Summary Table of Study Protocol

Title	Risk Prediction, Prognosis and Management of Cardiac Events Among Patients With Multiple Myeloma
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Date of last version of the protocol	13 September 2016
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Country(-ies) of Study	USA

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Marketing Authorisation Holder

Marketing authorisation holder(s)	*NA*
MAH Contact	*NA*

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I have read the attached protocol entitled Risk Prediction, Prognosis and Management of Cardiac Events among Patients with Multiple Myeloma, dated 13 September 2016, and agree to abide by all provisions set forth therein.

<<I agree to ensure that Financial Disclosure Statements will be completed by:

- *me (including, if applicable, my spouse {or legal partner] and dependent children)*
- *my Subinvestigators (including, if applicable, their spouses {or legal partners] and dependent children)*

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.>>

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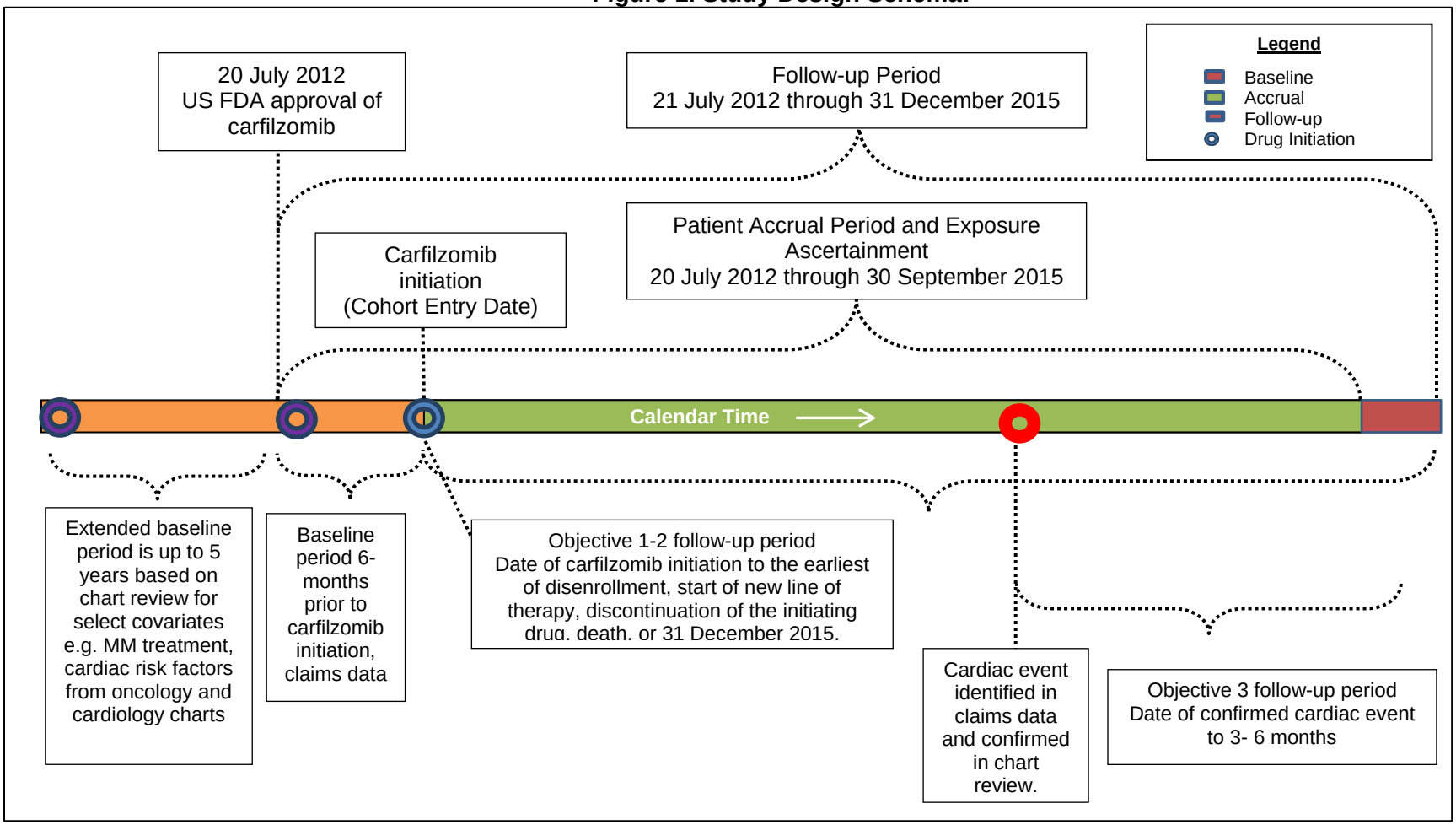
Anthony P Nunes

Signature	25/July/2016
Name of Investigator <<*Coordinating Investigator*>>	Date (DD Month YYYY)

Figure 1. Study Design Schema:



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2. List of Abbreviations

AE	Adverse Event
BNP	Brain Natriuretic Peptide
BSA	Body Surface Area
CI	Confidence Interval
CV	Cardiovascular
COPD	Chronic Obstructive Pulmonary Disease
CPT	Current Procedural Terminology
CTCAE	Common Terminology Criteria for Adverse Events
cTnT	Cardiac troponin
ECOG	Eastern Conference Oncology Group
EMR	Electronic Medical Record
ESRD	End Stage Renal Disease
FDA	The Food and Drug Administration
GAF	Global Assessment of Functioning
GI	Gastrointestinal
HCFCA	Health Care Financing Agency
HCPCS	Healthcare Common Procedure Coding System
ICD-9	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	International Classification of Diseases, 10th Revision, Clinical Modification
IHD	Ischemic Heart Disease
IRB	Institutional Review Board
LOT	Line of Therapy
LVEF	Left Ventricular Ejection Fraction
MM	Multiple Myeloma
NCCN	National Comprehensive Cancer Network
NDC	National Drug Codes
NT-pro-BNP	N-terminal-pro- Brain Natriuretic Peptide
ORD	Optum Research Database
OS	Overall Survival
PB	Privacy Board
SOP	Standard Operating Procedure
US	United States

3. Responsible Parties

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4. Abstracts

Study Title

Risk Prediction, Prognosis and Management of Cardiac Events among Patients with Multiple Myeloma

Study Background and Rationale

Carfilzomib (Kyprolis) is a proteasome inhibitor indicated for the treatment of patients with advanced multiple myeloma (MM). Cardiac events in patients with MM have been associated with several classes of anti-MM treatments, including chemotherapy agents, immunomodulatory drugs, and proteasome inhibitors.

While data on cardiovascular (CV) safety related to carfilzomib exists, uncertainties in the real world use of carfilzomib remain. The aim of this protocol is to address gaps in the current understanding of the occurrence of cardiac events among MM patients treated with carfilzomib using a real world data source.

Research Question and Objective(s)

Objective 1: Quantify the occurrence of preselected cardiac events in MM patients treated with carfilzomib

Objective 2: Describe predictors for preselected cardiac events in MM patients receiving carfilzomib

Objective 3: Describe the subsequent treatment and prognosis of cardiac events

Study Design/Type

This will be a retrospective cohort study of the relapsed/ refractory MM patients using enrollment, pharmacy, and medical claims from a large US commercial health insurance claims database and from a Medicare Advantage database, both affiliated with Optum, and chart review for eligible patients. Chart review will consist of oncology chart review for carfilzomib exposure and cardiology chart review for cardiac events.

Among patients with cardiac event claims, cardiology medical charts review will be used to confirm cardiac events. For patients with confirmed cardiac event, a more detailed patient history of risk factors will be abstracted from the cardiology medical chart.

Study Population or Data Resource

The cohort will be defined from two separate data sources.

1) Claims data: Cohort identification will be collected from claims data. Patients with evidence of MM and carfilzomib administration will be identified from the claims database. Potential cardiac events will be identified from claims data and later confirmed in cardiology charts.
2) Chart data: Cardiac event adjudication will be collected from chart data to obtain information typically not available in claims data.

a. Oncology charts: Oncology charts from the provider associated with carfilzomib administration will be sought for all carfilzomib initiators. Additional details on MM treatments will be abstracted from the oncology charts.

b. Cardiology charts: Among patients with an observed claim for a cardiac event of interest, cardiology charts will be requested and adjudicated for the claims-identified events. Additional details on the cardiac event including diagnoses, tests and observations pertinent to the diagnosis of cardiac events will be abstracted from the cardiology charts. For objective 3, details on the cardiac event treatments and patient prognosis will be abstracted from the cardiology charts.

Data derived from claims and chart information will be used for analysis of all study objectives.

Summary of Patient Eligibility Criteria

MM patients initiating carfilzomib will be identified from 21 July 2012 through 30 September 2015. Patients will be eligible for inclusion in the study upon meeting the following criteria:

- Complete medical coverage (Commercial or Medicare Advantage)
  - Patients with incomplete or conflicting enrollment dates, age, or sex will not be included
- Chart eligible at cohort entry
- At least 6-months of enrollment in the health plan prior to and including the cohort entry date.
- At least one diagnosis of MM (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9] 203.0x or 10th Revision [ICD-10] C90.0x) up to 5-years (as available) preceding the carfilzomib dispensation or administration date

Follow-up

Two separate follow-up periods are defined:

For objective 1 and 2, follow-up will extend from date of carfilzomib initiation to the earliest of disenrollment, start of new line of therapy, discontinuation of the initiating drug, death, or 31 December 2015.

For objective 3, evaluation of the treatments used and prognosis of patients with cardiac events, follow-up will extend beginning from confirmed cardiac event to 3 to 6 months.

Variables

- Outcome Variables

  For objectives 1 and 2, cardiac events will initially be identified within the claims databases and then confirmed in cardiology chart review.

- Preselected cardiac events of interest will be defined using claims-based algorithms. Cardiac events of interest include hypertension (overall and malignant), cardiac failure, ischemic heart disease, acute myocardial infarction, cardiac arrhythmias, conduction disorders, and cardiomyopathy.

- Cardiology charts corresponding to the cardiac events identified in the claims will be sought for chart review. Final definitions of select cardiac outcomes will be developed in collaboration with Optum epidemiologists, Amgen collaborators, and clinical consultants. Medical records associated with the potential cardiac events will be requested for outcome adjudication by cardiologist(s). In addition to the adjudication, the clinician(s) will abstract from the medical charts mentions of explicit diagnoses, tests and observations pertinent to the diagnosis of cardiac events.

For objective 3, subsequent treatment and prognosis of cardiac events will be assessed from cardiology charts. Signs of changes in cardiac function including diagnoses and treatments of dyspnea, venous engorgement, cyanosis and edema occurring after the chart-confirmed cardiac event will be sought as added indicators of prognosis.

Exposure Variables
Dispensations and administrations of carfilzomib will be identified within claims data through the presence of HCPCS. Exposures will be further classified according to line of therapy and treatment regimen at cohort enrollment.

– Other Covariates
Covariates will be assessed from the claims and medical charts, as available. Demographic attributes and other clinical characteristics will be determined on the cohort entry from claims data during the 6-month baseline period. From oncology and cardiology medical charts, vital signs and laboratory measures will be assessed over time.

Baseline covariates summary from claims and chart data:
- Socio-demographics
  - Age
  - Sex
  - Race/ethnicity
  - Geographic region
  - Weight
  - Height
  - Body surface areas (BSA)
  - Tobacco use
  - Alcohol use
  - Sedentary life style

- Comorbidities
- Comedications
- MM characteristics (e.g. stage, duration)
- Responses to prior therapy
- Vital signs (repeated over time)
  - Blood pressure
  - Heart rate
  - Respiratory rate
  - Pulse oximetry
- Laboratory values (repeated over time)

Data Analysis

Among the MM patients treated with carfilzomib, the occurrence of chart-confirmed cardiac events will be summarized, overall, by subtype and by key comorbidity strata within the MM patient population. The frequency and percent of claims-identified events as well as those of chart-adjudicated events will be reported for each cardiac event.

To describe predictors for preselected cardiac events in MM patients receiving carfilzomib, cross tabulations of confirmed cardiac events from medical chart review by treatment patterns, patient attributes, and potential cardiovascular risk factors will be presented. After assessment of univariate analyses, regression modeling will be used to evaluate the adjusted association between the potential risk factors and cardiac events.

Indicators of cardiac prognosis and treatment will be described overall, by line of therapy, by treatment regimen, and by refractory disease state. Indicators of prognosis will include claims based measures and chart-based measures.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
Start of data collection (Obtain Claims Data)	17 October 2016
Start Medical Record Procurement	31 January 2017
End of data collection (Complete Medical Record Procurement)	31 May 2017
Final report of study results	31 May 2018

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Multiple myeloma (MM) is the second-most common hematological malignancy and constitutes 1% of all cancers.(1) The prognosis of patients with MM has been improving in recent years, from a five-year survival rate of 29.6% in 1990, when melphalan and high-dose dexamethasone were the only available targeted therapies, to more than 45% in 2006 with the introduction of new drugs.(2) Immunomodulators (thalidomide, lenalidomide) and proteasome inhibitors (bortezomib, carfilzomib) are the cornerstones of current chemotherapy.(3; 4) In addition, high-dose dexamethasone, prednisone, vorinostat, doxorubicin, and other chemotherapeutic agents are used (either alone or in combination regimens) for the management of MM. Very little is known about the real world choice of different treatment regimens among MM patients in current oncology practice.

Carfilzomib is a proteasome inhibitor indicated for the treatment of patients with MM. From July 2012 to July 2015, the labeled indications and usage of carfilzomib specified treatment of patients with MM who had received at least two prior treatments (including bortezomib and an immunomodulator), with progression within 60 days of completing the last therapy.(5) The indications for usage were modified in 2015 and again in 2016 to include combinations with dexamethasone and lenalidomide.(6; 7)

The aim of the current protocol is to address gaps in the current understanding of the occurrence of cardiac events in relapsed/ refractory MM patients exposed to carfilzomib and subsequent treatment and prognosis relating to the events.

7.1.1 Background and Rationale

Cardiac events are not rare in patients with MM, particularly in elderly patients. These events may be due to age-related comorbidities, the effects of disease itself, or previous or current treatments received. Many factors have been associated with the development of cardiac diseases in patients with MM and MM-associated adverse events (AEs), such as chronic anemia, hemodynamically significant arteriovenous shunt, and hyperviscosity. (5) Amyloid light-chain amyloidosis is present in about 10% of patients with MM and can manifest as heart failure when the heart is involved. Cardiac events in patients with MM have been associated with several classes of anti-MM treatments, including chemotherapy agents, immunomodulatory drugs, and proteasome inhibitors. Systolic left ventricular dysfunction and overt heart failure are the most frequently reported treatment-related cardiac AEs associated with MM treatments. Studies suggest that patients receiving stem cell transplants, particularly those receiving allogeneic stem cell transplants, are at increased risk for cardiovascular (CV) disease.

While data on CV safety related to carfilzomib exists, uncertainties in the real world use of carfilzomib remain. Data from 526 patients with relapsed and/or refractory MM enrolled in Phase II trials and treated with a single agent (carfilzomib) indicate that any cardiac adverse event occurred in 22.1% of patients, hypertension in 14.3%, cardiac arrhythmia in 13.3%, and ischemic heart disease in 3.4%. Aggregated cardiac failure events including congestive heart failure, pulmonary edema and decreased left ventricular ejection fraction (LVEF) were reported in 7.2% of patients; with the severity of the majority of events classified as Grade 3 (severe) or 4 (life threatening) using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). (8) In a recent trial where a higher dose (56 mg/m2) of carfilzomib was utilized in a cohort of 44 relapsed/refractory MM patients who were heavily pre-treated, the prevalence of carfilzomib-related Grade 3/4 hypertension and heart failure (defined as left ventricular systolic dysfunction, pulmonary edema, and/or other criteria) increased to 25% and 11% respectively. (9) Hypertension necessitated carfilzomib dose reductions occurred in 11% of cohort patients. Although heart failure appears to be more prevalent during early treatment with carfilzomib, later presentations were observed after 12 and 14 cycles of treatment. In the ASPIRE trial, adverse cardiac events were observed with higher frequency during the first 18 cycles of carfilzomib than in later cycles. (10)

There is a need to accurately quantify the incidence of CV events, better describe comorbidities associated with these events that might lead to a better understanding of the mechanism of cardiotoxicity.

Prognosis and outcomes for patients who developed cardiac events depends on the severity of events, the patients' pulmonary and cardiovascular function, other co-morbid conditions, and the treatment history. Co-morbid conditions, which are prevalent in elderly MM patients, may increase the chance of having a cardiac event, as well as may affect the prognosis following a cardiac event. It is important to understand the full range of symptoms associated with cardiac events in MM patients during chemotherapy. The clinical presentation, management of cardiac events, and prognosis among MM patients during chemotherapy treatment has not been well studied in the real world practice setting. In this descriptive study, we intend to conduct to examine the evolution of cardiac events, the treatment options, and associated outcomes/prognosis in MM patients.

8. Research Question and Objectives

Objective 1: Quantify the occurrence of preselected cardiac events in MM patients treated with carfilzomib (claims plus chart review)

Objective 2: Describe predictors for preselected cardiac events in MM patients receiving carfilzomib (claims plus chart review)

Objective 3: Describe the subsequent treatment and prognosis of cardiac events (claims plus chart review)

9. Research Methods

9.1 Study Design

All objectives included in this protocol will be addressed within the context of a retrospective cohort study relying on the pharmacy and medical claims from a large US commercial health insurance claims database and from a Medicare Advantage database and chart review for eligible patients. Chart review will consist of oncology chart review for carfilzomib exposure and cardiology chart review for cardiac events. Based on prior work at Optum, medical charts will be available for a subset of patients from the medical claims. This subset is based on primary insurance providers who agree to share their medical chart data with Optum. Patients from these insurance providers are defined as charts eligible. Core eligibility and design features are the same for all objectives and are summarized in Table 1.

Table 1: Overview of eligibility and design elements by objective

Objective	Carfilzomib	Charts eligible	Oncology chart	Cardiac chart	Minimum baseline requirement in claims	Accrual Period 20-Jul-2012 through	Follow up period 21-Jul-2012 through
Objective 1	Yes	Yes	Yes	Yes	6-months	30-Sep-15	31-Dec-15
Objective 2	Yes	Yes	Yes	Yes	6-months	30-Sep-15	31-Dec-15
Objective 3	Yes	Yes	Yes	Yes	6-months	30-Sep-15	31-Dec-15

Cohort identification and data collection from claims:

Patients treated with carfilzomib will be identified from the claims database. Patients with evidence of MM and carfilzomib administration will be accrued from 20 July 2012 through 30 September 2015. Apparent line of therapy will be determined in the claims data based on algorithms developed by Amgen (as described in Section 9.2.2.1). To provide additional information for determining all lines of therapy MM treatments will be identified for at least 6 months and up to five years before the date of carfilzomib initiation in the claims data. Patients will be followed from their cohort entry date (initiation of carfilzomib) through the earliest of disenrollment, death, or 31 December 2015 to identify potential cardiac events during or within 30 days of carfilzomib administration.

Cardiac event adjudication and data collection from charts:

Oncology charts

Oncology charts from the provider associated with carfilzomib administration will be sought for all carfilzomib initiators. Additional details on MM treatments will be abstracted from the oncology charts.

Cardiology charts

Among patients with an observed claim for a cardiac event of interest, cardiology charts will be requested and adjudicated for the claims-identified events. Chart review will confirm or deny claims based cardiac events. Chart review will not identify cardiac events not listed in claims and no new cardiac events will be collected. Chart review will begin at date of confirmed cardiac event (chart review confirmation) to at least three months and up to 6 months after event, as available. Additional details on the cardiac event including diagnoses, tests and observations pertinent to the diagnosis of cardiac events will be abstracted from the cardiology charts. Adjudication of the cardiac events will be performed by cardiologist(s).

Data derived from claims and chart information will be used for analysis of all study objectives.

9.2 Setting and Study Population

9.2.1 Study Period

For the claims analysis for cohort creation and potential cardiac event identification, the full study period, including baseline, accrual, and follow-up, will extend from 20 July 2007 (allowing for up to five years of baseline data) through 31 December 2015. Patient accrual will occur from 20 July 2012 through 30 September 2015 (Figure 1). Ending accrual in September 2015 allows for a minimum of 3-months of follow-up to observe cardiac events. Individual patients will not be required to have a minimum follow-up period to be included in the analysis. Patient follow-up will be censored at the earliest of exit from the health plan, death, or 31 December 2015. Oncology charts will be requested for the same study periods for the claims, so that we can capture full MM treatment history. Cardiology charts will be requested for the 30 day period before the event until approximately 3 to 6 months.

9.2.2 Patient Eligibility

9.2.2.1 Inclusion Criteria

This study will include patients with MM initiating carfilzomib.

Carfilzomib will be identified through the presence of corresponding Healthcare Common Procedure Coding System (HCPCS) codes within the claims database.

Patients will be eligible for inclusion in the study upon meeting the following criteria:

- Complete medical coverage (Commercial or Medicare Advantage)
    - Patients with incomplete or conflicting enrollment dates, age, or sex will not be included
- Chart eligible at cohort entry. Chart eligible patients are patients from insurance providers who agree to share their medical chart data with Optum.
- At least 6-months of enrollment in the health plan prior to and including the cohort entry date.
- At least one diagnosis of MM (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9] 203.0x or 10th Revision [ICD-10] C90.0x) up to 5-years (as available) preceding the carfilzomib dispensation or administration date

- To identify the apparent line of therapy for the initiating carfilzomib, a full list of MM treatments will be utilized:
    - Proteasome inhibitors
        - Bortezomib
        - Carfilzomib
    - Immunomodulators
        - Thalidomide
        - Lenalidomide
        - Pomalidomide

- Alkylating agents
    - Melphalan
    - Cyclophosphamide
- Others
    - Bendamustine
    - Cisplatin
    - Doxorubicin
    - Liposomal doxorubicin
    - Etoposide
    - Panobinostat
    - Vincristine
    - Vorinostat

Starting with the earliest observed MM diagnosis (up to five years prior to cohort entry, as available), the apparent lines of therapy will be identified using the following logic based on previously defined algorithms in the ORRG approved Amgen Protocol 20150150:

- A line of therapy encompasses the time between the start of one line to the start of a next line.
- Each line of therapy may be comprised of a treated period (time on active treatment) and an untreated period (treatment gaps). Initiation dates and termination dates for each line of therapy will be based on dispensations and administrations observed in the claims.
- The start of treatment for the apparent first line will be defined as the earliest observed date a patient received any MM-related chemotherapy.
- The regimen for a line is defined as all drugs administered during the first 3 months of a line. If another agent is administered within 3 months of the first administration, it will be considered to be part of the combination regimen for that line of therapy.
- The end of the treated period for a line of therapy will be defined by either a 90-day gap for all drugs in the regimen or the initiation of a new drug that was not adjunctive to the existing regimen (i.e., a switch to a subsequent line of therapy). If a switch to a subsequent line of therapy does not occur, then the treated period

of the earlier line of therapy will cease at the end of the drug dispensing date + days supply, or the administration date + 12 days.

- The day following the end of the treated period for the earlier line of therapy signifies the start of a treatment gap between the earlier line of therapy and the subsequent line of therapy. The treatment gap ends when a subsequent line of therapy begins, or at the end of follow-up. Re-initiation of a prior line of therapy after a gap in all therapy of over 3 months constitutes a new line. If a switch to a subsequent line of therapy occurs, the duration of the treated period for the earlier line of therapy will be censored on the switch date and zero days will be included in the untreated period.

9.2.2.2 Exclusion Criteria

No exclusion criteria will be applied beyond what is implied through the inclusion criteria.

9.2.3 Baseline Period

The baseline period will be the six months of continuous enrollment in the health plan prior to cohort entry date, with the cohort entry date set as the initiation of carfilzomib treatment in the claims.

The baseline period for selected covariates will be at least 6-months, but up to 5-years prior to and including cohort entry, as available from the claims. Chart review will identify additional variables including MM history and treatments. See Section 9.2.7 for full list of covariates identified by chart and claim review.

9.2.4 Study Follow-up

Two separate follow-up periods are defined:

For objective 1 and 2, follow-up will extend from the day after the cohort entry date (carfilzomib initiation) to the earliest of disenrollment, start of new line of therapy, discontinuation of the carfilzomib, death, or 31 December 2015. Death will be identified through a linkage to the Social Security Administration's Death Master File, or by the

presence of a hospital discharge status indicative of death or a diagnosis code for sudden death (ICD-9 798.xx), and no claims after 30 days of the corresponding hospital discharge status or sudden death code.

For objective 3 analyses of the treatment and prognosis of cardiac events, follow-up extend on the date after the confirmed cardiac event until approximately 3 to 6 months.

9.2.5 Exposure Assessment

Dispensations and administrations of carfilzomib will be identified within claims data through the presence of HCPCS. Exposures will be further classified according to line of therapy and treatment regimen at cohort enrollment.

Determination of the actual line of therapy within the claims data may be limited if the length of enrollment prior to cohort entry is not sufficient to capture the incident MM diagnosis. For this reason, the apparent line of therapy within the claims data is likely to underestimate the true line of therapy for patients with shorter baseline periods. Therefore, medical chart will be sought to improve the characterization of time since MM diagnosis and true line of therapy. Additional exposure data will be abstracted from the medical charts, as available, including line of therapy associated with the initiating therapy and dosage, dose delays and dose reductions occurring during the line of therapy initiated on the index date. The listing of data elements relating to MM therapy to be abstracted will be detailed in the abstraction and adjudication forms. A preliminary list is provided in Appendix 1.

9.2.6 Outcome Assessment

For objectives 1 and 2, occurrence of cardiac events will be identified during the period of time extending from day of cohort entry through the earliest of carfilzomib discontinuation plus 30 days, death, or 31 December 2015. Cardiac events will initially be identified within the claims databases. Preselected cardiac events of interest are defined and related claims-based algorithms to identify potential cases are listed in Table 3. The intent is to identify cardiac events occurring during the active treatment of

carfilzomib. The active treatment period is defined from first administration of carfilzomib to 30 days after the last carfilzomib administration. Cardiac medical history will be collected during the baseline period. New and recurrent cardiac events will be collected during the active treatment period. For hypertensive events only, not including malignant hypertension, the analysis will be restricted to incident events only. Refer to Analysis Section 9.7.2 for full explanation of analysis for recurrent and incident events.

Table 3: Claims based identification of cardiac events of interest

Outcome	**ICD-9***	**Details**	**Claims in baseline period for potential event identification**	**Type of event**
Hypertension	401.XX, 402.XX, 403.XX, 404.XX, 405.XX, 437.2X	1 In-patient, 2 out-patient, hypertensive medication	No	Incident
Malignant hypertension (subset of hypertension)	402.0X, 403.0X, 404.0X, 405.0X, 437.2X	1 In-patient, 2 out-patient, hypertensive medication	Yes	Incident and recurrent
Heart Failure	428.X	Primary hospital discharge	Yes	Incident and recurrent
Ischemic heart disease (IHD)	410.xx, 411.xx, 413.xx, 414.xx	1 In-patient, 2 out-patient	Yes	Incident and recurrent
Acute Myocardial infarction (subset of IHD)	410.x	1 In-patient, 1 ER	Yes	Incident and recurrent
Cardiac arrhythmias	427.xx and 798.xx	Any position	Yes	Incident and recurrent
Conduction disorders	426.xx	1 In-patient, 2 out-patient	Yes	Incident and recurrent
Cardiomyopathy	425.x	1 In-patient, 2 out-patient	Yes	Incident and recurrent

* ICD-10 codes will be added as needed

Cardiology charts corresponding to the cardiac events identified in the claims will be sought for medical chart review and the following information related to cardiac diagnoses will be abstracted (as available):

- Brain Natriuretic Peptide (BNP)
- N-terminal-pro-BNP (NT-pro-BNP)
- Cardiac troponin T (cTnT)
- Electrocardiogram results
- Echocardiogram results

The cardiology chart abstraction effort will include records from 30 days prior to through 3 to 6 months after the claims diagnosis date.

As an assessment of the potential for false negatives within the claims data, the oncology chart obtained for the purposes of treatment assessment will be reviewed to identify cardiac events that were recorded in the medical charts but not identified in the claims environment.

For objective 3, subsequent treatment and prognosis of cardiac events will be assessed. From the claims data, indicators of prognosis will include site of care, length of stay, treatments received, and date of death (as available). Signs of changes in cardiac function including diagnoses and treatments of dyspnea, venous engorgement, cyanosis and edema occurring after the chart-confirmed cardiac event will be sought as added indicators of prognosis. Assessment of clinical symptoms/signs and treatments will rely on claims-based identification of dispensations, administrations, and procedures supplemented with cardiac chart review.

9.2.7 Covariate Assessment

Covariates will be ascertained from the claims and/or medical charts. Demographic attributes will be determined on the cohort entry date while other factors, unless otherwise specified, will be assessed in the 6-months baseline period.

Claims data:

Baseline covariates will include the following:

- Socio-demographics
  - Age
  - Sex
  - Race/ethnicity

- Geographic region

- Comorbidities
  - Acute renal failure
  - Anemia
  - Family history of cardiovascular disease
  - Cardiovascular diseases
    - Cardiomyopathy
    - Hypertension
    - Malignant hypertension
    - Cardiac failure
    - Ischemic heart disease
    - Cardiac arrhythmia
  - Conduction disorders
  - Cerebrovascular disease
  - COPD/emphysema
  - Diabetes
  - Dyspnea
  - Fractures/skeletal related events
  - Dyslipidemia
  - Hypercalcemia
  - Moderate to severe liver disease (hepatitis, cirrhosis)
  - Neutropenia
  - Other cancers
  - Peripheral neuropathy
  - Renal diseases including end stage renal disease (ESRD)
  - Thrombocytopenia
  - Thromboembolic events
  - Thyroid disorder/Parathyroid
  - Additional comorbidities to be empirically identified through review of the top 50 most commonly observed diagnoses within the baseline period

- Comedications
  - Prior MM treatments
  - Additional comedications to be empirically identified through review of the top 50 most commonly observed dispensations

(generics) or administrations (HCPCS J-codes) within the baseline period

- MM Characterization
    - Year of earliest observed MM diagnosis (up to 5-years prior to index date)
    - Indicator for whether earliest MM diagnoses is an incident diagnosis
        - Defined as at least 12 months of enrollment data prior to the earliest MM diagnosis with no MM diagnoses or chemotherapy.
    - Stem cell transplantation (up to 5-years prior to index date)
    - Anthracycline use
    - Prior radiation use
    - Treatment for anemia
        - Blood transfusion
        - Growth factors
        - Anticoagulation

Chart data:

A preliminary list of baseline covariates to be abstracted from charts is provided below. Other covariates will be assessed repeatedly at each line of therapy. The final list will be developed in collaboration with the clinical consultants.

- Socio-demographics
    - Weight (repeated over time)
    - Height (latest measure within 6-month baseline)
    - Body surface areas (BSA) (derived from height and weight)
    - Tobacco use (latest measure within 6-month baseline)
    - Alcohol use (latest measure within 6-month baseline)
    - Sedentary life style (yes/no)
- MM Characterization
    - Date of first diagnosis
    - Stem cell transplantation (up to 5-years prior to index date)
    - Anthracycline use
    - Prior radiation use
    - Performance at index date and at each line of therapy (as available)
        - Eastern Conference Oncology Group (ECOG) score
        - Global Assessment of Functioning (GAF) score

        - Kornofsky Scoring
    - Staging at cohort entry
    - Staging at first diagnosis
    - Cytogenetic mutation and/or risk category
    - Prior treatment and responses to prior therapy
        - Any prior refractory
        - Date of latest refractory
        - Any prior disease progression
        - Date of latest progression
- Vital Signs (repeated over time)
    - Blood pressure (systolic, diastolic)
    - Heart rate
    - Respiratory rate
    - Pulse oximetry
- Laboratory Values (repeated over time)
    - m-protein
    - Serum ferritin level
    - Bone marrow biopsy results (e.g. % plasma cells)
    - Plasmacytoma or bone lesions
    - Hemoglobin level
    - Liver test (ALT/AST, albumin)
    - Iron level (ferritin level)
    - Renal function test (blood urea nitrogen, and creatinine)
    - Serum β2-microglobulin
    - Creatinine clearance
    - C-reactive protein
    - Lactate dehydrogenase

9.2.8 Validity and Reliability

Potential cardiac events will be initially identified in claims data and confirmed through cardiology chart review. All cardiology charts will be reviewed by two clinical consultants. Agreement will be assessed for each reviewed chart, and if differences are

observed, the clinical consultants will discuss in order to provide a consensus assessment of cardiac events.

To assess of the potential for false negatives within the claims data, the oncology charts of patients will be reviewed to identify chart-recorded cardiac events that were not recorded in the claims environment. We will report the number of cardiac events mentioned in the oncology chart that were not captured by the claims based assessment of cardiac events. While the oncology chart should not be viewed as a gold standard in this case (since patients may receive their cardiac diagnosis elsewhere), this comparison may be informative with respect to the potential for false negatives when relying on the claims data.

For covariates where data are derived from claims and charts, the data from charts will be analyzed. Data from charts are expected to be more reliable as to the true status of the patient by including information that may not be captured in claims that include billing information only.

9.3 Data Sources

This study includes data from two medical insurance claims databases – the Optum Research Database (ORD) and the Medicare Advantage (including Part D) (MA-PD) Database. Each is described in detail below. Data from oncology and cardiology medical charts will be used for patients who are chart eligible as based on the healthcare providers. Based on prior work at Optum, medical charts will be available for a subset of patients from the medical claims. This subset is based on primary insurance providers who agree to share their medical chart data with Optum. Patients from these insurance providers are defined as charts eligible.

9.3.1 Data Sources: Optum Research Database (ORD) Commercial Claims Data

Optum has access to the Optum Research Database (ORD), a proprietary research database containing medical and pharmacy claims with linked enrollment information with data covering the period from 1993 to current. For 2011, data relating to approximately 12.8 million individuals with both medical and pharmacy benefit coverage are available. The data undergo regular audits and quality control procedures by the insurer and are updated monthly. The accessible information includes demographics,

pharmacy use, and all medical and facility claims, which provide data on services, procedures, and their accompanying diagnoses. The insured population from which the data are drawn is geographically diverse across the US and comprises approximately 3% to 4% of the US population.

The coding of medical claims conforms to insurance industry standards including:

- Use of designated claims forms (e.g., physicians use the HCFA-1500 format and hospitals use the UB-92 format)
- International Classification of Diseases, Ninth Edition (ICD-9) and Tenth Addition (ICD-10) diagnosis codes and procedure codes
- Current Procedural Terminology (CPT) codes
- Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes
- Cost information
- De-identified patient and provider codes

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. Pharmacy claims data allowing for longitudinal tracking of medication refill patterns and changes in medications include:

- National Drug Code (NDC)
- Drug name
- Dosage form
- Drug strength
- Fill date
- Days of supply
- Cost information
- De-identified patient and prescriber codes

Pharmacy claims are typically added to the research database within six weeks of dispensing. Approximately six months following the delivery of services are required for complete medical data.

Optum research activities utilize de-identified data from the ORD. Patient identifiers may be accessed in limited instances where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

9.3.2 Data Sources: Medicare Advantage (MA-PD) Claims Data

Medical and pharmacy claims data are available for approximately 3.6 million enrollees since 2006 that are enrolled in a managed Medicare program through an offering

associated with Optum. Pharmacy claims contain sufficient information to trace patients' pharmacy expenditures through the multiple phases of the Part D plans.

Patient identifiers may be accessed in limited instances where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

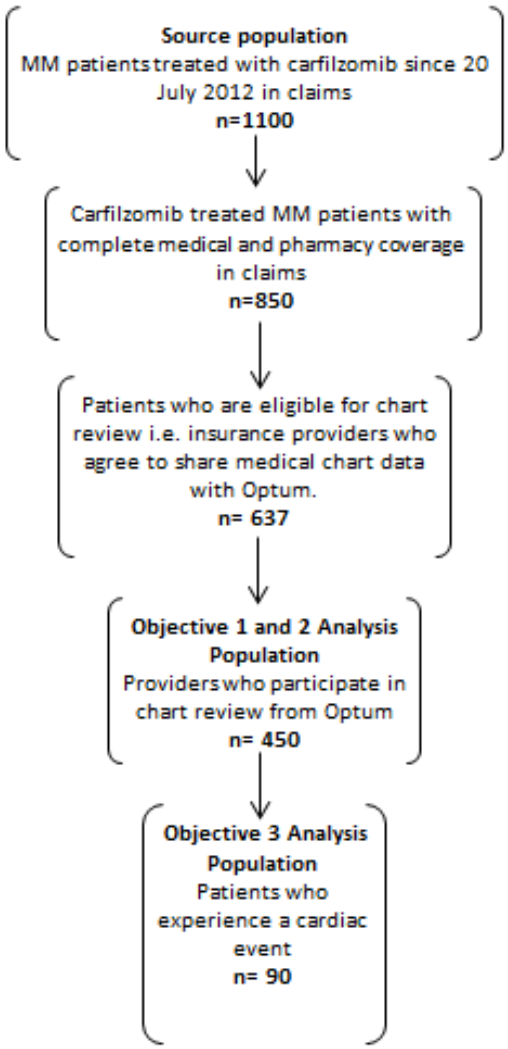
9.3.3 Data Sources: Medical Chart Abstraction

Optum will supplement the claims data with abstracted medical charts to better capture the extent and timing of MM therapies, occurrence of cardiac events, and vital signs and other laboratory measurements. The process of medical chart abstraction and the use of this information are described in Section 9.5

9.4 Study Size

The study population will consist of patients with MM exposed to carfilzomib. Since 20 July 2012, there were a total of 1,100 patients with an administration or dispensation of carfilzomib within the claims data. However, we assume that restricting to patients with medical and pharmacy coverage at the time of drug administration reduces the eligible population to approximately 850 carfilzomib patients. We expect 637 or 75% of patients will be chart eligible, and we anticipate obtaining 70% of charts from participating providers for chart review. As a result, we expect our carfilzomib cohort to be approximately 450 carfilzomib patients.

Assuming 20% of the population may experience a cardiac event of interest; the estimated sample size is approximately 90 patients. The flow chart below describes the study population used for the analysis. We are describing cardiac events from real world data and will report our findings. However, if the number of cardiac events is lower than expected, the analyses for objectives 2 and 3 will be re-evaluated.



9.5 Medical Chart Abstraction and Adjudication

9.5.1 Identifying and Obtaining Patient Charts

For the carfilzomib patients, the main oncology provider will be identified and an oncology chart will be sought from that site of care. In addition, among patients with claims-identified cardiac events of interest, the cardiology chart associated with the provider who diagnosed the cardiac event will be sought. While we expect cardiac events to be treated by a cardiologist, charts for primary care providers or other medical specialties will be sough if necessary. To identify the most relevant providers, Optum will perform a detailed review of the chronological listing of claims (claims profile) in order to determine the medical site of treatment most likely to yield a medical chart with

the necessary information. As a result, Optum will use chart providers as available, not limited to cardiologist or oncologists as listed in claims. Optum will contract with, train, and pay an outside vendor to perform the medical chart procurement of identified charts. Optum has historically been able to successfully obtain medical charts on approximately 70-80% of those that are requested

9.5.2 Development of the Abstraction and Pilot Adjudication Forms

Optum will retain practicing oncologists (maximum of 4, minimum of 2) and cardiologists (minimum of 2) for the purposes of developing the abstraction and adjudication tools. In collaboration with the oncologists, cardiologists, and Amgen, Optum will develop pilot abstraction form (for the oncology and cardiology charts) and an adjudication form (for the cardiology chart) based on a-priori expectations of the content or medical records. Preliminary lists of identified data elements to be abstracted from the medical records are provided in Appendix 1 and includes indicators of the occurrence, prognosis, and treatment of cardiac events, as well as those related to MM disease status.

A pilot abstraction and adjudication will be conducted. The medical abstracters will abstract a random sample of 25 oncology charts and 10 cardiology charts to test the assumptions embedded in the forms. Optum's epidemiologists and the clinical consultants will meet and refine both the abstraction and adjudication forms based on a review of the pilot abstractions and adjudications. However, if based on the pilot, we will not be able to collect the necessary details to meet the study objectives, the study will be terminated.

9.5.3 MM Abstraction Form

Based on the pilot abstraction results, if necessary, a final abstraction form will be developed. Using the refined abstraction form, medical chart abstraction will be conducted among all patients to ascertain patient attributes relating to clinical observations, MM disease status and line of therapy, and cardiovascular risk factors. The abstraction will be performed by the medical abstracter. The medical abstractor will be a qualified medical professional employed by Optum.

9.5.4 Cardiac Events Adjudication Form

Using the revised adjudication form, medical charts pertaining to the potential cardiac events will be used for outcome adjudication. Adjudication will be conducted by two cardiologists. If the adjudicated cardiac outcome differs between the clinicians, the cardiologists will meet to provide a consensus determination.

9.6 Review and Verification of Data Quality

The conduct and reporting of this study follows Optum Epidemiology's standard operating procedures (SOPs) that are consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org). In particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

The validation of analytic work typically involves a combination of a review of SAS program log and output files, independent coding, a review of program processes and documentation to ensure departmental SOPs are followed, and reconciliation of program code with the study analytic specifications to ensure populations and results are consistent with what is needed for the particular study. Individual programs are documented and revised as needed until sign-off by a validation analyst using a validation/programming log.

9.7 Data Analysis

9.7.1 Descriptive Analyses

Optum will describe the carfilzomib cohort with respect to relevant baseline characteristics such as demographics, medical and drug dispensing history, health care utilization, comorbidities, laboratory values, and clinical observations.

9.7.2 Primary Analyses

Objective 1: Quantify the occurrence of preselected cardiac events in MM patients treated with carfilzomib

Cardiac events (hypertension, malignant hypertension, heart failure, IHD, acute IHD, cardiac arrhythmias, conduction disorders, and cardiomyopathy) will initially be identified within the claims databases and confirmed or denied in the cardiac chart review (Refer to Section 9.5 for medical chart abstraction and adjudication process). The frequency and percent of confirmed cardiac events will be reported for each cardiac event. The occurrence of cardiac events will be summarized, overall, by subtype and by key comorbidity strata (e.g. history of cardiac event) within the carfilzomib treated MM patient population

Cardiac events occurring during the active treatment of carfilzomib will be reported. The active treatment period is defined as a cardiac event occurring within 30 days of carfilzomib administration. Incident events and recurrent events will be identified for all cardiac events. The prevalence rate and incidence rate for each cardiac event, except hypertension will be reported. For hypertension only, the incident rate will be reported during the active treatment period since hypertension is a chronic condition that is managed over time. Rates of cardiac events, defined as the number of patients with a cardiac event divided by the person-time at risk, will be estimated. The incident rate of hypertension will not include occurrences of events that also occurred during baseline and will be defined as the number of patients with hypertensive events divided by the person time at risk will be estimated.

Objective 2: Describe predictors for preselected cardiac/ events in MM patients receiving carfilzomib

Within the carfilzomib cohort, cross tabulations of confirmed cardiac events from medical chart review by treatment patterns, patient attributes, and potential cardiovascular risk factors will be presented. After assessment of univariate analyses, regression modeling will be used to evaluate the adjusted association between the potential risk factors and cardiac events.

Objective 3: Describe the subsequent treatment and prognosis of cardiac events

Indicators of cardiac prognosis and treatment will be described overall, by line of therapy, by treatment regimen, and by refractory disease state. Indicators of prognosis include claims based measures (site of care, length of stay, and decompensation) and

chart-based measures (adjudicated prognosis and select clinical observations; e.g. ECG or EKG results).

9.7.3 Planned Method of Analysis

9.7.3.1 General Considerations

For categorical indicators of covariates and events, distributions will be summarized as frequencies and percentages. Continuous variables will be summarized with means and standard deviations and/or medians and interquartile ranges. All data management and analyses will be conducted with SAS version 9.4.

9.7.3.2 Missing or Incomplete Data and Lost to Follow-up

For variables defined by the presence or absence of a particular procedure, disease, or drug dispensing within the claims data, the absence of an associated claim will be interpreted as indicating that the procedure was not conducted, the disease was not present, or the drug was not dispensed.

Determination of the actual line of therapy within the claims data may be limited if the length of enrollment prior to the cohort entry date is not sufficient to capture the incident MM diagnosis. For this reason, the apparent line of therapy within the claims data is likely to underestimate the true line of therapy for patients with shorter baseline periods.

After the data extracts are performed, a standard cleaning program will be utilized to delete medical claims and pharmacy claims where both quantity of drug and days supply equal zero. For the following demographic variables, individuals without relevant information or with conflicting information will not be included in the study:

- Age
- Sex
- Health plan enrollment date

9.7.3.3 Descriptive Analysis

9.7.3.3.1 Description of Study Enrollment

Study subjects are enrolled from Optum claims database and will be selected into the study cohort based on inclusion criteria (listed in Section 9.2.2.1) beginning 20 July 2007 extending through 31 December 2015 (refer to Figure 1).

9.7.3.3.2 Description of Subject/Patient Characteristics

Patient demographics and baseline covariates will be summarized. In addition, the 50 most common baseline diagnoses, procedures (including medication administrations), and medication dispensations will be reported based on claims data.

9.7.3.4 Sensitivity Analysis

9.7.3.4.1 Subgroup Analysis

Subgroups of interest include line of therapy, key comorbidities, and refractory disease state.

9.7.4 Analysis of Safety Endpoint(s)/Outcome(s)

Preselected cardiac events are safety endpoints. The main objective of this study is to describe predictors for developing cardiac events. The analysis methods are described above in Section 9.7.2.

9.8 Quality Control

The conduct and reporting of this study follows Optum Epidemiology's standard operating procedures (SOPs) that are consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org). In particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

The validation of analytic work typically involves a combination of a review of SAS program log and output files, independent coding, a review of program processes and documentation to ensure departmental SOPs are followed, and reconciliation of program

code with the study analytic specifications to ensure populations and results are consistent with what is needed for the particular study. Individual programs are documented and revised as needed until sign-off by a validation analyst using a validation/programming log.

9.9 Limitations of the Research Methods

This study is based on automated medical and prescription claims supplemented by information abstracted from the medical charts.

Claims data:

While claims data are extremely valuable for the efficient and effective examination of health care events, treatment patterns, health care resource utilization, and costs, all claims databases have certain inherent limitations because the claims are collected for the purpose of payment and not research. The presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over-the-counter or provided as samples by the physician will not be observed in the claims data. Presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Length of enrollment in the health plan may be limited due to individuals changing health insurance plans.

Chart data:

Abstraction of additional medical data from oncology and cardiology charts is crucial to understand the frequency and nature cardiac events in the treated MM population since administrative codes do not provide detail on cardiac severity, prognosis and outcomes. However, the availability of the requested data elements in medical charts is unknown. The medical charts to be sought will be manually chosen with the aim of ascertaining of the information of interest; the data must be recorded within the existing medical chart to be available to the research team. Information on MM treatments and cardiac events may not be charted uniformly or consistently between medical charts.

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

Exposure and MM:

Insurance claims and the process by which they are paid represent healthcare transactions. The codes attached to a claim may reflect the reason for the service rather than the true diagnosis (e.g. may reflect a diagnosis to be ruled out). Some patients may be misclassified as first line even though they may be second line or beyond. Some patients may obtain some prescription outside of the United Health care system, and their medication use and treatment patterns may thus be misclassified. Additionally, there may incomplete data on dates of chemotherapy administration. Claims used to define dates of chemotherapy administration and chemotherapy agents administered do not always identify an exact date of administration and the agents administered may be reported inconsistently or incorrectly. This may yield misleading or biased line algorithms if there is systematic error in the reported dates or therapeutic agents. The dates for disease progression may not be present so it may be difficult to accurately determine the disease progression first to occur in all patients. Therefore, we aim to minimize incomplete claims data by abstracting additional information on chemotherapy from medical charts.

Cardiac events:

Completeness of cardiac event prognosis and subsequent treatment information, especially clinical symptoms and signs, recorded for patients may be different by clinics or examining healthcare providers. This type of data is not collected for reimbursement purposes but for medical care only and healthcare providers may have different opinions on what is important in terms of clinical details to be recorded in the charts. For outcome assessment, detailed medical chart information will only be available for patients who are admitted to hospital or had an outpatient visit for treatment. Therefore, data will be biased towards more severe cases. This will be clearly indicated in any interpretation of the data.

9.9.1.2 Selection Bias

Eligible patients identified from claims may not be available for oncology and cardiology chart review. However, to characterize potential selection bias, patients with and without

chart review will be compared with respect to patient age, gender, treatment history, and co-morbidities at baseline from claims data.

9.9.1.3 Confounding

The analyses are descriptive; therefore, no hypothesis testing for causal association will be performed. For objective 2, we will adjust for potential confounders including patient, clinical, and treatment characteristics as outlined in the covariate list after assessment of univariate analysis. However residual confounding remains a possibility.

9.9.2 External Validity of Study Design

The results of this study may be generalizable to the US commercially insured population and to the Medicare Advantage population, and likely to the US population, assuming that medical treatments and care of the patients included in the databases is representative of the US as a whole.

10. Protection of Human Subjects

Optum will prepare and submit an application to a central institutional review board (IRB), the New England Institutional Review Board (NEIRB), and affiliated privacy board (PB) for approval of the study process and to obtain a Waiver of Patient Authorization for the medical chart retrieval. Optum will submit the study protocol to the central IRB and PB.

Internal review and approval processes are also required. Optum will provide general study information and a copy of the IRB and PB approval and waiver documents to the relevant data sources for approval to utilize such data source's data in the study.

10.1 Patient Confidentiality

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. All study reports will contain aggregated results only and will not identify individual patients or physicians. At no time during the study will Amgen receive patient identifying information

11. Collection of Safety Information and Product Complaints

Reporting of individual adverse events is not required for secondary data collection studies.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Optum is responsible for maintaining IRB approval for this study during its conduct. Protocol amendments will be made only with the prior approval of Amgen and Optum. The New England Institutional Review Board (NEIRB) must be informed of all amendments and give approval. Optum will send a copy of the approval letter from the NEIRB to Amgen.

Both Amgen and Optum reserve the right to terminate the study according to the contractual agreement. Optum is to notify the NEIRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

13.1 Publication Policy

Findings from this study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet Conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

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15. Appendix 1: Preliminary list of variables to be abstracted from medical charts

A preliminary list of variables to be abstracted from medical charts is provided below. The final set of variables, along with the abstraction and adjudication forms, will be developed in collaboration with clinical consultants.

Table A1: Preliminary list of variables to be abstracted from Oncology charts

Variable	Frequency of collection	Carfilzomib Cohort
MM related treatments		
Regimen, frequency, cycle	Index line of therapy	Yes
Dosages	Index line of therapy	Yes
Dose delay, dose reduction	Index line of therapy	Yes
Reasons for dose delay, reduction	Index line of therapy	Yes
Hydration related, infusion time and volume	Index line of therapy	Yes
Line of therapy	Index and prior lines of therapy	Yes
Duration of each line of therapy	Index and prior lines of therapy	Yes
Time to next line of therapy	Index and prior lines of therapy	Yes
Response data		
Refractory (yes/no)	Index and prior lines of therapy	Yes
Date of refractory	Index and prior lines of therapy	Yes
Disease progression (yes/no)	Index and prior lines of therapy	Yes
Date of disease progression	Index and prior lines of therapy	Yes
Responders: best response (complete, partial, MRD)	Index line of therapy	Yes
Non-responders: disease progression and date	Index line of therapy	Yes
Time to response	Index line of therapy	Yes

Duration of response	Index line of therapy	Yes
Time to next therapy	Index line of therapy	Yes
Clinical observations		
Weight	At enrollment and at each line	Yes
Height	At enrollment	Yes
Body surface areas (BSA)	At enrollment and at each line	Yes
Tobacco use	At enrollment	Yes
Alcohol use	At enrollment	Yes
Performance status (ECOG/ WHO Karnofsky)	At enrollment and at each line	Yes
ISS and DS (Durie-Salmon)	At enrollment and at each line	Yes
Cytogenetic risk	At enrollment	Yes
Blood pressure	At enrollment and at each line	Yes
Heart rate	At enrollment and at each line	Yes
Respiratory rate	At enrollment and at each line	Yes
Pulse oximetry or “need for oxygen supplementation for hypoxemia”	At enrollment and at each line	Yes
MM related labs		
m-protein	At enrollment and at each line	Yes
SFL ratio	At enrollment and at each line	Yes
Bone marrow biopsy results (e.g. % plasma cells)	At enrollment and at each line	Yes
Plasmacytoma or bone lesions	At enrollment and at each line	Yes
Hemoglobin level	At enrollment and at each line	Yes
Liver test (ALT/AST, albumin)	At enrollment and at each line	Yes
Iron level (ferritin level)	At enrollment and at each line	Yes
Renal function test (blood urea nitrogen, and creatinine)	At enrollment and at each line	Yes
Serum β2-microglobulin,	At enrollment and at each line	Yes
Creatinine clearance	At enrollment and at each line	Yes

C-reactive protein	At enrollment and at each line	Yes
Cardiac related tests		
BNP/pro-BNP	At enrollment and at each line	Yes
cardiac troponin T (cTnT)	At enrollment and at each line	Yes
troponin I (cTnI)cardiac troponin	At enrollment and at each line	Yes
EKG report	At enrollment and at each line	Yes
Echocardiogram reports	At enrollment and at each line	Yes

Table A2: Abstraction and adjudication of cardiac events from the cardiology charts corresponding to claims-identified events

Variable	**Frequency of collection**	**Carfilzomib Cohort**
Treatment related cardiac events		
Dyspnea	each line	Yes
Hypertension	each line	Yes
Malignant hypertension	each line	Yes
Pulmonary hypertension	each line	Yes
Cardiac failure	each line	Yes
Ischemic heart disease	each line	Yes
Cardiac arrhythmia	each line	Yes
Conduction disorders	each line	Yes
Cardiomyopathy	each line	Yes
Acute renal failure	each line	Yes
Treatment and prognosis of cardiac events and hospitalization		Yes
Any treatment and management during hospitalization (meds, procedures, surgeries, etc.)	Index line of therapy	Yes
Prognosis	Index line of therapy	Yes
Death and date of death	Index line of therapy	Yes
Causes of death	Index line of therapy	Yes