Study information

Title	Treatment and Clinical Characteristics in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) using Talazoparib and Enzalutamide (tala+enza) Combination Therapy
Protocol number	C3441073
Protocol version identifier	1.0
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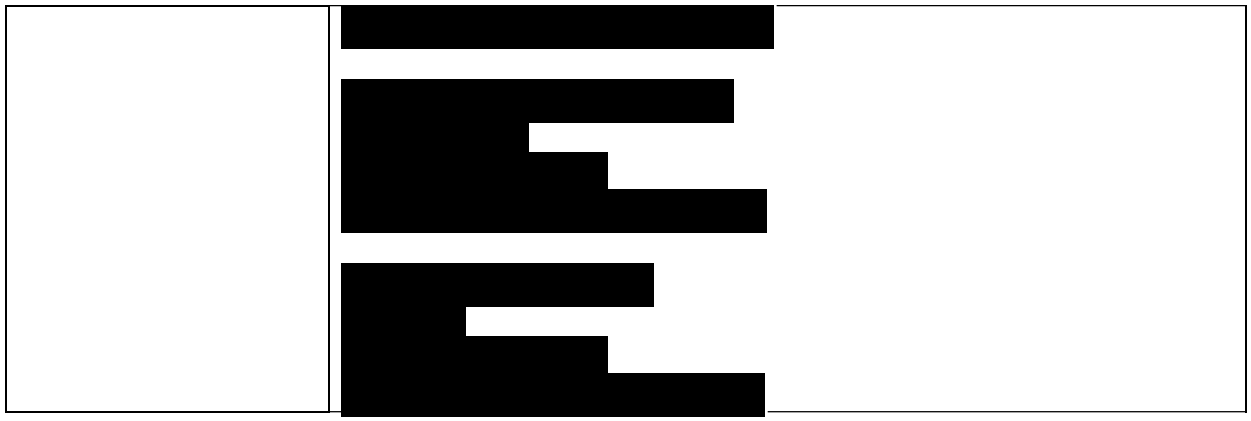
EU Post Authorization Study (PAS) register number	EUPAS1000000580
Active substance	L01XX56, L02BB03
Medicinal product	TALZENNA® (talazoparib) and XTANDI® (enzalutamide)
Research question and objectives	**Research question** What are the demographic, clinical, treatment, and anemia characteristics of patients with mCRPC using tala+enza combination therapy? **Objectives** 1. To determine the number of patients with a mCRPC diagnosis who were treated with tala+enza in combination on or after June 20, 2023 The following objectives will be evaluated among patients identified in Objective 1: 2. To describe demographic and clinical characteristics 3. To describe the prostate cancer-related treatments initiated prior to mCRPC diagnosis 4. To describe the genetic and biomarker testing patterns among patients who have undergone homologous recombination repair testing, including the timing and types of tests performed 5. To describe treatment patterns (eg, line of therapy, dosage, relative dose intensity, dose modification, treatment persistence, time from index to treatment modification, reasons for treatment modification) of tala+enza combination therapy

	6. To describe anemia characteristics (ie, hemoglobin level, severity), anemia management (eg, red blood cell transfusion, iron supplementation, erythropoiesis stimulating agents, treatment modification of talazoparib), and anemia resolution status
Country(ies) of study	United States
Author	[redacted]



1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First-line
2L	Second-line
ADT	Androgen deprivation therapy
AE	Adverse event
AEM	Adverse event monitoring
AESI	Adverse event of special interest
AG	Analysis Group
ALP	Alkaline phosphatase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ARPI	Androgen receptor pathway inhibitor
BMI	Body mass index
CCI	Quan-Charlson Comorbidity Index
CI	Confidence interval
CKD	Chronic kidney disease
CPT	Current Procedural Terminology
CTCAE	Common Terminology Criteria for Adverse Events
DCT	Data collection tool
EC	Ethics Committee
ECOG PS	Eastern Cooperative Oncology Group performance status
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HMA	Heads of Medicines Agencies
HR	Hazard ratio
HRR	Homologous recombination repair
HRRm	Homologous recombination repair mutations
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IQR	Interquartile range
IRB	Institutional Review Board
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LDH	Lactate dehydrogenase

LHRH	Luteinizing hormone-releasing hormone
LOINC	Logical Observation Identifier Names and Codes
LOT	Line of therapy
mCRPC	Metastatic castration-resistant prostate cancer
mCSPC	Metastatic castration-sensitive prostate cancer
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
MGB	Mass General Brigham
NIS	Non-interventional study
NOS	Not otherwise specified
PARP	Poly(ADP-ribose) polymerase
PASS	Post-Authorization Safety Study
PC	Prostate cancer
PSA	Prostate-specific antigen
RPDR	Research Patient Data Registry
rPFS	Radiographic progression-free survival
RWD	Real-world data
SD	Standard deviation
SSDI	Social Security Death Index
tala+enza	Talazoparib and enzalutamide
TNM	Tumor, node, and metastasis
US	United States
VUS	Variant of uncertain significance
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]

4. ABSTRACT

Title

Treatment and Clinical Characteristics in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) using Talazoparib and Enzalutamide (tala+enza) Combination Therapy

Version: 1.0

Date of protocol: 23 July 2025

Name and affiliation of main author

[redacted]

Rationale and background

Prostate cancer (PC) is the most common cancer in men in the United States (US), representing 29% of newly diagnosed cancers in men and responsible for an estimated 35,250 deaths in 2024. Metastatic PC can be further described by patient response to androgen deprivation therapy (ADT); patients with metastatic castration-sensitive PC (mCSPC) are treatment naïve or still responsive to ADT, while patients with metastatic castration-resistant PC (mCRPC) no longer respond to ADT. Homologous recombination repair mutations (HRRm) can increase sensitivity of tumors to treatment with poly(ADP-ribose) polymerase (PARP) inhibitors, including talazoparib.

In June 2023, the US Food and Drug Administration (FDA) approved the use of talazoparib and enzalutamide (tala+enza) in patients with HRRm+ mCRPC. Findings from the phase 3 TALAPRO-2 trial, among patients with mCRPC harboring HRRm, showed a significant improvement in the risk of disease progression or death (ie, radiographic progression-free survival), and overall survival for those treated with tala+enza compared to those treated with placebo with enzalutamide.

This non-interventional study (NIS) will be conducted using secondary data collection via structured codified data with human review of unstructured data (clinical notes) to describe the patient demographic, clinical (including HRRm status), treatment (including dose management, treatment persistence, and reasons for treatment discontinuation), and AEs characteristics in patients with mCRPC treated under real-world routine clinical care with tala+enza.

This NIS is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

Research question and objectives

Research Question
What are the demographic, clinical, treatment, and anemia characteristics of patients with mCRPC using tala+enza combination therapy?

Objectives

1. To determine the number of patients with a mCRPC diagnosis who were treated with tala+enza in combination on or after June 20, 2023

The following objectives will be evaluated among patients identified in Objective 1:

2. To describe demographic and clinical characteristics

3. To describe the prostate cancer-related treatments initiated prior to mCRPC diagnosis

4. To describe the genetic and biomarker testing patterns among patients who have undergone homologous recombination repair testing, including the timing and types of tests performed

5. To describe treatment patterns (eg, line of therapy, dosage, relative dose intensity, dose modification, treatment persistence, time from index to treatment modification, reasons for treatment modification) of tala+enza combination therapy

6. To describe anemia characteristics (ie, hemoglobin level, severity), anemia management (eg, red blood cell transfusion, iron supplementation, erythropoiesis stimulating agents, treatment modification of talazoparib), and anemia resolution status

Study design

This voluntary PASS study is a retrospective NIS that will be conducted using secondary data collection via structured codified data with human review of unstructured data (clinical notes) from the Mass General Brigham (MGB) Research Patient Data Registry (RPDR). This NIS does not have a comparison group.

The study population will include patients treated under real-world routine care with tala+enza combination therapy on or after June 20, 2023. The date of first observed prescription of tala+enza combination treatment will be defined as the index date. The pre-index period will be defined as time from the first clinical activity to the index date. The baseline period will be defined as time from the date of mCRPC diagnosis to the index date. The observation period, or post-index period, will be defined as the time from the index date to the end of follow-up, which is the earliest of date of death (identified from MGB facility/hospital records or clinical notes) or the end of data availability.

Population

Adult, male PC patients with prescription(s) for tala+enza combination treatment on or after June 20, 2023 will be identified. The source population comprises diverse real-world patients who have received care within the MGB healthcare system, as captured in the RPDR database. The MGB network primarily serves patients in Massachusetts and broader New England area.

<u>Inclusion criteria</u>
Patients must meet all of the following criteria to be eligible for inclusion in the study:

1. Male sex

2. Initiation of tala+enza combination treatment for mCRPC* on or after June 20, 2023
    - The date of first prescription of tala+enza combination will be defined as the index date
3. Aged ≥18 years as of index date
4. Diagnosis of PC (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]: C61) on or prior to index date
5. Diagnosis of mCRPC*, defined by diagnosis codes for both hormone resistance and metastatic disease, on or prior to index date

**Tala+enza combination therapy for mCRPC treatment will be confirmed in Objective 1 of the study.*

Exclusion criteria

There are no exclusion criteria for this study.

Variables

Among patients with prescription(s) for tala+enza combination treatment (ie, exposure), the demographic, clinical, and prostate cancer-related treatment characteristics (eg, age at index, race, ethnicity, index year, body mass index, comorbidities, PC characteristics at time of initial diagnosis, PC characteristics at the time of first evidence of mCRPC, HRRm, ECOG PS, laboratory assessments, cancer-related treatment history) will be assessed during the baseline or pre-index period, unless otherwise specified. Treatment patterns and anemia characteristics (ie, outcomes of interest) will be evaluated during the observation period.

Data sources

Longitudinal data from the MGB RPDR will be used to address the study objectives. The MGB RPDR is drawn from the EPIC EHR system of teaching hospitals affiliated with Harvard Medical School. This study will be conducted using mainly structured secondary data from the MGB RPDR database. To further supplement the structured data, key word searches and manual review of the unstructured physician clinical notes will be conducted to ascertain specific variables (eg, HRR mutation status, line of therapy) that may be unavailable in the structured data.

Study size

As all study objectives are descriptive in nature and do not involve hypothesis testing, no formal power calculation will be performed. Based on a preliminary assessment of patients with PC treated with tala+enza in MGB RPDR, between January 2013 and February 2024, over 107,000 patients with PC were identified, among which approximately 3,000 patients had mCRPC. Among patients with PC, 80 were treated with talazoparib, as identified based on keyword search in the unstructured physician notes.

Data analysis

Descriptive statistics will be presented using frequencies and proportions for categorical variables and means, standard deviations (SDs), medians, and interquartile ranges (IQRs) for continuous variables.

Milestones

Milestone	Planned Date
Registration in the HMA-EMA Catalogues of RWD studies	31 July 2025
Start of data collection	1 August 2025
End of data collection	31 October 2025
Final study report	31 December 2025

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Registration in the HMA-EMA Catalogues of RWD studies	31 July 2025
Start of data collection	1 August 2025
End of data collection	31 October 2025
Final study report	31 December 2025

7. RATIONALE AND BACKGROUND

Prostate cancer (PC) is the most common cancer in men in the United States (US), representing 29% of newly diagnosed cancers in men and responsible for an estimated 35,250 deaths in 2024.[1] Prognosis and survival differ significantly by disease state. While the 5-year survival rate approaches 100% for non-metastatic PC, approximately one third of these men will progress to metastatic disease, where the 5-year survival is only around 30% as of 2024.[2] Metastatic PC can be further described by patient response to androgen deprivation therapy (ADT); patients with metastatic castration-sensitive PC (mCSPC) are treatment naïve or still responsive to ADT, while patients with metastatic castration-resistant PC (mCRPC) no longer respond to ADT.[3] When treated appropriately with ADT, patients with mCSPC can achieve a median overall survival of 34 to 81 months.[3] However, when patients no longer respond to ADT, or have experienced relapse after ADT treatment, they then progress to mCRPC, where prognosis is less favorable in comparison, with a median survival ranging 9 to 32 months.[4-7]

Taxane chemotherapy (eg, docetaxel and cabazitaxel) used to be the standard first-line (1L) therapy for patients with mCRPC, until androgen receptor pathway inhibitors (ARPIs), such as abiraterone and enzalutamide, represented a breakthrough in the treatment of mCRPC, with significant quality of life and survival benefits.[4] Despite benefits from these new therapies, alterations in the homologous recombination repair (HRR) genes, found in approximately 25% of patients with mCRPC, are associated with poor clinical outcomes and earlier resistance to systemic therapies.[8] HRR mutations (HRRm) can increase sensitivity of tumors to treatment with poly(ADP-ribose) polymerase (PARP) inhibitors, including talazoparib.[9]

In June 2023, the US Food and Drug Administration (FDA) approved the use of talazoparib and enzalutamide (tala+enza) in patients with HRRm+ mCRPC. Final results from the phase 3 TALAPRO-2 trial, among patients with mCRPC harboring HRRm, showed a significant improvement in the risk of disease progression or death (hazard ratio [HR] for radiographic progression-free survival [rPFS]: 0.47; 95% confidence interval [CI]: 0.36-0.61, p<0.0001) and overall survival (HR: 0.62; 95% CI: 0.48-0.81, p=0.0005) for those treated with tala+enza compared to those treated with placebo with enzalutamide.[10-12] The TALAPRO-2 trial also reported results on the safety of tala+enza. The most common adverse events (AEs; all grades in ≥10% of patients) among those treated with tala+enza included anemia (43%) and neutropenia (20%). According to the label of talazoparib, monthly monitoring for complete blood counts and dose modification is recommended for patients with hemoglobin level <8g/dL, platelet count less than 50,000/µL, or neutrophil count <1,000/µL.[13]

Considering the relatively recent approval of the combination treatment, it will be valuable to gain insights into the demographic, clinical, and treatment characteristics of patients with mCRPC treated with the tala+enza combination treatment in the real-world setting. Additionally, this study may help generate real-world insights into AEs including anemia among this population and provide a better understanding of how dose reductions or treatment discontinuations related to talazoparib can be implemented to manage and resolve AEs in clinical practice.

This non-interventional study (NIS) will be conducted using secondary data collection via structured codified data with human review of unstructured data (clinical notes) to describe the patient demographic, clinical (including HRRm status), treatment (including dose management, treatment persistence, and reasons for treatment discontinuation), and AEs characteristics in patients with mCRPC treated under real-world routine clinical care with tala+enza.

This NIS is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

What are the demographic, clinical, treatment, and anemia characteristics of patients with mCRPC using tala+enza combination therapy?

8.2. Objectives

1. To determine the number of patients with a mCRPC diagnosis who were treated with tala+enza in combination on or after June 20, 2023

The following objectives will be evaluated among patients identified in Objective 1:

2. To describe demographic and clinical characteristics

3. To describe the prostate cancer-related treatments initiated prior to mCRPC diagnosis

4. To describe the genetic and biomarker testing patterns among patients who have undergone HRR testing, including the timing and types of tests performed

5. To describe treatment patterns (eg, line of therapy [LOT], dosage, relative dose intensity, dose modification, treatment persistence, time from index to treatment modification, reasons for treatment modification) of tala+enza combination therapy

6. To describe anemia characteristics (ie, hemoglobin level, severity), anemia management (eg, red blood cell transfusion, iron supplementation, erythropoiesis stimulating agents, treatment modification of talazoparib), and anemia resolution status

9. RESEARCH METHODS

9.1. Study Design

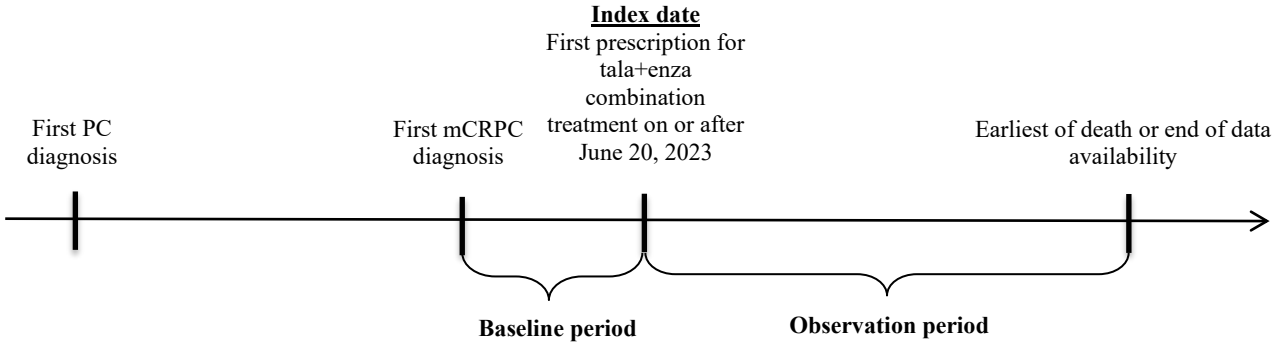
This voluntary PASS study is a retrospective NIS that will be conducted using secondary data collection via structured codified data with human review of unstructured data (clinical notes) from the Mass General Brigham (MGB) Research Patient Data Registry (RPDR). A retrospective design allows for efficient assessment of real-world patient characteristics and treatment patterns, leveraging existing data sources.[14] As all study objectives are descriptive in nature, this NIS does not have a comparison group.

The study population will include patients treated under real-world routine care with tala+enza combination therapy on or after June 20, 2023. The date of first observed prescription of tala+enza combination treatment will be defined as the index date. The pre-index period will be defined as time from the first clinical activity to the index date. The baseline period will be defined as time from the date of mCRPC diagnosis to the index date. The observation period, or post-index period, will be defined as the time from the index date to the end of follow-up, which is the earliest of date of death (identified from MGB facility/hospital records or clinical notes) or the end of data

availability. Treatment patterns and anemia characteristics (ie, primary outcomes of interest) will be evaluated during the observation period.

The study design scheme is depicted in **Figure 1**.

Figure 1. Study design scheme



9.2. Setting and Population

Adult, male PC patients with prescription(s) for tala+enza combination treatment on or after June 20, 2023 will be identified and followed until the end of follow-up, which is the earliest of date of death or the end of data availability. The source population comprises diverse real-world patients who have received care within the MGB healthcare system, as captured in the RPDR database (as further described in **Section 9.4)**. The MGB network primarily serves patients in Massachusetts and broader New England area. Although the population is largely drawn from academic medical settings, which may limit generalizability to community-based care across the US, the data source was selected for its comprehensive clinical data and ascertainment of a substantial number of patients treated with talazoparib following its recent approval.

9.2.1. Inclusion Criteria

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

1. Male sex
2. Initiation of tala+enza combination treatment for mCRPC* on or after June 20, 2023
    - The date of first prescription of tala+enza combination will be defined as the index date
3. Aged ≥18 years as of index date
4. Diagnosis of PC (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]: C61) on or prior to index date
5. Diagnosis of mCRPC*, defined by diagnosis codes for both hormone resistance and metastatic disease (see **Annex 3 Table 1**), on or prior to index date

**Tala+enza combination therapy for mCRPC treatment will be confirmed in Objective 1 of the study.*

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

9.3.1. Baseline Characteristics

Demographic, clinical, and cancer-related treatment characteristics will be assessed during the baseline or pre-index period, unless otherwise specified. If multiple measurements exist during the baseline or pre-index period, the measurement closest to the index date will be used, when appropriate.

Table 1. Baseline demographic, clinical, and cancer-related treatment characteristics

Variable	Role	Data Source (data table in MGB RPDR)	Operational Definition
Age at index date (continuous)	Baseline characteristics	Structured data (Patient dimension)	Patient age (continuous) in years
Age at index date (categorical)	Baseline characteristics	Structured data (Patient dimension)	Patient age (categorical): • 18-49 years • 50-64 years • 65-74 years • ⩾75 years
Race	Baseline characteristics	Structured data (Patient dimension)	Asian, Black or African American, White, Other/multiracial, Unknown
Ethnicity	Baseline characteristics	Structured data (Patient dimension)	Hispanic/Latino, Non-Hispanic/Latino, Unknown
Index year	Baseline characteristics	Structured data (Medications; Expanded medications) and/or unstructured data	Calendar year of index date
Body mass index (BMI; continuous)	Clinical characteristics	Structured data (Vitals)	BMI (continuous) in kg/m^2 as available, or as calculated based on height and weight
BMI (categorical)	Clinical characteristics	Structured data (Vitals)	BMI categories: • Underweight (<18.5 kg/m^2) • Normal weight (18.5 to <25 kg/m^2) • Overweight (25 to <30 kg/m^2) • Obese (30 to <40 kg/m^2) • Severe obesity (≥40 kg/m^2) • Unknown
Quan-Charlson Comorbidity Index (CCI) (assessed during the pre-index period)	Clinical characteristics	Structured data (Diagnosis)	See list of associated diagnosis codes in **Annex 3 Table 1**.
Prior medical history of anemia	Clinical characteristics	Structured data (Diagnosis; Labs)	Prior medical history of anemia based on diagnosis codes or hemoglobin measurement (<13.5 g/dL; yes, no)

Variable	Role	Data Source (data table in MGB RPDR)	Operational Definition
			If yes, anemia status, measured using hemoglobin: Grade 1 (10.0 – <13.5 g/dL), Grade 2 (8.0 – <10.0 g/dL), Grade 3 (6.5 – <8.0 g/dL), or Grade 4 (<6.5 g/dL)[a] See list of associated diagnosis codes in **Annex 3 Table 1**.
Prior medical history of chronic kidney disease (CKD)	Clinical characteristics	Structured data (Diagnosis; Procedures; Labs)	Prior medical history of CKD (yes, no) If yes, CKD stage, measured using estimated glomerular filtration rate (eGFR): Stage 1 (⩾ 90 mL/min/1.73m²), Stage 2 (60 – <90 mL/min/1.73m²), Stage 3a (45 – <60 mL/min/1.73m²), Stage 3b (30 – <45 mL/min/1.73m²), Stage 4 (15 – <30 mL/min/1.73m²), Stage 5 (<15 mL/min/1.73m²)[b] See list of associated diagnosis and procedure codes in **Annex 3 Table 1** and **Annex 3 Table 2**.
Time from initial PC diagnosis to index	PC characteristics at time of initial diagnosis	Structured (Diagnosis) and/or unstructured data	The time between the date of the patient's first recorded initial PC diagnosis and the index date
Histology	PC characteristics at time of initial diagnosis	Unstructured data	Adenocarcinoma, Non-adenocarcinoma
Tumor, node, and metastasis (TNM stage)	PC characteristics at time of initial diagnosis	Unstructured data	Stage I, Stage II, Stage III, Stage IV
Gleason score	PC characteristics at time of initial diagnosis	Unstructured data	Primary and secondary grade will be captured as available: • Low-grade (score ⩽ 6) • Intermediate-grade (score 7) • High-grade (score 8-10)
Gleason grade group	PC characteristics at time of initial diagnosis	Unstructured data	1, 2, 3, 4, 5
Tumor size	PC characteristics at time of initial diagnosis	Unstructured data	Tumor size reported in mm
Time from first mCRPC diagnosis to index	PC characteristics at time of first evidence of mCRPC	Structured (Diagnosis) and/or unstructured data	The time between the date of the patient's first recorded mCRPC diagnosis and the index date

Variable	Role	Data Source (data table in MGB RPDR)	Operational Definition
Bone metastases	PC characteristics at time of first evidence of mCRPC	Structured (Diagnosis) and/or unstructured data	Presence of bone metastases (yes, no) If yes, number of bone metastases (1, 2, 3, 4, ⩾5)
Metastases to other sites	PC characteristics at time of first evidence of mCRPC	Structured (Diagnosis) and/or unstructured data	Presence of metastases to other sites (yes, no) If yes, list sites of metastases, as available.
Timing of HRR test relative to index	HRR characteristics	Unstructured data	Timing of HRR test relative to index (before, after, not applicable) • If before, time from first available HRR test to index • If after, time from index to first available HRR test
Gene alteration status	HRR characteristics	Unstructured data	Deficient, Non-deficient, Variant of uncertain significance (VUS)/not otherwise specified (NOS), Unknown
Mutation status	HRR characteristics	Unstructured data	Eg, germline, somatic, both, neither
Source of sample	HRR characteristics	Unstructured data	Eg, blood, tissue, circulating DNA
Presence of gene mutation	HRR characteristics	Unstructured data	Eg, *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*; pending data availability
Eastern Cooperative Oncology Group performance status (ECOG PS)	Clinical characteristics	Unstructured data	0, 1, 2, 3, 4
Laboratory assessments (assessed during baseline and observation periods, separately)	Clinical characteristics	Structured data (Labs)	• Absolute neutrophil count (ANC), cells/µL • Alkaline phosphatase (ALP), IU/L • Estimated glomerular filtration rate, mL/min/1.73m² • Hemoglobin, g/dL • Lactate dehydrogenase (LDH), IU/L • Mean Corpuscular Volume (MCV), fL • Prostate-specific antigen (PSA), ng/mL • Testosterone, ng/dL See list of associated Logical Observation Identifier Names and Codes (LOINC) codes in **Annex 3 Table 4**.
Cancer-related treatment history (assessed prior to the baseline period, i.e. the period between first PC diagnosis and the first evidence of mCRPC)	Clinical characteristics	Structured (Medications; Procedures) and/or unstructured data	Type and duration of treatments, including but not limited to: • ADT (eg, orchiectomy [surgical castration], luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists)

Variable	Role	Data Source (data table in MGB RPDR)	Operational Definition
			• First-generation anti-androgens (eg, bicalutamide, flutamide, nilutamide) • Second-generation ARPIs (eg, enzalutamide, apalutamide, darolutamide) • Androgen synthesis inhibitors (eg, abiraterone) • Radiation therapy • Chemotherapy (docetaxel, cabazitaxel) See **Annex 3 Table 3** for full list of treatments. Associated procedure codes are listed in **Annex 3 Table 2**.

[a] Anemia status is categorized based on cut-offs identified by Common Terminology Criteria for Adverse Events (CTCAE).

[b] CKD stage is categorized based on cut-offs identified by the American Kidney Fund's Medical Advisory Committee.

9.3.2. Treatment Patterns and Adverse Events

The following measures will be evaluated during the observation period to inform treatment patterns and describe anemia characteristics.

Table 2. Treatment and anemia characteristics, management and outcomes

Variable	Role	Data Source	Operational Definition

Tala+enza treatment characteristics	Outcome	Structured (Medications; Expanded medications) and/or unstructured data	• LOT
			• Dosage (eg, 1L, 2L)
			  ○ Initial talazoparib treatment dose
			  ○ Subsequent talazoparib dose changes (discontinuation, interruption, reduction, increase)
			  ○ Initial enzalutamide treatment dose
			  ○ Subsequent enzalutamide dose changes (discontinuation, interruption, reduction, increase)
			• Duration of treatment
			• Treatment modification (ie, dose reduction/increase, treatment interruption, treatment discontinuation)
			  ○ Time from index to treatment modification
			  ○ Reason(s) for treatment modification (eg, due to toxicity including MDS and AML, progression, or death)
			• Concurrent treatment (if overlapping with tala+enza)

Variable	Role	Data Source	Operational Definition
			• Subsequent treatments (after discontinuing tala+enza)
Hemoglobin	Anemia characteristics	Structured data (Labs)	Hemoglobin reported in g/dL See list of associated LOINC codes in **Annex 3 Table 4**.
Anemia severity	Anemia characteristics	Structured data (Labs)	Severity[a] o Grade 1: 10.0 – <13.5 g/dL o Grade 2: 8.0 – <10.0 g/dL o Grade 3: 6.5 – <8.0 g/dL o Grade 4: < 6.5 g/dL
Time from index date to onset of anemia	Anemia characteristics	Structured data (Diagnosis; Labs)	The time from the index date to the first recorded instance of anemia, identified through diagnosis codes or hemoglobin lab values.
Time from index to onset of worse-grade anemia compared to baseline	Anemia characteristics	Structured data (Labs)	The time from the index date to the first occurrence of a hemoglobin value indicating a higher grade of anemia than observed at baseline.
Resolution status	Anemia characteristics	Structured data (Labs)	• Full resolution (ie, no anemia; if anemic at baseline) • Return to baseline (if anemic at baseline) • Return to lower than Grade 3 (if Grade 3 or higher at baseline)
Duration of anemia	Anemia characteristics	Structured data (Diagnosis; Labs)	Days from the onset of anemia to the resolution of anemia
Management of anemia	Anemia characteristics	Structured (Medications; Procedures) and/or unstructured data	Types of management of anemia, including but not limited to: • Treatment modification of talazoparib • Red blood cell transfusions • Iron supplementation • Erythropoiesis stimulating agents For a full list of treatment agents and associated procedure codes, see **Annex 3 Table 5**.
AEs with explicit causal attribution to ANY Pfizer product during the study period	AE	Structured (Diagnosis) and unstructured data	Date and verbatim text record of AE with explicit causal attribution to ANY Pfizer product during the study period that appeared in the medical chart/record/reviewed information.[b]

[a] Severity of anemia is categorized based on cut-offs identified by Common Terminology Criteria for Adverse Events (CTCAE).[15]

[b] To comply with CT24-WI-GL02-RF02B V6 Safety Reporting Language Secondary Data Collection Study Includes Protocol Required Human Review Of Unstructured Data.

Contingent on sample size and data availability, additional adverse events of special interest (AESI) and other events of special interest may be assessed. AESI include venous thromboembolism (embolic and thrombotic events [venous]), second primary malignancies (other than acute myeloid

leukemia [AML] or myelodysplastic syndromes [MDS]), pneumonitis, AML and MDS. Other additional events of special interest include neutropenia, thrombocytopenia, leukopenia, and lymphopenia.

9.4. Data Source

Longitudinal data from the MGB RPDR will be used to address the study objectives. The MGB RPDR is drawn from the EPIC EHR system of teaching hospitals affiliated with Harvard Medical School. The MGB RPDR aggregates de-identified hospital inpatient and outpatient clinical data from electronic health records (EHR) (2000-present; EPIC post-2015, legacy EHR systems pre-2015) from 8 EPIC hospitals affiliated with the Harvard Medical School in Massachusetts (Massachusetts General Hospital, Brigham and Women's Hospital, Brigham and Women's Faulkner Hospital, Massachusetts Eye and Ear Hospital, McLean Hospital, Newton-Wellesley Hospital, North Shore Medical Center, Spaulding Rehabilitation Hospital). Dana Farber Cancer Institute also contributes EHR data to the RPDR database.

At the core of MGB HealthCare's research infrastructure lies a suite of extensive data resources, comprising the MGB HealthCare Computer Infrastructure, Research Electronic Data Capture system, Center for Clinical Data Science, and RPDR. These resources collectively empower researchers, providing them with the necessary tools to conduct groundbreaking studies and enhancing the institution's capacity for scientific exploration and innovation. The MGB database gathers data from hospital systems and stores it in a single clinical data registry, or data warehouse, to allow for clinical research and to ensure the security of patient information. The database stores clinical information for more than 7 million patients and over 3 billion records. There were around 2.0 million active patients in 2021, and around 3.6 million "loyalty cohort" patients (ie, those with a MGB primary care provider). The average length of follow-up in the database is around 7 years.

Data elements include demographics, providers, visits, diagnoses, medications, procedures, laboratories, microbiology, and reports (eg, discharge, operative, and radiology). In addition to codified data, clinical variables can be additionally extracted from unstructured data (ie, health care provider notes, radiology reports, pathology reports, discharge summaries, and operative reports). Data are updated monthly. Mortality data are available for (1) patients whose death information had been linked to SSDI ≥3 years before the data cutoff (ie, mortality information sourced from SSDI for the most recent 3 years of data), for (2) patients whose death occurred in an MGB facility/hospital (ie, in-facility death), and for (3) patients whose death was reported by next of kin.

This study will be conducted using mainly structured secondary data from the MGB RPDR database. To further supplement the structured data, key word searches and manual review of the unstructured physician clinical notes will be conducted to ascertain specific variables (eg, HRR mutation status, LOT) that may be unavailable in the structured data.

9.5. Study Size

As all study objectives are descriptive in nature and do not involve hypothesis testing, no formal power calculation will be performed.

Table 3 describes a preliminary assessment of patients with PC treated with tala+enza in MGB RPDR. Between January 2013 and February 2024, over 107,000 patients with PC were identified,

among which approximately 3,000 patients had mCRPC. Among patients with PC, 80 were treated with talazoparib, as identified based on keyword search in the unstructured physician notes. As patients with PC are usually administered talazoparib along with enzalutamide, patients treated with talazoparib serves as a proxy for the number of patients receiving the combination treatment.

Table 3. Preliminary feasibility assessment in MGB RPDR

Criteria (01/01/2013- 02/29/2024)	Patients, n
1. Patients with mCRPC	
1a. Patients with ≥1 claim with a PC diagnosis (ICD-10-CM code: C61)	107,210
1b. Among (1a), patients with diagnosis for mCRPC: • ≥1 claim with a diagnosis for hormone resistance (ICD-10-CM code: Z19.2) AND • ≥1 claim with a diagnosis for metastatic disease (ICD-10-CM codes: C77.xx-C80.0, C7B) **OR** Any of the following terms in clinical notes: mcrpc, castration resistant, castration-resistant, castration resistance, castration-resistance	3,094
2. Among (1a), unstructured notes were used to identify patients who received talazoparib (Talzenna®).	80
3. Among (2), patients who received HRR testing (Current Procedural Terminology [CPT] codes: 81445, 81479, 81229, 81405, 81235, 81479 or any of the follow terms in clinical notes: HRR)	23

9.6. Data Management

All data used for this study will be stored in a database and only accessible through remote access to MGB computers, specifically through the Data Enclave. Analysis Group (AG) staff will serve as MGB researchers with direct access to MGB's data servers to conduct analyses.

9.6.1. Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A DCT is required and should be completed for each included patient. The completed original DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. MGB shall ensure that the DCTs are securely stored within the MGB system in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

MGB has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCTs must be signed by MGB or by an authorized staff member to attest that the data contained on the DCTs are true. Any corrections to entries made in the DCTs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the DCTs must match those charts.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, MGB agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, eg, DCTs and hospital records), copies of all DCTs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by MGB according to local regulations or as specified in the research agreement, whichever is longer. MGB must ensure that the records continue to be stored securely for so long as they are retained.

If MGB becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless MGB and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

MGB must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

Descriptive statistics will be presented using frequencies and proportions for categorical variables and means, standard deviations (SDs), medians, and interquartile ranges (IQRs) for continuous variables. Specific statistical methods to address each objective are described below. Data analyses will be conducted using SAS Enterprise Guide Version 7.1 or its latest version (SAS Institute, Inc., Cary, NC).

9.7.1. Objective 1: To determine the number of patients with mCRPC treated with tala+enza on or after June 20, 2023

Sample selection will be performed to identify adult, male patients with mCRPC, treated with tala+enza treatment in MGB RPDR on or after June 20, 2023. To do so, first, patients with PC will be identified from structured data. Then, among PC patients identified, those who have initiated talazoparib would be identified from structured data on medication and prescription. Lastly, a manual review of clinical notes for up to 100 charts will be conducted to confirm that all patients meet the inclusion criteria.

9.7.2. Objective 2: To describe demographic and clinical characteristics

Baseline demographic and clinical characteristics outlined in **Section 9.3.1** will be summarized for the study sample identified in **Section 9.7.1** using descriptive statistics, using means, SD, medians, and IQR for continuous variables, and frequencies and proportions for categorical variables.

9.7.3. Objective 3: To describe the prostate cancer-related treatments

Prostate cancer-related treatments initiated prior to mCRPC diagnosis, outlined in **Section 9.3.1**, will be summarized by treatment type and LOT, if available, for the study sample identified in **Section 9.7.1** using frequencies and proportion.

9.7.4. Objective 4: To describe the genetic and biomarker testing patterns among patients who have undergone HRR testing

Genetic and biomarker testing patterns will be summarized among those who have undergone HRR testing, identified in **Section 9.7.1**. The timing of HRR testing relative to index will be described. Gene alteration status, mutation status, and source of sample will be summarized using frequencies and proportions (as available).

9.7.5. Objective 5: To describe treatment patterns of tala+enza combination therapy

Treatment patterns will be summarized during the observation period for the study sample identified in **Section 9.7.1**. Treatment-related characteristics, including dose, relative dose intensity, and dose modifications, and treatment persistence, will be described using means, SD, medians, and IQR for continuous variables, and frequencies and proportions for categorical variables. Contingent on data availability, dose patterns (eg, no change, dose interruption followed by resumption at same dose, dose interruption followed by resolution at lower dose, permanent dose interruption, others) may also be described. Time from index to treatment modification will be assessed using Kaplan-Meier (KM) analysis. Reasons for treatment modification will be summarized using frequencies and proportions.

9.7.6. Objective 6: To describe anemia characteristics and how anemia is managed including treatment modification of talazoparib

For the study sample identified in **Section 9.7.1**, the rate of hemoglobin assessments during the observation period (ie, number of assessment divided by person-time to account for variable follow-up) will be reported. Additionally, hemoglobin levels at baseline and over the observation period (eg, 28 days after the last talazoparib dose, or before the start of next therapy, whichever occurs first) will be summarized using means, SDs, medians, and IQRs. Similarly, anemia status, severity and resolution of anemia will be summarized at baseline and over the observation period using frequencies and proportions.

Among patients who experienced anemia, the proportion of patients who experienced dose modifications of talazoparib will be summarized using frequencies and proportions. Time from index date to the onset of anemia, stratified by severity, will be described overall and by those who had talazoparib dose modifications of talazoparib using KM analysis. Similarly, duration of anemia, defined as the time from onset of anemia to the resolution of anemia (eg, full resolution, return to baseline, return to lower than Grade 3), will be described overall and stratified by severity, using KM analysis. Patients would be censored at 28 days after the last tala dose, the start of next therapy, death, or the end of data availability, whichever occurs first.

Additional AESI and other events of special interest may be assessed, contingent on sample size and pending data availability. AESI include venous thromboembolism (embolic and thrombotic events [venous]), second primary malignancies (other than AML or MDS), pneumonitis, AML and MDS. Other additional events of special interest include neutropenia, thrombocytopenia, leukopenia, and lymphopenia.

9.8. Quality Control

Best practice guidelines will be followed to ensure project quality, including structured organization of project materials (eg, data extracts, statistical software programs, output tables) and standard internal audit processes. The audit process confirms both the validity of the analytical approach and ensures accuracy of all programs and results. Outlined below are the key components of the quality control process.

Documentation and diagnostics applied to computer code development: The primary programmer at AG will be responsible for creating and documenting all project specific code, including comments as to why changes are made over the course of the project. In addition to evaluating diagnostic output independently, the programmer will evaluate this output with the entire project team before results tables are generated.

Independent code review: A secondary programmer will be assigned to the project for the purpose of performing code review. The code review programmer will review all programming line by line to confirm code is written with correct syntax and generates results as specified by the analysis plan. Issues identified by the code reviewer will be documented and resolved.

Validation of study results: AG will validate the results table to confirm that results are consistent across analysis tables and that the results make sense from a real-world perspective. Specifically, AG will closely review and audit all results tables for accuracy. Moreover, AG will check to make sure that all results are aligned with expectations and findings in the literature.

Peer review of final deliverables: In addition to AG reviewing all final reports before delivery, an internal, peer reviewer will also be assigned to evaluate final products. This peer reviewer will examine the final results and reports to ensure concordance among all final documents as well as to evaluate content for consistency.

9.9. Limitations of the Research Methods

Several limitations should be considered when interpreting results from this real-world study:

- This study relies on RWD from EHR, which may be subject to missing, incomplete, or inaccurately recorded information, particularly for variables not consistently captured in structured data. Moreover, the frequency of clinical assessments may vary across patients, introducing potential surveillance bias; patients who have more clinical encounters may have a higher likelihood of having outcomes or variables of interest recorded. This consideration may be potentially minimized by supplementing structured data with manual review of unstructured clinical notes to capture additional context and data elements.

- This analysis relies on diagnosis and procedure codes associated with medical records to determine patients with PC for sample selection and key study variables, including anemia characteristics. These codes are subject to misspecification and may lead to the mischaracterization of patients with PC. However, additionally implementing manual review of clinical notes to determine mCRPC stage may minimize these concerns.

- Treatment characteristics are based on medication prescription data, which indicates the date on which a drug was prescribed to a patient, but do not inform drug dispensing, medication fill status, or medication adherence and compliance. This may lead to the misclassification of treatment patterns.

- MGB RPDR's mortality data is primarily sourced from the SSDI. Due to the lag time with SSDI data, mortality for the most recent three years is not available in MGB RPDR. However, beyond data from the SSDI, additional information on death is available and supplemented by EHR data if the death occurred in an MGB facility/hospital; deaths reported to MGB by a next of kin can also be abstracted from patient charts.

- The data source includes patients receiving care at the affiliated medical centers within MGB RPDR, whom may not be demographically representative of the general patient population, as patients in the MGB system are more likely to be white and of higher socioeconomic status. As a result, the study findings may have limited generalizability.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site (ie, within the MGB system) in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. MGB will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, MGB shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the research agreement and applicable privacy laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC should be retained by MGB. Copies of IRB/EC approvals must be forwarded to Pfizer.

10.4. 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 described in Guidelines for Good Pharmacoepidemiology Practices,[17] Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),[18] Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making,[19] International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences,[20] European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology,[21] FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment,[22] FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data,[23] and FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.[24]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis

This study involves a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

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

11.2. Human Review of Unstructured Data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report safety events (AEs/SAEs) with explicit attribution to any Pfizer product that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE with such causality documented in the medical chart.

The requirements for reporting safety events on the "Non-Interventional Study Adverse Event Report Form for Protocols with Stipulated Active Collection of Adverse Events", herein after referred to as the NIS AEM Report Form are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the DCT and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy[(a)], breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, occupational exposure, and off-label use associated with the use of any Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

  [(a)] Exposure during pregnancy (EDP) reports are reportable using the NIS AEM Report Form and the EDP Supplemental Form, irrespective of the presence of an associated safety event.

  For exposure during pregnancy in studies of pregnant people, data on the exposure to talazoparib during pregnancy, are not reportable. However, if the mother or the fetus experiences any safety event (either serious or non-serious), the event must be reported without the event EDP.

- For these safety events with an explicit attribution or scenarios involving exposure to any Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up in related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than day/month/year (DD/MMM/YYYY) format.

All site/research staff members must complete the following Pfizer training requirements:

- "Your Reporting Responsibilities (YRR) with Supplemental Topics."

This training must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training statements must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current "*Your Reporting Responsibilities (YRR) with Supplemental Topics*" training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report will be submitted to Pfizer. Results from this study will also be submitted in the form of peer-reviewed publications and presented as an abstract or poster at scientific conferences.
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.

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14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

18. ANNEX 3. ADDITIONAL INFORMATION

Annex 3 Table 1. ICD-10-CM diagnosis codes

Condition	ICD-10-CM diagnosis codes
Cancer-related clinical characteristics	
Prostate cancer	• C61, Malignant neoplasm of prostate
Hormone resistance	• Z19.2, Hormone resistant malignancy status
Metastatic disease	• C77, Secondary and unspecified malignant neoplasm of lymph nodes • C78, Secondary malignant neoplasm of respiratory and digestive organs • C79, Secondary malignant neoplasm of other and unspecified sites • C80.0, Disseminated malignant neoplasm, unspecified • C7B, Secondary neuroendocrine tumors
Bone metastases	• C79.51, Secondary malignant neoplasm of bone
Comorbidities	
Anemia	• D46.0-D46.4, Refractory anemia • D50, Iron deficiency anemia • D51, Vitamin B12 deficiency anemia • D52, Folate deficiency anemia • D53, Other nutritional anemias • D55, Anemia due to enzyme disorders • D56, Thalassemia • D58, Other hereditary hemolytic anemias • D59.0-D59.4, D59.8-D59.9, Acquired hemolytic anemia • D60, Acquired pure red cell aplasia (erythroblastopenia) • D61, Other aplastic anemias and other bone marrow failure syndromes • D63, Anemia in chronic diseases classified elsewhere • D64, Other anemias
Chronic kidney disease (CKD)	• I12, Hypertensive CKD • I13, Hypertensive heart and CKD • N18, Chronic kidney disease • N19, Unspecified kidney failure • Z49.0, Preparatory care for renal dialysis • Z99.2, Dependence on renal dialysis
CCI	• I21, I22, I25.2, Myocardial infarction • I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43, I50, P29.0, Congestive heart failure • I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9, Peripheral vascular disease • G45, G46, H34.0, I60-I69, Cerebrovascular disease • F00-F03, F05.1, G30, G31.1, Dementia • I27.8, I27.9, J40-J47, J60-J67, J68.4, J70.1, J70.3, Chronic pulmonary disease • M05-M06, M31.5, M32-M34, M35.1, M35.3, M36.0, Rheumatic disease • K25-K28, Peptic ulcer disease • B18, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73, K74, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4, Mild liver disease • I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7, Moderate or severe liver disease

Condition	ICD-10-CM diagnosis codes
	• E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9, Diabetes without chronic complication • E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7, Diabetes with chronic complication • G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0-G83.4, G83.9, Hemiplegia or paraplegia • I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2, Renal disease • C00-C26, C30-C34, C37-C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97, Any malignancy including leukemia and lymphoma • C77–C80, Metastatic solid tumor • B20–B22, B24, HIV/AIDS

Abbreviations: CCI, Charlson comorbidity index; CKD, Chronic kidney disease; HIV/AIDS, Human immunodeficiency virus/acquired immunodeficiency syndrome; ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification.

Sources:

[A] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-83.

[B] Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol.* 2011;173(6):676-82.

Annex 3 Table 2. Procedure codes

Condition/ Procedure	Code type	Codes
Orchiectomy	CPT	54520, 54522, 54530, 54535, 54690
Hormone therapy	HCPCS	• J9217, J9218, J9219, J1950, J1951, J1954, J9152, Leuprolide • J9202, Goserelin • J3315, J3316, Triptorelin • J9155, Degarelix • S0175, Flutamide • S9560, Home injectable therapy; hormonal therapy (eg, leuprolide, goserelin)
	ICD-10-PCS	• XW0DXJ5, Apalutamide
Chemotherapy	HCPCS	• J9043, J9064, Cabazitaxel • J9045, Carboplatin • J9060, J9062 Cisplatin • J9171, J9172, Docetaxel • J9293, Mitoxantrone
Immunotherapies	HCPCS	• Q2043, Sipuleucel-T • J9271, Pembrolizumab
Radiopharmaceuticals	HCPCS	• A9607, A9513, Lutetium-177 • A9606, Radium-223
HRR testing	CPT	81445, 81479, 81229, 81405, 81235
Radiation therapy	CPT	• 77371-77525, 77750-77799, Radiation treatment delivery • 55860, 55862, 55865, Exposure of prostate (any approach) for insertion of radioactive substance • 79005-79999, Radiopharmaceutical therapy • 0394T-0395T, Electronic brachytherapy
	HCPCS	• C1715-C2699, Q3001, Brachytherapy • G6001-G6015, Radiation treatment delivery
Dialysis services and procedures, indicative of chronic kidney disease	CPT	90935-90999

Abbreviations: CPT: Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; HRR, Homologous recombination repair; ICD-10-PCS, International Classification of Diseases, 10th Revision, Procedure Coding System.

Annex 3 Table 3. Prostate cancer treatment agent text strings

Treatment Type[1]	Agent	Brand Name
Hormone therapies		
LHRH agonists	Leuprolide, leuprolide mesylate	Camcevi, Eligard, Lupron Depot, Viadur
	Goserelin	Zoladex
	Triptorelin	Trelstar
	Histrelin	Supprelin, Vantas
LHRH antagonists	Degarelix	Firmagon
	Relugolix	Orgovyx
First-generation anti-androgens	Bicalutamide	Casodex
	Flutamide	Eulexin
	Nilutamide	Nilandron
Second-generation ARPIs	Apalutamide	Erleada
	Darolutamide	Nubeqa
	Enzalutamide	Xtandi
Androgen synthesis inhibitors	Abiraterone	Yonsa, Zytiga
	Ketoconazole	Nizoral
Other treatments		
PARP inhibitor	Niraparib/abiraterone	Akeega
	Olaparib	Lynparza
	Rucaparib	Rubraca
	Talazoparib	Talzenna
Chemotherapeutic agents	Cabazitaxel	Jevtana
	Carboplatin	Paraplatin
	Cisplatin	Platinol
	Docetaxel	Taxotere
	Mitoxantrone	Novantrone
Immunotherapies	Sipuleucel-T	Provenge
	Pembrolizumab	Keytruda
Radiopharmaceuticals	Lutetium-177	Pluvicto
	Radium-223	Xofigo

Abbreviations: ARPI, Androgen receptor pathway inhibitor; LHRH, Luteinizing hormone-releasing hormone; PARP, poly(ADP-ribose) polymerase.

Note:
[1] The data source used to identify treatments, MGB RPDR, requires using text strings and not codes to identify drugs.

Source:
[A] Drugs and Supplements. Mayo Clinic. Accessed November 3, 2023. https://www.mayoclinic.org/drugs-supplements
[B] NCCN Guidelines for Patients: Advanced-Stage Prostate Cancer.

Annex 3 Table 4. LOINC codes for select laboratory assessments

Condition	LOINC codes[1]
ALP	1783-0, 6768-6, 77141-0
ANC	751-8, 753-4, 26499-4
eGFR	96591-3, 96592-1, 69405-9, 50384-7, 50210-4, 62238-1, 78006-4, 88293-6, 48643-1, 50044-7, 70969-1, 94677-2, 102097-3, 88294-4, 48642-3, 98979-8, 77147-7, 98980-6
Hemoglobin	718-7, 20509-6, 59260-0, 55782-7
LDH	14804-9, 14805-6
MCV	787-2, 30428-7
PSA	19195-7, 19197-3, 2857-1, 83112-3, 35741-8, 100716-0
Testosterone	2986-8, 14913-8, 83116-4, 105121-8, 83115-6, 49041-7, 70239-9, 96421-3

Abbreviations: ALP, Alkaline phosphatase; ANC, Absolute neutrophil count; eGFR, estimated glomerular filtration rate; LDH, Lactate dehydrogenase; MCV, Mean corpuscular volume; LOINC, Logical Observation Identifiers Names and Codes; PSA, Prostate-specific antigen.

Note:

[1] Pending data availability, text string search may be used in addition to LOINC codes for identifying relevant lab results.

Annex 3 Table 5. Anemia management related treatment agent text strings

Treatment Type[1]	Agent	Brand Name	Procedure codes
Iron supplementation	Ferrous sulfate, ferrous gluconate, ferrous fumarate, ferric sulfate, ferric maltol, ferric citrate, heme iron polypeptide, ferric pyrophosphate citrate, ferric carboxymaltose	Accrufer, Auryxia, Bifera, Duofer, Elite Iron, Ezfe, Femiron, Feosol, Fer-In-Sol, Feratab, Ferate, Fergon, Ferretts, Ferrex 150, Ferrimin, Ferro-Sequels, Ferrocite, Ferrousal, Hemocyte, iFerex 150, Nephro-Fer, Niferex, NovaFerrum, Nu-Iron, Poly-Iron, ProFe, Proferrin, Slow Fe, Slow Iron	HCPCS: J1437, J1439, J1443-J1445, J2916, J1756
Erythropoiesis stimulating agents	Darbepoetin alfa	Aranesp	HCPCS: J0881-J0882
	Epoetin alfa	Epogen, Procrit	HCPCS: J0885, Q4081
	Epoetin alfa-epbx	Retacrit	HCPCS: Q5105-Q5106
	Methoxy polyethylene glycol-epoetin beta	Mircera	HCPCS: J0887-J0888
Red blood cell (RBC) transfusion	-	-	ICD-10-PCS: 30250N0, 30250N1, 30253N0, 30253N1, 30260N0, 30260N1, 30263N0, 30263N1

Abbreviations: HCPCS, Healthcare Common Procedure Coding System; ICD-10-PS, International Classification of Diseases, 10th Revision, Procedure Coding System; RBC, Red blood cell.

Notes:
[1] The data source used to identify treatments, MGB RPDR, requires using text strings and not codes to identify drugs.

Sources:
[A] Drugs and Supplements. Mayo Clinic. Accessed November 3, 2023. https://www.mayoclinic.org/drugs-supplements