Challenges of identifying health utility data for patients with penta-refractory multiple myeloma to inform HTA reimbursement discussion for newer treatment options

HTA18

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Background/Introduction

- Multiple myeloma (MM) remains an incurable disease with most patients experiencing repeated periods of relapse and/or are resistant to therapy.
- Despite the advent of novel therapeutic strategies, and their inclusion in doublet and triplet regimens, MM in most patients will become refractory to proteasome inhibitors (PIs), immunomodulatory imide drugs (IMiDs), and monoclonal antibodies (mAbs).
- Penta-refractory MM (PR-MM) is refractory to two PIs, two IMiDs, and an anti-CD38 mAb. Patients with PR-MM have poor prognosis and limited treatment options.
- Health-state utility values (HSUVs) specific for the PR-MM population are required to calculate quality adjusted life years (QALYs) in the cost-effectiveness analyses for health interventions seeking reimbursement through health technology assessment (HTA), including MM novel treatments.
- HSUVs to produce QALY estimates, including those for the PR-MM population, are generally obtained from preference-based measures such as the EQ-5D questionnaire, but these measures are not always included in clinical trials.[1,2]

Objective

- To identify HSUVs for a PR-MM patient population to support economic evaluations for HTA of novel treatments.

Methods

- A systematic review was conducted to identify economic evaluations, healthcare costs and resource use, and health related quality of life (HRQoL) data (including HSUVs) in patients with RRMM, including PR-MM (PROSPERO: CRD42023397925).
- Searches were performed in February 2023, according to the principles of systematic reviews in the Cochrane Handbook, the Centre for Reviews and Dissemination (CRD), the National Institute for Health and Care Excellence (NICE) manual for health technology evaluations, and in line with the PRISMA-P checklist.[3-6]
- Records were screened by two researchers independently, against a predefined PICOS, summarised in **Table 1**.

Table 1: Summary of eligibility criteria (PICOS, publication types and limits) to identify HRQoL evidence in RRMM

Eligibility criteria	Inclusion Criteria	Exclusion criteria
Population(s)	Adults (≥18 years) with RRMM who have received ≥1 prior therapy [a]	Newly diagnosed/ untreated MM
Intervention/Comparators	Systemic therapies used to treat RRMM	NA
Outcomes	**HRQoL:** [b] • Any HRQoL outcomes (from generic or condition-specific measures) reporting utilities, disutilities or HRQoL scores.	
Study design	**HRQoL:** [b] • Economic evaluations • Randomised and non-randomised (comparative) clinical trials • Non-comparative single-arm studies • Early access treatment protocol (EAP) studies • Patient chart reviews • Patient and disease registry studies • Claims data analyses	• Case studies • Case reports • Animal studies • Studies/trials with < 20 participants
Publication types	• Full-text peer reviewed publications • Conference abstracts, posters and oral presentations (2021-2023) • HTA documents • Guidance documents • Horizon scanning documents • Trial protocols • Systematic reviews [c]	• Non-systematic reviews • Opinion pieces • Letters • Editorials • Commentaries • Press releases
Limits	**HRQoL records:** [b] • No restriction **Country:** • No restriction **Language:** • No restriction	

a Evidence across all lines of RRMM were eligible for inclusion for patients with PR-MM prioritised in an evidence hierarchy assessment, followed by records reporting utility values in proxy patient populations.
b The economic review also identified economic evaluations, healthcare cost and resource use data in a RRMM population but only the HRQoL evidence is reported here.
c Systematic reviews were included for reference tracking only.

Results

- Bibliographic database searching with additional handsearching identified 141 eligible records reporting HRQoL evidence in RRMM, of which 62 records reported utility values (**Figure 1**).
- No published records reported utility values in a PR-MM population.
- One record was identified reporting aggregate HRQoL data in a penta-exposed MM population (PE-MM), of which ≥50% of patients were penta-refractory, captured through the Functional Assessment of Cancer Therapy-General (FACT-G) and the disease-specific Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM) questionnaires,[7,8] alongside calculation of the FACT-MM Trial Outcome Index (FACT-MM TOI), comprised of summing the physical and functional subscales of FACT-G with the MM domain, to obtain an overall score. However, no utilities were reported.[9]
- In the absence of published utility values in a PR-MM population, 26 of 62 records were identified reporting utility values in wider patient populations (proxy-reported data) which were considered as evidence to support a cost-utility analysis (CUA) in PR-MM (**Figure 2**).
- The proxy populations considered included: PE-MM; triple-class refractory/triple-class exposed (TCR/TCE) MM; 5L+/heavily pre-treated RRMM; and double-class refractory/ double-class exposed (DCR/DCE) MM.
- Three studies plus one NICE Technology Appraisal (GID-TA10568) reported a range of utility values from 0.730 to 0.759 and 0.660 to 0.676 for the pre-progression and post-progression health states, respectively, in heavily pre-treated patients with either 5L+ TCE/TCR MM or patients who had received a median of 5 prior lines of therapy (**Table 2**).[10-13]
- The HSUVs identified in these heavily pre-treated RRMM populations were considered as the most appropriate evidence to support an economic model and meet the requirements of HTA for novel interventions in PR-MM, in lieu of published utility data in a PR-MM population.
- In a separate analysis, utility values were obtained from a PR-MM subpopulation by mapping scores from the FACT-G questionnaire to the EQ-5D-3L,[14] using unpublished patient level data (PLD) from a phase 2b, single-arm trial, via a published algorithm, to support a CUA in PR-MM.

Figure 1: PRISMA of HRQoL evidence identified in RRMM

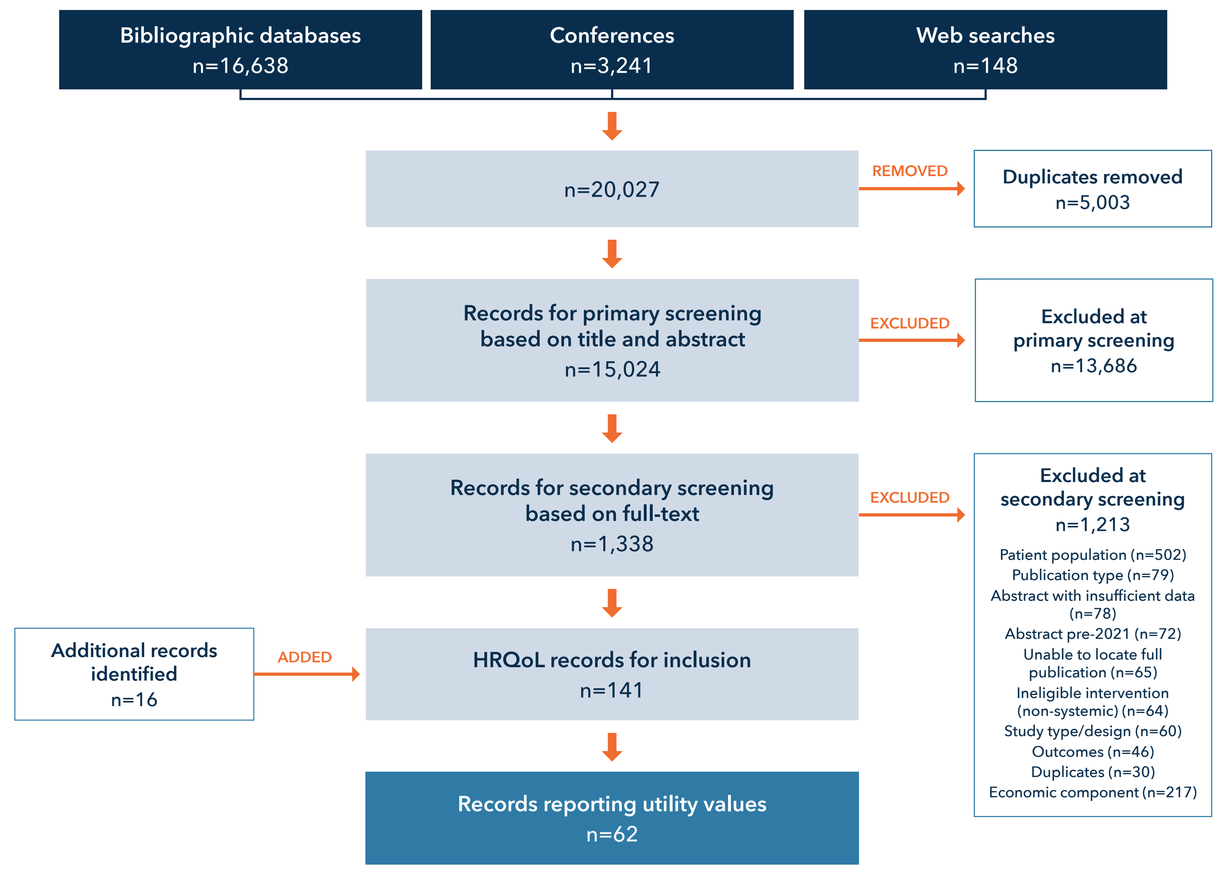
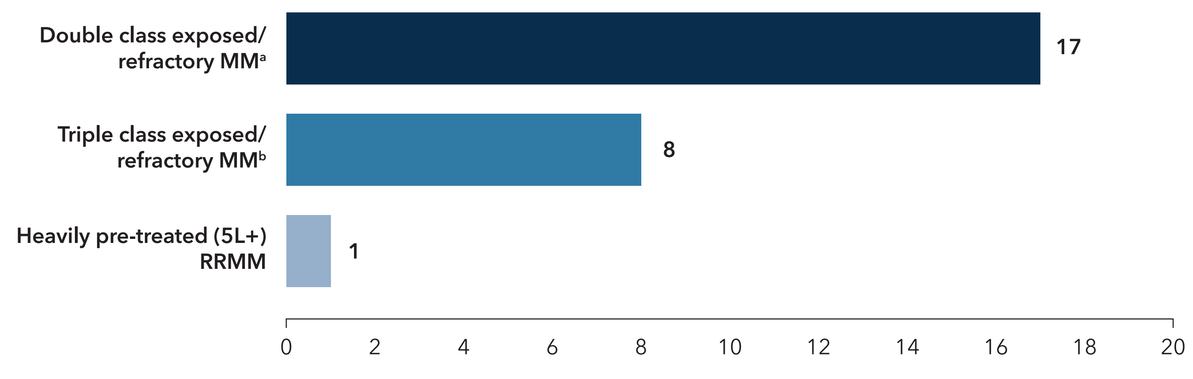


Table 2: Utility values reported in proxy patient populations of heavily pre-treated RRMM

Publication/ Record	Patient population	Utility source	Patient-reported outcome measure	Utility values: pre-progression	Utility values: post-progression
NICE Technology Appraisal [GID-TA10568][10]	5L+ TCR MM	DREAMM-2 [15]	EORTC QLQ-C30/ MY20 mapped to EQ-5D-3L	0.759 (on-treatment)	NR
Nikolaou *et al.* (2021)[11]	5L+ TCR MM	DREAMM-2 [15]	EORTC QLQ-C30/ MY20 mapped to EQ-5D-3L	0.731	0.664
Yang *et al.* (2021)[12]	5L+ TCE MM	DREAMM-2 [15]	EORTC QLQ-C30/ MY20 mapped to EQ-5D-3L	0.73	0.66
Pelligra *et al.* (2017)[13]	Heavily pre-treated RRMM (median of 5 prior lines)	MM-003 [16]	EQ-5D-3L	0.730	0.676 [a]

a Post-progression health state decrement of -0.054 applied to the pre-progression health state to estimate the post-progression utility value.

Figure 2: Number of records identified reporting utility values in proxy RRMM populations (n=26)



a Double-class exposed/double-class refractory are patients exposed (or refractory) to an IMiD and PI.
b Triple-class exposed/triple-class refractory are patients exposed (or refractory) to an IMiD, a PI, and an anti-CD38 mAb.

Conclusions

- Although robust data is required for CUA informing HTA of newer interventions in MM, identifying HSUVs in a PR-MM population is challenging.
- Of the 62 records identified reporting utility values for RRMM, there are currently no published utility values for patients with PR-MM.
- Utility values obtained from wider RRMM populations (proxy populations; e.g. heavily pre-treated [5L+] RRMM patients) provide a "next-best" source of evidence for economic evaluations, in lieu of data specifically in a PR-MM population.
- There is precedence for using proxy-reported populations in heavily pre-treated (5L+) RRMM to identify utility values for novel treatments undergoing HTA and reimbursement (e.g. GID-TA10568) in the absence of utility values in a PR-MM population.[10]
- Where utility values were identified from proxy patient populations of heavily pre-treated MM, the majority of these were derived from mapping disease-specific HRQoL measures in the absence of trial-based utilities derived from preference-based measures.
- There is currently a lack of health utility data reported for a PR-MM population to inform economic evaluations to support reimbursement of novel multiple myeloma treatments through HTA. Use of heavily pre-treated proxy populations and mapping HRQoL data from disease-specific questionnaires to preference-based measures are two options that can address this issue.

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Abbreviations
CUA, cost-utility analysis; DCE MM, double-class exposed multiple myeloma; DCR MM, double-class refractory multiple myeloma; EQ-5D, EuroQol five dimension; EQ-5D-3L, EuroQol five dimension-3 level; EORTC QLQ-C30/ MY20, European Organisation for Research and Treatment Core Quality of Life questionnaire/ Myeloma Module; FACT-G/MM/TOI, Functional Assessment of Cancer Therapy – General/Multiple Myeloma/Trial Outcome Index; GID, Guidance in Development; HSUVs, health-state utility values; HTA, Health Technology Assessment; IMiD, immunomodulatory imide drug; mAb, monoclonal antibody; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; NR, not reported; PI, proteasome inhibitor; PLD, patient-level data; PR-MM, penta-refractory multiple myeloma; PRISMA, Preferred reporting items for systematic reviews; QALY, quality adjusted life year; RRMM, relapsed and/ or refractory multiple myeloma; TCE MM, triple-class exposed multiple myeloma; TCR MM, triple-class refractory multiple myeloma; 5L+, fifth-line plus.

Disclosures
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