PCR73

Sensitivity of EuroQoL 5 dimensions (EQ-5D) to assess health-related quality of life for triple-class exposed relapsed/refractory multiple myeloma: KarMMa-3 case study exploring EQ-5D mapped from disease-specific instruments

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Introduction

- The EuroQoL 5 dimensions (EQ-5D) questionnaire is a generic preference-based measure of health-related quality of life (HRQoL) that includes 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[1]
- It is available in 2 versions based on the number of levels used to describe each dimension: EQ-5D 3 levels (EQ-5D-3L) and EQ-5D 5 levels (EQ-5D-5L)[2]
- Health state utility values (HSUVs) for economic models are used to provide quantitative measures of how strongly a person values a certain health state, and the UK National Institute for Health and Care Excellence (NICE) prefers EQ-5D-3L utilities reported by patients in the relevant population or, if EQ-5D is unavailable, mapping from a disease-specific measure[3]
- The challenge is that EQ-5D may not be sensitive to relapsed/refractory (RR) multiple myeloma (MM)-specific dimensions
  - EQ-5D may not fully capture disease-specific dimensions of health or the impact of new interventions on patient HRQoL[4,5]
- Consequently, disease-specific instruments are used to measure HRQoL, such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30)[6]
  - The multiple myeloma 20 (MY20) module captures disease-specific impacts, such as symptoms, side effects, and outcomes for patients with MM[7]
- To estimate HSUVs, several algorithms have been developed in various patient populations to map EORTC QLQ-C30 and MY20 to EQ-5D
- KarMMa-3 (NCT03651128) is an open-label, phase 3, randomized, controlled trial comparing the efficacy and safety of idecabtagene vicleucel (ide-cel), a chimeric antigen receptor T cell therapy targeting B-cell maturation antigen, versus standard regimens in patients with triple-class exposed (TCE) RRMM after 2–4 prior regimens[8]
  - Ide-cel showed statistically significant and clinically meaningful improvements in HRQoL compared with standard regimens, including key MM symptoms and functioning[9]
- TCE patients represent a severe and heavily pretreated subset of RRMM, and the sensitivity of EQ-5D to changes in HRQoL in this patient population is unknown and may be better captured with disease-specific instruments

Objective

- To compare the sensitivity of HSUVs to treatment effect in patients with TCE RRMM, based on the EQ-5D-3L crosswalked from EQ-5D-5L and EQ-5D-3L mapped from EORTC QLQ-C30 with/without MY20 utilizing KarMMa-3 HRQoL data

Methods

Identification of the most appropriate algorithms for mapping EORTC QLQ-C30 with/without MY20 to EQ-5D-3L for patients with TCE RRMM

- A targeted literature review was conducted using the Health Economics Research Centre database of mapping studies (updated October 2020),[10,11] with additional searches in April 2023 to identify more recent publications
- Only algorithms mapping EORTC QLQ-C30 with/without MY20 to EQ-5D-3L in populations that included at least some patients with MM and allowed for use of a tariff for the UK were included
- Additional consideration was given to validation of the algorithms,[12-14] and the use and acceptance in NICE technology appraisals of oncology therapies between January 2017 and May 2023
- Domains captured in the selected algorithms were compared versus:
  - Domains of interest specified a priori based on clinical relevance for patients with TCE RRMM
  - Domains showing statistically significant improvements for ide-cel versus standard regimens in KarMMa-3[9]

Utility estimates by health state and treatment

- HSUVs for KarMMa-3 were estimated using linear mixed-effects models, which accounted for repeated measures including a random slope and a 3-level variable of treatment and health state (ie, ide-cel pre-progression, standard regimens pre-progression, and post-progression):
  - EQ-5D-3L crosswalked from EQ-5D-5L using the algorithm by van Hout et al.[15]
  - EQ-5D-3L mapped from EORTC QLQ-C30 with/without MY20 based on the algorithms selected as most relevant

Sensitivity of utility estimates based on crosswalked (generic) versus mapped (disease-specific) EQ-5D-3L from KarMMa-3

- Differences in utilities were compared (coefficients and *P* values) between treatment arms and health states for each method

Results

Most appropriate mapping from EORTC QLQ-C30 with/without MY20 to EQ-5D-3L

- We selected 3[16-18] out of 5[16-20] identified algorithm publications to map EORTC QLQ-C30 with/without MY20 to EQ-5D-3L for KarMMa-3 based on the following assessment (**Table 1**):
  - Longworth et al.[17] included all EORTC QLQ-C30 domains except for global health, was the most widely used in prior NICE submissions, and was preferred in validation studies[12-14] (**Table 2**)
  - Kharroubi et al.[16] was the most comprehensive algorithm (all EORTC QLQ-C30 and MY20 domains) and aligned most closely with the domains of interest and those showing statistical significance in KarMMa-3 (**Table 3**)
  - Although both Proskorovsky et al.[18] algorithms with/without MY20 were the least comprehensive, previous validation studies and NICE submissions have used this mapping

Utility estimates by health state and treatment

- **Figure 1** provides an overview of the selected mapping algorithms and crosswalks used to estimate EQ-5D-3L from KarMMa-3 based on the EORTC QLQ-C30 with/without MY20 or EQ-5D-5L, respectively
- **Figure 2** illustrates the utility estimates for pre-progression for ide-cel and standard regimens and post-progression (overall)

Sensitivity of utility estimates based on crosswalked (generic) versus mapped (disease-specific) EQ-5D-3L from KarMMa-3

- Treatment effect for pre-progression utility for ide-cel versus standard regimens (**Table 4**)
  - Crosswalked: smallest (Δ 0.008) and not significant (*P* = 0.370)
  - Mapped: greatest with Kharroubi et al.[16] (Δ 0.036) and significant (*P* < 0.05) for all mapping algorithms
- The difference between pre- versus post-progression was significant for all models (**Table 4**)
  - Ide-cel
    - Crosswalked: smallest difference (Δ 0.073)
    - Mapped: greatest difference with Kharroubi et al.[16] (Δ 0.105)
  - Standard regimens
    - Crosswalked (Δ 0.065) and mapped estimates more similar (Δ 0.055 to 0.071), with Longworth et al.[17] showing greatest difference

Table 1. Identified algorithms mapping EORTC QLQ-C30 with/without MY20 to EQ-5D for patients with TCE RRMM

Citation	Algorithm characteristics							
	Included MY20	Population	Treatment	Observations, n	Patients, n	Method of regression in final model	EORTC domains included as model variables,[a] n	Tariff
Kharroubi et al.[16]	Yes	NDMM	Unspecified	2674	1658	OLS (Bayesian)	19 plus age and gender	UK
Longworth et al.[b,17]	No	Breast cancer, lung cancer, and NDMM	Varied	771	771	Response mapping	15 plus age and gender	Any
Proskorovsky et al.[18]	Yes	MM	Unspecified	154	154	OLS	QLQ-C30/MY20 = 6 QLQ-C30 = 5	UK
Versteegh et al.[19]	No	MM and NHL	Unspecified	723	137	OLS	11 questions	NL
Versteegh et al.[c,20]	No	MM, NHL, arthritis (poor health)	Tested published algorithms, including in press algorithm later published as Versteegh et al.[19], and developed a de novo algorithm using HAQ-DI for arthritis population					NL, UK

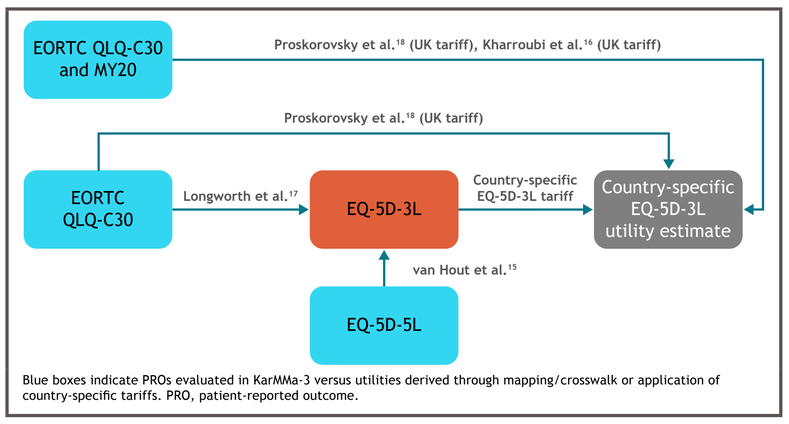
Text in blue indicates references that were selected for the HSUV mapping for KarMMa-3. [a]EORTC QLQ-C30 includes 15 domains and EORTC QLQ-MY20 includes 4 domains; [b]The algorithm presented in Longworth et al.[17] was published subsequently as Young et al.[21] and is referred to as such in some publications; [c]Excluded from further analysis since a de novo algorithm for EORTC QLQ-C30 in MM was not presented. HAQ-DI, Health Assessment Questionnaire Disability Index; NDMM, newly diagnosed MM; NHL, non-Hodgkin lymphoma; NL, Netherlands; OLS, ordinary least squares.

Table 2. Validation and use of the selected mapping algorithms in previous NICE submissions

Citation	Evaluated in validation reviews of mapping algorithms			Number of NICE appraisals	
	Arnold et al.[12]	Doble & Lorgelly[13]	Woodcock et al.[14]	Base case	Scenario
Kharroubi et al.[16]	No	No	No	0	0
Longworth et al.[a,17]	Yes[b]	Yes[b]	Yes	12	1
Proskorovsky et al.[c,18]	Yes	Yes	No	2	0

[a]The algorithm presented in Longworth et al.[17] was published subsequently as Young et al.[21] and is referred to as such in some publications; [b]Text in blue indicates preferred algorithms within the reviews or used most frequently in NICE appraisals; [c]Only EORTC QLQ-C30 mapping validated in review; algorithm with MY20 was not explored in validation studies.

Figure 1. Overview of mapping and crosswalk algorithms to inform utility estimates from KarMMa-3



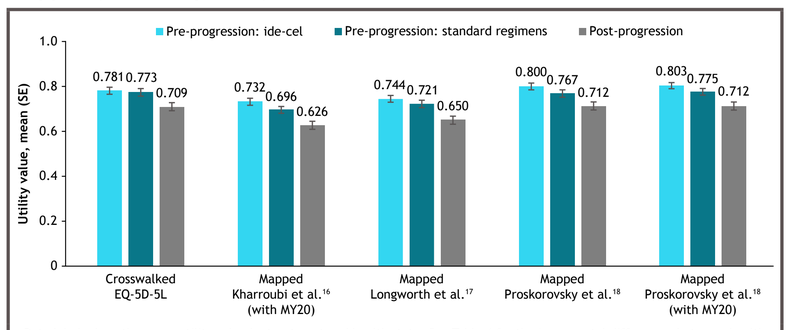
Blue boxes indicate PROs evaluated in KarMMa-3 versus utilities derived through mapping/crosswalk or application of country-specific tariffs. PRO, patient-reported outcome.

Table 3. Domains in mapping algorithms versus disease-specific domains of interest in KarMMa-3

Citation	EORTC QLQ-C30															EORTC QLQ-MY20				Additional covariates	
	Global health	Functional domains					Symptom domains									Disease symptoms	Side effects	Future perspective	Body image	Age	Sex
		Physical	Role	Emotional	Cognitive	Social	Fatigue	Nausea/ vomiting	Pain	Dyspnea	Insomnia	Appetite loss	Constipation	Diarrhea	Financial difficulties						
KarMMa-3 Primary domains of special interest[a]	✓	✓			✓		✓		✓							✓	✓				
KarMMa-3 Statistically significant difference in overall LS mean change from baseline between treatment arms[b]	✓	✓		✓	✓	✓	✓		✓	✓	✓		✓				✓	✓	✓		
Kharroubi et al.[16] (with MY20)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Longworth et al.[17]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓					✓	✓
Proskorovsky et al.[18]	✓	✓		✓					✓												
Proskorovsky et al.[18] (with MY20)	✓	✓							✓		✓							✓			

Cells with blue fill indicate domains that were flagged as clinically relevant or statistically significant in KarMMa-3 analyses; cells with teal fill indicate that the domain was included in the final model reported in the publications.[16-18] In the KarMMa-3 HRQoL analyses, *P* values are nominal without multiplicity testing. [a]Selected a priori based on clinical relevance and importance to the target population;[22] [b]Table 14 KarMMa-3 PRO report.[22] LS, least squares; PRO, patient-reported outcome.

Figure 2. HSUVs based on EQ-5D-3L estimates crosswalked (generic) versus mapped (disease-specific)



Data labels show the mean utility value by treatment and health state. See Table 4 for the incremental differences between health states for each algorithm. Number of patients included across ide-cel pre-progression scenarios ranged from 211 to 213; number of observations for ide-cel pre-progression scenarios ranged from 2284 to 2313. Number of patients included across standard regimens pre-progression scenarios ranged from 108 to 109; number of observations for standard regimens pre-progression scenarios ranged from 670 to 678. Number of patients included in post-progression (ide-cel and standard regimens combined) scenarios ranged from 134 to 137; number of observations for post-progression scenarios ranged from 330 to 348. SE, standard error.

Table 4. Summary of estimates from linear mixed-effects utility models

Scenario	Instrument measured and mapped to EQ-5D-3L	Coefficient (*P* value)				Range of predicted utilities
		Time (months)	Treatment/health state			
			Ide-cel vs standard regimens pre-progression	Ide-cel pre- vs post-progression	Standard regimens pre- vs post-progression	
Crosswalked utility (van Hout et al.[15])	EQ-5D-5L	0.001 (*P* = 0.354)	0.008 (*P* = 0.370)	0.073 (*P* < 0.001)	0.065 (*P* < 0.001)	−0.510 to 1.000
Kharroubi et al.[16] (with MY20)	EORTC QLQ-C30 and MY20	0.003 (*P* = 0.064)	0.036 (*P* < 0.001)	0.105 (*P* < 0.001)	0.069 (*P* < 0.001)	−0.197 to 1.031
Longworth et al.[17]	EORTC QLQ-C30	0.003 (*P* = 0.069)	0.023 (*P* < 0.007)	0.094 (*P* < 0.001)	0.071 (*P* < 0.001)	−0.368 to 0.954
Proskorovsky et al.[18]	EORTC QLQ-C30	0.002 (*P* = 0.122)	0.033 (*P* < 0.001)	0.088 (*P* < 0.001)	0.055 (*P* < 0.001)	−0.008 to 1.035
Proskorovsky et al.[18] (with MY20)	EORTC QLQ-C30 and MY20	0.003 (*P* = 0.041)	0.028 (*P* < 0.001)	0.091 (*P* < 0.001)	0.063 (*P* < 0.001)	0.029-1.076

Blue text indicates statistically significant results at a significance level of 0.05. Time (in months) is included in the model to account for repeated measures.

Discussion

- The EQ-5D generic measure may not be sensitive to capture changes in HRQoL and may not capture the MM-specific elements most important to patients with TCE RRMM
- Although the algorithm by Longworth et al.[17] is slightly less comprehensive than Kharroubi et al.[16], it has been validated and used in previous NICE submissions and still captures many disease-specific domains likely to be relevant to patients
- The findings of this study are limited by primary data collection issues common to PROs, including limited follow-up and/or completion, particularly post-progression
- The sensitivity of EQ-5D to health domains of interest for patients with TCE RRMM was not tested formally in this study[23]

Conclusions

- EQ-5D may not capture disease-specific elements that are most important and sensitive to change for patients with TCE RRMM
- All 4 mapping algorithms tested were able to detect a treatment-specific utility difference for the pre-progression health state that was not captured in the crosswalked EQ-5D-3L
- Decision makers should also consider HSUVs mapped from disease-specific measures to fully capture improvements in HRQoL with new interventions

References

1. Rabin R, de Charro F. *Ann Med* 2001;33:337-343.
2. Herdman M, et al. *Qual Life Res* 2011;20:1727-1736.
3. NICE health technology evaluations: the manual. https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Published January 31, 2022. Accessed September 29, 2023.
4. Versteegh MM, et al. *Value Health* 2012;15:504-513.
5. Shah KK, et al. *Patient* 2017;10:701-709.
6. Rowen D, et al. *Value Health* 2011;14:721-731.
7. Cocks K, et al. *Eur J Cancer* 2007;43:1670-1678.
8. Rodriguez-Otero P, et al. *N Engl J Med* 2023;388:1002-1014.
9. Delforge M, et al. *J Clin Oncol* 2023;41(16 Suppl):8032.
10. Dakin H, et al. *Health Qual Life Outcomes* 2018;16:31.
11. HERC Database of Mapping Studies, version 8.0. https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies. Updated October 14, 2020. Accessed April 29, 2023.
12. Arnold DT, et al. *Health Qual Life Outcomes* 2015;13:6.
13. Doble B, Lorgelly P. *Qual Life Res* 2016;25:891-911.
14. Woodcock F, et al. *Med Decis Making* 2018;38:954-967.
15. van Hout B, et al. *Value Health* 2012;15:708-715.
16. Kharroubi SA, et al. *Med Decis Making* 2015;35:351-360.
17. Longworth L, Rowen D. *Value Health* 2013;16:202-210.
18. Proskorovsky I, et al. *Health Qual Life Outcomes* 2014;12:35.
19. Versteegh MM, et al. *Value Health* 2012;15:504-513.
20. Versteegh MM, et al. *Health Qual Life Outcomes* 2010;8:141.
21. Young TA, et al. *Med Decis Mak* 2015;35:912-926.
22. Delforge M, et al. *HemaSphere* 2023;7[S3]:P905.
23. Hernández Alava M, et al. *Value Health* 2023;26:1398-1404.

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