoL is $\delta = \left\{\frac{E[W(H_t)]}{W'(H_u)}\right\}$.

ε is the certainty equivalence ratio, a measure of outcome variance between different treatment options, estimated from Mulligan et al (2024).[3]

$\frac{\omega_h}{\omega_c}$ is the ratio of elasticities from the utility functions with respect to health and consumption.

H_0, the health with disability, is defined as 1 if no prior disability is present.

$\frac{\omega_h}{\omega_c} * \frac{C_0}{H_0}$ can thus be reworked as $\left[\frac{C_0}{\omega_C H_0}\right]\omega_H$. The value for ω_H, the elasticity of utility with respect to QoL, was taken from Mulligan et al (2024), estimated through an expo-power utility model.[3] Following L&P (2023),[4] ω_C can be broken down as $\omega_C = \frac{U'(C_0)C_0}{U(C_0)}$ and further simplified to $K = \frac{U(C_0)}{U'(C_0)}$, which represents the traditional WTP threshold for consumption used in CEA.

Lastly, R is the disease severity ratio, depending on the average SCD-related health loss (measured as QALY decrement) and relative risk aversion in health, taken from Mulligan et al (2024).[3]

Sensitivity Analyses

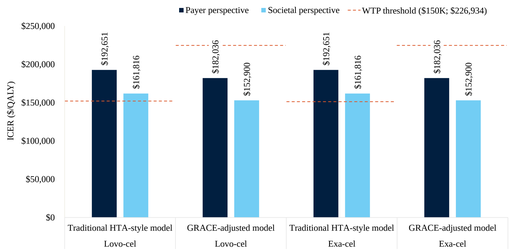
- To test the sensitivity of our model and assumptions, we ran sensitivity analyses for the GRACE-adjusted ICERs, including high-low scenarios for:
  i. Treatment uncertainty
  ii. Cost of treatment acquisition
  iii. Quality adjusted life year (QALY) gains

RESULTS

Base case results

- Without GRACE, the ICER for lovo-cel and exa-cel were $192,651 (direct) and $161,816 (societal).
- After implementing GRACE, ICERs decreased to $182,036 (direct) and $152,900 (societal) (**Figure 1**).
- Applying the GRACE framework increases WTP thresholds from the traditional values of $50,000, $100,000, and $150,000 per QALY to $75,645, $151,289, and $226,934 per QALY.
- In the traditional CEA following the Beaudoin et al (2023) approach,[2] lovo-cel and exa-cel had a value-based price (VBP) of $1.7M at a threshold of $150,000 per QALY, while the VBP after the GRACE adjustment was $2.3M for both.

Figure 1. Difference in ICER estimation for non-GRACE and GRACE models



Sensitivity analysis results

- For both therapies, for low certainty equivalence, the GRACE-ICER value is higher and for high certainty equivalence, we see a decrease in ICER values (**Table 2**).
- As the incremental healthcare cost of lovo-cel or exa-cel versus common care goes up, there is a significant increase in the GRACE-adjusted ICER.
- For higher QALY gains we find lower GRACE-adjusted ICER values; however, the difference in the ICER for lower and higher QALY is greater for exa-cel $96,261 than lovo-cel $53,467 (direct perspective) due to the larger uncertainty in outcomes reported by Beaudoin et al. (2023).[3]

Table 2. GRACE sensitivity analysis results

	Treatment Uncertainty		Incremental Healthcare Cost		Incremental QALYs	
	Low	High	Low	High	Low	High
Lovo-cel						
GRACE-ICER (direct)	$219,582	$155,456	$177,816	$243,794	$225,341	$171,874
GRACE-ICER (societal)	$184,436	$130,574	$147,317	$234,592	$189,273	$144,363
Exa-cel						
GRACE-ICER (direct)	$219,582	$155,456	$170,817	$244,515	$267,815	$171,554
GRACE-ICER (societal)	$184,436	$130,574	$138,059	$235,545	$224,948	$144,095

CONCLUSIONS

- This case study in SCD shows traditional CEA methods may overlook important sources of societal value that are quantitatively meaningful:
  - Implementing GRACE results in a **$10,615 (6%) and $8,916 (6%) decrease in the direct and societal ICERs,** respectively, for both gene therapies for SCD, lovo-cel and exa-cel.
  - Applying the GRACE framework, which accounts for disease severity, also **increases WTP thresholds by about 50%.**
- According to traditional HTA CEA, lovo-cel and exa-cel would not be considered cost-effective, however, using GRACE-adjusted ICER estimates, both therapies would be considered cost-effective at the highest GRACE-adjusted WTP threshold from a both a direct payer and societal perspective.
- Our study provides a roadmap of a potential approach for estimating needed parameters to incorporate GRACE model elements as described by L&P (2023).[4]
- By applying the GRACE method, HTAs can produce comprehensive and precise estimates of societal value, thereby facilitating more efficient and fair resource allocation.

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