Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

Journal:	*Pharmacoepidemiology and Drug Safety*
Manuscript ID	PDS-15-0194.R1
Wiley - Manuscript type:	Original Research Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Cid Ruzafa, Javier; Evidera, Retrospective Observational Studies Merinopoulou, Evie; Evidera, Retrospective Observational Studies Baggaley, Rebecca; London School of Hygiene & Tropical Medicine, Department of Infectious Disease Epidemiology Leighton, Pamela; Evidera, Retrospective Observational Studies Werther, Winifred; Onyx Pharmaceuticals, Inc., an Amgen subsidiary, Epidemiology Felici, Diana; Onyx Pharmaceuticals, Inc., an Amgen subsidiary, Epidemiology Cox, Andrew; Evidera, Retrospective Observational Studies
Keywords:	Epidemiology, multiple myeloma, prevalence, model, treatment line
Abstract:	Multiple myeloma (MM) is a progressive, malignant neoplasia with a worldwide, age-standardized annual incidence of 1.5 per 100,000 individuals and 5-year prevalence around 230,000 patients. Main favorable prognostic factors are younger age, low-moderate cytogenetic risk, and undergoing stem cell transplantation. Our aim was to estimate the size of the patient population with MM eligible to receive a new MM therapy at different lines of therapy in the US. Methods: We constructed a compartmental, differential equation model representing the flow of MM patients from diagnosis to death, via two possible treatment pathways and distinguished in four groups based on prognostic factors. Parameters were obtained from published references, available statistics, and assumptions. The model was used to estimate number of diagnosed MM patients and number of patient transitions from one line of therapy to the next over one-year. Model output included 95% credible intervals (CI) from probabilistic sensitivity analyses. Results: The base-case estimates were 80,219 patients living with MM, including 70,375 on treatment, 780 symptomatic untreated patients, and 9,064 asymptomatic untreated patients. Over a one-year period, the number of MM patients on treatment line 1 was estimated at 23,629 (CI 22,236-25,029), and the number of transitions from treatment line 1 to treatment line 2 estimated at 14,423. Conclusions:

	The size of the patient population with MM on different lines of therapy and in-patient subgroups of interest estimated from this epidemiologic model can be used to assess the number of patients who could benefit from new MM therapies and their corresponding budgetary impact.

Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

Running Head: Multiple myeloma lines of therapy: an epidemiologic model

Cid Ruzafa J[1], Merinopoulou E[1], Baggaley RF[2], Leighton P[1], Werther W[3], Felici D[3], Cox A[1]

[1] Retrospective Observational Studies, Evidera, London, UK; [2] Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK; [3] Onyx Pharmaceuticals, Inc., an Amgen subsidiary, South San Francisco, CA, USA

Keywords: Epidemiology, multiple myeloma, prevalence, model, treatment line

Key Points:

- The estimated number of patients with MM in the US provided by the epidemiology model was consistent with the figure reported by SEER.
- The distribution of the patient population with MM on different lines of therapy and in patient subgroups of interest can be estimated from the epidemiologic model.
- The size of the patient population with MM on different lines of therapy and in patient subgroups can be used to assess the number of patients who could benefit from new MM therapies, information required for budget impact analysis and to support the planning of healthcare services.

Word Count: 2,751 (excluding abstract, references, tables, etc.)

Sponsors/Conflict of Interest:

This work was funded by Onyx Pharmaceuticals. Cid Ruzafa J, Merinopoulou E, Baggaley R, Leighton P, and Cox A were employed by Evidera and served as consultants to Onyx Pharmaceuticals. Werther W and Felici D were employed by and own stock in Onyx Pharmaceuticals.

Corresponding Author:

Javier Cid
Evidera
Metro Building, 6th Floor,
1 Butterwick London, UK W6 8DL
Javier.Cid@evidera.com
Tel +34 932 213 441
Fax + 44 (0) 208 576 5195

This research represents original work and has not been published elsewhere in full or in part, besides in abstract form. Javier Cid takes responsibility for the integrity of the work as a whole.

ABSTRACT

Purpose:

Multiple myeloma (MM) is a progressive, malignant neoplasia with a worldwide, age-standardized annual incidence of 1.5 per 100,000 individuals and 5-year prevalence around 230,000 patients. Main favorable prognostic factors are younger age, low-moderate cytogenetic risk, and undergoing stem cell transplantation. Our aim was to estimate the size of the patient population with MM eligible to receive a new MM therapy at different lines of therapy in the US.

Methods:

We constructed a compartmental, differential equation model representing the flow of MM patients from diagnosis to death, via two possible treatment pathways and distinguished in four groups based on prognostic factors. Parameters were obtained from published references, available statistics, and assumptions. The model was used to estimate number of diagnosed MM patients and number of patient transitions from one line of therapy to the next over one-year. Model output included 95% credible intervals (CI) from probabilistic sensitivity analyses.

Results:

The base-case estimates were 80,219 patients living with MM, including 70,375 on treatment, 780 symptomatic untreated patients, and 9,064 asymptomatic untreated patients. Over a one-year period, the number of MM patients on treatment line 1 was estimated at 23,629 (CI 22,236-25,029), and the number of transitions from treatment line 1 to treatment line 2 estimated at 14,423.

Conclusions:

The size of the patient population with MM on different lines of therapy and in-patient subgroups of interest estimated from this epidemiologic model can be used to assess the number of patients who could benefit from new MM therapies and their corresponding budgetary impact.

Word count: 250

INTRODUCTION

Multiple myeloma (MM) is a progressive, hematologic malignancy originating from plasma cells and with the most negative long-term prognosis among lymphoid malignancies.[1,2] MM accounts for approximately 1% of all cancers and 10-12% of hematologic malignancies, with a worldwide age-standardized annual incidence of 1.5 per 100,000 or estimates of around 115,000 new cases per year, a rather small number compared to other cancers and chronic conditions.[2-4] MM has an estimated worldwide 5-year prevalence of around 230,000 patients.[4] Older age is associated with unfavorable outcomes,[1,5] and there are no apparent prognostic differences associated with gender.[1] The presence of certain chromosomal abnormalities is also a negative prognostic factor.[5-8]

MM treatment is intended to control the symptomatic disease and minimize organ damage; however, relapse is likely. From high-dose therapy followed by autologous stem cell transplantation for candidates in good condition,[7,9] to allogeneic stem cell transplantation (SCT) in young patients with high-risk disease,[7,10] and to novel agents introduced in recent years,[2,7,11,12] all are associated with prolonged survival of patients with this incurable disease.[5,7,9,13-15] More than 10 drugs and a greater number of drug combinations offer therapeutic options to patients who have relapsed or are refractory to previous treatments and can result in patients receiving multiple lines of therapy.[5,7] The prevalence of MM is likely to increase as a result of ageing societies and improved survival of patients. Multiple lines of therapy for an increasing number of patients with MM translate into increasing resource requirements at subsequent lines of therapy[16] and competition among MM treatment alternatives on pharmacoeconomic grounds.[17-19]

Epidemiologic information including disease incidence, prevalence and mortality are inputs for burden of disease and cost-effectiveness analyses that aim to inform policy-making, planning and research prioritization in health care.[20] Previous studies have used mathematical modeling techniques to project the prevalence of chronic conditions such as diabetes and chronic kidney disease into the near or distant future.[21-23] In oncology, an epidemiologic model was used to estimate disease prevalence and the absolute number of patients at first-, second-, and third line of therapy for gastrointestinal stromal tumors,[24] providing useful information for budget impact analysis and healthcare services planning.[20]

In the absence of current data on the number of patients with MM by line of therapy in the US, the objectives of this study were to estimate the current number of patients with MM who are potentially eligible to receive a new MM therapy at different lines of therapy in the US, and to estimate the corresponding number of patient transitions from one line of therapy to the next over a one-year period.

METHODS

Model Overview

The size of the patient population with MM in the US across lines of therapy and the number of patient transitions from one line of therapy to the next was estimated using a compartmental model that represents the flow of patients with MM from disease occurrence to death, via two possible treatment pathways (SCT eligible; SCT non-eligible) (Figure 1). To account for the impact of different risk factors on disease progression,[1,5-8] the model distinguished four groups of patients based on age at diagnosis and cytogenetic risk: older or younger than 65 years of age, and high or low/standard cytogenetic risk (Figure 1, as depicted by dotted lines).

All newly diagnosed patients with MM enter the model as symptomatic or asymptomatic. Asymptomatic patients are assumed to receive no treatment until symptom occurrence. Symptomatic patients can transition through two treatment pathways depending on whether they are eligible for an SCT or not. Patients in both pathways progress from one line of therapy to the next as they relapse. For patients eligible for a SCT, the first line of therapy represents induction, SCT and maintenance therapy post SCT. In each treatment line, patients are allowed to die from background mortality or mortality related to their condition. Eventually, all patients will die since the model assumes there is no cure for MM.

The model consists of a set of four differential equations which represent a mean approximation of the expected number of asymptomatic, symptomatic untreated, individuals who initiated on first line, and on subsequent treatment lines through time (Appendix A). The model parameters include estimates of MM incidence, mortality, and time to next treatment line (Table 1, Appendix A). The base case parameter values are shown in Table 1.

This model includes a number of assumptions necessary for its correct interpretation:

- Results for all lines beyond 17 are incorporated into the 17th line.
- Patients on the SCT pathway may have up to two SCTs along their line therapy trajectory.
- Asymptomatic MM (smoldering) is explicitly modeled, but no treatment is given.
- Patterns of co-morbidities (e.g., peripheral neuropathy) are not explicit.
- The model tracks time between starting one treatment line and starting the next. Treatment breaks and permanent discontinuations are not explicitly modelled.
- There is no stratification for academic versus community care (for settings where these different care types exist).
- Line of therapy is determined by disease progression, relapse, or drug toxicity resulting in a modification of the planned therapeutic approach.[25]
- Being in the high-risk cytogenetic group does not affect SCT eligibility.

- Survival probabilities are characterized by an exponential function.
- The length of each treatment line is shorter than the previous one. Minimum length of a treatment line is approximately one week (1/50 year).
- Relative rate of patients transitioning from one line to another is constant across all lines.
- MM-related mortality while symptomatic before first line treatment initiation is slightly higher (≈10%) than MM-related mortality while asymptomatic.
- MM attributable mortality declines in the first year because of plasma cell leukemia patient depletion from the cohort. It is relatively constant over the subsequent years (≈10% increase) but then increases, especially from the 6th line of therapy and beyond
- Forecasts are at the population level and not at the individual level.

Data Sources

To estimate the overall number of patients with MM, we used the incidence of MM obtained from Surveillance Epidemiology and End Results (SEER) Cancer Statistics[26] applied to the 2013 US population estimate from the US Census Bureau.[27] Mortality rates were obtained from 2007 US National Vital Statistics.[28] Other model parameters were obtained from targeted literature searches (Table 1). For each of these parameters, one or more references were identified from the literature. Internal validity of the parameter estimates obtained from the literature (or the degree to which the referenced studies are free from systematic error) is supported by the peer review process of such studies, consistency of results, and for some parameters, information provided from interviews with MM experts and market research surveys. External validity of the parameter estimates (or the degree to which those estimates can be applied to the overall population) is also expected, since the parameters' base-case values were chosen around mid-range values and the study results were consistent. Some references provided data in the format required by the model, while others required transformation. For example, survival figures expressed as percentage of surviving patients at a specific time after diagnosis or treatment initiation required transformation into yearly rates before they could be included in the model. No ethical committee approval was necessary for this study.

Sensitivity Analysis

Parametric uncertainty analyses were conducted through probabilistic sensitivity analysis (PSA). The PSA was performed on key selected model parameters[29] using Latin hypercube sampling (LHS).[30] This process involved two steps: first, parameters expected to influence model output were selected for inclusion in the PSA, and partial rank correlation coefficients (PRCCs) were then computed (Appendix B, Figure B-1) to illustrate the parameters that were the greatest sources of heterogeneity in model output.[31] Secondly, the PSA consisted

of varying the parameter values by sampling 1000 times from distributions specified by the mean value (deterministic model input) and standard errors (Appendix B, Table B2). Standard errors were selected to describe parameter variability observed in the data sources and expected in the broad population of patients with MM. Distributions were determined by the characteristics of the parameter and experience (e.g. beta distributions are usually considered for binomial data; gamma or log normal for right skew parameters; log normal for hazard ratios.[32])

Model Outcomes

Model outcomes include the size of the patient population with MM potentially eligible to receive a MM therapy at different lines of therapy in the US, as well as the corresponding number of patient transitions from one line of therapy to the next over a one-year period. The model is designed to report outcomes at equilibrium, which is judged to have been achieved when the model reaches a steady state, in that the number of patients in each line no longer fluctuates and remains stable. All model outcomes are stratified by the eight subgroups of interest resulting from the combination of SCT eligibility, age group, and cytogenetic risk group. Model outcomes also include 95% credible intervals (analogous to a confidence interval with estimates obtained from the sampling results) from the PSA for both the number of patients and their transitions at different lines of therapy. Ninety five percent (95%) credible intervals were defined by the upper and lower bounds of the distribution of model outcomes from the PSA leaving 2.5% of the values below and above, respectively.

RESULTS

Prevalence of MM

Model results are presented in Table 2. An estimated 80,219 patients were living with diagnosed MM in the US, of whom 70,375 patients were receiving treatment, 780 patients were symptomatic untreated and 9,064 patients were asymptomatic who are untreated and would be monitored for progression to symptomatic MM. Patient numbers stratified by SCT eligibility, age group, and cytogenetic risk group are shown in Table 2. Additionally, the model estimated that 19,330 patients with MM would die over a one-year period from background mortality and mortality attributable to MM.

Patient Transitions from One Line of Therapy to the Next

Table 3 reports the number of patient transitions from one line of therapy to the next over a one-year period, estimating that the total number of transitions experienced by the above patient population would be 96,259. A total of 18,689 patients diagnosed with MM are estimated to initiate first line therapy over a one-year period. Patients entering into treatment

line 17 and beyond were estimated at 167. Results stratified by SCT eligibility, age group, and cytogenetic risk group are also presented in Table 3.

PSA results

The results of the PSA are in Table 4, estimating 95% credible intervals (CI) for numbers of MM patients and the numbers of patient transitions from one line of therapy to the next. The results corresponding to the eight strata of interest defined by SCT eligibility, age group, and cytogenetic risk group are shown in Appendix C. The PSA model runtime was around three hours.

DISCUSSION

The current estimated number of patients with MM in the US is 80,219, with 70,375 on different lines of therapy. Over a one-year period, 19,330 deaths from all causes would be expected as well as 14,423 transitions from line 1 into line 2. The estimated number of patients initiating line 1 of therapy over one year is 18,689. Beyond line 17 of treatment, as anticipated, the patient prevalence was close to 0, although the number of transitions over a one year period could be larger as a consequence of the short time spent in those lines of therapy when the condition is so advanced.

The model estimates of the patient distribution across the different lines of therapy, from the first to 17th line and beyond, at a snapshot in time, differed from the patient transition breakdown over a one-year period. For early lines of therapy, lines 1 and 2, the number of patient transitions over a one-year period was smaller than the number of patients at a point in time, as a consequence of these patients spending long periods on treatment, or without receiving treatment but free of disease progression and drug toxicity.[25] At subsequent lines of therapy, the number of patient transitions decreased more slowly than the number of patients reflecting that the average patient spends shorter periods on successive treatment lines and eventually can transition through several lines of therapy over a one-year period.

The estimated number of patients with MM in the US provided by the model, 80,219, was consistent with the figure estimated by SEER for 2014 of 83,367 patients. Conversely, the number of patients with MM who died of this disease over a one-year period was estimated at 11,090 (SEER data from 2014),[26] while the model estimate was 16,670. This difference is larger than expected because one would anticipate that the number of deaths over a one-year period is somehow lower than the number of new patients being diagnosed, as a result of the range of novel therapeutic alternatives providing increased patient survival over time. The expected small difference between incident cases and patient mortality would translate into a continuous steady increase of the prevalence of MM. The observed large difference in

the SEER data between incident cases and patient mortality would result in the prevalence of patients with MM increasing greatly over a short period. We hypothesize that the large difference between the mortality estimates of the model and those of SEER could be attributable to SEER reporting only mortality attributed to MM and not all mortality experienced by patients with MM, and also to a proportion of deaths caused by MM not being correctly classified as such (resulting in apparently increased background mortality among patients with MM).

We have not identified any other epidemiologic models reporting on patients with MM. Nevertheless, there are several studies reporting on the use of epidemiologic models for other oncologic conditions such as prostate cancer,[33,34] breast cancer,[35] Hodgkin's lymphoma,[36,37] chronic myeloid leukemia,[38] and gastrointestinal stromal tumors.[24] The rationale for developing such models is consistent with the objectives of the model presented in this paper: while the epidemiology of these conditions is well documented, estimates of patient numbers and their distribution across subgroups of interest are scarce in the literature.[24,33,35-37] Other research groups have developed similar models for such predictive purposes.[34,38]

Estimates of numbers of patients in groups of interest produced by epidemiologic models can inform budget impact analysis and support planning of healthcare services by limiting the uncertainty associated with identifying patient numbers eligible for a given treatment.[20,34] This contribution can be especially relevant for conditions that have low frequency, and hence are difficult to study, but could qualify for orphan designation and the corresponding support for research and treatment development.[24,39]

The model used has a complex structure and requires a large number of parameters. This is the consequence of modelling a complex condition whose treatment is also complex. A positive aspect is that the reported estimates provide a detailed picture of the patient population with MM. On the other hand, complexity is a limitation when it comes to finding supportive data for the parameters that inform the model. As a consequence, some parameters are supported by only one or a few sources. This limitation is common to other modeling studies.[24] Some prognostic factors of the condition such as tumor staging or renal function[5] were not included separately in the model. One limitation of the model to estimate the real difference between incident cases and patient mortality is that, by definition, in the model at equilibrium the number of incident patients with MM is the same as the number of patients dying from MM and background mortality combined. Using this dynamic model to look at projections for how the MM patient population will change over time would be of interest but it is not within the scope of this project.

Further research on the epidemiology of patients with MM will support more robust parameter estimates that can be used in this and other models. Other parameters may become pertinent to modeling prevalence of lines of therapy in patients with MM, which may warrant additional research and model development. Different stratification variables, such as disease stage or new risk classification, may prove important in further research. Additionally, future real world study results reporting on patient population and subpopulations at different lines of therapy and transitioning across those lines will contribute data to validate the model outcomes.

In summary, the reported epidemiologic model estimates the size and the distribution of the patient population with MM stratified by subgroups of interest and the patients transitioning from one line of therapy to the next, corresponding to multiple disease relapses or treatment intolerances, and increasing burden as the condition progresses. This information can be used to assess the number of patients who could benefit from new MM therapies and their corresponding budgetary impact.

References

1. Monnereau A, Troussard X, Belot A, et al. Unbiased estimates of long-term net survival of hematological malignancy patients detailed by major subtypes in France. *International journal of cancer. Journal international du cancer.* 2013;132(10):2378-2387.

2. Palumbo A, Anderson K. Multiple myeloma. *The New England journal of medicine.* 2011;364(11):1046-1060.

3. Alexander DD, Mink PJ, Adami HO, et al. Multiple myeloma: a review of the epidemiologic literature. *International journal of cancer. Journal international du cancer.* 2007;120 Suppl 12:40-61.

4. GLOBOCAN. 2012 Incidence. 2012; http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed November 7, 2014.

5. Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clinic proceedings.* 2013;88(4):360-376.

6. Avet-Loiseau H, Hulin C, Campion L, et al. Chromosomal abnormalities are major prognostic factors in elderly patients with multiple myeloma: the intergroupe francophone du myelome experience. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(22):2806-2809.

7. Engelhardt M, Terpos E, Kleber M, et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica.* 2014;99(2):232-242.

8. Kapoor P, Fonseca R, Rajkumar SV, et al. Evidence for cytogenetic and fluorescence in situ hybridization risk stratification of newly diagnosed multiple myeloma in the era of novel therapie. *Mayo Clinic proceedings.* 2010;85(6):532-537.

9. Barlogie B, Attal M, Crowley J, et al. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(7):1209-1214.

10. Bashir Q, Khan H, Orlowski RZ, et al. Predictors of prolonged survival after allogeneic hematopoietic stem cell transplantation for multiple myeloma. *American journal of hematology.* 2012;87(3):272-276.

11. El Mahou S, Attal M, Jamard B, et al. Do new therapeutic approaches (autotransplants, thalidomide, dexamethasone) improve the survival of patients with multiple myeloma followed in a rheumatology department? *Clinical rheumatology.* 2006;25(2):175-182.

12. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood.* 2012;119(19):4375-4382.

13. Kaya H, Peressini B, Jawed I, et al. Impact of age, race and decade of treatment on overall survival in a critical population analysis of 40,000 multiple myeloma patients. *International journal of hematology.* 2012;95(1):64-70.

14. Lonial S, Anderson KC. Association of response endpoints with survival outcomes in multiple myeloma. *Leukemia.* 2014;28(2):258-268.

15. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood.* 2008;111(5):2521-2526.

16. Gaultney JG, Franken MG, Tan SS, et al. Real-world health care costs of relapsed/refractory multiple myeloma during the era of novel cancer agents. *Journal of clinical pharmacy and therapeutics.* 2013;38(1):41-47.

17. Green C, Bryant J, Takeda A, et al. Bortezomib for the treatment of multiple myeloma patients. *Health technology assessment.* 2009;13 Suppl 1:29-33.

18. Mehta J, Duff SB, Gupta S. Cost effectiveness of bortezomib in the treatment of advanced multiple myeloma. *Managed care interface.* 2004;17(9):52-61.

19. Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. *Journal of medical economics.* 2011;14(6):690-697.

20. Cid Ruzafa J, Cox A, Merinopoulou E, Baggaley RF, Leighton P, Desai K. An epidemiologic modelling application to pharmacoeconomics for improved healthcare planning. *Value in Health.* 2014;17(7):A587.

21. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Population health metrics.* 2010;8:29.

22. Brinks R, Tamayo T, Kowall B, Rathmann W. Prevalence of type 2 diabetes in Germany in 2040: estimates from an epidemiological model. *European journal of epidemiology.* 2012;27(10):791-797.

23. Levy AR, Perkins RM, Johnston KM, et al. An epidemiologic model to project the impact of changes in glomerular filtration rate on quality of life and survival among persons with chronic kidney disease. *International journal of nephrology and renovascular disease.* 2014;7:271-280.

24. Starczewska Amelio JM, Cid Ruzafa J, Desai K, et al. Prevalence of gastrointestinal stromal tumour (GIST) in the United Kingdom at different therapeutic lines: an epidemiologic model. *BMC cancer.* 2014;14:364.

25. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood.* 2011;117(18):4691-4695.

26. National Cancer Institute (NCI). SEER Cancer Statistics Factsheets: Myeloma. http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed November 7, 2014.

27. U.S. Census Bureau Population Division. Annual Estimates of the Population for the US, Regions, States, and Puerto Rico: April 1, 2010 to July 1, 2013 (NST-EST2013-01). Release Date: December 2013.; http://www.census.gov/popest/data/national/totals/2013/index.html Accessed November 7, 2014.

28. CDC/NCHS. National Vital Statistics System, Mortality. http://www.cdc.gov/nchs/data/dvs/MortFinal2007_Worktable23r.pdf. Accessed November 7, 2014.

29. McKay MD, Beckman RJ, Conover WJ. A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. Technometrics (JSTOR Abstract). *Am Stat Assoc.* 1979;21(2):239-245.

30. Blower SM, Dowlatabadi H. Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example. *Int Stat Rev.* 1994;62:229-243.

31. Iman RL, Helton JC, Campbell JE. An approach to sensitivity analysis of computer models: part I - introduction, input variable selection and preliminary assessment. *J Qual Technol.* 1981;13(174-183).

32. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making.* 2012;32(5):722-732.

33. Cure S, Martin M, Bracco A, Brown J, Kearney M. An epidemiological model of prostate cancer and progression to bone metastases in the United Kingdom. *Value in Health.* 2011;14:PCN18.

34. Vitale V, Asano E, Pereira ML. Budget impact analysis of abiraterone acetate in metastatic castration-resistant prostate cancer patients previously treated with docetaxel from the perspective of the Brazilian private health care system. *Value in Health.* 2013;16:A665.

35. Martin M, Kearney M, Bracco A, Brown J. An epidemiological model of breast cancer and progression to bone metastases in the United Kingdom. *Value in Health.* 2011;14:PCN19.

36. Abbe A, Lee A, Hamed A, Neumann F, Olivares R, Engert A. Epidemiologic modelling estimating the number of patients with relapsed Hodgkin lymphoma after autologous stem cell transplant in 5 European countries. *JNCCN.* 2013;11(3):243-244.

37. Lee A, Abbe A, Hamed A, Neumann F, Olivares R, Younes A. Epidemiologic model estimating number of Hodgkin lymphoma patients who relapsed after autologous

stecm cell transplant in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(15):e12554.

38. Fagnani F, Sartre J, Rota C, Bregman B, Gaudin AF. Projection of the patients' population treated for chronic myeloid leukemia in chronic phase in France: an epidemiological model at the horizon 2015. *Value in Health.* 2011:A233.

39. EMA. Human regulatory: orphan designation. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce. Accessed November 7, 2014.

40. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. *Blood.* 2007;109(8):3489-3495.

41. Avet-Loiseau H, Soulier J, Fermand JP, et al. Impact of high-risk cytogenetics and prior therapy on outcomes in patients with advanced relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone. *Leukemia.* 2010;24(3):623-628.

42. Gonsalves WI, Rajkumar SV, Gupta V, et al. Quantification of clonal circulating plasma cells in newly diagnosed multiple myeloma: implications for redefining high-risk myeloma. *Leukemia.* 2014;28(10):2060-2065.

43. Kapoor P, Kumar S, Fonseca R, et al. Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood.* 2009;114(3):518-521.

44. Konigsberg R, Zojer N, Ackermann J, et al. Predictive role of interphase cytogenetics for survival of patients with multiple myeloma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2000;18(4):804-812.

45. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia.* 2012;26(1):149-157.

46. Sellner L, Heiss C, Benner A, et al. Autologous retransplantation for patients with recurrent multiple myeloma: a single-center experience with 200 patients. *Cancer.* 2013;119(13):2438-2446.

47. Karlin L, Soulier J, Chandesris O, et al. Clinical and biological features of t(4;14) multiple myeloma: a prospective study. *Leukemia & lymphoma.* 2011;52(2):238-246.

48. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *The New England journal of medicine.* 2007;356(25):2582-2590.

49. Liwing J, Uttervall K, Lund J, et al. Improved survival in myeloma patients: starting to close in on the gap between elderly patients and a matched normal population. *British journal of haematology.* 2014;164(5):684-693.

50. Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *The New England journal of medicine.* 2013;369(5):438-447.

51. Al-Hamadani M, Hashmi SK, Go RS. Use of autologous hematopoietic cell transplantation as initial therapy in multiple myeloma and the impact of socio-geo-demographic factors in the era of novel agents. *American journal of hematology.* 2014;89(8):825-830.

52. Ludwig H, Durie BG, Bolejack V, et al. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. *Blood.* 2008;111(8):4039-4047.

53. Armoiry X, Fagnani F, Benboubker L, et al. Management of relapsed or refractory multiple myeloma in French hospitals and estimation of associated direct costs: a multi-centre retrospective cohort study. *Journal of clinical pharmacy and therapeutics.* 2011;36(1):19-26.

54. Wu W, Merriman K, Nabaah A, et al. The association of diabetes and anti-diabetic medications with clinical outcomes in multiple myeloma. *British journal of cancer.* 2014;111(3):628-636.

55. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(15):1993-1999.

56. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(5):830-834.

57. Bergsagel PL, Mateos MV, Gutierrez NC, Rajkumar SV, San Miguel JF. Improving overall survival and overcoming adverse prognosis in the treatment of cytogenetically high-risk multiple myeloma. *Blood.* 2013;121(6):884-892.

58. Hebraud B, Leleu X, Lauwers-Cances V, et al. Deletion of the 1p32 region is a major independent prognostic factor in young patients with myeloma: the IFM experience on 1195 patients. *Leukemia.* 2014;28(3):675-679.

59. Sasaki K, Lu G, Saliba RM, et al. Impact of t(11;14)(q13;q32) on the outcome of autologous hematopoietic cell transplantation in multiple myeloma. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation.* 2013;19(8):1227-1232.

60. Drake MB, Iacobelli S, van Biezen A, et al. Primary plasma cell leukemia and autologous stem cell transplantation. *Haematologica.* 2010;95(5):804-809.

61. El-Cheikh J, Crocchiolo R, Furst S, et al. Long-term outcome after allogeneic stem-cell transplantation with reduced-intensity conditioning in patients with multiple myeloma. *American journal of hematology.* 2013;88(5):370-374.

62. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma. *Cancer.* 2012;118(6):1585-1592.

63. Richardson PG, Barlogie B, Berenson J, et al. Clinical factors predictive of outcome with bortezomib in patients with relapsed, refractory multiple myeloma. *Blood.* 2005;106(9):2977-2981.

64. Richardson PG, Sonneveld P, Schuster MW, et al. Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed multiple myeloma. *British journal of haematology.* 2007;137(5):429-435.

65. San Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(4):448-455.

66. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *The New England journal of medicine.* 2008;359(9):906-917.

TABLES

Table 1. Model Base Case Parameter Values for the US

Parameter	Base Case	Units	Reference
Population			
Population size	316,128,839	persons	27
Background death rate of adults 40-64 years	0.008	proportion per year	28
Background death rate of adults ≥65 years	0.060	proportion per year	28
MM epidemiology			
Incidence of MM	0.000061	proportion per year	5,26
Proportion patients <65 years at MM diagnosis	38.00%	%	5,26
Proportion in high cytogenetic risk group at MM diagnosis	35.00%	%	5,6,9,40-46
Proportion symptomatic at MM diagnosis	87.50%	%	47-50
Median duration for progression from asymptomatic (smoldering) MM to symptomatic MM	58	months	47,48,50
MM-related death rate while asymptomatic (smoldering), <65 years, MM patients	0.0040	proportion per year	42,50
MM-related death rate while asymptomatic (smoldering), ≥65 years, MM patients	0.0400	proportion per year	42,50
MM-related death rate while symptomatic MM before treatment initiation, <65 years	0.0045	proportion per year	assumption
MM-related death rate while symptomatic MM before treatment initiation, ≥65 years	0.0450	proportion per year	assumption
Treatment initiation			
Time from diagnosis of symptomatic MM to treatment initiation	0.500	months	42,45
Proportion <65 years initiating SCT pathway	30.00%	%	51,52
Proportion ≥65 years initiating SCT pathway	10.00%	%	51,52
MM-related death rates on treatment pathway			
Patients <65 years, standard/low cytogenetic risk, non-SCT treatment pathway: treatment line 1	0.10	Proportion per year	11,53
MM-related death rate ratio: SCT compared to non-SCT	0.70	None (ratio)	9,54
MM-related death rate ratio: ≥65 year age group compared to <65 year age group	1.50	None (ratio)	9,49,52,55,56
MM-related death rate ratio: high cytogenetic risk group compared to standard/low cytogenetic risk group	2.25	None (ratio)	6,40,41,46,54,57-59

Parameter	Base Case	Units	Reference
MM-related death rate ratio: 2nd line compared to 1st line treatment	1.00	None (ratio)	1,15,60
MM-related death rate ratio: 3rd line compared to 2nd line treatment	1.10	None (ratio)	1,15,60
MM-related death rate ratio: 4th line compared to 3rd line treatment	1.15	None (ratio)	1,15,60
MM-related death rate ratio: 5th line compared to 4th line treatment	1.20	None (ratio)	1,15,60
MM-related death rate ratio: 6th line compared to 5th line treatment	1.25	None (ratio)	1,15,60
MM-related death rate ratio: 7th line compared to 6th line treatment	1.40	None (ratio)	1,15,60
MM-related death rate ratio: 8th line compared to 7th line treatment (applicable to subsequent lines, up to 17, compared to the previous line)	1.50	None (ratio)	1,15,60
Time to next line of treatment			
Treatment duration on treatment line 1* (patients <65 years, standard/low cytogenetic risk, SCT pathway)	35.0	Months	5,40,42,46,49,58,59,61,62
Time to next line of treatment: n+1th line compared to nth line treatment	0.80	None (ratio)	41
Time to next line of treatment: ≥65 year age group compared to <65 year age group	0.75	None (ratio)	63,64
Time to next line of treatment: high cytogenetic risk group compared to standard/low cytogenetic risk group	0.45	None (ratio)	6,40,41,43,46,57,58
Treatment duration on treatment line 1* (patients <65 years, standard/low cytogenetic risk, non-SCT pathway)	27.0	Months	42,43,49,65,66

* Defined as time between initiating treatment line 1 and initiating treatment line 2.

Table 2. Estimated Total Number of Prevalent MM Cases in the US by Line of Therapy and Patient Subgroups of Interest

Treatment Line	Total	SCT Eligibility				SCT Non Eligibility			
		Low/Standard Cytogenetic Risk		High Cytogenetic Risk		Low/Standard Cytogenetic Risk		High Cytogenetic Risk	
		<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs
Line 1	23,629	3,375	1,196	825	306	6,000	8,351	1,465	2,111
Line 2	15,350	2,287	742	562	198	4,017	5,201	985	1,358
Line 3	10,249	1,584	477	390	132	2,746	3,346	676	898
Line 4	6,966	1,114	314	274	89	1,901	2,201	469	604
Line 5	4,786	790	210	193	61	1,325	1,469	328	410
Line 6	3,301	561	142	136	42	925	987	229	279
Line 7	2,252	394	95	95	28	637	657	158	188
Line 8	1,501	271	62	65	19	428	427	106	123
Line 9	971	181	40	43	12	279	269	69	78
Line 10	605	116	25	27	7	175	164	43	48
Line 11	363	72	15	17	4	106	95	26	28
Line 12	206	43	8	10	2	61	52	15	15
Line 13	111	24	5	5	1	33	27	8	8
Line 14	54	12	2	3	0	17	13	4	3
Line 15	23	6	1	1	0	8	5	1	1
Line 16	7	2	0	0	0	3	2	0	0
Line 17 and greater	2	1	0	0	0	1	0	0	0
Total patients on treatment	70,375	10,833	3,333	2,646	901	18,662	23,266	4,582	6,152

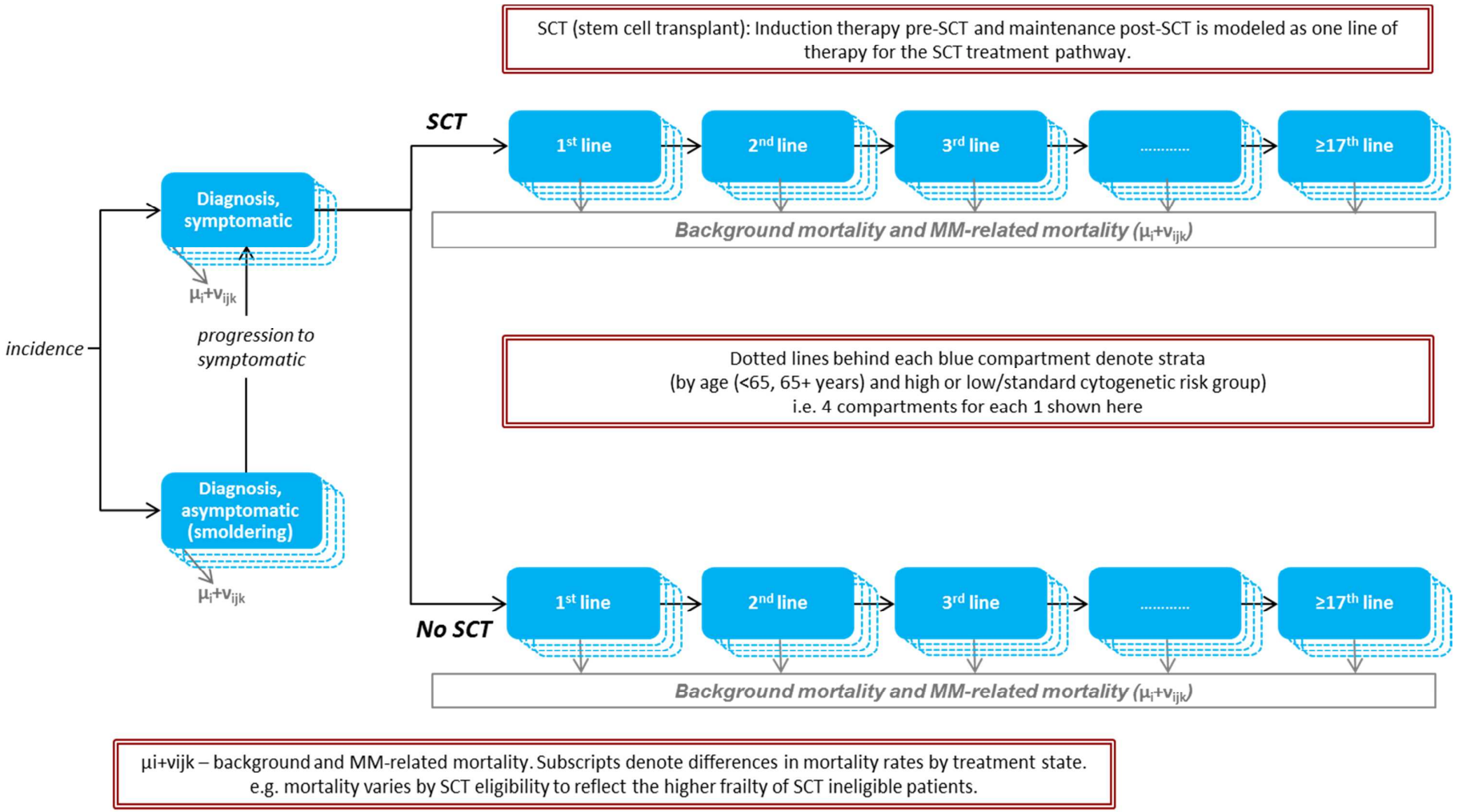
Table 3. Number of MM Patient Transitions in the US by Line of Therapy and Patient Subgroups of Interest

New Treatment Regimens	Total	SCT Eligibility				SCT Non Eligibility			
		Low/standard cytogenetic risk		High cytogenetic risk		Low/standard cytogenetic risk		High cytogenetic risk	
		<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs
Line 1	18,689	1,418	742	763	399	3,309	6,680	1,781	3,597
Line 2	14,423	1,155	545	627	309	2,661	4,928	1,440	2,758
Line 3	11,677	979	422	533	250	2,227	3,837	1,210	2,219
Line 4	9,715	848	339	463	208	1,902	3,085	1,038	1,832
Line 5	8,225	746	278	406	176	1,646	2,535	900	1,538
Line 6	7,038	662	233	358	150	1,433	2,113	786	1,303
Line 7	6,047	589	196	316	129	1,250	1,773	686	1,108
Line 8	5,131	518	164	275	109	1,075	1,472	590	928
Line 9	4,241	444	134	234	90	900	1,192	493	754
Line 10	3,396	370	107	193	72	730	934	399	591
Line 11	2,616	298	82	153	55	571	704	310	443
Line 12	1,920	230	60	116	40	427	505	229	313
Line 13	1,334	169	42	84	28	303	342	160	206
Line 14	862	117	28	57	17	202	215	103	123
Line 15	511	76	17	35	10	125	124	60	64
Line 16	267	45	9	19	5	70	63	30	26
Line 17 and greater	167	40	5	12	1	52	37	14	6
Total transitions	96,259	8,704	3,403	4,644	2,048	18,883	30,539	10,229	17,809

Table 4. Median and Credible Intervals of the Number of MM Patients and Number of Patient Transitions by Line of Therapy in the US

	Number of MM Patients			Number of Patient Therapy Line Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	23,584	22,236	25,029	18,696	18,558	18,817
Line 2	15,346	13,845	16,760	14,415	13,489	15,176
Line 3	10,234	8,908	11,515	11,658	10,348	12,811
Line 4	6,955	5,847	8,053	9,699	8,223	11,085
Line 5	4,778	3,893	5,685	8,214	6,670	9,744
Line 6	3,298	2,609	4,038	7,028	5,483	8,630
Line 7	2,252	1,723	2,850	6,042	4,531	7,669
Line 8	1,502	1,106	1,975	5,131	3,695	6,766
Line 9	975	687	1,338	4,244	2,919	5,872
Line 10	612	409	886	3,403	2,223	4,964
Line 11	369	232	568	2,629	1,612	4,075
Line 12	213	125	353	1,937	1,107	3,273
Line 13	116	63	210	1,350	714	2,487
Line 14	59	30	119	878	428	1,788
Line 15	28	13	63	525	236	1,212
Line 16	12	5	32	279	120	719
Line 17 and greater	9	5	22	192	77	523

Figure 1. Model to Assess Prevalence of Patients with MM at Different Treatment Lines



Appendix A: Model Parameters and Equations

Table A - 1. Model Parameters

	Description
$\boldsymbol{\beta_u}$	Incidence of MM (all stages) for demographic group u (proportion/year)
$\boldsymbol{P}$	Proportion of MM patients that is symptomatic at diagnosis*
$\boldsymbol{K}$	Progression rate of asymptomatic MM to symptomatic*
$\boldsymbol{\alpha}$	Progression rate of symptomatic MM to treatment* (per year)
$\boldsymbol{\mu_u}$	Background death rate for demographic group† $\boldsymbol{u}$ (per year)
$\boldsymbol{\theta_u}$	MM-related death rate for demographic group $\boldsymbol{u}$ as yet untreated, asymptomatic (per year)
$\boldsymbol{\varphi_u}$	MM-related death rate for demographic group $\boldsymbol{u}$ as yet untreated, symptomatic MM (per year)
$\boldsymbol{\psi_{uz}}$	Proportion symptomatic initiating first line of treatment within demographic group $\boldsymbol{u}$ who are assigned to each treatment pathway[1] $\boldsymbol{z}$
$\boldsymbol{\nu_{uzw}}$	MM-related death rate for demographic group $\boldsymbol{u}$ on treatment pathway $\boldsymbol{z}$ and line of therapy $\boldsymbol{w}$ (per year)
$\boldsymbol{1/\gamma_{uzw}}$	Time to next line of treatment for patients in demographic group u on treatment pathway $\boldsymbol{z}$ and line of therapy $\boldsymbol{w}$ (years)

MM = multiple myeloma

*Assumption that this parameter has the same value regardless of risk and age group.

†Demographic groups= <65 years and low/standard cytogenetic group; ≥65 years and low/standard cytogenetic group; <65 years and high cytogenetic group; ≥65 years and high cytogenetic group;

[1]Treatment pathways= at least one SCT is performed; no SCT is performed

Model Equations

The model initiates upon diagnosis with MM. Individuals flow between states in the model. Patients may be diagnosed with asymptomatic ($\boldsymbol{A_u}$) or symptomatic ($\boldsymbol{S_u}$) MM, where u is demographic group (currently four groups according to age group and cytogenetic risk group). Asymptomatics ($\boldsymbol{A_u}$) receive new cases with proportion ($\boldsymbol{1-P}$) of the total incidence $\boldsymbol{\beta_u}$. Individuals become symptomatic at rate $\boldsymbol{K}$. Symptomatics ($\boldsymbol{S_u}$) receive a proportion $\boldsymbol{P}$ of the incident cases directly and initiate treatment at a rate $\boldsymbol{\alpha}$ with proportions $\boldsymbol{\psi_{uz}}$ in each of the two treatment pathways. Asymptomatics experience MM-related mortality at rate $\boldsymbol{\theta_u}$whilst symptomatics experience MM-related mortality at rate $\boldsymbol{\varphi_u}$.

Each treatment state is represented by T_{uzw}, where u is demographic group, z is treatment pathway (currently: 1 = at least one SCT is performed; 2 = no SCT is performed), and w is line of therapy).Treated cases progress through 17 lines of treatment (index w from 1 to 17) at rate γ_{uzw} and experience MM-related mortality at rate ν_{uzw}. Asymptomatic, symptomatic, and treated individuals are all subject to background death rate μ_u.

Line of therapy is understood as one or more cycles of a planned treatment program (single agent, combination therapy, or sequence of treatments administered as planned). A new line of therapy is assumed to start when a planned treatment program is modified to include other drugs as a result of disease progression, relapse or toxicity, or when a planned period off-treatment is interrupted because additional treatment for MM is required.[25]

For patients undergoing SCTs, first-line treatment usually represents the package of treatments that are required for an SCT procedure (i.e., includes induction therapy as well as SCT). A second SCT is recorded as second-line treatment. In some cases, a first SCT could also take place at a line of therapy greater than line 1.

Asymptomatic MM:

$$\frac{dA_u}{dt} = \beta_u\,(1 - P) - A_u(K + \mu_u + \theta_u)$$

Where u = 1...4

Symptomatic MM, untreated:

$$\frac{dS_u}{dt} = \beta_u P + A_u K - S_u\,(\alpha + \mu_u + \varphi_u)$$

Where u =1...4

MM treatment stages

First-line treatment:

$$\frac{dT_{uzw}}{dt} = S_u \alpha \psi_{uz} - T_{uzw}(\mu_u + \nu_{uzw} + \gamma_{uzw})$$

Where u = 1...4; z = 1, 2; w = 1

Subsequent treatment lines (w > 1):

$$\frac{d\boldsymbol{T_{uzw}}}{d\boldsymbol{t}} = \boldsymbol{T_{uzw-1}\gamma_{uzw-1}} - \boldsymbol{T_{uzw}(\mu_u + \nu_{uzw} + \gamma_{uzw})}$$

Where $\boldsymbol{u}$ = 1...4; $\boldsymbol{z}$ = 1,2; $\boldsymbol{w}$ = 2…20

The values of MM-related death rates and MM time to next treatment (TTNT) durations for each MM treatment state are related to a baseline MM-related death rate and two baseline time to next line of treatment values:

- The baseline MM-related death rate is for MM patients on the first line of treatment, on the non-SCT pathway, < 65 years of age and in the low/standard cytogenetic risk group.
- MM-related death rates for all other treated MM health states are derived from the baseline rate using the following death rate relative risks (RR):
  - RR for patients ≥ 65 years compared to < 65 years
  - RR for patients in the high cytogenetic risk group compared to the low/standard-risk group
  - RR for patients on the SCT pathway compared to those on the non-SCT pathway
  - RR for patients on the n+1th line of treatment compared to those on the nth line of treatment
- The baseline TTNT values are for MM patients on the first line of treatment, < 65 years of age and in the low cytogenetic risk group. There is one baseline value for patients on the SCT treatment pathway and another value for patients on the non-SCT pathway.
- TTNT values for all other treated MM health states are derived from the baseline values using the following TTNT RRs:
  - RR for patients ≥ 65 years compared to < 65 years
  - RR for patients in the high cytogenetic risk group compared to the low/standard-risk group
  - RR for patients on the n+1th line of treatment compared to those on the nth line of treatment

Appendix B: Probabilistic Sensitivity Analysis

Based on model influence diagram face validity discussions, the parameters expected to influence model output selected for inclusion in the PSA were:

Population inputs:

1. Proportion patients < 65 years at MM diagnosis **(prop_young in Figure B-1 below)**
2. Proportion in low/standard cytogenetic risk group at MM diagnosis **(prop_lowrisk)**
3. Proportion symptomatic at MM diagnosis **(prop_sympt)**

Treatment inputs:

4. Proportion < 65 years initiating SCT pathway **(prop_less65_SCT)**
5. Baseline MM-related death rate; patients < 65 years, low/standard cytogenetic risk, non-SCT treatment pathway: treatment line 1 **(baseline MM death rate)**
6. MM-related death rate ratio: ≥ 65 year age group compared to < 65 year age group **(RR_mort_oldage)**
7. MM-related death rate ratio: high cytogenetic risk group compared to low/standard cytogenetic risk group **(RR_mort_highrisk)**

We used the LHS method[30]. Running the model with model parameters for the baseline country produced the PRCCs shown in **Figure B-1**. The magnitude of each PRCC quantifies the importance of each parameter, with the sign of the PRCC value indicating the specific qualitative relationship between the input and the output variable: positive values of PRCC imply that increasing the value of the input variable will lead to an increase in the output variable (number of forecasted patients with MM). As a general rule, parameters with the largest influence are defined as those with a PRCC greater than 0.4 or less than –0.4.

Figure B-1 shows that the parameters with the greatest influence on the model outcomes for the baseline country are all the MM-related death rates ratios [5-7 from list above], with the relationship being negative. Additionally, the proportion of patients in low cytogenetic risk group [2] and the proportion symptomatic [3] are shown to have a great positive influence on model outcomes. The observed low PRCCs for the proportion of young patients [1] and the proportion of young patients initiating SCT [4] imply that their influence on the model outcomes is expected to be low.

Figure B-2. Partial Rank Correlation Coefficients for Key Model Parameters

Table B - 2. Probabilistic Sensitivity Analysis Parameters

Parameter (unit)	Base Case	Standard Error	Distribution
Proportion patients <65 years at MM diagnosis	38.00%	1.80%	Beta
Proportion in high cytogenetic risk group at MM diagnosis	35.00%	2.50%	Beta
Proportion symptomatic at MM diagnosis	87.50%	1.50%	Beta
Proportion <65 years initiating SCT pathway	85.00%	2.5%	Beta
Proportion patients <65 years, standard/low cytogenetic risk, non-SCT treatment pathway: treatment line 1	0.100	0.010	Gamma
MM-related death rate ratio: ≥65 year age group compared to <65 year age group	1.50	0.15	Lognormal
MM-related death rate ratio: high cytogenetic risk group compared to standard/low cytogenetic risk group	2.25	0.25	Lognormal

Appendix C: PSA Results for Subgroups of Interest

Table C - 1. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients <65 Years, Low/Moderate Cytogenetic Risk and Eligible for SCT.

	Number of Patients			Number of Patient Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	3,357	2,792	4,030	1,414	1,177	1,693
Line 2	2,270	1,882	2,773	1,150	956	1,380
Line 3	1,570	1,284	1,929	972	806	1,187
Line 4	1,099	887	1,363	840	687	1,032
Line 5	774	618	976	734	593	911
Line 6	548	431	702	646	515	814
Line 7	384	297	503	570	449	732
Line 8	263	200	351	499	386	653
Line 9	175	129	240	425	324	568
Line 10	113	81	159	353	261	485
Line 11	70	49	102	283	204	398
Line 12	42	28	64	218	151	320
Line 13	24	15	39	160	107	247
Line 14	13	8	22	111	70	182
Line 15	7	4	12	72	43	128
Line 16	3	2	6	43	24	83
Line 17 and greater	5	4	7	43	21	95

Table C - 2. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients ≥65 Years, Low/Moderate Cytogenetic Risk and Eligible for SCT

	Number of Patients			Number of Patient Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	1,195	1,080	1,316	744	682	798
Line 2	740	643	846	545	492	600
Line 3	475	396	561	421	366	482
Line 4	314	248	383	338	282	400
Line 5	210	159	265	279	221	341
Line 6	142	102	186	233	176	294
Line 7	95	65	129	197	141	257
Line 8	63	40	90	165	112	223
Line 9	41	24	61	135	86	193
Line 10	25	14	41	108	63	163
Line 11	15	8	27	83	45	135
Line 12	9	4	17	62	30	108
Line 13	5	2	10	43	19	83
Line 14	3	1	6	29	11	61
Line 15	2	1	4	17	6	42
Line 16	1	1	2	10	3	26
Line 17 and greater	4	4	4	4	3	11

Table C - 3. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients <65 Years, High Cytogenetic Risk and Eligible for SCT

	Number of Patients			Number of Patient Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	822	631	1,033	759	608	940
Line 2	561	409	723	624	479	785
Line 3	388	265	528	532	389	687
Line 4	271	175	386	461	314	627
Line 5	192	116	282	402	260	572
Line 6	136	76	208	355	214	522
Line 7	95	49	153	315	176	480
Line 8	66	30	111	274	141	440
Line 9	44	18	79	235	108	398
Line 10	28	11	56	194	80	352
Line 11	18	6	38	154	57	306
Line 12	11	3	25	117	38	258
Line 13	6	2	17	85	23	209
Line 14	3	1	11	58	13	165
Line 15	2	1	6	37	7	123
Line 16	1	1	4	21	3	85
Line 17 and greater	4	4	5	8	3	42

Table C - 4. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients ≥65 Years, High Cytogenetic Risk and Eligible for SCT

	Number of Patients			Number of Patient Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	305	252	362	400	344	457
Line 2	199	148	247	308	254	366
Line 3	133	89	174	251	186	312
Line 4	90	55	124	209	140	274
Line 5	62	34	90	177	108	243
Line 6	43	22	66	151	84	220
Line 7	29	14	47	130	67	200
Line 8	20	8	34	110	51	179
Line 9	13	5	24	91	37	160
Line 10	8	3	17	73	26	140
Line 11	5	2	12	56	17	119
Line 12	3	1	8	41	10	98
Line 13	2	1	5	28	6	78
Line 14	1	1	3	18	3	59
Line 15	1	1	2	10	2	41
Line 16	1	1	2	5	1	26
Line 17 and greater	2	2	2	3	2	16

Table C - 5. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients <65 Years, Low/Moderate Cytogenetic Risk and Not Eligible for SCT

	Number of Patients			Number of Patient Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	6,011	5,350	6,686	3,309	2,967	3,675
Line 2	4,024	3,519	4,526	2,667	2,373	2,966
Line 3	2,757	2,373	3,136	2,232	1,951	2,510
Line 4	1,906	1,614	2,211	1,911	1,644	2,173
Line 5	1,330	1,106	1,567	1,651	1,398	1,915
Line 6	929	760	1,118	1,439	1,196	1,696
Line 7	641	512	792	1,256	1,027	1,512
Line 8	430	335	549	1,081	864	1,336
Line 9	281	211	371	905	704	1,154
Line 10	176	129	242	735	553	971
Line 11	107	74	154	574	418	789
Line 12	62	41	93	431	299	622
Line 13	34	21	55	307	204	464
Line 14	18	10	30	205	128	331
Line 15	9	5	16	128	75	221
Line 16	4	2	8	72	39	137
Line 17 and greater	5	4	8	61	29	133

Table C - 6. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients ≥65 Years, Low/Moderate Cytogenetic Risk and Not Eligible for SCT

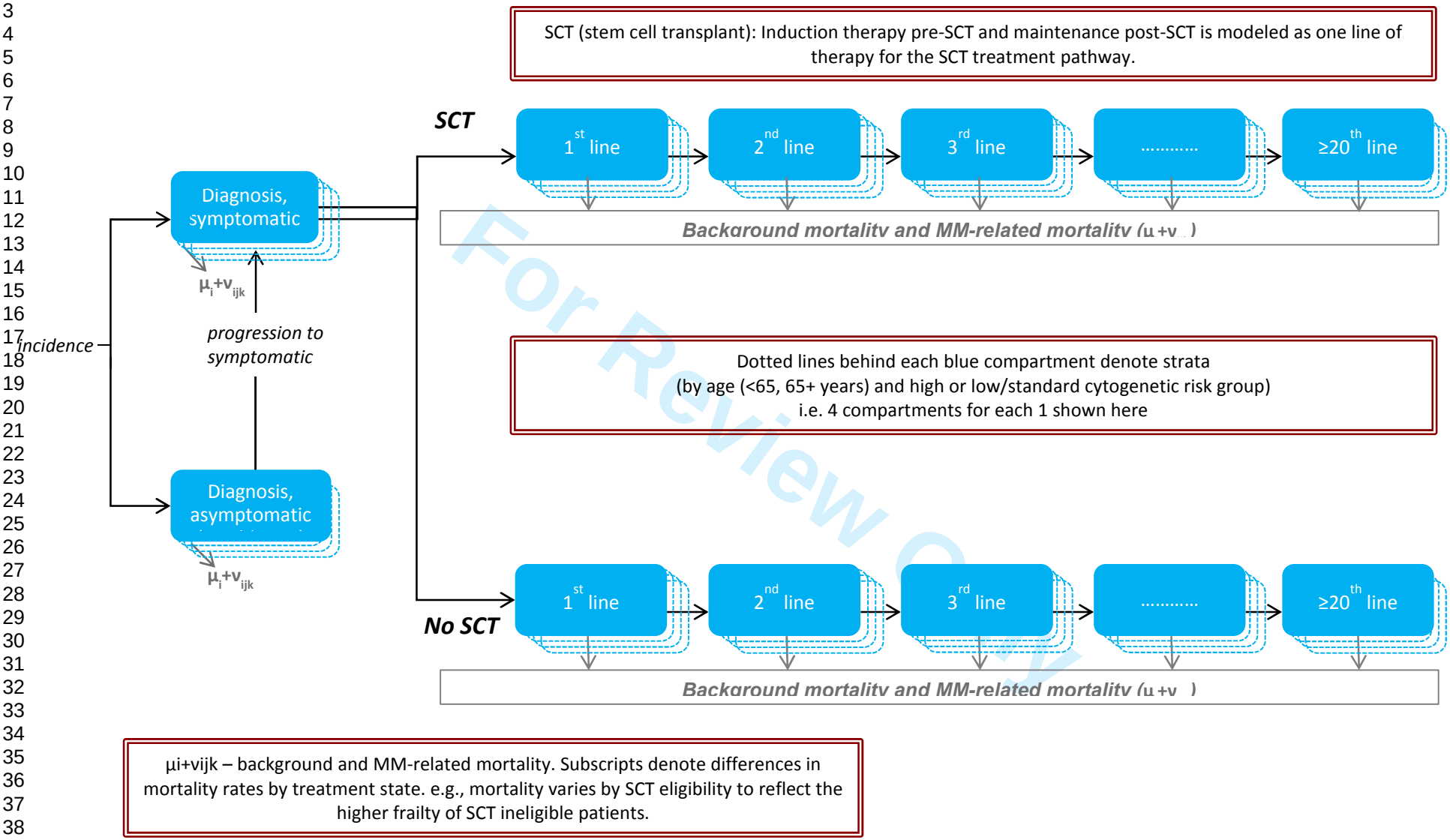
	Number of Patients			Number of Patient Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	8,341	7,522	9,219	6,689	6,133	7,180
Line 2	5,182	4,464	5,969	4,919	4,435	5,436
Line 3	3,338	2,723	4,001	3,820	3,290	4,400
Line 4	2,202	1,702	2,735	3,074	2,508	3,684
Line 5	1,472	1,078	1,897	2,533	1,958	3,146
Line 6	989	687	1,324	2,114	1,549	2,726
Line 7	660	430	924	1,773	1,231	2,375
Line 8	432	259	636	1,475	962	2,065
Line 9	273	152	429	1,199	720	1,766
Line 10	167	84	282	941	522	1,478
Line 11	97	44	180	709	358	1,201
Line 12	54	22	111	508	229	940
Line 13	29	10	65	344	136	703
Line 14	14	4	37	216	74	495
Line 15	7	2	19	122	36	323
Line 16	3	1	9	61	15	188
Line 17 and greater	3	3	7	33	7	130

Table C - 7. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients <65 Years, High Cytogenetic Risk and Not Eligible for SCT

	Number of Patients			Number of Patient Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	1,460	1,194	1,733	1,779	1,514	2,059
Line 2	979	747	1,220	1,436	1,174	1,705
Line 3	674	476	877	1,203	919	1,500
Line 4	470	305	641	1,035	731	1,347
Line 5	329	201	467	902	586	1,230
Line 6	230	131	345	788	482	1,118
Line 7	159	82	252	688	391	1,030
Line 8	107	49	183	591	305	938
Line 9	70	29	130	496	228	845
Line 10	45	16	91	402	162	748
Line 11	27	8	62	314	108	644
Line 12	16	4	41	232	67	540
Line 13	9	2	26	163	39	430
Line 14	5	1	16	107	20	330
Line 15	2	1	10	64	9	238
Line 16	1	1	6	34	4	153
Line 17 and greater	3	3	6	6	2	43

Table C - 8. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients ≥65 Years, High Cytogenetic Risk and Not Eligible for SCT

	Number of Patients			Number of Patient Transitions		
		95% Credible Interval			95% Credible Interval	
Treatment Lines	Median	Lower	Upper	Median	Lower	Upper
Line 1	2,106	1,718	2,512	3,597	3,090	4,111
Line 2	1,360	989	1,709	2,747	2,241	3,277
Line 3	902	580	1,205	2,217	1,612	2,787
Line 4	606	355	857	1,836	1,181	2,454
Line 5	413	219	619	1,540	903	2,177
Line 6	281	136	448	1,308	693	1,963
Line 7	189	82	324	1,109	537	1,770
Line 8	125	47	231	926	401	1,590
Line 9	80	26	163	754	284	1,397
Line 10	49	13	111	591	189	1,210
Line 11	29	7	75	442	117	1,005
Line 12	16	3	50	312	67	814
Line 13	9	2	32	204	34	629
Line 14	4	1	20	119	15	452
Line 15	2	1	12	60	6	292
Line 16	1	1	6	22	2	152
Line 17 and greater	1	1	2	4	1	39




1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
RR_mort_oldage
prop_young
prop_lowrisk
RR_mort_highrisk
prop_sympt
prop_less65_SCT
baseline MM death rate

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. Yes

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. No

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. No

6. In the past three years I have:

- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; No
- been paid as a consultant (or in a similar capacity by a company with a vested interest in the product being studies, on issues unrelated to the product being studied; No
- received research or educational support from a company with a vested interest in the product(s) being studied. No

7. A company whose product is being studied has provided funding to support the work on this project. No

---

If you have answered YES to any of the above questions, or if you have additional personal, commercial or academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been reimbursed by Safe Drug Ltd. for international conference attendance.

Representatives of Onyx Pharmaceuticals, an Amgen subsidiary, participated in this project providing scientific advise, reviewing the model and commenting on the manuscript.

---

8. Manuscript title (first six words are sufficient)

Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

9. Author's full name (a separate form must be submitted for each author)

Javier CID RUZAFA

10. In checking this box, I confirm I have completed this form to the best of my knowledge. ☒

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. n/a

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. n/a

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. No

6. In the past three years I have:

- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; No
- been paid as a consultant (or in a similar capacity by a company with a vested interest in the product being studies, on issues unrelated to the product being studied; No
- received research or educational support from a company with a vested interest in the product(s) being studied. No

7. A company whose product is being studied has provided funding to support the work on this project. No

---

If you have answered YES to any of the above questions, or if you have additional personal, commercial or academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been reimbursed by Safe Drug Ltd. for international conference attendance.

Evie Merinopoulou has been an employee of Evidera and served as paid consultant to Onyx Pharmaceuticals for the work in this study.

---

8. Manuscript title (first six words are sufficient)

Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

9. Author's full name (a separate form must be submitted for each author)

Evie Merinopoulou

10. In checking this box, I confirm I have completed this form to the best of my knowledge. ☒

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. n/a

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. n/a

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. No

6. In the past three years I have:

- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; No
- been paid as a consultant (or in a similar capacity by a company with a vested interest in the product being studies, on issues unrelated to the product being studied; No
- received research or educational support from a company with a vested interest in the product(s) being studied. No

7. A company whose product is being studied has provided funding to support the work on this project. No

---

If you have answered YES to any of the above questions, or if you have additional personal, commercial or academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been reimbursed by Safe Drug Ltd. for international conference attendance.

---

8. Manuscript title (first six words are sufficient)

Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

9. Author's full name (a separate form must be submitted for each author)

Rebecca F Baggaley

10. In checking this box, I confirm I have completed this form to the best of my knowledge. ☒

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. n/a

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. n/a

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. No

6. In the past three years I have:

- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; No
- been paid as a consultant (or in a similar capacity by a company with a vested interest in the product being studies, on issues unrelated to the product being studied; No
- received research or educational support from a company with a vested interest in the product(s) being studied. No

7. A company whose product is being studied has provided funding to support the work on this project. No

---

If you have answered YES to any of the above questions, or if you have additional personal, commercial or academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been reimbursed by Safe Drug Ltd. for international conference attendance.

This work was funded by Onyx Pharmaceuticals. Leighton P was employed by Evidera and served as consultant to Onyx Pharmaceuticals.

---

8. Manuscript title (first six words are sufficient)

Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

9. Author's full name (a separate form must be submitted for each author)

Pamela Leighton

10. In checking this box, I confirm I have completed this form to the best of my knowledge. ☒

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. n/a

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. n/a

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. Yes

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. Yes

6. In the past three years I have:

- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; No
- been paid as a consultant (or in a similar capacity by a company with a vested interest in the product being studies, on issues unrelated to the product being studied; No
- received research or educational support from a company with a vested interest in the product(s) being studied. No

7. A company whose product is being studied has provided funding to support the work on this project. No

---

If you have answered YES to any of the above questions, or if you have additional personal, commercial or academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been reimbursed by Safe Drug Ltd. for international conference attendance.

I am an employee of Onyx Pharmaceuticals, an Amgen Subsidiary, who funded this research.

---

8. Manuscript title (first six words are sufficient)

Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

9. Author's full name (a separate form must be submitted for each author)

Winifred Werther

10. In checking this box, I confirm I have completed this form to the best of my knowledge. ☒

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. n/a

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. n/a

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. Yes

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. Yes

6. In the past three years I have:

- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; Yes
- been paid as a consultant (or in a similar capacity by a company with a vested interest in the product being studies, on issues unrelated to the product being studied; Yes
- received research or educational support from a company with a vested interest in the product(s) being studied. No

7. A company whose product is being studied has provided funding to support the work on this project. No

---

If you have answered YES to any of the above questions, or if you have additional personal, commercial or academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been reimbursed by Safe Drug Ltd. for international conference attendance.

I have been paid as a consultant (or in a similar capacity) by Onyx, a subsidiary of Amgen, with a vested interest in the product being studied.

---

8. Manuscript title (first six words are sufficient)

Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

9. Author's full name (a separate form must be submitted for each author)

Diana Felici

10. In checking this box, I confirm I have completed this form to the best of my knowledge. ☒

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. n/a

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. n/a

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. No

6. In the past three years I have:

- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; No
- been paid as a consultant (or in a similar capacity by a company with a vested interest in the product being studies, on issues unrelated to the product being studied; No
- received research or educational support from a company with a vested interest in the product(s) being studied. No

7. A company whose product is being studied has provided funding to support the work on this project. No

---

If you have answered YES to any of the above questions, or if you have additional personal, commercial or academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been reimbursed by Safe Drug Ltd. for international conference attendance.

---

8. Manuscript title (first six words are sufficient)

Patient population with Multiple Myeloma and

9. Author's full name (a separate form must be submitted for each author)

Andrew Paul Cox

10. In checking this box, I confirm I have completed this form to the best of my knowledge. ☒

This form is available online by clicking here