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Adam Irving, Dennis Petrie, Anthony Harris, Laura Fanning, Erica M. Wood, Elizabeth Moore, Cameron Wellard, Neil Waters, Bradley Augustson, Gordon Cook, Francesca Gay, Georgia McCaughan, Peter Mollee, Andrew Spencer and Zoe K. McQuilten

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Adam Irving: Centre for Health Economics, Monash Business School; Transfusion Research Unit, Monash University (email: adam.irving@monash.edu); Dennis Petrie: Centre for Health Economics, Monash Business School, Monash University (email: dennis.petrie@monash.edu); Anthony Harris: Centre for Health Economics, Monash Business School, Monash University (email: anthony.harris@monash.edu); Laura Fanning: Centre for Health Economics

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Title

Discrete-event simulation for economic evaluation: A real-world, post-market cost-effectiveness analysis in multiple myeloma using registry data

Authors

Adam Irving[1,2*], Dennis Petrie[1], Anthony Harris[1], Laura Fanning[1], Erica M Wood[2], Elizabeth Moore [2], Cameron Wellard[2], Neil Waters[2], Bradley Augustson[3], Gordon Cook[4], Francesca Gay[5], Georgia McCaughan[6,7], Peter Mollee[8], Andrew Spencer[9], Zoe K McQuilten[2]

Affiliations

[1] Centre for Health Economics, Monash Business School, Monash University, Melbourne, Victoria, Australia

[2] Transfusion Research Unit, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

[3] Sir Charles Gairdner Hospital, Nedlands, Perth, Western Australia, Australia

[4] Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom

[5] Oncology and Hematology Department, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy

[6] Department of Haematology, St Vincent's Hospital Sydney, New South Wales, Australia

[7] School of Clinical Medicine, Faculty of Medicine and Health, University of New South Wales, Sydney, Australia

[8] Princess Alexandra Hospital, The University of Queensland, Brisbane, Queensland, Australia

[9] Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne, Victoria, Australia

*** Corresponding Author E-mail:** adam.irving@monash.edu

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Abstract

Background

Health technology assessments traditionally rely on cohort modelling using clinical trial data, leaving uncertainties about real-world cost-effectiveness. This post-market economic evaluation used individual-level modelling with a discrete-event simulation (DES) framework and registry data to estimate the real-world cost-effectiveness of bortezomib, lenalidomide and dexamethasone (VRd) in Australia which was listed for newly diagnosed multiple myeloma in 2019.

Methods

We conducted an economic evaluation of VRd versus No VRd using the EpiMAP Myeloma model, a DES model powered by risk equations from the Australia & New Zealand Myeloma and Related Diseases Registry. This approach captured individual patient heterogeneity and complex treatment pathways through up to nine lines of therapy. We assessed differences in quality-adjusted life-years (QALYs) and costs over a lifetime horizon, with bootstrapping to quantify uncertainty.

Results

VRd was associated with positive incremental QALYs (0.16; 95% CI: 0.10, 0.21) and incremental cost (A$10K; 95% CI: A$8K, A$11K). Improved response to first-line therapy with VRd was predicted to marginally increase receipt of autologous stem cell transplantation by 1.1% (95% CI: 0.6, 1.7%), significantly increase receipt of maintenance therapy by 13.8% (95% CI: 10.4%, 17.3%) and marginally offset further lines of therapy. VRd was the most cost-effective option in 95% of the bootstrap iterations at a willingness-to-pay threshold of $60K/QALY.

Conclusion

The 2019 decision to list VRd for newly diagnosed multiple myeloma has resulted in a somewhat cost-effective allocation of healthcare resources when judged against the traditional A$50K/QALY willingness-to-pay threshold. This analysis demonstrates how using individual-level modelling with registry data to perform economic evaluation can capture the interplay between patient characteristics, treatment decisions, and outcomes. Our findings provide

nuanced insights into the real-world cost-effectiveness of VRd, highlighting how post-market evaluations can inform refinement of funding decisions for complex therapeutic interventions.

Key points

- VRd treatment for newly diagnosed multiple myeloma provides modest health benefits at increased costs compared to previous standard treatments, making it cost-effective at slightly higher than traditional thresholds in Australia.
- Individual-level modelling using real-world patient registry data reveals that VRd improves response to initial therapy, increases use of stem cell transplantation and maintenance therapy, and slightly reduces the need for additional treatment lines.
- This study demonstrates how individual-level modelling with real-world data can provide more nuanced insights into treatment effectiveness than traditional methods, helping to inform policy decisions about funding expensive cancer therapies.

Statements and Declarations

The EpiMAP Myeloma project was supported by Medical Research Future Fund GNT1200706 and GNT2017480 and by National Health and Medical Research Council GNT2024876. The Australian and New Zealand Myeloma and Related Diseases Registry has received funding from Abbvie, Amgen, Antengene, Bristol-Myers Squibb, Celgene, Gilead, GSK, Janssen, Novartis, Pfizer, Sanofi, and Takeda. These funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

1 Introduction

Individual-level modelling approaches such as discrete-event simulation (DES) represent a significant methodological advancement in health economic evaluation that addresses fundamental limitations of traditional cohort models. While Markov cohort models have long been the standard for health technology assessment (HTA), they inherently aggregate patient experiences, obscuring the heterogeneity present in real-world patient populations and failing to capture how individual characteristics influence treatment outcomes in nonlinear ways.[1]

HTA bodies worldwide face significant challenges when evaluating complex therapies in heterogeneous diseases like multiple myeloma (MM). Traditional cohort models often struggle to account for the multifaceted nature of treatment pathways and individualised clinical decision-making that characterises modern oncology care. The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia has previously noted difficulties in assessing the cost-effectiveness of MM treatments due to discrepancies between clinical trial populations and real-world patient characteristics.[2] These challenges were evident in the 2019 PBAC assessment of VRd (bortezomib, lenalidomide & dexamethasone), where significant effort was devoted to reconciling trial-based efficacy with expected real-world effectiveness, particularly regarding the appropriate patient population.[3] The PBAC noted that while the pivotal SWOG S0777 trial was designed for patients "without intent for immediate autologous stem-cell transplant," approximately 69% were classified as having "intent to transplant" at baseline, with many patients ultimately receiving transplantation.

MM presents other unique challenges for economic evaluation due to its clinical heterogeneity and rapidly evolving therapeutic landscape. Treatment selection depends on complex patient-specific factors including age, comorbidities, cytogenetic risk, previous therapies, and transplant eligibility. The positioning of new therapies within the treatment pathway may influence not only immediate survival outcomes but also downstream treatment decisions, particularly regarding autologous stem cell transplantation (ASCT) eligibility and subsequent lines of therapy (LoTs). These dynamic treatment pathways create interdependencies between first-line therapy choice and later outcomes that traditional cohort models often fail to capture adequately.

Individual-level modelling such as DES naturally accommodates dynamic interactions between patient characteristics, treatment decisions, and downstream outcomes. Whereas

traditional cohort models require separate transition probabilities for each subgroup and additional health states to approximate patient history, DES tracks individual patient trajectories dynamically throughout the simulation. This enables more nuanced assessment of how first-line treatment choices influence subsequent interventions and outcomes—a critical consideration in chronic diseases with complex care pathways. As patients progress through multiple LoTs, DES can reveal emergent patterns that would remain hidden in state-transition approaches, providing insights into how treatment effects vary across different patient populations.

Regulatory agencies, including the PBAC in Australia, the National Institute for Health and Care Excellence in the United Kingdom, and the Canadian Agency for Drugs and Technologies in Health, increasingly recognise the value of DES in economic evaluations.[1, 4, 5] Despite its advantages, DES does present challenges, including increased computational complexity and more extensive data requirements. Efforts to improve the transparency and reproducibility of DES models will be key to their broader adoption in HTA processes.

The use of registry data to inform DES models represents a particularly valuable approach for capturing real-world treatment patterns and outcomes. Clinical registries like the Australia & New Zealand Myeloma and Related Diseases Registry (MRDR) offer several advantages over randomised clinical trials for economic evaluation. They capture broader patient populations with greater heterogeneity in baseline characteristics and comorbidities, longer follow-up durations, and more diverse treatment patterns reflecting actual clinical practice rather than protocol-driven care.[6] These features are particularly relevant for MM, where the patient population treated in routine practice frequently differs from those in pivotal trials due to eligibility criteria and selective recruitment.[7]

Registry data can also address specific limitations of clinical trials in MM, including inadequate representation of elderly and frail patients, limited information on treatment sequencing beyond progression, and incomplete capture of resource utilisation.[8] However, using registry data presents methodological challenges that DES is uniquely positioned to address. These include handling missing data through appropriate imputation techniques, accounting for selection bias through risk-adjustment models, and managing the complexity of time-varying covariates that influence treatment decisions and outcomes.[9, 10] By estimating risk equations derived from registry data, individual-level models can account for these factors in ways that would be prohibitively complex in traditional cohort models.

Previous economic evaluations of VRd and similar combination regimens in MM have largely relied on cohort models using clinical trial data. These traditional methodologies, including partitioned survival models and Markov cohort models, aggregate patients into homogeneous health states with fixed transition probabilities. Narsipur et al. conducted a cost-utility analysis comparing VRd to Rd using a partitioned survival model with three health states (progression-free, progressed disease, and death), parameterised exclusively with data from the SWOG S0777 trial. Their analysis demonstrated that in the US healthcare system, VRd was not cost-effective at a willingness-to-pay threshold of US$150K per quality-adjusted life year (QALY).[11] A key limitation of their analysis was that they calculated progression-free QALYs rather than traditional QALYs due to insufficient overall survival data from the trial at the time of analysis. This approach meant they applied utility weights only to the progression-free period and did not capture the post-progression period. This methodological compromise, combined with challenges in comparing across non-identical trial populations, introduced significant uncertainty into their cost-effectiveness estimates and limits direct comparability with other economic evaluations.

Similarly, the 2019 PBAC evaluation of VRd versus Rd in Australia faced methodological challenges in defining the appropriate population, estimating quality-of-life impacts, and determining the downstream effects of improved response rates on subsequent treatment decisions—including access to expensive salvage therapies such as carfilzomib- and daratumumab-based regimens.[3] These high-cost subsequent interventions significantly influence the overall cost-effectiveness of initial treatment choices, creating complex modelling dependencies that cohort models struggle to capture adequately, underscoring the need for more sophisticated individual-level modelling techniques that can better reflect real-world clinical practice.

The objective of this study was to demonstrate the practical application and advantages of individual-level modelling using a DES framework in post-market economic evaluation, using the case of VRd for newly diagnosed MM in Australia. By leveraging data from the MRDR, we showcase how individual-level modelling can overcome the limitations of traditional cohort models in capturing real-world complexity. We estimate real-world cost-effectiveness, which we define as cost-effectiveness estimated on patients whose characteristics and response to therapy reflect those of patients who actually receive the new therapy in routine clinical practice, rather than trial-based populations that may not be fully representative.

2 Methods

2.1 Economic Evaluation

This economic evaluation compared first-line VRd versus No VRd for patients predicted to be diagnosed with MM in Australia between 2025 and 2030. Unlike traditional economic evaluations that often select a single comparator regimen, our registry-based DES approach enabled the use of a realistic, weighted blend of alternative regimens that accurately reflects the treatments displaced when VRd was funded. The No VRd comparator was constructed by analysing changes in treatment patterns in the 2-year period immediately prior to VRd funding in Australia (2017-2018) with the most recent 2-year period (2023-2024). MRDR data showed that first-line VRd gained a 48.6% market share, primarily displacing VCd (bortezomib, cyclophosphamide & dexamethasone - decreasing from 75.6% to 25.8%, a 49.8% reduction) and 'other' regimens (a heterogenous group of less commonly used regimens - decreasing from 16.3% to 15.1%, a 1.2% reduction), while the use of Rd (lenalidomide & dexamethasone), the comparator assessed by PBAC in their 2019 evaluation of VRd, actually increased from 8.1% to 10.5%. By calculating the proportional displacement, we determined that the No VRd comparator should comprise 97.6% VCd and 2.4% 'other' regimens, representing the counterfactual scenario of what treatments patients would have received had VRd not been funded.

We conducted the economic evaluation from the perspective of the Australian healthcare system over a lifetime horizon. The primary outcomes were QALYs and costs, both discounted at the PBAC's recommended 5% per annum,[4] summarised as an incremental cost-effectiveness ratio (ICER) and compared with PBAC's traditional A$50K/QALY willingness-to-pay threshold. To ensure transparent reporting of methods and results, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist is presented in the Supplementary Information .[12]

2.2 The EpiMAP Myeloma Model

We conducted the economic evaluation using the EpiMAP (Epidemiological Modelling of Australian Patients) Myeloma model, a whole-care pathway, DES model designed to predict MM disease outcomes and treatment pathways at the individual patient level.[13] The model simulates individual patient trajectories through up to 9 LoTs, with each patient's pathway determined by risk predictions based on each individual's evolving clinical characteristics. The

model is powered by risk equations estimated and continuously updated using patient-level data from the MRDR, which captures comprehensive information on patient characteristics at diagnosis, treatment patterns, and clinical outcomes including response to treatment and accurately records death via linkage with Australia's National Death Index.[14]

Version 1.0 of the model, published in 2024, demonstrated strong predictive accuracy for OS in an out-of-sample prediction analysis.[13] For this analysis, we developed Version 2.0 of the EpiMAP Myeloma model, presented in Figure 1, which incorporates five key enhancements:

1. Adding a squared age term to all risk equations
2. Utilising the Revised International Staging System (R-ISS) score in all risk equations
3. Utilising a single comorbidity score in ASCT intent and receipt risk equations
4. Replacing previous anticancer regimen with previous best clinical response (BCR) when predicting next anticancer regimen
5. Modelling specific anticancer regimens at LoT 3 and LoT 4

The DES framework allows our model to capture emergent properties that cannot be predetermined in a state-transition approach. For example, the model can reveal how changes in first-line treatment affect the proportion of patients who receive ASCT, maintenance therapy, and subsequent LoTs without requiring these pathways to be explicitly programmed in advance.

2.3 Model Structure and Risk Equations

The DES approach allows us to incorporate a rich set of risk equations that determine all model outcomes including OS, anticancer regimen, response to therapy, anticancer therapy duration, ASCT intent and receipt, receipt of maintenance therapy, and treatment-free interval duration—providing a level of granularity not possible in traditional cohort modelling. All 5,030 MRDR patients diagnosed with MM between the registry's inception in 2012 and the end of 2024 were included in the risk equation estimations for this analysis. Multiple imputation using chained equations was used to impute missing data, the details of which have been previously published.[13]

Parametric survival analysis using the Weibull distribution was used to predict OS, anticancer therapy duration, and treatment-free interval duration, with this distribution selected over the exponential and Gompertz distributions based on lowest Akaike and Bayesian Information Criteria. The DES framework enables a dynamic competing risks framework, where the model

continuously recalculates survival times conditional on updated patient characteristics at each event, comparing these with other time-to-event predictions. The earliest predicted event determines the patient's next step in the simulation, creating individualised trajectories that better reflect real-world clinical complexity than the aggregated transitions of cohort models. This approach allows for the emergence of non-linear relationships between patient characteristics, treatment decisions, and outcomes that would be difficult to capture in traditional cohort models without exponentially increasing the number of health states. Logit models were used for binary outcomes such as ASCT intent and receipt, ordered logit was used for the 6-item BCR scale, and multinomial logit was used to select anticancer regimen. The covariates included in each risk equation were developed in collaboration with an advisory group of clinical MM experts and are included in the Supplementary Information.

The EpiMAP Myeloma model uses BCR as a surrogate outcome for OS. BCR is assessed using the International Myeloma Working Group (IMWG) uniform response criteria, a validated 6-item ordinal scale ranging from Complete Response to Progressive Disease.[15] The model assumes that novel therapies improve survival through their ability to achieve deeper responses, with the relationship between BCR and OS captured in the OS risk equation. The BCR risk equations included patient characteristics, treatment (either ASCT or anticancer regimen), and BCR to the previous LoT. This approach to modelling treatment effects represents another advantage of individual-level modelling compared to traditional cohort models. By using multinomial logit models to predict individual-level BCR, we capture heterogeneity in treatment effects across different patient populations. Unlike cohort models that typically apply constant hazard ratios or relative risks uniformly, our approach allows treatment effects to vary based on the observed relationships between patient attributes and treatment, providing a more nuanced representation of real-world effectiveness.

2.4 Study Cohort

Another important differentiating feature of DES compared to traditional cohort modelling is the requirement for a representative, individual-level study cohort rather than aggregate population parameters. We employed a multi-step approach to generate a representative study cohort with individual-level characteristics that match the Australian MM patients likely to receive VRd. We first obtained projected MM incidence data for 2025 to 2030 from a published statistical modelling study.[16] These projections provided the expected age and sex distribution of incident MM cases over the 5-year timeline of our analysis. The EpiMAP

Myeloma model requires five patient characteristics at diagnosis to begin the simulation – age, sex, Eastern Cooperative Oncology Group (ECOG) performance score, R-ISS stage, and comorbidity score. We combined the 2025 to 2030 incident MM population with all 5,030 MRDR patients and used multiple imputation with chained equations to predict ECOG status, R-ISS stage, and comorbidity score (based on age and sex). This process preserved the relationship between the covariates observed in the MRDR, creating a synthetic population that exhibits the same heterogeneity and covariate relationships as real patients.

We then used the EpiMAP Myeloma model to simulate the treatment pathways of this synthetic incident MM population to identify patients predicted to receive VRd at LoT 1. To minimise the influence of Monte Carlo error on the results, this process was repeated 10 times, combining each set of predicted patients into one study cohort representing 10 different potential VRd-receiving populations.[17] The disease outcomes and treatment pathways of each patient in the study cohort were then simulated with the EpiMAP Myeloma model under both the VRd and No VRd scenarios from the start of assigned LoT 1 therapy through till death. As our research question focussing on cost effectiveness and not budget impact, all patients in the study cohort were assumed to be diagnosed in 2025 and discounted accordingly.

2.5 Economic Data

As a reliable source of hospital and community costs of MM in Australia was not available, only treatment-related cost data were included in the analysis. This is akin to assuming that non-treatment hospital and community costs of MM do not vary between patients who receive VRd or No VRd at LoT 1. Anticancer dosing information was taken from the clinical practice guidelines published by Myeloma Australia's Medical and Scientific Advisory Group.[18] This dosing information was combined with height and weight data from the MRDR to calculate total drug dose per anticancer cycle. Published '*dispensed price for maximum quantity'* drug prices were taken from the Pharmaceutical Benefits Scheme website, utilising a 2024/25 cost year.[19] The cost of ASCT was derived from the 2024/25 Independent Health and Aged Care Pricing Authority's published price weights for admitted care as an average of Australian refined diagnosis-related groups for autologous haematopoietic stem cell transplant weighted by the number of separations.[20]

Quality-of-life utility weights were derived from Acaster et al.,[21] which demonstrated that MM patients experienced significantly improved quality of life during treatment-free intervals compared to periods on active therapy. This finding informed our decision to explicitly model

treatment-free interval duration as a distinct health state after each LoT in the EpiMAP Myeloma model. A full list of the treatment costs and utility weights utilised in the analysis are presented in the Supplementary Information.

2.6 Uncertainty

Our approach to quantifying uncertainty represents a significant advancement over traditional probabilistic sensitivity analysis (PSA) methods commonly used in cohort models. While traditional PSA typically draws parameter values independently from predefined distributions, our bootstrapping method captures the complex interdependencies between parameter estimates across and within our risk equations that are essential in individual-level modelling.

By bootstrapping patients with replacement from the MRDR dataset, reperforming multiple imputation, and re-estimating all risk equations for each bootstrap sample, we simultaneously capture uncertainty in both patient characteristics and treatment effects. This approach preserves the correlation structure between risk equation parameters that would be lost in standard PSA approaches. For example, if increased age reduces the probability of receiving ASCT and simultaneously increases mortality risk, these correlated effects are naturally preserved in our bootstrapping approach rather than being artificially separated. As each bootstrap sample generates slightly different risk equations, the relative importance of different patient characteristics in determining outcomes varies across bootstrap iterations.

This comprehensive approach to uncertainty quantification is particularly valuable in complex treatment pathways like MM, where sequential treatment decisions are interdependent and influenced by evolving patient characteristics. The resulting confidence intervals therefore reflect not just uncertainty in isolated parameters, but in the entire system of relationships that determine patient trajectories through the model.

2.7 Subgroup Analyses

Another advantage of using DES modelling is the ability to assess clinically meaningful differences in treatment pathways and outcomes by patient subgroups without requiring pre-specification of these subgroups in the model structure. We demonstrate this advantage using two subgroup analyses stratifying patients by whether they had Intent for ASCT at diagnosis and then further stratifying patients with No Intent for ASCT at diagnosis by age at diagnosis (<70 years versus ≥70 years). These subgroups are particularly relevant in MM management where treatment decisions and outcomes are heavily influenced by transplant eligibility and

age. ASCT remains a cornerstone of treatment for eligible patients, potentially amplifying the benefits of novel induction therapies like VRd. Meanwhile, age represents a critical determinant of treatment tolerance and efficacy in non-transplant candidates, with younger patients potentially deriving different benefits from intensified regimens compared to their older counterparts. By examining these clinically meaningful subgroups, we can identify potential heterogeneity in treatment effects that might be obscured in aggregated analyses. We stratify by Intent for ASCT at diagnosis rather than receipt of ASCT because receiving VRd changes the likelihood of receiving ASCT and we need to compare identical populations in both subgroups. These post-hoc subgroup analyses were implemented within our DES framework without requiring separate model structures or transition probabilities for each subgroup.

2.8 Data Availability

The MRDR Steering Committee approved the request to utilise fully anonymised MRDR data to build the EpiMAP Myeloma model and standalone ethics approval including a waiver of consent for the modelling study was provided by Monash University (Project ID 26371). The MRDR data are property of Monash University and not publicly available due to the sensitive patient information. De-identified data are available for research purposes upon successful application to the MRDR Steering Committee for researchers and projects that meet the criteria for access to confidential data, more information can be found at https://www.mrdr.net.au/. All simulations were performed using Stata 17,[22] using the built-in matrix programming language Mata on Monash University's 'MASSIVE' high-performance computing infrastructure.[23] To promote transparency and reproducibility, the Stata code for V2.0 of the EpiMAP Myeloma model used in this analysis has been made open source using the General Public License version 3 (GPLv3). All risk equation coefficients and the synthetic study cohort used in this analysis are available on the online repository for use with the simulation code. The online repository can be found at https://github.com/adam-irving/EpiMAP-Myeloma.

3 Results

Across the 10 sets of 17,571 patients diagnosed with MM in Australia between 2025 and 2030, between 4,779 and 5,018 were predicted to receive VRd at LoT 1. Combining all 10 sets of predicted VRd patients resulted in a total study cohort of 48,741 patients - 39% were over 70

years old at diagnosis, 59% were male, 14% had an ECOG score of 2 or above and 12% were in R-ISS stage 3.

The real-world cost-effectiveness results from the main analysis are presented in Table 1 with the associated cost-effectiveness plane and acceptability curves presented in Figure 2 and Figure 3, respectively.

Table 1: Real-world Cost-effectiveness Results

Outcome	VRd (95% CI)	No VRd (95% CI)	Incremental (95% CI)
QALYs	5.60 (5.33, 5.91)	5.44 (5.16, 5.73)	**0.16 (0.10, 0.21)**
Costs (A$)	124K (116K, 135K)	115K (106K, 125K)	**10K (8K, 11K)**

CI – confidence interval; QALY – quality-adjusted life-years; VRd – bortezomib, lenalidomide & dexamethasone

VRd was associated with a mean gain of 0.16 QALYs (95% CI: 0.10, 0.21) and a mean increase in costs of A$10K (95% CI: A$8K, A$11K) compared to No VRd. All 500 bootstrap iterations were in the Northeast quadrant of the cost-effectiveness plane (Figure 2), indicating consistent findings of both positive incremental QALYs and incremental costs. The cost-effectiveness acceptability curve (Figure 3) demonstrated that VRd is somewhat cost-effective, only 14% of the bootstrap iterations fell below the traditional A$50K/QALY willingness-to-pay threshold, with 95% of the iterations below the A$60K/QALY threshold.

Table 2 illustrates the key mechanisms in the model in which VRd impacts on both downstream QALYs and costs by comparing treatment pathways between the VRd and No VRd scenarios, including BCR to LoT 1.

Table 2: Treatment Pathways

Outcome	VRd	No VRd	Difference (95% CI)
LoT 1 BCR			
Complete Remission	15.8%	10.7%	5.1% (3.1%, 7.0%)
Very Good Partial Response	30.7%	25.5%	5.2% (3.5%, 6.9%)
Partial Response	29.3%	31.7%	-2.4% (-3.5%, -1.3%)
Minimal Response	5.3%	6.6%	-1.3% (-1.8%, -0.8%)
Stable Disease	13.2%	18.9%	-5.7% (-7.4%, -3.8%)
Progressive Disease	1.2%	1.9%	-0.7% (-0.9%, -0.4%)
Receipt of ASCT	42.1%	40.9%	1.1% (0.6%, 1.7%)
Receipt of Maintenance Therapy	49.2%	35.4%	13.8% (10.4%, 17.3%)
Receipt of LoT 2	67.2%	67.8%	-0.5% (-1.0%, -0.0%)
Receipt of LoT 3	54.9%	55.6%	-0.7% (-1.3%, -0.2%)
Receipt of LoT 4	45.9%	46.5%	-0.6% (-1.2%, -0.1%)
Receipt of LoT 5	36.7%	37.3%	-0.6% (-1.1%, -0.1%)
Receipt of LoT 6	25.9 %	26.5%	-0.6% (-1.1%, -0.2%)
Receipt of LoT 7	18.0%	18.5%	-0.5% (-0.9%, -0.2%)
Receipt of LoT 8	12.9%	13.3%	-0.4% (-0.8%, -0.1%)
Receipt of LoT 9	9.3%	9.7%	-0.3% (-0.7%, 0.0%)

ASCT – autologous stem cell transplant; BCR – best clinical response; CI – confidence interval; LoT – line of therapy; VRd – bortezomib, lenalidomide & dexamethasone

VRd was associated with an improvement in BCR to LoT 1, with significantly more patients experiencing Complete Remission or Very Good Partial Response. VRd was also associated with a small but statistically significant 1.1% (95% CI: 0.6%, 1.7%) increase in the proportion of patients who receiving ASCT, a large 13.8% (95% CI: 10.4%, 17.3%) increase in the proportion of patients who receive maintenance therapy, and small but significant decreases in the proportion of patients who receive subsequent LoTs.

Table 3 presents the results of the two subgroup analyses. The first subgroup analysis compared patients with Intent for ASCT at diagnosis with No Intent for ASCT at diagnosis. The second subgroup analysis focused only on patients with No Intent for ASCT at diagnosis and compared younger patients (<70 years at diagnosis) with older (≥70 years at diagnosis). The Supplementary Information contains cost-effectiveness acceptability curves for both subgroup analyses.

Table 3: Subgroup Analyses

Outcome	VRd (95% CI)	No VRd (95% CI)	Incremental (95% CI)
Intent for ASCT			
QALYs	6.07 (5.76, 6.43)	5.86 (5.56, 6.22)	**0.21 (0.14, 0.27)**
Costs (A$)	163K (151K, 176K)	151K (140K, 165K)	**12K (9K, 14K)**
No Intent for ASCT			
QALYs	4.91 (4.66, 5.18)	4.81 (4.57, 5.08)	**0.09 (0.04, 0.15)**
Costs (A$)	86K (78K, 94K)	78K (71K, 86K)	**7K (6K, 9K)**
No Intent for ASCT & <70 years			
QALYs	5.72 (5.45, 6.03)	5.57 (5.29, 5.90)	**0.15 (0.07, 0.24)**
Costs (A$)	143K (134K, 155K)	132K (122K, 143K)	**11K (8K, 15K)**
No Intent for ASCT & ≥70 years			
QALYs	4.18 (3.93, 4.50)	4.14 (3.90, 4.44)	**0.04 (-0.02, 0.10)**
Costs (A$)	57K (50K, 65K)	51K (44K, 59K)	**6K (4K, 7K)**

ASCT – autologous stem cell transplant; CI – confidence interval; QALY – quality-adjusted life-years; VRd – bortezomib, lenalidomide & dexamethasone

The results of the first subgroup analysis comparing Intent for ASCT versus No Intent for ASCT suggests that, compared with the main analysis, incremental QALYs and costs are both higher in the Intent for ASCT subgroup and both lower in the No Intent for ASCT subgroup. Cost-effectiveness is improved in the Intent for ASCT subgroup with 95% of the bootstrap iterations falling below the $56K/QALY willingness-to-pay threshold versus $79K/QALY for the No Intent for ASCT subgroup and $60K/QALY in the main analysis. When considering patients with No Intent for ASCT only, the second subgroup analysis results suggest that the incremental QALY gains are concentrated in younger patients (<70 years at diagnosis) compared to older patients (≥70 years at diagnosis) leading to inferior cost-effectiveness in older patients with No Intent for ASCT.

4 Discussion

4.1 Summary of key findings

Our post-market, real-world cost-effectiveness analysis using a DES framework and registry data revealed that VRd was only somewhat cost-effective at the traditional A$50K/QALY threshold. The model demonstrated that VRd was associated with a modest 0.16 QALY gains

(95% CI: 0.10, 0.21) and A$10K in increased costs (95% CI: A$8K, A$11K) compared to No VRd. The model also revealed that VRd significantly improved BCR to LoT 1, with 5.1% (95% CI: 3.1%, 7.0%) more patients achieving Complete Remission and 5.2% (95% CI: 3.5%, 6.9%) more achieving Very Good Partial Response compared to No VRd. This improved response profile led to a small but statistically significant 1.1% (95% CI: 0.6%, 1.7%) increase in receipt of ASCT and a large 13.8% (10.4%, 17.3%) increase in receipt of maintenance therapy. The model also captured small but significant reductions in the proportion of patients receiving subsequent LoTs, suggesting that improved early response may modify the entire treatment pathway. These interdependencies between first-line treatment choice and subsequent therapeutic decisions highlight the value of our DES approach in capturing the complex, dynamic nature of MM treatment pathways that would be difficult to model using traditional cohort models.

4.2 Comparison with literature

Given our economic evaluation compares VRd with No VRd, where No VRd contains 97.6% VCd it is not possible to directly compare our findings aligned with previous economic evaluations of VRd in MM which have compared against Rd. The 2019 PBAC recommendation for VRd produced a smaller ICER of A$15K-A$45K/QALY against Rd when using the intention-to-treat population from the pivotal SWOG S0777 clinical trial. However, similarly to our analysis, when restricted to the transplant-ineligible subgroup, this ICER increased to A$45K-A$75K/QALY. This shift reflects a critical limitation in the original trial data that our registry-based approach helps address. The SWOG S0777 trial recruited patients "without immediate intent for ASCT," but approximately 69% were classified as having "intent to transplant" at baseline, and many patients ultimately received transplantation. This population heterogeneity likely led to overestimating benefits when applying the results specifically to transplant-ineligible patients.

Narsipur et al. found that VRd was not cost-effective compared to Rd at a willingness-to-pay threshold of US$150K per QALY in the US healthcare system with an estimated an ICER of US$530K per PFQALY.[11] The significantly higher ICER in their study likely reflects differences in drug costs between healthcare systems and their methodological approach, which used progression-free survival rather than overall survival as the primary benefit measure. Importantly, their PFQALY methodology only accounted for quality-adjusted survival until disease progression, effectively assuming zero benefits and costs in the post-progression

period. This approach omits the potential downstream benefits of improved response to initial therapy on subsequent treatment effectiveness and overall survival, which our model explicitly captures through its whole-care pathway design.

4.3 Implications for policy and practice

Our research has several important implications for health policy, clinical practice, and health economic methodology. Selecting the appropriate comparator is a critical methodological decision in HTA that can significantly impact cost-effectiveness conclusions and subsequent policy decisions. The PBAC Public Summary Document indicates that the submission for VRd originally targeted ASCT-ineligible patients with Rd nominated as the primary comparator based on the prediction that "the utilisation of lenalidomide was expected to overtake bortezomib based regimens as the mainstay of first-line therapy by 2022."[3] While the PBAC considered both Rd and VMP (as a proxy for all bortezomib-based regimens) as relevant comparators, the economic evaluation predominantly focused on the comparison with Rd.

Our analysis of changes in anticancer regimen use in the MRDR between 2017-2018 and 2023-2024 revealed that VRd largely replaced VCd rather than Rd. Assuming the MRDR accurately represents Australia's MM treatment landscape, this suggests the economic evaluation considered by PBAC may have been based on a suboptimal comparator. This finding highlights the value of incorporating real-world treatment pattern data when HTA agencies determine appropriate counterfactuals for economic evaluations, potentially improving the accuracy of cost-effectiveness assessments and subsequent reimbursement decisions.

Notwithstanding this limitation, our findings suggest that the PBAC decision to list VRd for reimbursement for newly diagnosed MM in Australia was justified if considered at a slightly higher willingness-to-pay threshold than the traditional A$50K/QALY. This aligns with precedent where PBAC has accepted higher thresholds for rare conditions or where there is a lack of effective treatment alternatives.[24] The significant difference in treatment pathways observed in our model—including improved response rates, increases in ASCT and maintenance therapy, decreases in subsequent LoTs—highlights the value of considering downstream effects when making reimbursement decisions. Rather than evaluating treatments in isolation, our findings demonstrate the importance of assessing how a new therapy might modify the entire treatment pathway, potentially influencing the cost-effectiveness of subsequent interventions.

Our study demonstrates the feasibility and value of post-market economic evaluations using registry data. Such evaluations could become a standard component of HTA processes, providing a feedback loop that validates or refines initial reimbursement decisions based on real-world evidence. This approach is particularly valuable for high-cost therapies where significant uncertainty exists at the time of initial assessment. The whole-care pathway EpiMAP Myeloma model could serve as a common reference case for future HTA decisions in MM, enhancing consistency across evaluations of different interventions while reducing methodological heterogeneity. By maintaining and regularly updating this validated DES framework with the latest registry data, decision-makers could evaluate new treatments within the context of established pathways rather than in isolation, enabling cumulative knowledge building about comparative effectiveness. This would address a common critique of HTAs—that assessments often lack consistency in modelling approaches, comparators, and assumptions—while streamlining the evaluation process for emerging therapies in this rapidly evolving therapeutic landscape.

The use of DES modelling and registry data provides a template for future economic evaluations in oncology and other therapeutic areas characterised by complex treatment pathways and heterogeneous patient populations. As healthcare systems increasingly prioritise personalised medicine and value-based care, methods that can capture individual heterogeneity and dynamic treatment pathways will become increasingly important for supporting evolving healthcare priorities.

4.4 Strengths

The key strength of our study is the use of the MRDR, a comprehensive, ongoing national MM registry that captures detailed information on patient characteristics, treatment patterns, and outcomes in routine clinical practice. This provides a robust foundation for our real-world cost-effectiveness estimates, enhancing their relevance to decision-makers compared to models based solely on clinical trial data. In the future, risk equations for the EpiMAP Myeloma model can be updated with the latest MRDR data as it becomes available.

The DES modelling framework represents another significant methodological strength, allowing us to capture the complex, dynamic nature of MM treatment pathways in a way that traditional cohort models cannot. By simulating individual patient trajectories, we more accurately represent the heterogeneity of patient populations, the impact of patient characteristics on treatment decisions, and the downstream effects of therapy choices. This

approach avoids the artificial constraints of health states that characterise traditional cohort models, instead allowing the model structure to emerge naturally from the relationships estimated in our risk equations.

Our approach to uncertainty quantification, using bootstrapping to re-estimate risk equations and re-run simulations, provides a comprehensive assessment of parameter uncertainty that accounts for the complex interdependencies in our model. This offers decision-makers a clear understanding of the robustness of our cost-effectiveness estimates that goes beyond the separate PSA typical of cohort models, which often fail to capture correlations between parameters.

The open-source nature of our model code enhances transparency and reproducibility, addressing common criticisms of complex simulation models. This approach not only supports scientific rigour but also facilitates adaptation of our methods to other settings or therapeutic areas, potentially accelerating the adoption of advanced modelling techniques in health economic evaluation more broadly.

4.5 Limitations

Despite these strengths, our study has several limitations. While the MRDR provides comprehensive data on treatment patterns and outcomes, it may not capture all relevant patient characteristics that influence treatment selection and response. This could introduce confounding into our real-world estimates of treatment effects. Our cost analysis focused solely on treatment-related costs, excluding hospital and community costs due to data limitations. While this approach assumes these costs are similar between treatment arms, differences in disease progression rates could lead to differential resource utilisation beyond treatment costs.

The quality-of-life utility weights used in our model were derived from international literature rather than Australian-specific data. While this is a common approach in economic evaluations, it may not fully reflect the preferences and experiences of Australian MM patients. While our model captures treatment patterns observed in the registry up to 2024, future changes in clinical practice—such as the introduction of new therapies or changes in treatment sequencing—could alter the cost-effectiveness of VRd over time. This highlights the importance of ongoing registry data collection and periodic re-evaluation of cost-effectiveness as the treatment landscape evolves.

5 Conclusion

This analysis demonstrated the utility of individual-level modelling using registry data to estimate post-market, real-world cost-effectiveness that captures the downstream impacts of changes to the treatment pathway. By employing a DES model, we showed that VRd provides modest QALY gains at increased costs compared to alternative regimens and is only likely to have been cost-effective if judged against a slightly higher willingness-to-pay threshold than PBAC's traditional A$50K/QALY. This study highlights the importance of post-market economic evaluations and the value of individual-level modelling using registry data in informing ongoing policy discussions about high-cost cancer therapies.

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7 Figure Legend

Figure 1: EpiMAP Myeloma Model Diagram

Figure 1: Cost-effectiveness Plane

Figure 2: Cost-effectiveness Acceptability Curve

Supplementary Information

Table A1: CHEERS Checklist

Topic	No.	Item	Location
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Methods, Page 6
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract, Page 2
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introducti on
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	None
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Study Cohort
Setting and location	6	Provide relevant contextual information that may influence findings.	Economic Evaluatio n
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Economic Evaluatio n
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Economic Evaluatio n
Time horizon	9	State the time horizon for the study and why appropriate.	Economic Evaluatio n
Discount rate	10	Report the discount rate(s) and reason chosen.	Economic Evaluatio n
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Economic Evaluatio n
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Economic Data
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Economic Data
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Economic Data
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Supplemе ntary Appendix

Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	The EpiMAP Myeloma Model
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	The EpiMAP Myeloma Model
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Subgroup Analyses
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Subgroup Analyses
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Uncertainty
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	None
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Results, Supplementary Appendix
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	None
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	None
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	None
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	End of manuscript
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	End of manuscript

Table A2: Treatment Costs

Regimen	LoT	Cost	Usage
VCd	1	$902/cycle	4x 21-day cycles maximum
VRd	1	$1,776/cycle	5x 21-day cycles maximum
DVd	2	$12,110/cycle	28-day cycles until progression
Rd	2, 3, 4	$1,608/cycle	28-day cycles until progression
Kd	3, 4	$15,025/cycle	28-day cycles until progression
Pd	4	$2,291/cycle	28-day cycles until progression
'Other'[1]	All	$4,016/cycle	Assumed 28-day cycles until progression
ASCT	1	$41,723	One off
MNT[2]	1	$1,329/cycle	28-day cycles until progression

[1] 'Other' was calculated as the mean cost/cycle of VCd, VRd, Rd, Kd, DVd, Pd, VTd, TCd, Td and Vd
[2] Maintenance therapy was calculated as a weighted cost per 28-day cycle of R (67%) and T (33%) based on observed maintenance therapy data in the MRDR since 2020
ASCT – autologous stem cell transplant; C – cyclophosphamide; D – daratumumab; d - dexamethasone; K – carfilzomib; MNT – maintenance therapy; P – pomalidomide; Rd– lenalidomide; T – thalidomide; V – bortezomib

Table A3: EQ-5D utility weights - Acaster et al. (2012)

Treatment Phase	Utility weight
LoT 1	0.63
TFI 1	0.72
LoT 2	0.67
Later	0.63

LoT – line of therapy; TFI – treatment-free interval

Table A4: Risk Equations - Summary

Equation	Form	Covariates
Overall Survival	Parametric survival – Weibull	Age, Age^2, Male, cECOG, R-ISS, BCR interacted with LoT
Diagnosis to LoT 1 Interval	Parametric survival – Weibull	Age, Age^2, Male, cECOG, R-ISS, Planned ASCT
Treatment-free Interval	Parametric survival – Weibull	Age, Age^2, Male, cECOG, R-ISS, BCR
Anticancer Regimen	Multinomial logit	Age, Age^2, Male, cECOG, R-ISS, BCR
Anticancer Treatment Duration	Parametric survival – Weibull	Age, Age^2, Male, cECOG, R-ISS, Anticancer Regimen
Planned ASCT	Logit	Age, Age^2, Male, cECOG, R-ISS, Age ≥ 70, Age ≥75, Comorbidity Score†
Receipt of ASCT	Logit	Age, Age^2, Male, cECOG, R-ISS, Age ≥ 70, Age ≥ 75, Comorbidity Score†, BCR
Receipt of MNT	Logit	Age, Age^2, Male, cECOG, R-ISS, Receipt of ASCT, Anticancer Regimen, BCR
BCR to Anticancer Treatment	Ordered logit	Age, Age^2, Male, cECOG, R-ISS, Anticancer Regimen, BCR
BCR to ASCT	Ordered logit	Age, Age^2, Male, cECOG, R-ISS, BCR

†Comorbidity Score includes cardiac disease, pulmonary disease, diabetes, liver disease, peripheral neuropathy, and other malignancy
ASCT – autologous stem cell transplant; BCR – best clinical response, cECOG – collapsed Eastern Cooperative Oncology Group; R-ISS – revised international staging system; LoT – line of therapy; MNT – maintenance therapy

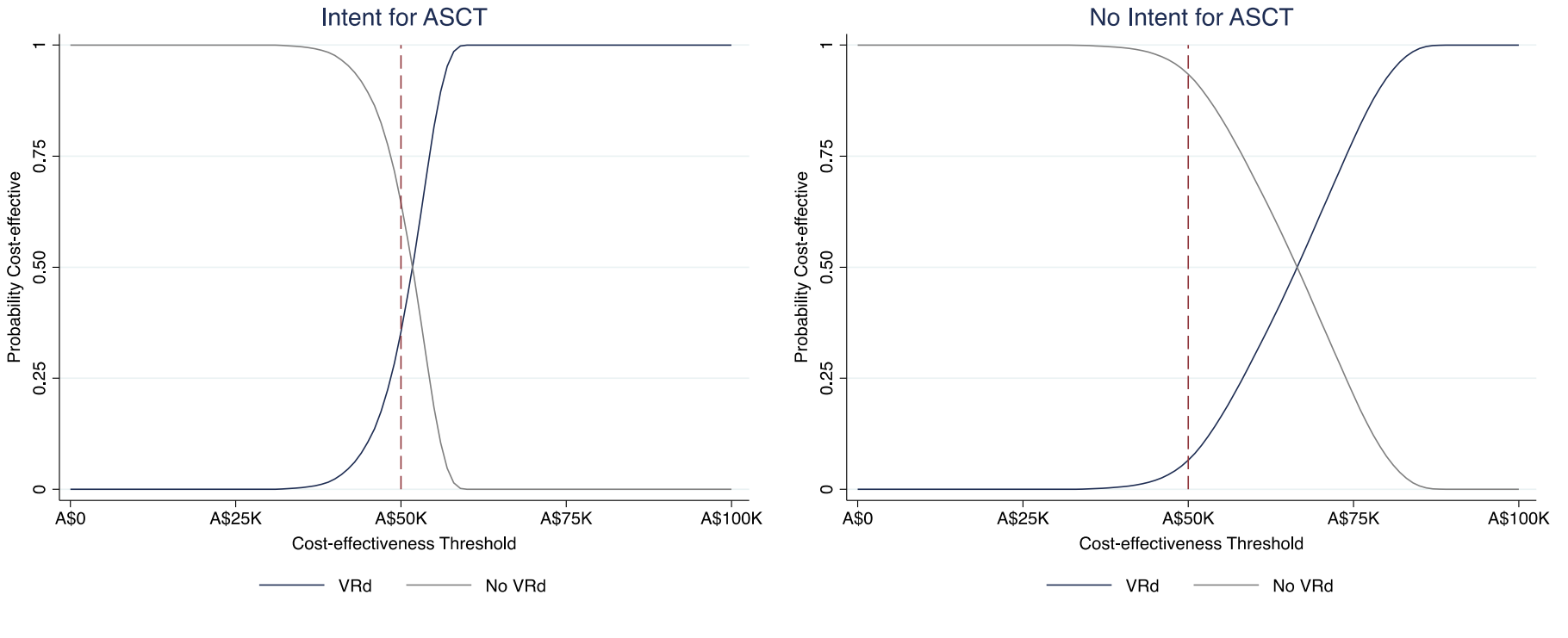

Figure A1: Intent for ASCT vs. No Intent for ASCT Subgroup Analysis - Cost-effectiveness Acceptability Curves

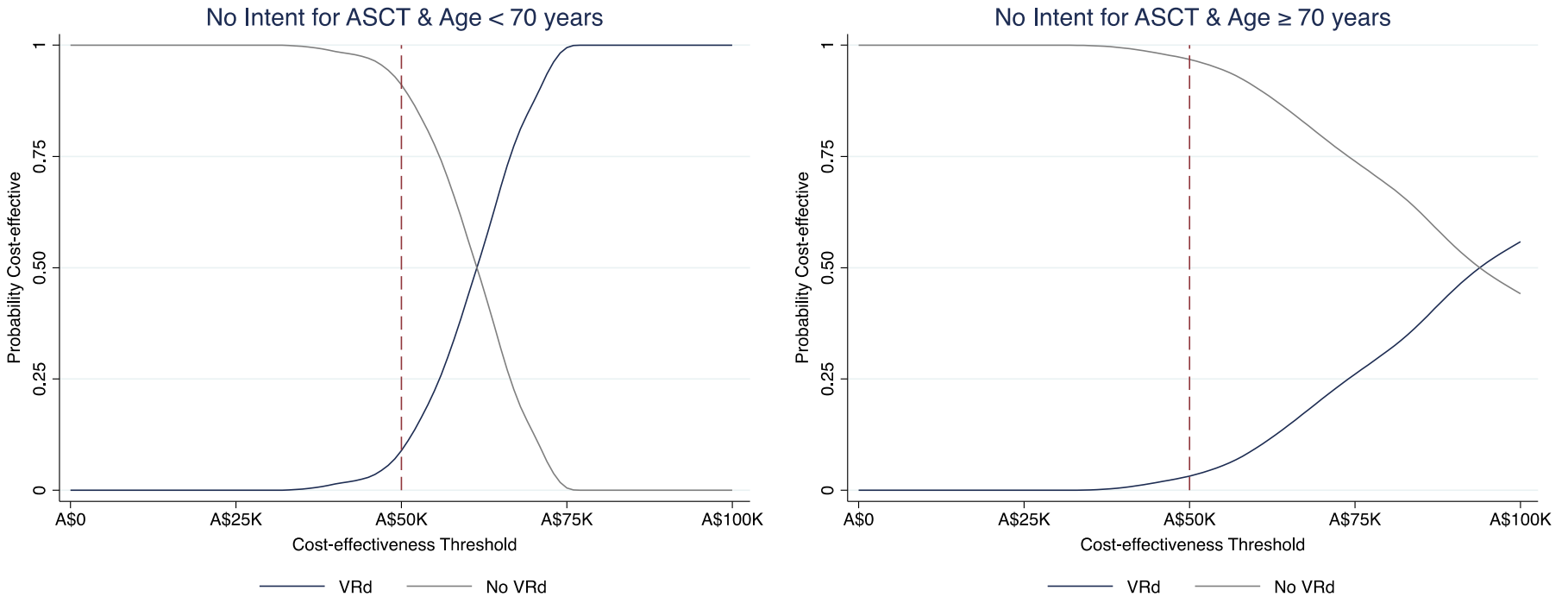

Figure A2: No Intent for ASCT – Age < 70 years vs. Age. ≥ 70 years Subgroup Analysis - Cost-effectiveness Acceptability Curves