User Guide

Economic Model to Establish the Costs Associated with Routes to Presentation for Patients with Myeloma in the UK

July 2020

This model and user guide were developed on a pro bono basis for Myeloma UK by Costello Medical

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Abbreviations

AE	Adverse event
A&E	Accident and emergency
ASCT	Autologous stem cell therapy
BNF	British National Formulary
BSA	Body surface area
BSBMT	British Society of Blood and Marrow Transplantation
CDF	Cancer Drugs Fund
CI	Confidence interval
CRAB	Hypercalcaemia, renal insufficiency, anaemia and bone disease
CTD	Cyclophosphamide, thalidomide and dexamethasone
D	Daratumumab monotherapy
DSA	Deterministic sensitivity analysis
DVd	Daratumumab, bortezomib and dexamethasone
eMIT	Electronic market information tool
e-RS	Electronic referral system
ESMO	European Society for Medical Oncology
FVd	Panobinostat, bortezomib and dexamethasone
GBP	Great British Pound (Sterling)
GP	General Practitioner
HDT	High-dose therapy
HES	Hospital episode statistics
HMRN	Haematological Malignancy Research Network
HRG	Healthcare resource group
HRQoL	Health-related quality of life
IRd	Ixazomib, lenalidomide and dexamethasone
IV	Intravenous
Kd	Carfilzomib and dexamethasone
MGUS	Monoclonal gammopathy of undetermined significance
MPT	Thalidomide, melphalan and prednisone
NCIN	National Cancer Intelligence Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
N/A	Not applicable
PAS	Patient Access Scheme
Pd	Pomalidomide and dexamethasone
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RBC	Red blood cell
Rd	Lenalidomide and dexamethasone
SCT	Stem cell transplant
SMM	Smouldering myeloma
SmPC	Summary of product characteristics
SRE	Skeletal-related events
TA	Technology appraisal
TWW	Two-week wait
UK	United Kingdom
VCd	Bortezomib, cyclophosphamide and dexamethasone
Vd	Bortezomib and dexamethasone
VMP	Bortezomib, melphalan and prednisone
VTd	Bortezomib, thalidomide and dexamethasone

NICE Technology Appraisals

A variety of model inputs have been sourced from prior technology appraisals conducted by the National Institute for Health and Care Excellence (NICE). Technology appraisals (TAs) are developed by the Centre for Health Technology Evaluation in NICE and are designed to provide recommendations, in the form of NICE guidance, on the use of new and existing medicines, products and treatments in the United Kingdom's National Health Service. The TAs which are referenced throughout this Model User Guide are as follows.

Identification number	**Title (year of publication)**
TA129	Bortezomib monotherapy for relapsed multiple myeloma (2007)
TA228	Bortezomib and thalidomide for the first-line treatment of multiple myeloma (2011)
TA311	Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (2014)
TA380	Panobinostat for treating multiple myeloma after at least 2 previous treatments (2016)
TA427	Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (2017)
TA510	Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (2018)
TA505	Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (2018)
TA573	Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (2019)
TA586	Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib (2019)
TA171	Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (2019)
TA587	Lenalidomide plus dexamethasone for previously untreated multiple myeloma (2019)

1 Executive Summary

1.1 Background

Myeloma is a relatively rare cancer with vague and overlapping symptoms, and patients often face considerable delays to diagnosis, particularly at the primary care level. Many patients have multiple general practitioner (GP) appointments and inappropriate referrals before a correct diagnosis is reached, with one-third of patients diagnosed following an emergency presentation.[1] Patients with myeloma who are diagnosed via the emergency route have considerably poorer prognosis than those presenting through other referral routes (e.g. GP referral or two-week-wait [TWW]).[1-3] For example, these patients often have additional complications, such as renal failure, and have aggressive disease with a higher need for chemotherapy and radiotherapy.[2] It was therefore hypothesised that delays to diagnosis result not only in poorer survival outcomes, but in a higher economic burden. Myeloma UK sought to quantify the economic costs associated with different routes of presentation for patients newly diagnosed with myeloma in the United Kingdom (UK), in order to build the case that more funding should be dedicated to myeloma diagnosis in clinical practice and research.

1.2 Methods

An economic model was developed to estimate the costs associated with different routes of presentation (emergency presentation, GP TWW, GP urgent, GP routine and consultant to consultant referral) for patients newly diagnosed with myeloma in the UK. The model employs a National Health Service (NHS) and Personal Social Services (PSS) perspective, utilising a decision tree framework to model treatment pathways over a lifetime time horizon.

The decision tree framework is largely based on a publication by Howell et al. (2017), who examined the impact of route of presentation on clinical characteristics and survival for a UK population of multiple myeloma patients.[2] Other model inputs were based on inputs used in recent models published in the disease area (in published National Institute for Health and Care Excellence [NICE] technology appraisals), or derived from targeted literature reviews and discussions with UK clinical experts. Costs were informed by established sources within the NHS, such as the British National Formulary (BNF) and the NHS reference costs 2017–2018.[4, 5]

Model outputs include a summary of patient numbers reaching each stage of the decision tree framework, the costs associated with each route of presentation based on these patient numbers (at the cohort level) and the costs per route of presentation (considering 1 patient per route). Costs are presented with and without the inclusion of monetised quality-adjusted life year (QALY) losses, representing the economic impact of reduced survival and health-related quality of life (HRQoL). The model allows for sensitivity analyses to be undertaken and contains a large range of user-adjustable settings to explore a variety of scenarios.

1.3 Results

For a patient diagnosed with myeloma in the UK, the model estimates a per patient undiscounted lifetime cost (averaged across referral routes) of approximately £168,000, of which approximately £119,000 constitutes treatment costs (acquisition, administration, monitoring and adverse event (AE) costs), £39,000 constitutes the costs of managing complications, and £10,000 constitutes end of life care. When monetised QALY losses are included, the per patient undiscounted lifetime costs are estimated to be approximately £395,000.

In line with Howell et al. (2017), the summary of patient numbers reaching each stage of the decision tree framework showed that more patients present via the emergency route than any other route, and therefore the associated total costs (at the cohort level) were highest for the emergency route. Disaggregated costs showed that treatment costs (especially for patients who were ineligible for stem cell transplant [SCT]) formed the most substantial contribution to the total costs associated with myeloma across each route of presentation.

Total costs per route of presentation (considering 1 patient per route) were similar across referral routes, but were highest for the emergency route. Disaggregated costs per route of presentation (considering 1 patient per route) showed that treatment costs were similar across referral routes, and marginally higher for the emergency, GP TWW and consultant to consultant routes. Treatment costs for patients with active treatment as first-line management constituted a larger proportion of the emergency costs, whereas treatment costs for patients with observation as first-line management (i.e. who had smouldering myeloma at diagnosis and subsequently progressed) were higher for the other routes. Complication and end of life care costs were considerably higher for the emergency route.

Sensitivity analyses were conducted on the costs per route of presentation (considering 1 patient per route) and highlighted that the proportion of patients reaching second line therapy for SCT-ineligible patients was the most influential parameter for the emergency, GP TWW and GP urgent routes, whilst the proportion of patients progressing from smouldering myeloma to active myeloma was the most influential parameter for the GP routine and consultant to consultant routes. Whilst the probabilistic results appeared to be consistent with the base case analysis, the sensitivity analyses indicate that there is considerable uncertainty in the results, warranting further investigation.

1.4 Discussion

The economic model describes the entire treatment pathway for UK patients with myeloma with high granularity, accounting for a large number of events and the associated costs from diagnosis to death. The model was built to closely align with current clinical guidelines and incorporated UK-specific inputs that were extensively validated with UK clinical experts. The model can therefore be considered an accurate reflection of UK clinical practice. However, the model has a number of limitations due to a lack of data with sufficient granularity to directly inform differences in inputs between routes of presentation. Examples include the probability of receiving different therapies at each stage of treatment (assumed to only depend on whether a patient was eligible or ineligible for SCT), the probability of patients reaching each line of therapy and the length of treatment/treatment-free intervals (assumed to be the same for all patients who receive active treatment). Finally, due to data limitations, it was assumed that active treatment was the same regardless of whether patients received active treatment at diagnosis or after a period of observation.

Considering total direct costs (i.e. excluding monetised QALYs) per route of presentation (1 patient per route), complication and end of life care costs were considerably higher for the emergency route, reflecting a cost benefit associated with earlier diagnosis. Whilst the model captures differences in the distribution of treatment costs across different parts of the decision tree framework, total treatment costs were similar across routes of presentation. It is plausible that a direct cost benefit associated with earlier diagnosis could exist in terms of treatment costs, but due to limited granularity of data, this is not currently captured in the model. When monetised QALY losses are included in the total costs per route, the emergency route is associated with considerably higher costs than all other routes. Key data gaps include whether prior observation facilitates a reduction in treatment costs, complications or survival and/or HRQoL benefits, and whether certain referral routes (i.e. earlier diagnosis) facilitate a reduction in treatment costs and/or HRQoL benefits for equivalent patients (e.g. for patients who receive active treatment at diagnosis and are eligible for SCT). These data gaps could be addressed through collection of individual patient data (e.g. from a comprehensive cancer or myeloma registry). The impact of earlier diagnosis on the most influential model parameters identified in the sensitivity analyses would be of particular interest.

1.5 Conclusion

This model comprehensively explores the factors that may drive differences in economic costs between routes of presentation for patients with multiple myeloma in the UK. The results suggest that there may be an economic benefit associated with earlier diagnosis through a reduction in complication and end of life care costs. By addressing the key data gaps relating to the impact of earlier diagnosis on treatment outcomes, costs and complications, the uncertainty surrounding the economic cost of delays in diagnosis for patients with myeloma in the UK could be reduced. This analysis thus provides a focus for future research aiming to build the economic case that more funding should be dedicated to myeloma diagnosis in clinical practice and research.

2 Introduction

Each year, around 5,500 individuals in the UK are diagnosed with myeloma, which is a type of blood cancer originating from plasma cells in the bone marrow.[6] As a relatively rare cancer with vague and overlapping symptoms, patients often face considerable delays to diagnosis, particularly at the primary care level. Many patients have multiple GP appointments and inappropriate referrals before a correct diagnosis is reached, and one-third of patients are diagnosed following an emergency presentation.[1] Delays to diagnosis result in poor survival outcomes, with survival varying considerably by route of presentation. For example, the National Cancer Intelligence Network (NCIN) reported a one-year relative survival rate of 62% for emergency presentations, compared to 88% for GP referrals, and 89% for the TWW pathway.[1] There is therefore a strong clinical argument for ensuring that delays to myeloma diagnoses are minimised, and that efforts are made to reduce the proportion of patients diagnosed via emergency presentation.

Patients who are diagnosed via the emergency route often have additional complications, such as renal failure, and have aggressive disease with a higher need for chemotherapy and radiotherapy.[2] It was therefore hypothesised that delays to diagnosis result not only in poorer survival outcomes, but in a higher economic burden. However, there is limited research into the costs associated with such delays, and the financial implications of different routes to diagnosis.

3 Model Objective

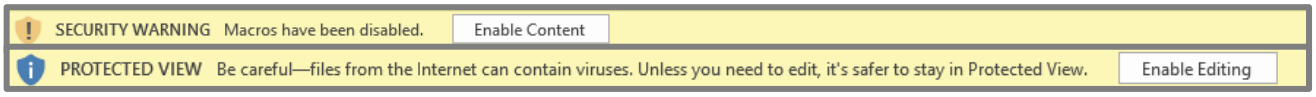
The primary objective of the economic model was to estimate the economic costs associated with different routes of presentation for patients newly diagnosed with myeloma in the United Kingdom (UK), to build the economic case that more funding should be dedicated to myeloma diagnosis in clinical practice and research. The model was built from the perspective of the UK National Health Service (NHS). The primary model output was the cost associated with each referral route for patients diagnosed with myeloma in the UK. Sensitivity analyses were conducted in order to test how robust the model is to different assumptions and highlight areas of model uncertainty that could be addressed through further research.

4 Methods

4.1 Model Navigation

4.1.1 Opening the model

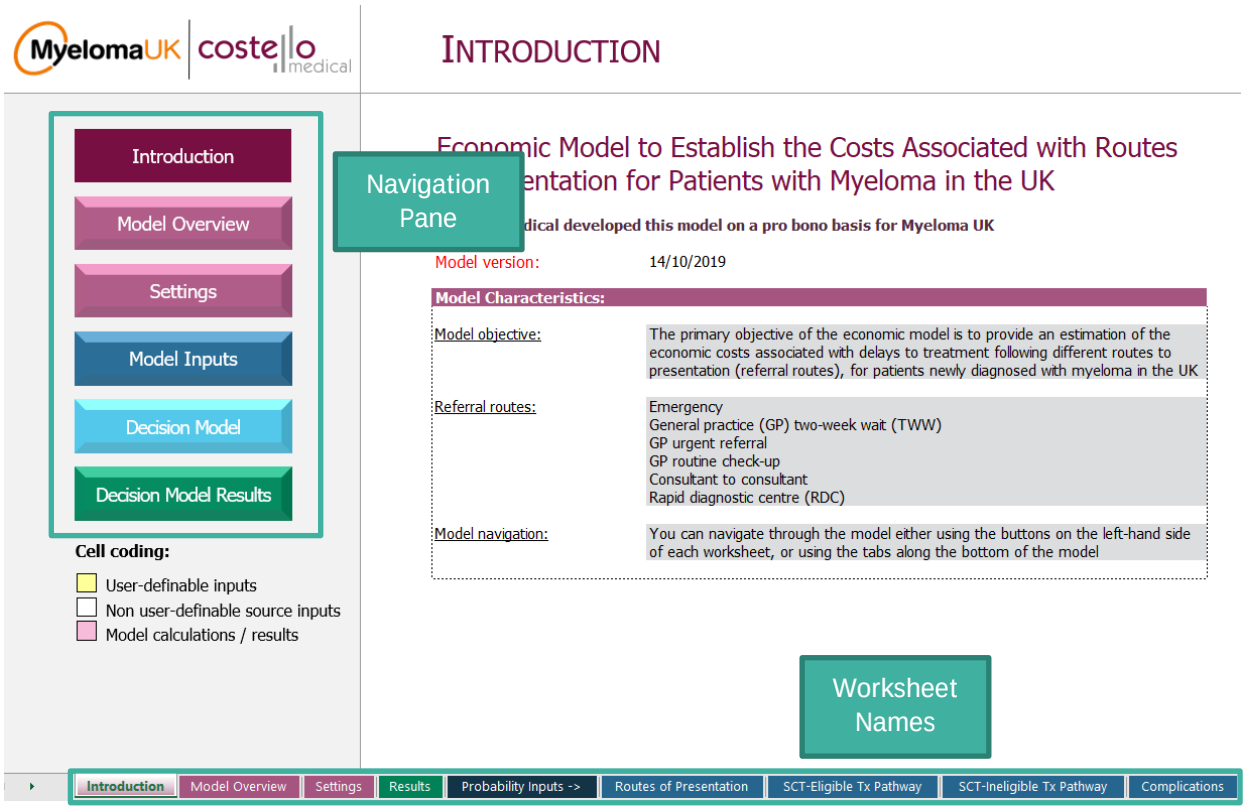
The first time that the model is opened, the user will need to click 'Enable Content' at the top of the screen and 'Enable Editing' to ensure the model can run with full functionality. The model is only compatible with Excel 2007 onwards.



4.1.2 Navigation

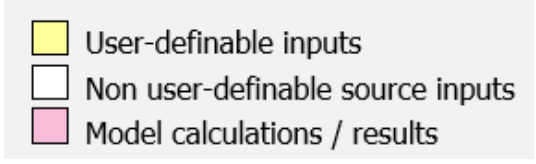
The model will automatically open on 'Introduction' worksheet, containing key model characteristics. The Navigation Pane can be found on the left-hand side of the 'Introduction' tab. These buttons can be pressed to move between the core sections of the model. It is also possible to navigate through the model by clicking on the Worksheet Names at the bottom of the screen, as shown in Figure 1.

Figure 1: Model Navigation



4.1.3 User adaptability

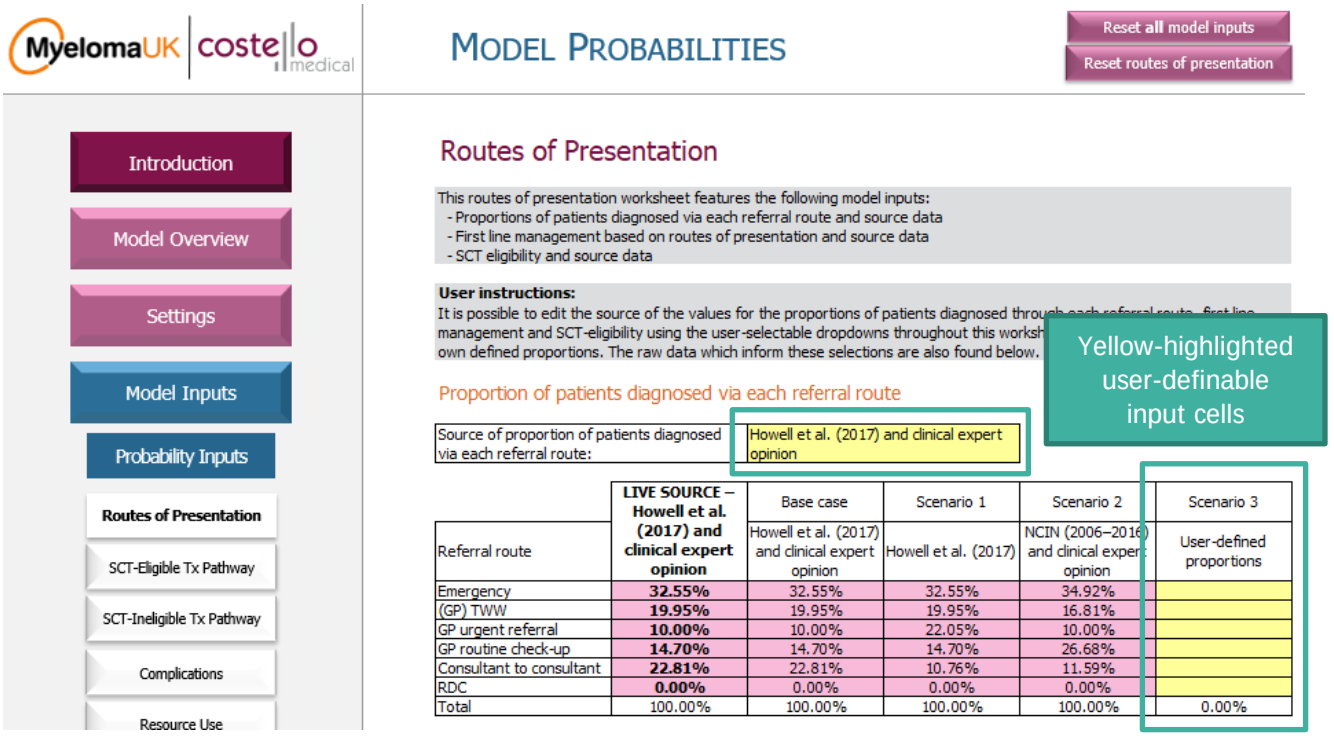
Cells in the model have been colour coded as follows:



The model has been built such that the user can adjust many of the inputs to evaluate the impact on the model results. Any cells that are user-definable have been coloured yellow. These cells can be manually edited, and the model results will update automatically.

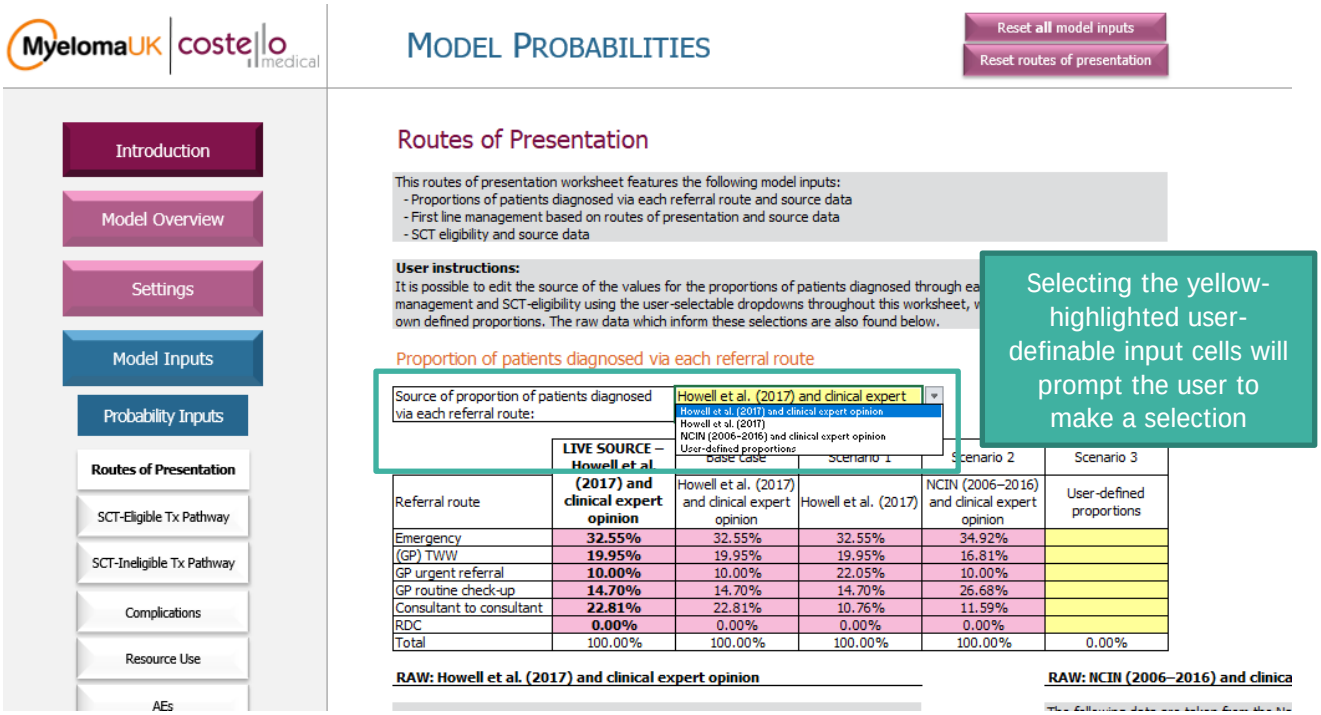
An example of the steps that should be taken to adjust user-definable inputs (yellow-highlighted) is shown in the figures below, for a scenario where the user wishes to adjust the proportions of patients diagnosed through each referral route (in the 'Routes of Presentation' worksheet).

Figure 2: Identifying user-defined inputs (step 1)



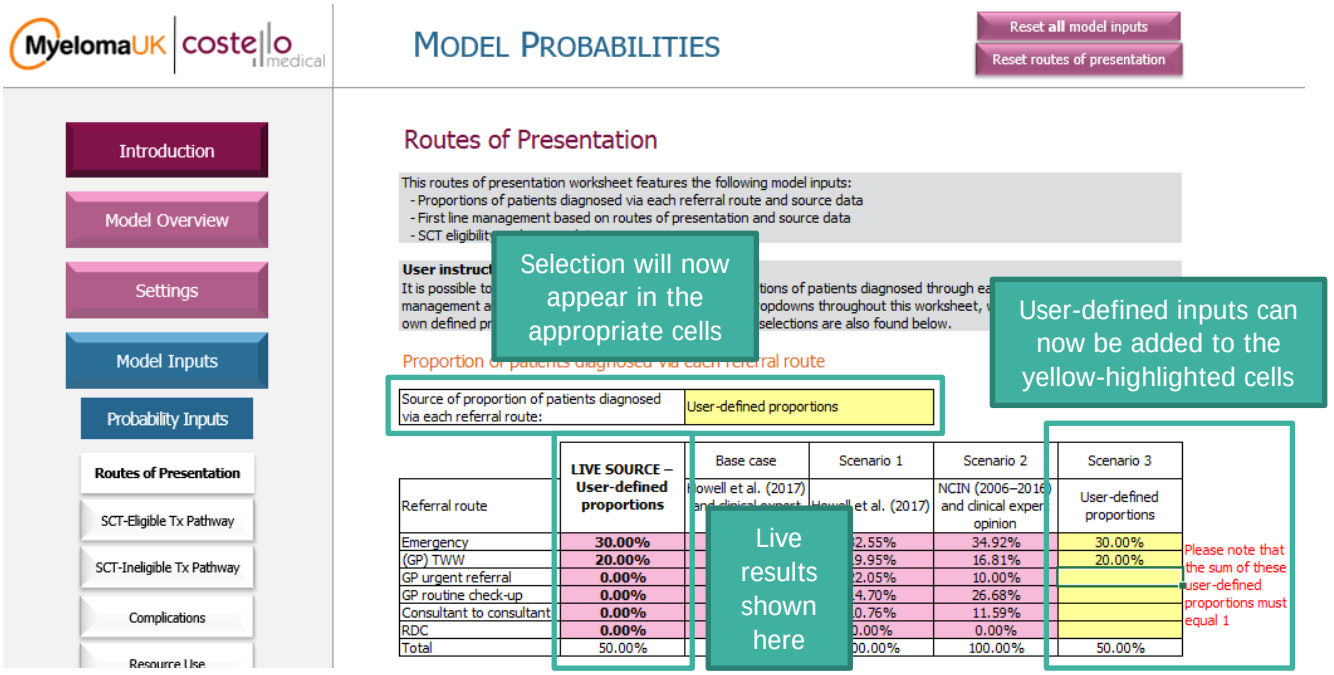
After identifying the appropriate user-definable cells, in this case the user-definable cells are presented alongside additional data sources, so it would be necessary to ensure that the correct source is being used in the model. You can ensure that this is the case by selecting an alternative option in the dropdown immediately preceding the inputs table, as shown in Figure 3 below.

Figure 3: Editing user-definable input cells (step 2)



When this dropdown selection is made, the updated choice of selection will appear in place of the base case selection. Once this has been completed, the user can input their own values in the appropriate cells, which will then be reflected in the 'LIVE' source column, as shown in Figure 4 below.

Figure 4: Editing user-definable results (step 3)



Should a user wish to undo any adjustments, the model includes the functionality to reset model inputs to their original values. If the user wishes to revert all model inputs, this can be done by selecting the 'Reset all model inputs' button on the 'Settings' worksheet(as shown in Figure 5 below). The model also includes the functionality to reset model inputs on each individual model input worksheet (an example of the 'Routes of Presentation' worksheet is given in Figure 6 below, with the reset all model inputs and reset worksheet-specific input commands are located at the top of each worksheet).

Figure 5: Reset all model inputs

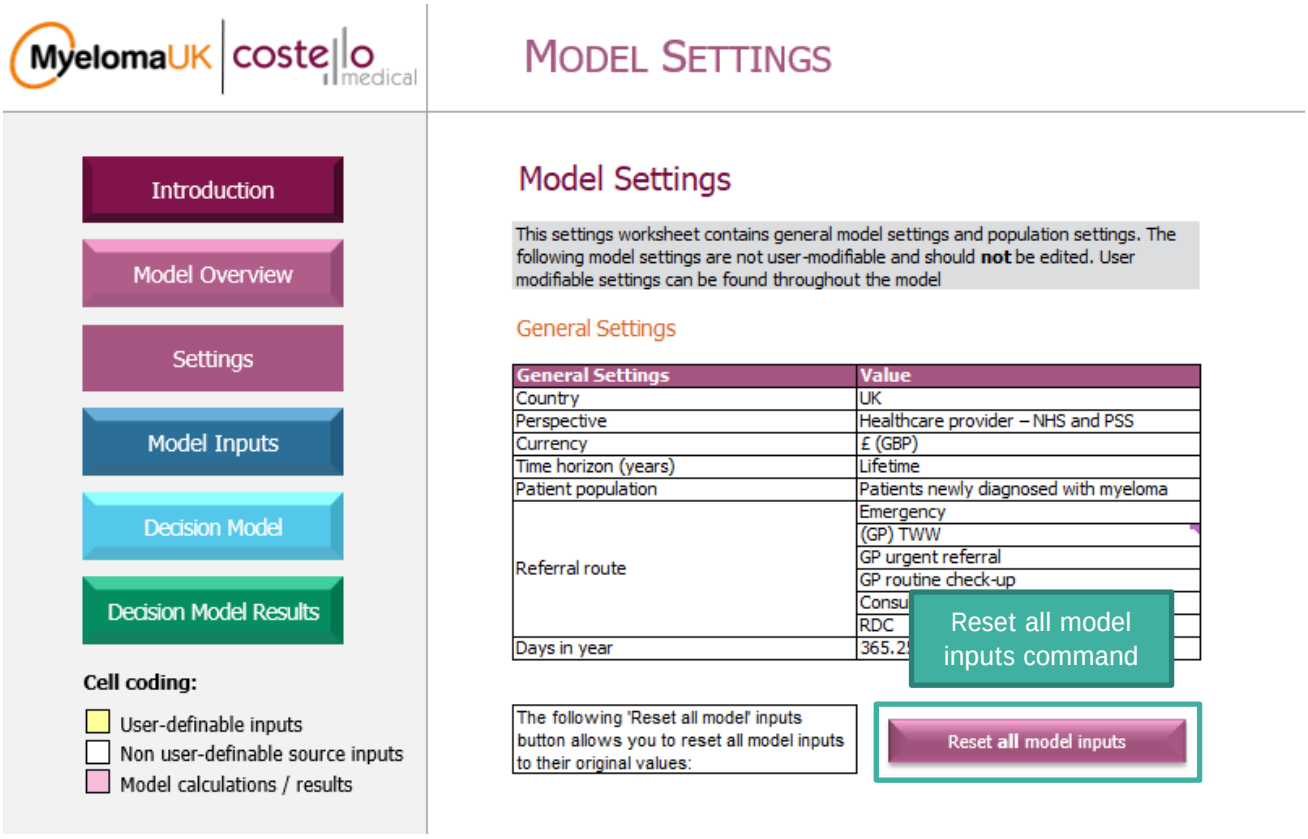
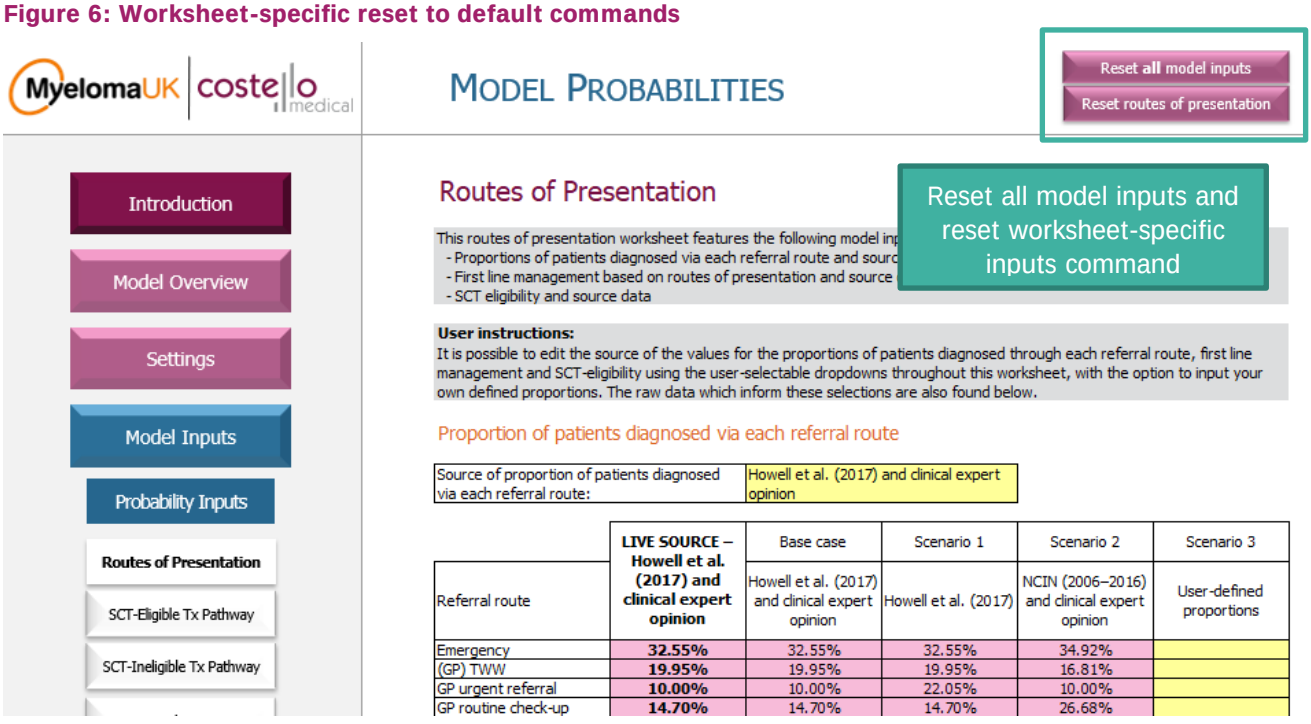


Figure 6: Worksheet-specific reset to default commands



4.2 General Model Characteristics

Table 1 provides an overview of the general model settings.

Table 1: Summary of model characteristics

Model characteristics	Specification
Target population	Patients diagnosed with myeloma in the UK
Country (Currency)	UK (GBP)
Perspective	NHS and PSS
Time horizon	Lifetime
Audience	Freely available to myeloma community
Routes of presentation	• Emergency • GP TWW • GP urgent referral • GP routine check-up • Consultant to consultant • RDC

Abbreviations: GBP: Great British Pound (Sterling); GP: general practitioner; NHS: National Health Service; PSS: Personal Social Services; RDC: Rapid Diagnostic Centre; TWW: two-week wait; UK: United Kingdom.

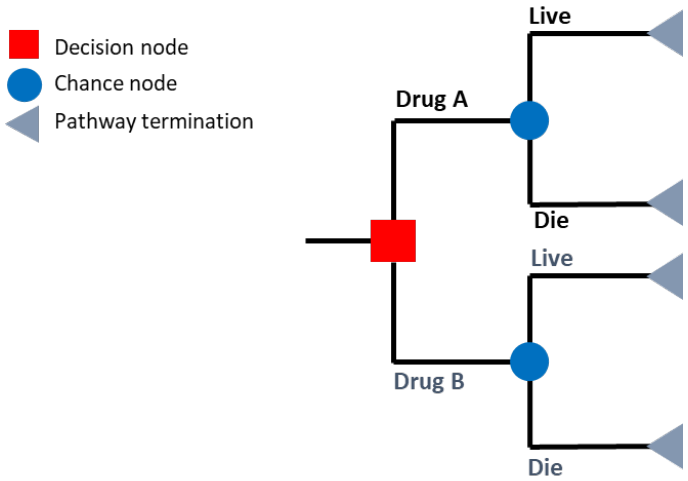
4.3 Model Structure

4.3.1 The decision tree

Decision tree modelling

A decision tree is an economic modelling technique which is based on an intuitive graphical representation of possible solutions to a decision, based on certain conditions. Generally, decision trees starts with a single box (analogous to the root of a tree), which then branch off into a number of alternative pathways. A simplified decision tree structure is shown in Figure 7.

Figure 7: The decision-tree framework



In Figure 7, the initial box is called a 'decision node', representing a choice between two (or more) mutually exclusive options (or 'branches'). In Figure 7, the choice is between Drug A and Drug B. The points where these branches divide, shown by the blue circles in Figure 7 are referred to as 'chance nodes', and each node is associated with a probability of an event occurring or not. That is, the probability of either living or dying conditional on having taken Drug A or Drug B. Outcomes and costs associated with each branch of the decision tree are multiplied by the branch probabilities, to calculate probability-weighted (i.e. expected) costs and outcomes for each of the options.

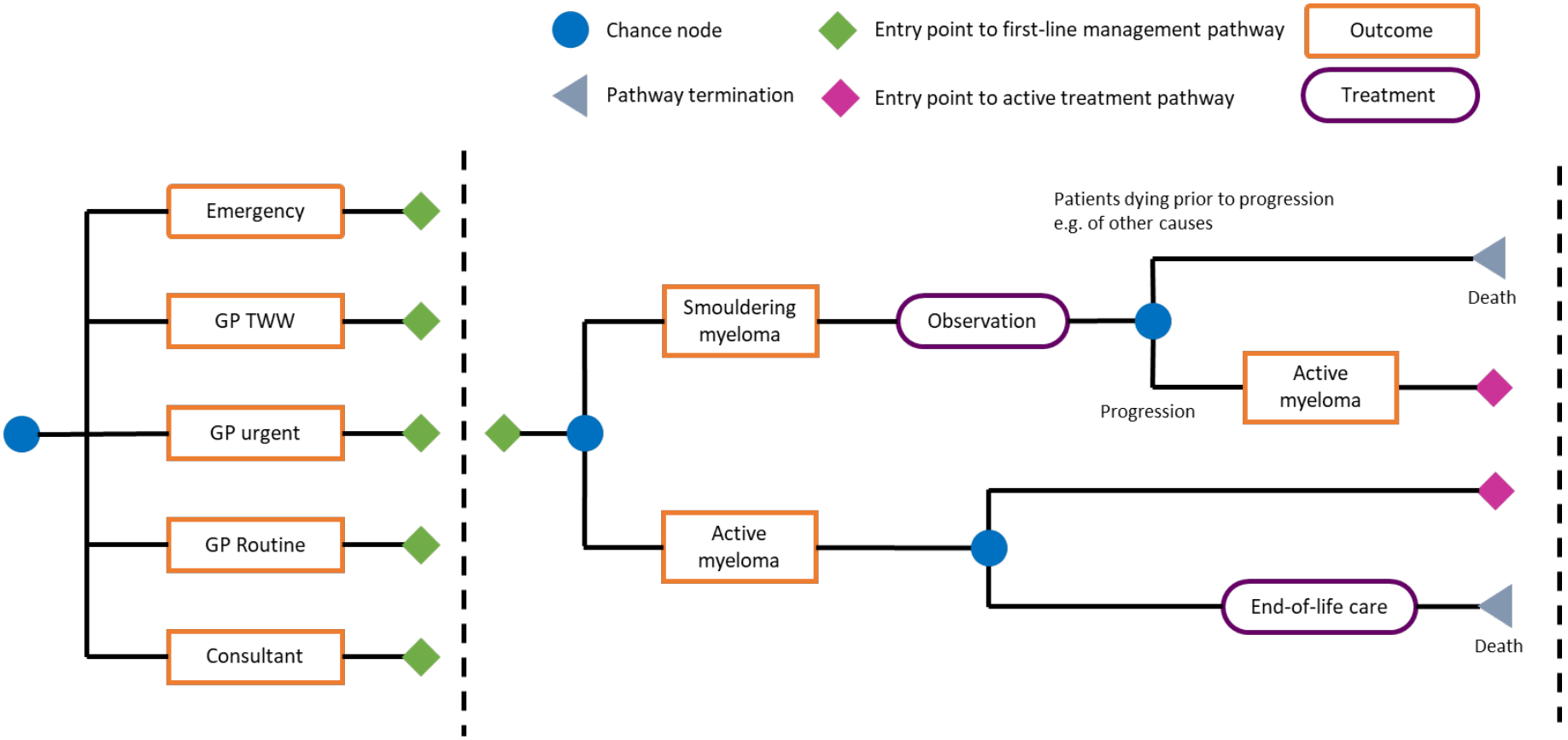
Decision tree frameworks are often used to conduct cost-effectiveness analyses for health care interventions; in these cases, the decision node represents the choice between a new intervention and an existing alternative, which can be associated with different branch probabilities, costs and outcomes. By comparing the expected costs and outcomes for the different interventions in an incremental analysis, a decision can be made regarding whether any additional benefit conferred by the new intervention would be worth any additional costs.

A decision-tree framework for Myeloma UK

This analysis does not aim to compare mutually exclusive options, but rather to model the existing treatment pathways for myeloma in current UK practice. As such, the model does not have a decision node, and could be considered to represent a single 'branch' of a decision tree, where all nodes in the model are chance nodes.

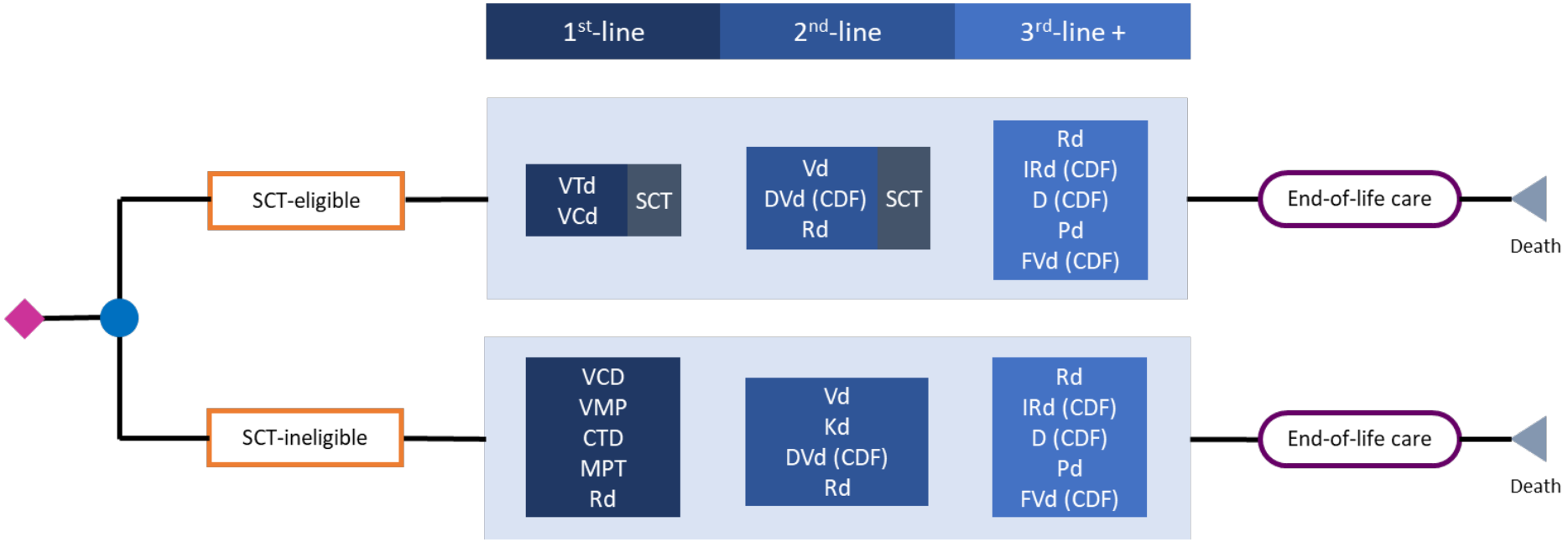
The economic model was developed in Microsoft Excel 2010 and a graphical representation of the decision tree structure in the base case model is given in Figure 8 and Figure 9. Figure 9 is an extension of Figure 8. Figure 8 shows the referral route followed by the first-line management strategy dependent on the type of diagnosis (asymptomatic versus symptomatic myeloma) and Figure 9 shows the treatment pathway for patients receiving active treatment.

Figure 8: Model structure: routes of presentation and first-line management



Abbreviations: GP: general practitioner; TWW: two-week wait.

Figure 9: Model structure: treatment pathway following initiation of active treatment



Abbreviations: CDF: Cancer Drugs Fund; D: daratumumab monotherapy; DVd; daratumumab, bortezomib and dexamethasone; CTd: cyclophosphamide, thalidomide and dexamethasone; FVd: panobinostat, bortezomib and dexamethasone; IRd: ixazomib, lenalidomide and dexamethasone; Kd: carfilzomib and dexamethasone; MPT: thalidomide, melphalan and prednisone; Pd: pomalidomide and dexamethasone; Rd: lenalidomide and dexamethasone; SCT: stem cell transplant; VCd: bortezomib, cyclophosphamide and dexamethasone; Vd: bortezomib and dexamethasone; VMP: bortezomib, melphalan and prednisone; VTd: bortezomib, thalidomide and dexamethasone.

4.3.2 Routes of presentation

The decision tree framework is largely based on Howell et al. (2017), who examined the impact of route of presentation on clinical characteristics and survival for multiple myeloma patients.[2] The study was set within the Haematological Malignancy Research Network (a UK population-based cohort instigated in 2004 to generate 'real world' data for research and clinical purposes), and included patients diagnosed with myeloma diagnosed between 1st July 2012 and 31st December 2013. The following referral routes were modelled, based on referral routes reported in Howell et al. (2017):[2]

- Emergency presentation
- General practitioner (GP) two-week wait (TWW)
- GP urgent
- GP routine
- (Hospital) Consultant to consultant

Howell et al. (2017) also note that an additional cohort were observed, for whom no referral route had been recorded.[2] Within this group, 65% of patients were already being monitored by haematology (often for a monoclonal gammopathy of undetermined significance [MGUS]), and 35% of patients had no details documented in hospital records.[2] However, given that no further data were reported in Howell et al. (2017) about this subgroup, the economic model did not consider these patients. Additionally, clinicians noted that due to the launch of the electronic referral system (e-RS) in 2015, the use of GP urgent referrals are expected to decline in UK practice. The model also includes a placeholder route for referral via an RDC. Whilst this route is becoming more relevant in clinical practice, no data were available to inform the movement of patients through this route, so all model inputs were set to zero. As such, the RDC route has not been included in this report.

4.3.3 First-line management

In line with Howell et al. (2017), following a diagnosis, the economic model reflects patients receiving one of the following three options as first-line management of myeloma:[2]

- Observation
- Chemotherapy/radiotherapy
- Supportive/palliative care

The European Society for Medical Oncology (ESMO) treatment guidelines suggest that patients diagnosed with asymptomatic smouldering myeloma (SMM) should not receive immediate treatment (i.e. should be observed), and that active treatment should be initiated upon progression to active myeloma.[7] Therefore, the following modelling assumptions were made:

- Patients reported to receive observation as first-line management in Howell et al. (2017) were assumed to have been diagnosed with asymptomatic SMM
- Patients reported to receive chemotherapy/radiotherapy or supportive/palliative care in Howell et al. (2017) were diagnosed with active myeloma
  - Those who receive chemotherapy/radiotherapy receive treatment in line with UK clinical practice
  - Those receiving only supportive/palliative care are at an end of life stage (due to an advanced stage of disease), and receive only end of life care

The appropriateness of these assumptions within the UK has been validated by clinical expert opinion, and with the study authors. As myeloma is not curable, all treatments could be described as being used with 'palliative' intent. However, the study authors confirmed that the supportive/palliative care described in the study represented solely end of life care. As such, this first-line management option will hereby be denoted 'end of life care'.

4.3.3.1 Observation

The ESMO treatment guidelines suggest that patients diagnosed with asymptomatic SMM should not receive immediate treatment (i.e. should be observed), and that active treatment should be initiated upon progression to active myeloma.[7] As such, only monitoring costs were included in the model for these patients. However, clinical experts highlighted that there has been a recent change in practice, and that a small proportion (<20%) of patients with SMM who are at a higher risk of developing myeloma may receive treatment. To reflect this recent change in practice, a small proportion (10%) of those who were reported to receive "observation" in Howell et al. (2017) were instead modelled to receive active treatment following diagnosis, in an analogous manner to those with a diagnosis of active myeloma.

4.3.3.2 Active treatment

The treatment landscape for multiple myeloma is complex and constantly evolving and so clinical experts note the difficulty in capturing a typical treatment pathway for a representative myeloma patient. As such, the economic model accounts for a number of possible treatment options at each of three stages (first-, second- and subsequent-lines [3+]) of the active treatment pathway using a "market basket" approach, where costs at each line of therapy represent a weighted average of the costs of the therapies in each market basket. Weights were based on the likelihood of receiving each treatment option at each stage. The probabilities associated with these likelihoods are explored later in this document and have been validated by clinical expert opinion.

1. SCT eligibility

SCT eligibility is an important consideration in determining the treatment pathway of patients diagnosed with myeloma. Following diagnosis of active myeloma, patients who are eligible for SCT receive treatments which differ from a patient who is ineligible for SCT. Age and fitness are important considerations in determining patient eligibility for SCT. For example, the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up advise that patients under the age of 65, or patients under the age of 70 and in good clinical condition receive SCT as standard treatment.[7] Clinical expert opinion confirmed the importance of these factors in determining treatment eligibility.

2. First-line therapy

SCT-eligible

NICE technology appraisal (TA) guidance (TA311) recommends bortezomib in combination with dexamethasone (Vd), or with dexamethasone and thalidomide (VTd), for the induction treatment of adults with previously untreated multiple myeloma who are eligible for SCT.[8] Clinicians confirmed that the majority of patients would receive VTd as an induction therapy. However, it was noted that another triplet therapy such as bortezomib, cyclophosphamide dexamethasone (VCd) would be preferred to bortezomib and dexamethasone (Vd). As such, the following therapies are considered in the model for induction treatment prior to SCT:

- VTd
- VCd

Following induction therapy, patients go on to receive high-dose therapy (HDT) and autologous SCT (ASCT) (or allogeneic SCT for a small number of younger patients).[6]

SCT-ineligible

As per BNF
guidance (TA228), thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma for patients who are ineligible for SCT.[9] Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for patients who are unable to tolerate or have contraindications to thalidomide. Clinical experts also noted that lenalidomide plus dexamethasone (Rd) has recently been recommended as an option for SCT-ineligible patients in the first-line setting for whom thalidomide is contraindicated or not tolerated (TA587).[10] Clinical

experts therefore consider the following combinations appropriate for inclusion within the economic model for the first-line treatment of myeloma for patients who are not eligible for SCT:

- VCd
- Bortezomib, melphalan and prednisone (VMP)
- Cyclophosphamide, thalidomide and dexamethasone (CTd)
- Thalidomide, melphalan and prednisone (MPT)
- Lenalidomide and dexamethasone (Rd)

Clinicians noted the constantly evolving nature of the myeloma treatment pathway, highlighting that CTd has generally taken the place of MPT. It was also noted that if MPT were still used in the first-line treatment of SCT ineligible patients, the proportion of patients receiving MPT would be very small.

3. Second-line therapy

As per NICE TA129, bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation.[11] In UK clinical practice, bortezomib is routinely used in combination with dexamethasone (Vd). Daratumumab in combination with bortezomib and dexamethasone (DVd) is recommended as an option for patients who have had one prior therapy (TA573).[12] Carfilzomib in combination with dexamethasone (Kd) is also recommended as an option for patients who have had only one prior therapy, which did not include bortezomib.[13] Clinical experts also noted that in addition to these treatment options, lenalidomide plus dexamethasone (Rd) was recently approved by NICE for patients who have had only one prior therapy that included bortezomib (TA586).[14]

SCT-eligible

All patients who are SCT-eligible at first-line are expected to receive bortezomib. As such, none of these patients are expected to receive Kd in the second-line setting. However, clinical experts confirmed that Vd, DVd and Rd were relevant in the second-line setting for those who had undergone an SCT, and highlighted that for some patients a second SCT may be considered. As such, the following therapies are considered in the model:

- Vd
- DVd
- Rd

SCT-ineligible

Clinical experts confirmed that all of the recommended therapies are relevant in the second-line setting for those who are ineligible for SCT, and as such, the following therapies are considered in the model:

- Vd
- Kd
- DVd
- Rd

Clinical experts noted that although Kd is used in Scotland, it is not commonly used in England and Wales.

4. Subsequent lines (3+)

Within the economic model, following first- and second-line therapies, subsequent lines (such as third- and fourth-lines) of treatment are grouped together. Clinicians confirmed that therapies for subsequent lines are common across both SCT-eligible and SCT-ineligible patients, and that further SCT would not be offered. In line with NICE guidance (TA505, TA171, TA510, TA427 and TA380) and clinical expert opinion, the following subsequent-line therapies (3+) were included in the model:[15-19]

- Rd
- Ixazomib, lenalidomide and dexamethasone (IRd)
- Daratumumab monotherapy (D)
- Pomalidomide and dexamethasone (Pd)
- Panobinostat, bortezomib and dexamethasone (FVd)

4.3.3.3 End of life care

As described in Section 4.3.5, end of life care included in the model accounts for the increased costs and resource use that patients are expected to incur in the weeks preceding their death, in a hospital setting, at a hospice or at home. Patients who receive end of life care as first line management are considered to have very poor prognosis and a short life expectancy, and thus end of life care was expected to differ for these patients.

4.3.4 Complications

The diagnosis of myeloma often follows one or more of the following clinical presentations (CRAB features):

- Hypercalcaemia
- Renal insufficiency
- Anaemia
- Bone disease

Given the elevated cost and resource use associated with these presenting symptoms, these complications were accounted for within the economic model.

4.3.5 End of life care

It was assumed that, prior to death, all patients who die of myeloma receive end of life care. End of life care defines the holistic approach taken by healthcare professionals to manage a patient's condition, with the aim of improving quality of life. End of life care often focusses on pain relief and symptom control.[20] As noted previously, myeloma is an incurable disease and so this end of life care accounts for the increased costs and resource use that patients are expected to incur in the weeks preceding their death, in a hospital setting, at a hospice or at home.

4.4 Model Inputs

4.4.1 Population inputs

The model considers all patients diagnosed with myeloma in the UK. The following patient characteristics are applied within the model and are used to establish drug acquisition costs, as described in Section 4.4.3.1. The following characteristics are applied in the 'Drug Acqu. & Admin. Costs' worksheet.

Table 2: Patient characteristics

Patient Characteristic	Value	Source
BSA	1.73	TA587[10]
Weight (kg)	71.5	

Abbreviations: BSA: body surface area.

4.4.2 Probability inputs

Probabilities reported below represent the likelihood of an event occurring. Subsequent probabilities (shown by the asterisk below) are conditional on the representative patient reaching the stage of the decision tree in question, given that an earlier event has occurred.

Based on the model structure in Figure 8 and Figure 9, decision tree probabilities pertaining to the following model inputs are required:

- Routes of presentation
- First-line management
- Complications (conditional on receiving a diagnosis of active myeloma)
- SCT eligibility (conditional on entering the active treatment pathway)
- Therapies received at each line of therapy, associated resource use and adverse events (conditional on SCT eligibility)
- End of life care

Many of the probability inputs included in the model are based on data reported in Howell et al. (2017), including routes of presentation, first-line management, complications and SCT eligibility.[2]

4.4.2.1 Routes of presentation

A summary of the probabilities associated with patients presenting through each referral route are shown in Table 3. In the base case analysis, the proportion of patients presenting via each referral route was based on the data reported in Howell et al. (2017), but the proportion of patients presenting via the "GP urgent" route was set to 10% based on clinical expert opinion, and the proportion of "consultant to consultant" referrals adjusted to compensate.[2]

Table 3: Probability of patients diagnosed through each route of presentation (base case): Howell et al. (2017) and clinical expert opinion

Referral route	Base case	Source
Emergency presentation	0.33	Howell et al. (2017)[2] and clinical expert opinion
GP TWW	0.20	
GP urgent	0.10	
GP routine	0.15	
Consultant to consultant	0.22	

Abbreviations: GP: general practitioner; TWW: two-week wait.

Scenarios: Routes of presentation

A scenario was included in the model where these proportions are based on the data from Howell et al. (2017) without adjustment.[2]

Table 4: Probability of patients diagnosed through each route of presentation: Howell et al. (2017)

Referral route	Scenario 1	Source
Emergency presentation	0.33	Howell et al. (2017)[2]
GP TWW	0.20	
GP urgent	0.22	
GP routine	0.15	
Consultant to consultant	0.11	

Abbreviations: GP: general practitioner; TWW: two-week wait.

The proportions of patients diagnosed by different routes of presentation are also available from the NCIN for 47,671 patients diagnosed with myeloma from 2006 to 2016, as presented in Table 5.[21]

Table 5: Probability of patients diagnosed through each route of presentation defined by NCIN

Referral route	Definition	Proportion of patients
Emergency presentation	An emergency route via A&E, emergency GP referral, emergency transfer, emergency consultant outpatient referral or emergency admission or attendance	0.34
TWW	Urgent GP referral with a suspicion of cancer, using the two week wait (TWW) guidelines	0.17
GP referral	Routine and urgent referrals where the patient was not referred under the TWW referral route	0.36
Other outpatient	An elective route starting with an outpatient appointment: either self-referral, consultant to consultant or other referral	0.11
Inpatient elective	Where no earlier admission can be found prior to admission from a waiting list, booked or planned	0.02
Unknown	No data available from inpatient or outpatient HES, CWT, screening within set time parameters or unknown referral	N/A

Abbreviations: A&E: accident and emergency; CWT: Cancer Waiting Times; GP: general practitioner; HES: Hospital Episode Statistics; NCIN: National Cancer Intelligence Network; TWW: two-week wait.

The NCIN did not report patient characteristics or first-line management according to referral route.[21] Therefore in order to use these data to inform a scenario in the model, the referral routes had to be mapped to those used in Howell et al. (2017) (see Table 6). Like the base case analysis, the proportion of GP urgent referrals was set to 10%, based on clinical expert opinion.

Table 6: Probability of patients diagnosed through each route of presentation: NCIN mapped to Howell et al. (2017)

Referral route (NCIN)	Referral route mapped to Howell et al. (2017)	Scenario 2	Source
Emergency presentation	Emergency presentation	0.33	NCIN 2006–2016[21] and clinical expert opinion
GP TWW	TWW	0.16	
GP referral	GP urgent	0.10[b]	
	GP routine	0.25	
Other outpatient	Consultant to consultant	0.11	
Inpatient elective[a]	No referral route	0.05[a]	
Unknown[a]			

[a] Not included in the model. [b] The probability of GP urgent referrals was set to 0.10, based on clinical expert opinion.
Abbreviations: GP: general practitioner; NCIN: National Cancer Intelligence Network; TWW: two-week wait.

4.4.2.2 First-Line management

The probabilities presented in Table 7 inform the likelihood of receiving one of three first-line management options for myeloma in the base case.

Table 7: Probability of first-line management option by referral route (base case)

Referral route	Chemotherapy / radiotherapy	Observation	Supportive / palliative care	Source
Emergency	0.77	0.08	0.15	Howell et al. (2017),[2] validated by clinical expert opinion
TWW	0.59	0.34	0.07	
GP urgent referral	0.58	0.31	0.11	
GP routine check-up	0.43	0.50	0.07	
Consultant to consultant	0.59	0.37	0.05	

Abbreviations: GP: general practitioner; TWW: two-week wait.

4.4.2.3 SCT eligibility for those receiving active treatment

The NICE draft scope for bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311; 2008) estimated that the proportion of patients eligible for SCT was 20%.[8] A more recent NICE partial review of TA171 suggests that 32% of patients would be eligible for SCT (based on data from BSBMT 2016).[15, 22] Based on the latest data from the BSBMT (2017), the proportion of patients receiving SCT was 35%.[23] Clinical experts agreed that it is reasonable to assume that one third of patients are eligible to receive SCT. The probabilities of patients being eligible and ineligible for SCT were therefore based on data from patients included in Howell et al. (2017), adjusted to match the more recent estimate of SCT-eligibility from the BSBMT (2017).[2, 23] This was achieved by adding a common factor of 23% to the proportions of patients receiving SCT across all routes such that 35% of all patients diagnosed with active myeloma (receiving active treatment of end of life care) are modelled to be eligible for SCT.

Table 8: Probability of being eligible for SCT by referral route (base case): Howell et al. (2017) adjusted based on BSBMT (2017)

Referral route	SCT-eligible[a]	SCT ineligible	Source
Proportions of those receiving active treatment			
Emergency	39.19%	60.81%	Howell et al. (2017) adjusted based on BSBMT (2017)[2, 23]
TWW	51.41%	48.59%	
GP urgent referral	40.89%	59.11%	
GP routine check-up	26.69%	73.31%	
Consultant to consultant	39.19%	60.81%	
Total	40.59%	59.41%	
Proportions of all patients with active myeloma (i.e. those receiving active treatment or end of life care)			
Total	35.00%	65.00%	BSBMT (2017)[23]

[a] Please note that the proportions of patients eligible for SCT based on Howell et al. (2017) have been adjusted by adding 23% across each route to reflect the expected total in current clinical practice (~35% of all patients diagnosed with active myeloma regardless of first-line management).
Abbreviations: GP: general practitioner; TWW: two-week wait.

Scenario: SCT Eligibility for those receiving active treatment

A scenario was included in the model where no adjustment was made to the proportions reported in Howell et al. (2017).[2]

Table 9: Probability of being eligible for SCT by referral route: unadjusted Howell et al. (2017) data

Referral route	SCT-eligible[a]	SCT ineligible
Proportions of those receiving active treatment		
Emergency	16.67%	83.33%
TWW	28.89%	71.11%
GP urgent referral	18.37%	81.63%
GP routine check-up	4.17%	95.83%
Consultant to consultant	16.67%	83.33%
Total	18.07%	81.93%
Proportions of all patients with active myeloma (i.e. those receiving active treatment or end of life care)		
Total	15.58%	84.42%

[a] Please note that the proportions of patients eligible for SCT based on Howell et al. (2017) have been adjusted by adding 23% across each route to reflect the expected total in current clinical practice (~35% of all patients diagnosed with active myeloma regardless of first-line management).
Abbreviations: GP: general practitioner; TWW: two-week wait.

4.4.2.4 Active treatment

Given the constantly evolving nature of the myeloma treatment pathway, a number of placeholder treatments were included in the economic model so that it can be modified to include new treatments, thereby increasing the longevity of the model. Note that these placeholder treatments have not received any weighting in the first model draft.

Lines of therapy

It was assumed that only a proportion of patients reach each line of therapy (i.e. a proportion of patients die or proceed to end of life care and then die, thus not continuing to the next line of therapy). These proportions were based on Yong et al. (2016), a large real-world study including 753 UK patients.[24] The proportions of patients who enter the active treatment pathway reaching first, second and subsequent (3+) lines of therapy are detailed in Table 10. Yong et al. (2016) reports that only 95% of patients reach first line therapy.[24] In the model, patients who don't reach first line therapy are already captured as those who receive end of life as first line management. To avoid double counting, the proportions reported in Table 10 (which are applied to all patient entering the active treatment pathway) represent the proportions of patients reaching each line in Yong et al. (2016) as a fraction of the 95% of patients who had already reached first line (e.g. 61%/95%=64.21%).

It is likely that patients who receive SCT are more likely to progress to second and subsequent lines of therapy. However, due to lack of data, it was assumed that the probability of progressing to second and subsequent lines is the same for both SCT-eligible and SCT-ineligible patients. Flexibility was included in the model such that the probability of progressing for the two populations can be altered.

Table 10: Proportion of patients who enter the active treatment pathway reaching later lines of therapy

Line of therapy	SCT-eligible	SCT-ineligible	Source
First line	100.00%	100.00%	Yong et al. (2016)[24]
Second line	64.21%	64.21%	
Subsequent lines (3+)	40.00%	40.00%	

Abbreviations: SCT: stem cell transplant.

SCT-eligible

The probabilities presented in Table 11 inform the likelihood of SCT-eligible patients receiving particular myeloma treatments at first and second lines of therapy. The probabilities associated with second line therapies are conditional on patients reaching second line.

Table 11: Treatment probabilities for SCT eligible patients

Treatment	Probability of receiving treatment	Source
First line (induction)		
VTd	0.80	Clinical expert opinion
VCd	0.20	
[Placeholder 1]	–	N/A
[Placeholder 2]	–	N/A
Subsequent SCT		
Did not undergo HDT-SCT post-induction	0.19	Proportion who underwent SCT after VTd induction therapy in TA311 (2014)[8]
HDT-SCT post-induction	0.81	
Auto SCT	0.97	BSBMT (2017)[23]
All SCT	0.03	BSBMT (2017)[23]
Second line		
Vd	0.20	Clinical expert opinion
Kd	0.00	
DVd	0.80	
Rd	0.00	Clinical expert opinion
[Placeholder 1]	–	N/A
[Placeholder 2]	–	N/A
Subsequent SCT		
Did not receive a second HDT-SCT	0.91	BSBMT (2017)[23]
HDT-SCT post-second line therapy	0.09[a]	
Auto SCT	0.97	BSBMT (2017)[23]
All SCT	0.03	BSBMT (2017)[23]

Abbreviations: BSBMT: British Society of Blood and Marrow Transplantation; DVd: daratumumab, bortezomib and dexamethasone; HDT: high-dose therapy; Kd: carfilzomib and dexamethasone; N/A: not applicable; Rd: lenalidomide plus dexamethasone; SCT: stem cell transplant; VCd: bortezomib cyclophosphamide dexamethasone; Vd: bortezomib and dexamethasone; VTd: bortezomib, thalidomide and dexamethasone.

SCT-ineligible

The probabilities presented in Table 12 inform the likelihood of SCT-ineligible patients receiving particular myeloma treatments at first and second lines of therapy. The probabilities associated with second line therapies are conditional on patients reaching second line.

Table 12: Treatment probabilities for SCT ineligible patients

Treatment	Probability of receiving treatment	Source
First line		
VMP	0.62	NICE part-review of TA171 (bortezomib market share as a proxy for thalidomide intolerance)[14] Clinical expert opinion indicates CTD is used in place of MPT[15]
VCd	0.00	
CTd	0.38	
MPT	0.00	
Rd	0.00	Clinical expert opinion
[Placeholder 1]	–	N/A
[Placeholder 2]	–	N/A
Second line		

Vd	0.10	Clinical expert opinion
Kd	0.10	
DVd	0.80	
Rd	0.00	Clinical expert opinion
[Placeholder 1]	–	N/A
[Placeholder 2]	–	N/A

Abbreviations: CTd: cyclophosphamide, thalidomide and dexamethasone; DVd: daratumumab, bortezomib and dexamethasone; Kd: carfilzomib and dexamethasone; MPT: thalidomide, melphalan and prednisone; N/A: not applicable; NICE: National Institute for Health and Care Excellence; Rd: lenalidomide plus dexamethasone; VCd: bortezomib, cyclophosphamide and dexamethasone; Vd: bortezomib and dexamethasone; VMP: bortezomib, melphalan and prednisone.

Subsequent Lines (3+)

Clinicians confirmed that therapies for subsequent lines are common across both SCT-eligible and SCT-ineligible patients. The probabilities presented in Table 13 inform the likelihood of patients receiving particular subsequent-line (3+) myeloma treatments.

Table 13: Subsequent-line (3+) treatment probabilities

Treatment	Probability of receiving treatment			Source
	After DVd	After Vd	After Kd	
IRd	0.46	0.22	0.22	TA573[12] and clinical expert opinion[a]
Rd	0.20	0.10	0.10	
D	0.00	0.56	0.56	
Pd	0.35	0.12	0.12	
FVd	0.00	0.00	0.00	N/A
[Placeholder 1]	–	–	–	N/A
[Placeholder 2]	–	–	–	N/A

[a]Note that IRd and Rd are assumed to be used in a 70%:30% ratio.
Abbreviations: D: daratumumab monotherapy; DVd: daratumumab, bortezomib and dexamethasone; FVd: panobinostat, bortezomib and dexamethasone; IRd: ixazomib, lenalidomide and dexamethasone; Kd: carfilzomib and dexamethasone; N/A: not applicable; Pd: pomalidomide and dexamethasone; Rd: lenalidomide and dexamethasone; Vd: bortezomib and dexamethasone.

4.4.2.5 Complications

1. Patients with active myeloma (active treatment or end of life care as first line management)

The complications presented in Table 14 are based on the CRAB features reported in Howell et al. (2017) and have been validated by clinical expert opinion.[2]

Table 14: Proportion of patients experiencing CRAB features at diagnosis by referral route

Referral route	Hypercalcaemia	Renal insufficiency	Anaemia	Bone disease	Source
Emergency	0.19	0.38	0.55	0.75	Howell et al. (2017)[2]
TWW	0.10	0.06	0.37	0.84	
GP urgent referral	0.02	0.18	0.51	0.71	
GP routine check-up	0.11	0.07	0.43	0.68	
Consultant to consultant	0.18	0.32	0.54	0.75	

Abbreviations: GP: general practitioner; TWW: two-week wait.

2. Patients with smouldering myeloma (observation as first line management) who progress

It was assumed that the probability of experiencing complications following observation was independent of the route by which patients originally presented. Probabilities were based on the CRAB features reported for the whole patient cohort from Howell et al. (2017).[2]

Table 15: Proportion of patients experiencing CRAB features who progress following observation by referral route

Referral route	Hypercalcaemia	Renal insufficiency	Anaemia	Bone disease	Source
Emergency	0.13	0.25	0.49	0.75	Howell et al. (2017)[2]
TWW	0.13	0.25	0.49	0.75	
GP urgent referral	0.13	0.25	0.49	0.75	
GP routine check-up	0.13	0.25	0.49	0.75	
Consultant to consultant	0.13	0.25	0.49	0.75	

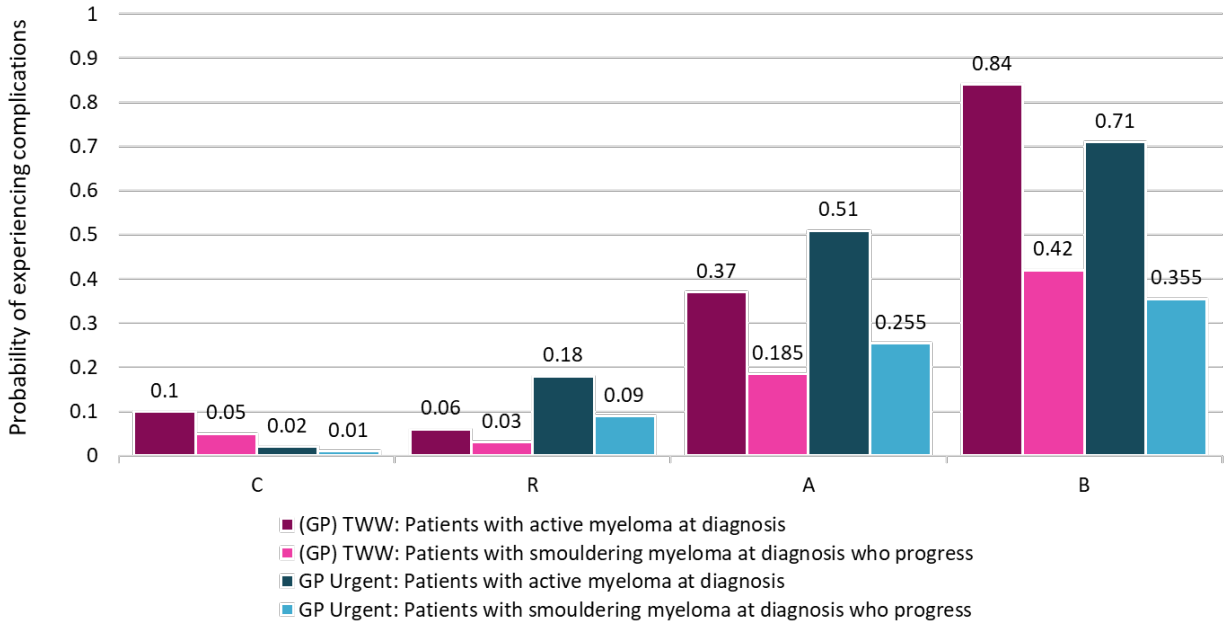
Abbreviations: GP: general practitioner; TWW: two-week wait.

The model includes the flexibility to modify the probability of experiencing complications for patients who initially receive observation as first-line management, but then progress to active myeloma and enter the active treatment pathway. Users can modify the proportion of complications avoided by patients who receive observation and then progress to active myeloma, which is assumed to apply equally across all four CRAB features and all routes of presentation i.e. if a value of 0.5 is selected then this will apply a 50% reduction in the proportion of patients with hypercalcemia, renal insufficiency, anaemia and bone disease, relative to the proportions currently applied for that route of presentation for patients with active myeloma at diagnosis, as shown in Figure 10. However, it may not be accurate to assume that early diagnosis (as would be the case with patients entering observation at first-line management) has the same impact on avoiding bone disease as avoiding anaemia, for example, and that it would have the same proportional impact across the routes of presentation. As such, a modification factor of 0 was used in the base case.

Table 16: Proportion of all complications avoided for patients who progress following observation

Parameter	Input	Source
Proportion of all complications avoided for patients who progress following observation	0.00	Assumption

Figure 10: Probability of experiencing complications for patients with active myeloma and patients with smouldering myeloma who progress (for a modification factor of 0.5)



Data presented for (GP) TWW and GP Urgent routes as examples. C, hypercalcemia; R, renal insufficiency; A, anaemia; B, bone disease.
Abbreviations: GP: general practitioner; TWW: two-week wait.

Hypercalcaemia

Management of hypercalcaemia was assumed to only be required for patients diagnosed with 'severe' hypercalcaemia. Within the economic model, where patients presenting with hypercalcaemia require treatment, patients are assumed to require intravenous (IV) fluids to manage the acute episode and then bisphosphonates for longer-term management.

Table 17: Probability of patients presenting with hypercalcaemia requiring treatment

Parameter	Probability	Source
Patients with hypercalcaemia requiring forced saline diuresis[a] and then drug therapy[b]	0.5	Assumption

[a]Note that patients receiving forced saline diuresis were assumed to receive normal saline for 1.5 hours intravenously followed by 40mg/hour frusemide intravenously.
[b]Note that drug therapy management of hypercalcaemia were assumed only to require a 30-60mg IV as a single infusion of bisphosphonate (e.g. pamidronate) lasting up to 4 hours.

Renal insufficiency

Evison et al. (2018) suggests that 3.4% of patients with newly-diagnosed myeloma require dialysis.[25] The proportion of patients presenting with renal complications who require dialysis was calculated based on the proportion of patients diagnosed via each route who presented with renal complications as per Howell et al. (2017),[2] such that the proportion of patients with newly-diagnosed myeloma modelled to require dialysis was 3.4% (see Table 18). The appropriateness of this figure has been validated by clinicians. Clinicians noted that between 3% and 4% of patients presenting with renal insufficiency would be expected to go onto long-term dialysis; 3.5% was used in the base case.

Table 18: Probability of requiring dialysis for patients with renal complications

Parameter	Proportion	Source
Patients with renal complications requiring dialysis	18.2%	Calculated such that the proportion of all patients requiring dialysis was 3.4%[a]
Proportion of all newly-diagnosed myeloma patients requiring dialysis	3.4%	Evison et al. (2018)[25]
Proportion of all newly-diagnosed myeloma patients presenting with renal complications	18.7%	Calculated based on routes of presentation and complication probabilities as per Howell et al. (2017)[2]
Patients with renal complications requiring dialysis	18.2%	Calculation (3.4%/18.7%)
Patients with renal complications requiring long-term dialysis	3.5%	Clinical expert opinion[b]

[a] Calculated such that the required proportion of all patients requiring dialysis is equivalent to the proportion reported in Evison et al. (2018) and shown in the row below.
[b] Clinicians noted that between 3% and 4% of patients presenting with renal insufficiency would be expected to go onto long-term dialysis; 3.5% was used in the base case.

Anaemia

Table 19 presents the likelihood of patients presenting with anaemia receiving treatment. The economic model assumed that patients presenting with anaemia receive one RBC blood transfusion.

Table 19: Probability of patients presenting with anaemia receiving interventions

Parameter	Probability (base case)	Source
Patients receiving erythropoietin	0.35	Clinical expert opinion[a]

Patients receiving one RBC blood transfusion[b]	0.05	Clinical expert opinion

[a]Note that clinicians estimated that between 30%-40% of patients presenting with anaemia would require erythropoietin. 35% was therefore used as a midpoint estimate in the model.
Abbreviations: RBC: red blood cell.

Bone disease

Ashcroft et al. (2018) report health care usage data for patients in the UK with bone lesions that were secondary to multiple myeloma.[26] It was assumed that the proportions of patients requiring treatment or experiencing skeletal-related events (SREs) in Ashcroft et al. (2018) can be applied to the patients presenting with bone disease via each route of presentation.

Clinicians confirmed that the following probability of patients receiving bisphosphonates due to bone disease would be appropriate for use within the economic model.

Table 20: Probability of patients presenting with bone disease receiving bisphosphonates

Parameter	Probability	Source
Patients presenting with bone disease receiving bisphosphonates	0.88	Ashcroft et al. (2018)[26] – proportion of UK patients with previous bisphosphate use and following diagnosis

Abbreviations: UK: United Kingdom.

Based on Ashcroft et al. (2018) and clinical expert opinion, the following distribution of bone disease-associated SREs were considered within the economic model.[26]

Table 21: Probability of SREs for patients presenting with bone disease at diagnosis

SRE	Probability of SREs	Source
Vertebral fracture	0.233	Ashcroft et al. (2018)[26] and clinical expert opinion
Non-vertebral fracture	0.163	
Radiation to bone	0.256	
Spinal cord compression	0.163	
Surgery to bone	0.186	

Abbreviations: SRE: skeletal-related event.

Based on Ashcroft et al. (2018) and clinical expert opinion, SREs were considered to occur at a rate of 2.6 per patient per year for patients who presented with bone disease at diagnosis.[26] A lower rate of SREs (0.4 per patient per year) was considered for patients with bone disease who progressed following observation, based on findings from Kim et al. (2019) and clinical expert opinion.[27] This study reports the incidence rate of SREs for patients with a baseline history of SREs (those who experienced SREs in the 12-month period prior to the diagnosis date through to 60 days on or after the diagnosis date) and for those without a baseline history of SREs.

It was assumed that patients in the model who present with bone disease at diagnosis have a "baseline history of SREs", whereas those who progress to active myeloma following a period of observation have "no baseline history" (since they were asymptomatic by definition at diagnosis). The rate of SREs for patients with bone disease who progressed following observation was calculated by applying the ratio between the rates reported for patients with no baseline history (n=21; 15.9 per 100 patient years) and patients with a baseline history (n=58; 103.2 per 100 patient years) to the rate reported in Ashcroft et al. (2018).

Table 22: Frequency of SREs for patients with bone disease

Parameter	Frequency	Source
Frequency of SREs per patient per year for patients presenting with bone disease at diagnosis	2.6	Ashcroft et al. (2018)[26]

Frequency of SREs per patient per year for patients with bone disease who progress following observation	0.4	Ratio between the rates reported for patients with and without baseline history of SREs in Kim et al. (2019)[27] applied to the rate from Ashcroft et al. (2018)[26]

Abbreviations: SRE: skeletal-related event.

4.4.2.6 Resource use (monitoring and laboratory tests)

Monitoring costs associated with treatment and follow-up have been included in the model. The frequency of laboratory tests and monitoring differs according to whether patients are on- or off-treatment, the line of therapy and the specific therapy received at each line. Laboratory tests and monitoring included items such as haematologist appointments, full blood counts, protein electrophoresis, liver function and renal function tests. The frequencies of such tests and monitoring were sourced from relevant NICE TAs for each therapy and applied for the duration of treatment-free or treatment intervals for the respective line of therapy as reported in Yong et al. (2016) (see Section 4.4.4) to calculate a total frequency across the model time horizon.[24] Where data were unavailable monitoring frequencies were assumed equivalent to the most similar alternative treatment option. A summary of the sources of different monitoring frequencies are presented in Table 23. Please see the model for individual frequencies.

Table 23: Summary of the sources of monitoring states and frequencies included in the model

Model state	Source / Assumption	
	Per week frequencies	Total duration
Off treatment		
Observation (i.e. patients with SMM)	TA573,[12] assumed equivalent to off-treatment frequencies	Monitoring was assumed to apply for the duration of time spent with SMM. This was estimated as the life years associated with SMM (see Section 4.4.5)
SCT-eligible patients: first, second and third-line treatment free intervals	Off-treatment frequencies derived from TA573[12]	The respective treatment-free intervals reported in Yong et al. (2016)[24] (see Table 43)
SCT-ineligible patients: first, second and third-line treatment free intervals		
First line		
SCT-eligible		
VTd	TA311[8]	Yong et al. (2016)[24] (see Table 43). Although treatment intervals were assumed to be the same for SCT-eligible and -ineligible patients (see Section 4.4.4), durations were applied independently so that total frequencies across the model time horizon update automatically should these durations be manually changed
VCd	In the absence of data, assumed equivalent to VTd (with the exception of tests for thalidomide-containing regimens only)[8]	
SCT-ineligible		
VCd	In the absence of data, assumed equivalent to VMP (as both contain bortezomib)[10]	Yong et al. (2016)[24] (see Table 43), applied independently for SCT-eligible and -ineligible patients
VMP	TA587[10]	
CTd	In the absence of data, assumed equivalent to MPT (as both contain thalidomide)[10]	
MPT	TA587[10]	

Rd	TA587[10]	
Second line		
SCT-eligible and -ineligible		
Vd	TA573[12]	Yong et al. (2016)[24] (see Table 43), applied independently for SCT-eligible and -ineligible patients
Kd		
DVd		
Rd	TA586[14]	
Subsequent (3+) lines		
SCT-eligible and -ineligible		
IRd	TA505[15]	Yong et al. (2016)[24] (see Table 43), applied independently for SCT-eligible and -ineligible patients
Rd	TA505[15]	
D	TA510[17] (these frequencies are the same as those used in TA573 and TA427)	
Pd		
FVd	TA380[19]	

Abbreviations: D: daratumumab monotherapy; DVd; daratumumab, bortezomib and dexamethasone; CTd: cyclophosphamide, thalidomide and dexamethasone; FVd: panobinostat, bortezomib and dexamethasone; IRd: ixazomib, lenalidomide and dexamethasone; Kd: carfilzomib and dexamethasone; MPT: thalidomide, melphalan and prednisone; Pd: pomalidomide and dexamethasone; Rd: lenalidomide and dexamethasone; SCT: stem cell transplant; SMM: smouldering myeloma; VCd: bortezomib, cyclophosphamide and dexamethasone; Vd: bortezomib and dexamethasone; VMP: bortezomib, melphalan and prednisone; VTd: bortexomib, thalidomide and dexamethasone.

4.4.2.7 Adverse events

In addition to disease-related complications, the economic model aimed to include any treatment-related AEs that represented a significant cost burden across treatment options. Clinical trial data or relevant data from prior TAs were identified to inform the cumulative probability of patients experiencing each AE for each treatment option at each line of therapy. It was assumed that patients did not experience treatment-related AEs when off-treatment. Where necessary, probabilities were adjusted to match the treatment durations used in the model to derive the treatment acquisition costs (see Section 4.4.3.1). As per the monitoring costs, AEs were applied independently for SCT-eligible and -ineligible patients even if the source of the probabilities was the same. Where data were unavailable, AE probabilities were assumed equivalent to the most similar alternative treatment option. A summary of these assumptions alongside the sources of different AEs are presented in Table 23. Please see the model for more details.

Table 24: Summary of the sources of AEs included in the model

Model state	Source / Assumption	
	AEs	Treatment duration adjustments
First line		
SCT-eligible		
VTd	GIMEMA trial, TA311[8]	No adjustment necessary, since the cumulative probability during the total treatment period was reported
VCd	In the absence of data, assumed equivalent to VTd[8]	
SCT-ineligible		
VCd	In the absence of data, assumed equivalent to VMP (as both contain bortezomib)[28]	Adjusted to match treatment duration observed in Yong el al. (2016)[24]
VMP	VISTA trial, Mateos et al. (2010)[28]	Adjusted to match the treatment duration recommended in the Velcade SPC[29]
CTd	In the absence of data, assumed equivalent to MPT (as both contain thalidomide)[30]	Adjusted to match the treatment duration recommended in the MMIX trial and TA228[9]
MPT	FIRST trial, Benboubker et al. (2014)[30]	Adjusted to match the treatment duration recommended in the Thalidomide SPC[31]

Rd		Adjusted to match the treatment duration recommended in the Revlimid SPC[32]
Second line		
SCT-eligible and -ineligible		
Vd	TA573[12]	No adjustment necessary, since the cumulative probability during the total treatment period was reported
Kd		
DVd		
Rd	TA586[14]	Adjusted to match treatment duration observed in Yong el al. (2016)[24]
Subsequent (3+) lines		
SCT-eligible and -ineligible		
IRd	TA505[15]	Adjusted to match treatment duration observed in Yong el al. (2016)[24]
Rd		
D	MMY002 trial,[33] TA505[15]	
Pd	MM-003 trial,[34] TA505[15]	
FVd	PANORAMA 2 trial,[35] TA505[15]	

Abbreviations: D: daratumumab monotherapy; DVd; daratumumab, bortezomib and dexamethasone; CTd: cyclophosphamide, thalidomide and dexamethasone; FVd: panobinostat, bortezomib and dexamethasone; IRd: ixazomib, lenalidomide and dexamethasone; Kd: carfilzomib and dexamethasone; MPT: thalidomide, melphalan and prednisone; Pd: pomalidomide and dexamethasone; Rd: lenalidomide and dexamethasone; SCT: stem cell transplant; SMM: smouldering myeloma; SPC: Summary of Product Characteristics; VCd: bortezomib, cyclophosphamide and dexamethasone; Vd: bortezomib and dexamethasone; VMP: bortezomib, melphalan and prednisone; VTd: bortexomib, thalidomide and dexamethasone.

Given that some of the included events (e.g. anaemia) could be related to either the underlying disease or result from treatment, it is possible that inclusion of these events as both complications and AEs could result in double-counting. However, these events are costed differently depending on their modelled cause; the management of disease-related complications at presentation is associated with higher costs (see Section 4.4.3).

4.4.2.8 End of life care

End of life care was broken down by either care provided in a hospital, hospice, nursing home or at home. A study by Howell et al. (2013) highlights that patients with haematological malignancies such as myeloma are more likely to die in hospital than patients with other types of cancer.[36] The study also found that the likelihood of dying in hospital is dependent on the time from diagnosis to death. As such, the probabilities of patients dying in each setting differ according to patients first-line management as reported in Howell et al. (2017).[2]

Patients receiving observation or chemotherapy/radiotherapy as first-line management

For patients receiving observation or chemotherapy/radiotherapy as first-line management, the probability of receiving end of life care in different settings is assumed to be approximately equal to the probabilities for all myeloma patients, as reported in Howell et al. (2013).[36]

Table 25: Probability of receiving end of life care in a particular setting: patients receiving observation of chemotherapy/radiotherapy as first-line management

Setting	Proportion of patients	Source
End of life care in hospital	0.645	Howell et al. (2013)[36]
End of life care in hospice	0.078	
End of life care in nursing home	0.120	
End of life care at home	0.157	

Patients receiving end of life care as first-line management

Patients who receive end of life care as first-line management are assumed to have an average life expectancy of 3 months following diagnosis. As such, the probability of dying in hospital is increased.

Table 26: Probability of receiving end of life care in a particular setting: patients receiving end of life care as first-line management

Setting	Proportion of patients[a]	Source
End of life care in hospital	0.800	Howell et al. (2013)[36]
End of life care in hospice	0.045	
End of life care in nursing home	0.065	
End of life care at home	0.091	

[a] These proportions are based on the risk of hospital versus non-hospital deaths across all malignancies for patients with a time from diagnosis to death of 0–3 months.

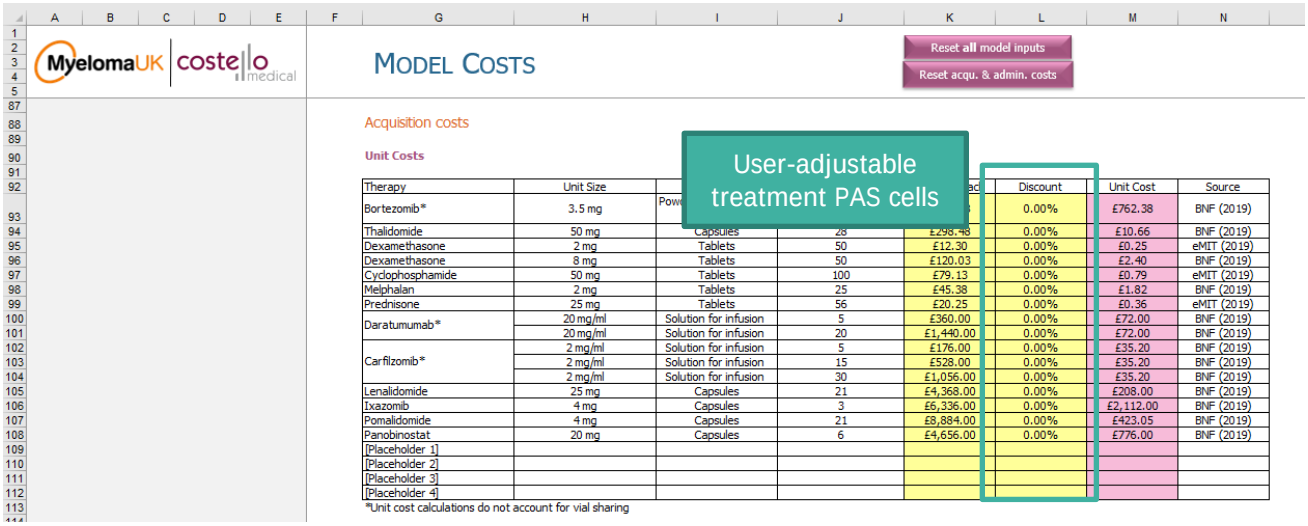
4.4.3 Cost inputs

Below is a description of the cost sources that were included in the economic model. Treatment acquisition costs, costs for SCT, administration costs, monitoring costs, costs associated with complications, adverse event and end of life costs are all shown below.

4.4.3.1 Treatment acquisition costs

Costs for treatments were taken from the BNF or electronic market information tool (eMIT).[4, 37] In some instances, drugs may have a confidential Patient Access Scheme (PAS) discount, and, although no discounts were applied to drug costs in the base case, the option to apply a simple discount to the list price was included as a user-adjustable input for every drug in the user-adjustable cells on the 'Drug Acqu. & Admin. Costs' worksheet (the yellow-highlighted cells under the 'Discount' heading in column L of the economic model, as shown in Figure 11 below). Drug acquisition unit cost calculations do not account for vial sharing.

Figure 11: Drug Acquisition Costs: As Seen in the Economic Model



The treatment acquisition unit costs adopted in the model are provided in Table 27 below.

Table 27: Unit costs

Therapy	Unit Size	Formulation	Pack Size	Cost per Pack	Source
Bortezomib*	3.5 mg	Powder for solution for injection	1	£762.38	BNF (2019)[4]
Thalidomide	50 mg	Capsules	28	£298.48	BNF (2019)[4]

Dexamethasone	2 mg	Tablets	50	£12.30	eMIT (2019)[37]
Dexamethasone	8 mg	Tablets	50	£120.03	BNF (2019)[4]
Cyclophosphamide	50 mg	Tablets	100	£79.13	eMIT (2019)[37]
Melphalan	2 mg	Tablets	25	£45.38	BNF (2019)[4]
Prednisone	25 mg	Tablets	56	£20.25	eMIT (2019)[37]
Daratumumab*	20 mg/ml	Solution for infusion	5	£360.00	BNF (2019)[4]
	20 mg/ml	Solution for infusion	20	£1,440.00	BNF (2019)[4]
Carfilzomib*	2 mg/ml	Solution for infusion	5	£176.00	BNF (2019)[4]
	2 mg/ml	Solution for infusion	15	£528.00	BNF (2019)[4]
	2 mg/ml	Solution for infusion	30	£1,056.00	BNF (2019)[4]
Lenalidomide	25 mg	Capsules	21	£4,368.00	BNF (2019)[4]
Ixazomib	4 mg	Capsules	3	£6,336.00	BNF (2019)[4]
Pomalidomide	4 mg	Capsules	21	£8,884.00	BNF (2019)[4]
Panobinostat	20 mg	Capsules	6	£4,656.00	BNF (2019)[4]

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool.

For treatment doses dependent on patient weight and/or body surface area (BSA), acquisition costs were calculated based on average dose requirements of the population under evaluation in the model (see Table 2). All dosing regimens used to calculate acquisition costs aimed to reflect those used in the clinical trials and align with the relevant summary of product characteristics (SPC).[37] The drug dosing regimens identified from the clinical trials are presented in Table 28 below.

Table 28: Drug dosing regimens

Treatment	Component	Dose	Dosing schedule per cycle	Cycle length	Number of cycles	Source
First line therapies for SCT-eligible patients						
VTd (induction)	Bortezomib	1.3 mg/m^2	Days 1,4,8,11	28 days	4	Velcade SPC,[29] GIMEMA trial, TA311[8]
	Thalidomide	Weeks 1-2: 50 mg Weeks 3-4: 100 mg Cycle 2: 200 mg	QD	28 days	4	
	Dexamethasone	40 mg	Days 1,2,4,5,8,9,11,12	28 days	4	
VCd (induction)	Bortezomib	1.3 mg/m^2	Days 1,4,8,11	21 days	4	EMN-02 trial, Cavo (2015)[38]
	Cyclophosphamide	500 mg/m^2	Days 1 and 8	21 days	4	
	Dexamethasone	40 mg	Days 1,2,4,5,8,9,11,12	21 days	4	
First line therapies for SCT-ineligible patients						
VCd	Bortezomib	1.3 mg/m^2	Days 1,8,15	28 days	Until progression	Jimenez Zepeda (2014)[39]
	Cyclophosphamide	300 mg/m^2	Days 1,8,15	28 days	Until progression	
	Dexamethasone	20-40mg	QW	28 days	Until progression	
VMP	Bortezomib	1.3 mg/m^2	Cycles 1-4: 1,4,8,11,22,25,29,32; Cycles 5-9: 1,8,22,29	6 weeks	9	Velcade SPC,[29] VISTA trial, Mateos (2010),[28] TA228[9]
	Melphalan	9 mg/m^2	QD on days 1-4	6 weeks	9	
	Prednisone	60 mg/m^2	QD on days 1-4	6 weeks	9	
CTd	Cyclophosphamide	500 mg	QW	28 days	9	Myeloma IX trial, Morgan (2011),[40] TA228[9]
	Thalidomide	Cycle 1: 50 mg Cycle 2: 100 mg Cycle 3+: 150 mg	QD	28 days	9	
	Dexamethasone (attenuated)	20mg	QD for 4 days	28 days	9	
MPT	Melphalan	9 mg/m^2	Days 1-4	6 weeks	8	Thalidomide SPC,[31] TA228[9]
	Prednisone	60 mg/m^2	Days 1-4	6 weeks	8	
	Thalidomide	150mg	QD	6 weeks	8	
Rd	Lenalidomide	25 mg	QD for 3 weeks	28 days	Until progression	Revlimid SPC[32]
	Dexamethasone	40 mg	Days 1,8,15,22	28 days	Until progression	
Second line therapies for SCT-eligible patients						
Vd	Bortezomib	1.3 mg/m^2	Days 1,4,8,11	21 days	8	Velcade SPC[29]
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	21 days	8	

Kd	Carfilzomib	Cycle 1, days 1,2: 20 mg/m^2 Otherwise 56 mg/m^2	Days 1,2,4,5,8,9,11,12	28 days	Until progression	Kyprolis SPC[41]
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	28 days	Until progression	
DVd	Daratumumab	16 mg/kg	Cycles 1-3: QW Cycles 4-8: once per cycle Cycles 9+: once per cycle	Cycles 1-8: 21 days Cycles 9+: 28 days	Until progression	Darzalex SPC[42]
	Bortezomib	1.3 mg/m^2	Days 1,4,8,11	Cycles 1-8: 21 days	8	
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	Cycles 1-8: 21 days	8	
Rd	Lenalidomide	25 mg	QD for 3 weeks	28 days	Until progression	Revlimid SPC[32]
	Dexamethasone	40 mg	Cycles 1-4: Days 1,2,3,4,9,10,11,12,17,18,19, 20 Cycles 5+: Days 1,2,3,4	28 days	Until progression	
Second line therapies for SCT-ineligible patients						
Vd	Bortezomib	1.3 mg/m^2	Days 1,4,8,11	21 days	8	Velcade SPC[29]
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	21 days	8	
Kd	Carfilzomib	Cycle 1, days 1,2: 20 mg/m^2 Otherwise 56 mg/m^2	Days 1,2,4,5,8,9,11,12	28 days	Until progression	Kyprolis SPC[41]
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	28 days	Until progression	
DVd	Daratumumab	16 mg/kg	Cycles 1-3: QW Cycles 4-8: once per cycle Cycles 9+: once per cycle	Cycles 1-8: 21 days Cycles 9+: 28 days	Until progression	Darzalex SPC[42]
	Bortezomib	1.3 mg/m^2	Days 1,4,8,11	Cycles 1-8: 21 days	8	
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	Cycles 1-8: 21 days	8	
Rd	Lenalidomide	25 mg	QD for 3 weeks	28 days	Until progression	Revlimid SmPC[42]

	Dexamethasone	40 mg	Cycles 1-4: Days 1,2,3,4,9,10,11,12,17,18,19, 20 Cycles 5+: Days 1,2,3,4	28 days	Until progression	
Subsequent (3+) line therapies for SCT-eligible patients						
IRd	Ixazomib	4 mg	QW for 3 weeks	28 days	Until progression	Ninlaro SPC[43]
	Lenalidomide	25 mg	QD for 3 weeks	28 days	Until progression	
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	28 days	Until progression	
Rd	Lenalidomide	25 mg	QD for 3 weeks	28 days	Until progression	Revlimid SPC[42]
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	28 days	Until progression	
D	Daratumumab	16 mg/kg	Cycles 1-2: QW Cycles 3-6: Every 2 weeks Cycles 7+: once per cycle	28 days	Until progression	Darzalex SPC[42]
Pd	Pomalidomide	4 mg	QD for 3 weeks	28 days	Until progression	Imnovid SPC[44]
	Dexamethasone	40 mg	Days 1,2,4,5,8,9,11,12	28 days	Until progression	
FVd	Panobinostat	20 mg	3 times weekly for 2 weeks	21 days	Until progression	Farydak SPC[45]
	Bortezomib	1.3 mg/m^2	Days 1,4,8,11	21 days	Until progression	
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	21 days	Until progression	
Subsequent (3+) line therapies for SCT-ineligible patients						
IRd	Ixazomib	4 mg	QW for 3 weeks	28 days	Until progression	Ninlaro SPC[43]
	Lenalidomide	25 mg	QD for 3 weeks	28 days	Until progression	
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	28 days	Until progression	
Rd	Lenalidomide	25 mg	QD for 3 weeks	28 days	Until progression	Revlimid SPC[42]
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	28 days	Until progression	
D	Daratumumab	16 mg/kg	Cycles 1-2: QW Cycles 3-6: Every 2 weeks Cycles 7+: once per cycle	28 days	Until progression	Darzalex SPC[42]
Pd	Pomalidomide	4 mg	QD for 3 weeks	28 days	Until progression	Imnovid SPC[44]
	Dexamethasone	40 mg	Days 1,2,4,5,8,9,11,12	28 days	Until progression	
FVd	Panobinostat	20 mg	3 times weekly for 2 weeks	21 days	Until progression	Farydak SPC[45]
	Bortezomib	1.3 mg/m^2	Days 1,4,8,11	21 days	Until progression	
	Dexamethasone	20 mg	Days 1,2,4,5,8,9,11,12	21 days	Until progression	

Abbreviations: CTd: cyclophosphamide, thalidomide and dexamethasone; D: daratumumab monotherapy; DVd: daratumumab, bortezomib and dexamethasone; FVd: panobinostat, bortezomib and dexamethasone; IRd: ixazomib, lenalidomide and dexamethasone; Kd: carfilzomib and dexamethasone; MPT: thalidomide, melphalan and prednisone; Pd: pomalidomide and dexamethasone; QD:

once a day; QW: once a week; Rd: lenalidomide and dexamethasone; SCT: stem cell transplant; SPC: Summary of Product Characteristics; VCd: bortezomib, cyclophosphamide and dexamethasone; Vd: bortezomib and dexamethasone; VMP: bortezomib, melphalan and prednisone; VTd: bortezomib, thalidomide and dexamethasone;

4.4.3.2 Costs for SCT

Costs for SCT align with those used in TA311 and were applied to the proportion of patients that receive SCT as part of the costs incurred in the decision tree.[8] Relevant unit cost and administration costs relating to mobilisation, harvest, ablation, transplant and post-transplant were incurred per patient receiving SCT and relevant costs were sourced from BNF, eMIT and NHS Reference Costs 2017–2018.[4, 5, 37] These costs are presented in Table 29 below.

Table 29: SCT cost calculations

Description	Intervention	Unit Cost	Source / assumption	Cost per transplant	Administration Cost	Source / assumption
Mobilisation	Cyclophosphamide (1.5 g/m^2 BSA)	£13.47	eMIT (1g powder for solution for injection, DHA014).[37] 1.73 m^2 BSA, 2.60 g per patient i.e. 3 x 1 g vials	£40.41	£247.74	NHS Reference Costs 2017–2018; SB12Z DCRDN, Deliver simple parenteral chemotherapy at first attendance, NHS Reference Costs 2017–18[5]
	G-CSF: Lenograstim 19.2 MU/m^2 daily	£62.54	BNF 2019 (1 vial of 33.6 MU).[4] 1.73 m^2 BSA. Duration ranged from 5 days to until neutrophil count stable	£62.54	N/A	Assume G-CSF given with cyclophosphamide, so no additional administration cost
Harvest	Peripheral blood stem cell harvest	N/A	N/A	N/A	£1,435.16	NHS Reference Costs 2017–2018; SA34Z DC, Peripheral blood stem cell harvest, NHS Reference Costs 2017–18[5]
Ablation	High dose melphalan 200 mg/m^2 (75%)	£137.37	BNF 2019 (50 mg powder for solution for injection).[4] Assume 1.73 m^2 BSA.	£892.91	£247.74	NHS Reference Costs 2017–2018; SB12Z DCRDN, NHS Reference Costs 2017–18[5]
	Immediate dose melphalan 140 mg/m^2 (25%)	£137.37			N/A	N/A
Transplant	Auto	N/A	N/A	N/A	£18,520.20	NHS Reference Costs 2017–2018; SA26A EL, Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over, NHS Reference Costs 2017–18[5]

	Allo	N/A	N/A	N/A	£26,739.65	NHS Reference Costs 2017–2018; SA27A, Peripheral Blood Stem Cell Transplant, Syngeneic, 19 years and over, NHS Reference Costs 2017–18[5]
Post-transplant	G-CSF: Lenograstim 19.2 MU/m^2 daily	£62.54	BNF 2019 (1 vial of 33.6 MU).[4] Assume 14 days of lenograstim use.	£875.56	N/A	N/A

Abbreviations: BNF: British National Formulary; BSA: body surface area; eMIT: electronic market information tool; G-CSF: granulocyte colony-stimulating factor; N/A: not applicable; NHS: National Health Service.

4.4.3.3 Administration costs

Both first- and subsequent-line (3+) therapies incurred administration costs which were sourced from NHS Reference Costs 2017–2018.[5] A one-off administration cost was applied on treatment initiation for regimens containing an oral therapy and ongoing per-administration costs were applied to regimens requiring infusions/injections. A summary of the administration costs associated with each therapy and adopted in the economic model are provided in Table 30 below.

Table 30: Administration costs

Therapy	Parameter	Cost	Details/code	Source/ justification
Bortezomib (SC)	Administration	£89.16	Specialist nursing, cancer related, adult, face to face (N10AF)	NHS Reference Costs 2017–18,[5] based on TA573[12]
Carfilzomib	Administration	£233.23	Deliver subsequent elements of a chemotherapy cycle (SB15Z Outpatient)	
Daratumumab	First administration	£375.52	Deliver complex chemotherapy, including prolonged infusion, at first attendance (SB14Z DCRDN)	
	Subsequent administration	£233.23	Deliver subsequent elements of a chemotherapy cycle (SB15Z Outpatient)	
	Blood sample (prior to first administration)	£3.10	-	
Thalidomide	Oral drug initiation	£131.61	Deliver exclusively oral chemotherapy (SB11Z Outpatient)	
Cyclophosphamide				
Melphalan				
Lenalidomide				
Ixazomib				
Pomalidomide				
Panobinostat				
Dexamethasone	No cost (not chemotherapy)	N/A	N/A	N/A
Prednisone				

Abbreviations: N/A: not applicable; NHS: National Health Service; SC: subcutaneous.

4.4.3.4 Monitoring costs

In addition to treatment acquisition and administration costs, monitoring costs associated with treatment and follow-up were included in the model. Unit costs were sourced from NHS Reference Costs 2017–2018.[5] These costs were applied in the model as described in Section 4.4.2.6, based on the frequencies reported in the 'Resource Use' worksheet of the economic model. The unit cost of each monitoring resource use element is provided in Table 31 below.

Table 31: Monitoring unit costs (NHS Reference Costs 2017–2018)

Laboratory test or monitoring	Unit cost	NHS Reference Cost Code
Bacterial investigation	£7.59	DAPS07: Microbiology
Biochemistry	£1.11	DAPS04: Clinical biochemistry
Blood testing-blood type	£2.51	DAPS05: Haematology
Blood testing-chemistry panel	£1.11	DAPS04: Clinical Biochemistry
Blood testing-FREELITE® test	£6.37	DAPS06: Immunology
Blood testing-haematology	£2.51	DAPS05: Haematology
Blood testing-immunofixation	£6.37	DAPS06: Immunology
Blood testing-serum protein electrophoresis	£1.11	DAPS04: Clinical Biochemistry
Bone densitometry	£77.45	RA50Z: Outpatient. Dexa Scan
Bone marrow aspirate	£495.98	SA33Z: Diagnostic Bone Marrow Extraction
Bone marrow trephine biopsy	£32.75	DAPS02: Histopathology and histology
Bone testing – X-rays	£77.45	RA50Z: Outpatient. Dexa Scan
Calcium	£1.11	DAPS04: Clinical biochemistry
Clotting	£2.51	DAPS05: Haematology
C-reactive protein	£6.37	DAPS06: Immunology
Creatine-clearance	£1.11	DAPS04: Clinical biochemistry
Erythrocyte sedimentation rate	£1.11	DAPS04: Clinical biochemistry
Full blood count	£2.51	DAPS05: Haematology
Haematologist appointment	£164.80	WF01A: Consultant led. Face-to-face follow-up attendance. Clinical haematology (303)
Immunofixation	£6.37	DAPS06: Immunology
Immunoglobulin	£1.11	DAPS04: Clinical biochemistry
International normalized ratio	£2.51	DAPS05: Haematology
Lactate dehydrogenase	£1.11	DAPS04: Clinical biochemistry
Liver function test	£1.11	DAPS04: Clinical biochemistry
Magnetic resonance imaging	£202.64	RA05Z: Outpatient. MRI scan of two or three areas with contrast.
Neuropathy	£1.11	DAPS04: Clinical biochemistry
Paraprotein measurements	£1.11	DAPS04: Clinical biochemistry
Plasma viscosity	£2.51	DAPS05: Haematology
Platelet Transfusion	£185.86	NHS Blood and DTS Pricing Proposals for 2017/18
Protein electrophoresis	£1.11	DAPS04: Clinical biochemistry
RBC Transfusion	£124.46	NHS Blood and DTS Pricing Proposals for 2017/18
Renal function test	£1.11	DAPS04: Clinical biochemistry
Serum albumin	£1.11	DAPS04: Clinical biochemistry
Serum B2 microglobulin	£1.11	DAPS04: Clinical biochemistry
Serum Erythropoietin level	£1.11	DAPS04: Clinical biochemistry
Serum free light chains	£1.11	DAPS04: Clinical biochemistry
Serum lactate dehydrogenase	£1.11	DAPS04: Clinical biochemistry
Skeletal Survey by X-Ray	£188.91	DAPF: Direct access plain film (six sites assumed)
Skeletal Survey by X-Ray individual sites	£31.49	DAPF: Direct access plain film
Thyroid function test	£1.11	DAPS04: Clinical biochemistry

Total urine protein	£1.11	DAPS04: Clinical biochemistry
Uric acid	£1.11	DAPS04: Clinical biochemistry
Urinalysis	£1.11	DAPS04: Clinical biochemistry
24-hour urine measurement	£1.11	DAPS04: Clinical biochemistry
24-hour urine for creatinine	£1.11	DAPS04: Clinical biochemistry
Urine immunofixation	£6.37	DAPS06: Immunology
Urine protein electrophoresis/light chains	£1.11	DAPS04: Clinical biochemistry

4.4.3.5 Complications

Additional healthcare costs were applied to patients presenting with CRAB complications; hypercalcaemia, renal insufficiency, anaemia and bone disease.

Severe hypercalcaemia

For patients diagnosed as having 'severe' hypercalcaemia, patients receive IV fluids to manage the acute episode and then bisphosphonates for longer-term management. The following one-off costs were applied.

Table 32: Drug costs

Drug	Dose	Source	Unit cost	Source
Sodium chloride solution for infusion	0.9% sodium chloride 2-4 L / 24h; one 2L bag	SPC for Sodium Chloride 0.9% Intravenous Infusion BP	£4.92	BNF (2019); Intraven sodium chloride 0.9% infusion 2litre bags[4]
Zoledronic acid	Single dose of 4 mg zoledronic acid	SPC for Zoledronic Acid 4 mg/100 ml solution for infusion	£3.44	eMIT (2019); Zoledronic Acid 4 mg/100 ml solution for infusion bags[37]

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; SPC: Summary of Product Characteristics.

Table 33: Resource use costs

Complication	Unit cost	Source
Severe hypercalcaemia	£4,196.31	NHS Reference Costs 2017–2018; Weighted average of KC05G-H: Fluid or Electrolyte Disorders, with interventions[5]

Abbreviations: NHS: National Health Service.

Renal insufficiency

The following complication management costs were incurred by patients presenting with renal insufficiency. A one-off "Dialysis for renal insufficiency" cost was applied to the proportion of patients with renal complications who require dialysis as reported in Table 18. For the proportion of patients requiring long-term dialysis (as reported in Table 18), patients were assumed to receive dialysis 3 days a week until death.[46] For patients with active treatment as first-line management, the "Long-term dialysis cost" was therefore applied 3 times a week for a weighted average of the total disease durations for SCT-eligible and -ineligible patients reported in Table 44. For patients with end of life care as first-line management, the "Long-term dialysis cost" was applied 3 times a week until death (i.e. for three months). Due to a lack of data, it was assumed that the probability of having renal insufficiency and requiring long-term dialysis does not differ between patients who are SCT-eligible, SCT-ineligible, or receiving end of life care as first line management.

Table 34: Resource use costs

Complication	Unit cost	Source

Dialysis for renal insufficiency	£271.06	NHS Reference Costs 2017–2018; LE01A: Haemodialysis for Acute Kidney Injury, 19 years and over[5]
Long-term dialysis	£151.44	NHS Reference Costs 2017–2018; LD01A: Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over[5]

Abbreviations: NHS: National Health Service.

Anaemia

The following costs were applied to patients presenting with anaemia.

Table 35: Drug costs

Drug	Dose	Source	Unit cost	Source
Erythropoietin	150 units/kg subcutaneously, 3 times per week, for 12 weeks	Epoetin Alfa Hexal SPC,[47] NICE TA323[48]	£33.18	BNF (2019): Eprex 1,000units/0.5ml solution for injection pre-filled syringes[4]
Anaemia patients receiving one RBC blood transfusion	N/A	N/A	£124.46	NHSBT Pricing Proposals for 2018–19[49]

Abbreviations: BNF: British National Formulary; NHSBT: National Health Service Blood and Transplant; NICE: National Institute for Health and Care Excellence; RBC: red blood cell; SmPC: Summary of Product Characteristics.

Table 36: Resource use costs

	Unit cost	Source
Anaemia	£1,077.36	NHS Reference Costs 2017–2018; Weighted average of SA08G-J: Other Haematological or Splenic Disorders[5]
Blood transfusion	£501.74	NHS Reference Costs 2017–2018; SA44A: Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over[5]

Abbreviations: NHS: National Health Service.

Bone disease

Patients presenting with bone disease incur the following bisphosphonate cost for the duration of treatment for bone disease.

Table 37: Drug costs

Drug	Dose	Source	Unit cost	Source
Zoledronic acid	4 mg zoledronic acid every 3 to 4 weeks	Zometa SPC[50]	£3.44	eMIT (2019); Zoledronic Acid 4 mg/100 ml solution for infusion bags[4]

Abbreviations: eMIT: electronic market information tool; NICE: National Institute for Health and Care Excellence: SmPC: Summary of Product Characteristics.

Patients presenting with bone disease were assumed to be treated in either an inpatient and/or outpatient setting in the economic model. Non-elective inpatient costs were sourced from the NHS Reference Costs 2017–2018, and are associated with a corresponding non-elective duration of stay. The inpatient costs used in the model were calculated by adjusting the identified inpatient costs based on the duration of inpatient stay as reported in Ashcroft et al. (2018), as shown in Table 38.[26] For patients receiving active treatment as first-line management, these costs were applied assuming 2.6 events per patient per year for a weighted average of the total disease durations for SCT-eligible and SCT-ineligible patients reported in Table 44. For patients with end of life care as first-line management, these costs were applied assuming 2.6 events per patient per year until death (i.e. for three months). For patients with observation as first-line management, these costs were applied assuming 0.4 events per patient per year following progression until death.

Table 38: Inpatient costs for SREs

SRE	Proportion of SREs requiring at least one inpatient stay	Duration of inpatient stay (mean)[a] (days)	Source	Non-elective inpatient cost	Non-elective duration of stay corresponding to the inpatient cost	Source (non-elective duration and cost)	Total cost per event
Vertebral fracture	40.0%	21.9	Ashcroft et al. (2018)[26]	£3,687.99	8.71	NHS Reference Costs 2017–2018; Weighted average of HD39D-H: Pathological Fractures[5]	£9,268.80
Non-vertebral fracture	57.1%	18.7		£3,687.99	8.71	NHS Reference Costs 2017–2018; Weighted average of HD39D-H: Pathological Fractures[5]	£7,914.45
Radiation to bone	9.1%	15.9		£6,437.41	N/A[b]	NHS Reference Costs 2017–2018; SC97Z: Same Day Radiotherapy Admission or Attendance (excluding Brachytherapy)[5]	£6,437.41
Spinal cord compression	74.4%	40.5		£5,098.13	10.89	NHS Reference Costs 2017–2018; Weighted average of HC30D-E: Spinal Tumours[5]	£18,954.67
Surgery to bone	50.0%	14.6		£3,893.92	8.16	NHS Reference Costs 2017–2018; Weighted average of HD40D-H: Malignancy, of Bone or Connective Tissue[5]	£6,971.18

[a]Duration of inpatient stay for each SRE was only reported pooled across a number of countries. An overall mean duration of inpatient stay was reported for the UK. The mean durations of inpatient stay for each SRE were adjusted by a common factor such that the overall mean was equal to that reported for the UK. [b]The cost for radiation to bone is a cost per event, so no adjustment was required.
Abbreviations: NHS: National Health Service; SRE: skeletal-related event.

The cost of an outpatient visit (as shown in Table 39) was assumed not to differ according to the SRE experienced. The total cost per event was calculated based on the mean number of visits required for each SRE reported in Ashcroft et al. (2018).[26] In the same manner as inpatient costs, for patients receiving active treatment as first-line management, these costs were applied assuming 2.6 events per patient per year for a weighted average of the total disease durations for SCT-eligible and SCT-ineligible patients reported in Table 44. For patients with end of life care as first-line management, these costs were applied assuming 2.6 events per patient per year until death (i.e. for three months). For patients with observation as first-line management, these costs were applied assuming 0.4 events per patient per year following progression until death.

Table 39: Outpatient appointment for SREs

	Cost per visit	Source
Outpatient appointment for SREs	£249.25	NHS Reference Costs 2017–2018; Consultant led outpatient attendance. Palliative Medicine (315)[5]

Abbreviations: NHS: National Health Service; SRE: skeletal related event.

Table 40: Outpatient visits required for SREs

SRE	Proportion of SREs requiring outpatient visit	Mean number of outpatient visits	Source	Total cost per event
Vertebral fracture	70.0%	2.5	Ashcroft et al. (2018)[26]	£623.12
Non-vertebral fracture	42.9%	1.9		£473.57
Radiation to bone	81.8%	1.5		£373.87
Spinal cord compression	42.9%	0.4		£99.70
Surgery to bone	50.0%	1.0		£249.25

Abbreviations: SRE: skeletal-related event.

4.4.3.6 AE costs

Costs associated with treatment-related adverse events were included in the economic model. These costs were applied in the model as described in Section 4.4.2.7, based on the frequencies reported in the 'AEs' worksheet of the economic model. These costs have been updated based on the most recent NHS Reference Costs 2017–2018 and are presented in Table 41 below.[5]

Table 41: AE unit costs

Adverse Event	Unit cost	NHS Reference Cost Code
Abdominal Pain	£645.12	FD05B: Abdominal Pain without interventions
Anaemia	£1,077.36	Weighted average of SA08G-J: Other Haematological or Splenic Disorders
Arterial embolism	£159.65	OPATT 303: Clinical Haematology
Asthenia	£163.58	OPATT 300: General Medicine
Back pain	£1,345.68	Weighted average of HC32H-K: Low Back Pain without Interventions
Cardiac failure	£1,979.71	Weighted average of EB03A-E: Heart Failure or Shock
Cataract	£893.74	Weighted average of BZ24E-G: Non-Surgical Ophthalmology without Intervention
Constipation	£149.00	OPATT 301: Gastroenterology
Deep-vein thrombosis	£159.65	OPATT 303: Clinical Haematology
Diarrhoea	£149.00	OPATT 301: Gastroenterology
Dyspnoea	£591.49	Weighted average of DZ19L-N: Other Respiratory Disorders without Interventions

Fatigue	£163.58	OPATT 300: General Medicine
Flatulence	£0.00	Assumed
Herpes Zoster	£163.58	OPATT 300: General Medicine
Hypercalcaemia	£1,362.12	Weighted average of KC05J-N: Fluid or Electrolyte Disorders, without interventions
Hyperglycaemia	£1,578.58	Weighted average of KB02G-K: Diabetes with Hyperglycaemic Disorders
Hypertension	£659.00	EB04Z: Hypertension
Hypocalcaemia	£1,362.12	Weighted average of KC05J-N: Fluid or Electrolyte Disorders, without interventions
Hypokalaemia	£1,362.12	Weighted average of KC05J-N: Fluid or Electrolyte Disorders, without interventions
Hypophosphatemia	£1,362.12	Weighted average of KC05J-N: Fluid or Electrolyte Disorders, without interventions
Ischaemic heart disease	£987.76	Weighted average of AA29C-F: Transient Ischaemic Attack
Leukopenia	£1,077.36	Weighted average of SA08G-J: Other Haematological or Splenic Disorders
Lymphopenia	£1,077.36	Weighted average of SA08G-J: Other Haematological or Splenic Disorders
Nausea	£163.58	OPATT 300: General Medicine
Neutropenia	£1,077.36	Weighted average of SA08G-J: Other Haematological or Splenic Disorders
Peripheral neuropathy - incl. motor, sensory and polyneuropathy	£167.23	OPATT 400: Neurology
Pneumonia	£1,633.55	Weighted average of DZ11R-V: Lobar, Atypical or Viral Pneumonia, without Interventions and DZ23L-N: Bronchopneumonia without Interventions
Pulmonary embolism	£1,318.38	Weighted average of DZ09L-Q: Pulmonary Embolus without Interventions
Pyrexia	£862.40	Weighted average of WJ07C: Fever of Unknown Origin without Interventions
Rash	£163.58	OPATT 300: General Medicine
Renal failure	£1,586.54	Weighted average of LA07L-P: Acute Kidney Injury without Interventions
Respiratory failure	£1,518.16	Weighted average of DZ27S-U: Respiratory Failure without Interventions
Respiratory tract infection	£157.98	OPATT 340: Respiratory Medicine
Septic shock	£1,838.89	Weighted average of WJ06G-J: Sepsis without Interventions
Thrombocytopenia	£640.09	Weighted average of SA12G-K: Thrombocytopenia
Vomiting	£163.58	OPATT 300: General Medicine

4.4.3.7 End of life care costs

A weighted average cost for end of life care is applied to patients upon entering the death state. End of life care is assumed to be distributed across hospital, hospice, nursing home or home services. The weekly end of life care cost for each setting, and the number of weeks for which this cost is applied in the economic model is presented in Table 42 below.

Table 42: Patients receiving active treatment or observation as first line management

End of life setting	Weekly cost	Number of weeks	Source

End of life care in hospital	£1,853.67	8	Costs based on National Audit Office (2008), inflated to 2017–18 cost year;[51] number of weeks based on TA427[18]
End of life care in hospice	£1,106.07	8	
End of life care in nursing home	£234.08	8	
End of life care at home	£234.08	8	

4.4.4 Duration of treatment

Durations of treatment and treatment-free intervals are reported in Yong et al. (2016) according to line of therapy.[24] These inputs are used throughout the model, for example, to inform treatment acquisition/administration costs and on- and off-treatment monitoring costs. The mean treatment and treatment-free intervals for subsequent (3+) lines of therapy were calculated based on the intervals for each individual line (third, fourth and fifth), and the proportions of patients reaching each of these lines, respectively (as reported in Table 10). Total disease durations are reported in Table 44; these are used to calculate complication costs as described in Section 4.4.3.5.

Table 43: Duration of treatment by line of therapy

Line of therapy	Mean treatment-free interval (months)	Mean duration of treatment (months)	Source
First line	2.00	8.00	Yong et al. (2016)[24]
Second line	16.00	9.00	
Subsequent (3+) lines	13.84	10.47	
Third line	11.00	8.00	
Fourth line	7.00	6.00	
Fifth line	3.00	4.00	

Abbreviations: SCT: stem cell transplant.

Table 44: Total disease duration

	Mean average disease duration (years)	Source
SCT-eligible	2.98	Calculated based on the duration of treatment and treatment-free intervals for each line of therapy reported in Yong et al. (2016)[24] and the proportion of patients reaching each line
SCT-ineligible	2.98	

Abbreviations: SCT: stem cell transplant.

4.4.5 Survival inputs

Patients who present via emergency presentation have poorer prognosis than those who present via other routes. Thus, whilst these patients may have higher costs per unit of time, these costs are accrued over shorter periods of time. In order to fully capture the economic costs associated with each route of presentation, it is important to account for the economic impact of utility losses associated with death, pain and suffering, as well as the direct costs.

The model applied a similar methodology to that used in some cost-of-illness models, where the utility losses associated with each route of presentation are estimated in terms of the number of QALYs lost compared with the general population (without myeloma). A QALY is a measure of the state of health of a patient or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life.[52] Quality of life, or 'utility', is measured on a scale where full health is valued as 1 and death as 0. One QALY is equal to 1 year of life in perfect health.

4.4.5.1 Calculating QALY losses

To calculate the QALY losses associated with each route of presentation, the QALYs accrued by patients presenting via each route were calculated, and then compared to the QALYs accrued by a gender- and age-matched population. This methodology is shown in the equation below.

QALYs accrued by a gender- and age-matched population – QALYs accrued by patients presenting via referral route = QALY losses associated with referral route

General population (without myeloma)

The average QALYs accrued across the model time horizon were calculated for a gender- and age-matched population without myeloma. This was done by estimating the number of patients in the cohort who remain alive each year from age 64 to 100 (based on mortality estimates from the ONS UK life tables 2016–18)[53] to calculate a total number of life years accrued across the model time horizon. Life years were adjusted based on utility values reported for the general population in Kind et al. (1999).[54] The life years and QALYs accrued across the model time horizon for the general population are reported in Table 45.

Table 45: Survival inputs for a gender- and age-matched population with myeloma

	Input	Source
Average LYs accrued	20.73	Calculated based on ONS UK life tables 2016–18[53]
Average QALYs accrued	15.67	

Abbreviations: LYs: life years; QALYs: quality-adjusted life years.

Patients receiving observation (i.e. who have smouldering myeloma)

To calculate QALYs accrued during observation, it was assumed that patients progress to active treatment in line with the rate that patients progress from asymptomatic SMM to active myeloma, based on Kyle et al. (2007).[55] Life years and QALYs were then calculated in an analogous manner to the general population, by estimating the number of patients in the cohort who remain in observation (i.e. who haven't progressed or died prior to progression due to other causes) each year from age 64 to 100.

It was assumed that patients with SMM had a higher risk of death (independent of the risk of death associated with progression) than the general population, so mortality estimates from the ONS UK life tables were adjusted by a standardised mortality ratio (SMR) of 2.1. This value corresponds to the value reported in Gregerson et al. (2001) for patients with MGUS;[56] it was assumed that this value was applicable to patients with SMM.

The life years and QALYs accrued by patients receiving observation are reported in Table 46. The proportion of patients who progress to active treatment is also reported; these patients are assumed to subsequently go on to receive the costs and QALYs associated with active treatment in the same manner as those who receive active treatment as first line management.

Table 46: Survival inputs for patients receiving observation

	Input	Source
Average LYs accrued	6.90	Calculated based on data reported in Kyle et al. (2007)[55]
Average QALYs accrued	5.33	
Proportion of patients who progress to active treatment	0.680.68	

Abbreviations: LYs: life years; QALYs: quality-adjusted life years.

Patients receiving active treatment

The QALYs accrued during active treatment were based on those reported in prior NICE TAs, and differed according to the therapy received in first line; given that these appraisals followed patients until death, it was assumed that these values included QALYs accrued on subsequent therapies.

Where data were unavailable, QALYs were assumed equivalent to alternative treatment options. QALYs accrued by patients receiving active treatment are reported in Table 47. Only discounted QALYs were reported in the relevant TA, and therefore these were used in the model; this was however inconsistent with the rest of the model, as no discounting assumptions were considered for costs or for other QALY estimates. The value of QALYs accrued on active treatment have therefore been undervalued compared with QALYs accrued in other states.

Table 47: Survival inputs for patients who receiving active treatment

Therapy	Total QALYs[a]	Source
SCT-eligible		
VTd	4.00	TA311;[8] VCd assumed equivalent to VTd
VCd	4.00	
SCT-ineligible		
VCd	3.62	TA228;[9] VCd and Rd assumed equivalent to VMP
VMP	3.62	
CTd	2.68	
MPT	3.64	
Rd	3.62	

[a]Discounted

Abbreviations: CTd: cyclophosphamide, thalidomide and dexamethasone; LYs: life years; MPT: thalidomide, melphalan and prednisone; QALYs: quality-adjusted life years; Rd: lenalidomide and dexamethasone; VCd: bortezomib, cyclophosphamide and dexamethasone; VMP: bortezomib, melphalan and prednisone; VTd: bortexomib, thalidomide and dexamethasone.

Patients receiving end of life care as first-line management

To calculate QALYs accrued by patients receiving end of life care as first-line management, based on feedback from clinical experts, it was assumed that patients in this state live for an average of only 3 months, as shown in Table 48. These patients were assumed to have utility equivalent to those with progressed disease.

Table 48: Survival inputs for patients receiving end of life care as first line management

	Input	Source
Average LYs accrued	0.25	Clinical expert opinion
Utility value	0.64	Post-progression utility value used in TA228,[9] TA171[16] and TA380[19]
Average QALYs accrued	0.16	Calculation

Abbreviations: LYs: life years; QALYs: quality-adjusted life years.

4.4.5.2 Calculating monetised QALY losses

To estimate the total economic costs associated with each route of presentation, QALY losses associated with each route were converted to monetary costs by assigning a monetary value to a QALY. This monetary value is highly contentious, and no method is widely accepted; the results where monetised QALY losses are included should therefore be interpreted with caution. However, this conversion has been included in the model as a tool to explore the impact that QALY losses may have on the total economic costs. In the base case, this was assumed to be £20,000 to reflect the lower limit of the NICE threshold for cost-effectiveness.[57]

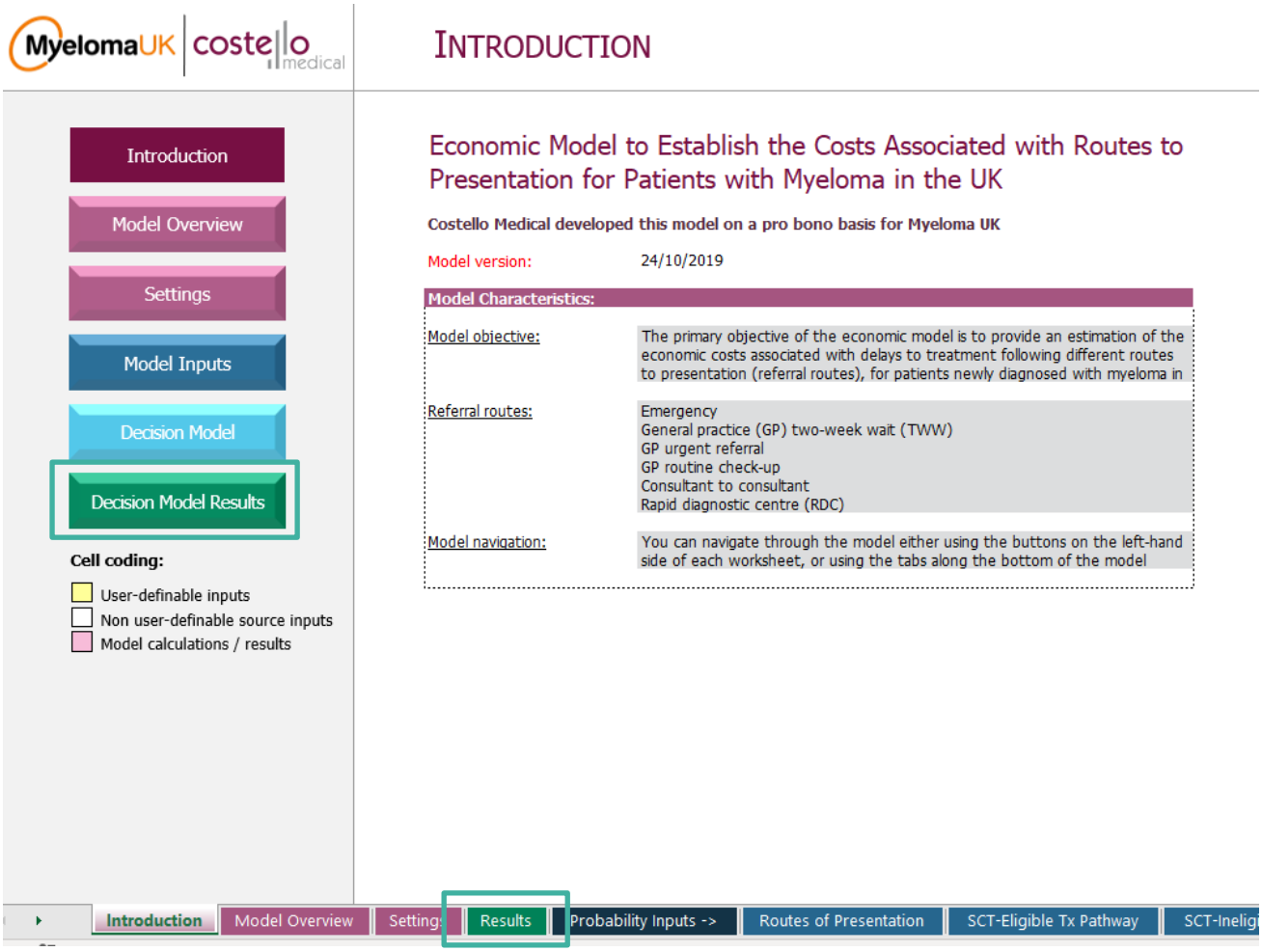
Scenarios: The monetary value of a QALY

Scenarios were included in the model where the monetary value of a QALY could be set to £30,000 to reflect the upper limit of the NICE threshold for cost-effectiveness,[57] or £60,000 based on estimate from the Department of Health.[58]

4.5 Model Outputs

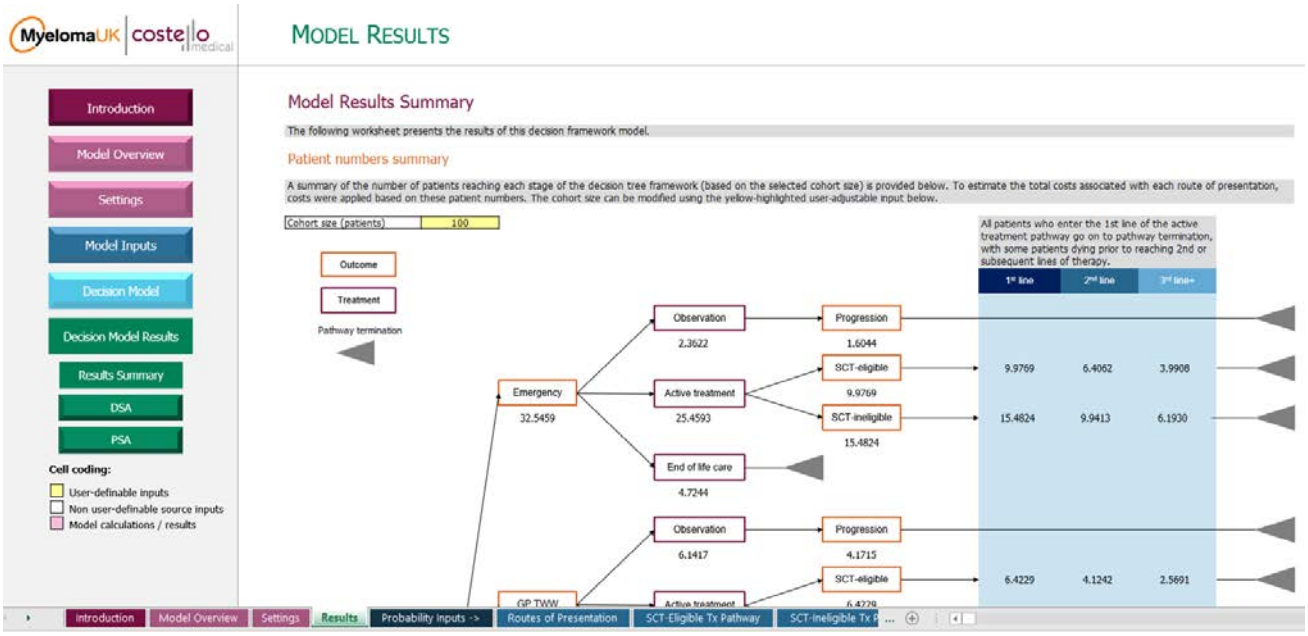
Model results are presented on the 'Results' worksheet, which can be reached by selecting any of the following links in the model, shown below in Figure 12 and shown by the green boxes.

Figure 12: Model results navigation



When the user has arrived on the 'Model Results' worksheet, the model will appear as is shown in Figure 13 below:

Figure 13: Model results screen view



The user can navigate the model results by scrolling throughout the worksheet, with model results presented in the following order as the user scrolls:

- Patient numbers summary (featuring a user-editable patient cohort size)
- Cost summary
  - Costs per route of presentation based on patient numbers as shown in the decision tree framework for a cohort of 100 patients
    - Total costs
    - Total QALY losses
    - Total costs (including monetised QALY losses)
    - Disaggregated costs
    - Disaggregated costs by first line management (active treatment, smouldering myeloma or end of life care as first-line management)
    - Disaggregated costs by cost category (treatment costs, complications and end of life care)
  - Costs per route of presentation (1 patient per route)
    - Total costs
    - Total QALY losses
    - Total costs (including monetised QALY losses)
    - Disaggregated costs
    - Disaggregated costs by first line management (active treatment, smouldering myeloma or end of life care as first-line management)
    - Disaggregated costs by cost category (treatment costs, complications and end of life care)
  - Selected costs for specific patient pathways (1 patient per pathway)

Model results are presented numerically as well as graphically and are presented in the 'Results' worksheet as per the order shown above. Model results are presented and discussed in Section 5 of this document.

4.6 Sensitivity Analyses

The final model output within the model 'Results' worksheet, which follows the results described in Section 4.5, are the sensitivity analyses. Sensitivity analyses were conducted to address elements of uncertainty in the model and to explore the robustness of the model results.

- A deterministic sensitivity analysis (DSA), which tests uncertainty in individual model parameters of interest sequentially, was used to identify the principal drivers of uncertainty in the model results. The DSA tested the sensitivity of the costs per route, calculated assuming 1 patient presents via each route. Variables which are grouped together as well as variables that were dependant on other model variables were excluded from the DSA.
- A probabilistic sensitivity analysis (PSA) was also conducted, which randomly samples all input values from relevant probability distributions associated with each treatment to assess the combined uncertainty of the costs per route of presentation (calculated assuming 1 patient presents via each route). The PSA involved 1,000 probabilistic simulations.

The results of the sensitivity deterministic and probabilistic sensitivity analyses are presented and discussed in Section 5.1.5 of this document. It is possible to re-run either the deterministic or probabilistic sensitivity analyses if model inputs have been updated, by selecting the 'Run DSA/PSA' buttons, as shown in Figure 14 and Figure 15 below.

Figure 14: Deterministic sensitivity analysis screen view

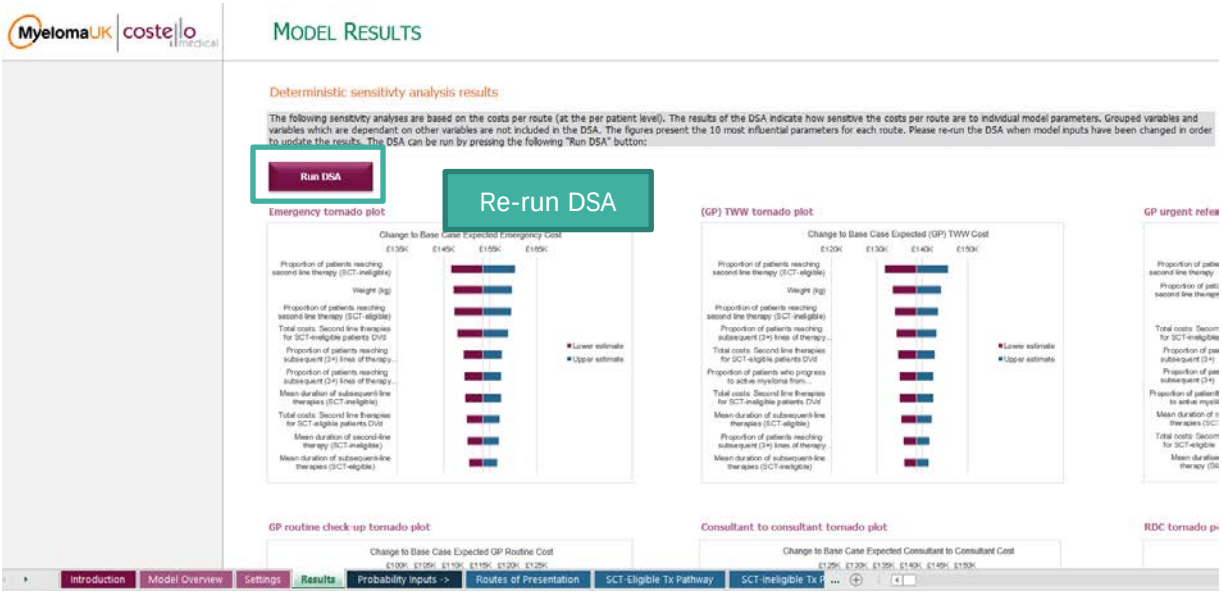
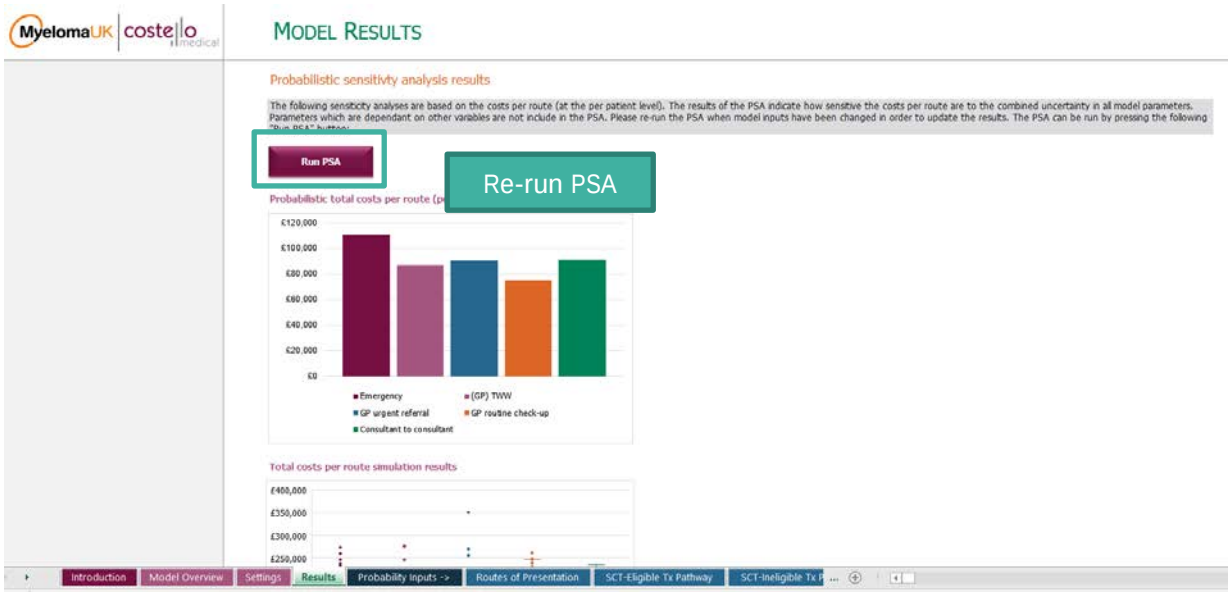


Figure 15: Probabilistic sensitivity analysis screen view



5 Results

5.1 Base Case Results

The model base case results are presented in the figures below. Please note that the drug list prices of the treatment regimens have been used to calculate the results, however, confidential patient access agreements may be in place which could result in reduced total drug costs for each route of presentation.

5.1.1 Total costs (across all referral routes)

Total costs per patient (cohort = 1)

For a patient diagnosed with myeloma in the UK, the model estimates a per patient undiscounted lifetime cost of approximately £168,000, of which £119,000 constitutes treatment costs (acquisition, administration, monitoring and AE costs), £39,000 constitutes the costs of managing complications, and £10,000 constitutes end of life care. When monetised QALY losses are included in the economic costs, the per patient undiscounted lifetime costs are estimated to be approximately £395,000.

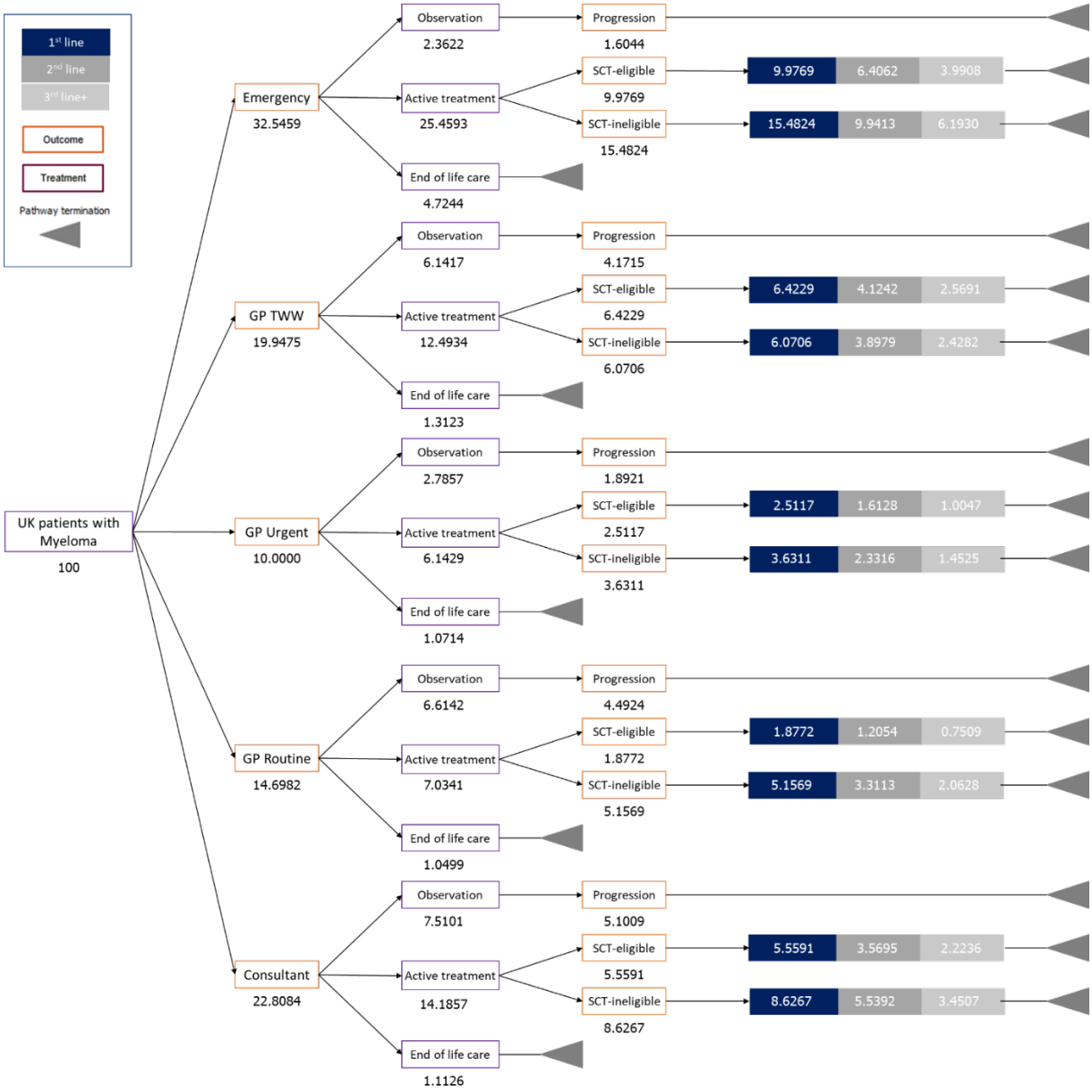
Total costs for UK incident population (cohort = 5,700)

For the incident population of patients with myeloma in the UK (~5,700 patients), the model estimates total lifetime undiscounted direct costs of £957 million, of which £325 million is associated with the emergency route.

5.1.2 Patient numbers summary (cohort = 100)

Figure 16 provides a cohort level summary of the patient numbers at each stage of the decision tree framework, where a cohort size of 100 patients has been assumed. The numbers presented alongside each stage of the decision model framework represent the number of patients who, based on the probabilities in the model, arrive at each stage of the decision model framework.

Figure 16: Patient numbers summary (cohort size of 100)



Abbreviations: GP: general practitioner; SCT: stem cell transplant; UK: United Kingdom.

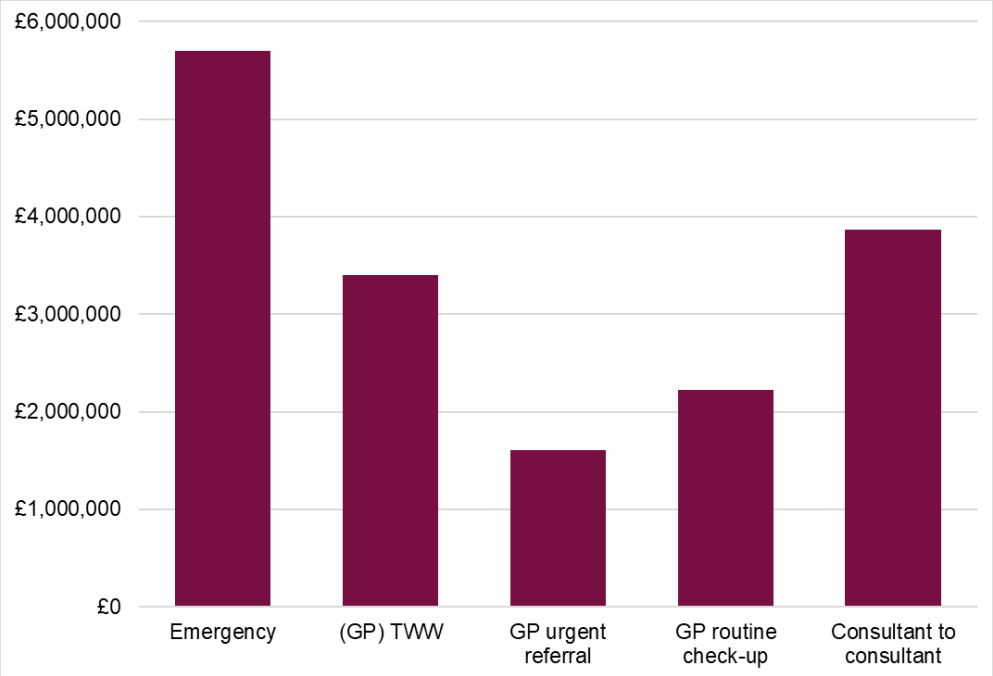
5.1.3 Costs per route of presentation (cohort = 100)

Total and disaggregated costs are provided below for each referral route based on the patient numbers shown in the decision tree framework above (for a cohort size of 100 patients). Changing the cohort size will change these costs accordingly.

5.1.3.1 Total costs and QALY losses (cohort = 100)

Figure 17 shows the costs associated with each referral route based on the cohort of 100 patients entering the decision tree framework. Given that the more patients present through the emergency route than the other referral routes, emergency presentation is the most costly route to diagnosis at a cohort level.

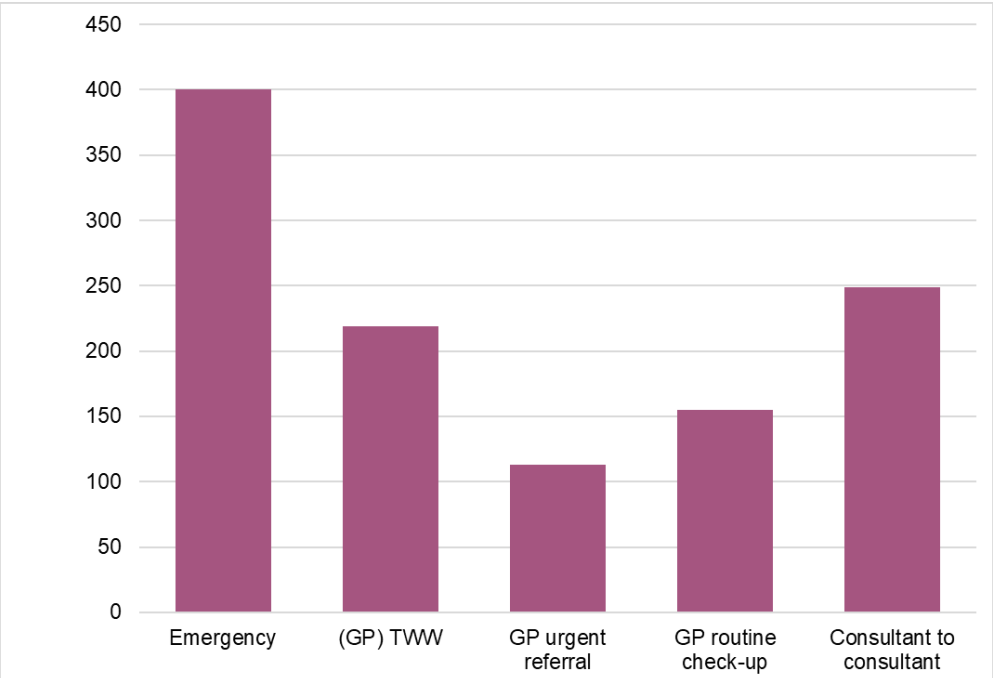
Figure 17: Total costs (cohort = 100)



Abbreviations: GP: general practitioner; TWW: two-week wait.

Figure 18 presents the QALY losses associated with each referral route based on the cohort of 100 patients entering the decision tree framework. The emergency referral route is associated with the greatest QALY losses.

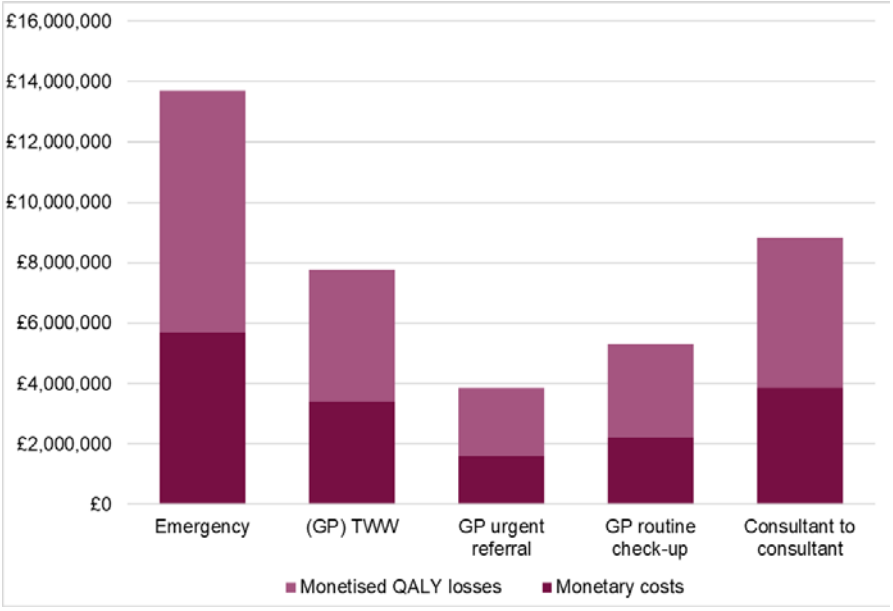
Figure 18: Total QALY losses (cohort = 100)



Abbreviations: GP: general practitioner; QALY: quality-adjusted life year; TWW: two-week wait.

By quantifying the monetary value of a lost QALY (see Section 4.4.5.2), Figure 19 presents the total economic costs associated with each referral route as the sum of direct monetary costs and monetised QALY losses. The ordering of results does not change, with the emergency referral route being the most costly. When a QALY is valued at £20,000, QALY losses form a greater proportion of the economic costs associated with each route than the direct monetary costs.

Figure 19: Total costs (including monetised QALY losses) (cohort = 100)

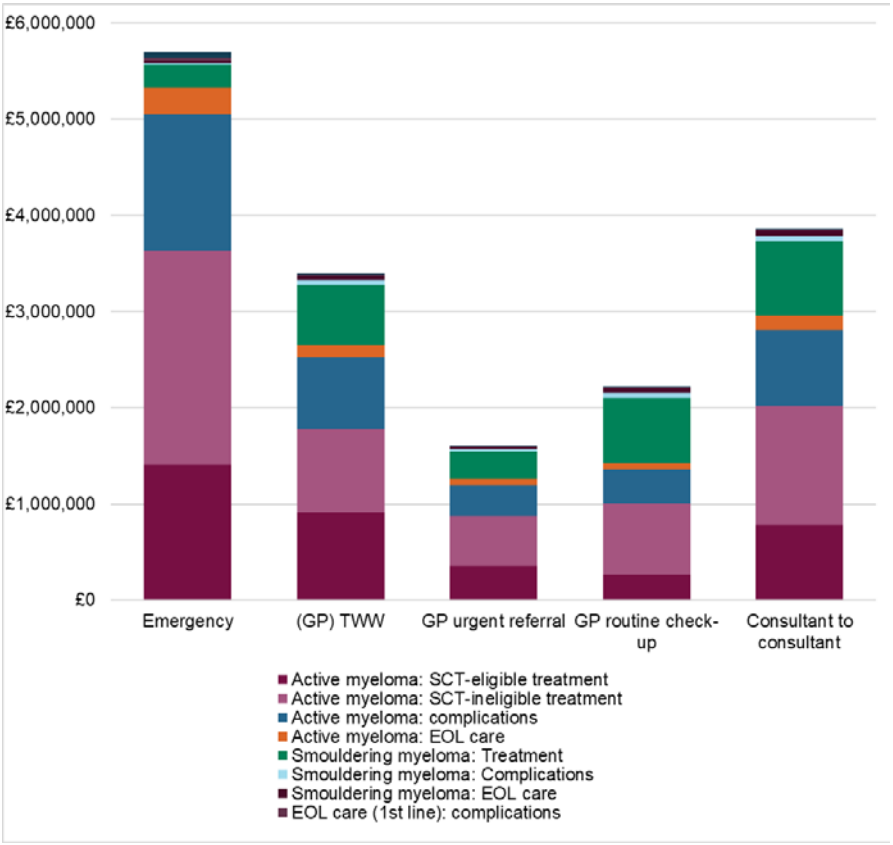


Abbreviations: GP: general practitioner; QALY: quality-adjusted life year; TWW: two-week wait.

5.1.3.2 Disaggregated costs and QALYs (cohort = 100)

Figure 20 provides a disaggregated summary of Figure 17, showing the break-down of costs which contribute to total costs. These do not include monetised QALY losses. Across all referral routes, the modelled cost of treatment for SCT-ineligible patients with active myeloma is the most substantial contribution to the total cost associated with the treatment of myeloma across each referral route.

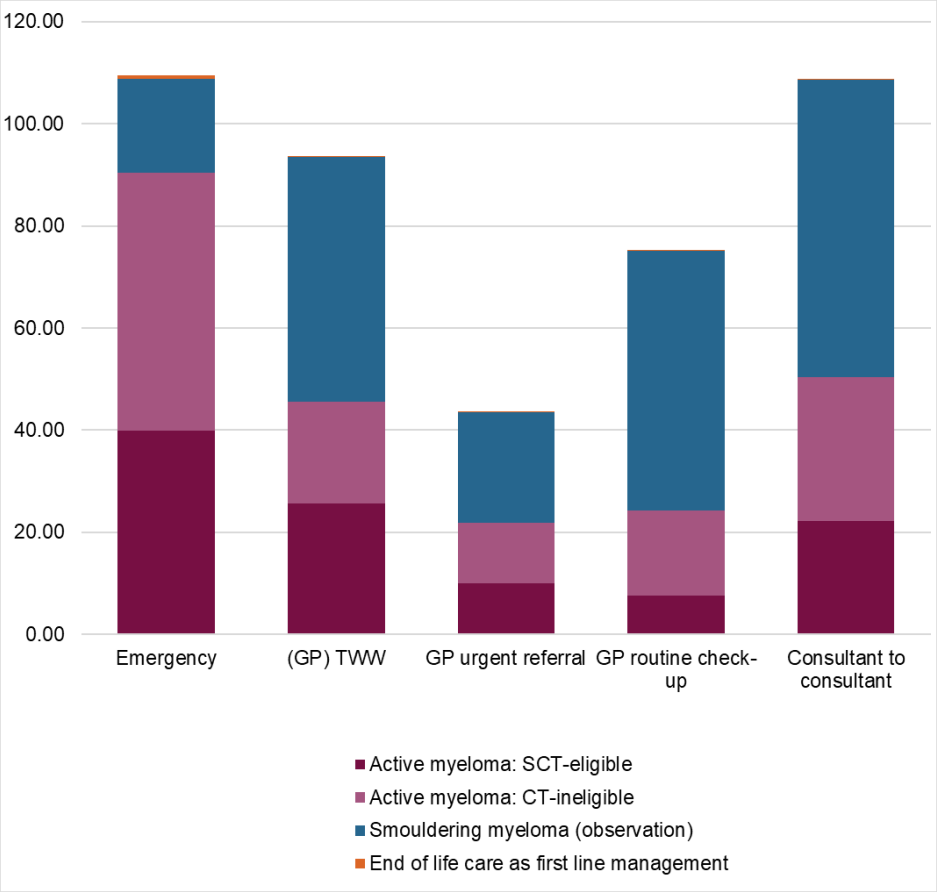
Figure 20: Disaggregated costs (cohort = 100)



Abbreviations: EOL: end of life; GP: general practitioner; SCT: stem cell transplant; TWW: two-week wait.

Figure 21 provides a breakdown of the total QALYs accrued by patients presenting via each referral route, based on a cohort of 100 patients entering the decision tree framework. Despite a larger number of patients presenting through the emergency route than the other referral routes, emergency presentation is not associated with the largest number of QALYs accrued. This appears to be because fewer patients in the emergency route receive observation as first line management, and patients in observation gain considerably more QALYs than those receiving active treatment or end of life care as first line management.

Figure 21: Disaggregated QALYs (cohort = 100)



Abbreviations: GP: general practitioner; SCT: stem cell transplant; TWW: two-week wait.

5.1.4 Costs per route of presentation (1 patient per route)

The costs for each route of presentation (total costs and disaggregated costs) at the per patient level are presented below. These costs are calculated assuming 1 patient presents via each route. As these costs are calculated without reflecting the different numbers of patients that would enter each route (as shown in the decision tree framework in Figure 16), changing to cohort size does not change these costs, and they allow direct comparisons between the referral routes.

5.1.4.1 Total costs and QALY losses per route of presentation (1 patient per route)

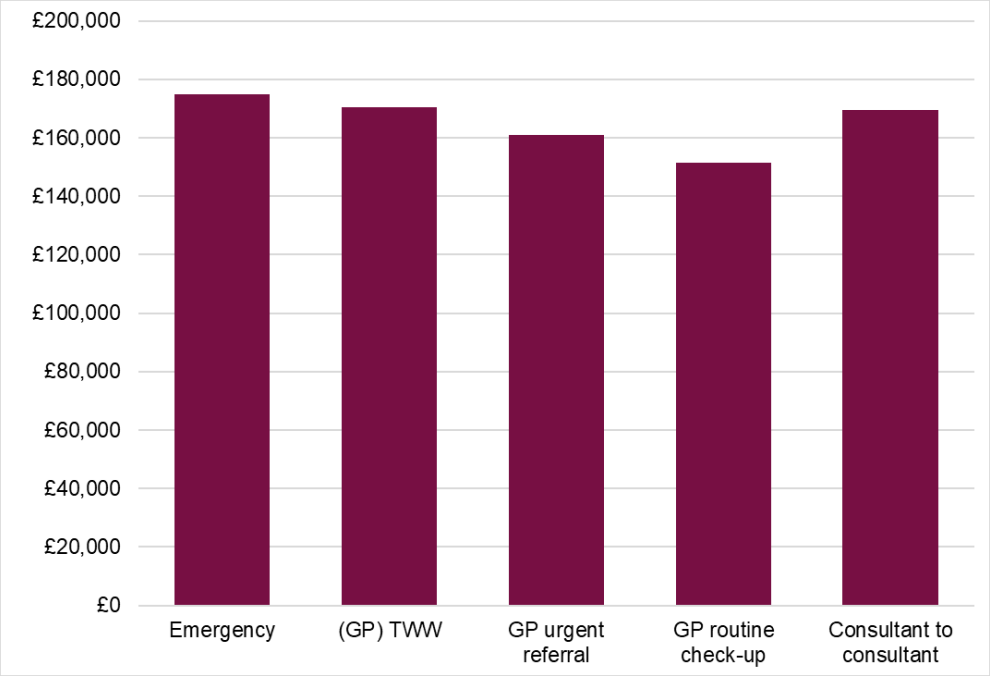
The total costs per route, total QALY losses per route and total costs including monetised QALY losses at the per patient level are presented in Figure 22, Figure 23 and Figure 24, respectively. These results show that presenting via the emergency route is associated with the highest total costs and highest QALY losses.

Whilst the emergency route was the costliest, differences in total costs (excluding monetised QALYs) were minimal between the emergency, TWW and consultant to consultant routes. Total costs were marginally lower for the GP urgent and GP routine check-up routes.

Differences in QALY losses between the emergency and non-emergency routes were more pronounced. The higher total QALY losses associated with the emergency route are expected, given the poor prognosis for

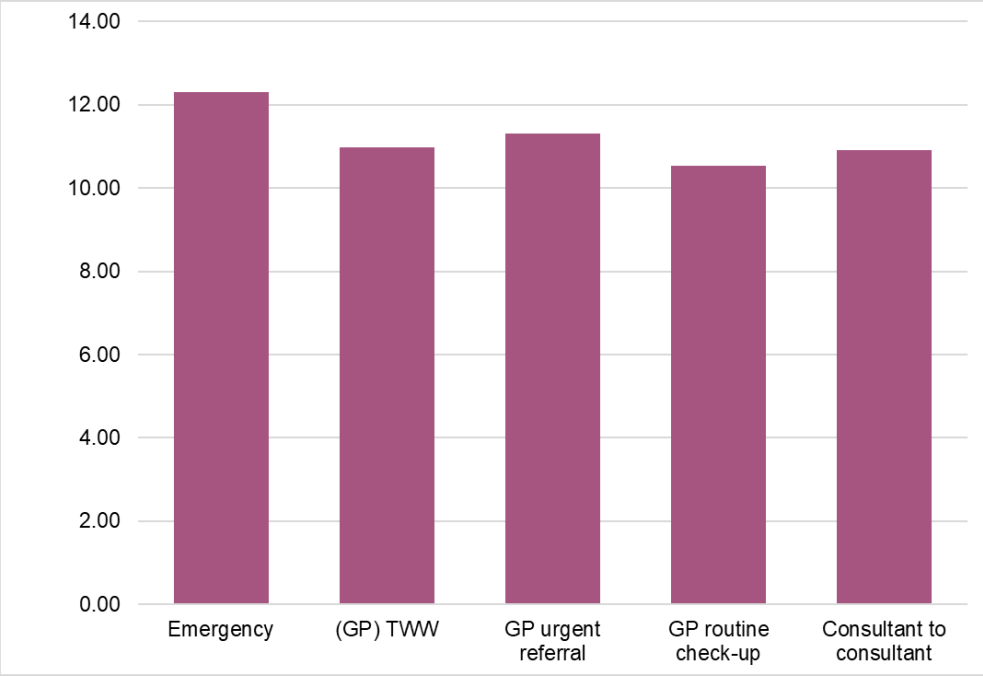
patients presenting via the emergency route, and the reduced probability of receiving observation compared with the other referral routes. QALY losses associated with the other routes of presentation are largely similar, with the GP routine check-up route providing lowest QALY losses.

Figure 22: Total costs (1 patient per route)



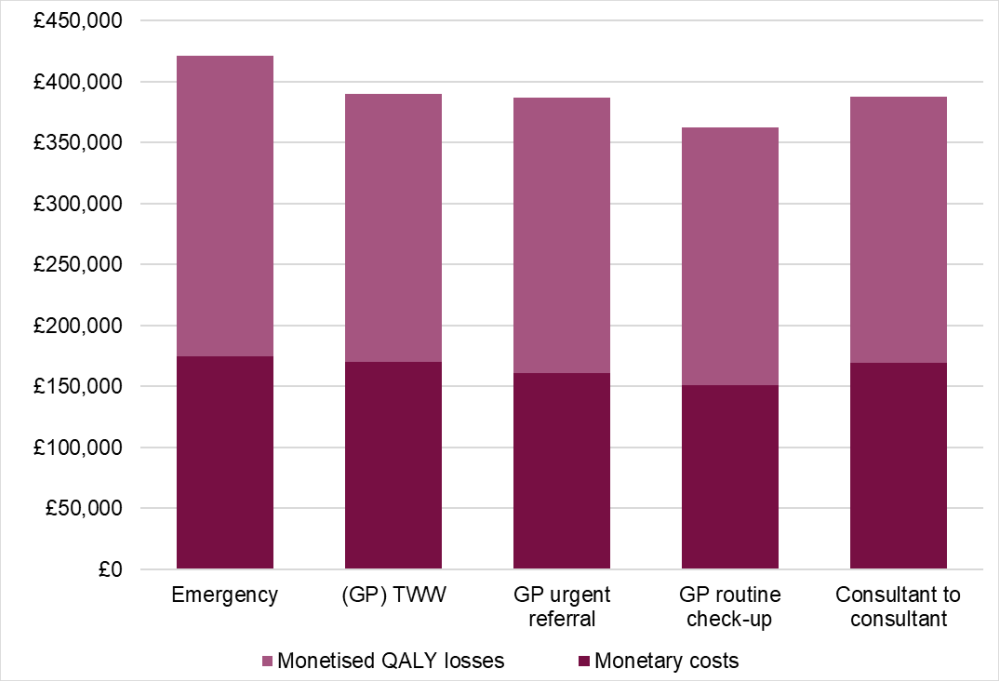
Abbreviations: GP: general practitioner; TWW: two-week wait.

Figure 23: Total QALY losses (1 patient per route)



Abbreviations: GP: general practitioner; TWW: two-week wait.

Figure 24: Total costs (including monetised QALY losses) (1 patient per route)



Abbreviations: GP: general practitioner; QALY: quality-adjusted life year; TWW: two-week wait.

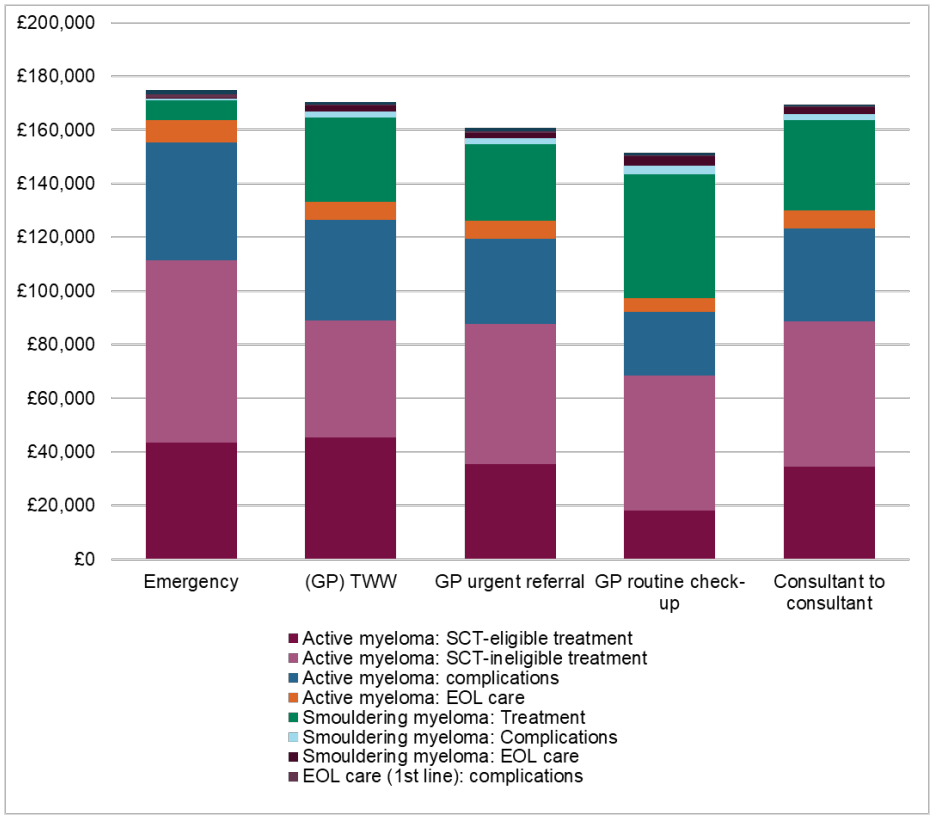
5.1.4.2 Disaggregated costs (1 patient per route)

Disaggregated costs and QALYs per route are presented in Figure 25 and Figure 26, respectively and disaggregated costs by cost category (treatment, complication and end of life care) are presented in Figure 27.

The disaggregated costs show there were considerable differences in the distribution of costs across different parts of the decision tree framework. Treatment costs were similar across referral routes, and marginally higher for the emergency, GP TWW and consultant to consultant routes. Treatment costs for patients with active treatment as first-line management constituted a larger proportion of the emergency costs, whereas treatment costs for patients with observation as first-line management (who then progressed from SMM) were higher for the other routes. Complication and end of life care costs were considerably higher for the emergency route, reflecting a cost benefit associated with earlier diagnosis.

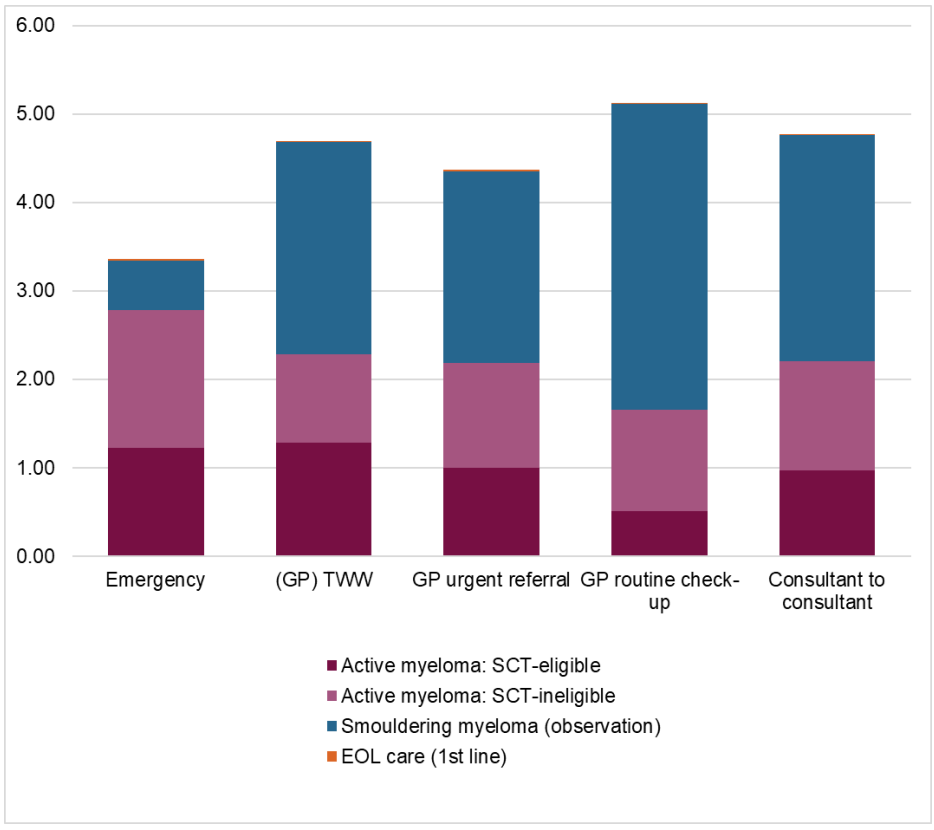
The disaggregated QALYs show that the emergency route has the lowest number of QALYs accrued during observation.

Figure 25: Disaggregated costs (1 patient per route)



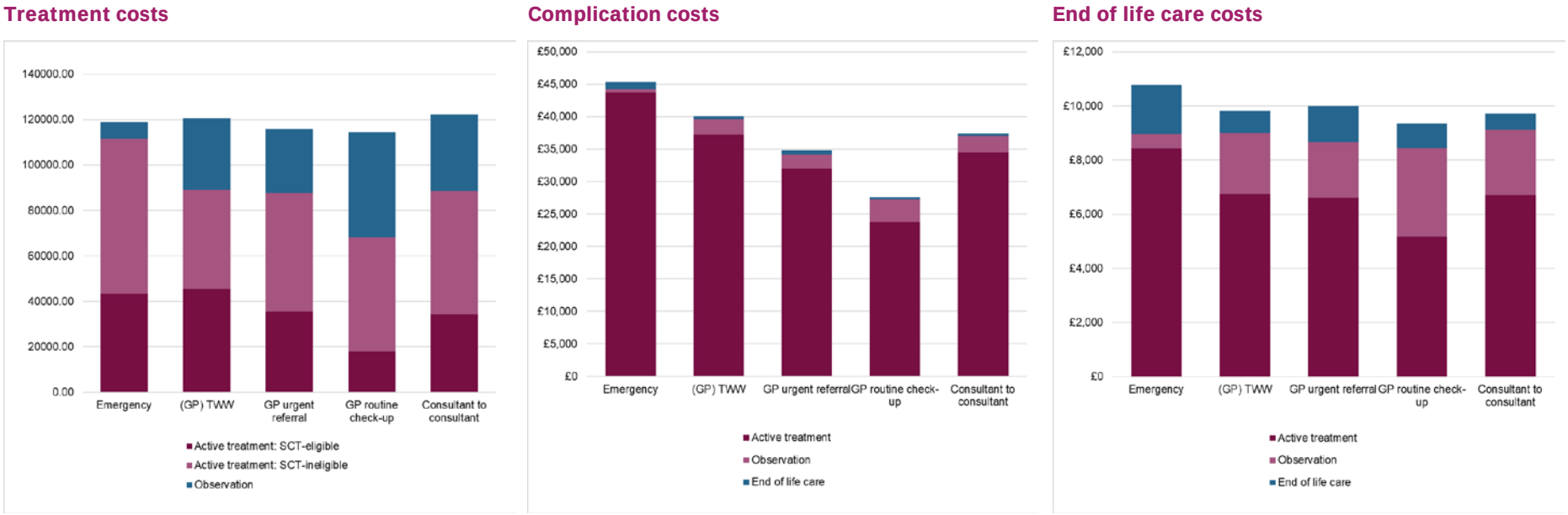
Abbreviations: EOL: end of life; GP: general practitioner; SCT: stem cell transplant; TWW: two-week wait.

Figure 26: Disaggregated QALYs (1 patient per route)



Abbreviations: GP: general practitioner; SCT: stem cell transplant; TWW: two-week wait.

Figure 27: Disaggregated costs by cost category (1 patient per route)



Abbreviations: GP: general practitioner; SCT: stem cell transplant; TWW: two-week wait.

5.1.5 Selected costs for specific patient pathways (1 patient per pathway)

Costs associated with specific patient types are presented in Table 49. These costs are calculated for 1 patient following the specified pathway. For example, the assumed treatment costs for a patient who presents via the emergency route, receives active treatment as first line management and is eligible for SCT are £141,386.74 (using base case assumptions and inputs).

The costs shown in Table 49 highlight some of the assumptions underlying the model. Firstly, the costs for some patient types do not differ between routes of presentation. For example, treatment costs are assumed to be dependent only on SCT eligibility, and therefore the treatment costs for an SCT-eligible patient are the same regardless of the route by which a patient presents. Differences in treatment costs between routes (as shown in Figure 25) are therefore driven by the probability of entering the active treatment pathway at diagnosis, and the probability of being eligible or ineligible for SCT. In contrast, since complication costs depend on the probabilities of presenting with CRAB complications at diagnosis, which differ according to the route of presentation, complication costs differ between referral routes (as shown via differentiated colours in Table 49).

Secondly, specific costs for some patient pathways do not differ depending on their first-line management. For example, whether an SCT-eligible patient receives active treatment as first-line management or after being observed (i.e. early diagnosis), the model assumes that SCT-eligible patients accrue the same treatment cost (which is also the same regardless of route of presentation, as described above). As such, the model does not capture any treatment cost benefits that may be associated with earlier diagnosis; treatment costs are simply “delayed” until a patient progresses. This may go some way to explaining why total costs per route of presentation (1 patient per route, as shown in Figure 22) are largely similar across routes of presentation, but differ once monetised QALY losses are included (as shown in Figure 25). On the other hand, the model does capture any complication cost benefits associated with earlier diagnosis; complication costs are higher for patients receiving active treatment as first-line management than for patients progressing after observation (i.e. early diagnosis). This is a result of the lower rate of SREs experienced by patients after observation (see Section 4.4.2.5).

These assumptions are discussed further in Section 6.2.1.

Table 49: Selected costs for specific patient pathways (at the per patient level)

Route of presentation	Patients with active treatment as first line management				Patients with observation as first line management				Patients with end of life care as first-line management	
	Treatment costs		Complication costs (from diagnosis)	End of life care costs	Treatment costs		Complication costs (from progression)	End of life care costs	Complication costs	End of life care costs
	SCT-eligible (from diagnosis)	SCT-ineligible (from diagnosis)			SCT-eligible patient (from progression)	SCT-ineligible patient (from progression)				
Emergency	£141,386.74	£143,263.31	£55,889.56	£10,773.85	£141,386.74	£143,263.31	£10,622.11	£10,773.85	£7,142.59	£12,547.49
(GP) TWW	£141,386.74	£143,263.31	£59,474.66	£10,773.85	£141,386.74	£143,263.31	£10,622.11	£10,773.85	£6,520.46	£12,547.49
GP urgent referral	£141,386.74	£143,263.31	£52,175.62	£10,773.85	£141,386.74	£143,263.31	£10,622.11	£10,773.85	£6,342.56	£12,547.49
GP routine check-up	£141,386.74	£143,263.31	£49,662.97	£10,773.85	£141,386.74	£143,263.31	£10,622.11	£10,773.85	£5,931.47	£12,547.49
Consultant to consultant	£141,386.74	£143,263.31	£55,495.26	£10,773.85	£141,386.74	£143,263.31	£10,622.11	£10,773.85	£7,023.07	£12,547.49

Costs that are equal across different pathways are assigned the same colour.

Abbreviations: GP: general practitioner; SCT: stem cell transplant; TWW: two-week wait.

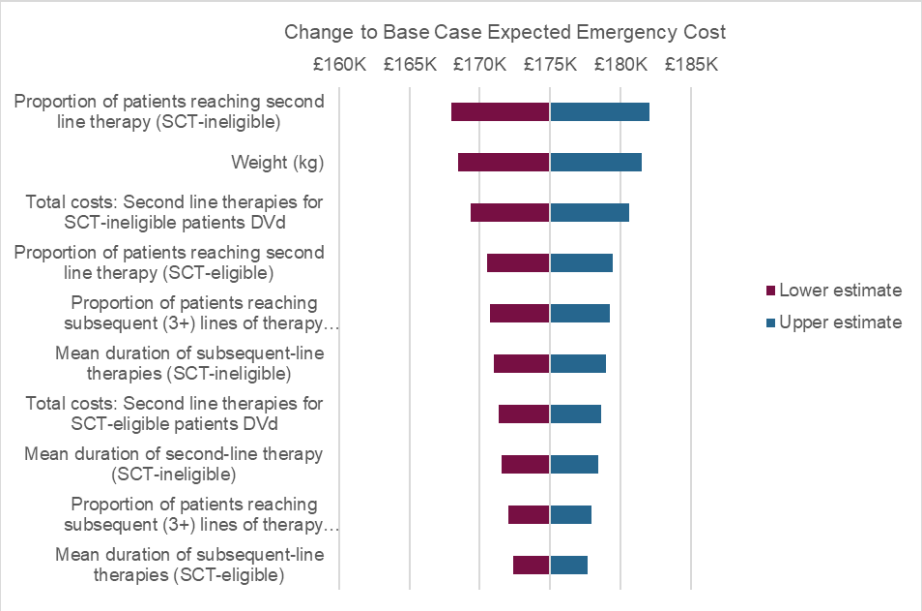
5.2 Sensitivity Analyses

Sensitivity analyses were conducted to address elements of uncertainty in the model and to explore the robustness of the model results. Sensitivity was measured by varying all model parameters by 20%.

5.2.1 Deterministic sensitivity analysis results (1 patient per route)

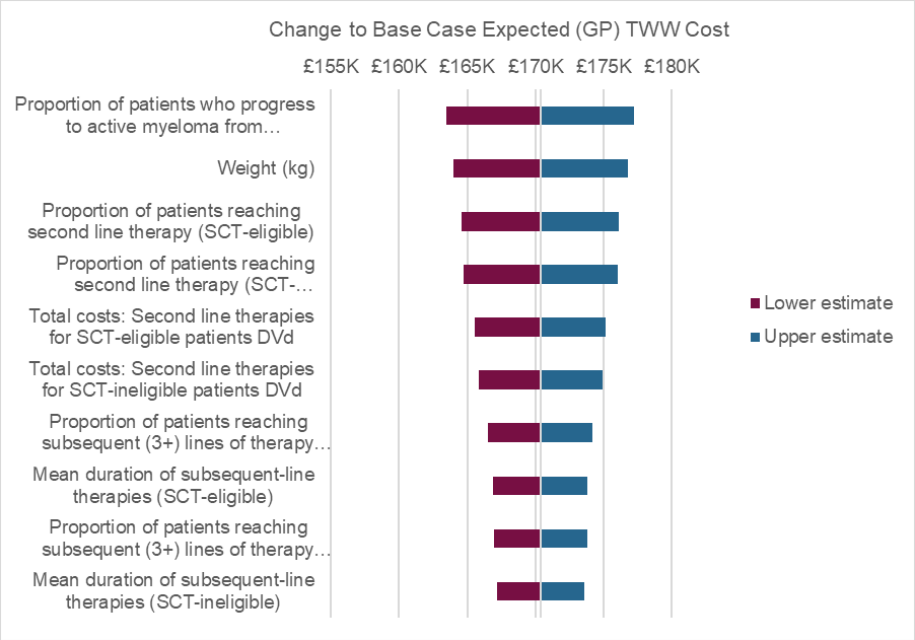
The results of the DSA are displayed in the tornado plots below, which graphically display the parameters to which each route of presentation was found to be most sensitive. The DSA tested the sensitivity of the costs per route of presentation assuming 1 patient presents via each route. The proportion of patients reaching second line therapy for SCT-ineligible patients was found to be the most influential parameter for the emergency and GP Urgent routes, whilst the proportion of patients progressing from smouldering myeloma to active myeloma was the most influential parameter for the (GP) TWW, GP Routine and consultant to consultant routes.

Figure 28: Tornado Plot, Emergency



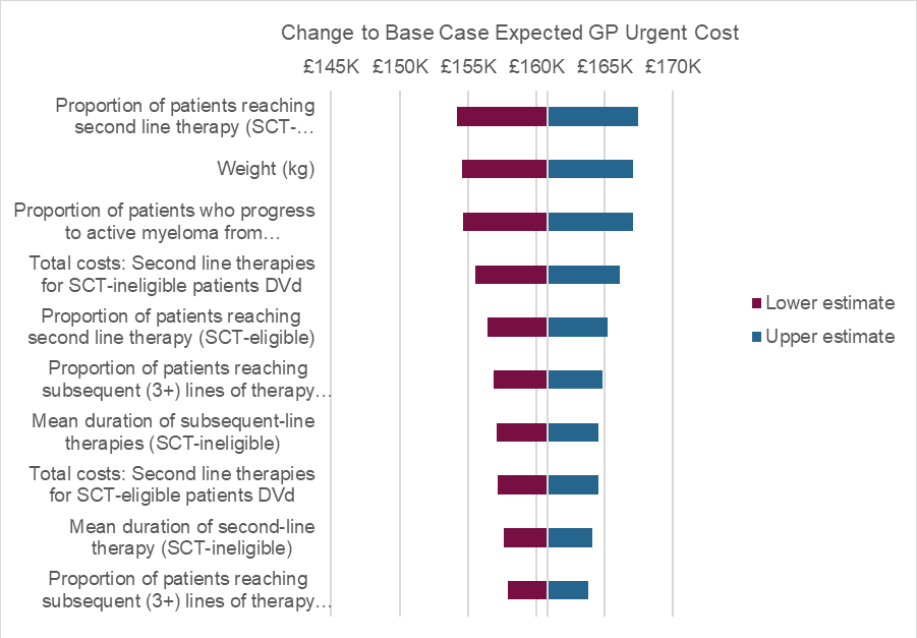
Abbreviations: DVd: daratumumab, bortezomib and dexamethasone; SCT: stem cell transplant.

Figure 29: Tornado Plot, (GP) TWW



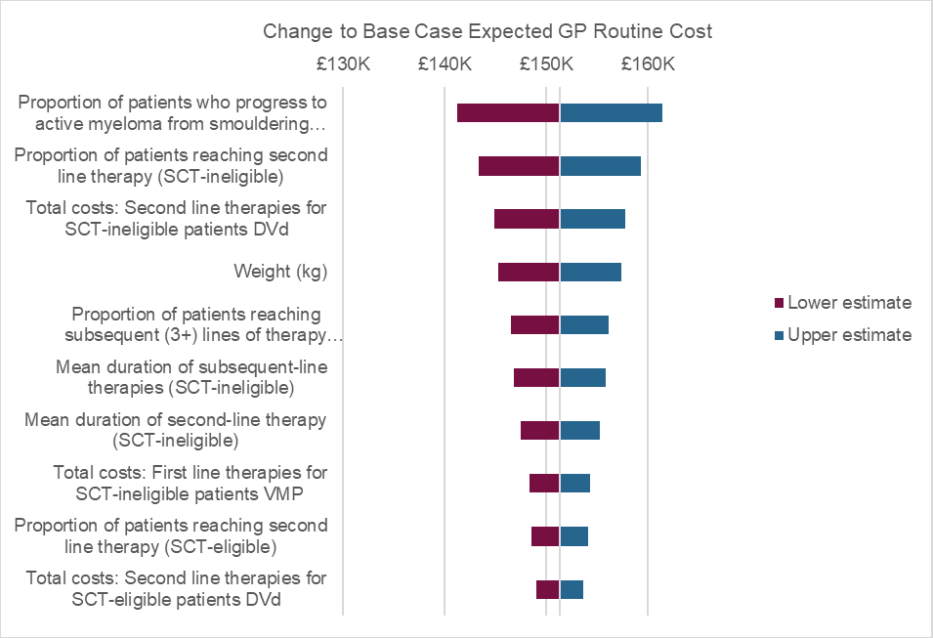
Abbreviations: DVd: daratumumab, bortezomib and dexamethasone; SCT: stem cell transplant.

Figure 30: Tornado Plot, GP Urgent



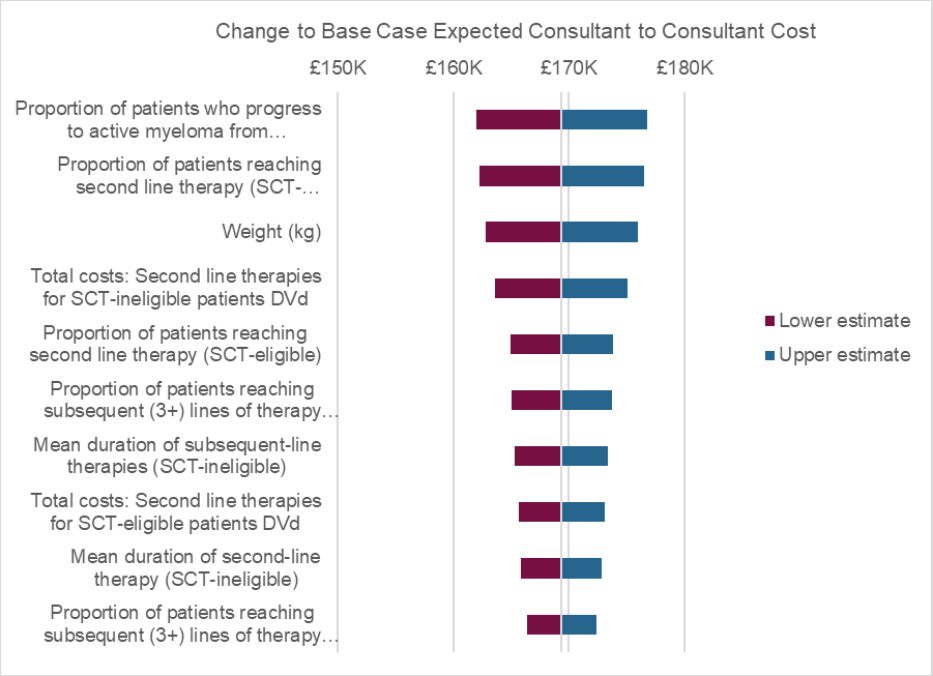
Abbreviations: DVd: daratumumab, bortezomib and dexamethasone; SCT: stem cell transplant.

Figure 31: Tornado Plot, GP Routine



Abbreviations: DVd: daratumumab, bortezomib and dexamethasone; SCT: stem cell transplant.

Figure 32: Tornado Plot, consultant to consultant

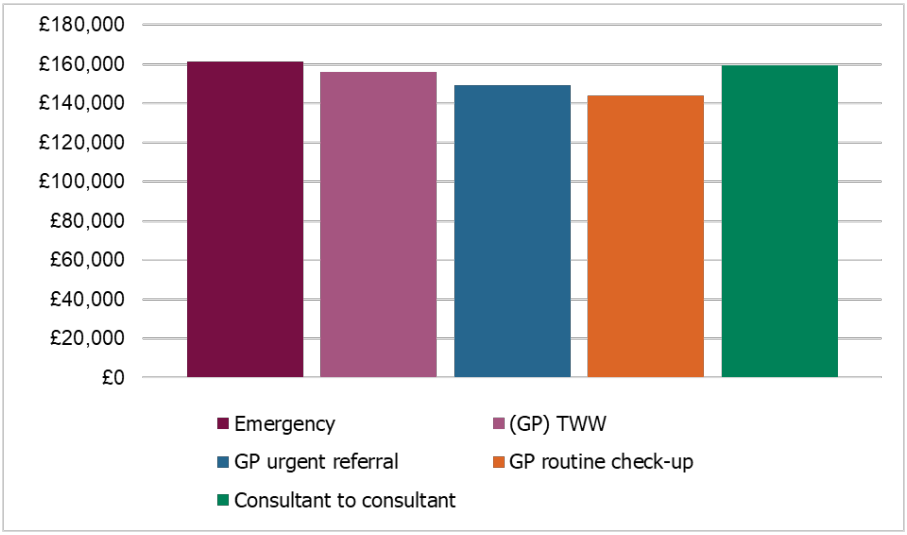


Abbreviations: DVd: daratumumab, bortezomib and dexamethasone; SCT: stem cell transplant.

5.2.2 Probabilistic sensitivity analysis results (1 patient per route)

The results of the PSA (based on costs per route of presentation, calculated assuming 1 patient presents via each route) are shown in Figure 33 and Figure 34. Figure 33 presents the average probabilistic total costs per route of presentation across all 1,000 simulations. The ordering of the referral routes from most costly to least costly appeared to be consistent with the base case analysis (Figure 22).

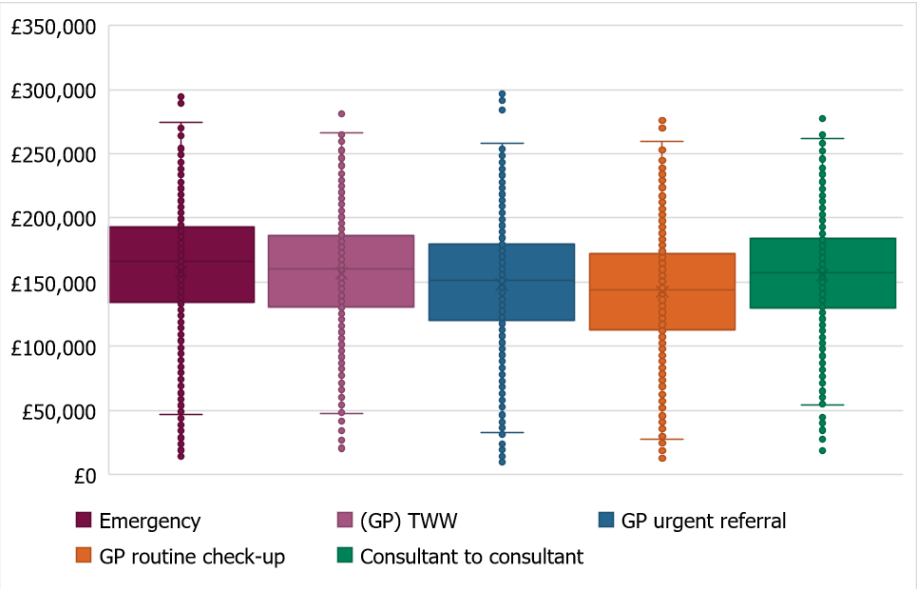
Figure 33: Probabilistic total costs (1 patient per route)



Abbreviations: GP: general practitioner; TWW: two-week wait.

Figure 34 presents the results of each probabilistic simulation, where each dot on the figure represents the cost calculated for each model simulation Whilst individual simulations varied between £0 and over £250,000, the mean values appear to be similar to the base case analysis. For the emergency route, the median result is slightly higher than the mean, indicating that the simulations are skewed towards the costly end (i.e. lower outliers may be dragging down the mean). The interquartile range (IQR) also appears to be slightly wider for the emergency route than the other referral routes, suggesting that the costs for the emergency route are more sensitive to the combined uncertainty in the parameters.

Figure 34: Probabilistic total costs (1 patient per route) simulation results



A box a whisker plot has been superimposed over the individual simulations. The central horizontal line indicates the median result, the upper and lower boundaries of the box represent the upper and lower quartiles and the "x" represents the mean of the results. Simulations that lie outside the whiskers (which extend 1.5 times the interquartile range [IQR] above and below the upper and lower quartiles) are considered to be outliers.
Abbreviations: GP: general practitioner; TWW: two-week wait.

6 Discussion and Conclusions

6.1 Model Strengths

The model considered the entire treatment pathway for UK patients with myeloma, from diagnosis to death. The model has high granularity, accounting for a large number of events and the associated costs, including treatment acquisition and administration costs, monitoring costs, and costs associated with complications, AEs and end of life care. A targeted literature review was undertaken to identify data sources to inform the inputs in the model. The majority of data sources are UK-specific, ensuring relevance to the UK setting.

The comprehensive consultation of UK clinical experts during the model development is a strength of the approach taken. UK clinical experts in myeloma were consulted on the structure of the model, as well as validating appropriate data sources and inputs. Furthermore, the model has been closely aligned with current clinical guidelines (ESMO guidelines and NICE TA guidance), and care has been taken to ensure the model will remain relevant in areas where the guidelines are expected to change. For example, the model includes a placeholder route of presentation via an RDC, as well as placeholders for additional therapies at each line of treatment.

Flexibility is another key strength of the model. The majority of inputs in the model are user-adjustable, allowing straightforward investigation of alternative parameter values. Furthermore, where multiple input sources were identified, the model includes the option for the primary source to be changed by the user. The calculation of results is also flexible, as the user can choose the size of the cohort being considered or consider results at a per-patient level.

6.2 Model Assumptions and Limitations

All modelling necessitates assumptions to be made, which need to be taken into account when interpreting the outputs of any model. A summary of the key limitations and assumptions are presented in Table 50.

Table 50: List of assumptions for the base case analysis

Model aspect	Assumption/limitation	Justification	Mitigating steps
Time-dependency	• The model utilises a decision tree framework, and therefore time-dependency is not accounted for in the economic model. All modelled costs and benefits are applied in the model instantaneously • Costs are not discounted (where the value decreases in the future), and QALYs are discounted inconsistently. QALYs for the general population, patients receiving observation and patients receiving end of life care as first line management were not discounted, whereas QALYs accrued in the active treatment pathway (which were based on values reported in NICE TAs) were discounted. The value of QALYs accrued on active treatment have therefore been undervalued compared with QALYs accrued in other states. • The model results may therefore not accurately reflect the costs and benefits which could have been realised if the costs and benefits were acquired in real time. For example, the costs associated with routes where higher proportions of patients receive observation as first line management may have been overestimated, since the active treatment costs accrued by these patients were not discounted.	• A more complex model would have been required to account for time-dependency, and this was out of the scope of this research	-
Routes of presentation	• The modelled referral routes were limited to the following based on Howell et al. (2017): emergency, TWW, GP	• Howell et al. (2017) was the only publication identified that included the characteristics of patients presenting via	• The model permits users to modify the routes of presentation probabilities,

	urgent referral, GP routine check-up or consultant to consultant.[2] • The patients included in Howell et al. (2017) were diagnosed between 1st July 2012 and 31st December 2013.[2] Myeloma is a rapidly evolving disease area, so it is unclear whether the data reported in this study is still relevant to the present day. This limitation applies to all probabilities included in the model that were based on Howell et al. (2017); routes of presentation, first line management, complications and SCT eligibility.	different referral routes, which were required to inform subsequent steps in the decision tree framework.[2] • Howell et al. (2017) is set within the HMRN and therefore reflects real-world practice for patients with myeloma in the UK.[2] • All probabilities based on Howell et al. (2017) were validated with UK clinical experts to ensure that they were generalisable to current practice.	meaning that more up-to-date data can be included when it becomes available. • The model includes a scenario where routes of presentation probabilities are based on more recent data from the NCIN (for patients diagnosed between 2006 and 2016) – please note that in this scenario (and if user inputs are selected), subsequent probabilities are still based on Howell et al. (2017), compromising the internal consistency of the model. If the proportions of patients presenting via each route are changed, it is unclear whether the characteristics of patients within each route would remain the same. • More recent data describing the characteristics of patients presenting via different referral routes could be collected to update the model. • A placeholder route for referral via an RDC was also included in the model, since this is becoming more relevant in clinical practice.
First line management	• Following a diagnosis, patients were modelled to receive one of the following three options for the first-line management of the disease based on Howell et al. (2017): active treatment, observation or end of life care.[2]	• UK clinical experts confirmed that these represent the available first line management options available to patients in current practice.	• A small proportion (10%) of those who were reported to receive “observation” in Howell et al. (2017) were instead modelled to receive active treatment following diagnosis, to reflect recent changes in practice. • The model permits users to modify the first line management probabilities.

SCT-eligibility	• All probabilities prior to and including SCT eligibility are conditional on referral route. • After this point in the decision tree framework, branching probabilities are no longer conditional on referral route; instead, treatments received (and thus the acquisition, administration, monitoring and AE costs accrued) by patients who enter the active treatment pathway become conditional on SCT status alone. • I.e. whilst costs differ between the SCT-eligible and SCT-ineligible treatment pathways, all patients who enter the SCT-eligible treatment pathway accrue the same costs, regardless of referral route by which they presented (as shown in Table 49). As such, the model may not be capturing all cost differences between referral routes.	• Clinical experts agreed that SCT eligibility is the most important consideration in determining the treatment pathway of patients diagnosed with myeloma, so it is reasonable to assume that treatment pathways are similar for patients who are eligible or ineligible for SCT across referral routes. • No data were identified to directly inform the treatments received by patients presenting via different referral routes, so a simplifying assumption was required.	• This is an inherent limitation of the current model structure (discussed further in Section 6.2.1). • It would be feasible to extend the model to include treatment pathways that were conditional on referral route, should this data become available, but this would increase the complexity of the model.
Treatment pathways	• The economic model does not capture individual treatment pathways. • Instead, a number of possible treatment options at each stage of the active treatment pathway were modelled using a "market basket" approach, where costs at each line of therapy represent a weighted average of the costs of the therapies in each market basket.	• The treatment landscape for multiple myeloma is complex and constantly evolving and so capturing a typical treatment pathway for a representative myeloma patient is difficult. • Capturing individual treatment pathways would require a much more complex individual patient model, beyond the scope of this research. • Treatment options included were based on published NICE guidance and UK clinical expert opinion.	• The model permits users to modify the market basket probabilities. • Placeholder treatments have been included in the model, so that additional treatments can be added to the model should the treatment pathway change.

Lines of therapy	• The model assumes that only a proportion of patients reach each line of therapy (i.e. a proportion of patients proceed to end of life care and then die, thus not continuing to the next line of therapy). • In the model, the probabilities that patients reach second or subsequent lines (3+) are not conditional on referral route or SCT eligibility. This assumption may not reflect reality because, for example, it may be more likely that patients who receive SCT are more likely to progress to second and subsequent lines of therapy than those who do not. Thus, the model may not be capturing all cost differences between referral routes. • In sensitivity analyses, these probabilities were found to be in the top 10 most influential parameters for all referral routes, and the proportion of SCT-eligible patients reaching second line was the most influential for the emergency and (GP) TWW routes. This is because the treatment acquisition costs for second and subsequent line therapies form a large proportion of the total costs.	• These proportions were based on Yong et al. (2016), a large real-world study including 753 UK patients, so were considered generalisable to UK practice.[24] • No data were identified to directly inform the probability of patients reaching each line of therapy conditional on SCT eligibility or referral route.	• Flexibility was included in the model such that the probability of progressing to second and subsequent lines of therapy can be altered between SCT-eligible and SCT-ineligible patients. • It would be feasible to extend the model to include proportions that were conditional on referral route, should this data become available, but this would increase the complexity of the model.
Treatment duration	• Mean durations of treatment and treatment-free intervals reported in Yong et al. (2016) are used in the model to inform treatment acquisition/administration costs and on- and off-treatment monitoring costs.[24] • In the model, these are not conditional on referral route or SCT eligibility. This	• No data were identified to directly inform the probability of patients reaching each line of therapy conditional on SCT eligibility or referral route.	• Flexibility was included in the model such that treatment and treatment-free intervals can be altered between SCT-eligible and SCT-ineligible patients. • It would be feasible to extend the model to include treatment and treatment-free intervals that were conditional on referral route, should this data become available,

	assumption may not reflect reality because, for example, it may be more likely that patients who receive SCT have longer treatment-free intervals than those who do not. Thus, the model may not be capturing all cost differences between referral routes. • In sensitivity analyses, mean durations of treatment for second and subsequent (3+) therapies were found to be in the top 10 most influential parameters for most referral routes.		but this would increase the complexity of the model.
Complications	• In the model, complication costs are applied to patients with active myeloma (active treatment or end of life care as first line management) conditional on route of presentation, based on probabilities of presenting with CRAB complications reported in Howell et al. (2017).[2] • The model assumes that the probability of presenting with CRAB complications is not conditional on first line management received, i.e. probabilities were assumed to be the same for patients who received active treatment or end of life care as first line management. This assumption may not reflect reality because, for example, you might expect patients receiving end of life care to have a higher probability of experiencing CRAB complications given that they are likely to be at a more advanced stage of disease. Thus, the model may not be capturing all cost differences between referral routes.	• There were limitations in the granularity of the data reported in Howell et al. (2017).[2] • No data were identified to inform the probabilities of experiencing CRAB complications by first line management received. • It was considered plausible by clinical experts that the rate of SREs would be lower for patients who progress following a period of observation compared with those who receive active treatment at diagnosis (e.g. because preventative steps could be taken to reduce the rate of SREs such as prescribing bisphosphonates). As such, in the absence of alternative data, it was considered appropriate to use data from Kim et al. (2019) to inform the SRE rate following observation.[27] Due to uncertainty in generalisability, rates reported in Kim et al. (2019) were not used directly in the model, but were	• It would be feasible to extend the model to include complications that were conditional on referral route, should this data become available, but this would increase the complexity of the model. • Probabilities associated with complications were not found to be in the top 10 most influential parameters in sensitivity analyses, so this assumption is unlikely to have a substantial impact on the results.

	• Similarly, the probability of having renal insufficiency and requiring long-term dialysis was assumed to be the same for patients who received active treatment or end of life care as first line management. • A lower rate of SREs was considered for patients with bone disease who progressed following observation, based on findings from Kim et al. (2019).[27] However, these data are subject to uncertainty given the small patient numbers included in the study and the limited follow up. In addition, this study is based in the US, and thus the findings may not be generalisable to UK clinical practice due to differences in patient populations and SRE definitions.	used to adjust the UK-specific SRE rate reported in Ashcroft et al. (2018).[26]	
Progression from smouldering myeloma	• In the model, treatment and complication costs are not conditional on the point at which patients enter the active treatment pathway; whether a patient enters the active treatment pathway at diagnosis or following observation (i.e. early diagnosis), the model assumes that patients accrue the same treatment and complication costs (as shown in Table 49). • As such, the model does not capture any cost benefits that may be associated with earlier diagnosis; treatment and complication costs are simply "delayed" until a patient progresses. • It is plausible that some treatment and complication costs would be mitigated through observation e.g. by taking	• No data were identified to inform whether assumptions for patients entering the active treatment pathway following observation should differ from patients entering the active treatment pathway at diagnosis.	• This is an inherent limitation of the current model structure (discussed further in Section 6.2.1). • The model includes the flexibility to modify the probability of experiencing complications for patients who initially receive observation as first-line management, but then progress to active myeloma and enter the active treatment pathway. • It would be feasible to extend the model to include treatment pathways that were conditional on referral route, should this data become available, but this would increase the complexity of the model.

	preventative measures to avoid complications.		
Accounting for the economic impact of differences in survival	• The model accounted for utility losses associated with each route of presentation in terms of the monetised QALYs lost compared with the general population (without myeloma). • This monetary value of a QALY is highly contentious, and no method is widely accepted. • In the base case, this was assumed to be £20,000 to reflect the lower limit of the NICE threshold for cost-effectiveness.[57]	• The most conservative estimate of the monetary value of a QALY was included in the base case analysis, and thus likely underestimates the economic impact of reductions in survival (and quality of life).	• A variety of sources were included in the model to explore the uncertainty in this parameter.

Abbreviations: GP: general practitioner; HMRN: Haematological Malignancy Research Network; NCIN: National Cancer Intelligence Network; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life year; SCT: stem cell transplant; TWW: two-week wait.

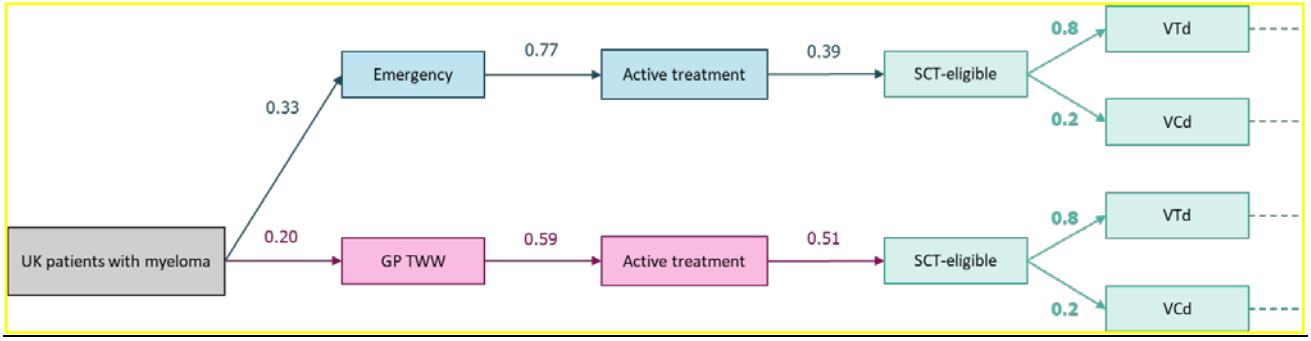
6.2.1 Probabilities (and other non-cost inputs) that are not conditional on route of presentation

As would be expected, all unit cost inputs included in the model are independent of referral route (i.e. the unit cost of a dexamethasone tablet or the cost of a haematology appointment). Differences in total costs between referral routes are therefore driven by differences in probabilities (and other non-cost inputs such as treatment durations) between referral routes. In principle, all probabilities included in the decision tree framework could be conditional on route of presentation. However, in order to inform all probabilities across the model time horizon, individual patient data capturing the occurrence of all events post-diagnosis (until death) would be required. This kind of data is rarely available in the public domain, and only summary data were identified to inform the model.

6.2.1.1 Probabilities following SCT eligibility

Of the publications identified, the data in Howell et al. (2017) had the highest level of granularity, providing data stratified by referral route for complications at diagnosis, first line management received, and for those patients who received active treatment as first line management whether they went on to receive SCT.[2] Therefore, as discussed in Table 50, all probabilities prior to and including SCT eligibility in the model are conditional on referral route. After this point in the decision tree framework, treatments received (and thus the acquisition, administration, monitoring and AE costs accrued) become conditional on SCT status alone. This is shown in Figure 35; probabilities differ between the emergency and TWW branches up to the point where patients are deemed to be eligible for SCT, but subsequent branching probabilities are common across routes.

Figure 35: Comparison of decision tree framework branches for SCT-eligible patients who present via the emergency or TWW routes



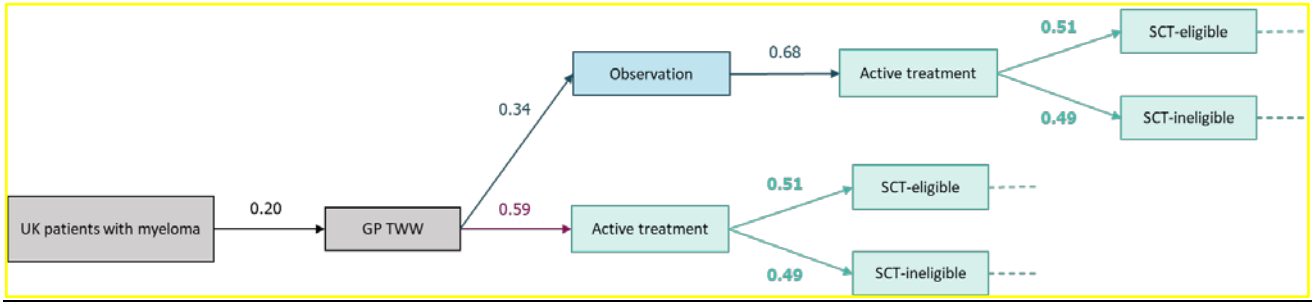
Please note that only specific branches of the decision tree framework are shown.
Abbreviations: GP: general practitioner; SCT: stem cell transplant; TWW: two-week wait.

If probabilities (and other non-cost inputs) are expected to differ between referral routes for any branches subsequent to SCT eligibility, individual patient data could be collected (e.g. from a comprehensive cancer or myeloma registry) to inform these probabilities, and the model could be extended to incorporate these data.

6.2.1.2 Probabilities following observation

Howell et al. (2017) does not provide data on subsequent events experienced by patients who received observation as first-line management (i.e. were diagnosed with smouldering myeloma). Given the time horizon of the model, some patients who receive observation as first-line management are modelled to progress to active myeloma and initiate treatment. For any particular route, it was assumed that branching probabilities (and other non-cost inputs such as treatment durations) following entry into the active treatment pathway were not conditional on the first line management received due to lack of data. This is shown in Figure 35; whether patients receive active treatment as first-line management or after observation, subsequent branching probabilities are the same.

Figure 36: Comparison of decision tree framework branches for patients who present via the TWW route and receive active treatment at diagnosis or following observation



Please note that only specific branches of the decision tree framework are shown.
Abbreviations: GP: general practitioner; SCT: stem cell transplant; TWW: two-week wait.

The implication of this assumption is that the model does not capture cost benefits that may be associated with earlier diagnosis; treatment costs are simply "delayed" until a patient progresses. If some treatment costs would be mitigated through observation (i.e. earlier diagnosis), the model would be overestimating the costs for referral routes where the proportion of patients receiving observation is higher. This would have the smallest impact on the emergency route, where the majority of patients enter the active treatment pathway at diagnosis.

If the parameters informing the active treatment pathway (SCT eligibility, treatments received, treatment durations, etc.) are expected to differ between patients initiating active treatment at diagnosis or following observation, data to inform these parameters could be collected and incorporated into the model.

6.3 Interpreting the Model Results

For a patient diagnosed with myeloma in the UK, the model estimates an average per patient undiscounted lifetime cost of approximately £168,000, of which £119,000 constitutes treatment costs (acquisition, administration, monitoring and AE costs), £39,000 constitutes the costs of managing complications, and £10,000 constitutes end of life care. This seems plausible based on estimates from other sources; a study by de Oliveira et al. (2016) estimated the undiscounted net lifetime cost of myeloma care (i.e. the cost difference between patients and matched non-myeloma control subjects) in Ontario, Canada, to be around £90,000 ($119,958 2009 Canadian dollars).[59] This was based on patients diagnosed between 1997 and 2007; this time period is prior to the recommendation of the majority of novel myeloma therapies (bortezomib was only recommended by the Canadian Agency for Drugs and Technologies in Health [CADTH] in 2012), so the cost of myeloma care may be substantially higher than this estimate in UK clinical practice. It is also unclear whether this estimate includes the costs of managing complications. When monetised QALY losses are included in the economic costs, the per patient undiscounted lifetime costs are estimated to be approximately £395,000.

Data reported in Howell et al. (2017) and from the NCIN indicate that more patients present via the emergency route than any other route, and the model reflects this, showing the total costs at the cohort level to be highest for the emergency route. For the incident population of patients with myeloma in the UK (~5,700 patients), the model estimates total lifetime undiscounted direct costs of £957 million, of which £325 million is associated with the emergency route.

Considering total direct costs (i.e. excluding monetised QALYs) per route of presentation (1 patient per route), complication and end of life care costs were considerably higher for the emergency route, reflecting a cost benefit associated with earlier diagnosis (Figure 27). As a result, the emergency route was associated with marginally higher total direct costs than the non-emergency routes (Figure 22), providing an economic argument for earlier diagnosis. However, despite the differences in patient characteristics between routes of presentation, total treatment costs appear to be similar across routes of presentation (Figure 27), which may explain why there are only minimal differences in total direct costs:

1. Costs for patients with an initial diagnosis of active myeloma form a larger contribution to the total costs of the emergency route than for the other routes. In contrast, costs for patients with an initial

diagnosis of smouldering myeloma form a much larger contribution to the total costs of other routes of presentation. As shown in Section 5.1.5 and discussed in Section 6.2.1, it was assumed that treatment costs are not conditional on the point at which patients enter the active treatment pathway, so patients with an initial diagnosis of smouldering myeloma accrue the same costs as those with an initial diagnosis of active myeloma. As such, total treatment costs (across those with an initial diagnosis of active or smouldering myeloma) are relatively similar between referral routes.

2. There are also differences in the contributions from the SCT-eligible and SCT-ineligible treatment pathways to the treatment costs. However, treatment costs for an SCT-eligible or SCT-ineligible patient are largely similar, since the proportions of patients progressing to second and subsequent lines of therapy and treatment durations are assumed to be independent of SCT status.
3. There are two groups of patients in the model who do not accrue treatment costs: those who receive end of life care as first line management and those who those who receive observation as first line management who die prior to progression. The proportions of patients in these two groups may therefore drive differences in costs between routes of presentation. However, there appears to be an inverse relationship between these two proportions: the proportion of patients receiving end of life care as first line management is higher for the emergency route, resulting in decreased costs relative to the other referral routes, but the proportion of those who receive observation as first line management is lower, resulting in increased costs relative to the other referral routes. As such, cost differences may cancel out to some extent.

It is plausible that a cost benefit associated with earlier diagnosis exists in terms of treatment costs (e.g. patients who are diagnosed earlier may have a better response to treatment and thus have shorter treatment intervals). However, due to structural limitations of the modelling approach arising from limited granularity of data (see Section 6.2) a cost benefit in terms of treatment costs is not captured in the model. It is also plausible that earlier diagnosis is associated with higher treatment costs (e.g. patients have better survival and thus require treatment for longer periods of time), but for the same reasons, a cost impact is currently not captured in the model. These limitations could be mitigated through collection of individual patient data (e.g. from a comprehensive cancer or myeloma registry).

When monetised QALY losses are included in the total costs per route of presentation (1 patient per route), the emergency route is associated with considerably higher costs than all other routes (Figure 24). This is because observation is associated with a substantial QALY gain, whilst very few QALYs are accrued for those who receive end of life care as first line management. Given the poor prognosis for patients presenting via the emergency route, there is a reduced probability of receiving observation compared with the other referral routes, and a higher probability of receiving end of life care, so QALY losses are higher for this route.

However, these results should be interpreted with caution, as they may be subject to lead time bias. Observation does not involve active management, so observation does not change the probability of progressing from smouldering myeloma to active myeloma, it only enables more accurate identification of the point where a patient progresses. Therefore, whilst it is plausible that receiving observation as first line management might result in a survival or HRQoL benefit following progression to active myeloma (since treatment can be initiated as soon as it is needed), QALYs gained whilst in observation are merely co-incidental, and are not reflecting a survival or HRQoL benefit facilitated by earlier diagnosis. The fact that referral routes with a higher proportion of patients receiving observation as first line management are associated with fewer QALY losses could therefore be considered an artefact, and does not necessarily provide evidence for an economic benefit of earlier diagnosis. In fact, as described in Section 6.2.1.2 for treatment and complication costs, it was assumed that the QALYs gained following entry into the active treatment pathway are not conditional on first line management received (i.e. observation was not associated with survival or HRQoL benefit following progression to active myeloma). On the other hand, QALYs gained via a smaller proportion of patients receiving end of life care as first line management does reflect a survival or HRQoL benefit facilitated by earlier diagnosis – diagnosing patients earlier such that they are still able to receive active treatment is likely to confer a survival or HRQoL benefit. Further research would need to be conducted to explore whether prior observation (i.e. earlier diagnosis) facilitates a survival or HRQoL benefit compared with patients who enter the active treatment pathway at diagnosis.

6.4 Conclusions

In summary, the results suggest that there may be an economic benefit associated with earlier diagnosis through a reduction in complication and end of life care costs. The analysis highlights two important data gaps that could be addressed through further research and would help to reduce uncertainty in the economic cost of myeloma diagnosis and treatment:

- The benefits of earlier diagnosis through prior observation; does prior observation facilitate a reduction in treatment costs, complications or survival and/or HRQoL benefits?
- The benefits of earlier diagnosis, independent of prior observation; do certain referral routes (i.e. earlier diagnosis) facilitate a reduction in treatment costs and/or HRQoL benefits for equivalent patients (e.g. for patients who receive active treatment at diagnosis and are eligible for SCT)?

This model comprehensively explores the factors that may drive differences in economic costs between routes of presentation for patients with multiple myeloma in the UK. The analysis provides a focus for future research aiming to build the economic case that more funding should be dedicated to myeloma diagnosis in clinical practice and research.

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