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CADTH Health Technology Review

Optimal Pharmacotherapy for Transplant-Ineligible Multiple Myeloma: Project Protocol

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Protocol

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Table of Contents

Tables

Figure

Abbreviations

HR	hazard ratio
IMiD	immunomodulatory drugs
MM	multiple myeloma
NMA	network meta-analysis
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PFS	progression-free disease
QALY	quality-adjusted life-year
r/r	relapsed and/or refractory
RCT	randomized controlled trial
SLR	systematic literature review
TE	time to next event
TTP	time to progression

Introduction and Rationale

Symptomatic multiple myeloma (MM) is an incurable plasma cell neoplasm, characterized by an overgrowth of plasma cells in the bone marrow. It represents 1.5% of all new cancers in Canada, with an estimated 3,400 new cases annually.[1] MM accounts for approximately 10% of all hematologic malignancies.[2] Symptomatic myeloma affects older adults, with the average age at diagnosis being 62 years for men and 61 years for women, and only 4% of cases are diagnosed in individuals younger than 45 years of age.[3] In Canada, the 5-year net survival rate for MM is 44%, with a higher incidence in males.[2] MM had the second-largest increase in male cancer incidence in 2019, with an annual percentage change of 2.6%.[4]

The preferred first-line therapy for newly diagnosed MM patients is high-dose chemotherapy followed by autologous stem cell transplantation.[5] However, the majority of patients will not be eligible for this procedure because of health risks or other issues.[6] A number of multi-drug regimens can be offered to these patients as first- or subsequent-line of therapy. The choice of drug therapy may depend on patient characteristics, personal preferences, experience with previous therapies, and funding by regional cancer centres. Table 1 and Table 2 list all regimens for first- and subsequent-lines of MM treatment that are in use or being considered for public reimbursement in Canada.

Table 1: Treatment Regimens for Newly Diagnosed Transplant-Ineligible MM

Treatment regimen	Reviewed by CADTH pCODR
Bortezomib + melphalan + prednisone	No
Cyclophosphamide + bortezomib + dexamethasone	No
Cyclophosphamide + bortezomib + prednisone	No
Daratumumab + bortezomib + melphalan + prednisone	Yes
Daratumumab + cyclophosphamide + bortezomib + dexamethasone	No
Daratumumab + lenalidomide + dexamethasone	Yes
Lenalidomide + bortezomib + dexamethasone	Yes
Lenalidomide + dexamethasone	Yes

MM = multiple myeloma; pCODR = pan-Canadian Oncology Drug Review.
Note: These regimens for newly diagnosed transplant-ineligible MM are as per the indication reviewed by CADTH pCODR or are according to the provincial funding status.

Table 2: Treatment Regimens for Relapsed or Refractory MM

Treatment regimen	Reviewed by CADTH pCODR
Bortezomib + dexamethasone	No
Carfilzomib + dexamethasone ± cyclophosphamide[a]	Yes
Carfilzomib + lenalidomide + dexamethasone	Yes
Carfilzomib + pomalidomide + dexamethasone	No
Cyclophosphamide + bortezomib + dexamethasone	No
Daratumumab + bortezomib + dexamethasone	Yes
Daratumumab + lenalidomide + dexamethasone	Yes
Daratumumab + pomalidomide + dexamethasone	No
Lenalidomide + dexamethasone ± cyclophosphamide[a]	Yes
Idecabtagene vicleucel	No[b]
Isatuximab + pomalidomide + dexamethasone	Yes[c]

Treatment regimen	Reviewed by CADTH pCODR
Pomalidomide + bortezomib + dexamethasone	Yes
Pomalidomide + dexamethasone ± cyclophosphamide[a]	Yes

MM = multiple myeloma
[a] The addition of cyclophosphamide was not reviewed by the CADTH pan-Canadian Oncology Drug Review (pCODR).

[b] The sponsor filed the submission with CADTH and the submission is under review.
[c] This was presented at the January 2021 pCODR Expert Review Committee meeting.

Note: These regimens for relapsed or refractory MM are as per the indication reviewed by CADTH pCODR or are according to the provincial funding status.

By hitting multiple molecular targets simultaneously, these drug combinations can often control disease and delay its progression. For example, lenalidomide and other members of the immunomodulatory class of drugs (IMiDs) have immune-modulating and proapoptotic activities on blood cancer cells. Bortezomib is a proteasome inhibitor that inhibits cell survival pathways and modulates the tumour microenvironment and marrow niche. Melphalan is an alkylating chemotherapeutic agent. Corticosteroids like prednisone and dexamethasone dampen the activity of immune cells, including myeloma cells. Finally, daratumumab and isatuximab are monoclonal antibodies directed against cluster of differentiation 38, or CD38, which is expressed on plasma cells. Additional members of these classes such as pomalidomide (an analogue of lenalidomide), carfilzomib, and ixazomib (analogues of bortezomib) can be given to patients with relapsed or refractory MM after failure of primary agents. Many drugs are in development for MM, including venetoclax, selinexor, various bispecific T-cell engagers, and chimeric antigen receptor T-cell therapies directed against the B-cell maturation antigen marker and other plasma cell–specific targets.

Despite an abundance of clinical literature on drugs for MM, head-to-head comparisons of first-line drug regimens for transplant-ineligible patients are few and, as a result, uncertainty remains regarding their relative effectiveness and safety. As well, clear information on the real-world performance of front-line strategies is missing. The same situation prevails for subsequent-line therapies for relapsed or refractory MM. As a result, it is difficult to predict the fate of MM patients initiating therapy and the optimal sequencing of MM treatments is clouded with uncertainty.

Two network meta-analyses (NMAs) were performed to synthesize direct and indirect evidence from previously published clinical trials in MM, with the aim of enabling a comparison of all treatments studied. In 2019, Blommestein et al.[6] performed a systematic literature review (SLR) and NMA of 24 phase III randomized controlled trials (RCTs) including 21 treatments for newly diagnosed MM published between January 1999 and March 2016. Based on the extracted hazard ratios (HRs) of the different treatment options, they found daratumumab-bortezomib-melphalan-prednisone and bortezomib-melphalan-prednisone-thalidomide, with bortezomib-thalidomide maintenance to be the most effective treatments sequence. Earlier, van Beurden-Tan et al.[7] (2017) examined treatment outcomes for relapsed and/or refractory (r/r) MM using the same approach (i.e., SLR and NMA). Their network was based on 17 phase III RCTs conducted between January 1999 and March 2016, including 18 treatment options. For r/r MM, the treatment combination of daratumumab-lenalidomide-dexamethasone provided the best results in HRs considered. Both NMAs provide a rather complete overview of the relative efficacy of all available treatment options and sequences for newly diagnosed and r/r MM until the year 2016. However, since then, long-term results of trials such as the ALCYONE and OPTIMISMM have become available, and results from the MAIA trial are available, necessitating an update of these NMAs.[8-10]

Following a topic prioritization process, the Provincial Advisory Group (PAG), which provides advice to CADTH, selected MM first-line drugs for patients ineligible for stem cell transplant as the preferred topic for the development of an Optimal Use project. PAG members also mentioned that any CADTH work on subsequent treatments and sequencing would be of high value. PAG members noted the high amount of resources consumed for MM treatment in cancer centres and highlighted the complex array of therapeutic options. Evidence on the relative clinical and cost-effectiveness of multi-drug regimens and their sequencing across the treatment pathway is generally not included in CADTH reimbursement reviews, thus preventing recommendations on sequencing — an issue that is consistently acknowledged by the CADTH pCODR Expert Review Committee (pERC).

To fill this gap in sequencing, CADTH is developing a Therapeutic Review project. While publicly available list prices will be included in the economic model, this presents uncertainty around the true cost-effectiveness of sequences, as net prices are confidential. Therefore, a pERC recommendation will be developed, if appropriate.

To inform the final scope of the Therapeutic Review and protocol development, a proposed scope was posted to the CADTH website for stakeholder feedback (www.cadth.ca). Patient group input was also solicited.

Objectives

The aim of this project is to compare the clinical and cost-effectiveness of treatments for patients with MM who are ineligible for stem cell transplantation. More specifically, this will be done for newly diagnosed MM and r/r MM separately. Furthermore, this project aims to determine an optimal treatment sequence based on the clinical and cost-effectiveness profile of these sequences.

Deliverables

The following deliverables are planned:

- a Science Report, including updated comparative efficacy and safety results of previously published NMAs of treatments for patients with multiple myeloma who are ineligible for stem cell transplantation or r/r MM
- an economics report including costs and cost-effectiveness of treatments and treatment sequences for newly diagnosed patients with MM who are ineligible for stem cell transplantation
- a pERC Recommendation Report (if applicable) based on the Science and Economic Report.

Policy Question(s)

The policy question defined for this research is:

- In what sequences should drugs for transplant-ineligible MM be reimbursed to maximize clinical and cost-effectiveness while considering patient safety, characteristics, experience, and preferences?

Research Questions

The project will address the following research questions:

1. What is the comparative efficacy and safety of drug combinations for newly diagnosed, previously untreated MM in patients who are not eligible for autologous stem cell transplant?
2. What is the comparative efficacy and safety of drug combinations for MM in patients who have relapsed or are refractory to first-line drugs?
3. What is the cost-effectiveness of various treatment sequences for transplant-ineligible MM patients?

Supplemental Questions

1. What are the patient experiences with respect to living with MM?
2. What are the patient expectations and preferences regarding MM treatment?

Methods

Clinical Review

Literature Search Methods

The literature search will be performed by an experienced biomedical information specialist using a peer-reviewed search strategy.

Published literature will be identified by searching the following bibliographic databases: Embase (inception to March 2021), MEDLINE ALL (inception to March 2021) via Ovid, and the Cochrane CENTRAL register of Trials (inception to March 2021). The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts are multiple myeloma and randomized controlled trials.

Methodological filters will be applied to limit retrieval to RCTs. Where possible, retrieval will be limited to the human population. Retrieval will not be limited by publication date but will be limited to English-language results. Conference abstracts will be excluded from the search results. Regular alerts will be established to update the search until the CADTH recommendations, based on this review, are finalized. Regular search updates will be performed on databases that do not provide alert services.

Data Source(s)

Key data will be obtained from published, peer-reviewed scientific articles identified through the literature review. This will include clinical information such as progression-free survival (PFS).

Eligibility Criteria

Study Selection

Two reviewers will independently screen titles and abstracts for relevance to the clinical research questions. Full texts of potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the pre-determined selection criteria (Table 1). The 2 reviewers will then compare their chosen included and excluded studies; disagreements will be discussed until consensus is reached. In case of persistent disagreement, a third reviewer will be consulted for settlement. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Inclusion and Exclusion Criteria

The selection criteria for Research Question 1 (i.e., "What is the comparative efficacy and safety of drug combinations for newly diagnosed, previously untreated MM in patients who are not eligible for autologous stem cell transplant?") are summarized in Table 3.

Studies will be excluded if they are in languages other than English, do not meet the selection criteria aforementioned, provide results of a qualitative or non-comparative study, are extension studies, or present preliminary results in abstract form. Duplicate publications, narrative reviews, and editorials will also be excluded. In addition, the following observational study designs will be excluded: before and after studies, single-arm cohort studies with historical controls, case series, and case reports. Abstracts will be excluded unless they present supplementary data for an RCT that has another full-text publication that may be used to assess the risk of bias.

Table 3: Selection Criteria for Newly Diagnosed Patients

Population(s)	Adult patients with newly diagnosed, previously untreated MM who are receiving non-transplant–based therapy first line. Subgroups of interest: • Patients with high-risk cytogenetics • Age groups (< 75, ≥ 75 years) • ECOG score
Intervention(s)	Combinations with at least one of the following drugs: • Bortezomib • Daratumumab • Dexamethasone • Lenalidomide • Prednisone • Thalidomide[a] • Melphalan[a] • Carfilzomib

	• Ixazomib[a] • Cyclophosphamide
Comparator(s)	• Any other intervention identified as aforementioned • Placebo
Outcome(s)	• PFS • TTP • MRD-negative status (descriptively) • Health-related quality of life[b] • Severe adverse events (Grade ≥ 3)
Study Design(s)	Published phase III RCTs

ECOG = Eastern Cooperative Oncology Group; MM = multiple myeloma; MRD = minimal residual disease; PFS = progression-free survival; RCT = randomized controlled trial; TTP = time to progression.

[a] While these regimens are not used in Canada, their inclusion would strengthen the indirect treatment comparison (ITC) network. See Table 1 for the list of first-line regimens that are relevant for Canadian decision-makers.

[b] Health-related quality of life will not be included as an outcome in the ITC; CADTH will provide a summary of Health-related quality of life evidence based on previous CADTH reviews.

The selection criteria for Research Question 2 (i.e., "What is the comparative efficacy and safety of drug combinations for MM in patients who have relapsed or are refractory to first-line drugs?") are summarized in Table 4.

Table 4: Selection Criteria for Subsequent Treatment Lines

Population(s)	Patients with r/r MM (any prior drug experience). Subgroups of interest: • Patients with high-risk cytogenetics • Age groups (< 75, ≥ 75 years) • ECOG score • Number of prior lines of therapy
Intervention(s)	Combinations with at least one of the following drugs: • Bortezomib • Carfilzomib • Daratumumab • Dexamethasone • Elotuzumab • Idecabtagene vicleucel • Isatuximab • Ixazomib[a] • Lenalidomide • Pomalidomide • Prednisone • Thalidomide[a]
Comparator(s)	• Any other intervention identified as aforementioned • Placebo
Outcome(s)	• PFS • TTP • Health-related quality of life[b] • Severe adverse events (Grade ≥ 3)

Study Design(s)	Published phase III RCTs

ECOG = Eastern Cooperative Oncology Group; MM = multiple myeloma; PFS = progression-free survival; RCT = randomized controlled trial; r/r = relapsed/refractory; TTP = time to progression

[a] While these regimens are not used in Canada, their inclusion would strengthen the ITC network. See Table 2 for the list of first-line regimens that are relevant for Canadian decision-makers.

[b] Health-related quality of life will not be included as an outcome in the ITC; CADTH will provide a summary of health-related quality of life evidence based on previous CADTH reviews.

The same exclusion criteria as for newly diagnosed patients will be employed.

Data Extraction and Critical Appraisal

All information will be extracted using a standardized data abstraction form, which will be developed, piloted, and modified, as necessary. Extraction will include characteristics of trial participants, including inclusion and exclusion criteria; type of interventions, including dose, duration, and co-medication; and results of the clinical safety and efficacy/effectiveness outcomes of the intervention. All data will be extracted by 1 reviewer and checked for accuracy by a second independent reviewer.

The original primary publication for each unique study included will be used for data extraction, except where multiple publications for a single primary study are found. Multiple publications for a unique study (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study) will be handled by extracting the most recently adjudicated data for each outcome specified a priori.

Data on the subgroups of interest (see Table 3 and Table 4) will be extracted from the literature identified through the SLR when available.

Data on health-related quality of life will be extracted from a single reviewer at CADTH based on past submissions to CADTH and will be summarized narratively.

Patient insights from past submissions to CADTH will be extracted by a patient engagement officer and summarized narratively.

Quality Assessment

Quality assessment will be conducted using the Cochrane Collaboration tool for assessing risk of bias.

Data Analysis and Synthesis

Clinical

Included studies from the literature search will be classified based on study populations and relevant comparisons. Subsequently, a Bayesian NMA will be conducted using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) and WinBUGS code based on Dias et al.[11] Both fixed- and random-effects NMAs will be conducted, including both vague and informative priors on the between-study variance for random-effects meta-analyses. Based on the previously conducted NMAs,[6,12] it is expected that a random-effects model will be more appropriate, as this allows for between-study heterogeneity that was observed in trials investigating the melphalan-prednisone-thalidomide regimen, for instance. Trace plots and the Brooks-Gelman-Rubin statistic will be used to assess convergence. Three chains will be fit in WinBUGS for each analysis, with at least 40,000 iterations and burn-on of at least 40,000 iterations.

NMA summary treatment effects will be presented along with 95% credible intervals.

Patient Input

CADTH will summarize input received by patient groups for past reviews of MM drugs. We will also conduct a Rapid Response on the experiences of MM patients and the considerations that factor into their decision-making when selecting a treatment regimen.

CADTH will seek additional insights from patient groups to complement the input received for previous drug reviews and address any perceived gaps in the qualitative literature. Specific questions outlined in Appendix 2 on the following topics will be developed to guide patient groups in providing key information:

- experiences of newly diagnosed patients and patients with r/r MM and how they have shaped their perspectives around treatment
- patients' expectations, needs, and personal preferences in terms of health outcomes and treatment features
- challenges with drug regimens and how they have affected patients' perspectives and preferences around treatment.

CADTH may also conduct interviews with representatives of patient groups who submit input, as well as transplant-ineligible patients who have experience with MM pharmacotherapy, to clarify issues raised in the patient group submissions. This information will be used to provide further insight into how patients' needs, preferences, and more factor into their decision-making when selecting an appropriate drug therapy.

Patient group submissions will be summarized in the final report, along with input received for drug reviews and findings from the Rapid Response. Notes from the interviews and verbatim pieces of text will be also incorporated into the summary. The complete summary and the original patient group submissions will be shared with the research team and members of the CADTH pERC and used to inform the committee's discussions around the optimal sequencing of therapies.

The original patient group submissions will be included as an appendix in the final report. The name of the submitting patient groups and all conflict of interest information will be included in the posted patient group submissions; however, the names of the authors, including the names of individual patients or caregivers and other identifying details, will be redacted before posting to the CADTH website.

Economic Analysis

Economic Evaluation

An economic evaluation will be conducted to evaluate the cost-effectiveness of various treatment sequences for transplant-ineligible MM patients.

Primary Economic Analysis

To assess the costs and health outcomes associated with the various treatment sequences for transplant-ineligible MM patients, a decision-analytic model will be adapted based on previously conducted discrete event simulations.[12,13] Treatment sequences for the economic model will be determined based on data availability and relevance for Canadian clinical practice. The appropriate number of treatment lines will be determined based on feedback from the clinical experts and members of the pCODR PAG.

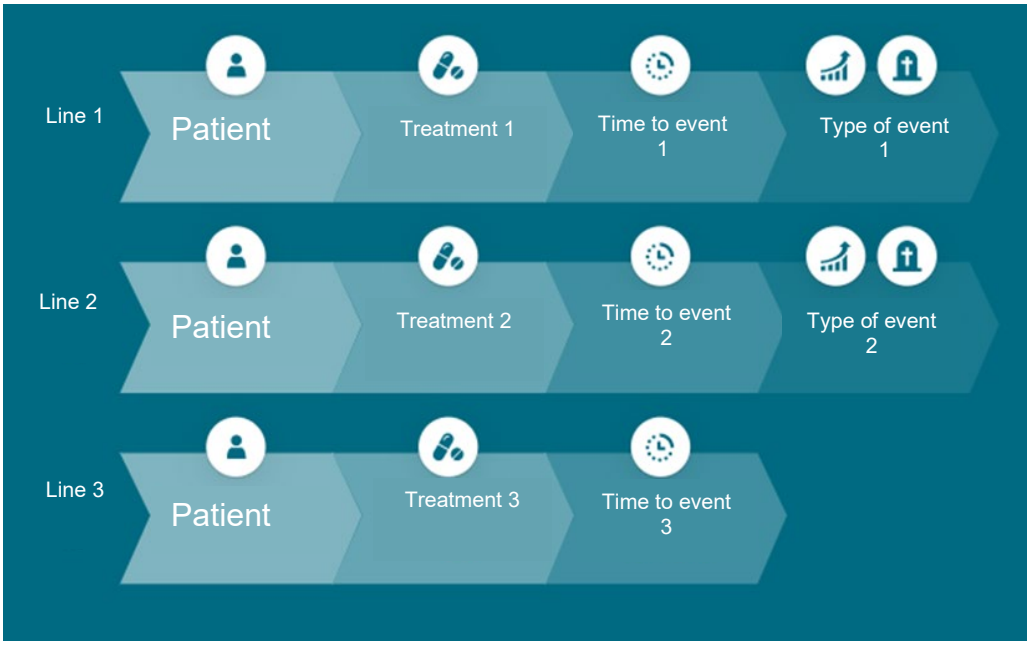
The patient cohort will be described by specific risk factors and clinical characteristics that will be identified from the clinical review and Canadian real-world data. Separate patient subgroups may be assessed based on feedback from clinical experts consulted for this project and the availability of subgroup data.

Model Design

The model used for this project will be based on an adaptation of a patient-level simulation model for transplant-ineligible patients with MM.[12,13] The original model was a discrete event simulation, with disease progression driven by the occurrence of the initiation of a new treatment line or death, with up to 3 lines of treatment modelled (see Figure 1). For the first- and second-line treatments, possible events will be either the start of the next line of treatment or death. Upon an individual entering third-line treatment, only time to death will be modelled. This model may be adapted accordingly to capture beyond 3 treatment lines.

Depending on availability, real-world data may be used in the base case to model the time to event. Specifically, time to next treatment and overall survival data from patients treated in Canadian clinical practice are parameters of interest to ensure generalizability. Furthermore, real-world data will be used to inform baseline parameters describing patient and disease characteristics.

Figure 1: Schematic Representation of the Multiple Myeloma Model



Note: In this figure, 3 lines of treatment are presented.

To derive time to next event (TTE), individual regression models for each line of treatment will be used. For the first-line treatment regression model, patient and disease characteristics along with treatment will be the model coefficients; for subsequent treatment regression models, patient and disease characteristics will be the model coefficients. For all treatment settings, logistic regressions in which TTE, treatment and, depending on data availability, patient and disease characteristics as coefficients will be used to determine the type of event (i.e., next line of treatment or death). TTE (as a proxy for time to progression) was selected as the outcome measure because the initiation of a new line of treatment or death is associated with changing costs and effects.

As a discrete event simulation, the model will simulate individual patients, each with their own patient and disease characteristics. For each patient, costs and effects will be estimated and combined to determine the total costs and effects for a representative patient cohort. Outputs to the model will include TTE, overall survival (defined as time from start of first-line treatment to death), quality-adjusted life-years (QALYs), and costs.

Further details of the model will be developed based on feedback from the CADTH clinical review team and consultation with clinical experts to ensure that it reflects current clinical literature and clinical practice. Checks on the internal and external validity of the model will be performed to assess for any logical discrepancies. Regression analyses will be performed in R, and the decision-analytic model will be constructed in Microsoft Excel 365.

Perspective

The primary perspective in the model will be that of a Canadian publicly funded health care system (i.e., provincial ministry of health).

Resource Use and Cost Data

The costs captured will reflect the perspective of the economic analysis. The costs include those related to the treatment regimens (e.g., drug costs, administration costs), disease management (e.g., hospitalization, outpatients visits, laboratory testing), and event-related costs (e.g., adverse events of treatment). Costs will be adjusted based on the expected time to event. Canadian-specific costs will be used, when available. If unavailable, costs will be estimated from the medical literature and, ideally, from comparable health systems. If necessary, costs will be inflated to 2021 costs using the general Consumer Price Index in Canada.

Utilities

Utilities and disutilities associated with each event will be obtained from a focused literature search and expert opinion may be used if the data are not available. Canadian sources will be preferred, where available.

Clinical Parameters

Parameters describing the natural history of transplant-ineligible patients with MM will be identified from peer-reviewed medical literature. To estimate the comparative clinical efficacy of treatment sequences, the outcomes from the NMA (HRs of PFS) will be combined within the regression models. The 95% credible interval will be used to incorporate uncertainty of the treatments' effectiveness.

Adverse events of Grade 3 and higher will be modelled based on data provided from the included RCTs.

Outcomes

The expected costs and QALYs associated with different treatment strategies, over the model's time horizon, will be estimated. QALYs will represent the main clinical outcome modelled, as this represents a single multi-dimensional measure and can capture the effect of the disease and its treatment on patients' morbidity and mortality. The primary economic outcome calculated will be the incremental cost-effectiveness ratios, measured in terms of the incremental cost per QALY gained, of the treatment strategies on the cost-effectiveness efficiency frontier.

In addition, costs and QALYs will be reported in a disaggregate manner. Additional outcomes, such as life-years and time on each line of treatment, will also be reported.

Time Horizon and Discounting

As MM is a lifelong condition and this analysis is exploring treatment sequences over a patient's lifetime, a lifetime time horizon will be considered to account for all relevant clinical and cost consequences of treatment.

Per existing guidelines, discounting will be set at 1.5% per year for both costs and QALYs, with sensitivity analysis conducted on this value (e.g., 0% and 5%).

Validation

We will validate the treatment duration by line of treatment and per treatment sequences with observed real-world data sources. Furthermore, we will compare our estimated

treatment duration with PFS as observed in clinical trials. In addition, we will compare the outputs of this model, adapted to the Canadian setting, with the outputs estimated in the original model that was based on the Dutch estimates. Finally, we will validate outcomes per line of treatment and per treatment sequence with clinical experts. This comparison will both include absolute outcomes (e.g., life-years) and relative differences between treatments.

Sensitivity Analysis

The base-case analysis will represent the probabilistic findings, capturing the extent to which parameter uncertainty may impact the incremental cost-effectiveness findings. Results of the probabilistic analysis will be presented on a cost-effectiveness acceptability curve whereby interventions on the efficiency frontier will be highlighted across different willingness-to-pay thresholds.

Uncertainty in the model will be further evaluated in a number of ways. Scenario and subgroup analyses will be performed to evaluate key model assumptions, while retaining the model's probabilistic element. Subgroups may include patients with high-risk cytogenetics, different age groups (< 75years, ≥ 75 years) and for different Eastern Cooperative Oncology Group scores. Scenario analyses may include different scenarios from the NMA that informs the treatment effectiveness parameters (e.g., random- versus fixed-effect NMA), setting a lower proportion of patients receiving treatment (e.g., assign treatment costs to 80% of the patients), or setting different treatment duration times. Further scenarios will be discussed with clinical experts.

Other analyses to address parameter uncertainty may include varying sets of related inputs (e.g., treatment effect) or extreme scenarios (e.g., best- and worst-case analysis, threshold scenarios).

Assumptions

During the course of the development of the economic model, assumptions and limitations will be identified and acknowledged in the report. Where possible, assumptions will be tested by conducting the appropriate sensitivity analyses.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All Ovid
- Embase.com
- Cochrane Central Register of Controlled Trials (CCTR)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: April 6, 2021

Alerts: Monthly search updates until project completion.

Study types: randomized controlled trials (phase III).

Limits

- Publication date limit: no limit-present
- Humans
- Language limit: English

Table 5: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*****	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.kw	Author keyword (Embase);
.nm	Name of substance word (MEDLINE)

Multi-Database Strategy

1. Medline All Ovid:

(Multiple Myeloma/ OR (myelom*).ab,ti,kw.) AND (Bortezomib/ OR Lenalidomide/ OR Bendamustine Hydrochloride/ OR daratumumab.nm. OR carfilzomib.nm. OR Panobinostat/ OR Thalidomide/ OR Prednisone/ OR Dexamethasone/ OR Melphalan/ OR (bortezomib OR lenalidomid* OR bendamustin* OR daratumumab* OR carfilzomib* OR panobinostat* OR belrapzo* OR bendamustin* OR bendeka* OR thalidomid* OR prednison* OR dexamethason* OR melphalan* OR cc-5013 OR cc5013 OR cdc-501 OR cdc-5013 OR cdc501 OR cdc5013 OR cimet-3393 OR cytostasan* OR darzalex* OR enmd-0997 OR enmd0997 OR farydak* OR humax-CD38 OR imet-3393 OR imet3393 OR imid-3 OR imid3 OR kyprolis* OR lbh-589 OR lbh-589a OR lbh-589b OR lbh589 OR lbh589a OR lbh589b OR ldp-341 OR ldp341 OR levact* OR mg-341 OR mg341 OR mln-341 OR mln341 OR nvp-lbh-589 OR nvp-lbh589 OR panobinostat-lactate* OR pr-171 OR pr171 OR ps-341 OR ps341 OR revimid* OR revlimid* OR ribomustin* OR ribomustine* OR ribovact* OR sdx-105 OR sdx105 OR syp-1512 OR syp1512 OR treanda* OR velcade* OR zimet-3393 OR zimet3393 OR contergan OR distaval OR isomin OR k-17 OR kedavon OR kevadon OR neurosedin OR neurosedyne OR nsc-66847 OR sedalis OR shin-naito OR softenon OR synovir OR talimol OR talizer OR telagan OR telargan OR thado OR thalidomid* OR thalix OR thalomid* OR adrecort* OR adrenocot* OR aeroseb-dex* OR aflucoson* OR aflucosone* OR alanine-nitrogen-mustard* OR alfalyl* OR alkeran* OR anaflogistico* OR ancortone* OR arcodexan* OR artrosone* OR azium* OR bidexol* OR biocortone* OR

calonat* OR cb3025* OR cb-3025* OR cebedex* OR cetadexon* OR colisone* OR colofoam* OR corsona* OR cortan* OR cortastat* OR cortidelt* OR cortidex* OR cortidexason* OR cortidron* OR cortiprex* OR cortisumman* OR cutason* OR dacorten* OR dacortin* OR dalalone* OR danasone* OR decacortin* OR decadeltoson* OR decaderm* OR decadion* OR decadran* OR decadron* OR decaesadril* OR decaject* OR decamethasone* OR decasone* OR decaspray* OR decasterolone* OR decdan* OR decilone* OR decofluor* OR decortancyl* OR decortin* OR decortisyl* OR de-cortisyl* OR dectancyl* OR dehydrocortison* OR dekacort* OR dekortin* OR delitisone* OR dellacort* OR delladec* OR deltacorten* OR deltacortison* OR deltacorton* OR delta-dome* OR deltafluoren* OR deltafluorene* OR deltasone* OR deltison* OR deltisona* OR deltra* OR dergramin* OR deronil* OR desacort* OR desacortone* OR desadrene* OR desalark* OR desameton* OR desigdron* OR de-sone-la* OR dexacen-4* OR dexachel* OR dexacort* OR dexacortal* OR dexacorten* OR dexacortin* OR dexacortisyl* OR dexa-cortisyl* OR dexa-dabrosan* OR dexadabroson* OR dexadecadrol* OR dexadrol* OR dexagel* OR dexagen* OR dexahelvacort* OR dexakorti* OR dexa-korti* OR dexalien* OR dexalocal* OR dexame* OR dexamecortin* OR dexameson* OR dexamesone* OR dexametason* OR dexameth* OR dexamethason* OR dexamethazon* OR dexamethonium* OR dexamonozon* OR dexane* OR dexano* OR dexa-p* OR dexapot* OR dexa-scherosan* OR dexascheroson* OR dexascherozon* OR dexa-scherozon* OR dexascherozone* OR dexa-scherozone* OR dexason* OR dexasone* OR dexinoral* OR dexionil* OR dexmethsone* OR dexona* OR dexone* OR dexpak-taperpak* OR dextelan* OR dextenza* OR dextrasone* OR dexycu* OR dezone* OR diadreson* OR di-adreson* OR dibasona* OR doxamethasone* OR drazone* OR encorton* OR enkorton* OR esacortene* OR evomela* OR exadion* OR exadione* OR ex-s1* OR fernisone* OR firmalone* OR fluormethylprednisolon* OR fluormethylprednisolone* OR fluormethyl-prednisolone* OR fluormone* OR fluorocort* OR fluorodelta* OR fluoromethylprednisolone* OR fortecortin* OR gammacorten* OR gammacortene* OR grosodexon* OR grosodexone* OR hemady* OR hexadecadiol* OR hexadecadrol* OR hexadiol* OR hexadrol* OR hostacortin* OR insone* OR isnacort* OR isoptodex* OR isopto-dex* OR isoptomaxidex* OR isopto-maxidex* OR levofalan* OR levo-ortho-sarcolysine* OR levo-phenylalanine-mustard* OR levo-sarcolysin* OR liquid-pred* OR lodotra* OR lokalison-f* OR loverine* OR l-phenylalanine-mustard* OR l-sarcolysin* OR luxazone* OR marvidione* OR maxidex* OR mediamethasone* OR megacortin* OR me-korti* OR melfalan* OR melphalan-hydrochloride* OR melphalon* OR melphelan* OR mephameson* OR mephamesone* OR meprison* OR metacortandracin* OR metasolon* OR metasolone* OR methazone-ion* OR methazonion* OR methazon-ion* OR methazonione* OR meticorten* OR metisone-lafi* OR mexasone* OR millicorten* OR millicortenol* OR mk125* OR mk-125* OR mymethasone* OR neoforderx* OR neofordex* OR nisomethasona* OR nisona* OR novocort* OR nsc10023* OR nsc-10023* OR nsc34521* OR nsc-34521* OR nsc8806* OR nsc-8806* OR oftan-dexa* OR opticorten* OR opticortinol* OR oradexan* OR oradexon* OR oradexone* OR orasone* OR orgadrone* OR orisane* OR ozurdex* OR panafcort* OR paracort* OR pehacort* OR phenylalanine-2037* OR pidexon* OR policort* OR posurdex* OR precort* OR prednicen* OR prednicorm* OR prednicot* OR prednidib* OR predni-f* OR prednison* OR prednitone* OR prodexona* OR prodexone* OR pronison* OR pronizone* OR pulmison* OR rayos* OR rectodelt* OR sanamethasone* OR santenson* OR santeson* OR sawasone* OR servisone* OR sk15673* OR sk-15673* OR solurex* OR spoloven* OR steerometz* OR sterapred* OR sterasone* OR thilodexine* OR triamcimetil* OR ultracorten* OR urtilone* OR vexamet* OR visumetazone* OR visumethazone* OR winpred* OR ixazomib* OR isatuximab* OR cyclophosphamid* OR pomalidomid* OR idecabtagen* OR vicleucel* OR elotuzumab* OR Abecma* OR Actimid* OR B-518 OR B518 OR bb-2121 OR bb2121 OR bms-901608 OR bms901608 OR carloxan OR CC4047 OR CC-4047 OR Chloroethylaminophenylalanine OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cycloblastin* OR cyclo-cell OR cyclofos-amide OR cyclofosfamid* OR cyclophar OR cyclophosphan* OR cyclostin OR cycloxan OR cyphos OR cytophosphan* OR cytoxan OR D2UX06XLB5 OR empliciti OR endocyclo-phosphate OR endoxan* OR enduxan* OR Fiasone OR genoxal OR Hu-38SB19 OR Hu38SB19 OR huluc63 OR Ide-cel OR IMID-3 OR IMID3 OR Imidan OR Imnovid* OR Isomin OR Kevadon OR ledoxan* OR mitoxan OR MLN-9708 OR MLN9708 OR Neaufatin OR neosan OR neosar OR Neosedyn OR Neosydyn OR Nerosedyn OR Neufatin OR Neurodyn OR Neurosedin OR Nevrodyn OR noristan OR nsc-26271 OR nsc-2671 OR pdl-063 OR pdl063 OR Pomalyst* OR prednisolone-f OR procytox* OR R30772KCU0 OR SAR-650984 OR SAR650984 OR Sarclisa* OR semdoxan OR sendoxan OR syklofosfamid OR Turbinaire OR Valgraine OR Wojtab OR ((((new* ADJ3 diagnos*) OR first-line OR untreat* OR naive)) AND (transplant* ADJ6 (ineligib* OR non-eligib* OR not-eligib*))) OR ((relaps* OR refractor*) ADJ3 myeloma*)).ab,ti.) NOT ((exp child/ OR exp infant/ OR pediatrics/ OR adolescent/) NOT exp adult/) AND english.la. NOT (exp animals/ NOT humans/) AND (Randomized Controlled Trial/ OR Controlled Clinical Trial/ OR Pragmatic Clinical Trial/ OR Pragmatic Clinical Trials as Topic/ OR Clinical Trial, Phase III/ OR Clinical Trials, Phase III as Topic/ OR Randomized Controlled Trials as Topic/ OR Controlled Clinical Trials as Topic/ OR Random Allocation/ OR Double-Blind Method/ OR Single-Blind Method/ OR Placebos/ OR Control Groups/ OR Systematic Review/ OR Systematic Reviews as Topic/ OR Meta-Analysis/ OR Network Meta-Analysis/ OR Meta-Analysis as Topic/ OR Technology Assessment, Biomedical/ OR ((random* or sham or placebo*) OR ((singl* or doubl*) ADJ (blind* or dumm* or mask*)) OR ((tripl* or trebl*) ADJ (blind* or dumm* or mask*)) OR (control* ADJ3 (study or studies or trial* or group*)) OR (Nonrandom* or non-random* or quasi-random* or quasirandom*) OR allocated OR ((open-label) ADJ5 (study or studies or trial*)) OR ((equivalence or superiority or non-inferiority or noninferiority) ADJ3 (study or studies or trial*)) OR pragmatic-stud* OR ((pragmatic or practical) ADJ3 trial*) OR ((quasiexperimental or quasi-experimental) ADJ3 (study or studies or trial*)) OR (phase ADJ (III or 3) ADJ3 (study or studies or trial*)) OR ((systematic* ADJ3 (review* or overview*)) or (methodologic* ADJ3 (review* or overview*))) OR ((quantitative ADJ3 (review* or overview* or synthes*)) or (research ADJ3 (integrati* or overview*))) OR ((integrative ADJ3 (review* or overview*)) or (collaborative ADJ3 (review* or overview*)) or (pool* ADJ3 analy*)) OR (data-synthes* or data-extraction* or data-abstraction*) OR (handsearch* or hand-search*) OR (mantel-haenszel or peto or der-simonian or dersimonian or fixed-effect* or latin-square*)

OR (met-analy* or met-analy* or technology-assessment* or HTA or HTAs or technology-overview* or technology-appraisal*) OR (meta-regression* or metaregression*) OR (meta-analy* or metaanaly* or systematic-review* or biomedical-technology-assessment* or bio-medical-technology-assessment*) OR (medline or cochrane or pubmed or medlars or embase or cinahl) OR (cochrane or (health ADJ2 technology-assessment) or evidence-report) OR (comparative ADJ3 (efficacy or effectiveness)) OR (outcomes-research or relative-effectiveness) OR ((indirect or indirect-treatment or mixed-treatment or bayesian) ADJ3 comparison*) OR (meta-analysis or systematic-review) OR (multi* ADJ3 treatment ADJ3 comparison*) OR (mixed ADJ3 treatment ADJ3 (meta-analy* or metaanaly*)) OR Umbrella-review* OR (multi* ADJ2 paramet* ADJ2 evidence ADJ2 synthesis) OR (multiparamet* ADJ2 evidence ADJ2 synthesis) OR (multi-paramet* ADJ2 evidence ADJ2 synthesis)).ab,ti.)

2. Embase.com:

('multiple myeloma'/de OR 'myeloma'/de OR 'myeloma cell'/de OR (myelom*):ab,ti,kw) AND (bortezomib/mj OR lenalidomide/mj OR bendamustine/mj OR daratumumab/mj OR carfilzomib/mj OR panobinostat/mj OR thalidomide/mj OR prednisone/mj OR dexamethasone/mj/exp OR melphalan/mj OR (bortezomib OR lenalidomid* OR bendamustin* OR daratumumab* OR carfilzomib* OR panobinostat* OR belrapzo* OR bendamustin* OR bendeka* OR thalidomid* OR prednison* OR dexamethason* OR melphalan* OR cc-5013 OR cc5013 OR cdc-501 OR cdc-5013 OR cdc501 OR cdc5013 OR cimet-3393 OR cytostasan* OR darzalex* OR enmd-0997 OR enmd0997 OR farydak* OR humax-CD38 OR imet-3393 OR imet3393 OR imid-3 OR imid3 OR kyprolis* OR lbh-589 OR lbh-589a OR lbh-589b OR lbh589 OR lbh589a OR lbh589b OR ldp-341 OR ldp341 OR levact* OR mg-341 OR mg341 OR mln-341 OR mln341 OR nvp-lbh-589 OR nvp-lbh589 OR panobinostat-lactate* OR pr-171 OR pr171 OR ps-341 OR ps341 OR revimid* OR revlimid* OR ribomustin* OR ribomustine* OR ribovact* OR sdx-105 OR sdx105 OR syp-1512 OR syp1512 OR treanda* OR velcade* OR zimet-3393 OR zimet3393 OR contergan OR distaval OR isomin OR k-17 OR kedavon OR kevadon OR neurosedin OR neurosedyne OR nsc-66847 OR sedalis OR shin-naito OR softenon OR synovir OR talimol OR talizer OR telagan OR telargan OR thado OR thalidomid* OR thalix OR thalomid* OR adrecort* OR adrenocot* OR aeroseb-dex* OR aflucoson* OR aflucosone* OR alanine-nitrogen-mustard* OR alfalyl* OR alkeran* OR anaflogistico* OR ancortone* OR arcodexan* OR artrosone* OR azium* OR bidexol* OR biocortone* OR calonat* OR cb3025* OR cb-3025* OR cebedex* OR cetadexon* OR colisone* OR colofoam* OR corsona* OR cortan* OR cortastat* OR cortidelt* OR cortidex* OR cortidexason* OR cortidron* OR cortiprex* OR cortisumman* OR cutason* OR dacorten* OR dacortin* OR dalalone* OR danasone* OR decacortin* OR decadeltoson* OR decaderm* OR decadion* OR decadran* OR decadron* OR decaesadril* OR decaject* OR decamethasone* OR decasone* OR decaspray* OR decasterolone* OR decdan* OR decilone* OR decofluor* OR decortancyl* OR decortin* OR decortisyl* OR de-cortisyl* OR dectancyl* OR dehydrocortison* OR dekacort* OR dekortin* OR delitisone* OR dellacort* OR delladec* OR deltacorten* OR deltacortison* OR deltacorton* OR delta-dome* OR deltafluoren* OR deltafluorene* OR deltasone* OR deltison* OR deltisona* OR deltra* OR dergramin* OR deronil* OR desacort* OR desacortone* OR desadrene* OR desalark* OR desameton* OR desigdron* OR de-sone-la* OR dexacen-4* OR dexachel* OR dexacort* OR dexacortal* OR dexacorten* OR dexacortin* OR dexacortisyl* OR dexa-cortisyl* OR dexa-dabrosan* OR dexadabroson* OR dexadecadrol* OR dexadrol* OR dexagel* OR dexagen* OR dexahelvacort* OR dexakorti* OR dexa-korti* OR dexalien* OR dexalocal* OR dexame* OR dexamecortin* OR dexameson* OR dexamesone* OR dexametason* OR dexameth* OR dexamethason* OR dexamethazon* OR dexamethonium* OR dexamonozon* OR dexane* OR dexano* OR dexa-p* OR dexapot* OR dexa-scherosan* OR dexascheroson* OR dexascherozon* OR dexa-scherozon* OR dexascherozone* OR dexa-scherozone* OR dexason* OR dexasone* OR dexinoral* OR dexionil* OR dexmethsone* OR dexona* OR dexone* OR dexpak-taperpak* OR dextelan* OR dextenza* OR dextrasone* OR dexycu* OR dezone* OR diadreson* OR di-adreson* OR dibasona* OR doxamethasone* OR drazone* OR encorton* OR enkorton* OR esacortene* OR evomela* OR exadion* OR exadione* OR ex-s1* OR fernisone* OR firmalone* OR fluormethylprednisolon* OR fluormethylprednisolone* OR fluormethyl-prednisolone* OR fluormone* OR fluorocort* OR fluorodelta* OR fluoromethylprednisolone* OR fortecortin* OR gammacorten* OR gammacortene* OR grosodexon* OR grosodexone* OR hemady* OR hexadecadiol* OR hexadecadrol* OR hexadiol* OR hexadrol* OR hostacortin* OR insone* OR isnacort* OR isoptodex* OR isopto-dex* OR isoptomaxidex* OR isopto-maxidex* OR levofalan* OR levo-ortho-sarcolysine* OR levo-phenylalanine-mustard* OR levo-sarcolysin* OR liquid-pred* OR lodotra* OR lokalison-f* OR loverine* OR l-phenylalanine-mustard* OR l-sarcolysin* OR luxazone* OR marvidione* OR maxidex* OR mediamethasone* OR megacortin* OR me-korti* OR melfalan* OR melphalan-hydrochloride* OR melphalon* OR melphelan* OR mephameson* OR mephamesone* OR meprison* OR metacortandracin* OR metasolon* OR metasolone* OR methazone-ion* OR methazonion* OR methazon-ion* OR methazonione* OR meticorten* OR metisone-lafi* OR mexasone* OR millicorten* OR millicortenol* OR mk125* OR mk-125* OR mymethasone* OR neoforderx* OR neofordex* OR nisomethasona* OR nisona* OR novocort* OR nsc10023* OR nsc-10023* OR nsc34521* OR nsc-34521* OR nsc8806* OR nsc-8806* OR oftan-dexa* OR opticorten* OR opticortinol* OR oradexan* OR oradexon* OR oradexone* OR orasone* OR orgadrone* OR orisane* OR ozurdex* OR panafcort* OR paracort* OR pehacort* OR phenylalanine-2037* OR pidexon* OR policort* OR posurdex* OR precort* OR prednicen* OR prednicorm* OR prednicot* OR prednidib* OR predni-f* OR prednison* OR prednitone* OR prodexona* OR prodexone* OR pronison* OR pronizone* OR pulmison* OR rayos* OR rectodelt* OR sanamethasone* OR santenson* OR santeson* OR sawasone* OR servisone* OR sk15673* OR sk-15673* OR solurex* OR spoloven* OR steerometz* OR sterapred* OR sterasone* OR thilodexine* OR triamcimetil* OR ultracorten* OR urtilone* OR vexamet* OR visumetazone* OR visumethazone* OR winpred* OR ixazomib* OR isatuximab* OR cyclophosphamid* OR pomalidomid* OR idecabtagen* OR vicleucel* OR elotuzumab* OR Abecma* OR Actimid* OR B-518 OR

B518 OR bb-2121 OR bb2121 OR bms-901608 OR bms901608 OR carloxan OR CC4047 OR CC-4047 OR Chloroethylaminophenylalanine OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cycloblastin* OR cyclo-cell OR cyclofosamide OR cyclofosfamid* OR cyclophar OR cyclophosphan* OR cyclostin OR cycloxan OR cyphos OR cytophosphan* OR cytoxan OR D2UX06XLB5 OR empliciti OR endocyclo-phosphate OR endoxan* OR enduxan* OR Fiasone OR genoxal OR Hu-38SB19 OR Hu38SB19 OR huluc63 OR Ide-cel OR IMID-3 OR IMID3 OR Imidan OR Imnovid* OR Isomin OR Kevadon OR ledoxan* OR mitoxan OR MLN-9708 OR MLN9708 OR Neaufatin OR neosan OR neosar OR Neosedyn OR Neosydyn OR Nerosedyn OR Neufatin OR Neurodyn OR Neurosedin OR Nevrodyn OR noristan OR nsc-26271 OR nsc-2671 OR pdl-063 OR pdl063 OR Pomalyst* OR prednisolone-f OR procytox* OR R30772KCU0 OR SAR-650984 OR SAR650984 OR Sarclisa* OR semdoxan OR sendoxan OR syklofosfamid OR Turbinaire OR Valgraine OR Wojtab OR ((((new* NEAR/3 diagnos*) OR first-line OR untreat* OR naive)) AND (transplant* NEAR/6 (ineligib* OR non-eligib* OR not-eligib*))) OR ((relaps* OR refractor*) NEAR/3 myeloma*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT (juvenile/exp NOT adult/exp) AND [english]/lim AND ('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR 'pragmatic trial'/exp OR 'phase 3 clinical trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial (topic)'/exp OR Randomization/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR Placebo/exp OR 'control group'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'biomedical technology assessment'/exp OR ((random* or sham or placebo*) OR ((singl* or doubl*) NEXT/1 (blind* or dumm* or mask*)) OR ((tripl* or trebl*) NEXT/1 (blind* or dumm* or mask*)) OR (control* NEAR/3 (study or studies or trial* or group*)) OR (Nonrandom* or non-random* or quasi-random* or quasirandom*) OR allocated OR ((open-label) NEAR/5 (study or studies or trial*)) OR ((equivalence or superiority or non-inferiority or noninferiority) NEAR/3 (study or studies or trial*)) OR pragmatic-stud* OR ((pragmatic or practical) NEAR/3 trial*) OR ((quasiexperimental or quasi-experimental) NEAR/3 (study or studies or trial*)) OR (phase NEXT/1 (III or 3) NEAR/3 (study or studies or trial*)) OR ((systematic* NEAR/3 (review* or overview*)) or (methodologic* NEAR/3 (review* or overview*))) OR ((quantitative NEAR/3 (review* or overview* or synthes*)) or (research NEAR/3 (integrati* or overview*))) OR ((integrative NEAR/3 (review* or overview*)) or (collaborative NEAR/3 (review* or overview*)) or (pool* NEAR/3 analy*)) OR (data-synthes* or data-extraction* or data-abstraction*) OR (handsearch* or hand-search*) OR (mantel-haenszel or peto or der-simonian or dersimonian or fixed-effect* or latin-square*) OR (met-analy* or met-analy* or technology-assessment* or HTA or HTAs or technology-overview* or technology-appraisal*) OR (meta-regression* or metaregression*) OR (meta-analy* or metaanaly* or systematic-review* or biomedical-technology-assessment* or bio-medical-technology-assessment*) OR (medline or cochrane or pubmed or medlars or embase or cinahl) OR (cochrane or (health NEAR/2 technology-assessment) or evidence-report) OR (comparative NEAR/3 (efficacy or effectiveness)) OR (outcomes-research or relative-effectiveness) OR ((indirect or indirect-treatment or mixed-treatment or bayesian) NEAR/3 comparison*) OR (meta-analysis or systematic-review) OR (multi* NEAR/3 treatment NEAR/3 comparison*) OR (mixed NEAR/3 treatment NEAR/3 (meta-analy* or metaanaly*)) OR Umbrella-review* OR (multi* NEAR/2 paramet* NEAR/2 evidence NEAR/2 synthesis) OR (multiparamet* NEAR/2 evidence NEAR/2 synthesis) OR (multi-paramet* NEAR/2 evidence NEAR/2 synthesis)):ab,ti)

3. Cochrane Central Register of Controlled Trials:

((myelom*):ab,ti,kw) AND ((bortezomib OR lenalidomid* OR bendamustin* OR daratumumab* OR carfilzomib* OR panobinostat* OR belrapzo* OR bendamustin* OR bendeka* OR thalidomid* OR prednison* OR dexamethason* OR melphalan*):ab,ti)

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture completed registered clinical trials with results. [Studies With Results | Multiple Myeloma | Phase 3]

Appendix 2: Call for Patient Input Questions

1. **We will be summarizing patient input we've received from patient groups for past reviews of multiple myeloma (MM) drugs. To add to this, we would like to learn more from transplant-ineligible individuals about their experiences living with MM.**
   - What aspects of the disease are most challenging? Most important to control?
   - How has patients' quality of life and day-to-day life been affected by this disease?
   - Are newly diagnosed patients' experiences different from patients with relapsed/refractory MM? How have these experiences shaped their perspective and preferences regarding treatments?
2. **Much like their experiences with MM, patients' needs and preferences vary when it comes to treatment outcomes. We want to learn more about how personal preferences, experiences with previous therapies, and more factor into their decision-making when looking for a treatment regimen that is right for them.**
   - What does a successful treatment look like for newly diagnosed patients trying a first-line drug regimen? For relapsed or refractory patients trying subsequent-line therapies?
   - What challenges did patients who have tried several drug regimens experience? How have these challenges affected their perspectives and preferences regarding treatments? Describe the range of challenges and identify those most frequently experienced.
   - What health outcomes were most important to patients when weighing their treatment options (e.g., managing symptoms, improving quality of life, fewer side effects)? What treatment features (e.g., ease of use, route of administration)? Describe the range of health outcomes and treatment features, and identify those most frequently reported.
3. **In addition to treatment outcomes, other considerations can help guide treatment sequences for transplant-ineligible MM patients.**
   - What other factors do patients think about when selecting a treatment regimen that is right for them (e.g., financial concerns, geographic location)?
   - Are there factors specific to patients and health care settings in certain communities or subpopulations across Canada that need to be considered?
   - Are there potential or actual challenges and inequalities around patients' ability to use and/or access treatment?