# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## Study information

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| **Title** | Real-world treatment patterns and clinical outcomes for patients with relapsed/refractory multiple myeloma (RRMM) who received Elranatamab |
| **Protocol number** | C1071050 |
| **Protocol version identifier** | 1.0 |
| **Date** | 16 December 2025 |
| **EU Post Authorization Study (PAS) register number** | EUPAS1000000852 |
| **Active substance** | L01FX32 |
| **Medicinal product** | ELREXFIO™ (Elranatamab) |
| **Research question and objectives** | **Research question:**<br>Among patients with RRMM treated with Elra in a real-world setting, what are the demographic and clinical characteristics, treatment patterns, response rates, and the incidence of real-world AEs (as well as their treatment and related outcomes)?<br>**Primary objectives:**<br>In patients with RRMM treated with Elra in real-world clinical practice:<br>• Describe real-world baseline demographic and clinical characteristics.<br>• Describe treatment patterns in all lines of therapy prior to receipt of Elra, during the Elra- containing line of therapy (LOT), and of the first subsequent LOT following the Elra-containing LOT (for those who have a subsequent LOT).<br>• Assess rwORR to Elra treatment.<br>• Examine the incidence and treatment of and outcomes (dose or schedule change, therapy hold, therapy discontinuation, hospitalization) related to the following AEs:<br>○ ICANS<br>○ CRS |

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| | ○ Peripheral Neuropathy<br>■ Peripheral neuropathy<br>■ Sensory neuropathy<br>■ Motor neuropathy<br>○ Bacterial Infection<br>■ Sepsis<br>■ Bacteremia<br>■ Pneumonia (if documented as bacterial)<br>○ Viral Infection (non-COVID)<br>■ Adenovirus<br>■ Influenza<br>■ Rhinovirus<br>■ Hepatitis B Virus (acute or reactivation)<br>○ Lower Respiratory Infections (LRI)<br>■ Pneumonia<br>■ Pneumonitis (with infectious component)<br>■ Bronchiolitis<br>■ Tracheitis<br>○ Overall Infections (OI)<br>○ Hypogammaglobulinemia<br>■ Hypogammaglobulinemia<br>■ Low Immunoglobulin (Ig) G<br>■ Low IgA<br>■ Low IgM<br>■ Low IgE<br>■ Low IgD<br>• Time from first administration of Elra to onset or worsening of baseline real-world adverse events (rwAEs) will be estimated, as well as resolution status and time to resolution (for those that were noted to be resolved)<br>**Secondary Objectives**<br>To describe real-world patient characteristics, treatment patterns, ORR, and AEs among RRMM patients treated with Elra in the following subgroups of interest, based on baseline characteristics:<br>• Presence of extramedullary disease |

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| | • High cytogenetic risk<br>• Renal impairment *(depending on sample size)*<br>• Elderly population (over 81)<br>• Setting of care for Elra step-up dose administration (inpatient vs. outpatient)<br>Patient characteristics and treatment patterns will also be reported by the following groupings, which are conditional and based on outcomes:<br>• Severity of AEs that develop or worsen on or after the start of treatment with Elra<br>• Safety grade of 2 and above and safety grade <2 (only available for ICANS and CRS that develops or worsens on or after the start of treatment with Elra)<br>• CRS and ICANS by setting of care for Elra step-up dose administration |
| **Country(ies) of study** | United States of America |
| **Author** | Redacted<br>Pfizer Inc.<br>66 Hudson Boulevard East, New York, NY 10001 |

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## 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| BCMA | B-cell maturation antigen |
| BMI | Body mass index |
| CAR T | Chimeric Antigen Receptor T-cell therapy |
| CCI | Charlson comorbidity index |
| CGS | Consensus Genomic Staging |
| CI | Confidential interval |
| CR | Complete response |
| CRS | Cytokine release syndrome |
| ECOG | Eastern Cooperative Oncology Group |
| EHR | Electronic health record |
| Elra | Elranatamab |
| ETL | Extract, Transform, and Load |
| FDA | U.S. Food and Drug Administration |
| FLC | Free light chain |
| FHRD | Redacted Research Database |
| ICANS | Immune Effector Cell-Associated Neurotoxicity Syndrome |
| ICD | International classification of disease |
| Ig | Immunoglobulin |
| IMiD | Immunomodulatory drug |
| IMWG | International Myeloma Working Group |
| IMS | International Myeloma System |

| | |
|---|---|
| IQR | Interquartile range |
| IRB | Institutional Review Board |
| ISS | International Staging System |
| 1L | First line of therapy |
| 5L | Fifth line of therapy |
| LCMM | Light chain multiple myeloma |
| LOT | Line of therapy |
| LRI | Lower Respiratory Infections |
| MM | Multiple Myeloma |
| ML | Machine learning |
| NCCN | National Comprehensive Cancer Network |
| NIS | Non-interventional Study |
| NLP | Natural language processing |
| ORR | Overall response rate |
| OI | Overall Infections |
| PHI | Protected Health Information |
| PR | Partial response |
| QA | Quality assurance |
| QC | Quality control |
| RRMM | Relapsed/refractory multiple myeloma |
| rwAE | Real-world adverse event |
| RWD | Real-World Data |
| RWE | Real-World Evidence |
| SCT | Stem cell transplant |
| SEER | Surveillance, Epidemiology and End Results Program |

| | |
|---|---|
| SES | Socioeconomic Status |
| SPEP | Serum Protein Electrophoresis |
| SQL | Structured Query Language |
| UPEP | Urine Protein Electrophoresis |
| USA | United States of America |
| VGPR | Very good partial response |

## 2. RESPONSIBLE PARTIES

## 3. ABSTRACT

**Title:** Real-world treatment patterns and clinical outcomes for patients with relapsed/refractory multiple myeloma (RRMM) who received elranatamab

**Version:** 1.0

**Date:** 16 December 2025

**Authors:** Redacted

**Rationale and background:** Elranatamab (Elra), a bispecific antibody that targets B-cell maturation antigen (BCMA), received accelerated approval by the U.S. Food and Drug Administration (FDA) in 2023 for the treatment of adult patients with RRMM who have received at least four prior lines of therapy. Although clinical trials provide critical efficacy and safety data, real-world evidence (RWE) is needed to understand treatment patterns, effectiveness, and safety outcomes in broader patient populations outside controlled trial settings. This study aims to fill this evidence gap by comprehensively characterizing the treatment patterns, real-world overall response rate (rwORR), and adverse events (AEs) among RRMM patients treated with Elra.

**Research question and objectives**: Among patients with RRMM treated with Elranatamab in a real-world setting, what are the demographic and clinical characteristics, treatment patterns, response rates, incidence of real-world Adverse Events (rwAEs), treatment and related outcomes?

**Research question:**

Among patients with RRMM treated with Elra in a real-world setting, what are the demographic and clinical characteristics, treatment patterns, response rates, and the incidence of real-world AEs (as well as their treatment and related outcomes)?

**Primary objectives:**

In patients with RRMM treated with Elra in real-world clinical practice:

- Describe real-world baseline demographic and clinical characteristics.
- Describe treatment patterns in all lines of therapy prior to receipt of Elra, during the Elra-containing line of therapy (LOT), and of the first subsequent LOT following the Elra-containing LOT (for those who have a subsequent LOT).
- Assess rwORR to Elra treatment.
- Examine the incidence and treatment of and outcomes (dose or schedule change, therapy hold, therapy discontinuation, hospitalization) related to the following AEs:
    - ICANS
    - CRS
    - Peripheral Neuropathy
        - Peripheral neuropathy
        - Sensory neuropathy
        - Motor neuropathy
    - Bacterial Infection

        - Sepsis
        - Bacteremia
        - Pneumonia (if documented as bacterial)
    - Viral Infection (non-COVID)
        - Adenovirus
        - Influenza
        - Rhinovirus
        - Hepatitis B Virus (acute or reactivation)
    - Lower Respiratory Infections (LRI)
        - Pneumonia
        - Pneumonitis (with infectious component)
        - Bronchiolitis
        - Tracheitis
    - Overall Infections (OI)
    - Hypogammaglobulinemia
        - Hypogammaglobulinemia
        - Low Immunoglobulin (Ig) G
        - Low IgA
        - Low IgM
        - Low IgE
        - Low IgD
- Time from first administration of Elra to onset or worsening of baseline real-world adverse events (rwAEs) will be estimated, as well as resolution status and time to resolution (for those that were noted to be resolved)

**Secondary Objectives**

To describe real-world patient characteristics, treatment patterns, ORR, and AEs among RRMM patients treated with Elra in the following subgroups of interest, based on baseline characteristics:

- Presence of extramedullary disease
- High cytogenetic risk
- Renal impairment *(depending on sample size)*
- Elderly population (over 81)
- Setting of care for Elra step-up dose administration (inpatient vs. outpatient)

Patient characteristics and treatment patterns will also be reported by the following groupings, which are conditional and based on outcomes:

- Severity of AEs that develop or worsen on or after the start of treatment with Elra

- Safety grade of 2 and above and safety grade <2 (*only available for ICANS and CRS that develops or worsens on or after the start of treatment with Elra)*
- CRS and ICANS by setting of care for Elra step-up dose administration

**Study design:** This is a retrospective, observational cohort study using de-identified electronic health record (EHR)-derived data from the Redacted. The study will evaluate real-world patient characteristics, treatment patterns, rwORR, and AEs among RRMM patients treated with Elra and in specific sub-populations of interest.

**Study Population**: US patients diagnosed with MM on or after January 1, 2013, who received Elra treatment. This study will be conducted using the Redacted. The database includes data from a large, demographically and geographically diverse network of oncology practices across the United States, encompassing both community oncology clinics and academic medical centers.

**Study Outcomes Variables:** Real-world overall response rate (rwORR), incidence and treatment of AEs, and outcomes related to AEs (dose or schedule change, therapy hold, therapy discontinuation, hospitalization). These will be reported for the overall cohort and subgroups based on baseline characteristics (presence of extramedullary disease, high cytogenetic risk, performance status, renal impairment [*if sample size allows*], age [81 years of age and older], and setting of care for Elra step-up dose administration (inpatient vs. outpatient). Baseline characteristics and treatment patterns will also be reported by the following groupings, which are conditional and based on outcomes: severity of AEs that occur during the follow-up period, as well as safety grade 2 and above, and safety grade <2 [*only available for immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome* (*CRS)*], and CRS and ICANS by setting of care for Elra step-up dose administration.

**Data Source(s):** The FHRD is a longitudinal database derived from EHRs from cancer care providers across the United States.

**Study Size:** Approximately 120 patients

**Data Analysis:** Descriptive statistics will be used to summarize demographics, clinical characteristics, treatment patterns, incidence of AEs, and rwORR. For continuous variables, the descriptive statistics will include medians, interquartile range (IQR), means, standard deviations, and minimum and maximum values (as applicable). For categorical variables, frequencies, and percentages will be generated. The number of patients with missing data will be reported for all variables. Levels of categorical variables may be combined to account for small sample sizes. Statistical testing for comparison of outcomes variables will not be conducted.

**Milestones:**

| Milestone | Planned Date |
|---|---|
| **Start date of data collection** | 30-Jan-2026 |
| **End date of data collection** | 02-Feb-2026 |
| **Registration in the HMA-EMA Catalogues of RWD Studies** | 29-Jan-2026 |
| **Final Study Report** | 01-Feb-2027 |

## 4. AMENDMENTS AND UPDATES

None.

## 5. MILESTONES

| Milestone | Planned Date |
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| **Start date of data collection** | 30-Jan-2026 |
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| **Final Study Report** | 01-Feb-2027 |

## 6. RATIONALE AND BACKGROUND

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells, monoclonal protein production, and progressive end-organ damage [1]. MM accounts for approximately 1–2% of all cancers and ~10% of hematologic malignancies worldwide, with an estimated 35,000 new cases annually in the United States [2,3]. Despite advances in therapeutic options over the past two decades, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies, MM remains largely incurable, and most patients eventually relapse [4].

Patients with RRMM who are triple-class exposed or refractory to PI, IMiD, and anti-CD38 antibodies face poor outcomes, with median progression-free survival (PFS) often less than 6 months and overall survival (OS) typically less than 1 year [5,6]. This underscores the critical need for novel therapies with distinct mechanisms of action in later-line settings.

Elranatamab (Elra) is a bispecific antibody that targets B-cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells, redirecting T-cell cytotoxicity against malignant plasma cells [7]. Clinical trials, including the pivotal phase 2 MagnetisMM-3 study, have demonstrated that Elra induces deep and durable responses in heavily pretreated RRMM patients, with an overall response rate (ORR) of ~60% and manageable toxicity profile [8]. The most common AEs include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which are typically low-grade and manageable with appropriate mitigation strategies [9].

Based on these results, elranatamab received accelerated approval from the U.S. Food and Drug Administration (FDA) on 14 August 2023 for the treatment of adult patients with RRMM who have received at least four prior lines of therapy, including a PI, an IMiD, and an anti-CD38 antibody [10]. While pivotal clinical trials provide critical efficacy and safety data, real-world evidence (RWE) is needed to understand treatment patterns, effectiveness, and safety outcomes in broader patient populations outside of controlled trial settings. In particular, RWE can help characterize:

- Patient characteristics and prior treatment histories of Elra users;
- Patterns of Elra initiation and sequencing in routine clinical practice;
- Real-world effectiveness, including response, progression-free, and overall survival;
- Safety outcomes, including incidence and management of CRS, ICANS, infections, cytopenias, and other AEs in diverse clinical settings.

Recently, in real-world settings, compassionate use programs and retrospective studies have provided additional insights. Malard et al. reported that in a French compassionate use study of Elra in RRMM (n=101), the ORR was 51.5%, with efficacy and safety largely consistent with the MagnetisMM-3 trial. CRS (45%, all grade 1–2) and infections (49% overall; 24% grade ≥3) were the most common toxicities, emphasizing the importance of proactive safety monitoring in clinical practice [11]. Similarly, a retrospective analysis at Moffitt Cancer Center confirmed encouraging outcomes in heavily pretreated RRMM patients treated with Elra, showing clinically meaningful responses and durable benefit with an ORR consistent with trial data, though rates of treatment modifications due to AEs were higher in real-world practice [12]. Such real-world analyses provide valuable context for treatment effectiveness and tolerability in routine practice. However, real-world data (RWD) on Elra remain limited, particularly with respect to detailed safety outcomes and consistency of ORR across diverse clinical practice settings. This study aims to address this evidence gap by systematically evaluating real-world treatment patterns, ORR, and safety outcomes of Elra, complementing the clinical trial findings. Findings from this study will provide

important insights to clinicians, patients, and regulators regarding the role of Elra in the treatment of RRMM.

This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer.

## 7. RESEARCH QUESTION AND OBJECTIVES

**Research question:**

Among patients with RRMM treated with Elra in a real-world setting, what are the demographic and clinical characteristics, treatment patterns, response rates, and the incidence of real-world AEs (as well as their treatment and related outcomes)?

**Primary objectives:**

In patients with RRMM treated with Elra in real-world clinical practice:

- Describe real-world baseline demographic and clinical characteristics.
- Describe treatment patterns in all lines of therapy prior to receipt of Elra, during the Elra-containing line of therapy (LOT), and of the first subsequent LOT following the Elra-containing LOT (for those who have a subsequent LOT).
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    - Overall Infections (OI)
    - Hypogammaglobulinemia
        - Hypogammaglobulinemia
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        - Low IgD
- Time from first administration of Elra to onset or worsening of baseline real-world adverse events (rwAEs) will be estimated, as well as resolution status and time to resolution (for those that were noted to be resolved)

**Secondary Objectives**

To describe real-world patient characteristics, treatment patterns, ORR, and AEs among RRMM patients treated with Elra in the following subgroups of interest, based on baseline characteristics:

- Presence of extramedullary disease
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- Setting of care for Elra step-up dose administration (inpatient vs. outpatient)

Patient characteristics and treatment patterns will also be reported by the following groupings, which are conditional and based on outcomes:

- Severity of AEs that develop or worsen on or after the start of treatment with Elra
- Safety grade of 2 and above and safety grade <2 (*only available for ICANS and CRS that develops or worsens on or after the start of treatment with Elra)*
- CRS and ICANS by setting of care for Elra step-up dose administration

## 8. RESEARCH METHODS

### 8.1. Study Design

This is a retrospective, observational cohort study of patients with RRMM using the FRedacted de-identified electronic health record (EHR)-derived database. The dataset generated for the study will include all protocol-required, retrospective patient-level data available for eligible patients within the study period. This retrospective cohort design was chosen to leverage existing EHR data, enabling comprehensive assessment of real-world treatment patterns and clinical and safety outcomes in a diverse RRMM population of patients treated with Elra and provides insights into routine clinical practice across diverse settings, which may not be fully represented in clinical trials. No formal comparison group is included, as the study aims to describe outcomes in Elra treated patients. A retrospective cohort design was deemed most appropriate for this study given the following rationale: exposure (i.e., Elra treatment) has already occurred, outcomes can be

ascertained from existing data, and the goal is to estimate incidence and describe associations rather than establish causality. The data is optimized for retrospective analysis given that it supports descriptive endpoints without formal comparisons, which is appropriate given the sample size of N~120 patients and study objectives. The primary endpoints are the rwORR to Elra as well as the incidence and management of adverse events as outlined in the primary objectives. Secondary endpoints are subgroup analyses describing real-world patient characteristics, treatment patterns, overall response rate (ORR), and adverse events (AEs) among RRMM patients treated with Elranatamab, stratified by baseline factors such as extramedullary disease, cytogenetic risk, renal impairment, age, and setting of care. Additional subgroup analyses will report outcomes by severity and grade of AEs, and by setting of care for step-up dosing. All endpoints will be summarized using descriptive statistics (means, medians, IQRs); no formal statistical comparisons will be performed.

**Study Period**

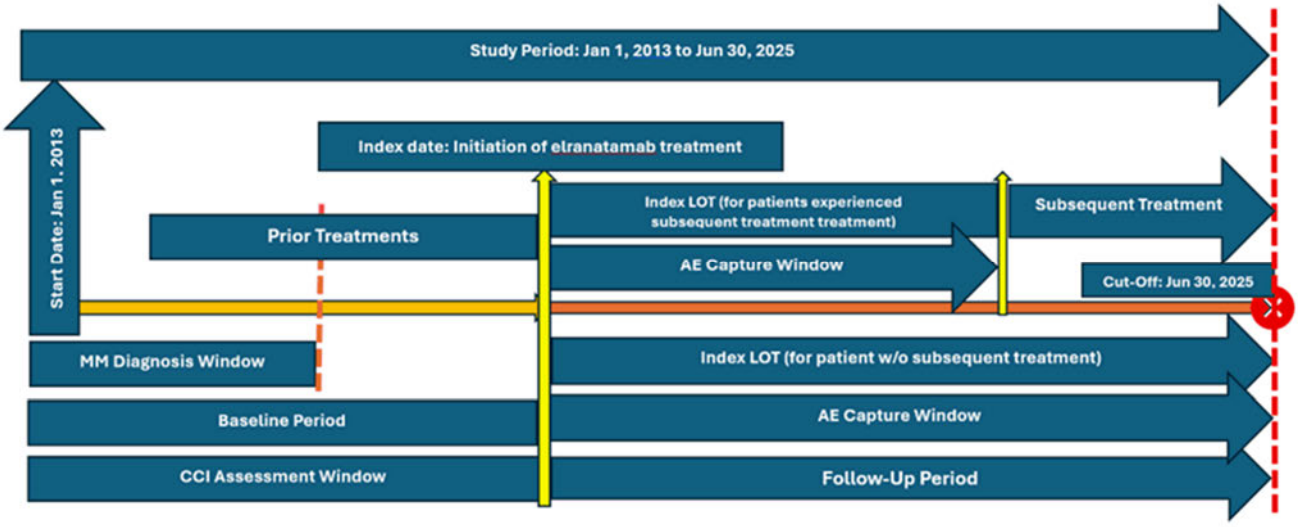
The study observation period will begin on January 01, 2013, and extend up to the data cutoff date of June 30, 2025. The index date will be defined as the date of the first documented administration of Elra on or after August 14, 2023 (date of FDA approval). Baseline characteristics will be assessed within the baseline window, generally defined as from the patient's date of initial diagnosis with multiple myeloma to index date with the closest measurement to index date being used. The follow-up period will be defined as the time from index date through the date of death, last confirmed activity, or data-cutoff, whichever occurs first.

Figure 1. below illustrates the overall study design. The study will describe the real-world treatment patterns and evaluate real-world outcomes among adult patients with RRMM who received Elra in routine clinical practice.

**Figure 1. Study Design Scheme**

This figure illustrates the study design, including key time windows and follow-up periods.

The index date refers to the date of initial treatment with elranatamab on or after 14 August 2023. The study period spans from 01 January 2013 (start date) to 30 June 2025 (data cutoff). The multiple myeloma (MM) diagnosis window extends from 01 January 2013 to the index date. The baseline period is from 01 January 2013 to the index date. The Charlson Comorbidity Index (CCI) assessment window will be evaluated prior to the index date; for patients with multiple CCI-related tests within the baseline period, the test value on or closest to the index date will be selected. Prior treatments include all therapies received after MM diagnosis and before the index date. Index LOT refers to the elranatamab-containing line of therapy corresponding to the index date. Patients will be followed from the index date to the earliest of death, last confirmed activity date (defined as a recording of vital information, medication administration, laboratory test/result being reported, or last abstracted therapy date), or data cutoff. The adverse event (AE) capture window spans from the index date to the earliest of death, last confirmed activity date, initiation of a new LOT, or data cutoff. Subsequent treatment refers to the first line of therapy after elranatamab treatment, if available.




## 8.2. Setting

This study will be conducted using the Redacted The database includes data from a large, demographically and geographically diverse network of oncology practices across the United States, encompassing both community oncology clinics and academic medical centers. The database includes data from over 280 cancer clinics (~800 sites of care) in a majority community oncology setting, representing more than 2.2 million active US cancer patients available for analysis. Redacted network includes ~80% patients from community practices and ~20% patients from academic centers, roughly in-line with where patients are receiving their cancer care in the US. Redacted data are sourced directly from routine clinical practice and include structured information (e.g., demographics, laboratory results, prescribing records) as well as unstructured data curated through technology-enabled abstraction of physician notes, pathology reports, and radiology reports. Data are longitudinal and refreshed monthly, enabling the capture of real-world treatment patterns, clinical outcomes, and safety events as they occur in practice. This setting reflects the routine clinical management of patients with relapsed/refractory multiple myeloma outside the controlled conditions of clinical trials, providing the opportunity to evaluate the use of Elra in a broader, more heterogeneous patient population.

**Study population** : Adult patients (aged 18 years and older) diagnosed with relapse/refractory multiple myeloma (RRMM) who received Elra treatment.

**Place**: Oncology practices participating in the Redacted (~80% patients from community practices and ~20% patients from academic centers) across the United States, roughly in-line with where patients are receiving their cancer care in the US.

**Time Period**: The study observation period begins on January 1, 2013, and extends up to the data cutoff date of June 30, 2025. The index date is defined as the date of the first documented administration of Elra on or after August 14, 2023 (the date of FDA approval).

### 8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients included in FHRD

- Has at least two documented clinical visits, on different days in the Redacted database on or after January 1, 2013

2. Has an International Classification of Diseases (ICD) diagnosis of MM using (ICD-9: 203.0x or ICD-10 C90.0x, C90)
3. Has evidence of treatment of Elra, on or after MM diagnosis and on or after 14 August 2023 (date of FDA approval)
4. Aged 18+ years as of first initiation of Elra
5. Prior to Elra initiation, has evidence of treatment with a proteasome inhibitor (bortezomib, carfilzomib, ixazomib), an IMiD (thalidomide, lenalidomide, pomalidomide), and an anti-CD38 (daratumumab, isatuximab)

### 8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Lacking relevant unstructured documents in the Redacted database
2. Receipt of Elra in combination with any other agents
3. Receipt of clinical study drugs, indicating participation in a clinical study.

## 8.3. Variables

The variables listed below in Table 1 will be used to characterize patients' baseline information, clinical characteristics, real-world treatment patterns, and clinical outcomes. For baseline characteristics, values closest to the index date will be used unless otherwise noted. The full code can be found in Annex 3.

**Table 1. Study Variables**

| (Outcome) Variable | Role | Operational Definition | Assessment Period |
|---|---|---|---|
| Follow-up period | Outcome | Follow-up period is defined as length of time from the index date to the earliest of date of death, last confirmed activity date (defined as a recording of vital information, a medication administration, a laboratory test/result being reported or last abstracted therapy date), or data cutoff. | From index date to data cutoff date |
| rwORR<br>● Partial response (PR)<br>● Very good partial response (VGPR) or better | Outcome | rwORR will be defined as the proportion of patients who had at least one PR, VGPR, or better assessment, among patients with a baseline lab value and a subsequent lab value.<br><br>PR and VGPR will be derived from enhanced M spike and free light chain (FLC) lab values based on IMWG criteria [12]. | During Elra-containing LOT |
| **(Safety) Variable** | | **Operational Definition** | **Assessment Period** |

| | | | |
|---|---|---|---|
| Presence of rwAE at baseline | Baseline characteristic / Exposure | Number and proportion of patients who have evidence of the respective rwAE during the baseline period (defined here as 30 days prior to index LOT up to one day before index LOT) | 30 days prior to the day before the index date |
| Incidence of new rwAEs during the index LOT | Outcome | The number and proportion of patients with evidence of first onset of the respective rwAE during the index LOT (first Elra-containing LOT) among the total number of patients in the cohort. | During Elra-containing LOT |
| Worsening of pre-existing rwAEs | Outcome | The number and proportion of patients with pre-existing rwAE (defined above as “presence of rwAE at baseline”) who experienced a worsening of the rwAE during the AE examination period divided by the total number of patients in the cohort will be reported.<br>The AE is considered to worsen if:<br>• The AE is present at baseline (ie, present within 30 days prior to index date) and is later documented to be worse/increased as compared to the status at baseline<br>• The AE is present at baseline, resolves, and then recurs during the AE examination period | During Elra-containing LOT |
| Time to AE onset or worsening | Outcome | Time (in days) from index date to documented onset date of the rwAE or the initial worsening of baseline rwAE. | During Elra-containing LOT |
| AE-related outcome(s) | Outcome | Clinician-documented outcomes related to the selected rwAEs that occurred during the index LOT, as determined by abstraction, among patients with the selected AE, including:<br>• Dose or schedule change - the dose was modified as a result of the rwAE or if the rwAE caused a change in treatment schedule (not a delay, but a change to the treatment schedule).<br>• Therapy hold - the therapy of interest was held or delayed as a result of the rwAE. A therapy hold is defined as a temporary suspension of the planned dosing schedule.<br>• Therapy discontinuation - any component drug of the referenced treatment is discontinued (and not restarted) as a result of the rwAE.<br>• Treatment for the AE - if any treatment (does not have to be pharmacological) is taken by the patient or recommended, prescribed, or administered by the clinician to treat the rwAE | During Elra-containing LOT |

| | | | |
|---|---|---|---|
| | | • Hospitalization - the patient was hospitalized during the time of or as a result of the rwAE<br>• No outcome related to the AE - the AE did not result in any of the above therapy changes, additional treatment, or hospitalization<br>Note: These categories are not mutually exclusive and more than one can be selected and reported. | |

| | | | |
|---|---|---|---|
| Therapy attribution | Outcome | Level of attribution for the selected rwAE of interest as determined by the treating clinician, among patients with the selected AE:<br>• Definite attribution - there is explicit clinician documentation that the rwAE is directly due to the referenced therapy (e.g., 'is due to treatment')<br>• Likely attribution - there is explicit clinician documentation that the rwAE might be due to the referenced therapy (e.g., 'possibly related to drug')<br>• Not attributed - there is explicit clinician documentation that the rwAE is not due to the referenced therapy or that the rwAE is due to another condition unrelated to reference therapy (e.g., 'not related to therapy')<br>• No documentation - there is no explicit clinician documentation that the rwAE is or is not due to the referenced therapy (e.g., 'patient presents with significant viral infection - will hold therapy' without attribution of the viral infection is considered not documented) | During Elra-containing LOT |
| Clinician-documented severity | Outcome | Severity of the selected rwAE of interest as determined by the treating clinician, among patients with the selected AE:<br>• Mild<br>• Moderate<br>• Severe<br>• Life-threatening<br>• Fatal<br>• Not documented | During Elra-containing LOT |

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| Resolution | Outcome | Clinician-documented resolution status of the selected rwAE of interest, among patients with the selected AE:<br>• Resolved - The patient has recovered completely from the AE of interest; or the patient has returned to baseline status, for those with AE at baseline and there are no permanent impairments to the patient's health as a result of the AE of interest.<br>• Resolving - The AE at the end of the LOT is reducing in grade or severity, or there is explicit documentation that the AE is "improving," "resolving," "marked improvement," "not as significant," or "getting better"<br>• Resolved with sequelae - The patient has recovered from the AE of interest, but a permanent or long-standing impairment to the patient's health has resulted from the AE of interest.<br>• Ongoing - The patient has not yet fully recovered from the AE of interest; or there is documentation that the AE is still occurring but not resolving at the end of the LOT; or there is documentation that the AE is the reason to discontinue therapy.<br>• Fatal - There is clinician documentation that the patient expired directly as a result of the AE.<br>• Not documented - There is no documented resolution of the AE. | During Elra-containing LOT |
| Time to resolution | Outcome | Time (in days) from rwAE start to date of resolution, for rwAEs marked as Resolved" or "Resolved with sequelae" | During Elra-containing LOT |
| CRS/ICANS | Outcome | • Clinician-reported grade of AE (available only for CRS/ICANS; note that the scales will not be standardized between clinicians)<br>○ 1<br>○ 2<br>○ 3<br>○ 4<br>○ 5<br>○ Not documented<br>○ | During Elra-containing LOT |
| Treatment for/Prevention of | Outcome | • Indication of Tocilizumab administration (Yes/No), date(s) of administration | During Elra-containing LOT |

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| CRS/ICANS | | (MM/DD/YYYY, as available)<br>• Indication of Dexamethasone or other steroid administration (Yes/No), start date and end date (MM/DD/YYYY, as availablfe)<br>• Indicator of siltuximab, anakinra, and/or methylprednisolone administration (Yes/No) | |
| Peripheral Neuropathy | Outcome | • Treatment:<br>○ Indication of administration neuropathic pain medication (Yes/No) | During Elra-containing LOT |
| Bacterial Infection | Outcome | • Treatment:<br>○ Indication of administration of antibiotics (Yes/No) | During Elra-containing LOT |
| Viral Infection (non-COVID) | Outcome | • Treatment:<br>○ Indication of antiviral medications (Yes/No) | During Elra-containing LOT |
| Hypogammaglobulinemia | Outcome | • Evidence of hypogammaglobulinemia (Yes/No)<br>• Treatment:<br>○ Indication of administration of Ig replacement therapy (Yes/No)<br>Note: Severity information will not be available for this rwAE. | During Elra-containing LOT |
| **(Baseline and/or Covariate) Variable** | **Role** | **Operational Definition** | **Assessment Period** |
| Year of initial MM diagnosis | Baseline characteristic | Categorical:<br>• 2013-2015<br>• 2016-2018<br>• 2019-2021<br>• 2022<br>• 2023<br>• 2024<br>• 2025 | At initial diagnosis of MM |

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| Age at index date | Baseline characteristic | Age at index date (continuous)<br>• Definition: Age at the index date is calculated as:<br>Age = Year of index date − BirthYear (from Redacted Demographics table).<br>• Source and Transformation: BirthYear reflects the year of birth recorded in the EHR.<br><br>Note: To meet de-identification requirements, Redacted transforms the BirthYear of patients older than 85 years at the data cutoff year. Approximately 9% of patients may have a transformed BirthYear, with a median difference of four years (IQR: 2–6 years). It is not possible to identify which records were transformed [13].<br><br>Implication for calculation: For patients with BirthYear ≤ (data cutoff year − 85), the calculated age should be considered a minimum estimate (eg, "≥ calculated age"). | At index date |
| Age at index date | Baseline characteristic | Age at index (categorical)<br>• < 81<br>• ≥ 81<br>Note: To meet de-identification requirements, Redacted transforms the BirthYear of patients older than 85 years at the data cutoff year. Approximately 9% of patients may have a transformed BirthYear, with a median difference of four years (IQR: 2–6 years). It is not possible to identify which records were transformed [13]<br><br>Implication for calculation: For patients with BirthYear ≤ (data cutoff year − 85), the calculated age should be considered a minimum estimate (e.g., "≥ calculated age"). | At index date |
| Birth sex | Baseline characteristic | Patient sex:<br>• Male<br>• Female<br>• Unknown<br>Note: Values in the sex variable likely reflect a patient's sex at birth, which reflects limitations in how EHR software systems have collected sex and gender identity information. | As of index date |

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| Race | Baseline characteristic | Patient race:<br>• White<br>• Black or African American<br>• Asian<br>• Other Race<br>• Unknown<br>Note: "Other Race" includes patients who identified as American Indian, Alaska Native, Native Hawaiian, Other Pacific Islander, or mixed races | As of index date |
| Patient region | Baseline characteristic | • Midwest<br>• South<br>• West<br>• Northeast<br>• Unknown<br>States are mapped to regions based on USA Census Bureau<br>Note: Patients from academic practices have unknown state values. | As of index date |
| Ethnicity | Baseline characteristic | Patient ethnicity:<br>• Not Hispanic or Latino<br>• Hispanic or Latino<br>• Unknown | As of index date |
| Socioeconomic status (SES) | Baseline characteristic | Based on the SES index, which is an area-level measure that provides insight into the socioeconomic conditions of the neighborhoods where patients reside. Provides the relevant SES Index quintile for a patient's block group based on 2015-2019 Census data:<br>• 1 - Lowest SES<br>• 2<br>• 3<br>• 4<br>• 5 - Highest SES | As of index date |
| Insurance type at index | Baseline characteristic | Insurance type:<br>• Commercial/Private<br>• Medicare<br>• Medicaid<br>• Other government programs (eg, VA, Military, Tricare)<br>• Self-pay/Uninsured<br>• Unknown/Missing | As of index date |

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| Practice type at index | Baseline characteristic | Practice type:<br>• Academic<br>• Community<br>• Both | As of index date |
| Body mass index (BMI) at Index | Baseline characteristic | Continuous ($kg/m^2$), calculated based on structured data or patients' height and weight from the Vitals table.<br>Determined using WHO BMI Categories:<br>• Underweight: <18.5 (May reflect frailty or cachexia; often rare in MM)<br>• Normal Weight: 18.5-24.9<br>• Overweight: 25.0-29.9 (Mildly elevated risk for some AEs)<br>• Obese (Class I-III): >=30.0 | The baseline window for BMI will start 30 days prior to index date and end 7 days after index date. The closest BMI value to index date within the time window will be used. If the absolute time difference is the same, the BMI value that precedes the index date will be used. For patients with multiple BMI values on the same day, the highest eligible BMI value will be selected. |
| Eastern Cooperative Oncology Group (ECOG) at index | Baseline characteristic | ECOG performance status (PS) on or prior to index date:<br>• 0<br>• 1<br>• ≥ 2<br>• Unknown | The baseline window for ECOG will start 30 days prior to index date and end 7 days after index date. The closest ECOG value to index date within the time window will be used. If the absolute time difference is the same, the ECOG value that precedes the index date will be used. For patients with multiple ECOG values on the same day, the highest eligible ECOG value will be selected. |
| International Staging System (ISS) stage at initial diagnosis | Baseline characteristic | • Stage I<br>• Stage II<br>• Stage III<br>• Unknown/not documented | Baseline period |
| Monoclonal protein (M-spike) testing | Baseline characteristic | Test closest to index date (latest test on or prior to index date)**:** | Baseline period |

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| | | • Date electrophoresis test<br>• Specimen collected for each electrophoresis test (serum, urine, unknown/not documented)<br>• Documented and standardized units<br>• M spike value<br>• Immunofixation results<br>• TestID | For patients with multiple M-spike tests within the baseline period, the test value on or closest to the index date will be selected. If there are multiple tests on the same day, the highest value will be used. |
| FISH cytogenetics testing | Baseline characteristic | Test closest to index date (latest test on or prior to index date):<br>• Date of specimen collection<br>• Indication of testing and whether abnormalities were identified (e.g., present, absent) for the following markers: t(14;16), t(11;14), t(4;14), t(6;14), t(14;20), deletion 17p, deletion 13q, deletion 1p, amplification 1q21, trisomy, other chromosome 1 abnormalities | Baseline period<br><br>For patients with multiple FISH cytogenetics tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used. |
| Karyotyping | Baseline characteristic | Test closest to index date (latest test on or prior to index date):<br>• Date of specimen collection<br>• Indication of testing and results for:<br>  ○ Number of chromosomes<br>  ○ Detection of abnormalities: trisomy, deletion 13<br>  ○ Ploidy: hyperdiploid, hypodiploid, unknown, not documented | Baseline period<br><br>For patients with multiple tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used. |
| Cytogenetic risk category | Baseline characteristic | Recently, in September of 2025, the International Myeloma Society (IMS) and the International Myeloma Working Group (IMWG) have released new recommendations for defining high-risk MM based on genomic tools. This new consensus definition, known as IMS-IMWG Consensus Genomic Staging (CGS), aims to more accurately identify patients with a poor prognosis [14]. Recognizing that RWD sources may not fully capture the granular detail required by the 'new' high-risk cytogenetic definition, we will employ a dual classification approach, integrating both the established ('old') and revised ('new') criteria for this study.<br><br>***New Definition***<br><br>The IMS-IMWG CGS of high-risk MM requires sequencing-based analyses and relies on the | Baseline period<br><br>Cytogenetic classification is based upon cytogenetic tests prior to and up to 60 days after the diagnosis date. For patients with multiple tests within the assessment period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used. |

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| | | presence of at least one of the following abnormalities:<br>• del(17p) with a clonal fraction greater than 20%, a TP53 mutation, or both.*<br>• An IgH translocation, including t(4;14), t(14;16), or t(14;20), along with gain or amplification of the long arm of chromosome 1 (1q+), del(1p32), or both.<br>• Monoallelic del(1p32) along with 1q+ or biallelic del(1p32).**<br>• High levels of β2-microglobulin (≥5.5 mg/L) with normal creatinine (<1.2 mg/dL).<br>*The guidelines also emphasize the importance of genomic sequencing for all MM patients and recommend that FISH testing be performed on plasma cell-enriched samples with a minimum purity of 70%. Risk assessments should be conducted at both diagnosis and relapse, with testing currently limited to bone marrow samples.*<br><br>**This will not be available in the current dataset.*<br>***The cytogenetic abstraction approach of the current dataset does not get to the level of granularity of monoallelic or biallelic deletion.*<br><br>***Old Definition***<br><br>Cytogenetic classification adapted from mSMART treatment guidelines and National Comprehensive Cancer Network (NCCN) Guidelines (Dispenzieri et al., 2007; Kumar et al., 2009; Mikhael et al., 2013; mSMART 2023; NCCN 2023)<br>• High risk: FISH del 17p, t(4;14), t(14;16), t(14;20), 1q21 gain/1q21 amplification<br>• Standard risk: t(11;14), t(6;14), trisomy<br>• Unknown: patients without documented cytogenetic tests<br>Note: Cytogenetic classification is based upon cytogenetic tests prior to and up to 60 days after the diagnosis date. | |
| Myeloma protein Ig class | Baseline characteristic | Patient's protein Ig class | Baseline period |

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| | | • IgA<br>• IgD<br>• IgE<br>• IgG<br>• IgM<br>• Not Documented<br>Note: These categories are not mutually exclusive and patients may present with multiple Ig classes for their myeloma proteins. Thus, each category may be displayed separately in results. | For patients with multiple tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used. |
| Involved light chain type | Baseline characteristic | Patient's involved light chain type<br>• Kappa<br>• Lambda<br>• Not Documented<br>Note: These categories are not mutually exclusive and patients may present with multiple involved light chain types. Thus, each category may be displayed separately in results. | Baseline period<br><br>For patients with multiple tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used. |
| Oligosecretory status (*exploratory variable)* | Baseline characteristic | Based on existed reports [15, 16], Oligo-Secretory Disease Status will be defined as Serum M protein < 1 g/dL AND urine M protein < 200 mg/day.<br>• Handling:<br>○ Latest Urine Protein Electrophoresis (UPEP) and Serum Protein Electrophoresis (SPEP) from baseline will be used<br>○ Make sure tests have valid units (mg for UPEP, g/dL for SPEP).<br>○ For FLC: latest serum test (kappa or lambda), mg/L units, elevated if outside normal range; but since the ratio itself cannot ensure that one type of FLC is elevated or low, we wouldn't be able to rely on this alone to identify FLC elevated<br>Looser Definitions *(if full capture for above is not possible):*<br>• Allow either UPEP or SPEP instead of requiring both. | Baseline period<br><br>For patients with multiple tests within the baseline period, the test value closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used. |
| Light chain MM (LCMM) status *(exploratory variable)* | Baseline characteristic | • Based on existing reports [15, 16], LCMM Status will be defined as<br>Absence of M spike AND elevated FLC (kappa or gamma). | Baseline period |

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| | | ○ Free kappa light chain (normal 3.3 – 19.4 mg/l)<br>○ Free lambda light chain (normal 5.71 – 26.3 mg/1)<br>○ Free kappa/lambda ratio (normal 0.26-1.65 mg/l)<br>Handling:<br>• Use latest UPEP, SPEP, and FLC from baseline.<br>• For Mspike: no unit restriction since we are interested in tests that did not identify presence of Mspike; if multiple assessments same day, keep one with M spike detected; use IFEM spike if Mspike missing.<br>• For FLC: latest serum test (kappa or lambda), mg/L units, elevated if outside normal range ; but since the ratio itself cannot ensure that one type of FLC is elevated or low, we wouldn't be able to rely on this alone to identify FLC elevated<br>Looser Definitions *(if full capture for above is not possible):*<br>• Allow either UPEP or SPEP instead of requiring both.<br>• For FLC: Consider dropping ratio criterion and rely on kappa/lambda only. | For patients with multiple tests within the baseline period, the test value closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used. |
| Renal impairment | Baseline characteristic | Categorical, using National Kidney Foundation (NFK) criteria and structured lab values.<br>The NFK defines renal impairment as:<br>• G1: glomerular filtration rate (GFR) 90 mL/min/1.73 $m^2$ and above with evidence of kidney disease, such as hematuria or proteinuria<br>• G2: GFR 60 to 89 mL/min/1.73 $m^2$<br>• G3a: GFR 45 to 59 mL/min/1.73 $m^2$<br>• G3b: GFR 30 to 44 mL/min/1.73 $m^2$<br>• G4: GFR 15 to 29 mL/min/1.73 $m^2$<br>• G5: GFR less than 15 mL/min/1.73 $m^2$ or treatment by dialysis<br><br>For the current study, categories will be collapsed, as follows:<br><br>Moderate RI or no RI | Baseline period<br><br>For patients with multiple tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used. |

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| | | • No RI: CrCl ≥40 mL/min<br>• Moderate RI: CrCl 30–39 mL/min<br>Severe RI<br>• Severe RI: CrCl <30 mL/min<br>• Dialysis | |
| Presence of extramedullary disease at diagnosis | Baseline characteristic | • Yes<br>• No | As of diagnosis date<br><br>For patients with multiple tests within the baseline period, the test value on or closest to diagnosis date will be selected. |
| Charlson comorbidity index (CCI) Score | Baseline characteristic | Assessed at any time prior to index date: CCI score, a derived measure created from the list of CCI comorbidities identified via ICD-9 and/or ICD-10 codes (Please see Annex 3 for more details).<br>• 0: no comorbidity<br>• 1-2: moderate<br>• ≥3: high burden | As of index date |
| Simplified frailty score | Baseline characteristic | Frailty will be evaluated using the simplified frailty score described by Facon et al. [17], which incorporates age, CCI, and ECOG PS. Age, CCI, and ECOG PS are each categorized according to predefined thresholds, and points are assigned to each category. The total frailty score is calculated by summing the points from all three components.* Patients are then classified as frail or non-frail based on the total score, with higher scores indicating greater frailty. This classification will be used to stratify patients for efficacy and safety analyses.<br>• Non-frail: 0 - 1<br>• Frail: ≥2<br><br>*Relevant details regarding how points will be assigned to each factor:<br>• Age:<br>○ ≤75 yrs = 0 points<br>○ 76-80 yrs = 1 point<br>○ >80 yrs = 2 points<br>• CCI:<br>○ ≤1 = 0 points<br>○ >1 = 1 point<br>• ECOG PS:<br>○ 0 = 0 points | As of index date |

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| | | ○ 1 = 1 point<br>○ ≥2 = 2 points | |
| Prior receipt of Chimeric Antigen Receptor T (CAR T)-cell therapy | Baseline characteristic | Indicates whether a patient received treatment with CAR T-cell therapy at any time prior to the index LOT:<br>• Yes<br>• No | Baseline period |
| Penta-drug exposure | Baseline characteristic | Indicates whether a patient had penta-drug exposure prior to the index LOT, defined as follows:<br>• ≥ 2 distinct treatment(s) for PIs (bortezomib, carfilzomib, or ixazomib)<br>• ≥ 2 distinct treatment(s) for IMiDs (lenalidomide, thalidomide, or pomalidomide)<br>• ≥ 1 treatment(s) for CD38 mAbs (daratumumab, isatuximab) | Baseline period |
| Prior receipt of autologous Stem cell transplant (SCT) | Baseline characteristic | Indicates whether a patient received autologous SCT at any time prior to the index LOT:<br>• Yes<br>• No | Baseline period |
| Prior receipt of allogeneic SCT | Baseline characteristic | Indicates whether a patient received allogeneic SCT at any time prior to the index LOT:<br>• Yes<br>• No | Baseline period |
| **(Treatment Patterns) Variable** | **Role** | **Operational Definition** | **Assessment Period** |
| Number of lines of systemic therapy prior to index LOT | Baseline characteristic / Exposure | Median with range<br>Categorical, number of LOTs received prior to the index date:<br>• 3<br>• 4<br>• 5+ | Baseline period |
| Prior treatments | Baseline characteristic / Exposure | For each prior LOT:<br>• Number of Line<br>• Drug class(es) received<br>• Treatment sequencing via Sankey diagrams<br>• Autologous SCT received prior to LOT (y/n)<br>• Allogeneic SCT received prior to LOT (y/n) | Baseline period |
| Index regimen | Exposure | Full regimen received in index LOT (first elra-containing LOT) | Index LOT |

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| First subsequent LOT after receiving Elra | Exposure | Subsequent 1st LOT following Elra treatment:<br>• Drug class(es) received<br>• Top 20 specific treatment regimens received<br>• Autologous SCT received prior to LOT (y/n)<br>• Allogeneic SCT received prior to LOT (y/n)<br>• The number of patients with no subsequent LOT after the elra-containing LOT will also be reported | From the initiation of a new LOT after the end of the Elra-containing LOT |
| Time from initial MM diagnosis date to index Elra treatment | Baseline characteristic / Exposure | Time (in months) from the initial diagnosis of MM to the start date of the index LOT (first Elra-containing line). | Baseline period to index date |
| Duration of treatment with Elra | Effect modifier | Time (in months) from the first administration of Elra to last administration of Elra | As of index date |
| Setting of care for Elra administration | Sub-group identifier | Reported for step-up dose 1, step-up dose 2, and the first treatment dose of Elra; categorical:<br>• Inpatient<br>• Outpatient<br>• Not documented | Index LOT |
| Timing of dosing periods | Effect modifier | Timing of the various dosing periods will be reported (for patients with the available follow-up time)<br>• Index date (day 1) to day 8: defined as the first 8 days post-index date, inclusive. Also defined as day 1 to day 8. (STEP UP DOSE PERIOD)<br>• Day 9 to day 168: defined as the period from day 9 to day 168 post-index date. (aka MAINTENANCE PERIOD 1 – the period in which Elra would be expected to be administered once weekly)<br>• Day 169+: defined as the period from day 169 post-index date to end of follow-up period. (aka MAINTENANCE PERIOD 2 – the period in which Elra would be expected to be administered every 2 weeks Q2W depending on individual response)<br>• Overall follow-up (day 1 to end of follow-up period): defined as the period from index date to end of follow-up period | Follow-up period |
| Dosing | Effect modifier | Reported for each administration of Elra, including step-up doses; distribution of dosing: | During Elra containing LOT |

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| | | • 12 mg<br>• 32 mg<br>• 76 mg<br>• Not recorded | |

### 8.4. Data Sources

As recommended in the draft FDA Guidance for Industry RWD: Assessing EHRs and Medical Claims Data To Support Regulatory Decision Making for Drug and Biological Products (September 2021), a description of the FHRD, data source management, and processing are provided.

The FHRD is a longitudinal database derived from EHRs and other RWD sources from cancer care providers across the US. FHRD is classified as structured or unstructured. Structured data refers to data points that are organized in a predefined manner, such as drop-down fields that reside in an EHR (e.g., a patient's sex or date of birth). Redacted harmonizes structured data to a standard terminology. Structured data is not provided directly to sponsors in the delivery of real-world datasets. Unstructured data refers to information that is not organized in a pre-existing field, such as free text from physician notes, or other non-standardized information in computer documents (such as PDF-based radiology reports) in an EHR. Unstructured data is not provided directly to sponsors in the delivery of real-world datasets.

The patient population within the FHRD evolves over time, based on the patients cared for in the Redacted network practices. Only patients from practices that have given Redacted appropriate data rights are included in the FHRD. For patients treated in the Redacted, the entire patient chart in the EHR is available to Flatiron, enabling a longitudinal data view of patients' health care with resolution at the disease and treatment level. Characteristics of patients in the FHRD have been compared to other data sources, such as Surveillance, Epidemiology, and End Results Program (SEER) and National Program for Cancer Registries (NPCR), and found to be broadly representative [18].

Redacted employs rigorous validation processes for abstracted data derived from EHR sources to ensure accuracy and reliability. Specially trained oncology abstractors use a proprietary abstraction platform (Patient Manager®) following documented procedures and best practice guidelines. Quality assurance includes inter-rater agreement checks, where a subset of records is independently abstracted by two abstractors and discrepancies are investigated, as well as technology-enabled oversight through automated and manual reviews. Additionally, performance for AI-assisted variables used in cohort selection is continually monitored against a fully abstracted reference standard, maintaining sensitivity thresholds of ≥95%. Linkage between structured and abstracted data is performed using a common patient identifier, and derived variables (e.g., lines of therapy) are created using deterministic rules reviewed by cross-functional teams. These measures collectively ensure that abstracted data are fit-for-purpose for retrospective research.

### 8.5. Study Size

There are no a priori hypothesis specified , thus sample size calculations are not applicable. This study will use descriptive statistics to estimate the outcomes; thus, no sample size calculations were conducted. After applying all inclusion/exclusion criteria, there will be approximately 120 patients available for the overall cohort.

## 8.6. Data Management

Redacted employs an Extract, Transform, and Load (ETL) process, a series of operations that move raw data from its source systems into Flatiron's research databases to prepare structured data for use in real-world datasets.

The ETL process primarily leverages Structured Query Language (SQL), a Redacted proprietary orchestration tool, and Python to process data in a consistent and reproducible manner. Through ETL, structured data is harmonized using domain-specific mapping policies to conform to a common data model, enabling disparate data sources to be integrated into a single, standardized dataset. Structured data are extracted from multiple EHR systems and other external supplementary sources. The mechanisms and cadence of extraction vary by source system. Defined business logic governs how data is extracted for each EHR type. To ensure reliability, the extraction process is monitored through automated alerting mechanisms that check whether data are extracted at the expected cadence and accurately reflect their source. Any anomalies detected through these alerts are investigated and remediated as needed.

Once extracted, structured EHR data fields are transformed and standardized to ensure suitability for downstream research deliverables. This includes mapping data elements such as diagnoses, laboratory values, and medication administrations to a common vocabulary, normalizing them across different EHR systems. Redacted medical informatics mapping process establishes this common vocabulary. For example, multiple "albumin" terms captured across EHRs are harmonized into a single standardized albumin variable. Terms referring to different concepts (eg, albumin-related but not equivalent measures) are excluded from that mapping. Redacted uses a technology-enabled mapping system that automates terminology management, supplemented by manual review and quality control (QC) from Flatiron's technical and medical informatics teams. Items that cannot be automatically mapped undergo manual adjudication to ensure accuracy. In the load phase, the transformed and harmonized structured data are published as a research-ready dataset at a cadence aligned with project needs.

Before publication, the dataset undergoes both automated and manual quality checks. For example, new builds are compared to prior versions to identify unexpected changes in data volume, composition, or quality (eg, unusually high proportions of nulls in specific fields). More granular analyses may also be performed, for instance, evaluating additions or drops of specific LOINC codes for particular sites in the laboratory table, to ensure data stability and integrity across releases.

## 8.7. Data Analysis

### 8.7.1. Overview of Analysis

All analyses will be descriptive in nature, and no formal statistical comparisons will be performed. Analyses will be completed using R version 4.1.3.

**Derived and Transformed Data**

Patients' treatment will be derived using Redacted LOT business rules. Specifically, an oncologist-defined, rule-based approach is applied to sequences and combinations of abstracted oral therapy spans, medication administrations, and non-cancelled medication orders. These business rules are developed specific to MM. Generally, 5L+ treatment is defined based on the first systemic Elra administration after receiving at least 4 prior lines of treatments. Evidence of prior treatment is included to allow for minor misclassification of the number of LOTs.

Patients' baseline comorbidities will be summarized by CCI score, which will be a derived measure created from the list of CCI comorbidities identified via ICD-9 and/or ICD-10 codes (see Annex 3).

**Bias Control Procedures:**

- Selection bias: Transparent patient attrition counts will be reported; patients who do not meet the inclusion criteria will be excluded.
- Information bias: Only lab values with valid units will be used, an explicit “Not documented” category will be reported where applicable.
- Confounding: This analysis is primarily descriptive and no comparison models will be performed.
- Censoring bias: Consistent Kaplan-Meier censoring rules as defined in Section 8.7.2 will be applied where applicable.

### 8.7.2. Primary Analyses

Baseline demographic and clinical characteristics will be described for the overall study cohort. Continuous variables will be described in terms of means, medians, IQR, SD, and range. Categorical variables will be reported as patient numbers and percentages of the population. Variable categories and definitions are described above in Table 1 of this protocol.

**Additional Details on Demographic and Clinical Characteristics:**

- BMI will be assessed as a continuous variable (kg/m²), calculated from structured data or patients’ height and weight from the Vitals table. BMI will be categorized according to WHO criteria: Underweight (<18.5; may reflect frailty or cachexia and is often rare in MM), Normal Weight (18.5−24.9), Overweight (25.0−29.9; mildly elevated risk for some AEs), and Obese (Class I−III; ≥30.0).
- ECOG performance status (PS) will be assessed on or prior to the index date and included in all baseline summaries.
- Charlson Comorbidity Index (CCI) will be assessed at any time prior to the index date. CCI will be derived from ICD-9 and/or ICD-10 codes (see Appendix B for details) and categorized as follows: 0 (no comorbidity), 1−2 (moderate), and ≥3 (high burden).
- Frailty will be evaluated using the simplified frailty score described by Facon et al., which incorporates age, CCI, and ECOG PS. Each component will be categorized according to predefined thresholds and assigned points. The total frailty score will be calculated by summing the points from all three components. Patients will be classified as non-frail (score 0−1) or frail (score ≥2), and this classification will be used to stratify patients for efficacy and safety analyses.
- Renal impairment will be assessed according to IMWG criteria: serum creatinine >2.0 mg/dL (177 umol/L) or creatinine clearance <40 ml/min (by Cockcroft-Gault or MDRD).
- Cytogenetic classification will be based on cytogenetic tests performed prior to and up to 60 days after the diagnosis date. For patients with multiple tests within the assessment period, the test value on or closest to the index date will be selected; if multiple tests occur on the same day, the highest value will be used. High-risk and standard-risk categories will be assigned according to both the IMS-IMWG Consensus Genomic Staging (September 2025) and legacy mSMART/NCCN guidelines. High-risk features will include FISH del 17p, t(4;14), t(14;16), t(14;20), and 1q21 gain/amplification. Standard risk will include t(11;14), t(6;14), and trisomy. Patients without documented cytogenetic tests will be classified as “unknown.”

- Oligo-Secretory Disease Status will be explored and defined as serum M protein <1 g/dL AND urine M protein <200 mg/day. The latest UPEP and SPEP from baseline will be used, ensuring valid units (mg for UPEP, g/dL for SPEP). For free light chain (FLC), the latest serum test (kappa or lambda) in mg/L units will be included and considered elevated if outside the normal range. If full capture is not possible, either UPEP or SPEP will be allowed instead of requiring both.
- LCMM Status will be explored and defined as absence of M spike AND elevated FLC. The latest UPEP, SPEP, and FLC from baseline will be used. For Mspike, no unit restriction will be applied; if multiple assessments occur on the same day, one with M spike detected will be retained, and IFEM spike will be used if Mspike is missing. For FLC, the latest serum test (kappa or lambda) in mg/L units will be included and considered elevated if outside the normal range. If full capture is not possible, either UPEP or SPEP will be allowed instead of requiring both, and the ratio criterion may be dropped in favor of kappa/lambda only

Treatment patterns will be displayed in Sankey diagrams with corresponding tables presenting frequency and proportion of treatment type (both drug classes and top 20 individual regimens) by line. Sankey diagrams illustrate cohort-level switch to next treatment or no subsequent treatment due to death or censoring at last confirmed activity captured in the EHR. The number and proportion of patients who proceed to subsequent LOT will be described by line names. Patients who receive autologous and allogeneic SCT prior to each LOT will be described among patients receiving each LOT of interest.

For the index line (first Elra-containing line), the line number will be noted, as well as the full regimen received. Time from the end of the prior LOT to the start of the index LOT will be reported in days. Duration of treatment with Elra will be reported in months. For step-up dose 1, step-up dose 2, and the first treatment dose of Elra, setting of care and practice setting will be reported.

**Additional Details on Index Treatment:**

- The line number in which the index treatment (first ELRA-containing regimen) occurred will be reported.
- Timing of dosing periods will be reported for patients with available follow-up:
    - Step-up dose period: Index date (day 1) to day 8 (first 8 days post-index, inclusive)
    - Maintenance Period 1: Day 9 to day 168 (once weekly)
    - Maintenance Period 2: Day 169+ (every 2 weeks Q2W depending on response)
    - Overall follow-up: day 1 to end of follow-up period
- Doses will be reported for each administration of Elra, including step-up doses; distribution of dosing: 12mg, 32mg, 76mg, not recorded.
- Setting of care for Elra administration will be reported for step-up dose 1, step-up dose 2, and first treatment dose.
- Index LOT treatment duration is defined as length of time from index date to earliest of date of death, last confirmed activity date (vital information, medication administration, lab result, or last abstracted therapy date), initiation of new LOT, or data cutoff.
- Practice type for patients receiving ELRA treatment will be captured.

rwORR will be reported as the number and proportion of patients who have at least one rwPR or rwVGPR or better during the index LOT out of the total number of patients in the cohort, along with 95% confidential interval (CI) estimates. Each rwR category will also be reported among patients with available response information.

**Additional Details on rwORR Capture:**

- rwORR will be defined as the proportion of patients who had at least one PR, VGPR, or better assessment, among patients with a baseline lab value and a subsequent lab value.
- PR and VGPR will be derived from enhanced M spike and free light chain lab values based on IMWG criteria.

Incidence of real-world AEs will be reported as the number and proportion of patients with first onset or worsening of the selected rwAE type that occurred during the follow-up period. The window for rwAE capture will be 30 days prior to the start of the line (for the AE to be considered present at baseline) through the end of the LOT. Numbers and proportions of patients with a drug-attributable (ie, “definite attribution” and “likely attribution,” respectively) rwAE will also be reported.

The proportion of patients with documented presence of each rwAE type and type of outcome related to the rwAE (including therapy discontinuation, dose or schedule change, therapy hold, treatment for the rwAE, and hospitalization) will be presented. Therapy attribution of rwAEs will be reported as numbers and proportions of patients by each rwAE type and therapy attribution category, including definite attribution, likely attribution, not attributed, and no documentation. Resolution of rwAEs will be reported as the proportion of patients with each documented resolution status type (resolved, resolving, resolved with sequelae, ongoing, fatal, not documented), for each rwAE. Time to resolution will be reported in days for those rwAEs that are noted to be resolved or resolved with sequelae.

**Additional Details on rwAE Capture:**

- Baseline rwAE prevalence: The number and proportion of patients who have evidence of the respective rwAE during the baseline period (defined as 30 days prior to index LOT up to one day before index LOT) will be reported.
- Incident rwAEs: The number and proportion of patients without any pre-existing rwAEs (no occurrence of the AE within 30 days prior to the index date) who experience one or more rwAE during the AE examination period will be calculated and divided by the total number of patients in the cohort.
- Worsening of pre-existing rwAEs: The number and proportion of patients with one or more pre-existing rwAEs who experience a worsening of the rwAE (or worsening of one or more of the pre-existing rwAEs) during the AE examination period will be calculated and divided by the total number of patients in the cohort. Worsening is defined as the AE being present at baseline and documented to be worse/increased compared to baseline status, or the AE is present at baseline, resolves, and then recurs during the AE examination period.
- Clinician-documented outcomes: Outcomes related to the selected rwAEs that occurred during the index LOT, as determined by abstraction, will include: dose or schedule change, therapy hold, therapy discontinuation, treatment for the AE, hospitalization, and no outcome related to the AE. These categories are not mutually exclusive and more than one can be selected and reported.

- Therapy attribution: The level of attribution for the selected rwAE of interest, as determined by the treating clinician, will be reported for each rwAE type: definite attribution, likely attribution, not attributed, and no documentation.
- Severity: The severity of the selected rwAE of interest, as determined by the treating clinician, will be reported for each rwAE type.
- Resolution status and timing: Clinician-documented resolution status of the selected rwAE of interest will be reported for each rwAE type: resolved, resolving, resolved with sequelae, ongoing, fatal, not documented. Time to resolution (in days) will be calculated from rwAE start to date of resolution for rwAEs marked as "resolved" or "resolved with sequelae".

Time from Elra start date to onset or worsening of rwAEs will be estimated using Kaplan-Meier methods. Time-at-risk will be indexed to Elra initiation, and the onset date of the specific rwAE. Patients without evidence of the rwAE will be censored at the end of the LOT. Median time to onset of rwAE and the corresponding 95% CI will be reported. In the event that the rwAE is resolved, median time to resolution of the rwAE and the corresponding 95% CI will also be reported.

No statistical comparisons of the rwAE incidence rates or outcomes will be made.

### 8.7.3. Secondary Analyses

The same outcomes analysis as the above will be conducted in the following subgroups: Presence of extramedullary disease, high cytogenetic risk, performance status, renal impairment (*if sample size allows*), age (81 years of age and older), and setting of care for Elra step-up dose administration (inpatient vs. outpatient). They will also be conducted in the following groupings, conditional on outcomes: severity of AEs, safety grade 2 and above (*only available for ICANS and CRS*), and CRS and ICANS by setting of care for Elra step-up dose administration. No statistical comparisons of the rwAE incidence rates will be made across groupings.

### 8.7.4. Sensitivity Analyses

To maximize sample size for the current study, all patients meeting criteria up to the data cutoff date (June 30, 2025) will be included, without applying a criterion to allow for minimum potential follow-up time. To address this we will conduct two sensitivity analysis: one, where we rerun the rwORR and rwAE analyses restricting the cohort to patients indexed at least 3 months prior to data cutoff, and then a second rwORR and rwAE analyses including only those indexed at least 6 months prior to data cutoff to see the impact of follow-up time on the results.

## 8.8. Quality Control

Redacted is committed to conducting high quality research intended to comply with regulatory requirements, industry best practices, and internal quality commitments. These inputs drive the implementation and ongoing development, enhancement, and maintenance of the QMS. Redacted research QMS is derived from defined principles outlined in ICH guidance documents and life science industry best practices. Redacted QMS is the foundation for the oversight activities which occur throughout the research lifecycle that support integrity of Redacted software systems, the curation and cleaning of data originating from structured and unstructured data sources, and the conduct of analytic studies.

Flatiron's quality assurance (QA) and QC activities aim to understand and improve the quality of our data, as well as provide oversight to the data collection process and conduct of analyses. Activities for this protocol fall into these categories:

- Operational procedures: These are documented processes which allow Redacted to employ consistency in completing tasks, anticipate potential roadblocks, as well as increase efficiency and facilitate planning.
- Quality procedures: These are processes intended to provide oversight of protocol-related activities to ensure that data are generated, documented (recorded), and reported in line with requirements (e.g., Flatiron's processes).
- System controls: These are processes built into technical systems and/or workflows to provide programmatic oversight and efficiency through (e.g., software).

Throughout the data lifecycle, Redacted employs both automated and manual monitoring to ensure data quality and integrity. Automated alerting mechanisms continuously check extraction cadence and data fidelity, flagging anomalies for prompt investigation and remediation. Prior to dataset publication, comprehensive quality checks—including comparisons to previous builds and granular analyses of data elements—are performed to detect unexpected changes or inconsistencies. These monitoring activities are supplemented by manual review and adjudication, ensuring that data meet rigorous standards for research.

## 8.9. Strengths and Limitations of the Research Methods

**Generalizability:**

The data source for this study largely draws from community oncology centers in the US, though patients treated in academic practices are also included, which may lead to a skewed pattern of treatment (eg, less aggressive treatment tendencies). External validity may be limited as oncology practices included in this study are part of the database's oncology practice network, which may not represent all oncology practice sites within the US. Consequently, generalizability of the results to the overall US population as well as non-US populations may be limited. Also, although the present study is descriptive, the study cohort has small sample size which limits the ability to generalize to the target population as a result of increased random error.

Additionally, the patients with RRMM included in this study are heavily-pretreated, and the diversity of prior treatment exposures and sequencing strategies may influence the response outcomes with Elra. For example, variations in the timing and order of proteasome inhibitors, IMiDs, and anti-CD38 monoclonal antibodies, and other BCMA-targeted agents may affect subsequent disease biology and sensitivity to Elra. Such heterogeneity in treatment histories is difficult to fully control for in retrospective analysis, and therefore, caution should be exercised when attempting to evaluate rwORR and safety data across these Elra treatment cohorts.

**Data Collection/Ascertainment**

EHR-based data in the FHRD is collected primarily for the clinical management of oncology patients and not for research purposes. The proposed study is therefore subject to the availability and level of granularity provided in the source data and, by extension, in the FHRD. This means there may be data not included or not included at an optimal level of granularity for the purpose of analyses described in the proposed study.

Evidence of exposure to treatments may be limited in the FHRD if patients are treated outside of the Redacted clinical network. This may result in a misclassified line of treatments. However, capture of treatments from unstructured data (e.g., review of clinical notes) is used to mitigate the potential for this source of misclassification. Additionally, treatments for additional malignancies may be incorrectly included in a LOT as the rules are not able to attribute medication administration or orders to the disease of interest. This likely will not be an issue as regimens are selected based on known standards of care for MM.

Because the rwAEs assessed in the present study are identified *a priori*, additional rwAEs outside of the pre-specified list that occur will not be included. Further, information on the grade or severity of rwAEs will not be available to examine the incidence by grade or to contextualize the outcomes and management of the rwAEs.

Specific to the outcomes and management of rwAEs, ascertainment is dependent upon clinician documentation, which may be missing. Thus, it is possible that the proportion of patients who die or who are hospitalized due to a rwAE may be underestimated, as there could be cases in which this occurs, but it is not documented. For management of the rwAEs, structured data will be used to assess treatments given to treat the rwAEs. The structured data cannot be confirmed as given for treatment of the rwAEs; thus, patients may be misclassified. This is mitigated by only assessing structured data in instances when patients have abstracted evidence confirming they received any treatment for the rwAEs and by only looking at structured data after the onset of the rwAEs.

Elra was approved on August 14, 2023, as a 5L+ regimen for the treatment of RRMM. As a result of the relatively recent approval, there are not enough patients in the FHRD to adequately characterize the incidence and outcomes of rwAEs in this population. Furthermore, given the relatively small sample size (approximately 120 patients), the study is not powered to detect or robustly assess rare adverse events. Therefore, no formal statistical inference will be made for rare AEs, and findings will be descriptive only.

**Measurement validity and granularity**

Treatments for additional malignancies may be incorrectly included in the LOT rules specific to the MM. Tumor characteristics and/or diagnoses may be misclassified if the documentation in the patient chart was entered erroneously.

**Missingness**

The lack of availability of data on certain variables, missingness in data obtained from the EHR, and loss-to-follow-up could introduce bias due to unmeasured confounding. Relatedly, certain variables may not be available with full completeness, such as race, ethnicity, stage, and ECOG. Baseline comorbidities and CCI score carry methodological limitations due to the included conditions being identified via ICD-9 and -10 codes which are susceptible to under-reporting and missingness in this dataset. Other primary malignancies will be identified via ICD-9 and -10 codes and there may be a degree of missingness in their reporting.

Flatiron's BirthYear Transformation may potentially impact the elderly patient population in this study. As outlined in Table 1, Redacted adjusts BirthYear for elderly patients; therefore, some individuals may appear younger than their true age. This could result in an underestimation of age at index date for the oldest patients (≥85 years). All age-related analyses and interpretations will consider this limitation. If precise age information for elderly patients is critical, a custom data extract from Redacted may be requested under privacy safeguards.

LOT are derived from EHR data using Redacted oncologist-defined, rules-based algorithms based on structured medication administrations, structured non-cancelled orders, and abstracted oral/intravenous antineoplastic therapies. As a result, a patient's treatment assignment and/or sequencing may be misclassified if underlying treatment data is missing or if treatment is ordered but not received. And also, treatments received for additional primary malignancies (other than MM) may be incorrectly included in LOT.

Regarding Cytogenetic Risk Classification, the recently proposed IMS-IMWG CGS definition of high-risk MM incorporates genomic abnormalities beyond the traditional criteria. However, some of these variables are not available in the current dataset; in particular, del(17p) with a clonal fraction >20%, TP53 mutation, or both, as well as monoallelic del(1p32) with 1q+ or biallelic del(1p32) are

recognized as high-risk features, but are not captured. As a result, some patients who would be considered high risk under CGS may be misclassified as standard risk, potentially leading to an underestimation of the prevalence and impact of high-risk cytogenetics in our study. Nevertheless, by employing both established ("old") and revised ("new") definitions where feasible, we provide a pragmatic framework for cytogenetic risk stratification in the context of RWD.

IMWG frailty score is considered to be a strong prognostic indicator of clinical outcomes in MM. This frailty score is not a variable in the current dataset, as activities of daily living are not captured; however, the simplified IMWG frailty score consists of ECOG, CCI, and age. A retrospective observational study such as this one can only capture an abstracted rwAE if it is documented by the clinician in the EHR in the course of standard care. Additionally, only the first instance of an AE is abstracted when there is documentation of an AE multiple times while receiving the therapy of interest. Clinicians may not document conditions that occur that do not result in changes in treatment relevant to that clinician's area of practice or do not result in a condition that is eligible for reimbursement of treatment. A condition also may not be reported to the clinician by a patient and therefore will not be reflected in this study. Attribution of the rwAE to the therapy is also only reported if it is documented by the clinician; as such, there will be a level of missingness associated with this variable.

In addition, patients may also be lost-to-follow-up if they seek treatment or care in practices outside of the Redacted network leading to potentially incomplete patient-level clinical information. As such, the end of clinical activities only reflects the most recent clinical activity as recorded by cancer care providers in the FHRD.

### 8.10. Other Aspects

Not applicable.

## 9. PROTECTION OF HUMAN PARTICIPANTS

### 9.1. Patient Information

This study involves data that exists in a de-identified/anonymized structured format and contains no patient personal information.

### 9.2. Patient Consent

As this study involves de-identified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

### 9.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

IRB is not required for this study as it uses EHR available de-identified secondary data sources and is considered exempt from the requirements for "human subjects research" in the US.

### 9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices. Flatiron's dataset from which the data for this study was extracted is covered by the Redacted Real-World Evidence Parent Protocol approved initially by the New England IRB and then by Copernicus Group Independent Review Board. Additionally, a sub-study protocol was also submitted as a supplement in addition to the parent protocol and provided to the IRB for approval. IRB approval

was in place for the duration of research activities and documentation for IRB submissions, approvals, and continuing review are retained by Redacted

In addition, the study design and conduct are guided by the Guidelines for Good Epidemiologic Practice, including the 2005 FDA Good Pharmacoepidemiology Practices (GPP), Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, and the 2015 International Society of Pharmacoepidemiology GPP.[19-20]

## 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exists as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

## 11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

### Study Report

The completed study will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

### Publication

The results of the present study will be used to develop an abstract to be submitted to the congress in 2026.

In collaboration with Pfizer, the manuscript will communicate the findings of the study conducted for the core task above. The Redacted project team will work closely with Pfizer to identify the most appropriate target journal for the manuscript.

Pfizer policy or guidance covering publications of study data will be observed to determine when and how the results will be communicated. Authorship for all publications will comply with ICMJE criteria. Each author will have participated sufficiently in the work to take public responsibility for the content (www.icmje.org/recommendations/browse/roles-andresponsibilities/defining-the-role-of-authors-and-contributors.html).

## 12. REFERENCES

1. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2022;97(8):1086-1107. doi:10.1002/ajh.26590
2. National Cancer Institute, Surveillance Research Program, SEER Program. *SEER Cancer Statistics Review*. https://seer.cancer.gov/csr/. Accessed November 20, 2025.
3. Siegel RL, et al. Cancer Statistics, 2023. *CA Cancer J Clin.*

4. Kumar SK, et al. Continued improvement in survival in multiple myeloma. *J Clin Oncol.* 2014.
5. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33(9):2266-2275. doi:10.1038/s41375-019-0435-7
6. Ghandi et al., 2019 OR other real-world refractory MM survival papers.
7. Harrison SJ, et al. Mechanism and early development of elranatamab. *Clin Lymphoma Myeloma Leuk.* 2022.
8. Bahlis NJ, et al. MagnetisMM-3: Elranatamab in RRMM. *NEJM.* 2023.
9. Clinical trial safety data (ASH 2022/2023 abstracts).
10. U.S. Food and Drug Administration. FDA grants accelerated approval to elranatamab bcmm for multiple myeloma. FDA. August 14, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-elranatamab-bcmm-multiple-myeloma. Accessed November 20, 2025.
11. Malard F, Bobin A, Labopin M, et al. Elranatamab monotherapy in the real-word setting in relapsed-refractory multiple myeloma: results of the French compassionate use program on behalf of the IFM. *Blood Cancer J.* 2024;14(1):219. Published 2024 Dec 18. doi:10.1038/s41408-024-01200-w
12. Grajales-Cruz A, Hansen D, Castaneda O, et al. Safety and efficacy of standard of care (SOC) elranatamab in patients with relapsed/refractory multiple myeloma: a single-center experience. *Blood.* 2024;144(19):7832. doi:10.1182/blood-2024-204276.
13. Sharon Zhang. BirthYear Overview and Data Considerations. Flatiron Health. 2023.
14. Robinson K. IMS-IMWG Releases New Consensus Definition of High-Risk MM Based on Genomic. ASH Clinical news. September, 2025.
15. Silva C, Costa A, Paiva D, et al. Light-Chain Multiple Myeloma: A Diagnostic Challenge. *Cureus*. 2021;13(10):e19131. Published 2021 Oct 29. doi:10.7759/cureus.19131
16. Pavan M, Ashwini KA, Ravi R, Suratkal LH. Complete remission of lambda light chain myeloma presenting with acute renal failure following treatment with bortezomib and steroids. *Indian J Nephrol*. 2010;20(2):94-96. doi:10.4103/0971-4065.65304
17. Facon T, Dimopoulos MA, Meuleman N, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. *Leukemia*. 2020;34(1):224-233. doi:10.1038/s41375-019-0539-0
18. Ma X, Long L, Moon S, et al. Comparison of Population Characteristics in Real-World Clinical Oncology Databases in the US: Flatiron Health, SEER, and NPCR. *medRxiv.* 2023;2020.03.16.20037143.
19. FDA. Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Published online 2005. https://www.fda.gov/files/drugs/published/Good-Pharmacovigilance-Practices-and-Pharmacoepidemiologic-Assessment-March-2005.pdf.
20. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets. U.S. Food and Drug Administration. Published May 2013.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic

21. International Myeloma Working Group. (n.d.). IMWG uniform response criteria for multiple myeloma. Retrieved from https://www.myeloma.org/resource-library/international-myeloma-working-group-imwg-uniform-response-criteria-multiple

## 13. LIST OF TABLES



## 14. LIST OF FIGURES



## ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

## ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable/not required.

## ANNEX 3. ADDITIONAL INFORMATION

Table shells for data analysis and results reporting

## DESCRIPTION OF THE Redacted DATA SOURCE AND OVERVIEW OF Redacted

### A.1 Introduction

The FHRD is a longitudinal database derived from EHRs and other RWD sources from cancer care providers across the United States. Redacted operates a real-world oncology data platform that aggregates and processes patient-level data such as demographics, diagnostic information, extent of disease, laboratory values, treatments, and patient outcomes. This detailed information facilitates insight into real-world cancer care, permitting hypothesis generation and retrospective research.

The primary source for Redacted data is EHRs. De-identified data originated from approximately 280 US cancer clinics (~800 sites of care). The majority of patients in the database (approximately 75%) originate from community oncology settings; relative community/academic proportions may vary depending on study cohort.

Patients are routinely included in research datasets based on confirmation of defined criteria (eg, the type of tumor of interest and stage of disease). Redacted employs data handling best practices to maximize the inclusion of relevant treatment history, as available in the patient's EHR.

In addition to data available in the EHR, data from secondary sources (such as databases from commercial, government, claims, genomics, or other RWD sources of clinical information collected in the routine care of patients) may also be included.

Redacted EHR data are classified as *structured* or *unstructured*.

- **Structured data** refers to data points that are organized in a predefined manner, such as drop-down fields that reside in an EHR (e.g., a patient's sex or date of birth). Redacted harmonizes structured data to a standard terminology. One specific example of harmonized data is diagnosis codes that are mapped to ICD-9 and ICD-10 codes. Structured data are not directly used in research deliverables for external sponsors.
- **Unstructured data** refers to information that is not organized in a pre-existing field, such as free text from physician notes or as other non-standardized information in computer documents (such as portable document format [PDF]-based radiology reports) in an EHR. Unstructured data are not directly used in research deliverables for external sponsors.

EHR data are processed using extraction, harmonization, abstraction, and/or derivation to create data variables of interest based on standardized processes. This results in the study-specific research dataset used in deliverables for external sponsors.

- **Extraction** results from retrieving data out of structured data or from the retrieval of unstructured data into structured data through automated techniques using artificial intelligence (eg, NLP and machine learning [ML]) and document searching techniques. Similar to abstracted data, extracted data supports Redacted ability to incorporate key information from the EHR. Examples of extracted data are diagnosis codes, demographics, ECOG performance status, and laboratory results.
- **Harmonization** results when individual data elements are mapped to controlled vocabularies that support the clinical use case and translate data in a consistent way. This achieves semantic consistency and representation of oncology data to support interoperability, data quality, and accuracy. An example of harmonization is mapping disease stage using disease-specific staging systems such as American Joint Committee on Cancer, Ann Arbor Staging system, International Prognostic Scoring System, and others (based on the cancer type of interest).
- **Abstraction** results from the manual abstraction of unstructured data into structured data using specially trained human abstractors. Unstructured data are processed through Redacted s proprietary, technology-enabled abstraction software platform, which supports Redacted ability to incorporate key information from the EHR (e.g., data points, clinician interpretation of digital images). Examples of abstracted data are disease stage, biomarker testing results, and oral antineoplastic therapies that are organized in discharge notes, physician notes, pathology reports, and other documents.
- **Derivation** results when multiple data components are combined with established deterministic rules. Examples of derived data include LOTs and patient date of death. One specific example of derived data is three different medications that are grouped together into a treatment sequence or LOT based on established deterministic rules.

### A.2 Data management and processing

Following data extraction, harmonization, and abstraction, the processed data are used to create research cohorts, and the data are available for analysis. EHR data may also be linked to other external data sources (eg, genomics data and claims data).

Datasets comprising the combined extracted, harmonized, abstracted, and derived data are stored

securely at Redacted or our data partners. Datasets are de-identified prior to use in deliverables shared with external research partners.

### A.2.1 Structured data processing

Redacted uses an Extract-Transform-Load (ETL) process (i.e., a set of processes that are performed when moving raw data from its source into a database) for preparing structured data for real-world datasets. The ETL process primarily leverages SQL, a Redacted proprietary orchestration tool, and Python programming languages, which work with data in a consistently reproducible fashion. Structured data flows into the FHRD using the ETL process, during which data are harmonized using domain-specific mapping policies for specific mapping concepts to conform to a common data model. This allows disparate data sources to be output to a single, standardized dataset.

### A.2.2 Unstructured data processing

Since there is an increased likelihood of patient information such as diagnosis, stage, histology, key outcomes, etc., being omitted if relying on structured EHR fields alone, Redacted has developed an approach to abstract unstructured data. Unstructured data are abstracted by specially trained human abstractors using Patient Manager®, Redacted proprietary software that supports the efficiency and accuracy of the process. Patient Manager® uses a layer of technology that facilitates document classification, visual organization, and abstraction workflow management. Indexed EHR documents are ingested from the EHR system, categorized (e.g., clinic note, pathology report), converted to a standard format (eg, PDF) with text extracted for digital recognition (e.g., optical character recognition) and stored in a central documents database. Data obtained through the abstraction of unstructured data are stored in the Patient Manager® Database.

Redacted data abstractors are qualified by training and experience, assessed through external experience (eg, direct experience with oncology and/or research) as well as Redacted specific training and experience (eg, training on abstraction procedures, Redacted systems). Abstracted data are obtained from unstructured data using the Patient Manager® system in accordance with internal operating procedures (often referred to as abstraction P&Ps), documented best practice guidelines, and review/oversight controls. Documented processes, including oversight, tracking, and quality checks, are in place to optimize the quality of abstracted data.

### A.2.3 Combining structured and unstructured data

After the above steps, the data is combined as follows:

1. Extracted and abstracted data flow into the study-specific database and are combined by relying on a common patient identifier.
2. Derived data variables and tables are created by applying defined algorithms that combine structured and/or abstracted data. For example, LOTs are derived using disease-specific deterministic rules, and this data can then be used for cohort selection for studies based on a specific treatment line. Drug episodes are also derived to facilitate analyses related to treatment span, such as duration of treatment or time to treatment discontinuation.
3. The combined dataset is de-identified and used in research deliverables.

### A.3 Data QA and QC

RWD is considered fit-for-purpose when it is of sufficient quality as well as relevant, robust, and representative within a given clinical and regulatory context. Maintaining data quality dimensions, such as accuracy, reliability, relevance, and completeness, is a continual, dynamic process throughout the study.

QA/QC oversight activities for real-world dataset(s) are conducted during the course of a study following documented business processes and procedures. At a high level, QA/QC oversight activities for curating real-world datasets can be grouped into the following areas:

- **Operational and process oversight**: Documented standard operating procedures allow Redacted to consistently complete study-related activities, anticipate potential risks, increase efficiency, and facilitate planning. Examples of operational processes are described below:
    - Structured data are extracted and harmonized in accordance with defined processes.
        - Structured data are extracted from source EHR systems from the site of clinical care alongside other external data (e.g., mortality data sources), in accordance with defined business processes to ensure secure and timely extracts.
        - Harmonization of structured data across data sources is done to standardize coding and/or terminology without changing the original meaning and context of the data. Defined harmonization processes are used and reviewed periodically to ensure they are up to date and consistent with source data, use cases, and standards.
    - Unstructured data is abstracted using controlled abstraction forms and in accordance with specific defined procedures.
        - Controlled abstraction forms are developed for abstractors to consistently abstract unstructured data in accordance with written instructions.
    - Data are derived by applying established deterministic rules to multiple data components.
    - Deterministic rules are developed collaboratively by a cross-functional team, and the derived data that are the output of these rules are reviewed periodically.
- **Data quality oversight**: Activities are designed to provide oversight during the extraction, abstraction, and derivation of RWD to ensure that data are generated, documented, and reported according to Redacted processes. An overview of quality processes is described below:
    - Extraction
        - Quality oversight is provided using automated checks designed to monitor the extraction process and generate alerts should the extracted data be determined to be incomplete, inaccurate, or sufficiently out-of-date in comparison to the source data. Automated alerts for NLP-extracted data are designed to monitor the stability (e.g., stability of month-over-month predictions) and performance (e.g., performance of models as compared with expectations).
    - Harmonization
        - Quality checks are performed on processes governing structured data harmonization to ensure consistency in mapping per the established mapping guidelines.
    - Abstraction
        - Manual (i.e., human review) and technology-enabled (i.e., programmatic) data review and oversight of unstructured data is provided by a cross-functional team (e.g., oncology, statistical, clinical data, engineering).
        - Inter-rater agreement for a percentage of abstracted RWD variables (i.e., the same abstraction form for the same patient is processed by two different abstractors independently, and the result of the two different abstraction tasks is compared) is

monitored and an investigation performed when an issue is identified.

- Performance for artificial intelligence–derived variables used for cohort selection are continually monitored by comparing against a fully abstracted reference standard to ensure they are highly sensitive (e.g., greater than or equal to 95% sensitivity).

- Derivation
  - Automated pipeline tests on derived data code changes are conducted to verify acceptable output parameters are met according to specified requirements.

- **Systems oversight**: These processes are built into technical systems and/or workflows to provide programmatic oversight and efficiency. Redacted software is developed in accordance with Good Engineering Practices (GEP; International Society for Pharmaceutical Engineering, 2021) for each phase of the software development lifecycle. An overview of system processes is described below.
  - System changes logs/change control to ensure traceability
    - Each code change has a unique ID (e.g., tag) automatically generated by Redacted source code repository
  - Data provenance and traceability to source documentation
    - Source data elements are archived in Redacted Data Hosting Cloud Provider for a minimum of seven years
    - Transparency in data provenance with audit trails throughout the data lifecycle
    - The state of the codebase during final delivery (i.e., commit reference) is archived
  - Abstraction system ensures only trained staff complete abstraction
  - Software is developed in accordance with GEP, including defined review, testing, and oversight of electronic systems
    - Redacted GEP Guideline provides guidance for each phase of the software development lifecycle, which includes: Analyze, Design, Develop, Test, and Deploy

### A.4 References

Bennett C, Block J, Drinan M, et.al. ISPE Good Practice Guide: Good Engineering Practice, 2nd Ed. International Society for Pharmaceutical Engineering, 2021.

## ICD-9/ICD-10 CODES USED TO IDENTIFY CCI

| CCI Condition | ICD-9 | ICD-10 |
|---|---|---|
| Myocardial infarction | 410, 412 | I21, I22, I252 |
| Congestive heart failure | 39891, 40201, 40211, 40291,40401, 40403, 40411, 40413, 40491, 40493, 428, 4254 - 4259 | I099, I110, I130, I132, I255, I420, I43, I50, P290, I425 - I429 |
| Peripheral vascular disease | 0930, 440, 441, 4471, 5571, 5579, V434, 4431 - 4439 | I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959 |

| | | |
|---|---|---|
| Cerebrovascular disease | 36234, 430 - 438 | G45, G46, H340, I6 |
| Dementia | 290, 2941, 3312 | F051, G30, G311, F00 - F03 |
| Chronic pulmonary disease | 4168, 4169, 5064, 5081, 5088, 490 - 505 | I278, I279, J684, J701, J703, J40 - J47, J60 - J67 |
| Rheumatic disease | 4465, 7148, 725, 7100 – 7104, 7140 - 7142 | M05, M06, M315, M32, M33, M34, M351, M353, M360 |
| Peptic ulcer disease | 531 - 534 | K25 - K28 |
| Mild chronic liver disease | 07022, 07023, 07032, 07033, 07044, 07054, 0706, 0709, 570, 571, 5733, 5734, 5738, 5739, V427 | B18, K709, K717, K73, K74, K760, K768, K769, Z944, K700 - K703, K713 - K715, K762 - K764 |
| Moderate or severe chronic liver disease | 4560 – 4562, 5722 - 5728 | I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767 |
| Diabetes with chronic complications | 2504, 2505, 2506, 2507 | E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E132, E133, E134, E135, E137 |
| Diabetes without chronic complications | 2500, 2501, 2502, 2503, 2508, 2509 | E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E130, E131, E136, E138, E139 |
| Hemiplegia | 3341, 342, 343, 3449, 3440 - 3446 | G041, G114, G801, G802, G81, G82, G839, G830 - G834 |
| Renal disease | 40301, 40311, 40391, 40402, 40403, 40412, 40413, 40492, 40493, 582, 585, 586, 5880, V420, V451, V56, 5830 - 5837 | I120, I131, N18, N19, N250, Z940, Z992, N032 - N037, N052 - N057, Z490 - Z492 |
| HIV/AIDS | 044 | B20, B21, B22, B24 |

LOT RULES - MM

1. THERAPIES ELIGIBLE FOR INCLUSION IN LINES OF THERAPY

1.1. Systemic treatment, as evidenced by an order or administration of an antineoplastic or steroid (IV dexamethasone, oral dexamethasone, and oral prednisone) recorded in the EHR, are included in lines of therapy (LOT) [rule implemented: 12/31/15, updated 9/30/19]

1.1.1. A “drug episode” of systemic therapy is defined as an administration or a non-canceled order for non-abstracted therapies

1.2. Oral therapy information is captured from unstructured data and included in lines of therapy. Treatment with oral therapies is reported in spans, where treatment extends from a start date to a defined end date. Multiple treatment spans are reported for a specific oral therapy when that drug is stopped or held for at least 60 days and then restarted [rule implemented: 12/31/15]

1.3. All dates of bone marrow transplants, including both autologous and allogeneic transplants, are captured from unstructured data and are included in lines of therapy. The date of the transplant is defined as the date on which the transplanted cells are infused [rule implemented: 12/31/15]

1.4. Radiotherapy and surgery are not included in lines of therapy [rule implemented: 12/31/15]

1.5. IV/SC therapy information for selecting agents of interest is captured from unstructured data and included in lines of therapy. Treatment with IV/SC therapy coming from unstructured data is reported in spans, where treatment extends from a start date to a defined end date. Multiple treatment spans are reported for a drug or drugs when that therapy is stopped or held for at least 60 days and then restarted [rule implemented: 11/30/23]

1.6. The following therapy is excluded from lines of therapy: mesna. [rule implemented: 12/31/16, updated 6/30/23]

1.7. Structured IV or SC orders that are contradicted by abstracted IV or SC data will not be considered in lines of therapy [rule implemented 11/30/23]

1.8. CAR-T cellular therapy infusion date is captured from unstructured data and included in lines of therapy [rule implemented: 4/29/22]

1.9. Therapies (including supportive agents, e.g., corticosteroids) given within 30 days post-CAR-T cellular therapy are excluded from lines of therapy [rule implemented: 4/29/22]

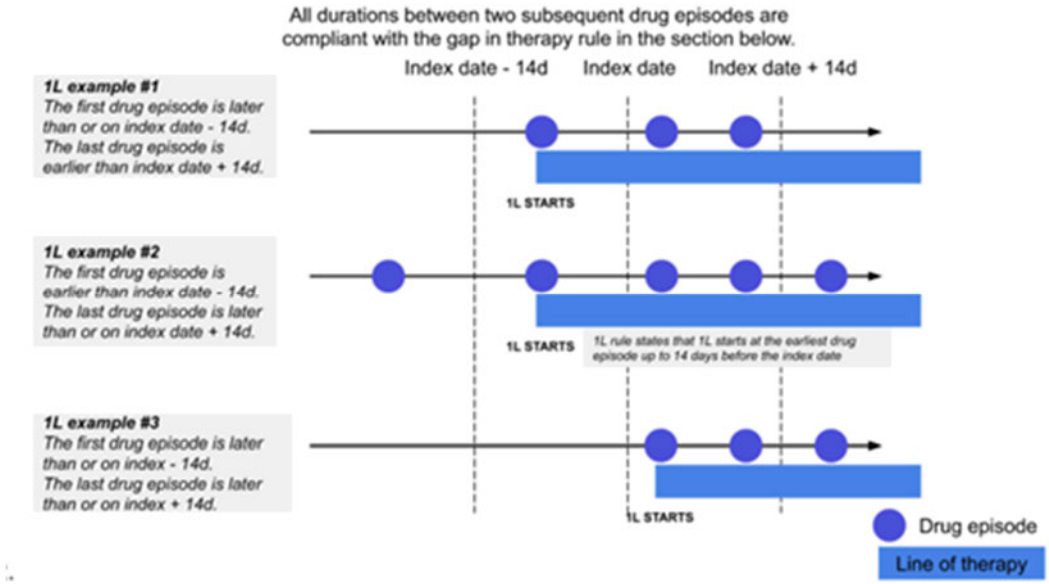
1.10. Structured IV or SC orders will not be considered in lines of therapy [rule implemented 4/30/25]

2. INDEX DATE

2.1. The index date is defined as the patient's date of diagnosis with MM, as identified from unstructured data [rule implemented: 12/31/15]

3. START OF FIRST LOT (1L)

3.1. The start of the 1L is defined as the date of first drug episode of an eligible therapy that is given after or up to 14 days before the index date, and after the start of structured activity (earliest structured visit or therapy). Only an abstracted oral or an abstracted IV or SC therapy can start 1L before the start of structured activity [rule implemented: 12/31/15, updated: 11/30/23]




3.2. Transplants are not eligible to be the start of the 1L. For cases where a transplant appears as the first treatment after the index date and start of structured activity, the transplant is marked as Line Zero (as noted below) [rule implemented: 06/30/17]

3.3. LINE ZERO: To indicate patients for whom, therapy data may be missing, Line Zero is created in patients whose start of MM treatment (as captured through unstructured data) is more than 30 days before the start of structured activity. In these patients, Line Zero extends from the start of MM treatment to the start of structured activity [rule implemented: 12/31/15]

3.3.1. Line Zero does not contain information on specific therapies

3.3.2. Note: For some patients, Line Zero will extend beyond the patient's start of structured activity. Line Zero contains all treatments that occurred before the start of structured treatment

3.3.3. Note: For some patients, Line Zero will be named Transplant if the transplant would otherwise have been the start of their 1L. These patients likely had other therapy prior to their start of structured activity

4. DEFINITION OF A LOT

4.1. The definition of a LOT is generally the first eligible drug episode plus other eligible drugs given within 28 days. The name of the "regimen" for that LOT is the combination of therapies in that line, unless otherwise noted [rule implemented: 12/31/15; amended [12/31/2016]

4.2. The LOT allows for three days of overlap between abstracted agents (oral, IV, or subcutaneous) and any other drug without rolling them up into a single line [rule implemented: 9/30/17; updated 11/30/23]

4.2.1. For example, if abstractors report that a patient stopped lenalidomide on 10/6 and initiated pomalidomide on 10/4, the stop date of lenalidomide

will be backdated to 10/3 and the two agents will be reported as distinct monotherapy lines

4.3. CAR-T cellular therapy infusions always advance a LOT. Any treatments started within 14 days before CAR-T cell infusion as part of a conditioning regimen are ineligible for LOT [rule implemented: 4/29/22]

5. MAINTENANCE

5.1. Bortezomib, lenalidomide, thalidomide, daratumumab, daratumumab/hyaluronidase-fihj (daratumumab and daratumumab/hyaluronidase-fihj are considered equivalent), and ixazomib are eligible to be considered maintenance therapy. Maintenance therapy does not advance the line number and can also apply to Line Zero. It is considered maintenance when one of these drugs is used as monotherapy and meets one of the following criteria: [rule implemented: 12/31/15, updated 9/30/2019, updated 7/31/20; updated 10/31/21; updated 6/30/23]:

5.1.1. Monotherapy duration more than 60 days (allowing for stops/starts of abstracted oral spans without addition of other treatments) follows a combination therapy that lasts more than 30 days (monotherapy start date must be within 180 days of the end of combination) [rule amended 8/30/2022]

5.1.1.1. For patients receiving daratumumab or daratumumab/hyaluronidase-fihj, in order for it to qualify as maintenance, the combination therapy must also include daratumumab or daratumumab/hyaluronidase-fihj [rule added 6/30/2023]

OR

5.2. Monotherapy (with no minimum duration requirement) follows transplant by less than 365 days with no interim antineoplastic treatment [rule amended 8/30/2022]

5.2.1. Pomalidomide, thalidomide, and lenalidomide are eligible to be considered maintenance therapy when given with: [rule implemented 6/30/25]

5.2.1.1. Carfilzomib OR bortezomib OR ixazomib

5.2.1.2. Isatuximab-irfc OR daratumumab OR daratumumab/hyaluronidase-fihj

6. GAP IN THERAPY

N/A

7. CHANGES PERMITTED WITHIN A LOT

7.1. When an abstracted transplant date occurs during a line, the transplant does not advance the LOT. The name “transplant” is assigned to the portion of the line starting on the transplant date and ending at either initiation of post-transplant maintenance or the start of the subsequent line. Any structured treatment or abstracted therapy (oral, IV, or subcutaneous) given between seven days prior to

and 30 days after the transplant date are ineligible for LOT [rule implemented: 12/31/15; rule last updated 11/30/23]

7.2. For the following substitutions, the line will be named according to the drug given for the longest duration within the line:

7.2.1. Substitution of dexamethasone for prednisone and vice versa does not advance the LOT [rule implemented: 12/31/15]

7.2.2. Substitution of rituximab for rituximab/hyaluronidase and vice versa does not advance the LOT [rule implemented: 9/30/19]

7.2.3. Substitution of daratumumab for daratumumab/hyaluronidase and vice versa does not advance the LOT [rule implemented: 07/31/20]

7.2.4. Substitution of the reference product for a biosimilar or vice versa does not advance the LOT (e.g, trastuzumab and trastuzumab-anns) [rule implemented: 8/28/20]

7.3. The addition of an *imid drug within the first 90 days of a regimen that had not previously contained an *imid does not advance the LOT (*imids = lenalidomide, pomalidomide, thalidomide). Note: the drugs in the initial regimen must overlap with this *imid drug for this rule to be applied [rule implemented: 12/31/2016]

7.4. The addition of a proteasome inhibitor within the first 90 days of a regimen that had not previously contained a proteasome inhibitor does not advance the LOT (proteasome inhibitor drugs = bortezomib, carfilzomib, or ixazomib) Note: the drugs in the initial regimen must overlap with this proteasome inhibitor for this rule to be applied [rule implemented: 12/31/2016]

7.5. The addition of lenalidomide in 1L to a line that already contained cyclophosphamide does not advance the LOT and cyclophosphamide is removed from the LOT name. Note: this switch must occur within 60 days of line start for this rule to be applied [rule implemented: 6/30/22]

7.6. Resuming the same regimen after transplant that was previously administered immediately prior to transplant does not advance the line and will be labeled as a consolidation phase. The presence of a Clinical Study Drug will not impact the rule [rule implemented: 3/31/25]

8. CHANGES NOT PERMITTED WITHIN A LOT

N/A

9. LOT END DATE

9.1. For the most recent LOT, the LOT end date is defined as:

9.1.1. [For patients with no recorded date of death] the date of last patient-level confirmed activity (i.e., the last record of patient vitals, medication administrations, reported laboratory tests/results, or abstracted oral episode).

9.1.2. [For patients with a recorded date of death] the earlier date of the date of death and the last patient-level confirmed activity (i.e., the last record of patient vitals, medication administrations, reported laboratory tests/results, or abstracted oral episode) (Note that for patient privacy and de-

identification purposes, date of death is generalized to the last day of the month of death).

9.1.3. When available, the abstracted end date for an abstracted treatment span is used as the LOT end date instead of its corresponding structured order

9.2. For all other lines, the end date is the day before the start date of the next LOT

10. INTERNATIONAL MARKET CONSIDERATIONS (UK, Germany, and Japan)

10.1. Cyclophosphamide administered only once within the year prior to transplant is excluded from Lines of Therapy.

Steroids (dexamethasone, prednisone, prednisolone, methylprednisolone) do not advance a LOT.

# Document Approval Record

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